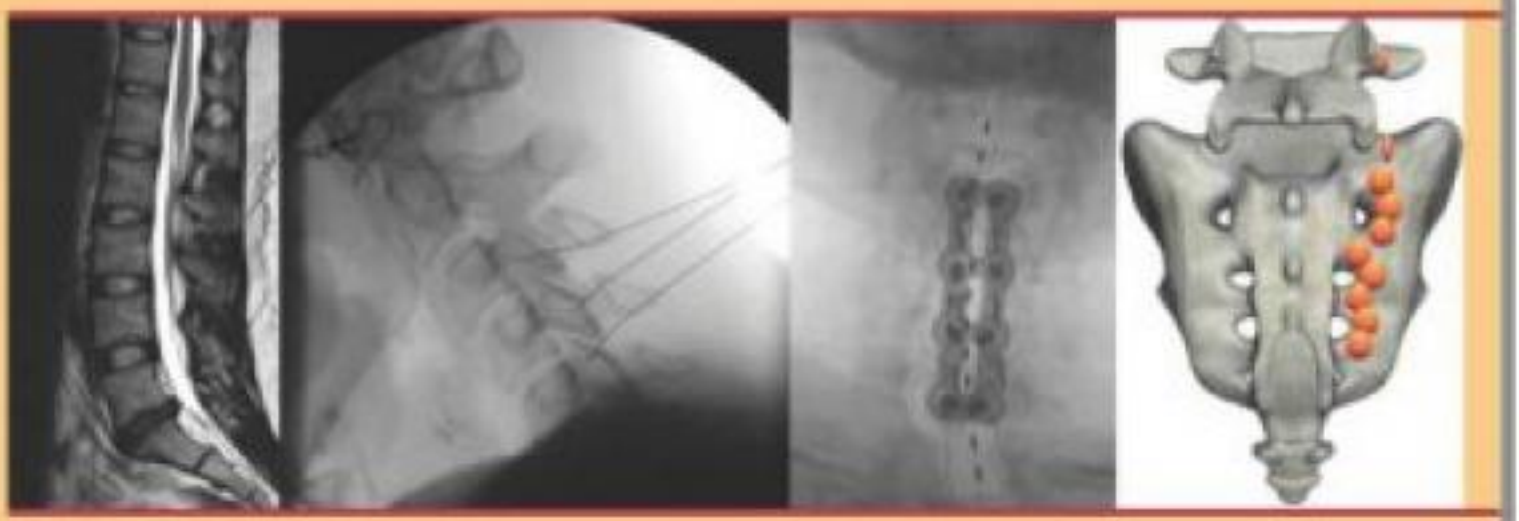
Essentials of Pain Medicine

3rd Edition



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Essentials of
Pain Medicine

Third Edition

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To Robert E. Molloy, MD, who served as an editor of the first two editions of Essentials of Pain Medicine. *Dr. Molloy spent his entire academic career at Northwestern University, Chicago, where he served as the residency program director for 19 years. We, the editors and associate editors, express our profound gratitude to Bob Molloy. His clinical experience is clearly demonstrated in the chapters he wrote and reviewed.*

To my wife, Juliet, for your love and counsel.
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Honorio T. Benzon

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Spencer S. Liu

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Samer Narouze

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In fond remembrance of my parents.
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Preface

The third edition of this book shows maturation. We, the editors, have changed the name to *Essentials of Pain Medicine* to emphasize its mission: the discussion of pain and its management. Consonant with this objective, we have deleted several chapters on regional anesthesia, including chapters on local anesthetics, spinal anesthesia, epidural anesthesia, combined spinal-epidural anesthesia, and caudal anesthesia, as well as chapters on complications of or controversies surrounding neuraxial and peripheral nerve blockade. We simply feel these topics are covered fully in textbooks on regional anesthesia. Realizing that the pain medicine practitioner performs peripheral nerve blocks, we updated the chapters on this topic. Yet, pain medicine has expanded in its scope since the previous edition. We therefore have added chapters on the *Diagnostic and Statistical Manual of Mental Disorders* and pain management, chronic pain after surgery, joint injections, and ultrasound-guided interventional pain procedures.

All the chapters are revised and updated. Key points have been added at the end of the chapters. In light of the complexity of pain and its management, we have added an editor, Dr. Steven P. Cohen, and Drs. Robert W. Hurley, Samer Narouze, Khalid M. Malik, and Kenneth D. Candido as associate editors. They are all experts in specific areas of pain medicine. We welcome them and appreciate their contributions.

The editors and associate editors of the third edition of *Essentials of Pain Medicine* have more than 100 years' clinical experience and have witnessed tremendous improvements in pain management. Once reliant on drugs that were ineffective or saddled with numerous side effects, we now employ drugs that are effective and have minimal side effects. The next few years will bring about the use of receptor-specific medications. Interventional procedures have progressed from blind approaches to fluoroscopy-guided techniques. Today, the use of ultrasound is generating intense interest within the pain medicine community. To the patient suffering from pain, there is continued hope. Indeed, the future looks promising.

Individually, we are grateful to the people closest to us, and to those who helped shape our careers. Collectively, we thank those connected with the publishing of this book, especially Pamela Hetherington. Without their help, this book would not have come to fruition.

The editors and associate editors

Basic Considerations

CHAPTER 1

Anatomy and Physiology of Somatosensory and Pain Processing

Srinivasa N. Raja, MD ❂ **Patrick M. Dougherty,** PhD

Pain is a physiological consequence of tissue injury that serves a vital protective function. For example, clinical observations of patients with congenital insensitivity to pain and patients with leprosy have clearly demonstrated that the absence of pain results in repeated injuries and disabilities. However, pain can become a disease when it occurs or persists in the absence of tissue damage or following appropriate healing of injured tissues. This chronic pain is disabling, has considerable negative impact on quality of life of the individual, and has profound economic impact on the family and society.

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] This definition acknowledges that pain is not only a sensory experience, but may be associated with affective and cognitive responses. The definition also recognizes that the relationship between pain and tissue damage is not necessarily correlated. Thus, an understanding of the anatomic substrates and physiologic mechanisms by which noxious and non-noxious stimuli are perceived provides the essential background to apprehend the mechanisms of acute and chronic pain, and the sites of action of pharmacologic therapies for pain.

SOMATOSENSATION, NOCICEPTION, AND PAIN

Somatosensation is the physiologic process by which neural substrates are activated by physical stimuli resulting in the perception of what we describe as touch, pressure, and pain. Nociception is the physiologic process of activation of neural pathways by stimuli that are potentially or currently damaging to tissue. In experimental situations, a stimulus is considered nociceptive based on an animal's behavioral avoidance or escape response or by studying the activity evoked by the stimulus in specialized groups of afferent fibers. Clinically, the degree of nociception is inferred by overt evidence of tissue damage. Pain, in contrast to nociception, is a conscious experience. While the stimulus-induced activation of afferent neural pathways plays an important role, other factors such as alterations in somatosensory processing following injury to tissues and/or nerves and psychosocial factors may influence the overall perception of pain. The experience of pain, particularly chronic pain, often results in suffering. Suffering results from a multitude of factors that includes loss of physical function, social isolation, family distress, and a sense of inadequacy or spiritual loss. This chapter briefly reviews the basic anatomy and physiology of the neural pathways that respond to somatosensory stimuli, especially nociceptive stimuli, and emphasizes the plasticity in this system following an injury. This knowledge is fundamental in the evaluation and subsequent management of patients with painful disorders.

The sequence of events by which a stimulus is perceived involves four processes: (1) transduction, (2) transmission, (3) modulation, and (4) perception (Fig. 1-1). Transduction occurs in the peripheral terminals of primary afferent neurons where different forms of energy (e.g., mechanical, heat, chemical, or cold) are converted to electrical activity (action potentials). Transmission is the process by which electrical activity induced by a stimulus is conducted through the nervous system. There are three major components of the transmission system. The peripheral sensory cells in the dorsal root ganglia transmit impulses from the site of transduction at their peripheral terminal to the spinal cord where the central terminals synapse with second-order neurons. The spinal neurons are the second component in the transmission network. These cells send projections to the thalamus and various brainstem and diencephalic structures. Finally, neurons of the brainstem and diencephalon form the third component of the transmission network as they project to various cortical sites. Modulation is the process whereby neural activity may be altered along the pain transmission pathway. A major site of modulation occurs within the dorsal horn of the spinal cord. Modulation at this level of processing involves a multitude of neurotransmitter systems that will be discussed in Chapter 2. Activation of pain modulation systems usually results in less activity in the pain transmission pathway following a noxious stimulus. Examples of activation of this process include stress-induced analgesia. However, in some circumstances modulation can also result in an enhancement of pain signaling. Perception is the final stage of the pain-signaling process by which neural activity in the somatosensory transmission pathway results in a subjective sensation of pain. It is presumed that this process results from the concerted activation of primary and secondary somatosensory and limbic cortices.

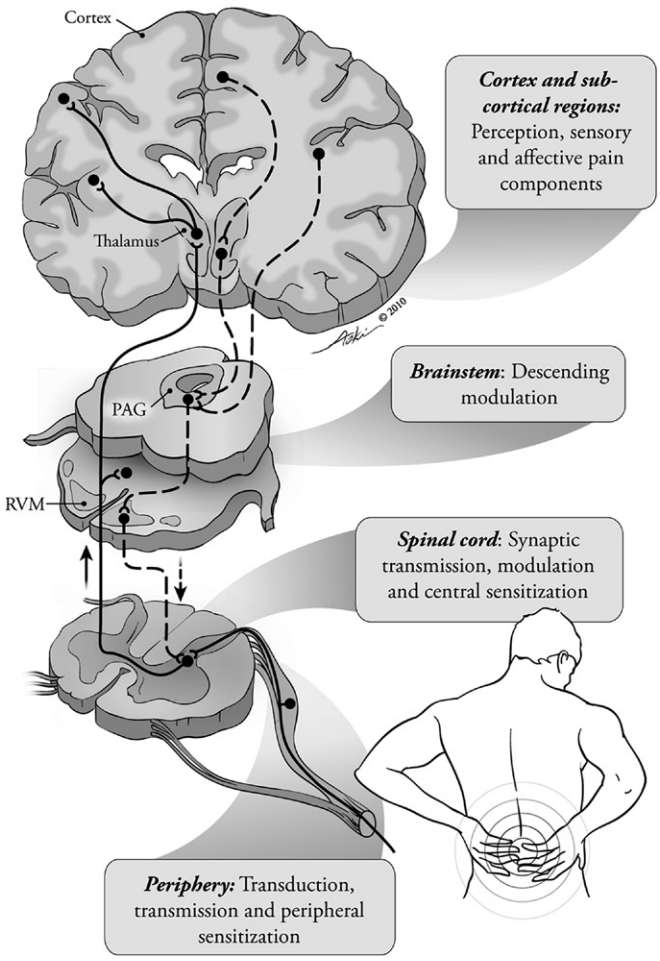

FIGURE 1-1 Schematic of pain-signaling mechanisms involved in transduction, transmission, modulation, and perception of pain. Ascending afferent and descending modulatory pathways are shown.

PERIPHERAL MECHANISMS

In general, somatosensation begins with activation of primary afferent fibers. These fibers are part of the peripheral nervous system with cell bodies located in the dorsal root ganglia. Primary afferent fibers are initially classified based on their conduction velocity and the cutaneous stimuli by which they are activated. Information on the intensity of a given stimulus is coded by the frequency of impulses in a population of primary afferents with a generally monotonic relationship between the stimulus intensity and the number of impulses generated by afferent fibers. There are three classes of primary afferent fibers in skin based on conduction velocity that may be activated by a given cutaneous stimulus.[2,3] The fastest-conducting fibers are the large-diameter myelinated A-beta (Aβ) fibers. When activated they do not normally transmit the sensation of pain, but rather of light touch, pressure, or hair movement. The axons of nociceptive neurons are generally unmyelinated C fibers or thinly myelinated A-delta (Aδ) fibers. Nociceptors have the capacity to respond to intense heat, cold, mechanical, and chemical stimuli. The functional role of the Aδ- and C-fiber nociceptors may be different. The C fibers (0.3 to 3.0 μM) conduct at velocities of less than 2 m/s and are the predominant (>75%) type of afferent fiber in peripheral nerves. Recordings from C fibers in humans suggest that C-fiber activity is associated with a prolonged burning sensation. In contrast, activation of faster-conducting (5 to 20 m/s) Aδ fibers evokes a sharp, intense, tingling sensation. The combined activation of these two groups of afferents, such as by an intense brief heat stimulus, results in a dual-pain sensation[4] as Aδ fibers convey the rapid-onset *first pain* sensation, a pricking pain, while C fibers mediate the slower-onset, burning *second pain* sensation that follows brief intense heat stimulation to the skin. Combined, Aδ- and C-fiber nociceptors encode and transmit information to the central nervous system concerning the intensity, location, and duration of noxious stimuli.

Nociceptive afferents are further subclassified based on the molecules expressed on their cell surface (e.g., receptors, glyco-conjugates), based on the molecules they store and release (e.g., peptides), and based on the enzymes they contain. While none of these cell markers is completely specific for the peripheral target tissue innervated, the percentage of dorsal root ganglion cells positive for a given marker differs significantly among target tissues. For example, almost all visceral afferents are peptidergic, but only about half of the afferents projecting to the skin are,[5] and only a small percentage of the nonpeptidergic afferents, characterized by binding the plant lectin IB4 from *Griffonia simplicifolia*,[6] project to muscle.[7,8] Similarly, the central projection areas of peptidergic and nonpeptidergic afferents differ with peptidergic fibers mainly projecting to lamina I and lamina II outer, and IB4 binding (nonpeptidergic) afferents projecting preferably to lamina II inner (e.g., Silverman and Kruger,[6] but see also Woodbury et al.[9]). Most peptidergic neurons express the tyrosine kinase receptor A (trk A), suggesting that they depend on nerve growth factor (NGF) for survival.[10] In contrast, most IB4-positive dorsal root ganglion cells do not express trk A[11] (see also Kashiba et al.[12]), but express one of the GDNF family receptors (GDNFRα1–4) together with receptor tyrosine kinase Ret.[13,14] Peptidergic and nonpeptidergic neurons also express different patterns of receptors involved in signal transduction, and they may therefore display different sensitivities to a given stimulus. Thus, the $P2X_3$ receptor, which mediates nociceptor excitation by ATP, is primarily expressed in IB4-positive neurons.[15] In contrast, the vanilloid receptor 1 (VR1/TRPV1), which mediates responses to heat, capsaicin, and protons, is expressed in only a minority of IB4-positive cells in mice,[16] and IB4-positive neurons are less responsive to these stimuli than their IB4-negative counterparts.[17,18] The role of these various peptides and receptors, in addition to others, in pain transmission is discussed in greater detail in Chapter 2.

SPINAL MECHANISMS

The first synapse in somatosensory processing of information from the body surface occurs at either the spinal dorsal horn or in the dorsal column nuclei at the spinal cord–brainstem junction.[19] Somatosensory processing for information from the face is similarly processed either in the spinal trigeminal nucleus (pain and temperature) or in the chief sensory nucleus of the trigeminal nerve located in the midpons region of the brainstem. Both nociceptive

and nonnociceptive fibers provide inputs to both of these initial targets. However, under normal circumstances the dorsal column nuclei and the chief sensory nucleus can be considered to selectively process inputs from the large myelinated Aβ-fiber classes related to light touch, while the spinal dorsal horn and spinal trigeminal nucleus process inputs of the nociceptive Aδ and C fibers. This separation of modalities in the somatosensory system is the basis for the localization of neural lesions based on quantitative sensory examination.

Nociceptive primary afferent fibers terminate in a highly ordered way in the spinal dorsal horn on the same side of the body of their origin.[20,21] The dorsal horn is anatomically organized in the form of layers or laminae as first recognized by Rexed in the cat[22] (Fig. 1-2). The unmyelinated C fibers terminate primarily in the most superficial lamina (I and II outer), while the thinly myelinated Aδ fibers end in lamina I, and in laminae III to V. Collaterals of the large myelinated fibers (Aβ) terminate laminae III to V of the dorsal horn.

Two predominant types of second-order nociceptive spinal and spinal trigeminal projection neurons have been identified: wide-dynamic-range neurons (WDR) and nociceptive-specific (NS) neurons.[19] WDR cells are especially concentrated in the deeper laminae of the dorsal horn (III to V) where they receive input from both low-threshold Aβ and nociceptive Aδ and C fibers, and hence are activated by both innocuous and noxious stimuli. However, the responses of WDR cells to these stimuli are graded so that the noxious stimuli evoke a greater response than non-noxious stimuli. WDR spinal projection neurons in monkeys have an average spontaneous discharge rate of approximately 11 Hz, average responses to innocuous cutaneous stimulation by a soft, camel-hair brush of approximately 25 Hz, and average responses to noxious mechanical stimulation by a small arterial clip applied to the skin of approximately 50 Hz (Fig. 1-3).

In contrast to WDR cells, NS projection cells respond only to noxious stimuli under physiologic conditions. The majority of NS cells are found in the superficial laminae of the dorsal horn (I and outer II). These cells have a lower rate of spontaneous activity than WDR cells averaging about 3 to 5 Hz. The discharge rates to the noxious stimuli of NS cells are comparable to those of WDR cells averaging about 50 Hz (Fig. 1-4).

The axons of both the WDR and NS second-order neurons cross the midline near the level of the cell body, gather into bundles of ascending fibers in the contralateral, anterolateral spinal region, and then ascend toward targets in the brainstem and diencephalon (Fig. 1-5). The conduction velocity of the WDR cells is usually faster than that of the NS cells (approximately 30 m/s versus 12 m/s). Additionally, the axons of the NS cells that largely arise from laminae I of the dorsal horn and those of the WDR cells arising primarily from laminae III to V tend to run in slightly different positions in the anterolateral spinal funiculus. In the anterolateral spinal column, the NS cell axons are found in the dorsal medial region, while axons of WDR cells are more concentrated in the ventral lateral region.

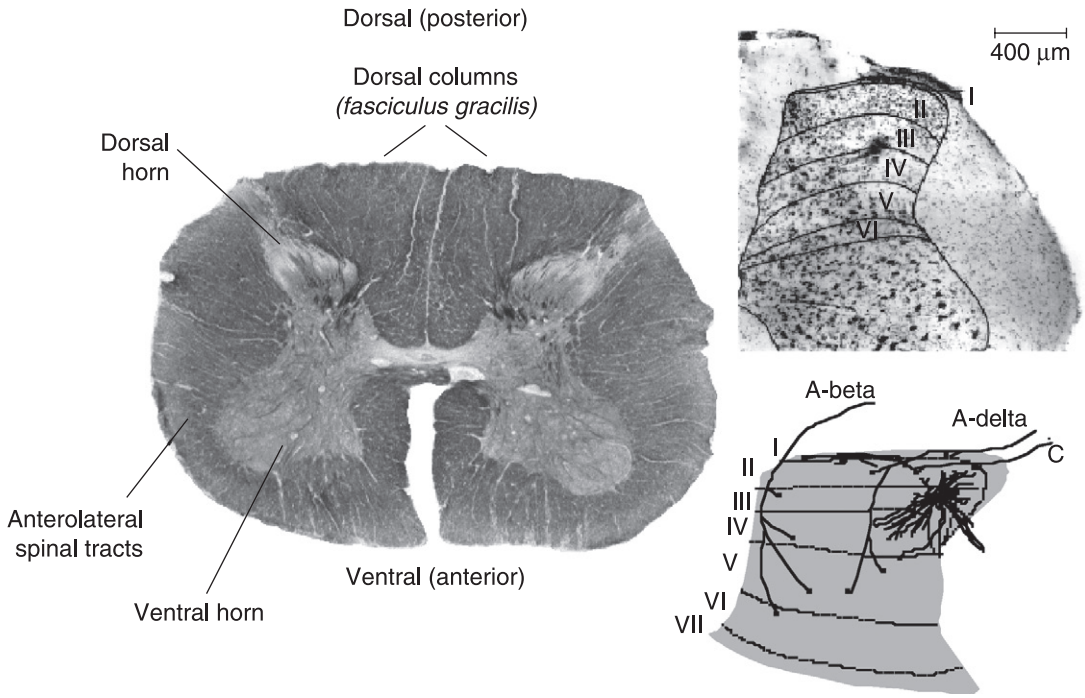

FIGURE 1-2 Histologic sections and schematic diagrams of the spinal dorsal horn. The histologic section at left from human lumbar spinal cord is labeled to show the relationship between the major spinal somatosensory structures. The histologic section at top right is from rat spinal cord. The outer heavy lines show the boundary of the spinal gray matter, while the inner heavy lines show the boundaries of Rexed's laminae. These boundaries are established by the histologic characteristics of each zone, and the layers are identified by the numerals at the right of the dorsal horn boundary. Finally, the schematic at the bottom right illustrates the pattern of primary afferent innervation to the non-human primate spinal dorsal horn. The large myelinated (Aβ) fibers segregate to the dorsal aspect of an entering rootlet and then course medially in the dorsal horn and terminate in layers III to V. The small myelinated (Aδ) fibers and C fibers, which carry nociceptive information, segregate ventrally in the entering roots, course laterally in the dorsal horn, and then largely terminate in the more superficial layers (I and II) of the dorsal horn. The cell profiles inserted in laminae I and II to IV are representative of superficial and deep classes of spinothalamic neurons.

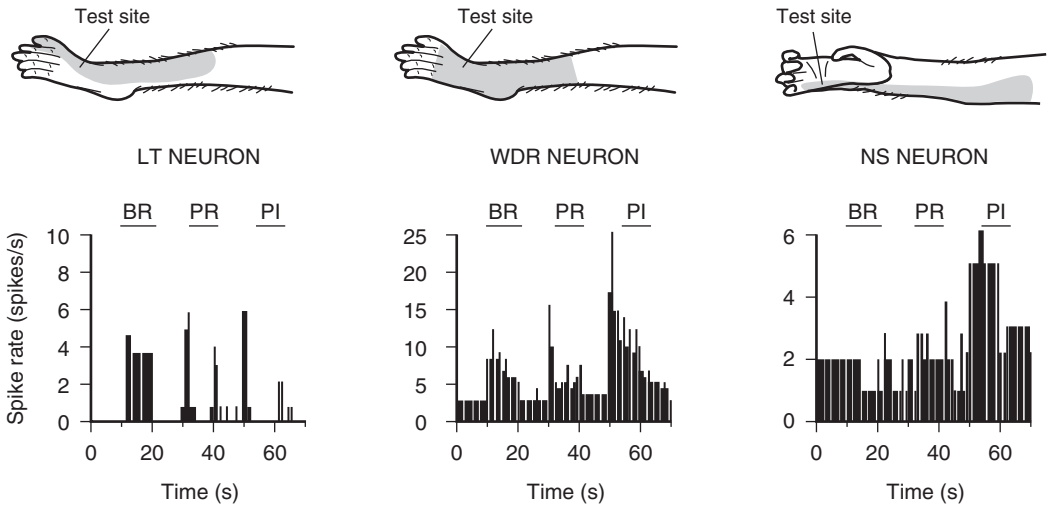

FIGURE 1-3 The rate histograms show responses of primate spinothalamic tract neurons representative of low threshold (LT), wide-dynamic-range (WDR), and nociceptive-specific (NS) classes. The responses of these cells were evoked by application of a series of mechanical stimuli of graded intensity to multiple sites across the receptive field for each cell. The times and sites of each stimulus application are indicated by the lines and labels at the top of each histogram. The brush stimulus (BR) was provided by a soft, camel-hair brush, while a large arterial clip was used to produce innocuous pressure (PR), and a small arterial clip was used to produce a noxious pinch (PI) sensation. The WDR cell in the center shows responses that are graded with the intensity of the stimuli. The NS neuron at the right shows no significant responses to any stimuli but the most intense, while the LT neuron on the left responds to innocuous brushing of the skin alone (the transient responses with the application and removal of the arterial clips are due to the touch stimuli provided at contact). The diagrams of the hind limbs show the receptive field locations of each neuron (*shaded region*) and the site on the skin where each of the mechanical stimuli was applied (*spots*).

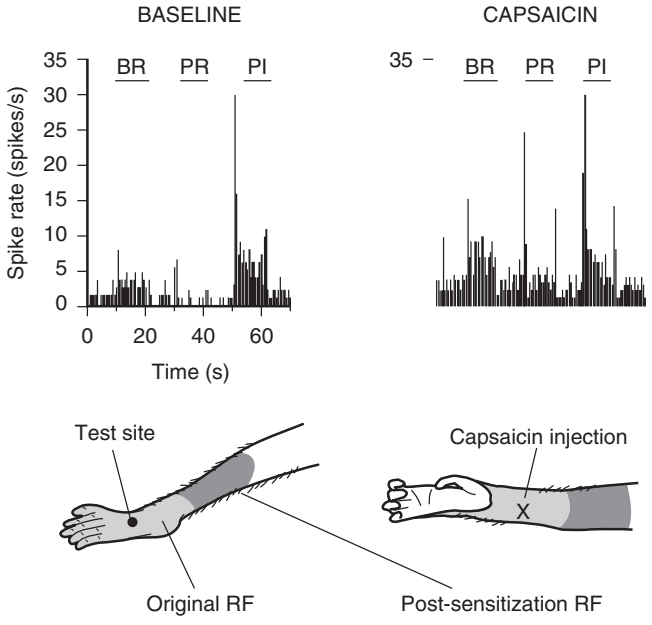

FIGURE 1-4 The rate histograms show the background activity and responses of a representative wide-dynamic-range, spinothalamic tract neuron to mechanical stimulation of the hindlimb before and after sensitization by an intradermal injection of capsaicin. The baseline responses to the mechanical stimuli are shown on the left, while the matching records after capsaicin are shown on the right. The mechanical stimuli were applied to the spot shown on the drawing of the leg at the bottom. The *X* shows the site at which capsaicin was delivered. The *light gray* area shows the receptive field during the baseline recordings, while the *dark gray* area shows the expansion in the receptive field induced by capsaicin.

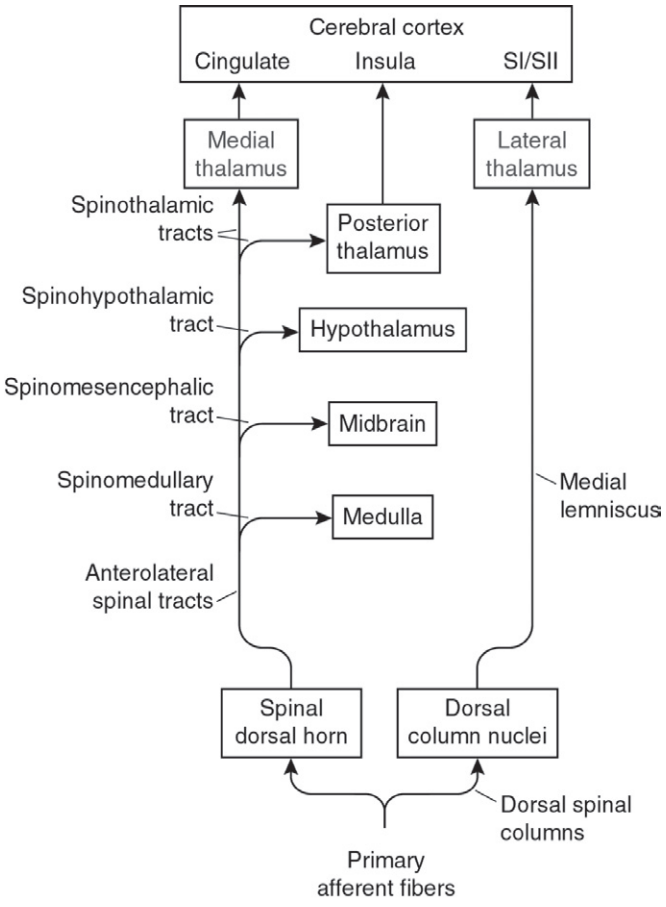

FIGURE 1-5 Schematic diagram summarizing the central nociceptive pathways. Each box represents the discrete anatomic locations at which noxious stimuli are processed and/or registered. The lines indicate the neural pathways that interconnect each of the anatomic locations.

SPINAL MODULATION

The concept of modulation of noxious inputs at spinal levels was highlighted by the gate control theory of Melzack and Wall.[23] This theory suggested that input along low-threshold (Aβ) fibers inhibits the responses of WDR cells to nociceptive input. The theory was offered as an explanation for the efficacy of transcutaneous electrical stimulation for pain relief. Subsequent studies have identified intrinsic spinal neurons that release a plethora of neurotransmitters in the spinal cord that play a role in the modulation of nociceptive impulses. Furthermore, a number of inputs to the dorsal horn from various brainstem sites have been shown to also modulate peripheral inputs as well as outputs of intrinsic cells.[24,25] Both types of modulation, that arising in the local network of cells at the spinal levels as well as that from the descending inputs, can result in either augmented or inhibited output from spinal cord pain-signaling neurons. It is the combined effects of spinal excitatory and inhibitory systems that determine what messages are delivered to the higher levels of the central nervous system (CNS).

A special type of spinal modulation that is observed under certain circumstances is known as central sensitization.[26] In this phenomenon, the capacity for transmission in the nociceptive system is changed or shows neuronal plasticity. The result of this plasticity is that following a noxious stimulus of sufficient intensity and duration, such as a surgical incision, the coding of pain-signaling neurons for a given stimulus may be increased. One example of central plasticity is the phenomenon of wind-up, whereby repeated stimulation of C fibers at intervals of 0.5 to 1 Hz results in a progressive increase in the number of discharges evoked by each volley.[27] In addition to an increase in discharges evoked by a given stimulus, sensitized spinal neurons also show an expansion of receptive field size and an increase in spontaneous discharge rate. WDR cells tend to become sensitized more readily than do NS cells. However, in those circumstances where NS cells do show sensitization they often acquire novel responsiveness to innocuous stimuli and hence could be recategorized as WDR neurons. The neurochemistry of central sensitization is discussed in Chapter 2. Better understanding of the pharmacology of this and other types of plasticity will have profound consequences in the development of new analgesic pharmacotherapies.

SUPRASPINAL MECHANISMS

Supraspinal structures involved in somatosensory processing include brainstem, diencephalic, and cortical sites.[28] There are two sets of somatosensory inputs to the brainstem and diencephalon. First, many axons and axon collaterals of the spinal projection neurons that ascend in the anterolateral spinal quadrant depart this ascending tract to terminate in a number of nuclei of the brainstem and midbrain. These target sites include brainstem autonomic regulatory sites that influence cardiovascular and respiratory functions, while in the midbrain there are multiple inputs to centers from which both descending as well as ascending (e.g., to thalamus) modulation of somatosensory processing is evoked. The remainder of the so-called anterolateral system fibers continues through the brainstem and midbrain to terminate in diencephalic structures, including the hypothalamus and posterior, lateral, and medial regions of the thalamus (see Fig. 1-5).

The second set of somatosensory inputs to the brain stem includes those primary afferent fibers that ascend in the dorsal (posterior) columns of the spinal cord to form their first synapse at the dorsal column nuclei. These inputs are organized so that the fibers from the lower extremities synapse most medially in the nucleus gracilis and inputs from the upper extremities synapse laterally in the nucleus cuneatus. The trunk is represented in regions of both nuclei. Comparative inputs from the face are processed in the chief sensory nucleus of the trigeminal nerve located at the origin site of cranial nerve five in the midpons of the brainstem. The axons of the second-order cells in the dorsal column nuclei cross the midline and form the medial lemniscus on the contralateral side of the brainstem. These fibers then ascend through the brainstem and midbrain acquiring the functionally related fibers from the trigeminal nerve as they pass and continue on to provide the second somatosensory input to the diencephalon as they terminate in the ventral posterior lateral (VPL) nucleus (inputs from the body) and ventral posterior medial (VPM) nucleus (inputs from the face) of the thalamus.

The somatosensory inputs to the cortex include the third-order projections from thalamic somatosensory relay neurons of VPL and VPM as well as third- (and higher-) order neurons projecting from brainstem and midbrain relay neurons.[29,30] Some of these projections are highly organized and quite specific. For example, the cells in the core of VPL that receive inputs from the dorsal column–medial lemniscus fibers project to cortical areas SI and SII. The neurons in the posterior region of the lateral thalamus receiving inputs from the anterolateral system project to SII and the retro-insular areas of cortex, while medial thalamic nuclei ultimately project to the anterior cingulate cortex. Similarly, somatosensory relay neurons of the midbrain parabrachial nucleus project specifically to the amygdaloid nucleus of the neocortex. On the other hand, other third-order projections into cortex are quite diffuse. Outputs from cells of the brainstem reticular activating system that receive somatosensory inputs from the spinoreticular tract, for example, project throughout the neocortex.

In addition to peripheral and spinal mechanisms of nociceptive processing and modulation, there are several cortical regions that consistently have been shown to be involved in acute and chronic pain states. While the exact brain areas included in what has been coined the "pain matrix" have been the focus of debate, the primary and secondary somatosensory cortices, insula, anterior cingulate cortex, prefrontal cortex, and several nuclei of the thalamus have consistently been shown to be active in imaging studies of acute and chronic pain states. Additionally, most pharmacologically induced analgesia has been shown to have effects in these brain regions. The "pain matrix" has further been categorized as comprising the lateral pathway, which encodes for the sensory-discriminative aspect of pain perception, and the medial pathway, which encodes for the affective component of pain perception. Brain structures

involved in the affective component of pain processing are required for encoding the unpleasant and aversive aspects of pain, which is critical for self-preservation. A case study of several patients with unilateral ischemic damage to the insular cortex exhibited pain *asymbolia*, as evidenced by a lack of or inappropriate emotional response to multiple painful stimuli applied over the entire body. Moreover, these patients failed to learn appropriate escape or protective responses in response to the painful stimuli.[31] Another example of the role of cortical structures in the experience of pain is the placebo analgesic effect. Previous studies have shown that the placebo effect is at least partially mediated by activation of the endogenous opioid system, and μ-opioid receptors are highly localized within structures of the pain matrix.[32,33] Recent studies using PET and the selective μ-opioid radiotracer[11] [11C]carfentanil have shown that the placebo-mediated activation of the endogenous opioid system is predominantly located in the pain matrix structures such as the anterior cingulate, prefrontal cortex, insula, medial thalamus, amygdala, and periaqueductal gray.[34,35]

SUPRASPINAL MODULATION OF NOCICEPTION

Several lines of research have clearly indicated that plasticity and modulation of somatosensory signaling occur at brainstem, midbrain, and diencephalic levels. Examples of plasticity of responses of dorsal column neurons following intradermal injection of the irritant capsaicin have been documented in the rat and monkey. Similarly, with the development of acute inflammation and following deafferentation, neurons of the thalamus alter their patterns of spontaneous discharge so that a large increase in bursting of these cells is observed. Ascending modulation from the brainstem dorsal raphe nucleus also influences signaling of thalamic neurons.

Descending modulation of nociception at the supraspinal level is a well-established phenomenon that can have both inhibitory and facilitatory effects on primary afferent neurons in the dorsal horn. This modulation is important for the attenuation of acute pain, and the facilitatory aspect has been implicated in the establishment and maintenance of chronic pain states. There are many different sites and pathways involved in descending modulation. Highlighting the complexity of this phenomenon, the vast majority of these anatomic sites have been shown to have inhibitory and facilitatory effects. The best characterized pathway is the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) pathway. The PAG and RVM receive descending projections from a variety of cortical and limbic sites known to be involved in the affective component of pain processing such as the anterior cingulate cortex, amygdala, and prefrontal cortex. Activation of these structures results in pro- or anti-nociceptive effects and requires the PAG and RVM.[36,37] The PAG has few direct projections to the spinal cord and instead projects to the RVM, which sends either inhibitory or excitatory impulses to nociceptive projection and WDR neurons in the superficial and deep layers of the dorsal horn of the spinal cord.

It is hypothesized that the RVM is able to facilitate both inhibitory and facilitatory effects on the dorsal horn via different types of neurons termed "ON" and "OFF" cells.[38] These contrasting cell types have distinctly different functional characteristics. OFF cells are tonically active except during nociceptive input and activated by known analgesics such as morphine. In contrast, ON cells become more active during nociceptive input and are inhibited by morphine.[38–40] It is generally accepted that OFF cells are required for descending inhibition.

While the evidence supporting the role of ON cells in descending facilitation is mixed, several studies have shown that activation of ON cells within the RVM induces hyperalgesia. For example, the peptide cholecystokinin (CCK) induces mechanical and thermal hyperalgesia when directly injected into the RVM and this direct CCK administration has been shown to preferentially activate ON cells.[41,42] Additionally, ON cells are activated, and OFF cells suppressed, in models of chronic pain.[43,44] Descending facilitation via ON cell activation is thought to induce hyperalgesia by upregulating spinal dynorphin, which is linked to the increased release of excitatory neurotransmitters from primary afferent neurons, which can lead to central sensitization and chronic pain.[45] ON cell activation and the subsequent cascade of facilitatory effects in the spinal cord are also implicated in opioid-induced hyperalgesia resulting from chronic opioid exposure.[46,47]

Recent studies indicate that in addition to functional changes in neurons, microglia and astrocytes may also play an important role in the central sensitization process. Other central neuroplastic changes that may contribute to neuropathic pain states include deafferentation hyperactivity that may occur following spinal cord or avulsion injuries, loss of large-fiber afferent inhibition, reorganization of central connections of primary afferent fibers, and excitatory descending modulatory mechanisms. Central, and to a lesser extent peripheral sensitization, are considered to be the prime culprits responsible for pain induced by innocuous stimuli (*allodynia*), and increased pain to normally noxious stimuli (*hyperalgesia*), that are commonly observed in neuropathic pain states.

KEY POINTS

- The processes resulting in a noxious stimulus-inducing pain are transduction, transmission, modulation, and perception.
- Nociceptors in the periphery respond to intense heat, cold, mechanical, or chemical stimuli, and encode the intensity, location, and duration of noxious stimuli.
- The dorsal horn is anatomically organized in laminae. Unmyelinated C fibers terminate in Rexed's laminae I and II, and large myelinated fibers terminate in the laminae III to V.
- Two types of second-order nociceptive spinal and spinal trigeminal projection neurons are wide-dynamic-range (WDR) and nociceptive-specific (NS). WDR cells receive input from both Aβ and nociceptive (C and Aδ) fibers.
- The somatosensory system is composed of two main signaling channels. The anterolateral system is the primary pain-signaling channel. In contrast, the dorsal

column–medial lemniscal system is primarily a high-speed, very discrete signaling channel for innocuous stimuli.

- Several cortical regions, referred to as the "pain matrix," have been shown to be involved in acute and chronic pain states. These regions include the primary and secondary somatosensory cortices, insula, anterior cingulate cortex prefrontal cortex, amygdala, and several nuclei of the thalamus.
- Descending modulation of nociception from supraspinal level sites can have both inhibitory and facilitatory effects on spinal dorsal horn neuronal activity. Descending modulation may be important for the attenuation of acute pain. However, descending facilitatory activity has been implicated in the establishment and maintenance of chronic pain states.
- Derangements can occur in both the ascending and descending signaling systems at any and all levels that result in the generation of chronic pain.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 2

Neurochemistry of Somatosensory and Pain Processing

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Expertise in the neurochemistry of somatosensory processing provides clinicians with the knowledge needed to control pain transmission at two levels: first, at transduction of injury-related signals by nociceptors in skin, and second, by modification of pain transmission through the central nervous system (CNS).

NEUROCHEMISTRY OF PAIN TRANSDUCTION

Numerous chemicals are released in skin following tissue injury that either directly activate nociceptors or that increase the general excitability of nociceptors. The graphical summary of many of these mediators shown in Figure 2-1 reveals that these are numerous. As such, these mediators are frequently referred to simply as an "inflammatory soup."

Inflammatory Soup: Several of the key "ingredients" of this soup include the following components.

Bradykinin, a potent vasodilating peptide, plays a critical role in inflammatory pain and hyperalgesia via actions on two G-protein–coupled receptors: the constitutively expressed B2 receptor, and the B1 receptor, the expression of which is increased following tissue injury (see Cray[1] and Couture et al.[2] for reviews). Following injury, bradykinin is released by kininogens and produces acute pain in man by activation of unmyelinated and myelinated nociceptors.[3] Bradykinin also produces transient heat hyperalgesia in humans by sensitization of nociceptors through activation of phospholipase C (PLC), protein kinase C (PKC), the production of eicosanoids and nitric oxide (NO), and modulation of the TRPV1 (VR1) channel (see below).

Low pH (excess free H^+) of inflamed tissue also contributes to the pain and hyperalgesia associated with inflammation. Low pH selectively causes activation and sensitization of nociceptors to mechanical stimuli by opening dorsal root ganglion neuron specific acid-sensing ion channels (DRASIC/ASIC-3, see Waldemann[4] for review). Excitation of nociceptors by protons does not undergo tachyphylaxis or adaptation, and a synergistic excitatory effect of protons and a combination of inflammatory mediators has been reported.[5,6]

Serotonin, which is released from platelets in response to platelet activating factor derived from mast cell degranulation, leads to pain by directly activating nociceptors.[7] In humans, direct application of serotonin to a blister base produced pain.[8] Serotonin also potentiates bradykinin-induced pain and nociceptor activation.

Histamine is released from mast cells by Substance P and calcitonin gene–related peptide (CGRP). These neuropeptides are derived from activated nociceptors and produce a variety of responses, including vasodilation and edema. Exogenous histamine applied to the skin produces itch but not pain.[9] Nevertheless, histamine excites polymodal visceral nociceptors and potentiates the responses of nociceptors to bradykinin and heat.[10]

Eicosanoids are a large family of arachidonic acid metabolites that include the *prostaglandins*, *thromboxanes*, and *leukotrienes*. Eicosanoids directly activate articular afferents and sensitize these, as well as those in skin and viscera, to natural stimuli and other endogenous chemicals (for reviews see Cunha and Ferreira[11] and Schaible et al.[12]). Prostaglandins, synthesized by the constitutive enzyme, COX-1, and by the inducible enzyme COX-2,[13] reduce the activation threshold of tetrodotoxin-resistant Na^+ currents in nociceptors, increase intracellular cAMP levels, and increase the excitability of sensory neurons. Leukotrienes, metabolites of the lipoxygenase pathway, are released by macrophages and mast cells, contribute to hyperalgesia and sensitization to mechanical stimuli by acting on G-protein–coupled receptors (GPCR) and by serving as chemoattractants for cytokine-producing cells,[14] and result in further sensitization of primary afferents.

Nitric oxide (NO) released by damaged afferents and acting on soluble guanylyl cyclase (sGC) can further sensitize nearby neurons, augmenting pain and inflammation in both GPCR and non–GPCR-mediated pathways.[15] Direct injection of NO into the skin produces acute pain in humans,[16] and mechanical sensitivity in an animal model of neuropathic pain was decreased following administration of the NO synthase inhibitor L-NAME.[17]

Adenosine and its mono- and poly-phosphate derivates (AMP, ADP, ATP) are increased in the extracellular space with tissue injury and inflammation (for reviews see Hamilton and McNahon[18] and Ralevic and Burnstock[19]). Like serotonin, adenosine induces pain in humans by direct activation of nociceptors. ATP also induces pain in humans and activates C-nociceptors in healthy human skin, but does not sensitize C fibers to mechanical or heat stimuli. It is thought that ATP activates nociceptive neurons in normal skin via the purinergic receptors $P2X_3$ and the heteromeric $P2X_2/P2X_3$ receptor[20] (discussed below).

Cytokines (e.g., *interleukin-1*β (*IL-1*β); *tumor necrosis factor* α (*TNF*α); *interleukin-6* (*IL-6*)) are released by a variety of cells, such as macrophages, astrocytes, and Schwann cells, to regulate inflammatory cell responses (see Cunha and Ferreira[11] for review), but also promote pain signaling. Both IL-1β and TNFα directly excite and sensitize nociceptive afferent fibers to thermal and mechanical stimuli, and IL-6 in combination with its soluble IL-6 receptor also sensitizes nociceptors to heat. Clinical studies show that TNFα levels are increased in synovial fluid of painful joints and treatment with antibodies against TNFα improves symptoms accompanying rheumatoid arthritis, including pain.[21] Further contributing to pain and inflammation is the fact that Schwann cells express receptors for

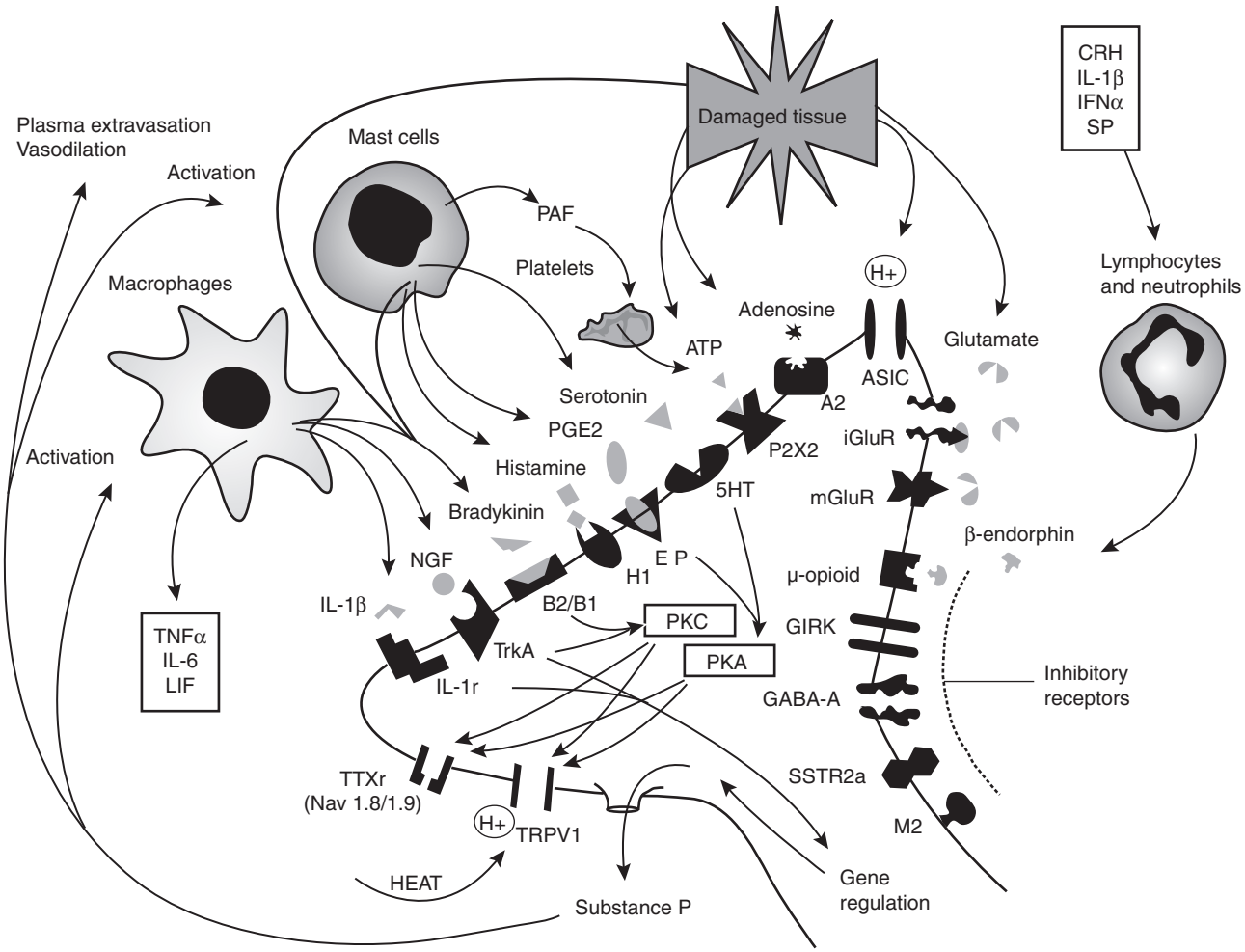

FIGURE 2-1 Schematic diagram of the neurochemistry of somatosensory processing at peripheral sensory nerve endings.

certain cytokines, such as TNF, IFN, IL-1, and IL-6. Activation of these receptors triggers a cascade of downstream reactions, including downregulation of myelin synthesis, increased expression of nerve growth factor receptors, dedifferentiation, and proliferation. The activated Schwann cells then begin to synthesize and release proinflammatory cytokines, affecting neighboring Schwann cells, and thus closing a positive feedback loop that can sustain pain.

Further, a subset of chemotactic cytokines, the *ckemokines*, plays a role in the development of ongoing pain. For instance, monocyte chemoattractant protein 1 (MCP1) and its receptor CCR2 are upregulated in primary afferent fibers and DRG cells following nerve injury, and injection of MCP1 in control animals creates a state of mechanical allodynia.[22] Additionally, mice lacking the CCR2 receptor are less susceptible to neuropathic pain.[23]

Excitatory amino acid (EAA) receptors play a role in the modulation of nociception. Researchers have reported the presence of such receptors on dorsal root ganglion cells and on the presynaptic terminals of primary afferents (see Carlton[24]). Peripheral injection of glutamate activates nociceptors by binding to both ligand-gated ion channels (ionotropic glutamate receptors, iGlu) and G-protein–coupled metabotropic (mGlu) type 1 and type 5 (mGluR1, mGluR5) receptors on unmyelinated axons. Neurons in the DRG labeled for mGluR5 also express vanilloid receptors (VR1) characteristic of nociceptive neurons.[25]

Nerve growth factor (NGF) may contribute to inflammatory pain via direct and indirect mechanisms. Inflammatory mediators, such as cytokines, increase NGF production in inflamed tissues (see McMahon[26]). In turn, NGF stimulates mast cells to release histamine and serotonin, which can sensitize primary afferent fibers. Further, NGF itself may directly sensitize nociceptors and can alter the distribution of A-δ fibers such that a greater proportion of fibers have nociceptor properties.[27] Heat hyperalgesia can be induced by NGF acting directly on the peripheral terminals of primary afferent fibers.[28] NGF is implicated in the inflammation-induced changes in nociceptor response properties, such as an increase in the incidence of ongoing activity, increase in maximum fiber frequency, and changes in the configuration of the action potential of DRG neurons. NGF-induced hyperalgesia may be mediated via its actions on the TTXr sodium channel, Nav 1.8 and by potentiating the responses of the VR1 receptor.[28]

Proteinases such as *thrombin*, *trypsin*, and *tryptase*, although not traditionally considered part of the inflammatory soup, are gaining increasing attention as mediators of pain and inflammation for their actions on *proteinase-activated receptors (PAR)*.[29] There are four classes of PAR, with PAR1 and PAR2 being implicated strongly in pain and inflammation. Both receptor types are located in the periphery on nerve fiber endings. Activation of PAR1 via thrombin leads to the release of histamine, substance P, CGRP, and cytokines. Activation of PAR2 by trypsin and tryptase creates a cascade of inflammatory reactions, including prostaglandin and bradykinin release, which would further sensitize unmyelinated primary afferents. The net effect of activation of these receptors is sensitivity to both mechanical and thermal stimuli.

Matrix metalloproteinases (MMP) comprise a large family of endopeptidases that have only recently been found to contribute to pain. MMP-2, and possibly MMP-9, has been suggested to be related to diabetic neuropathy. MMPs serve as a macrophage chemoattractant and convert the cytokine TNFα into its active form. Following injury, microglia release MMPs, and at least one MMP, MMP-3, is upregulated in DRG cells.[30] Use of the MMP-3 inhibitor minocycline protects against chemotherapy-induced hypersensitivity. Further, research using other MMP antagonists has found decreased MMP-mediated degradation of myelin basic protein, decreased macrophage infiltration, and subsequent decreased mechanical sensitivity.[31] At this time, the mechanisms and receptors involved in MMP-related pain induction have not been fully explored.

Peripheral Anti-Hyperalgesic Mechanisms: In contrast to the mediators discussed above, there are also numerous mediators released into inflamed or injured tissue that act to limit pain transmission.

Opioids are also a component of the inflammatory soup (see Machelska and Stein[32] for review). The peripheral terminals of afferent fibers contain receptors for opioids, but the number of receptors present is upregulated during inflammation. Further, inflammatory cells such as macrophages, monocytes, and lymphocytes induced by interleukin 1β and corticotropin-releasing hormone (CRH) originating from the inflamed tissue may serve to increase the amount of endogenous opioids in the tissue. Peripheral endogenous opioids may also be activated by endothelin-1 (ET-1), which is a potent vasoactive peptide, synthesized and released by epithelia after tissue injury.[33] Paradoxically, ET-1 can trigger pain by activating ET_A receptors on nociceptors or analgesia through its actions on ET_B receptors. Activation of ET_B receptors on keratinocytes by ET-1 results in release of β-endorphins and analgesia that is mediated via peripheral μ– and κ–opioid receptors that are linked to G-protein–coupled, inward-rectifying potassium channels (GIRKs).

Acetylcholine is released into injured tissue from non-neuronal sources and modulates pain via its effects on nicotinic or muscarinic receptors. Nicotinic agonists have weak excitatory effects on C-nociceptors and induce a mild sensitization to heat but no alterations in mechanical responsiveness. In contrast, muscarinic agonists desensitizes C-nociceptors to mechanical and heat stimuli.[34] Mice with targeted deletions of the M2 receptor show enhanced responsiveness of nociceptive fibers to noxious stimuli (see Wess[35] for review) indicating a tonic inhibitory role for this mediator.

Gamma amino butyric acid (GABA) may have a peripheral role in pain transmission similar to the bimodal actions of acetylcholine. $GABA_A$ receptors are located on unmyelinated primary afferents and activation of these receptors by low doses of the agonist muscimol decrease pain, whereas high doses potentiate pain.[36] $GABA_A$ receptors have also been found in DRG cells and on their central terminals in the dorsal horn, and direct application of GABA antagonists to DRG cells decrease hypersensitivity in an animal model of neuropathic pain.[37]

Somatostatin (SST) is a peptide commonly associated with the GI system that may also serve as an antinociceptive agent. Type 2a receptors (SSTR2a) are present in about 10% of unmyelinated primary afferent fibers innervating the glabrous skin of the rat,[38] and intraplantar administration of the SST receptor agonist, octreotide, reduces the phase II response after formalin injection. In addition, octreotide reduces the response of CMHs to heat stimuli and attenuates the thermal responses of nociceptors sensitized by bradykinin. SST also inhibits the release of cholecystokinin, which has been shown to have nociceptive properties. The peripheral effects of SST agonists may be mediated by a direct effect on primary afferents or by its anti-inflammatory effects.

Peripheral Second Messenger Pathways: Inflammation is associated with the release of a host of chemical mediators. These agents may mediate pain by directly activating nociceptors, such as is primarily discussed above. However, they may also produce more enduring changes in the sensory neuron, such as early post-translational changes or even longer-lasting transcription-dependent changes in effector genes in DRG cells (see Kidd and Urban[39] and Woolf and Costigan[40]). The early post-translational changes include phosphorylation of transducer molecules (e.g., VR1 receptor) and voltage-gated ion channels (e.g., sodium channels) in the peripheral terminals of nociceptors (peripheral sensitization). A classic example of these changes is seen in the *vanilloid receptor TRPV1* (also known as VR1). This receptor is present on a subpopulation of primary afferent fibers that are activated by capsaicin, heat, and protons. Inflammatory mediators, such as bradykinin and NGF, lower the threshold of TRPV1-mediated, heat-induced currents in DRG neurons and increase the proportion of DRG cells that respond to capsaicin.[41,42] These changes occur by phospholipase C (PLC)–dependent phosphorylation by protein kinase (PKC), by phosphorylation by protein kinase A (PKA),[43,44] and by hydrolysis of the membrane phospholipid, phosphatidylinositol-4-5-biphophate (PIP_2).[28] PKA and PKC also induce a short-term sensitization of nociceptors to heat by modulating the activity of tetrodotoxin-resistant sodium currents.[45,46] Additionally, increases in the activity of the various transcription factors, including cAMP-responsive, element-binding protein (CREB)[47] and the mitogen-activated protein kinases (MAPK), most especially, the extracellular signal-regulated kinases (ERK), the c-Jun amino-terminal kinases (JNK) and the p38 enzymes[48–50] produce even longer-term changes in TRPV1 following inflammation in primary afferent fibers.

NEUROCHEMISTRY OF PAIN TRANSMISSION

As reviewed in the previous chapter, the anterolateral and dorsal column-medial lemniscal pathways mediate pain transmission throughout the CNS, with differences between these paths being determined by anatomy and physiology of constituent neurons. However, unlike the differences in anatomy and physiology between the anterolateral and dorsal column–medial lemniscal systems, the neurochemistry of somatosensory processing in both is very similar. Both systems involve three classes of transmitter compounds, excitatory neurotransmitters, inhibitory neurotransmitters, and neuropeptides that are found in three anatomical compartments: sensory afferent terminals, local circuit terminals, and descending (or ascending) modulatory circuit terminals (Fig. 2-2).

Excitatory Neurotransmitters: The amino acids glutamate and aspartate constitute the main excitatory neurotransmitters found at synapses throughout the somatosensory system. Thus, transmission between primary afferent fibers and spinal neurons,[51] between spinal neurons and thalamic neurons,[52] and so on, are dependent on the four receptor types for glutamate and aspartate in the somatosensory system. These receptors are named for the synthetic agonists that best activate them; they include the *N-methyl-D-aspartate (NMDA)*,[53] the *kainate*, the *AMPA ((R,S)-a-amino-3-hydroxy-5-methlyisoxazole-4-propionic acid) receptors*, and the *metabotropic receptors*.[54] The latter three are often collectively referred to as the non-NMDA receptors. The AMPA and kainate receptors gate sodium channels and mediate the majority of the fast synaptic afferent signaling for all modalities and intensities of stimuli. The NMDA receptor is recruited only by intense and/or prolonged somatosensory stimuli that are sufficient to relieve the tonic magnesium block that regulates its divalent cation channel. Persistent activation of NMDA receptors leads to sensitization of dorsal horn neurons that includes an increase in receptive field size, decreased activation threshold, and prolonged depolarization. Multiple factors influence NMDA receptor–related sensitization. For instance, the release of bradykinin leads to increases in spinal glutamate released by astrocytes and neurons.[55] This glutamate activates NMDA receptors, augmenting central sensitization.

In addition to the release of glutamate from neurons, activated glial cells can release glutamate. In certain pain conditions, such as chemotherapy-induced neuropathy, glial glutamate transporters GLAST and GLT-1 are downregulated, leading to decreased reuptake of spinal glutamate and subsequent spillover of glutamate to extrasynaptic receptor sites.[56]

The metabotropic glutamate receptors (mGluR) are a family of G-protein–linked sites involved in more long-term cellular changes. When activated, the group I mGluR's are coupled to $G_{q/11}$ that activates phospholipase C liberating inositol phosphate which in turn results in the release of cytosolic calcium and activation of protein

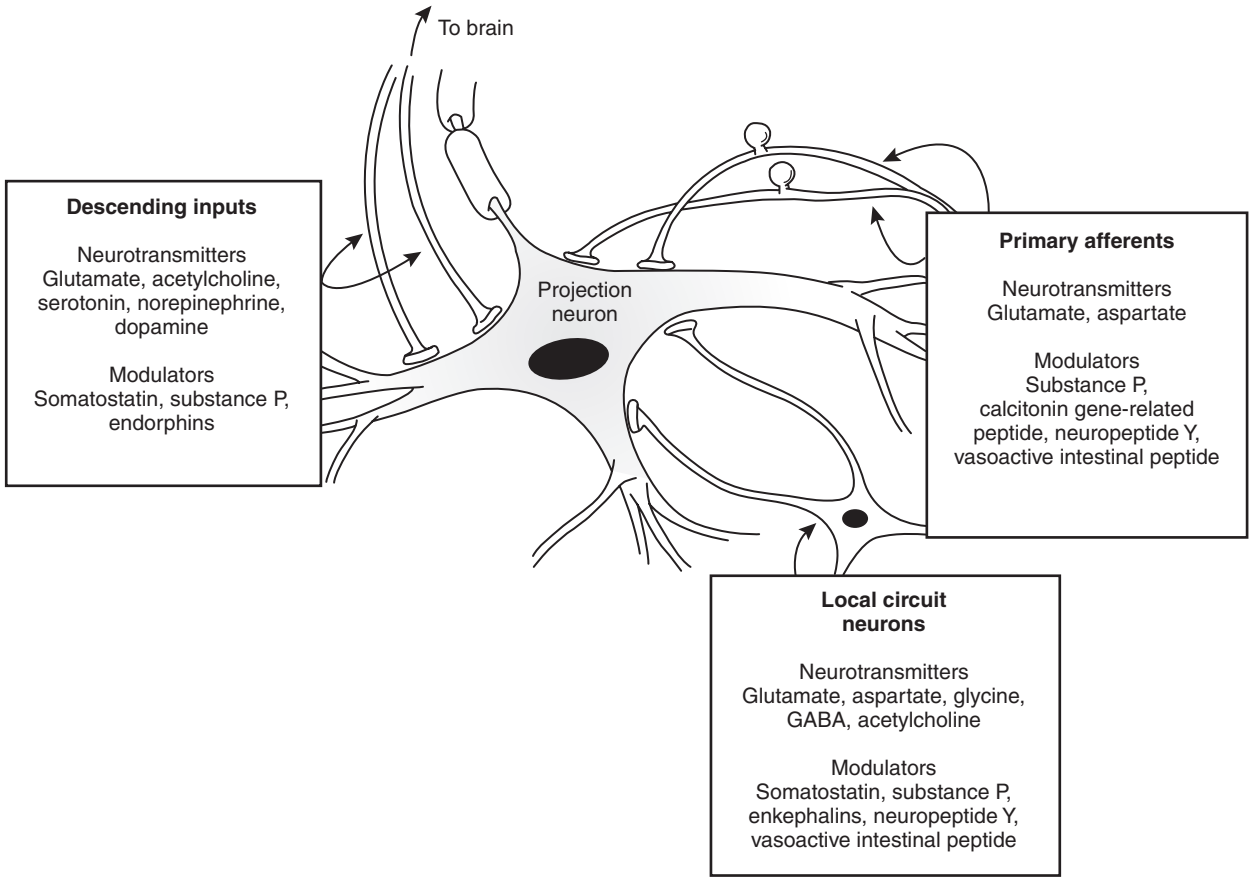

FIGURE 2-2 Schematic diagram of the neurochemistry of somatosensory processing in the spinal dorsal horn.

kinase C. The group II and III metabotropic receptors are negatively coupled by G_i/G_o to adenyl cyclase and so reduce intracellular cyclic AMP and protein kinase A activity. Given the complexity of these receptor transduction mechanisms, it should come as no surprise that activation of mGluR's can result in the modulation of multiple cellular kinases, receptors, ion channels, and transcription factors and so have complex and sometimes variable effects on somatosensory and pain processing. However, as a general rule the group I mGluR's have cooperative effects with NMDA receptors in promoting cellular excitability and pain signaling, while the group II and III mGluR's most often have inhibitory effects on pain transmission.

Adenosine triphosphate (ATP) also modulates somatosensory transmission. The primary receptor for ATP is the P2X family of receptors, which is composed of seven subunits expressed in six homomeric and at least four heteromeric subtypes.[57] These receptors are present on the central terminals of primary afferent fibers innervating neurons in lamina V and II of the dorsal horn where they function to increase the release of the glutamate. The P2 class of receptors, both the ionotropic P2X and the GPCR P2Y classes, further play a unique role in glial-mediated pain sensitivity. The binding of ATP to P2 receptors on microglia changes the phenotype of these cells to include increased expression of P2 and cytokine receptors. These now activated microglia begin to secrete inflammatory mediators such as cytokines, nerve growth factor, and NO. These factors serve to sustain pain and inflammation.[58] In support of these findings, researchers have found that mice lacking either the P2X4 or the P2X7 showed decreased sensitivity to mechanical and thermal stimulation in an animal model of pain.

Inhibitory Neurotransmitters: The amino acids *glycine* and *gamma-amino-butyric acid (GABA)* are the chief inhibitory neurotransmitters in the somatosensory system. Glycine is the chief inhibitory amino acid at spinal levels while GABA predominates at higher levels. There are two receptor sites for glycine, a chloride-linked, strychnine-sensitive receptor and a strychnine-insensitive regulatory site on the NMDA glutamate receptors. GABA is found in local circuit neurons of spinal laminae I, II, and III. Three types of GABA receptors have been identified. The $GABA_A$ receptor is linked to a chloride channel and modulated by barbiturates, benzodiazepines and alcohol. Selective $GABA_A$ agonists include muscimol and selective antagonists include gabazine. A $GABA_A$-mediated link between large myelinated fibers and C-fiber nociceptors has been proposed as a mechanism for the development of allodynia following intradermal injection of the irritant capsaicin.[59] Additionally, a selective loss of inhibitory interneurons at both spinal and thalamic levels has been suggested as contributing to some neuropathic pain conditions.[60] The $GABA_B$ receptor has been associated with both a potassium ionophore and with a G-protein–linked complex. Baclofen is a selective $GABA_B$ receptor agonist and phaclofen is a selective antagonist. Finally, the newly described $GABA_C$ receptor has also been described as associated with a potassium channel ionophore. Cis-4-aminocrotonic acid (CACA) is a selective agonist for this site, but there is no selective antagonist for $GABA_C$ receptors at present. $GABA_C$ receptors do not appear to have any role in the modulation of somatosensory information.

Norepinephrine is another abundant inhibitory neurotransmitter, and is especially important in descending brainstem projections to the dorsal horn.[61,62] The inhibitory effects of norepinephrine in the spinal cord appear to be twofold by directly activating inhibitory GABAergic interneurons and by also inhibiting excitatory interneurons.[63] The adrenergic receptors include two broad classes termed the *alpha-* and *beta-receptors*, each of which in turn have several subtypes. The α2-adrenergic receptor is the primary form found in the spinal dorsal horn that has an inhibitory role on the processing of sensory information. However, it should be noted that the function of norepinephrine following injury to the nervous systems might become reversed from an inhibitory, analgesic role into one of promoting and or sustaining an ongoing chronic pain state.

Serotonin is also involved in descending pathways to the spinal dorsal horn, predominantly from the midbrain raphe nuclei.[61,64] There are multiple serotonin receptor subtypes including 5HT-1, 2, and 3 receptors, and each of these major types also has several subtypes. Due to controversy concerning which of these subtypes mediate the analgesic properties of serotonin, interest in serotonin as a clinically useful target for the treatment of pain has waned. In part, this controversy may be due to the fact that some serotonin receptor subtypes promote nociception while others are inhibitory. If more selective tools are developed with which to dissect this pharmacology, serotonin may regain its former status as potentially useful clinical target.

The inhibitory and antinociceptive nature of norepinephrine and serotonin is further evidenced by the abundance of literature showing that many antidepressants that modulate both of these neurotransmitters, including duloxetine and amitriptyline, have analgesic properties in humans and in animal models of pain. Currently, it is thought that the antinociceptive effects are mediated by activation of α-1 adenoreceptors and 5HT2 receptors,[65] leading to descending inhibition.

Adenosine is another important inhibitory neurotransmitter at spinal levels.[66] There are at least two types of adenosine receptors termed the *A1* and *A2 sites*. Occupation of these sites by adenosine results in G-protein–mediated alterations of cyclic AMP levels in target cells. However, both elevations as well as decreases in cAMP formation have been reported in various conditions. Adenosine may mediate a portion of the analgesia produced by brainstem norepinephrine projections to the spinal cord and appears to have especially robust analgesic properties in neuropathic pain conditions.

Acetylcholine (Ach) is yet another neurotransmitter that mediates antinociception at the level of the spinal dorsal horn.[67] Stimulation of the vagus nerve results in inhibition of pain transmission, and it is likely that this effect is mediated by Ach. Ach may also contribute to the analgesia produced by the α2-adrenergic receptor agonist clonidine. The antinociceptive effects of acetylcholine appear mediated by the muscarinic and not by the nicotinic acetylcholine receptor subtypes.

Neuropeptides: In addition to the excitatory and inhibitory neurotransmitters discussed above, there are

multiple known neuropeptides that contribute to signaling of somatosensory information. While some of these could be classified as excitatory compounds and others as inhibitory, we have separated these into a section of their own because of the distinct profile of action of these compounds as opposed to the neurotransmitters. Unlike the very rapid onset and termination of action of the transmitters, neuropeptides tend to have more gradual onset of effects as well as much more prolonged duration of action once released.

Substance P and *neurokinin A* serve as excitatory neuropeptides in the somatosensory system.[68,69] The receptors for these peptides include the neurokinin 1 and 2 sites, each of which have been associated with elevation of intracellular calcium levels, perhaps through liberation of inositol phosphate. These two peptides may be present in intrinsic neurons of the spinal dorsal horn and thalamus but are especially concentrated in primary afferent fibers. At the spinal level, these peptides are only released following application of noxious stimuli which are sufficient to produce sustained discharges in C-nociceptors, although some small myelinated (Aδ) fibers may also contain substance P. Instead of signaling as synaptic transmitters, these peptides tend to spread throughout the dorsal horn potentially acting on multiple synapses some distance from their point of release. It has been suggested that stimuli of particular modalities (e.g., mechanical vs. thermal) are associated with selective release of one peptide versus another; however, this suggestion has not been corroborated. Activation of neurokinin 1 and/or 2 receptors by substance P and/or neurokinin A are generally accepted as key steps needed for the induction of sensitization, and hence the expression of hyperalgesia following cutaneous injury. It has been further proposed that the mechanism of neurokinin receptor involvement in the expression of sensitization is through facilitation of the synaptic actions of the excitatory amino acid neurotransmitters.

CGRP, like substance P, is expressed predominantly by small, unmyelinated primary afferent fibers, and it is also found in DRG cells and in the superficial layers of the spinal cord. Both CGRP and substance P synthesis and release are increased by another excitatory peptide, neuropeptide Y. Spinal release of CGRP has an excitatory effect on wide dynamic range neurons, and administration of the CGRP antagonist CGRP8-37 reverses this activity. Intrathecal administration of CGRP has been shown by some researchers to produce mechanical hypersensitivity, although it should be noted that others have failed to replicate this finding. Interestingly, the function of CGRP released within the brain seems to be antithetic to the peripheral and spinal effects, with release of this peptide within the PAG producing antinociceptive results.

Cholecystokinin (CCK) is a hormone peptide normally involved in digestion; however, it is also involved in the maintenance of pain. Some researchers contend that this effect is achieved via descending facilitation of nociceptive output from the rostral ventromedial medulla,[70] while others propose that CCK blocks the descending antinociceptive effects of endogenous opioids within the periaqueductal gray.[71] Coadministration of a CCK antagonist along with traditional exogenous opioids results in augmented analgesia, and even opioid tolerance reversal. Currently, more work is needed to better understand the mechanisms and therapeutic uses of CCK antagonists.

Somatostatin, the *enkephalins*, and possibly *dynorphin*, are included as inhibitory neuropeptides at spinal level. These peptides are contained in both intrinsic neurons of the dorsal horn and in the fibers descending to the dorsal horn from various brainstem nuclei. The endorphins are another class of inhibitory neuropeptides. The receptor types for the opioid peptides include the mu, delta and kappa receptor subtypes, and these receptors are found at all levels of the somatosensory system. These receptors are associated with modulation of both intracellular cAMP and potassium levels. There is also an important cooperative functional link between μ-opioid and α2-adrenergic receptors that have yet to be fully exploited for clinical applications.

Cannabinoids are present in the peripheral and central nervous systems and play a role in inhibiting pain. At this point, the CB1 receptor within the (CNS) seems to be a likely target for pharmacologic interventions. The CB1 receptor agonist Sativex is very effective at decreasing neuropathic pain, but has sedative side effects. CT3 has decreased (CNS) bioavailability, and therefore fewer side effects, and yet is still efficient at producing analgesia.

Peroxisome Proliferator-Activated Receptors (PPARs): The receptors discussed up to this point have been limited to those contained on the cell surface; however, the PPARs represent a class of nuclear receptors which serve as transcription factors. PPAR stimulation plays an important role in suppressing inflammation, and PPAR agonists have been shown to inhibit the development of pain. Based on this line of research, it follows that PPARs may offer a novel means to decrease pain. Future research attempting to utilize these receptor agonists as analgesics will have to overcome the serious side effects of increased adiposity and fluid retention.[72] PPARs, such as PPARγ, are located in the brain and spinal cord. Although at this time, it is unclear how these receptors become activated following injury, once activated they mediate inflammatory substances such as substance P, CGRP, and cytokines. In turn, mediation of these and other factors allows for inhibition of inflammation and pain.

Central Signal Propagation and Second Messenger Systems: The movement of various ions and the activity of cellular enzymes and metabolites are essential in the propagation of bioelectric signals in the (CNS). Alterations to these factors can drastically reduce or augment signal propagation, and ultimately somatosensory perception. Ion movement relies on proteins that form ion channels, and these proteins can function as second messenger enzymes. The actions of these proteins can be blocked by a number of agents and many of these have been studied as putative analgesics. However, since ion channels and second messengers are found in all neural elements, the effects of compounds acting at these sites are not specific to pain circuitry. Side effects are therefore often encountered with these drugs that limit their usefulness. There are four ion channels involved in pain signal propagation in the CNS, those for sodium, calcium, potassium, and chloride.

Sodium channels serve as the key to propagation of neural impulses throughout the nervous system, as the opening of these channels is the primary event underlying the depolarization of nerve membranes, and sodium currents in dorsal horn neurons are mediated by at least three types of tetrodotoxin sensitive channels. The local anesthetics lidocaine and bupivacaine physically block sodium channels, preventing the movement of sodium across the membrane. Prolonged infusions of local anesthetics for postoperative pain in humans became widespread in the 1990s[73–75] and cancer and chronic nonmalignant pain are treated with continuous infusions of intrathecal local anesthetics outside of the hospital.[76,77] Side effects are, however, common,[76–79] and include delayed urinary retention, paresthesia, paresis/gait impairment, periods of orthostatic hypotension, bradypnea, and dyspnea. Recent advances in the understanding of sodium channel subtypes present novel means of achieving pain relief. Both the Nav1.7 and Nav1.8 subtypes are expressed throughout the central and peripheral nervous system and are critical in action potential generation in peripheral nociceptors. Clinically, patients with absent or nonfunctioning Nav1.7 channels experience congenital insensitivity to pain, and overactivity of this subtype is associated with certain chronic pain conditions. The anticonvulsant carbamazepine produces analgesia, presumably by inhibiting Nav1.7. Further, mice lacking Nav1.8 display decreased pain responding, and the Nav1.8 selective blocker A-803467 alleviates neuropathic and inflammatory pain in animals.

Potassium is the second main cation of the neuronal action potential. There are four families of potassium channels, with the voltage-gated channels and the inwardly rectifying channels being strongly implicated to play a role in pain.[80] Opening of voltage-gated potassium channels allows outward positive current flow from neurons, such as during repolarization following an action potential. Blockade of these channels initially prolongs generation of action potentials. Continued application, however, prevents repolarization and so ultimately produces a failure to generate action potentials. The inwardly rectifying channels establish and regulate the resting membrane potential. Recent evidence has implicated a potential for potassium channels to serve as targets for the treatment of pain. Nitric oxide has been found to activate ATP-sensitive potassium channels (K(ATP)) and contribute to the maintenance of neuropathic pain, although the exact mechanisms of this effect are yet to be uncovered. Administration of the potassium channel blocker Retigabine reversed surgically induced neuropathic pain in an animal model.

Calcium ions are not directly involved in action potential propagation, but instead are essential for the release of neurotransmitters following synaptic depolarization.[81] At least four different types of calcium channels, the L-, N-, T-, and P-types, have been identified in dorsal horn neurons. There are numerous chemical antagonists of L-type calcium channels,[81] whereas N-type calcium channels are blocked using toxins of *Conus magnus*.[82] P-channels are especially prevalent in Purkinje cells and are sensitive to venom toxins of the funnel web spider (*Agelenopsis aperta*).[81] T-channels are involved in the regulation of neuronal excitability and pacemaker activity,[83] and are blocked by some omega conotoxins. Antinociceptive effects have been shown for N-, L-, and P-type calcium channels in animals,[82–86] and for L- and N-type channels in humans.[87]

Chloride ions are also a major contributor to signal propagation, and three major classes of chloride channels have been identified.[88] The first class identified was the ligand-gated chloride channels, including those of the gamma-aminobutyric acid type A ($GABA_A$) and glycine receptors, and these are common in dorsal horn neurons. The second class, also likely common at spinal levels, is the voltage-gated chloride channel. The final chloride channel class is activated by cyclic adenosine monophosphate and may include only the cystic fibrosis transmembrane regulator. Activation of chloride currents usually results in hyperpolarization of neurons, and facilitation of these hyperpolarizing currents underlies the mechanisms of many depressant drugs. However, the $GABA_A$ receptors on primary afferent terminals gate a chloride channel that allows efflux, instead of the normal influx, of chloride with a net effect therefore of depolarizing primary afferent terminals. Chloride channel antagonists such as bicuculline and strychnine have not been given to relieve pain, but instead to produce an experimental pain state characterized by a pronounced opiate-refractory allodynia.[60,89,90] These compounds were also used to exacerbate the anatomical consequences of nerve constriction injury.[91]

Finally, the role of second messenger systems on pain sensitivity has been examined in a number of studies. Increases in the levels of membrane-bound protein kinase C have been found following both nerve injury and intraplantar injection of formalin.[92,93] Spinal infusion of phorbol esters to activate protein kinase C increases the behavioral response to intraplantar formalin and increases the spontaneous and evoked activity of primate spinothalamic tract neurons. In contrast, antagonists for protein kinase C decrease pain behavior following nerve injury,[92] intraplantar formalin,[93] intraspinal N-methyl-D-aspartate and intradermal capsaicin. Similarly, inhibition of phospholipase C[94] or phospholipase A[95] (needed for release of co-factors to protein kinase C) reduced hyperalgesia following intraplantar formalin and zymosan, respectively. Further evidence comes from the finding that animals engineered with defects in protein kinase C had less pain following nerve injury,[96] while those engineered with defects in protein kinase A had decreased responses to formalin, capsaicin, and hind paw inflammation.[97]

Based on this abundance of research, many second messenger systems could become targets for clinical pain treatment. At present, however, the role of these systems in pain management is indirect through the action of various drugs that interact with surface receptors linked to G-proteins. Receptors linked to G_S (receptors associated with $\beta\gamma\alpha$ S subunits) include the β1-adrenergic, dopaminergic type 1, and adenosine type 2 receptors. Those that activate $G_{Sq,12}$ ($\beta\gamma\alpha$ q,12) include the serotonin 2C, α1-adrenergic, histamine, thromboxane A2, metabotropic glutamate, and the muscarinic type 1, 3, and 5 receptors. Finally, G_i-($\beta\gamma\alpha$) linked receptors include the adenosine 1, serotonin 1B, gamma-aminobutyric acid type B, muscarinic 2, and μ-, δ-, and κ-opioid receptors.[98] Neurotransmitter receptors linked

to G_S and $G_{q,12}$ generally increase pain transmission while G_I-linked receptors inhibit pain signaling.[98–101]

SUMMARY

Throughout the nervous system, many interrelated factors contribute to pain. In the periphery, mediators such as bradykinin, cytokines, and second messenger pathways facilitate the mechanisms of each other and lead to increased nociceptive transmission to the spinal cord. Within the spinal cord, many of these same elements work to convert acute pain into chronic conditions. This transition may occur via changes in gene regulation, receptor expression, glial activation, and through central sensitization. Attempts to alleviate pain have been made by altering many of the chemical mediators involved in pain, with varied levels of success. Future research will no doubt continue to expand our understanding of the neurochemistry of pain and will add to the means by which pain can be alleviated.

KEY POINTS

- The excitatory amino acids glutamate and aspartate are the key excitatory neurotransmitters in the somatosensory system.
- The four types of excitatory amino acid receptors are the NMDA, AMPA, kainite, and metabotropic receptors.
- GABA and glycine are the key inhibitory neurotransmitters.
- Substance P is the key excitatory neuropeptide in the somatosensory system.
- The enkephalins and somatostatin are the key inhibitory neuropeptides in the somatosensory system.

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CHAPTER 3

Taxonomy: Definition of Pain Terms and Chronic Pain Syndromes

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Acute pain—Pain resulting from nociceptor activation due to damage to tissues. Acute pain typically resolves once the tissue damage is repaired.

Analgesia—Absence of pain in response to a stimulus that is normally painful.

Anesthesia—Absence of all sensory modalities.

Anesthesia dolorosa—Pain in an area or region that is anesthetic.

Carpal tunnel syndrome—Pain in the hand, usually occurring at night, due to entrapment of the median nerve in the carpal tunnel. The quality of the pain is a pins-and-needles sensation, stinging, burning, or aching. There may be decreased sensation on the tips of the first to third fingers, positive Tinel's sign, and, rarely, atrophy of the thenar muscles. A nerve conduction study shows delayed conduction across the carpal tunnel. The syndrome is caused by compression of the median nerve in the wrist between the carpal bones and the flexor retinaculum (transverse carpal ligament).

Central pain—Regional pain caused by a primary lesion or dysfunction in the central nervous system, usually associated with abnormal sensibility to temperature and to noxious stimulation.

Chronic pain—Pain that outlasts an initial insult to tissues. Nociceptive pathways remain active, often with symptoms greater than the underlying pathology would suggest.

Complex regional pain syndrome (CRPS)—A term describing a variety of painful conditions following injury that appear regionally, having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event, often resulting in significant impairment of motor function, and showing variable progression over time. CRPS is a term for disorders previously called reflex sympathetic dystrophy (RSD).

CRPS type I (RSD)

1. Type I is a syndrome that develops after an initiating noxious event.
2. Spontaneous pain or allodynia/hyperalgesia occurs, which is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event.
3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

CRPS type II (causalgia)

1. Type II is a syndrome that develops after a nerve injury. Spontaneous pain or allodynia/hyperalgesia occurs, and is not necessarily limited to the territory of the injured nerve.
2. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.
3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Chronic pain—Pain that persists beyond the course of an acute disease or a reasonable time for an injury to heal or that is associated with a chronic pathologic process that causes continuous pain or the pain recurs at intervals of months or years. Some investigators use duration of ≥6 months to designate pain as chronic.

Comprehensive pain center—Center dedicated to managing a full spectrum of chronic pain syndromes using multiple disciplines and modalities.

Cubital tunnel syndrome—Entrapment of the ulnar nerve in a fibro-osseous tunnel formed by the trochlear groove between the olecranon process and the medial epicondyle of the humerus. A myofascial covering converts the groove to a tunnel, which causes the nerve entrapment. There is pain, numbness, and paresthesia in the distribution of the ulnar nerve and, sometimes, weakness and atrophy in the same distribution. Tinel's sign is positive at the elbow. Nerve conduction velocity shows slowing of conduction in the ulnar nerve across the elbow. The intrinsic muscles of the hand may show signs of denervation. Surgery may be required to decompress the entrapment or to transpose the ulnar nerve.

Deafferentation pain—Pain due to loss of sensory input into the central nervous system. This may occur with lesions of peripheral nerves such as avulsion of the brachial plexus or due to pathology of the central nervous system.

Disability—Loss of ability to perform a specific task in a standard or normal fashion.

Dysesthesia—An unpleasant abnormal evoked sensation, whether spontaneous or evoked.

Fibromyalgia—Diffuse musculoskeletal aching and pain with multiple predictable tender points. There is pain on digital palpation in at least 11 of 18 tender sites:

- Occiput: bilateral, at the suboccipital muscle insertions.
- Low cervical: bilateral, at the anterior aspects of the intertransverse process at C5–C7.
- Trapezius: bilateral, at the midpoint of the upper border.
- Supraspinatus: bilateral, at the origins above the scapula spine near the medial border.

- Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
- Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
- Gluteal: bilateral, in the upper outer quadrants of the buttocks in the anterior fold of muscle.
- Greater trochanter: bilateral, posterior to the trochanteric prominence.
- Knees: bilateral, at the medial fat pad proximal to the joint line.

Hyperalgesia—An increased response to a stimulus that is normally painful.

Hyperesthesia—Increased sensitivity to stimulation; this excludes the special senses.

Hyperpathia—A painful syndrome, characterized by increased reaction to a stimulus, especially a repetitive stimulus, as well as increased threshold.

Hypoalgesia—Diminished sensitivity to noxious stimulation.

Hypoesthesia—Diminished sensitivity to stimulation; this excludes the special senses.

Lateral epicondylitis (tennis elbow)—Pain in the lateral epicondylar region of the elbow due to strain or partial tear of the extensor tendon of the wrist. The pain may radiate to the lateral forearm or to the upper arm. There is pain in the elbow during grasping and supination of the wrist and on repeated wrist dorsiflexion. Physical examination shows tenderness of the wrist extensor tendon approximately 5 cm distal to the epicondyle.

Modality-oriented pain center—Facility that offers one specific therapeutic modality for an array of chronic pain disorders. For example, an interventional center may provide nerve blocks and other procedures for back pain, neck pain, CRPS, and other syndromes.

Multidisciplinary pain management—Treatment of chronic pain by professionals from multiple disciplines (physical therapy, psychology, rehabilitation medicine, anesthesiology, and others) in a group setting (typically approximately 10 patients). Centers are usually quite large due to the amount of space needed to perform time-consuming multidisciplinary evaluations and therapies in groups.

Neuralgia—Pain in the distribution of a nerve or nerves.

Neuritis—Inflammation of a nerve or nerves. (Not to be used unless inflammation is thought to be present.)

Neurogenic pain—Pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system.

Neuropathic pain—Pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous systems.

Central neuropathic pain—A lesion in the central nervous system causing pain. These include thalamic pain syndrome, poststroke pain, and postspinal cord injury pain.

Peripheral neuropathic pain—Pain caused by a lesion or dysfunction of the central nervous system. Examples are postherpetic neuralgia (PHN), painful diabetic neuropathy (PDN), and complex regional pain syndrome (CRPS).

Neuropathy—A disturbance of function or pathologic change in a nerve. This may involve one nerve (mononeuropathy), several nerves (mononeuropathy multiplex), or it may be bilateral or symmetrical (polyneuropathy).

Nociceptive pain—Pain caused by activation of nociceptive afferent fibers. This type of pain satisfies the criteria for pain transmission, that is, transmission to the spinal cord, thalamus, and then to the cerebral cortex.

Somatic pain—Pain carried along the sensory fibers; this pain is usually discrete and intense.

Visceral pain—Pain carried by the sympathetic fibers; this pain is diffuse and poorly localized.

Nociceptor—A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged.

Noxious stimulus—A stimulus that is actually or potentially damaging to body tissue.

Pain—An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of damage.

Pain of psychological origin

- Delusional or hallucinatory: pain of psychological origin and attributed by the patient to a specific delusional cause.
- Hysterical, conversion, or hypochondriac: pain specifically attributable to the thought process, emotional state, or personality of the patient in the absence of an organic or delusional cause or tension mechanism.
- Pain associated with depression: pain occurring in the course of a depressive illness, not preceding the depression and not attributable to any other cause.

Pain threshold—The least experience of pain that a subject can recognize.

Pain tolerance level—The greatest level of pain that a subject is prepared to tolerate.

Paresthesia—An abnormal sensation, whether spontaneous or evoked. (Note: Paresthesia is an abnormal sensation that is not unpleasant, while dysesthesia is an abnormal sensation that is considered unpleasant. Dysesthesia does not include all abnormal sensations, but only those that are unpleasant.)

Peripheral neuropathy—Constant or intermittent burning, aching, or lancinating limb pain due to generalized or focal diseases of peripheral nerves.

Phantom pain—Pain referred to a surgically removed limb or portion thereof.

Piriformis syndrome—Pain in the buttock and posterior thigh due to myofascial injury of the piriformis muscle itself or dysfunction of the sacroiliac joint or pain in the posterior leg and foot, groin, and perineum due to entrapment of the sciatic or other nerves by the piriformis muscle within the greater sciatic foramen, or a combination of these causes.

Post-thoracotomy pain syndrome—Pain along a thoracotomy scar persisting at least 2 months after a thoracotomy. There is an aching sensation in the distribution of the surgical incision. Sensory loss and tenderness may be present along the thoracotomy scar. A trigger

point may be present, secondary to a neuroma, that responds to a trigger-point injection.

Radicular pain—Pain perceived as arising in a limb or the trunk wall caused by ectopic activation of nociceptive afferent fibers in a spinal nerve or its roots or other neuropathic mechanisms. The pain is usually lancinating and travels in a narrow band. Etiologic causes include anatomic lesions affecting the spinal nerve and dorsal root ganglion including herniated intervertebral disc and spinal stenosis.

Radiculopathy—Objective loss of sensory and/or motor function as a result of conduction block in axons of a spinal nerve or its roots. Symptoms include numbness and weakness in the distribution of the affected nerve. Neurologic examination and diagnostic tests confirm the neurologic abnormality. (Note: Radicular pain and radiculopathy are not synonymous. The former is a symptom caused by ectopic impulse generation. The latter relates to objective neurological signs due to conduction block. The two conditions may coexist and may be caused by the same lesion.)

Raynaud's disease—Episodic attacks of aching, burning pain associated with vasoconstriction of the arteries of the extremities in response to cold or emotional stimuli.

Raynaud's phenomenon—Attacks like those of Raynaud's disease but related to one or more other disease processes. Systemic and vascular diseases such as collagen disease, arteriosclerosis obliterans, nerve injuries, and occupational trauma may all contribute to the development of Raynaud's phenomenon.

Referred pain—Pain perceived as occurring in a region of the body topographically distinct from the region in which the actual source of pain is located.

Somatic—Derived from the Greek word for "body." Although somatosensory input refers to sensory signals from all tissues of the body including skin, viscera, muscles, and joints, it usually signifies input from body tissue other than the viscera.

Stump pain—Pain at the site of an extremity amputation.

Suffering—A state of severe distress associated with events that threaten the intactness of the person; it may or may not be associated with pain.

Stylohyoid process syndrome (Eagle's syndrome)—Pain following trauma in the region of a calcified stylohyoid ligament.

Syndrome-oriented pain center—A center that is specialized to provide thorough and wide-reaching care for patients suffering from a specific chronic pain syndrome. Examples include fibromyalgia clinics and back pain centers.

Thoracic outlet syndrome—Pain in the root of the neck, head, and shoulder, radiating down the arm into the hand due to compression of the brachial plexus by the hypertrophied muscle, congenital bands, post-traumatic fibrosis, the cervical rib or band, or the malformed first thoracic rib.

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Clinical Evaluation and Diagnostic Examinations

CHAPTER 4

Physical Examination of the Patient with Pain

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The physical examination of a patient with pain is the most significant diagnostic tool, surpassed in importance only by the pain history. The goals of the physical examination include developing the patient's trust, gaining insight into the impact of pain on the patient's level of functioning, and ultimately identifying potential pain generators and other neurologic derangements. To simplify and focus what can be a complex physical examination, methodical templates that are easily reproducible, efficient, and targeted toward a specific region should be developed. A comprehensive physical examination that identifies anatomic and physiologic pain generation is an invaluable diagnostic tool. The pain physical exam is a comprehensive neurologic assessment that can be divided into four main categories: sensation, motor, reflexes, and coordination.

SENSATION AND SENSORY EXAMINATION

One of the major goals of sensory examination is determining which fibers, neuronal types, or neural tracts are involved in the transmission of each patient's specific pain. Classically, pain first starts with the activation of peripheral nociceptors. There are three broad classes of nociceptors differentiated based on the type of noxious stimuli they detect: mechanical nociceptors respond to pinch and pinprick, heat nociceptors respond to a temperature greater than 45°C, and polymodal nociceptors respond equally to mechanical, heat, and chemical noxious stimuli. Once the nociceptor is activated, the generated impulse is then transmitted to the central nervous system (CNS) via A-δ and C-fibers. A-δ fibers are responsible for "fast" or quickly sensed pain, while C-fibers are responsible for "slow" pain. Fast pain is transmitted by small myelinated A-δ fibers at a rate of 2 to 30 m/s and is typically characterized as a sharp, shooting pain. Slow pain is transmitted by even smaller unmyelinated C-fibers at a rate of less than 2 m/s, and is characterized as a dull, poorly localized burning pain. The patient's description of symptoms can help to elucidate the type of pain fibers being activated. For example, a dull and diffuse nonfocal pain complaint would be more suggestive of C-fiber activation.

Sensory alterations should be described in standardized terms in order to create a more universal record of symptoms. Hyperesthesia is a sensation out of proportion to the stimuli applied. Hyperesthesia is further divided into hyperalgesia and allodynia. Hyperalgesia is severe pain in response to mild noxious stimuli, such as a pinprick. Allodynia is the sensation of pain in response to a non-noxious stimuli (e.g., light touch, fabric on skin). Allodynia is a physical examination finding in many neuropathic pain states and its distribution, frequently nondermatomal, should be documented.[1]

If a deficit is identified during an initial gross sensory examination, a more in-depth investigation of the affected region should be performed using the contralateral side as a control (when possible). C-fibers are tested using both painful stimulus (pinprick) and warm temperature. A-δ fibers are tested with a pinprick and cold.

Even in the most painful pathologic states, sensory deficits are mild and focal and patients retain intact sensory tracts. Sensory dissociation is a state in which patients present with loss of fine touch and proprioception in the same region in which pain and temperature sensing are intact. Patients report a sharp sensation to a pinprick in an area without fine touch or proprioception. This constellation of symptoms (or the converse—intact proprioception and fine touch without temperature and pain intact) can occur with lesions that interrupt fibers at the spinal cord level. The symptoms can be explained by the geography of the respective neural tracts in the spinal cord. For example, the posterior columns house the tracts that transmit proprioception and light touch, whereas the anterolateral cord carries the spinothalamic tract (pain, temperature) and motor tract. A syrinx can cause a progressive myelopathy that presents as a central high cervical cord syndrome with a sensory deficit in a cape or shawl distribution, and neck, shoulder, and arm muscle wasting.

A-β fibers are examined through light touch, vibration, and joint position. Vibration is tested with a 128-Hz tuning fork and has increased value when combined with joint position testing. Isolated decreased vibratory sense is an early sign of large-fiber (A-β) neuropathy, and if combined with position sense deficit indicates posterior column disease or peripheral nerve involvement. Posterior column disease is

also indicated by the loss of graphesthesia or the ability to interpret a number outlined on the patient's palm or calf. The inability to perceive isolated joint position is indicative of parietal lobe dysfunction or peripheral nerve lesion.[1,2]

Anatomically, lesions can be divided into central (brain and spinal cord), spinal nerve root (dermatomal), and peripheral nerve lesions.[3] Careful comparison of an individual patient's sensory deficits relative to classic dermatome charts and known peripheral cutaneous nerve maps (Figs. 4-1 and 4-2) allows practitioners to identify potential causative lesions. Dermatomes are most accurate and exhibit the least variability distally (in the digits). Through comparison with established maps, it is possible to first differentiate between central and peripheral lesions, and then even pinpoint the anatomic location of a lesion (Table 4-1) without expensive and invasive testing and imaging.

While not yet fully validated and accepted, quantitative sensory testing (QST) can be helpful with complex patients; currently QST is predominantly used in research. QST involves using computer-guided precise measured sensory stimuli and then recording the responses fully objectively (i.e., the patient pushes a button when he/she feels pain and the computer records at what level of stimulus the patient's pain threshold was reached). QST should increase inter-rater reliability and create easily reproducible and comparable exams, although the equipment is costly and the techniques are time-consuming.

MOTOR EXAMINATION

Identifying a deficit in motor function and then comparing this with known motor innervation charts can help isolate a lesion. The motor examination begins with inspection. Detailed visual inspection can reveal hypertrophy, atrophy, and fasciculations, among other pathologies. Hypertrophy is suggestive of overuse, while atrophy and fasciculations occur with lower motor neuron disorders. Following inspection, palpation is a valuable tool to identify pain generators, specifically myofascial trigger points. Tone, the sensation of resistance felt as one manipulates a joint through its expected range of motion with the patient relaxed, is described in terms of hypotonia and hypertonia. *Hypotonia*, a decrease in the normal expected muscular resistance to passive manipulation, is due to a depression of alpha or gamma motor unit activity either centrally or peripherally. Hypotonia can be seen in polyneuropathy, myopathy, and certain spinal cord lesions. *Hypertonia*, a greater-than-expected normal resistance to passive joint manipulation, is divided into spasticity and rigidity. *Spasticity* is defined as a velocity-dependent increase in tone with joint movement. Spasticity

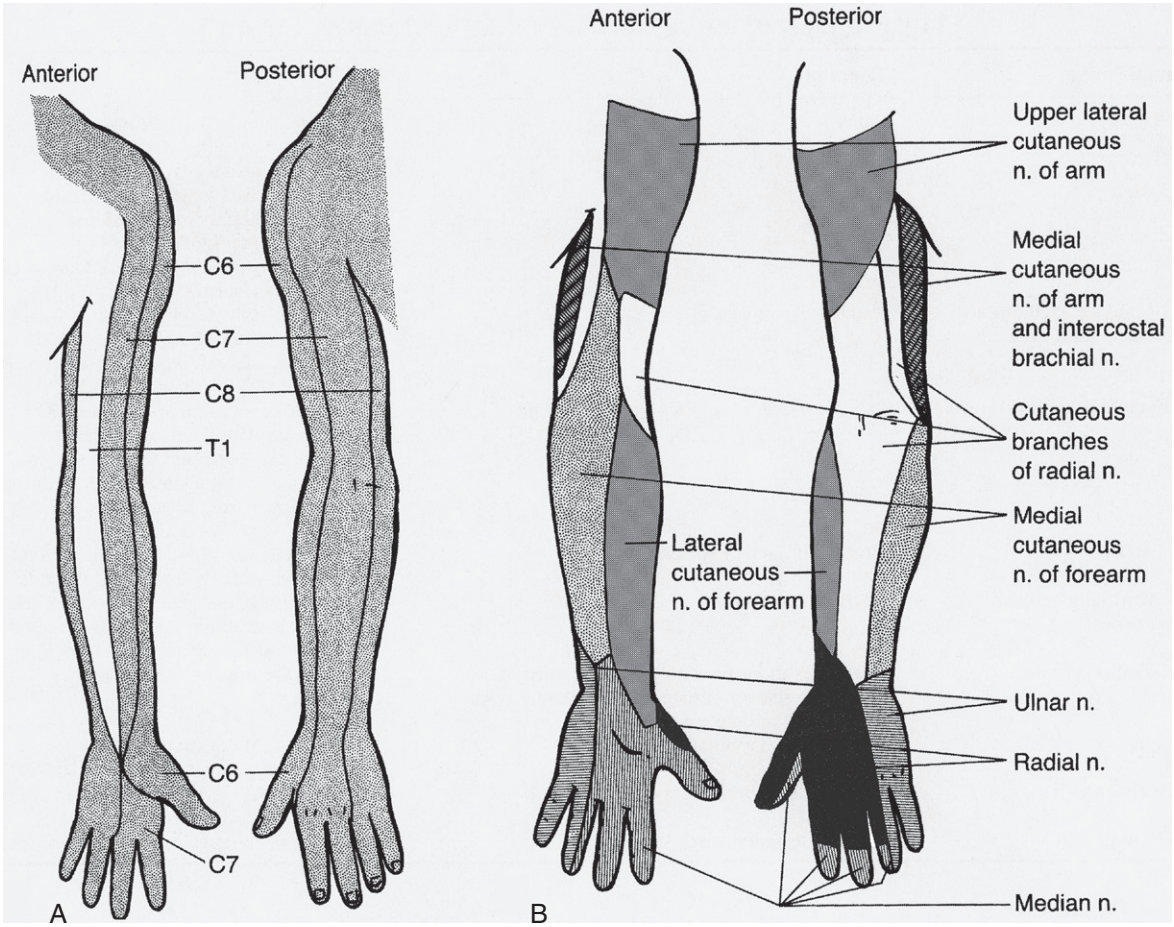

FIGURE 4-1 **A,** Cutaneous distribution of the cervical roots. **B,** Cutaneous distribution of the peripheral nerves of the upper extremity. *(Redrawn from Wedel DJ: Nerve blocks. In: Miller RD, editor:* Anesthesia, *ed 4. New York: Churchill Livingstone, 1994, p 1537.)*

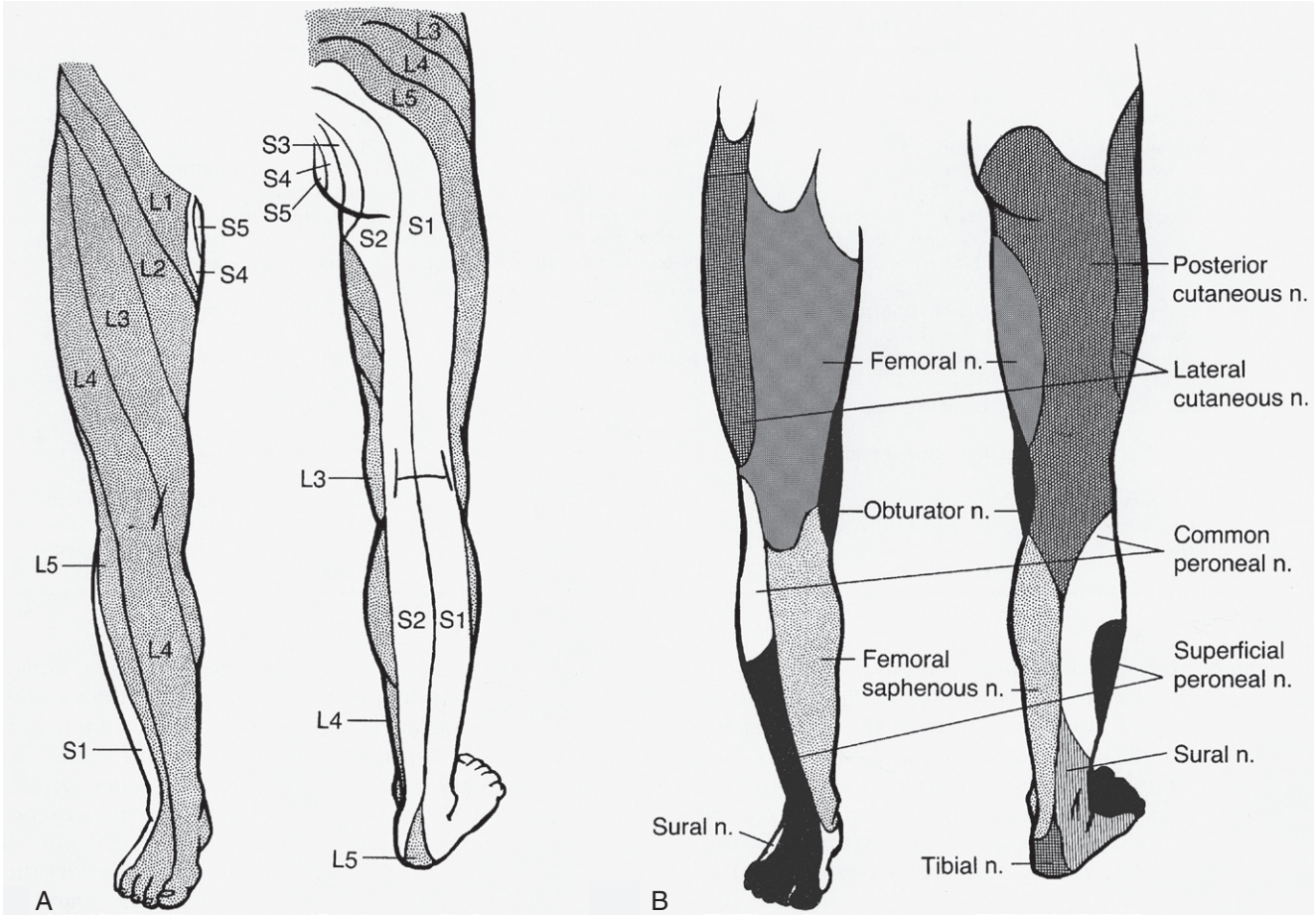

FIGURE 4-2 **A,** Cutaneous distribution of the lumbosacral nerves. **B,** Cutaneous distribution of the peripheral nerves of the lower extremity. *(Redrawn from Wedel DJ: Nerve blocks. In: Miller RD, editor:* Anesthesia, *ed 4. New York: Churchill Livingstone,1994, p 1547.)*

TABLE 4–1 Sensory Innervation Landmarks by Dermatome

Dermatome	Landmark
C4	Shoulder
C5	Lateral aspect of the elbow
C6	Thumb
C7	Middle finger
C8	Little finger
T1	Medial aspect of the elbow
T2	Axilla
T3–T11	Corresponding intercostal space
T4	Nipple line
T10	Umbilicus
T12	Inguinal ligament at midline
L1	Halfway between T12 and L2
L2	Mid-anterior thigh
L3	Medial femoral condyle
L4	Medial malleolus
L5	Dorsum of foot
S1	Lateral heel
S2	Popliteal fossa at midline
S3	Ischial tuberosity
S4–S5	Perianal area

is seen with excitation of spinal reflex arcs or with loss of descending inhibitory control in the reticulospinal or rubrospinal tracts. Spasticity is commonly seen after brain and spinal cord injury and stroke and in multiple sclerosis. *Rigidity*, a generalized increase in muscle tone, is characteristic of extrapyramidal diseases, and is due to lesions in the nigrostriatal system. Finally, isolated voluntary muscle strength is tested and graded from 0 to 5 (normal strength). Table 4-2 describes the standard muscle strength grading system. This test is effort dependent and a patient in pain may not be able to give full effort. If a "giveaway" component to muscle weakness is suspected, this should be documented, as the

TABLE 4–2 Standard Muscle Grading System

Grade	Description
0	No movement
1	Trace movement, no joint movement
2	Full range of motion with gravity eliminated
3	Full range of motion against gravity
4	Full range of motion against gravity and partial resistance
5 (normal)	Full range of motion against gravity and full resistance

classic scoring system may then overestimate the degree of weakness. Even more subtle deficits can be identified by comparing bilateral muscle groups. Even when muscle strength is 5/5 on both sides, relative weakness of the dominant limb can suggest pathology. For example, a weak right-hand grip (vs. the left hand) in a right-hand dominant patient may suggest a right-sided radicular disease or carpal tunnel syndrome. Greater proximal muscle weakness, in contrast to distal muscle weakness, indicates myopathy. Greater distal muscle weakness, compared to proximal muscle weakness, indicates polyneuropathy. Single innervation muscle weakness indicates a peripheral nerve lesion or a radiculopathy (if one nerve root provides all motor innervation for the given muscle).[1,4]

REFLEXES AND COORDINATION

In coordination with the sensory and motor examinations, deep-tendon reflexes (muscle stretch reflexes) serve as a valuable guide to the anatomic localization of a lesion. Similar to motor and sensory tests, specific reflexes are activated at specific spinal levels. The most commonly tested reflexes are listed in Table 4-3. A standardized grading system for deep-tendon reflexes from 0 to 4 is presented in Table 4-4. In cases of hypoactive reflexes, distraction techniques such as Jendrassik's maneuver (hooking the digits of both hands together and attempting to forcibly separate both hands) can be employed to better elucidate between true loss of reflex and examination artifact. The voluntary contraction of muscles not being tested results in facilitation of underactive reflexes and can provide a more accurate assessment of the reflex. Clonus, a grade-four reflex, is characterized by rhythmic, uniphasic muscle contractions in response to sudden sustained muscle stretch. Clonus is not always an abnormal finding but may be indicative of an upper motor neuron disease. Plantar reflex testing (elicited with sharp stimulus on the lateral aspect of the sole of the foot) should be documented in terms of an up-going (Babinski's sign) or down-going great toe. Babinski first noted the great toe moving upward and the toes fanning outward in response to a key scratch along the lateral plantar surface of the foot in patients with pyramidal lesions. We now know Babinski's sign can be seen with many upper motor neuron diseases, and is also a normal variant in children up until 12 to 18 months of age. In the hand, one can elicit a Hoffman's sign, which is thumb and index finger flexion with tapping of the distal third or fourth digit. This is indicative of an upper motor-neuron disease. Ultimately, the confidence level in the localization of a lesion is quite high when confirmed by sensory, motor, and reflex derangements.[1,5]

Coordination and gait testing is a sensitive indicator of cerebellar function and equilibrium. Cerebellar function is tested by traditional finger-nose-finger and heel-knee-shin tests. Equilibrium is assessed by observation of normal gait, heel-and-toe walk, and tandem gait testing (heel-to-toe walking in a straight line).[6] Equilibrium is further tested by Romberg's test (having a patient stand with feet together and eyes closed). Romberg's test is positive when the patient sways and loses balance with eyes closed and is suggestive of mild lesions of the sensory, vestibular, or proprioceptive systems.

TABLE 4–3 Nerve Root Level Tested for Common Reflexes

Nerve Root Level	Reflex
S1–S2	Achilles reflex
L3–L4	Patellar reflex
C5–C6	Biceps reflex
C7–C8	Triceps reflex

TABLE 4–4 Deep-Tendon Reflex Grading System

Grade	Description
0	No response
1+	Reduced, less than expected
2+	Normal
3+	Greater than expected, moderately hyperactive
4+	Hyperactive with clonus

DIRECTED PAIN EXAMINATION TEMPLATE

The goal of using directed examinations and templates is to develop a standardized and consistent examination. Templates can increase consistency and reproducibility of exams, which allows patients to be better tracked over a period of time by multiple practitioners. A standard template should include inspection, palpation, percussion, range of motion, motor examination, sensory examination, reflexes, and additional regional provocative tests if indicated. Table 4-5 lists a sample template. When using region-specific templates, it should be noted whether pain is concordant (in the usual location, nature, and intensity) or discordant (different from the patient's usual complaint).

The examination should begin with inspection and description of the affected region with attention to symmetry and the cutaneous landmarks. Signs of infection or rash, surgical or traumatic scars, sudomotor alterations, cutaneous discoloration, and abnormal hair growth should be noted (particularly when interventions are being considered). Subcutaneous alterations such as edema and muscular

TABLE 4–5 Directed Pain Examination Template

Examination	Observation
Inspection	Cutaneous landmarks, symmetry, temperature
Palpation	Gross sensory changes, masses, trigger points, pulses
Percussion	Tinel's sign, fractures
Range of Motor Innervation	Described in degrees, reason for motion limitation
	Graded 0–5, correlated with examination
Sensory Reflexes	Dermatomal distribution of changes, examination description of affected fibers
	Graded 0–4
Provocative	Description of concordant vs. tests disconcordant pain, appropriate for region

atrophy or hypertrophy and masses should also be documented and further evaluated when indicated. In addition to visual inspection, the cutaneous temperature should be measured in suspected cases of sympathetically mediated pain.

After inspection, palpation of superficial structures can help to differentiate visualized lesions. Lymph nodes, discrete trigger points, and lipomas can look very similar, but with palpation each lesion can be distinguished. Tenderness to palpation over specific structures suggests that these entities are pain generators. For example, tenderness to palpation over the greater trochanter may be suggestive of trochanteric bursitis. Palpation is dependent on the patient tolerating touch. Patients with allodynia, dysesthesia, hyperesthesia, or other sensory derangements often are unable to tolerate palpation. When tolerated, palpation should be performed in a systematic, comprehensive manner from the least to most painful area with standard pressure. This permits an appreciation of the normal tissues against which to compare the painful region. The objectives of palpation are to identify and delineate subcutaneous masses, edema, and muscle contractures; assess pulses; and to localize tender trigger points. Remember that unless the pain is bilateral, there is a contralateral structure that can be palpated and used as a control in most patients.

Similar to palpation, percussion is dependent on the patient tolerating touch. Pain on percussion of bony structures can indicate a fracture, abscess, or infection. Percussion of spinous processes is often done to determine whether a vertebral body fracture is a true pain generator or an incidental finding. Pain on percussion over a sensory nerve, or Tinel's sign, can indicate nerve entrapment or the presence of a neuroma. Tinel's signs are frequently noted on wrist examination for carpal tunnel syndrome and on the scalp for occipital neuralgia.

Range of motion (ROM) is an active test limited by the patient's effort and report of limitation. The possibilities of range of motion depend on the body location or joint. For example, in the shoulder the movements include flexion, extension, abduction, adduction, and external and internal rotation. The range of motion for each possible movement is described in terms of maximum degrees of movement the patient performed and the reported reason for any limitation. Each joint has generally agreed upon normal limits of motion. Joint, connective tissue, or ligamentous laxity can result in supranormal ROM, whereas pain and structural abnormalities (strictures, arthritis) can limit ROM.

An in-depth knowledge and understanding of the examined region is vital in order to integrate the results of sensory, motor, and reflex examinations, and come to a meaningful conclusion about the localization and nature of the lesion.

The combination of a global neurologic examination and a template-driven focal regional examination should provide the information needed to diagnose most common pain pathologies and rule out rarer diagnoses. All regionally directed pain examinations have evolved specific provocative pain tests for many of the potential pain-generating structures. Region specificity allows the practitioner to focus on the tests that will have a high specificity and sensitivity for the pathologies being diagnosed and avoid low yield maneuvers. Since these maneuvers are unique to each area, a detailed knowledge of the anatomy and function of the local structures is essential.[7]

GENERAL OBSERVATIONS

The physical examination should begin as soon as the patient walks into the examination room. Observations regarding the patient's mannerisms, coordination, interpersonal interactions, and gait can provide insight into the patient's mental, emotional, and physical status. Early observations in a less obvious setting (such as the waiting room) provide a basis against which to measure pain behaviors and gait abnormalities. During history taking, it is key to develop trust and basic insight into mental status to determine how detailed a mental status examination is warranted.[8] By establishing the nature of the patient's complaint during the history, the physical examination can be efficiently directed toward the affected region.

General assessment should include obtaining vital signs. The vital signs are an objective indication of the patient's general health status and may be used to rule out relative contraindications to interventions (fever, uncontrolled hypertension).

MENTAL STATUS EXAMINATION

Based on observations made while obtaining the history, a mental status examination can be performed and documented as an indicator of general health status. A basic mental examination is described in Table 4-6. Descriptors of the general mental status include the patient's level of consciousness; alertness; orientation to person, place, and time; and demeanor toward the examiner.[9] Signs of mental deterioration should correlate with the patient's history or initiate a search for an underlying pathology. The examiner should be especially vigilant for signs of undiagnosed depression, which is frequently associated with chronic pain.

GAIT

In general terms, gait is divided into two main phases, swing and stance, which are further subdivided into several components. Although there are numerous detailed descriptions of normal and pathologic gaits and their analysis, for a directed pain physical examination, it suffices to describe the gait as normal, antalgic, or abnormal. An antalgic gait is characterized by the avoidance of bearing weight on an affected limb or joint secondary to pain. An abnormal non-antalgic gait is a broad category that includes balance, neurologic, and musculoskeletal disorders. Included in gait analysis should be the observation of tilts, pelvic motion and tilt, and drifting. As most gait abnormalities are not specific for a particular pathology,

TABLE 4–6 Brief Mental Examination

Orientation to person and place, date repetition
Ability to name objects (e.g., pen, watch)
Memory immediate at 1 min, and at 5 min; repeat the names of three objects
Ability to calculate serial 7s, or if patient refuses have them spell "world" backward
Signs of cognitive deficits, aphasia

further investigation is almost always indicated to detect the cause.[6]

EXAMINATION OF THE DIFFERENT REGIONS OF THE BODY

Based on location, innervation, and function, the pain physical examination can be broadly divided into face, cervical region, thoracic region, and lumbosacral region. Obviously with such broad definitions, overlap occurs and the examination should be tailored to the patient's signs and symptoms.

FACE

A directed examination of the face is largely based on cranial nerve testing. Table 4-7 provides a description of a detailed strategy. Inspection of the face begins by observing the cutaneous landmarks for signs of infection, herpetic lesions, sudomotor changes, and scarring (both traumatic and postherpetic). Oral inspection is indicated since intraoral lesions frequently refer pain to distant facial regions. It is also crucial to observe the symmetry of the face; signs of asymmetry should be investigated. Facial palpation is important to identify masses, sensory changes, and tenderness over the sinuses. Percussion can confirm sinus tenderness and distal neurologic derangements. The most common facial percussive test is Chvostek's test (masseter spasm with tapping of the angle of the mandible, which suggests hypocalcemia). The only major articulation in the face is the temporomandibular joint (TMJ), which can dislocate, freeze, or be crepitant with pathology during ROM testing. A facial examination is indicated in headache patients secondary to referred pain patterns (supraorbital neuralgia, sinus headache, or headache secondary to TMJ syndrome).[5,10]

CERVICAL AND THORACIC REGIONS AND UPPER EXTREMITIES

A directed cervical examination includes the upper thorax, head, shoulders, and upper extremities, as pain can be referred to these areas. Inspection should focus on symmetry, muscle condition, and the position of the head, shoulder, and upper extremity at rest. Non-neutral neck positions can worsen neck pain from a plethora of different pathologies. Additionally the upper extremities should be examined for sudomotor changes and cutaneous temperature alterations when indicated. Palpation in the cervical and trunk region can identify muscle spasms, myofascial trigger points, enlarged lymph nodes, occipital nerve entrapment, and pain over the bony posterior spine elements that suggests facet arthropathy. Upper extremity palpation should identify gross sensory changes and pulse symmetry.

The normal cervical ROMs are flexion, 0° to 60°; extension, 0° to 25°; bilateral lateral flexion, 0° to 25°; and bilateral lateral rotation, 0° to 80°. Any reduction in active range of motion should be documented with the reported reason for limitation. Pain in a dermatomal pattern often indicates a spinal cord or nerve root lesion. Having the patient trace radiating limb pain all the way into the digits can elucidate which nerve root is affected.[5,10] The remainder of the examination of the cervical region is based on cervical motor, sensory, and reflex examinations, which are best reviewed in an integrated manner. Table 4-8 lists appropriate tests for the C4–T1 nerve roots.[1]

TABLE 4–7 Cranial Nerve Examination: Summary of Cranial Nerve Functions and Tests

Cranial Nerve	Function	Test
I. Olfactory	Smell	Use coffee, mint, and so on held to each nostril separately; consider basal frontal tumor in unilateral dysfunction
II. Optic	Vision	Assess optic disc, visual acuity; name number of fingers in central and peripheral quadrants; direct and consensual pupil reflex; note Marcus-Gunn pupil (paradoxically dilating pupil)
III, IV, and VI. Oculomotor, trochlear, and abducens	Extraocular muscles	Pupil size; visually track objects in eight cardinal directions; note diplopia (greatest on side of lesion); accommodation; note Horner's pupil (miosis, ptosis, anhydrosis)
V. Trigeminal: motor and sensory	Facial sensation, muscles of mastication	Cotton-tipped swab/pinprick to all three branches; recall bilateral forehead innervation (peripheral lesion spares forehead, central lesion affects forehead); note atrophy, jaw deviation to side of lesion
VII. Facial	Muscles of facial expression	Wrinkle forehead, close eyes tightly, smile, purse lips, puff cheeks; corneal reflex
VIII. Vestibulocochlear (acoustic)	Hearing, equilibrium	Use timing fork, compare side to side; Rinne's test for air conduction (AC) vs. bone conduction (BC) (BC > AC); Weber's test for sensorineural hearing
IX. Glossopharyngeal	Palate elevation; taste to posterior third of tongue; sensation to posterior tongue, pharynx, middle ear, and dura	Palate elevates away from the lesion; check gag reflex
X. Vagus	Muscles of pharynx, larynx	Check for vocal cord paralysis, hoarse or nasal voice
XI. Accessory	Muscles of larynx, sternocleidomastoid, trapezius	Shoulder shrug, sternocleidomastoid strength
XII. Hypoglossal	Intrinsic tongue muscles	Protrusion of tongue; deviates toward lesion

TABLE 4–8 Cervical Region Nerve Root Testing

Root Level	Nerve	Muscle(s) Tested	Position	Action	Sensory	Reflex
C4	Dorsal scapular	Levator scapulae	Sitting	Shoulder shrug	Shoulders	None
C5	Musculocutaneous lateral arm (C5–6)	Biceps	Forearm fully supinated, elbow flexed 90°	Patient attempts further flexion against resistance	Lateral forearm, first and second finger	Biceps
C6	Radial (C5–6)	Extensor carpi, radialis, longus, and brevis	Elbow flexed at 45°, wrist extended	Maintain extension against resistance	Middle finger	Brachioradialis
C7	Radial (C6–8)	Triceps	Shoulder slightly abducted, elbow slightly flexed	Extend forearm against gravity	Middle finger	Triceps
C8	Anterior interosseous (median) (C7–8)	Flexor digitorum profundus		Finger flexion of middle finger	Fourth, fifth finger medial forearm	None
T1	Ulnar, deep branch (C8–T1)	Dorsal interossei	Patient extends and spreads all fingers	Examiner pushes patient's fingers together, patient resists	Medial arm	None

Provocative Tests

The distraction test is a maneuver that evaluates the effect of cervical traction on a patient's pain perception. The patient's head is slightly elevated superiorly, off-loading the cervical spine. This motion allows widening of the neural foramina, relieving compression caused by neural foraminal stenosis. In contrast, the cervical compression test involves downward pressure on the head, causing compression of the cervical spine and narrowing of the foramina. A Spurling's (neck compression) test, which is performed by gently axially loading the cervical spine while extending the neck and rotating the head, is considered positive if it elicits radicular symptoms ipsilaterally. The exacerbation of symptoms indicates foraminal stenosis. A Valsalva maneuver may also be helpful in delineating pathology in the cervical spine. An increase in intrathecal pressure develops with this maneuver, and increased pain may be secondary to compression of the disc material or tumor.

The presence of a rotator cuff derangement can cause pain in the shoulder. The drop-arm test may help identify the presence of a tear in the rotator cuff. In this test, the patient with rotator cuff dysfunction will not be able to retain the arm in an abducted position. Other tests include shoulder ROM testing and pain provocation with a baseball pitching motion against resistance. A full-thickness rotator cuff tear can be most accurately diagnosed with a combination of three positive findings: painful arc, the drop-arm sign, and weakness in external rotation.[11] The Yergason test examines the integrity of the biceps tendon in its bony groove in the humerus. In this maneuver the patient flexes the elbow. The examiner grasps the elbow and wrist of the patient and attempts to rotate the arm externally while the patient resists the maneuver. Instability of the tendon is manifested by the presence of pain in the area of the tendon. Patients with lateral epicondylitis pain can have their symptoms reproduced by the tennis elbow test. The test involves wrist extension by the patient as the lateral forearm is stabilized by the examiner. An attempt to flex the wrist is made while the patient resists. In the presence of lateral epicondylitis, the patient will notice tenderness in the area.

A positive ulnar Tinel's sign is elicited at the elbow by tapping over the groove between the olecranon and the medial epicondyle and causing pain or numbness in ulnar distribution. A positive median nerve Tinel's sign is elicited by tapping on the carpal tunnel, and is suggestive of carpal tunnel syndrome. Similarly, Phalen's sign, paresthesias, or pain in the fingers when flexing the patient's wrists and placing the dorsal hand surfaces together for a minute, may also indicate median nerve dysfunction at the level of the carpal tunnel.

THORACIC REGION

Thoracic spine pathology can result in pain in the thorax, abdomen, and back. Inspection should focus on cutaneous landmarks and the presence of herpetic lesions, ecchymotic lesions, or masses. The thoracic spine, rib cage, and sternum to a degree all function as one unit to transmit loads and torque into the lumbosacral spine. Because loads are shared and there is not a great deal of mobility, in the absence of trauma, surgery, and congenital defects, clinically significant thoracic degenerative changes are not very common. Detection of thoracic kyphosis or scoliosis is an important indicator of thoracic alignment and possible neural and intrathoracic compression. Thoracic palpation should mainly focus on ruling out rib and spine fractures. Palpation of the abdominal wall may differentiate between superficial and deep pain generators. Deep palpation can detect pulsatile masses consistent with an abdominal aortic aneurysm that can present as low thoracic back pain. Once again, sensory examination can be guided by dermatome charts. This is especially true in postherpetic neuralgia and post-thoracotomy lesions. There are no true ROM, motor, or reflex examinations truly specific to the thoracic region.

LUMBOSACRAL REGION

The lumbosacral region is the most common location of pain complaints and contains the most potential pain-generating structures. Similar to the other regional

examinations, a structured evaluation begins with inspection. A global inspection of the patient's gait and posture at rest reveals signs of asymmetry (including pelvic tilts and obliquities) and the degree of spinal curvature. Major lumbar scoliosis, kyphosis, and excess lordosis can usually be assessed with inspection and palpation except in the very obese. Inspection of any postsurgical scars is important as the superficial scar alone can alter which interventional techniques are suitable. Lower extremity inspection includes vigilance for sudomotor and temperature changes.[5]

Palpation in the lumbar spine begins with identification of the bony landmarks, specifically the iliac crests. The horizontal line connecting the iliac crests roughly estimates the L4–L5 level. Identification of this landmark provides a reference point against which to orient any further observations. Common bony structure pain generators in the lumbar region include the facet joints, sacroiliac joints, and the coccyx. Soft tissue palpation is important to evaluate paraspinous muscle tone, the localization of trigger points, and the presence of masses such as lipomas. Pain on palpation over the iliac crest can indicate cluneal nerve entrapment.[12]

The normal lumbar spine ROMs are flexion, 0° to 90°; extension, 0° to 30°; bilateral lateral flexion, 0° to 25°; and bilateral lateral rotation, 0° to 60°.[5] Chapter 43 provides a review of the possible causes of limitation of ROM and pain. Generally, pain on flexion hints at a possible disc lesion, whereas pain on extension can indicate a facet arthropathy or myofascial pain generator.

Similar to the cervical region, the confidence in lumbosacral lesions localized by confirmatory muscle, sensory and reflex test results is extremely high. Table 4-9 provides an integrated sensory, motor, and reflex test outline for L2–S1. In addition to specific nerve root tests, two complementary tests are heel walk (dorsiflexion), which tests L4–L5 function, and toe walk (plantar flexion), which tests S1–S2 integrity.

Multiple provocative tests described for the lumbar region are presented in Chapter 43. The majority of tests are directed toward pathology in the disc and nerve roots, facet joints, sacroiliac joint, hip, and piriformis muscle. The most frequently performed test for nerve root irritation is the straight leg raise, which is specific for a radicular pathology when pain radiates distal to the knee. This test provokes lumbar radicular symptoms by applying a stretch force to these nerves, which is accentuated by ankle dorsiflexion. The slumped-seat test is a similar exam except in the seated position. Facet arthropathy can be diagnosed by eliciting pain with facet loading maneuvers (lateral flexion, lateral rotation, and extension). Patrick Faber test, Gaenslen's test, Yeoman's test, posterior shear test are tests for sacroiliac joint dysfunction.[12] If a patient exhibits at least three of these findings, sacroiliac joint dysfunction should be considered. It is hard to distinguish normal from abnormal sacroiliac joint response with the Gillet test (see Chapter 47 on sacroiliac joint syndrome). Tests for piriformis syndrome include the Pace, Laseque, and Freiberg signs, described in detail in Chapter 47 on piriformis syndrome. General tests for intrathecal lesions include the Kernig test for meningeal irritation, the Valsalva, and the Milgram test for intrathecal pathology. In the Kernig test, a supine patient flexes the chin onto the chest. A positive sign is when the patient complains of pain in the spine. The Milgram test involves a supine patient raising the leg a few inches off the examination table. The inability of the patient to hold this position for 30 seconds may indicate an intrathecal lesion.[1,13]

Provocative tests, by their nature, rely on honest patient cooperation and effort, and their validity can be greatly diminished by lack of patient participation, pain behaviors, and secondary gains. The Hoover test and Waddell's signs can help with a confounding patient. The Hoover test may be used to confirm the presence of malingering with regards to paralysis of the legs. In this test, the patient is supine and the examiner raises one leg of the patient while the other hand of the examiner is underneath the patient's other (supine) leg. The tendency is for the patient to press down on the supine leg (the downward movement of the heel of the foot is felt by the examiner's hands), the absence of movement of the supine leg indicates true leg paralysis.[12] Although controversial, Waddell's signs are a measurement of patient pain behaviors and provide

TABLE 4–9 Lumbar Region Nerve Root Testing

Root Level	Nerve	Muscle(s) Tested	Position	Action	Sensory	Reflex
L2	Femoral (L2–L4)	Psoas, iliacus	Patellar Hip and knee flexed at 90°	Hip and knee, upper thigh flexed at 90°	Anterior upper thigh	Patellar
L3	Femoral (L2–L4)	Quadriceps femoris	Supine, hip flexed, knee flexed at 90°	Extend knee against resistance	Anterior lower thigh	Patellar
L4	Deep anterior (L4–L5)	Tibialis	Ankle dorsiflexed, peroneal anterior heel walk	Maintain extension against resistance	Knee walk	Patellar*
L5	Deep lateral calf, peroneal hamstring (L4–L5)	Extensor hallucis longus	Great toe extended	Maintain extension	Web between big and second toe	Medial hamstring
	Superficial peroneal	Peroneus longus and brevis	Foot everted	Maintain eversion against resistance	Dorsum of foot	
S1	Sciatic (L5–S2)	Hamstrings	Prone, knee flexed toe walk	Maintain flexion against resistance	Foot (except medial aspect)	Achilles

** Patellar reflex is mainly secondary to L4.*

indications of a nonorganic source for the patient's pain. There are five potential Waddell's signs; the presence of three or more positive signs is a strong indication of a nonorganic source for the patient's pain. The five signs or tests are tenderness, simulation testing, distraction testing, regional disturbances, and overreaction. Tenderness is a deep or diffuse nondermatomal report of pain to a superficial stimulus most often a light skin roll or pinch. Simulation testing is a report of pain in the lumbar region to axial loading of the head or to body rotation with the shoulders and pelvis in line. Distraction testing is repetition and comparison of the results of a provocative test in an obvious and less obvious nonstandard fashion; the most common is sitting versus supine straight leg raise tests. If the results are contrary, this is considered positive. Regional disturbances are primarily motor, and include sensory deficits that do not follow an anatomic distribution. They can be a nondermatomal distribution of sensory change, such as a glove and stocking distribution or complete limb weakness. Finally, overreaction in the context of cultural variation includes disproportionate verbal and facial expressions, unconventional anatomic movements and postures, and inappropriate responses to the examination. These examinations simply suggest that there may not be an organic or anatomic source for the patient's pain, but placing the results of the physical examination in the context of the patient's effort and can provide support for the results.[5,12]

CONCLUSION

The physical examination is secondary in importance only to the pain history. In addition to developing the patient's trust, a complementary physical examination should explore the complaints raised in the history and provide information that confirms or rejects the proposed explanations for the symptoms. Oftentimes, costly imaging studies and painful invasive testing can be avoided by performing a simple yet thorough physical exam. In order to gain a meaningful understanding of the patient's symptoms, the physical examination should be based on anatomic and physiologic principles. Following a brief global assessment of the patient's health, the pain examination should be focused toward the affected region and consistently performed in a structured pattern using templates and standard "normal" charts and maps. Supported by confirmatory physical examination findings and appropriate provocative testing, one can have a high degree of confidence in the working diagnosis. Ultimately, a physical examination that fulfills these criteria is an invaluable component in establishing the correct diagnosis in a pain patient.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 5

Pain Assessment

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INTRODUCTION

By its very definition, pain is an internal, subjective experience that cannot be directly observed by others or measured by the use of physiologic markers or bioassays. The assessment of pain, therefore, relies largely (and in many cases exclusively) upon the use of self-report. Though the self-report of pain or any other construct is subject to a number of biases, a good deal of effort has been invested in testing and refining self-report methodology within the field of human pain research. The purpose of this chapter is to provide an overview of this research, to critically evaluate pain assessment tools, and to assist clinicians and researchers in selecting the pain assessment methods best suited to serve their purposes.

CHALLENGES OF PAIN MEASUREMENT

Assessing pain requires measurement tools that are valid and reliable, as well as an ability to communicate (using language, movements, etc.). However, even when these basic requirements are met, additional challenges abound. For example, over what time-frame is pain to be measured? By nature, most pain conditions are fairly variable, and it is sometimes unclear how representative (of a patient's global pain experience) ratings of current or recent pain might be. Many ratings scales do query current pain, or pain over the past week, but longer timeframes are often used and these many introduce additional memory biases.[1] In addition, pain is a multidimensional experience incorporating sensory and affective components that are correlated but which may be assessed separately.[2] Generally, most self-report pain assessment tools described below focus on pain intensity ratings over a relatively brief and recent period of time (e.g., the past week).

TYPES OF SELF-REPORT PAIN SCALES

A variety of pain assessment scales are available for evaluating the intensity of acute and chronic pain. Multiple types of scales are widely used and well-validated in both research and clinical settings.[3,4] The three most commonly used methods to quantify the pain experience (pain intensity, usually) are verbal rating scales, numerical rating scales, and visual analog scales.

VERBAL RATING SCALES (VRS)

A VRS generally consists of a series of adjectives (or phrases), ordered from least intense (or unpleasant) to most intense (or unpleasant). An adequate VRS should span a maximum possible range of the pain experience (e.g., from "no pain" to "extremely intense pain"). Patients are asked to select the adjective or phrase that best characterizes their level of pain. Dozens of VRS have been described and validated; one of the more common examples appears in Table 5-1.[5]

In general, a VRS is scored by assigning each adjective or phrase a number according to its rank (e.g., 0 to 4 in the example in Table 5-1). The strengths of the VRS include simplicity, ease of administration and scoring, as well as face validity (i.e., they appear to directly measure exactly what they purport to measure, such as the intensity of pain). In addition, because they are so easy to comprehend, compliance rates for the VRS can be superior to the rates obtained with other scales, especially within certain populations such as the elderly.[6] The VRS has demonstrated good reliability (e.g., consistency over short periods of time) in a number of studies. The validity of the VRS has also been repeatedly established; these scales correlate positively with other self-report measures of pain intensity and with pain behaviors.[7]

Despite its substantial strengths, the VRS also exhibits a number of weaknesses, based on which other pain researchers have hesitated to recommend these scales. First, the scoring method for VRS assumes equal intervals between adjectives. That is, the change in pain from "none" to "mild" is quantified identically with the change in pain from "moderate" to "severe." This assumption is rarely tested, and is likely often violated. This property of the VRS poses difficulties in both the interpretation and analysis of VRS-derived data. Second, in order to properly use a VRS, a patient must both be familiar with all of the words used on the scale, and must be able to find one that accurately describes his or her pain. Some past reviews of the pain assessment literature have indicated that the VRS is being used less often in pain outcome research than has been the case in the past.[8]

NUMERICAL RATING SCALES (NRS)

An NRS typically consists of a series of numbers with verbal anchors representing the entire possible range of pain intensity. Generally, patients rate their pain from 0 to 10, from 0 to 20, or from 0 to 100. Zero represents "no pain" whereas the 10, 20, or 100 represents the opposite end of the pain continuum (e.g., "the most intense pain imaginable,," "pain as intense as it could be,," "maximum pain"). See Figure 5-1 for an example. Like verbal rating scales, the NRS have well-documented validity; they correlate positively with other measures of pain and show sensitivity to treatments that are expected to affect pain.[3,9] The NRS can be administered verbally or in a written format, is simple and easily understood, and is easily administered and scored. The principal weakness of the NRS is that, statistically, it does not have ratio qualities.[10] That is, numerically equal intervals on the scale (e.g., the difference

TABLE 5–1 Verbal Rating Scale (VRS) for Pain Intensity

None	0
Mild	1
Moderate	2
Severe	3
Very Severe	4

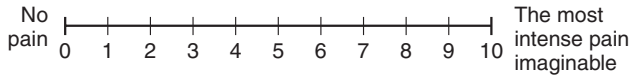


FIGURE 5-1 Sample numerical rating scale (NRS) for pain intensity.

between 1 and 3 and the difference between 7 and 9) may not represent equivalent intervals in terms of scaling the intensity of pain. One other limitation of most NRS measures of pain is that individuals' ratings of a given pain experience can be altered in idiosyncratic ways by the choice of anchors on the upper end of the scale. For example, women and men use systematically different events to contextualize the anchor of "most intense pain imaginable," and this can significantly affect studies of gender differences in the experience of pain.[11]

VISUAL ANALOG SCALES (VAS)

A VAS consists of a line, often 10 cm long, with verbal anchors at either end, similar to an NRS (e.g., "no pain" on the far left and "the most intense pain imaginable" on the far right). The patient places a mark at a point on the line corresponding to the patient's rating of pain intensity. The line may be depicted with a horizontal or vertical orientation, though a horizontal line is generally preferred (Figure 5-2). Recent versions include the mechanical VAS, which uses a sliding marker superimposed on a horizontal VAS drawn on a ruler,[12] and is easily scored from the back, which includes numbers for each marker placement. The VAS has often been recommended as the measure of choice for assessment of pain intensity. Substantial evidence supports its validity, and the VAS is sensitive to treatment effects. Though most studies suggest minimal differences in sensitivity among rating scales, significant differences that do emerge generally favor a VAS over a VRS or an NRS. In addition, VAS scores correlate with pain behaviors, and VAS scores do show ratio-level scoring properties.

The VAS does possess some limitations, however. It can be difficult to administer to patients with perceptual-motor problems, which are rather common in the context of chronically painful conditions. In addition, a VAS is generally scored using a ruler (the score is the number of centimeters or millimeters from the end of the line), making scoring more time consuming and adding additional possible sources of bias or error. Finally, relative to other rating scales, use of a VAS produces higher noncompletion rates among certain populations, primarily among those with cognitive limitations and among elderly samples (see below).

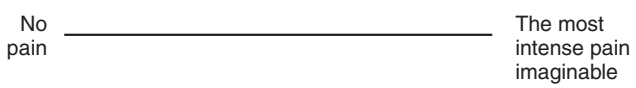


FIGURE 5-2 Sample visual analog scale (VAS) for pain intensity.

MCGILL PAIN QUESTIONNAIRE (MPQ)

The MPQ[13] and its brief analog, the short-form MPQ,[14] are among the most widely used measures of pain. In general, the MPQ is considered to be a multidimensional measure of pain quality; however, it also yields numerical indices of several dimensions of the pain experience. Researchers[15] have proposed three dimensions of the experience of pain: sensory-discriminative, affective-motivational, and cognitive-evaluative. The MPQ was created to assess these multiple aspects of pain. It consists of 20 sets of verbal descriptors, ordered in intensity from lowest to highest. These sets of descriptors are divided into those assessing the sensory (10 sets), affective (5 sets), evaluative (1 set), and miscellaneous (4 sets) dimensions of pain. Patients select the words that describe their pain, and their word selections are converted into a pain rating index, based on the sum of all of the words after they are assigned a rank value, as well as the total number of words chosen. In addition, the MPQ contains a present pain intensity VRS (i.e., the PPI), ordered from "mild" to "excruciating."

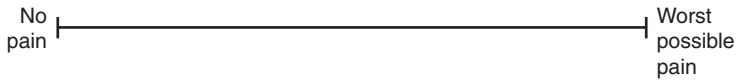
The more frequently used short form of the MPQ consists of 15 representative words that form the sensory (11 items) and affective (4 items) categories of the original MPQ. Each descriptor is ranked on a 0 ("none") to 3 ("severe") intensity scale. The PPI, along with a VAS, are also included (Figure 5-3). The short form correlates highly with the original scale, can discriminate among different pain conditions, and may be easier than the original scale for geriatric patients to use.[6]

PAIN RELIEF

Studies of interventions designed to reduce pain often include a post-treatment assessment of pain relief in addition to measures of pain intensity obtained at both baseline and post-treatment. Pain relief is often measured using a VAS, a VRS with gradations of relief (e.g., "none," "slight," "moderate," "complete"), or an NRS assessing the percentage of relief. Although conceptually attractive, measures of pain relief have demonstrated problems with validity. For example, a significant minority of patients report at least moderate relief on these scales when an analysis of sequential pain ratings (i.e., pre-treatment compared to post-treatment) reveals *increases* in reported pain intensity. In one trial, whereas average pain ratings increased by 28% early in the study, approximately 90% of patients reported some degree of relief on a VAS.[16] This phenomenon (i.e., the apparent over-reporting of relief) seems to be due in part to a memory for past pain as being substantially greater than previous ratings would indicate.[1]

	None	Mild	Moderate	Severe
Throbbing	0)_____	1)_____	2)_____	3)_____
Shooting	0)_____	1)_____	2)_____	3)_____
Stabbing	0)_____	1)_____	2)_____	3)_____
Sharp	0)_____	1)_____	2)_____	3)_____
Cramping	0)_____	1)_____	2)_____	3)_____
Gnawing	0)_____	1)_____	2)_____	3)_____
Hot-burning	0)_____	1)_____	2)_____	3)_____
Aching	0)_____	1)_____	2)_____	3)_____
Heavy	0)_____	1)_____	2)_____	3)_____
Tender	0)_____	1)_____	2)_____	3)_____
Splitting	0)_____	1)_____	2)_____	3)_____
Tiring-exhausting	0)_____	1)_____	2)_____	3)_____
Sickening	0)_____	1)_____	2)_____	3)_____
Fearful	0)_____	1)_____	2)_____	3)_____
Punishing-cruel	0)_____	1)_____	2)_____	3)_____

Rate the intensity of your pain on the two scales below. Make a mark on the line to indicate where your pain falls between *No pain* and *Worst possible pain* and then circle the appropriate number on the second scale.



Circle one of the following words that best describes your current pain:

0 No pain
1 Mild
2 Discomforting
3 Distressing
4 Excruciating

FIGURE 5-3 The short-form MPQ. *(Reprinted from Melzack R: The Short Form McGill Pain Questionnaire*, Pain *30:191–197, 1987.)*

MULTIDIMENSIONAL ASSESSMENT IN CLINICAL TRIALS

Though a full exploration of recommendations for outcome assessment in analgesic trials is beyond the score of this chapter, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has produced a series of publications on this issue. Interested readers should consult one of the IMMPACT position papers (e.g., Dworkin et al.[17]). In brief, this group of experts has reviewed measures of pain intensity, physical functioning, emotional functioning, and other pain-relevant outcome domains, making recommendations for the selection of outcome measures for clinical trials of pain treatments.

ADDITIONAL CONSIDERATIONS:

Differentiating Types of Pain: There has been a good deal of interest in the development of self-report measures of neuropathic pain; indeed, the MPQ has been studied in this context, and over recent years several screening tools for distinguishing neuropathic from nociceptive pain have

been validated.[18] The PainDETECT assessment system, which relies on a set of self-report questions about symptoms, was designed to detect neuropathic pain in patients with low back pain; it has been validated in large studies with thousands of patients, and has been reported to achieve reasonable sensitivity and specificity in identifying patients with neuropathic back pain. Other questionnaires such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale and the Neuropathic Pain Questionnaire (NPQ) have also been studied as indicators of the presence of neuropathic pain. However, whereas some validity studies suggest good results, several persistent issues have plagued the research in this area. The first is that while the definition of neuropathic pain indicates that a lesion or dysfunction must be present in the nervous system, this can often be difficult to establish in patients with chronic pain, creating a questionable "gold standard" against which the diagnostic accuracy of a questionnaire can be measured. Second, multiple studies strongly suggest that the endorsement of classically "neuropathic" symptoms (e.g., shooting pain, numbness and tingling, etc.) is strongly influenced by other patient characteristics, such as emotional distress,[19] indicating that a wide variety of factors are likely to contribute to self-report of the presence of neuropathic pain.

Daily Diaries: In trials of pain treatments, daily diaries are gradually becoming the standard for assessing pain-related symptoms in order to minimize memory biases that threaten the validity of global retrospective ratings of pain.[20,21] Participants are generally asked to complete measures of pain and related symptoms one or more times per day, often for 1-2 weeks. Because pain reports can have substantial day-to-day variability, aggregated (averaged) ratings have been demonstrated to be more reliable[22] and sensitive to treatment effects[23] than retrospective measures of pain. In general, recent research has favored electronic dairies; in comparison to paper-and-pencil diaries, electronic diaries (e.g., usually implemented using a PDA, cell phone, or similar tool), have been repeatedly shown to demonstrate superior compliance rates and patient satisfaction. Electronic diaries incorporate several features that enhance reliability, including: date/time stamping of all diary entries, and automatic rejection of erroneous data.

BEHAVIORAL OBSERVATION

Though pain is by definition a private and subjective experience, its manifestations are often apparent to others. People in pain may communicate their discomfort by vocalizations, facial expressions, body postures, and actions. These verbal and nonverbal behaviors have been termed pain behaviors, and they have emerged as an important component of behavioral models of pain. Numerous pain behavior coding systems have been developed, though many of them are specific to particular pain conditions. For example, the osteoarthritis (OA) pain behavior coding system[24] assesses the position, movement, and specific pain behaviors (e.g., guarding, rubbing, flexing) observed in OA patients during standardized tasks. Assessment of pain behaviors can be valuable in establishing a patient's level of physical functioning (e.g., the amount of activity engaged in), in analyzing the factors that may reinforce displays of pain (e.g., solicitous responses from others), or in assessing pain in nonverbal individuals. A review of the literature in this area concluded that although pain behaviors and self-report of pain are moderately related, these measures are not interchangeable.[25] Interestingly, correspondence between pain report and pain behavior was lower in the context of chronic pain than acute pain and, not surprisingly, was highest when observation and verbal report of pain were recorded at the same time.

Many recent behavioral observation studies have focused on facial expressions in response to pain.[26] To date, a number of observational systems have been developed for evaluating pain-related facial expressions in a relatively "objective" manner. Early studies used the Facial Action Coding System to characterize the facial expressions of adults responding to a variety of pain induction tasks. Numerous elements of facial expressions (e.g., upper lip raising, mouth opening, eye closure) were found to be related to pain ratings, and the relative consistency with which the same actions were associated with pain across numerous samples supported the concept of a potentially universal set of "pain expressions." Indeed, striking similarities have been observed between the facial actions associated with pain in middle-aged adults, the elderly, children, and neonates.[26] This commonality of pain-related facial expression suggests that it may be a crucial assessment tool in situations in which verbal report is unavailable, as is the case with very young children, or individuals with verbal communication deficits.

EXPERIMENTAL PAIN ASSESSMENT

Administration of standardized noxious stimulation under controlled conditions constitutes an important subdiscipline within the field of pain.[27] Several modalities of noxious stimulation are commonly used to induce pain (e.g., thermal, mechanical, electrical, chemical, ischemic); typical parameters that are measured include pain threshold, pain tolerance, and ratings of suprathreshold noxious stimuli using an NRS, VAS, or VRS. The clinical relevance of experimental pain assessment is gradually being established; quantitative sensory testing can be used to subtype patients with chronically painful conditions,[28] to identify mechanisms of chronic pain,[29] and to prospectively predict postoperative pain.[30]

PSYCHOPHYSIOLOGIC ASSESSMENT

Psychophysiologic data serve a number of important functions in the assessment of acute and chronic pain. First, they are a prerequisite for performing biofeedback or related procedures in which patients are taught to bring physiological processes under some degree of voluntary control. Second, psychophysiologic measures can help to elucidate some of the concomitants of pain not easily measured by self-report (i.e., arousal, central processing of information related to noxious stimulation). It should be noted that none of the following measures constitute "objective" measures of pain, which is by definition dependent on self-report, and none can substitute for some type of patient rating of their experience of pain.

Surface electromyography (EMG) is often used to record levels of local muscle tension in the context of musculoskeletal pain syndromes such as low back pain or tension headache, in which heightened muscle tension is thought to contribute to the experience of pain.[31,32] Electroencephalography (EEG) has been used in a number of studies to assess brain responses to noxious stimulation. Although EEG's spatial resolution is rather limited, its temporal resolution is quite good; several studies have now shown that EEG-measured cortical responses to standardized noxious stimuli are enhanced in patients with chronic pain relative to healthy controls.[33] Heart rate and blood pressure are frequently assessed in the context of experimental pain administration. However, while resting blood pressure and pain responses are inversely correlated,[34] no consistent relationships between cardiovascular reactivity and pain responses have been observed. Collectively, psychophysiologic measures can provide unique information about pain responses; they cannot, however, serve as proxy measures for the experience of pain.

FUNCTIONAL NEUROIMAGING

Imaging of pain processing in the human brain has attracted considerable research attention over the past 10 to 15 years.[35] Functional neuroimaging methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) allow noninvasive assessment of the neurophysiology of pain processing in the brain (and, recently, the spinal cord as well). Most of these studies have been based on measurement of brain responses to acute pain stimuli (often in healthy subjects); brain activity is measured during periods of pain and pain-free periods, and the difference between these two measurements is considered an index of pain-related neurophysiologic processes in the brain. Although the cost and the necessity of sophisticated, expensive equipment make it unlikely that functional neuroimaging will become a routine part of clinical assessment in the near future, these brain imaging studies have rapidly advanced our understanding of the central nervous system's processing of pain-related information, and functional neuroimaging methods show great promise in several key areas of pain assessment. These include: refining the mechanism-based classification of pain syndromes, evaluating abnormalities of pain processing in individuals with communication or cognitive deficits, studying the pharmacokinetic and pharmacodynamic properties of analgesic drugs, identifying dysfunctional areas of processing in the nervous system that can serve as analgesic drug targets, and finally, revolutionizing pre-clinical drug development. This last application is the subject of much current interest, and many experts have proposed using functional neuroimaging as a primary preclinical tool to study, in healthy volunteers, the effects of various putative analgesic agents on pain-related brain activation.[35]

SPECIAL POPULATIONS

CHILDREN

The assessment of pain in children obviously presents a number of challenges to healthcare professionals. Many providers may (inaccurately) assume that children cannot reliably provide information about their pain. In fact, many pain assessment tools for use specifically in children have been developed and validated, and factors similar to those that influence pain in adults (e.g., the presence and magnitude of tissue damage, affective state, social responses) have been shown to relate in similar ways to children's pain.[36,37]

Over a dozen behavioral pain rating scales for infants have been developed. Although demonstration of the validity of these scales is often difficult, many have been shown to be consistently reliable. As an example, one of the more commonly used measures is the Neonatal Infant Pain Scale (NIPS),[38] which codes the presence and intensity of six pain-related behaviors: facial expressions, crying, breathing, arm movement, leg movement, and arousal state. Among older children who can more readily self-report sensory and affective experiences, researchers have suggested that direct questioning (e.g., "How is your pain today?"), although clinically useful, is particularly susceptible to bias and demand characteristics. Standardized pain assessment scales have been developed for children of various ages, some of them specific to particular ethnic groups. For example, among these are the FACES Scale and the Oucher Scale[39] which do not require language and are used for younger children (see Chapter 34 on pediatric postoperative pain). Pain thermometers, consisting of a vertical NRS superimposed on a VAS shaped to resemble a thermometer, have also been widely used, while for children over 6 years, a standard VAS is a valid and reliable measures of pain.[40]

THE ELDERLY

The past several decades have witnessed a steady increase in research related to pain in the elderly. Most pain assessment tools that have been validated in middle-aged adults have also been psychometrically examined in older subjects. In general, this body of research indicates that increasing age is associated with a higher frequency of incomplete or non-scorable responses on a VAS, but not on a VRS or NRS. Across studies, VAS failure rates in cognitively intact elderly samples range from 7% to 30% of respondents, with the percentages increasing substantially (up to 73%) in cognitively impaired samples.[6] Studies of preferences indicate that, in general, a VAS is rated as one of the least preferred measures among the elderly while a VRS often receives the highest preference scores. In addition, it has been suggested that the MPQ (long form) is inappropriate for use in elderly samples due to its complexity and time requirements. Although research does not support the contention that the elderly make more errors on the MPQ, several studies have now shown that older adults report less pain on the MPQ (i.e., choose fewer words) even when NRS- or VRS-rated pain does not differ.[41,42] These findings may suggest that the MPQ assesses the construct of pain differently across age-groups, and caution may be warranted before using this instrument with older samples.

Collectively, recent finding suggest that a VRS produces the fewest "failure" responses among samples of cognitively intact and cognitively impaired elderly subjects while a VAS produces the largest number. It is therefore recommended that studies of pain in the elderly use, at minimum, a VRS to assess pain intensity. Moreover, some

research suggest that the use of behavioral pain indicators may be preferable as among individuals with cognitive impairments, as these patients tend to underreport pain intensity on standard self-report measures, but show preserved indices of pain behaviors.[43,44]

BIASES IN PAIN MEASUREMENT

In many cases, formal and informal clinical judgments of a patient's pain-related symptoms are likely to drive diagnostic and treatment-planning decisions. Inaccurate assessments of pain have a number of substantive consequences; underestimation of pain can lead to improper management, unnecessary suffering and delay in recovery, whereas overestimation of pain can lead to overtreatment and potentially to adverse iatrogenic consequences. A number of studies have examined the congruence, or lack thereof, between patient reports of pain and healthcare providers' assessments of patients' pain. In general, findings from this body of research suggest that a good deal of caution is warranted when medical professionals attempt to estimate patients' levels of pain. Collectively, healthcare providers are suboptimal estimators of patients' pain symptoms. In one study,[45] agreement scores (i.e., kappa statistics) between nurses and postsurgical pain patients ranged from 0.01 to 0.12, which indicates no significant correlation between nurse and patient ratings of pain. In a study of cancer patients and their providers, no correlations between patients' VAS pain ratings and ratings of patient pain made by nurses, house officers or oncology fellows were significant.[46] Moreover, there is little evidence for the validity of expert judgments regarding the prognosis of patients in pain. For example, among back pain patients followed longitudinally, no relationship was observed between providers' estimates of patients' rehabilitation potential and actual rehabilitation outcomes.[47]

In addition, healthcare providers tend to systematically underestimate and undertreat pain-related symptoms. (See Tait et al.[48] for a recent review.) These patterns have been found across a range of providers, settings, and painful conditions. The majority of studies examining the congruence between health professional and patient ratings of pain have used samples of nurses. One study found that 43% of nurses underestimated the pain experienced by burn patients during a therapeutic procedure and nurses also overestimated the amount of pain relief following administration of analgesic medication.[49] This systematic pattern appears to be related to certain provider, patient, and situational factors. Vulnerable patient groups are particularly susceptible to pain undertreatment, including people with such neurocognitive deficits as Alzheimer's disease. Characteristics of healthcare providers, such as their training and experience, may also affect the extent to which pain is misjudged. In fact, increased experience seems to predispose providers to underestimate pain severity.[48] This finding may inspire pessimism, as increasing exposure to patients in pain seems to result in less empathetic responses (i.e., greater underestimation of patients' pain). On the other hand, there are reasons for optimism as some studies have suggested that appropriate training and education can reverse this underestimation bias in longtime practitioners.[48]

SUMMARY AND RECOMMENDATIONS

Although pain is a private and subjective experience, a wide array of valid and reliable measurement tools is available. Any study of pain should include at least one self-report measure, and it is often beneficial to use either multiple measures or a multidimensional measure of pain (e.g., the short form of the MPQ, which includes both verbal descriptors and a VAS). A review of the extensive cancer pain literature indicated that single-item VAS, VRS, and NRS all showed good validity and reliability, and it was concluded that no one of these measures was consistently superior.[7] However, we can advise that in studies of elderly or cognitively compromised subjects, use of a VRS or NRS is strongly preferable to use of a VAS. Pain relief should be measured using sequential ratings (i.e., changes from pretreatment to post-treatment) rather than a retrospective impression. Daily diaries may be extremely useful in reducing the memory biases associated with recall of pain, and in obtaining a more precise sense of the variability in day-to-day pain symptoms. Behavioral observation, experimental pain assessment, and psychophysiologic assessment are all useful and potentially informative adjunctive measures of pain responses, but none can substitute for self-report of the pain experience. The one exception to this standard is infants, in whom coding of behavioral or facial responses is the current gold standard for pain assessment. For slightly older children, a pictorial scale such as the FACES Scale or Oucher Scale may be used, whereas in children who are 6 or older, a standard VAS may be the optimal choice. Finally, substantial research suggests that healthcare professionals, no matter how expert, are not reliable judges of patients' report of pain. Their estimates are both inaccurate and systematically biased in the direction of underestimation.

The assessment of pain is vitally important to both clinicians and researchers. Self-report is the most direct manner of assessing pain and a variety of self-report measurement options exist. In this chapter, we have attempted to provide those with an interest in treating or studying pain with some of the requisite information on which to base choices regarding pain assessment. Measures should be selected with as complete a knowledge as possible of their properties, strengths, and limitations.

KEY POINTS

- Pain is a subjective, private, internal experience
- While there is currently no "objective" measure of pain, a number of self-report pain assessment tools have proven to be valid and reliable
- Specialized pain assessment scales are available for special populations (e.g., children)
- Psychophysiologic, behavioral, and functional neuroimaging-based assessment methods cannot substitute for an individual's self-reported pain experience
- Biases in estimating another person's pain are common, and healthcare providers tend to underestimate and undertreat patients' pain

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 6

Psychological Evaluation and Testing

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Chronic pain is a multifaceted, subjective experience that is best understood as a complex interaction of physiological, psychological, and environmental variables. Extensive research has documented the role cognitive, emotional, and social factors play in the etiology and maintenance of chronic pain.[1] Thus, comprehensive assessment of chronic pain includes psychological evaluation. This chapter provides an overview of the key components of a psychological evaluation for chronic pain—the clinical interview including behavioral observation and the use of standardized testing instruments.

CLINICAL INTERVIEW

While structured clinical interviews are available, most practitioners elect to conduct semistructured interviews with pain patients. The clinical interview addresses multiple aspects of the individual's cognitive, medical, educational, social, employment, and psychiatric history. The interview will include an assessment of mental status to determine if the individual is sufficiently cognitively intact to participate in the assessment and future treatments. Should concerns regarding cognitive impairments emerge, closer examination of cognitive functioning or a referral for a full neuropsychological evaluation is appropriate. If available, the practitioner may draw on collateral sources of information, such as significant others or family members. As part of the clinical interview, the psychologist will gather extensive information regarding the individual's pain history and experience.

The clinical interview is the cornerstone of the psychological evaluation due to the subjective nature of the pain experience and the relatively limited set of standardized psychological measures that have normative data for chronic pain patients. Some individuals with chronic pain may be reluctant to participate in a psychological evaluation, due to the stigma associated with psychiatric illness or the concern that the provider may be suggesting that the pain is psychologically based. Referring physicians and other providers can reduce these concerns by informing patients that psychological evaluation is a routine component of comprehensive pain management. The practitioner conducting the psychological evaluation can establish credibility by beginning the interview with a focus on the patient's pain experience. Once rapport is established, it is easier to progress to cognitive, social and psychological aspects of the interview. It is critical to evaluate the cognitive-affective variables involved in chronic pain. Symptoms of depression and anxiety are common among patients with chronic pain,[2] and closely correlated are cognitions that render the person more vulnerable to increased pain and suffering.[3] An important objective of the interview is to identify any psychiatric conditions that might exacerbate pain or complicate treatment, such as psychosis, substance dependence, or a personality disorder. Finally, observation of pain behaviors can provide important information about the person's overall pain experience, coping, and the extent of pain-related disability. Pain behaviors—such as ability to sit through the interview, verbal complaints and other sounds (e.g., grunting and moaning), facial expressions (e.g., grimacing, wincing), and bodily gestures (e.g., bracing when changing positions, moving in a distorted fashion)—are noted during the interview.

STANDARDIZED TESTING

One of the important elements a psychologist contributes in the overall assessment of a pain patient is expertise in the use of standardized testing instruments, which can provide data on the individual's functioning relative to normative samples. Key assessment domains are presented here, along with instruments commonly used in the psychological evaluation of persons with chronic pain. (The assessment of pain is included in other chapters of this volume.) Practitioners typically select the critical domains for a given patient and use one measure to assess that domain in the evaluation.

PAIN-RELATED DISABILITY AND BEHAVIOR

A number of validated questionnaires are available to assess a person's perceived disability. The Brief Pain Inventory (BPI) was developed to measure pain severity and pain-related interference in patients diagnosed with cancer.[4] Later research extended its use to non–cancer pain assessment, including heterogeneous pain conditions,[5] osteoarthritis,[6] and neuropathic pain.[7] The most widely used version of this scale uses an 11-point numeric rating scale (where 0 = no interference and 10 = interferes completely) to assess pain-related interference in seven areas: general activity, mood, walking ability, normal work including outside the home and housework, relations with other people, enjoyment of life, and sleep.[4] The timeframe for assessment can vary from "the past week"[4] to "the past 24 hr."[7] The BPI has been used to demonstrate the efficacy of pain medication in a variety of chronic painful conditions[6] and appears to be sensitive to treatment-related change. Formatted in a similar way, the Pain Disability Index (PDI) provides an alternative to the BPI.[8] It consists of seven questions assessing disability due to pain in the following domains: family/home, recreation, social activities, occupation, sexual behavior, self-care, and life support activities. Each item is rated on an 11-point scale (0 = no disability to 10 = total disability) and the responses are summed. The PDI is also sensitive to change following pain treatment.[9]

The Sickness Impact Profile (SIP) is a behaviorally based checklist of 136 yes/no items, measuring psychosocial and physical dysfunction across 12 categories of functioning: sleep and rest, eating, work, home management, recreation

and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication. The SIP is widely used with chronic pain patients and has sound psychometric properties[10]; however, some clinicians argue that the SIP's usefulness is limited by its length and its complex scoring algorithm. With only 24 questions, the Roland-Morris Disability Questionnaire was developed from a subset of SIP items and tailored for more focused use with chronic low back pain patients. This measure has become one of a select group of standard outcome measures in the back pain literature.[11,12] Although primarily used for the assessment of function in low back pain, some investigators have used this shorter scale to assess function in heterogeneous groups of patients seen through multidisciplinary programs. A later analysis identified 20 items SIP that were most sensitive to change in patients with low back pain, only seven of which were included in the Roland-Morris scale.[13,14] Other instruments in common usage include the Chronic Disability Index (CDI), a short (nine-item) yes/no checklist covering nine general activities that are typically difficult for people with back pain, such as walking, sleeping, putting on footware[15]; and the Oswestry Low Back Pain Disability Questionnaire, a brief scale that provides a percentage score reflecting the amount of restriction that pain imposes on the individual. Scores have been shown to be sensitive to treatment.[16]

NEGATIVE AFFECT

The extent of disability in pain patients does not correlate strongly with the extent of physical impairment.[17] The biopsychosocial pain model suggests this discrepancy is related to the psychological, social, and contextual variables that interact with physical factors to determine the individual's experience with pain and disability. Thus, the assessment of negative affect, such as depression and anxiety, as well as negative cognitions is an essential component of pain assessment.

There are several commonly used standardized measures. The Beck Depression Inventory (BDI) is a multiple-choice measure that asks individuals to endorse descriptive statements in 21 areas of depressive symptomatology, such as sadness, energy level, concentration, guilt, and suicidal ideation.[18] Although brief and easy to score and interpret, the BDI may overestimate the degree of depression among chronic pain patients because of its focus on a number of somatic and vegetative symptoms.

The Center for Epidemiological Studies Depression Scale (CES-D)[19] was originally developed for use in general-population epidemiologic studies. Respondents are asked to report the frequency with which they have experienced each of 20 symptoms during the past week on a 4-point scale. Like the BDI, the CES-D is brief and has excellent psychometric properties. Similar to the BDI, it has been criticized for possibly overestimating the prevalence and severity of depression among pain populations. Comparative analysis suggests that the CES-D and BDI are relatively comparable, with the CES-D demonstrating greater sensitivity and the BDI exhibiting better specificity.[20] Another commonly used instrument is the Zung Depression Inventory, which may be more appropriate for medical populations and offers the advantages of allowing a lower reading level and interview-based administration.[21]

Anxiety is a negative affective experience that can exacerbate the pain experience and complicate recovery. The Beck Anxiety Inventory (BAI) was developed to assesses anxiety and discriminate it from depression.[22] The scale consists of 21 items, each describing a common symptom of anxiety. The respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3. One instrument designed to measure anxiety specific to pain patients is the Pain Anxiety Symptoms Scale (PASS).[23] The PASS uses a 6-point scale and asks respondents to rate the frequency with which they experience several dimensions of anxiety, including somatic, cognitive, fear, and escape/avoidance concerns.

PAIN-RELATED COGNITION

Closely interconnected with negative affects among individuals with chronic pain are negative cognitions—habitually maladaptive ways of perceiving and thinking about situations—which can lead to a cascade of negative emotions and behaviors. Among pain patients, examples might include a tendency to over-focus on the pain, fearful anticipation of extreme pain, or the belief that any amount of pain signals tissue damage or reinjury and should be avoided at all costs. Indeed, data suggests that a strong anticipation of pain and reinjury or negative thoughts regarding pain-related experience, referred to as catastrophizing[24] can lead to fear-related avoidance of activity. These fears can produce a negative reinforcement loop supporting the persistence of avoidance behaviors and functional limitations.[25–27]

Several instruments are available to measure various beliefs, attitudes, and expectancies about pain. The Survey of Pain Attitudes–Revised[28] is a 57-item instrument utilizing a 5-point Likert scale, assessing seven pain-specific attitudes, including perceptions of pain control, disability, and harm, as well as beliefs surrounding pain medication, the role of emotions in their pain experience, and the expectation that other people should be more supportive of their pain concerns. The Pain Beliefs and Perceptions Inventory[29] has 16 items that tap three dimensions of pain-related beliefs: future expectancies about pain and its persistence, the nature of pain and its symptomatology, and self-blame surrounding pain. The Pain Catastrophizing Scale[30] is designed to measure individuals' tendencies to focus on pain-related thoughts and exaggerate the significance of painful stimuli. Kinesiophobia is the term for excessive fear of pain and reinjury with physical movement, which can lead to avoidance behaviors and may serve to exacerbate and maintain pain-related disability.[31] The Tampa Scale of Kinesphobia[32] has 17 items and assesses excessive fear of physical activity related to the perceived threat of pain. Similarly, the Fear-Avoidance Beliefs Questionnaire[33] consists of 16 items that measure beliefs concerning the risk of harm from general physical activities and also from work-specific activities.

Locus of control refers to an individual's belief about his or her ability to influence outcomes in life. As applied to chronic pain, locus of control refers to the extent to

which patients believe they can influence or ameliorate the intensity and impact of their pain experience. The Pain Locus of Control scale[34] was adapted from the HealthLocus of Control Scale for this purpose, and may be useful in predicting pain treatment outcomes.[35]

COPING

Coping involves the use of diverse strategies and techniques in an effort to manage a variety of stressors, including pain. Some pain-specific coping strategies are related to poor outcomes among chronic pain patients,[2] and psychological interventions can improve these strategies. Several pain specific coping measures are available. The Coping Strategies Questionnaire[36] is a 50-item measure assessing the extent to which patients engage in a variety of cognitive and behavioral coping strategies when they experience pain, including diverting attention, reinterpreting pain sensations, coping self-statements, ignoring the pain, praying or hoping, increasing activity, and perceiving a measure of control over the pain. The Chronic Pain Coping Inventory[28] is a 65-item scale focused on behavioral strategies of coping that might be encouraged, or discouraged, in a multidisciplinary pain treatment program, including guarding, resting, asking for assistance, relaxation, task persistence, exercise/stretch, seeking social support, coping self-statements, and medication use.

PSYCHOPATHOLOGY

Other instruments are useful when the clinician needs a broader assessment of psychiatric illnesses and personality variables that might impact the functioning of pain patients. The Minnesota Multiphasic Personality Inventory (MMPI), and its successor, the MMPI-2, is the most widely used, and extensively researched, instrument for measuring psychopathology and personality variables.[37] The MMPI-2 is a measure with 567 true/false items, yielding three core validity scales and 10 clinical scales. The validity scales determine the patient's response set and motivation. The 10 clinical scales tap such dimensions such as concern with bodily symptoms, depression, defensive strategies, rebelliousness and antisocial tendencies, suspiciousness, worry and anxiety, and odd thinking. In addition to the primary clinical scales, the MMPI-2 has numerous subscales that measure more specific symptoms, traits, and behaviors, including: anger, family problems, social alienation, addiction potential, and negative treatment indicators. With the development of more narrowly defined pain inventories, the utility of the MMPI-2 for pain assessment has been questioned, due to its length, frequency of items relating to physical symptoms, and lack of predictive validity among populations with chronic pain.[38] Other investigators argue for the ongoing relevance of the MMPI-2 in pain assessment, pointing to abundant research supporting its value in identifying comorbid psychopathology and personality features among pain patients that can complicate the treatment process[38] and a "disability profile" associated with greater physical and emotional disability in response to pain.[39]

Two other instruments are commonly used to assess psycholopathology. The Millon Clinical Multiaxial Inventory–III[40] has 175 true/false items, yielding 14 personality disorder scales (e.g., avoidant, dependent, passive-aggressive, and histrionic) and 10 clinical syndrome scales (e.g., anxiety, somatoform, mood disorders, and substance abuse). While originally developed for psychiatric populations, the scale has been used with pain populations to assess levels of psychopathology[41,42] and predict back surgery outcomes.[43] The Symptom Checklist-90-Revised (SCL-90-R),[44] is a shorter instrument that has been used for assessing psychopathology among chronic pain patients. With 90 items, the SCL-90-R assesses nine different types of psychological disturbance and yields three global measures of distress. Although often favored for its briefer length and reduced likelihood of patient resistance due to focus on symptoms, it has not demonstrated predictive validity with regard to treatment outcome.

SUBSTANCE USE

The prevalence of alcohol abuse and dependence in persons with chronic pain is significant.[45] Comprehensive medical and psychological evaluations should include screening for substance use and abuse. Two widely used measures are the CAGE[46] and AUDIT.[47] The most widely used, the CAGE, is typically administered verbally and is comprised of four screening questions: (1) Have you ever tried to Cut down on your alcohol or drug use? (2) Do you get Annoyed when people comment on your drinking or drug use? (3) Do you feel Guilty about things you have done while drinking or using drugs? (4) Do you need an Eye opener to get started in the morning? A positive response to two or more of these questions is indicative of substance abuse.

MULTIDIMENSIONAL INSTRUMENTS

When clinicians do not have the need, or opportunity, to administer a battery of assessment instruments, multidimensional measures might be used in the evaluation of pain and its emotional and behavioral correlates. One of the most widely used and studied of these instruments is the Multidimensional Pain Inventory (MPI).[48] This 56-item measure assesses psychosocial, cognitive, and behavioral aspects of pain, including pain severity and interference; activity levels, including household chores and work; family relationships and social activities; pain-specific support from spouse or partner; perceived life control; and negative affect. This measure is valuable in its ability to assess multiple dimensions of pain, its relative brevity, and its demonstrated sensitivity to treatment effects. In addition, the MPI provides overall classification of people's coping styles as being "dysfunctional," "interpersonally distressed," or "adaptive coper." However, research on the validity, utility, and distinctiveness of these coping classifications has yielded mixed results.[49,50]

Another multidimensional instrument widely used among pain patients, and other medical populations, is the Millon Behavioral Health Inventory (MBHI),[51] and its successor, the Millon Behavioral Medicine Diagnostic (MBMD).[51] With 150 items, the MBHI assesses multiple relevant domains, including coping styles (e.g., introversive, inhibited, confident, cooperative) and psychogenic attitudes (e.g., recent stress, premorbid pessimism, somatic anxiety). Some

studies, but not all,[52] have found specific subscales to be effective in predicting treatment outcomes.[43,53,54] Slightly longer than its predecessor, with 165 true/false items, the MBMD assesses a wide range of domains, including: negative health habits (e.g., smoking, inactivity, alcohol, and drug use), psychiatric indications (e.g., anxiety, depression), coping styles, stress moderators (e.g., future pessimism, social isolation, and pain sensitivity), and treatment prognostics (e.g., problematic compliance, utilization excess, and medication abuse). While the validation of this instrument is still early and ongoing, some studies have supported the utility of the instrument in predicting treatment response in pain patients.[55]

The Battery for Health Improvement–II[56] is designed to assess the biopsychosocial variables relevant for pain patients. Normed on patients in physical rehabilitation and chronic pain treatment settings, the BHI-II has 217 items and offers information about several domains of functioning, including physical symptoms (e.g., somatic, pain, and functional complaints); affective functioning (e.g., depression, anxiety, and hostility); personality and behavior problems (e.g., substance abuse and chronic maladjustment); and psychosocial issues (e.g., family dysfunction, violence history, and doctor dissatisfaction). A shorter version the Brief Battery for Health Improvement–2 (BHI-II),[56] has 63 items and focuses on the physical and affective symptoms related to pain, and provides information on functioning relative to both medical and community populations.

SPECIAL TOPICS

PREINTERVENTIONAL PAIN PROCEDURE EVALUATIONS

There has been an increase in the use of interventional pain procedures including surgically implanted spinal cord stimulators (SCS) for treating chronic or intractable pain. Pain intervention specialists have found, however, that despite meeting appropriate medical criteria for this class of interventions, a significant number of patients fail to find benefit from these therapies, leading to the consideration of how psychosocial factors may impact outcomes.[57]

The European Federation of IASP Chapters presented a consensus document on neuromodulation treatment of pain that established psychosocial exclusion criteria for SCS implantation: (1) major psychiatric disorders (active psychosis, severe depression or hypochondriasis, and somatization disorder); (2) poor compliance and/or insufficient understanding of the therapy; (3) lack of appropriate social support; (4) drug and alcohol abuse; and (5) drug-seeking behavior. Additional risk factors to assess include unrealistic expectations for pain treatments, cognitive deficits that impair ability to understand, or manage, an implantable device, presence of active suicidal or homicidal intentions, severe sleep disturbance, the presence of personality disorders, and pain-related litigation.[58] While none of the above criteria necessarily serves as permanent exclusion from SCS surgery, these guidelines suggest areas that require additional evaluation and intervention to minimize the risk for complications and maximize likelihood of good outcomes. Thus, increasingly, preinterventional psychological assessment is being included as part of the treatment planning for SCS and related procedures. Indeed, many third party payers are requiring psychological evaluation prior to SCS. These evaluations have several goals, including (1) screening for major psychopathology and cognitive impairments, (2) assessing treatment expectations and ability to follow through on postintervention care and rehabilitation, (3) recommending interventions to address psychosocial factors that may impede optimal outcome, (4) educating the patient as to the procedure and their role in maximizing treatment outcome, and (5) identifying the individual's psychosocial strengths that aid in recovery. It is important to note that both physical and psychological criteria for patient selection for surgery are somewhat imprecise and the predictive ability of psychological measures is relatively mixed. Excellent detailed discussions of these procedures are available elsewhere.[59–61]

OPIOID MEDICATION MISUSE

Opioid medications are a vital tool in the management of severe pain; however, the use of these drugs may give rise to concerns, in both patients and providers, regarding the potential of misuse. Precise rates of opioid medication misuse have been difficult to establish, but some estimates of prescription drug abuse have ranged from 3.2% to 18.9%,[62] which corresponds with estimates of drug addiction rates in the general population. When physicians become reluctant to prescribe opiate pain medication out of fear of fostering addiction, this can result in the undertreatment of pain.[63] Poorly controlled pain, in turn, might prompt drug-seeking behavior by patients. Such behavior has been termed pseudoaddiction, because it is not a true signal of opiate misuse, as much as it reflects inadequate pain relief. Nevertheless, the risk for addiction exists with opiate pain medications, and physicians are challenged to minimize this risk while finding the optimum dosing for adequate pain control. If questionable behaviors arise, such as overusing pain medications or requesting early refills, the physician must assess if these behaviors stem from the under-treatment of pain or from misuse, a distinction that is not often straightforward.[64]

Some tools available to assess for the presence of addiction include patient interviews, questionnaires, and lab tests; however, the assessment process is not precise, and clinical judgment is required. Self-report measures to assist in this assessment are in the early stages of development. These include the Pain Medication Questionnaire[65] and the Screener and Opiate Assessment of Patients with Pain–Revised.[66] While validations studies have demonstrated some promise for these instruments in identifying problematic usage of opioid medications,[67,68] they have not yet progressed in their development to stand as reliable predictors of opiate misuse.[69]

SYMPTOM EXAGGERATION AND MALINGERING

It is not unusual for clinicians to suspect that some pain complaints and behaviors exceed what might reasonably be expected for the person's medical status. When symptom exaggeration is suspected, it is important to consider that this might occur for a range of reasons

related to internal psychological processes or environmental contingencies. While there is no one assessment tool that can definitely establish symptom exaggeration or malingering, multiple strategies, including both behavioral observations and standardized testing can be utilized. These include (1) inconsistencies between physical findings and the patient's self-presentation, (2) overly impaired performance, (3) lack of specific diagnostic signs of impairment, (4) nonorganic physical findings, and (5) evidence derived from psychological testing. Some investigators have cautioned that behavioral inconsistencies can be a misleading indicator of symptom exaggeration, as individuals in pain can normally present with some behavioral inconsistencies.[70]

Psychological test data including the validity and clinical scales on the MMPI-2[71] and patterns of responding to cognitive testing[72–74] can be useful in identifying patients who are engaged in symptom exaggeration or malingering.

CONCLUSION

A comprehensive, multidisciplinary assessment is needed to develop a helpful treatment plan for persons with chronic pain. Psychological evaluation is necessary to assess the psychological, behavioral, and social factors that should be considered in treatment planning. This assessment includes both the clinical interview and the use of instruments that are reliable and valid. Effective psychological evaluation should provide a case formulation and specific recommendations that are useful to both the patient and other health-care providers.

KEY POINTS

- Psychological evaluations for pain and disability typically include psychological testing and an interview.
- Key domains for assessment include pain-related disability, negative affect, pain-related cognitions, coping strategies, psychopathology, and substance use. Multidimensional instruments offer the potential of assessing selected key domains as well as social factors.
- When interventional pain therapy is being considered, it is advisable to obtain a specialized psychological consultation that includes evaluation, education, and if necessary, intervention.
- Psychological evaluation as part of chronic opioid therapy can provide valuable information to both the patient and provider regarding addiction concerns.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 7

Diagnostic and Statistical Manual of Mental Disorders and Pain Management

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INTRODUCTION

Somatoform disorders are grouped together by the presence of physical symptoms suggesting a general medical condition. These symptoms are not explained fully by a general medical condition, or by the effects of substances or other mental disorders. There is no diagnosable medical condition to fully account for the physical symptoms, and there must be a significant functional impairment. In contrast to factitious disorders and malingering, the symptoms in somatoform disorders are involuntary. In this chapter we will cover somatization disorder, undifferentiated somatoform disorder, conversion disorder, pain disorder, factitious disorder, malingering, and hypochondriasis. For completeness, we will also mention dyspareunia and vaginismus. Although these are not somatoform disorders, they are *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* conditions that may manifest with a pain component.

SOMATIZATION DISORDER

Undesired and unpleasant bodily experiences can unfortunately be common features of everyday life. Typically these include pain, fatigue, nausea, imbalance, dystonia, dyspnea, and paresthesias. For the vast majority of people, these episodes are transient. A minority of individuals decide to seek medical help, typically when the experience persists, becomes severe or disabling, or is accompanied by the fearful belief that the sensation is a symptom of bodily disease. Somatization has been described as a tendency to experience and communicate somatic distress and symptoms unaccounted by pathologic findings, to attribute them to physical illness, and to seek medical help for them.[1] Kellner noted that 60% to 80% of the general population experiences one or more somatic symptoms in any given week.[2] When somatic symptoms seem out of proportion to objective findings, physicians should consider major depressive disorder (common things being common) before entertaining a diagnosis of somatoform disorder. The differential diagnosis should also include unrecognized organic disease, anxiety, substance abuse, cognitive dysfunction, and psychosis. Patients who persist in searching for a medical cause for their functional symptoms risk invasive diagnostic procedures and unnecessary surgery, and the unwarranted costs of these examinations further strain limited medical resources.

The essential feature of somatization disorder (historically referred to as hysteria or Briquet's syndrome) is a pattern of recurring, multiple, clinically significant somatic complaints that may result in medical treatment or functional impairments (Table 7-1).[3] The somatic complaints begin before age 30 and occur over a period of many years (Criterion A).[3] There must be a history of pain related to at least four different anatomic sites or functions, at least two gastrointestinal symptoms, and one sexual symptom other than pain, as well as one symptom suggesting presence of a neurologic condition (Criterion B).[3] The symptoms cannot be fully explained by a general medical condition or effects of a substance, and the complaints themselves or associated functional impairments are in excess of what would be expected based on objective findings (Criterion C).[3] It must also be clarified that symptoms in this disorder may not be intentionally feigned or produced as in factitious disorder or malingering (Criterion D).[3] The approach to patients with many unexplained symptoms must include a thorough history and examination, consisting at a minimum of medical history, individual and family psychiatric history, social history, current medications, and laboratory or diagnostic imaging results. The somatic symptoms can be numerous and overwhelming for the time-constrained clinician. For this reason, Othmer and DeSouza have developed an abbreviated list of seven symptoms that can be employed to screen for the disorder (Table 7-2).[4] If two or more symptoms are present, there is a high likelihood of somatization disorder. The presence of three symptoms accurately identified 91% of patients with somatization disorder with a sensitivity of 87% and a specificity of 95%. Objective physical examination findings are often lacking and laboratory results are typically unrevealing. Three features that suggest somatization as opposed to a general medical condition are multiple organ system involvement, early onset, and chronic course without objective signs, and absence of laboratory abnormalities. Nonetheless, it remains imperative to rule out general medical conditions that may manifest with vague somatic symptoms.

In terms of associated features, individuals with somatization disorder usually describe complaints in exaggerated terms or grandiose fashion, often lacking specific facts. They are often inconsistent historians and may seek evaluation by many physicians concurrently. These patients may also display evidence of mood disturbance such as depression or prominent anxiety symptoms, antisocial behavior, suicidal ideation, and interpersonal problems.

Somatization disorder is far more common in women than men, with lifetime prevalence rates of 0.2% to 2% among women and less than 0.2% in men.[3] This disorder is observed in 10% to 20% of female first-degree biological relatives of women with the disorder, whereas male relatives show an increased incidence of alcoholism and sociopathy.[5] The tendency to somatization has been linked to childhood trauma via insecure attachment and maladaptive patterns of interpersonal communication in seeking care.[6,7] In addition, women with somatization disorder have a 75% chance of carrying another psychiatric diagnosis (most commonly an affective or anxiety disorder, or alcohol

TABLE 7–1 Diagnostic Criteria for Somatization Disorder[3]

Criterion A	A history of many physical complaints beginning before age 30 that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.
Criterion B	Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance:
	1. Four pain symptoms: a history of pain related to at least four different sites or functions (e.g., head, abdomen, back, joints, extremities, chest, rectum, during menstruation, during sexual intercourse, or during urination).
	2. Two gastrointestinal symptoms: a history of at least two gastrointestinal symptoms other than pain (e.g., nausea, bloating, vomiting other than during pregnancy, diarrhea, or intolerance of several different foods).
	3. One sexual symptom: a history of at least one sexual or reproductive symptom other than pain (e.g., sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy).
	4. One pseudoneurologic symptom: a history of at least one symptom or deficit suggesting a neurologic condition not limited to pain (conversion symptoms such as impaired coordination or balance, paralysis, or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures; dissociative symptoms such as amnesia; or loss of consciousness other than fainting).
Criterion C	Either (1) or (2):
	1. After appropriate investigation, each of the symptoms in Criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g., a drug of abuse or medication).
	2. When there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings.
Criterion D	The symptoms are not intentionally produced or feigned (as in factitious disorder or malingering).

TABLE 7–2 Screening Test for Somatization Disorder[4]

Mnemonic	Symptom	System
Somatization	Shortness of breath	Respiratory
Disorder	Dysmenorrhea	Female reproductive
Besets	Burning in sex organ	Psychosexual
Ladies	Lump in throat (difficulty swallowing)	Pseudoneurologic
And	Amnesia	Pseudoneurologic
Vexes	Vomiting	Gastrointestinal
Physicians	Painful extremities	Skeletal muscle

or substance use).[8] Unfortunately, the course of somatization disorder is chronic and fluctuating, and rarely remits completely.

UNDIFFERENTIATED SOMATOFORM DISORDER

This is a residual category for persistent somatoform presentations that do not meet full criteria for one of the specific somatoform disorders. The essential feature of this disorder is one or more physical complaints persisting for at least 6 mo. Frequent complaints include chronic fatigue, loss of appetite, and gastrointestinal or genitourinary symptoms that cannot be explained by a general medical condition or a substance, and are often excessive in nature (Table 7-3).[3] Again the symptoms must not be intentionally produced or feigned as in factitious disorder (with motivation to assume the sick role) or malingering (where more external incentives are present such as financial reward or relief of work duties). The highest frequency of unexplained physical complaints occurs in young women of low socioeconomic status. If the physical complaints have persisted for less than 6 mo, a diagnosis of somatoform disorder not otherwise specified should be made.

CONVERSION DISORDER

The essential feature of this disorder is the presence of symptoms or deficits affecting voluntary motor or sensory function that suggest a neurologic or other general medical condition (Criterion A, see Table 7-4).[3] Motor symptoms or deficits include impaired coordination or balance, paralysis, aphonia, dysphagia, and urinary retention. Sensory symptoms include loss of touch or pain sensation, diplopia, blindness, deafness, and hallucinations. Symptoms may also include seizures or convulsions. The primary evidence for the psychological cause consists of a temporal relationship between symptom onset and psychologically meaningful environmental precipitants or stressors (Criterion B).[3] Presenting symptoms may seem implausible and may strongly depend on the patient's level of education. Conversion symptoms typically do not conform to anatomic pathways and physiologic mechanisms but instead follow the individual's conceptualization of a condition. For example, "paralysis" may involve an inability to perform a specific movement or move an entire body part rather than a deficit corresponding to patterns of motor innervation. There may be unacknowledged strength in antagonistic muscles, normal muscle tone, and intact reflexes. Electromyograms (EMGs), evoked responses of vision and hearing, fundoscopic examinations, pulmonary function tests, and barium swallows are examples of tests that should be normal. A diagnosis of

TABLE 7–3 Diagnostic Criteria for Undifferentiated Somatoform Disorder[3]

Criterion A	One or more physical complaints (e.g., fatigue, loss of appetite, gastrointestinal or urinary complaints).
Criterion B	Either (1) or (2): 1. After appropriate investigation, the symptoms cannot be fully explained by known general medical condition or direct effects of a substance (e.g., a drug of abuse or medication). 2. When there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings.
Criterion C	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Criterion D	The duration of the disturbance is at least 6 mo.
Criterion E	The disturbance is not better accounted for by another mental disorder (e.g., another somatoform disorder, sexual dysfunction, mood disorder, anxiety disorder, sleep disorder, or psychotic disorder).
Criterion F	The symptoms are not intentionally produced or feigned (as in factitious disorder or malingering).

TABLE 7–4 Diagnostic Criteria for Conversion Disorder[3]

Criterion A	One or more symptoms or deficits affecting voluntary motor or sensory function that suggest a neurologic or other general medical condition.
Criterion B	Psychological factors are judged to be associated with symptom or deficit because the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors.
Criterion C	The symptom or deficit is not intentionally produced or feigned (as in factitious disorder or malingering).
Criterion D	The symptom or deficit cannot, after appropriate investigation, be fully explained by a general medical condition, or by the direct effects of a substance, or as a culturally sanctioned behavior or experience.
Criterion E	The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.
Criterion F	The symptom or deficit is not limited to pain or sexual dysfunction, does not occur exclusively during the course of somatization disorder, and is not better accounted for by another mental disorder.

conversion disorder should only be made after a thorough medical investigation has been performed to rule out an etiologic, neurologic, or general medical condition. Because a general medical etiology for an apparent diagnosis of conversion disorder may take years to manifest, it is important to re-evaluate this diagnosis periodically. The presence of a neurologic condition does not preclude a diagnosis of conversion disorder, and as many as one-third of individuals with conversion symptoms have a current or prior neurologic condition. Conversion disorder may be diagnosed in the presence of a neurologic disorder if the symptoms are not fully explained given the severity of the organic diagnosis. Again the symptoms must not be intentionally feigned or produced (Criterion C).[3] Conversion disorder may not be diagnosed if symptoms can be completely explained by a general medical or neurologic condition, the effects of a substance, or the result of a culturally sanctioned behavior (Criterion D), or if symptoms are limited to pain or sexual dysfunction, occur only during the course of somatization disorder, or are better explained by another psychiatric diagnosis (Criterion F).[3] The symptoms must be significant enough to cause emotional distress, marked impairments in social or occupational functioning, or the seeking of medical attention for the complaints (Criterion E).[3]

The onset of conversion disorder is typically between the ages of 10 and 35. Prevalence data exhibit wide ranges, with numbers ranging from 11/100,000 to 500/100,000 in general population samples.[3] In children with conversion symptoms, the gender ratio is equal; in adults, conversion is two to five times more common in women than men. Symptoms tend to be of acute onset and short duration, with recurrence common. Especially in women, symptoms are much more common on the left side of the body than the right. Women presenting with conversion symptoms may eventually progress to meeting criteria for somatization disorder. There is an association between conversion disorder and antisocial personality disorder in males. Conversion disorder has been reported to be more common in rural populations, individuals of lower socioeconomic status, and individuals less knowledgeable about medical and psychological concepts. Factors associated with a good prognosis include acute onset, presence of stress at time of onset, a short interval between onset and treatment, and higher intelligence level. Symptoms of paralysis, aphonia, and blindness portend a good prognosis, whereas tremor and seizures do not.

PAIN DISORDER

The diagnosis of pain disorder is new to the *DSM-IV* and is not found in earlier editions of the manual. Prior editions contained diagnoses such as "psychogenic pain

TABLE 7–5 Diagnostic Criteria for Pain Disorder[3]

Criterion A	The pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Criterion B	Psychological factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of the pain.
Criterion C	The symptom or deficit is not intentionally produced or feigned.
Criterion D	The pain is not better accounted for by a mood, anxiety, or psychotic disorder and does not meet criteria for dyspareunia.

disorder" and "somatoform pain disorder." The essential feature of pain disorder is pain that is the predominant focus of the clinical presentation and is of sufficient severity to warrant clinical attention.[3] The diagnostic criteria for pain disorder are listed in Table 7-5. The criteria state that psychological factors should be involved, to some degree, in the onset or maintenance of the pain. Making this assessment is the diagnostic challenge. ICD-9 codes for two separate subtypes exist, depending on whether the pain is associated with psychological factors alone (307.80) or with a medical condition along with psychological factors (307.89). Of note, the verbiage "associated with" is used since it is often difficult to determine the chronological order of the pain, psychological factor(s), and medical condition.[9] A third subtype of pain disorder that is not considered a mental disorder is included in order to facilitate a differential diagnosis and address the myth that when psychological factors play a role in one's pain the pain is somehow not as "real" as when psychological factors are not an issue.[9] This subtype, "pain disorder associated with a general medical condition," is listed on Axis III and is coded based on the associated medical condition or the location of the pain.

Given the range of subtypes, it is clear that a significant number of patients encountered in the practice of pain management will meet the criteria for pain disorder. Patients with this diagnosis may be dealing with inability to meet work, school, and family demands; substance dependence and/or abuse; sleep disorder; depression; anxiety; social isolation; and possibly even suicidal ideation. Of note, the *DSM-IV* states that psychological problems such as depression and anxiety can coexist with, or result from, pain disorder.

FACTITIOUS DISORDER

Common to both factitious disorder and malingering is the intentional production of physical and/or psychological symptoms (Criterion A).[3] In factitious disorder, the motivation is the psychological need to assume the sick role (Criterion B); external incentives for the patient's behavior (e.g., financial gain, avoiding work duties, obtaining opioid medications) should be absent (Criterion C).[3] Patients may complain about nonexistent symptoms, create objective signs (e.g., warming skin to create erythema, using psychoactive drugs to suggest a mental disorder), or exaggerate symptoms of a previous diagnosis. Components of the history suggesting this diagnosis include the following: multiple hospital admissions or office visits, knowledge of medical terminology, vague and unverifiable history, chronic illness at a young age, difficulty with interpersonal relationships and few visitors in the inpatient setting, comorbid personality disorders, or substance abuse disorder. Unfortunately, psychiatric treatment has not been shown to be effective, and this disorder is usually just "managed" rather than cured. It is best to avoid confrontation with these patients, as they will not likely admit to their actions. If possible, it is best to offer them therapies with minimal consequences and "allow them to save face."[10]

MALINGERING

In malingering, the intentional falsification of physical and/or psychological symptoms is motivated by external factors (e.g., economic gain, avoiding legal responsibility, avoiding military service, or avoiding domestic duties). Clues that suggest a diagnosis of malingering include the following: medico-legal context of the presentation, marked discrepancy between claimed stress or disability and objective findings, lack of cooperation during the diagnostic evaluation, and the presence of antisocial personality disorder. The prevalence of malingering in the population of chronic pain patients who are seeking compensation has been estimated to be 25% to 50%.[11] Malingering can be extremely difficult to diagnose and, according to one estimate, adds up to $150 billion in costs to the health insurance industry.[12] Three types of malingering have been described.[13] In pure malingering, patients fabricate symptoms that do not exist at all. In partial malingering, symptoms that do exist are exaggerated. Lastly, in false imputation, patients attempt to blame real symptoms on an unrelated event. For example, a patient may injure his hand during a home repair project but attempts to blame the injury on a motor vehicle accident that he is involved in a week later. In addition, some cases of malingering may involve a parent fabricating an illness in his or her child, again for the purpose of external gain (such as social benefits). The phrase "malingering by proxy" has been suggested to describe this scenario.[13]

Successful identification of the malingering patient remains difficult. Some advocate looking for inconsistencies in the physical exam and making use of Waddell's signs (Table 7-6). While Waddell's signs may be predictors of poor response to medical interventions, they are not thought to be able to discriminate between organic and nonorganic pain.[14,15] Other suggestions for detecting malingering include checking shoes for uneven wear in patients with a limp, examining hands for calluses or cuts in patients claiming an inability to work, or observing an absence of associated injury in patients claiming to have fainted or fallen.[16] In the absence of objective evidence of malingering, psychological testing such as the Minnesota Multiphasic Personality Disorder, ed 2 or the Symptom Checklist-90-Revision can be helpful in detecting exaggerations and inconsistencies in a history.[17]

TABLE 7–6 Waddell's Signs

Category	Signs
Tenderness	Superficial: light pinching causing pain = positive Nonanatomic: deep tenderness over a wide area = positive
Simulation	Axial loading: downward pressure on the head causing low back pain = positive Rotation: examiner holds shoulders and hips in the same plane and rotates patient; pain = positive
Distraction	Straight leg raise causes pain when formally tested, but straightening the leg with hip flexed 90° to check Babinski does not
Regional	Weakness: multiple muscles not enervated by the same root Sensation: glove and stocking loss of sensation
Overreaction	Excessive show of emotion

HYPOCHONDRIASIS

Central to the diagnosis of hypochondriasis is the preoccupation with fears of having, or the idea that one has, a serious disease based on a misinterpretation of one or more bodily signs or symptoms (Criterion A).[3] The remaining criteria (Table 7-7) state that the preoccupation must have a duration of longer than 6 mo and may not be better accounted for by another mental disorder. Normal sensations of joint movement, muscle tension, and bowel activity may be misinterpreted as pathologic conditions, and depending on the location and nature of the complaint, patients may be referred to a pain specialist for help in diagnosing their "significant" pain. Escobar et al. estimate the prevalence of hypochondriasis in the primary care setting to be around 3%, and so one can assume the incidence in the pain population is at least that, if not higher.[18] Despite an extensive negative workup, the patient's fears persist. Some have insight into the fact that levels of concern are excessive, while others lack this awareness. This subset can be coded with the specifier "with poor insight."

Young adulthood is the most common age of onset of hypochondriasis, although this can vary. Some patients have a history of serious illness as a child, while others have experienced a family member who suffered from significant health problems. Over time, patients develop a history of doctor shopping, and they may also undergo numerous invasive procedures. Work, family life, and social life can all become strained. As with all the somatoform disorders, a general medical condition needs to be ruled out. In addition, other disorders that could account for the symptoms (generalized anxiety disorder, major depressive disorder, obsessive-compulsive disorder) need to be screened for. Treatment of hypochondriasis is difficult. Education, cognitive therapy, and behavioral therapy offer the best chance of remission. Frequent medical exams and benign therapies (heat, bracing, etc.) can be helpful. There may also be a role for selective serotonin reuptake inhibitors (SSRIs) in some patients.[10]

TABLE 7–7 Diagnostic Criteria for Hypochondriasis[3]

Criterion A	Preoccupation with fears of having, or the idea that one has, a serious disease based on the person's misinterpretation of bodily symptoms.
Criterion B	The preoccupation persists despite appropriate medical evaluation and reassurance.
Criterion C	The belief in Criterion A is not of delusional intensity (as in delusional disorder, somatic type) and is not restricted to a circumscribed concern about appearance (as in body dysmorphic disorder).
Criterion D	The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Criterion E	The duration of the disturbance is at least 6 mo.
Criterion F	The preoccupation is not better accounted for by generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, a major depressive episode, separation anxiety, or another somatoform disorder.

DYSPAREUNIA (NOT DUE TO A GENERAL MEDICAL CONDITION)

While dyspareunia is a diagnosis rarely encountered by the pain physician, it is included here for completeness. The criteria for its diagnosis may be found in Table 7-8. Of note, pain with intercourse, by itself, is not sufficient to make the diagnosis. It must be accompanied by marked distress or interpersonal difficulty. Up to 15% of females and 5% of males are estimated to suffer from dyspareunia.[10] Younger females and those with a negative attitude toward sex or a history of sexual abuse are more likely to have this diagnosis. The condition limits one's ability to develop meaningful sexual relationships and disrupts existing ones. The course of illness is often chronic, and treatment centers on psychological counseling.[3]

VAGINISMUS (NOT DUE TO A GENERAL MEDICAL CONDITION)

With similar criteria as dyspareunia, vaginismus is recurrent or persistent involuntary contraction of the perineal muscles surrounding the outer third of the vagina when penetration is attempted (Table 7-9). Contractions may be mild, causing some tightness and discomfort, or severe enough to prevent penetration. The condition may be lifelong or acquired after a sexual trauma or general medical condition. Treatments can include pelvic floor control exercises, insertion or dilation training, and addressing the emotional component of the disorder.[10]

TABLE 7–8 Diagnostic Criteria for Dyspareunia[3]

Criterion A	Recurrent or persistent genital pain associated with sexual intercourse in either man or woman.
Criterion B	The disturbance causes marked distress or interpersonal difficulty.
Criterion C	The disturbance is not caused exclusively by vaginismus of lack of lubrication, is not better accounted for by another Axis I disorder (except another sexual dysfunction), and is not due exclusively to the direct physiologic effects of a substance (e.g., a drug of abuse or medication) or a general medical condition.

TABLE 7–9 Diagnostic Criteria for Vaginismus[3]

Criterion A	Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse.
Criterion B	The disturbance causes marked distress or interpersonal difficulty.
Criterion C	The disturbance is not better accounted for by another Axis I disorder (e.g., somatization disorder) and is not due exclusively to the direct physiologic effects of a general medical condition.

KEY POINTS

- Somatoform disorders involve somatic complaints that cannot be explained by any general medical or neurologic condition, the effects of a substance, or a culturally sanctioned behavior.
- Somatization disorder is a polysymptomatic entity beginning before 30 years of age, extending over a period of years, and is characterized by a constellation of pain, gastrointestinal, sexual, and pseudoneurologic symptoms.
- Undifferentiated somatoform disorder involves one or more physical complaints of at least 6 mo duration, but does not meet criteria for somatization disorder.
- Conversion disorder is hallmarked by presence of symptoms or deficits involving voluntary motor or sensory function, often temporally related to psychological stressors.
- A significant number of patients in the chronic pain setting are likely to meet criteria for a diagnosis of pain disorder.
- Physical and psychological symptoms in somatoform disorders are not intentionally feigned or produced as in factitious disorder (patient is motivated to assume a sick role) or malingering (motivation is toward external gain).
- Curative treatment in factitious disorder is unlikely and management is typically the best option.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 8

Neurophysiologic Testing for Pain

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Electrophysiologic testing when properly applied is a useful tool for the evaluation of patients with pain. Understanding the indications and limitations of each test is absolutely essential for appropriate diagnosis and subsequent treatment.

Electrophysiologic studies are a very sensitive indicator of central and peripheral nervous system involvement but do not indicate underlying disease. For example, testing can diagnose radiculopathy but cannot determine if it is caused by osteophytes, a herniated disc, or diabetes. This chapter describes conventional electrophysiologic tests such as electromyography (EMG), and short-latency somatosensory-evoked potentials (SSEPs), as well as newer techniques, including quantitative sensory testing (QST), laser-evoked potentials (LEPs), and contact heat–evoked potentials (CHEPs). Invasive testing such as microneurography will not be discussed here.

The role of the sympathetic nervous system in the production of pain is complex and controversial; nonetheless, testing of the autonomic function is also important for the evaluation of pain complaints because it gives an objective measure of small nerve fiber involvement as well as evidence of therapeutic interventions such as sympathetic nerve blocks. The most frequent referrals to the autonomic laboratory are patients with painful peripheral neuropathy, such as diabetic polyneuropathy, and so-called complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD). Based on accuracy, reproducibility, and easiness to perform, sudomotor function tests such as the sympathetic skin response (SSR) and quantitative sudomotor axon reflex test (QSART), are discussed here. Other quantitative autonomic measures for adrenergic function (Valsalva maneuver, head-up tilt) and for cardiovagal function (heart rate variability to deep breathing) are beyond the scope of this discussion. Finally, although controversial, the value of nociceptive reflexes, such as the blink reflex, masseter inhibitory reflex (MIR), and flexor reflex for the evaluation of neuropathic pain will be discussed briefly.

ELECTROMYOGRAPHY (EMG)

When strictly defined, EMG indicates only a needle examination of muscles. However, EMG is often used to include both needle studies and nerve conduction studies. Nerve conduction studies are often referred to by the letters NCV, with "V" standing for velocity, although nerve conduction studies measure more than velocity. For clarity, we use EMG/NCV to indicate the combination of needle electromyography and nerve conduction studies.[1,2]

EMG/NCV is extremely useful in the evaluation of the peripheral nervous system. Indeed, the three most common diagnoses in EMG laboratories—peripheral neuropathy, carpal tunnel syndrome, and lumbosacral radiculopathy—all cause pain. EMG/NCV can identify the anatomic site of injury (anterior horn cell, spinal root, plexus, nerve, neuromuscular junction, or muscle), the type of neurons or fibers involved (motor, sensory, or autonomic), the nature of pathologic alteration (demyelination, or axonal degeneration), time course (acute, subacute, or chronic), and severity of injury.[1,2]

By stimulating a peripheral nerve with supramaximal intensity, compound muscle action potential (CMAP) for motor nerve and sensory nerve action potential (SNAP) for sensory nerve are recorded. The amplitude of action potentials as well as the time from stimulation to response is recorded. Latency is the interval between the onset of a stimulus and the onset of a response, expressed in milliseconds. Conduction velocity is obtained by dividing the distance between two stimulation points (mm) of the same nerve by the difference between proximal and distal latencies (ms). This calculated velocity, expressed in meters per second (m/s) represents the conduction velocity of the fastest nerve fibers between two points of stimulation. It is important to note that studies may be normal if a disorder is limited to small nerve fibers such as Aδ and C-fibers.[1,2]

The amplitude of CMAP is measured from baseline to negative peak in millivolts, and the amplitude of SNAP is measured from the first positive peak to negative peak in microvolts. Most laboratories have their own normal values for major motor and sensory nerves with minor differences occurring among laboratories. A lower temperature will prolong distal latencies, reduce conduction velocities, and increase the amplitude of CMAP and SNAP. Age also affects NCVs. Adult values are not attained until 4 years of age, and they decline after age 60 years at a rate of 1 to 2 m/s per decade. Waveform analysis of CMAP and SNAP help estimate normal versus abnormal nerve function (Fig. 8-1). The amplitude of a response should be similar when the same nerve is stimulated proximally and distally. A 20% to 50% reduction between distal and proximal stimulation of a motor nerve suggests an abnormal block in conduction between two stimulation points. Many laboratories are now computerized and the area under an action potential curve can be calculated. Greater than 20% to 40% reduction in area also suggests conduction block. A significant reduction in amplitude from proximal to distal stimulation sites without a reduction in area under the response curve, and a significant increase in duration (>15%) suggest temporal dispersion resulting from a relative desynchronization of the components of an action potential, which is due to different rates of conduction of each nerve fiber. This also suggests nerve pathology between the proximal and distal stimulation sites.[1,2]

The H-reflex is the electrophysiologic equivalent of a muscle stretch reflex. A sensory nerve is stimulated with submaximal intensity, and a late motor response is recorded owing to reflex activation of motor neurons. In adults, H-reflexes are easily obtained from soleus muscle and less easily from flexor carpi radialis muscle following the stimulation of tibial and median nerves, respectively. The tibial H-reflex is useful in identifying S1 radiculopathy.

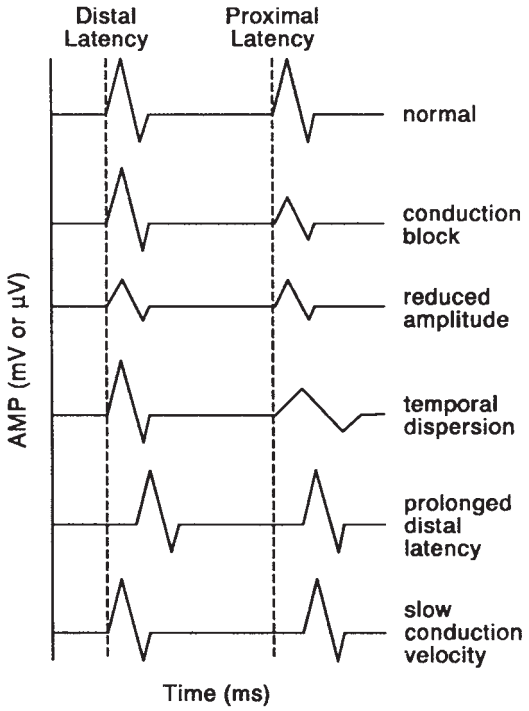

FIGURE 8-1 Schematic representation of normal and pathologic findings obtained from an NCV study.

F-waves are late response recorded from muscle after supramaximal stimulation of a motor nerve. F-waves represent a response to a stimulus that travels first to and then from the cord via motor pathways; thus, F-waves are useful in studying the proximal portion of motor nerves (Fig. 8-2). Unfortunately, there is no consensus as to methodology for obtaining responses, and to the patterns of abnormality to be identified. Repetitive nerve stimulation (RNS) studies are used primarily for evaluation of neuromuscular junction disorders like myasthenia gravis. As such they are not typically useful in the evaluation of pain, and therefore will not be discussed further. The electrical activity in a muscle can be measured using disposable needle electrodes. Needle examination is performed in proper steps. An examiner observes activity on insertion of a needle (insertion activity), activity when the needle is maintained in a relaxed muscle (spontaneous activity), and activity during varying degrees of voluntary muscle contraction. The electrical activity is evaluated by sight and sound, as specific activities have specific wave forms and characteristic sounds. Observations are made by the electromyographer during the study; therefore the results of a needle examination are dependent on the experience of the examiner.[1,2]

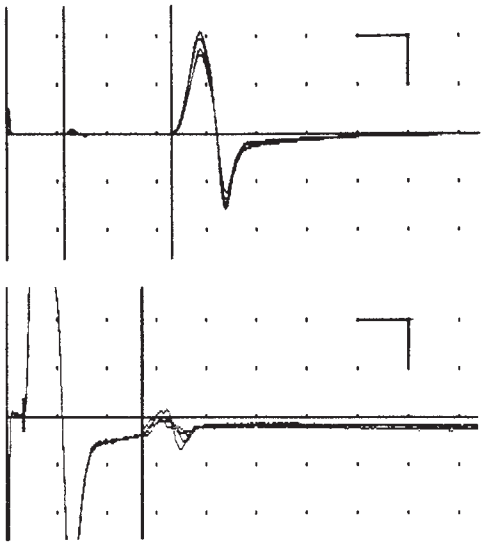

FIGURE 8-2 H-reflex with tibial nerve stimulation (top); time marker 10 ms; amplitude marker 5 mV. F-response with median nerve stimulation (bottom); time marker 10 ms; amplitude marker 1 mV.

Insertion activity, also referred to as injury potential, is caused by movement of the needle electrode, resulting in mechanical damage to the muscle fibers. Increased insertion activity consists of unsustained fibrillation potentials and positive sharp waves. A muscle at rest should be electrically silent. Spontaneous activity in a resting muscle usually suggests a pathologic condition. The type and significance of various spontaneous activities are summarized in Table 8-1, and some examples are shown in Figure 8-3. As a muscle contracts, motor unit action potentials (MUAPs) are observed. MUAP represents the summation of muscle fiber action potentials of a given motor unit. With increasing voluntary muscle contraction, individual motor units fire more frequently, and more motor units are recruited to fire. The term "onset frequency" is used to describe the firing rate of a single MUAP maintained at the lowest voluntary muscle contraction (normally <10 Hz). Recruitment frequency is defined as the frequency of first MUAP when the second MUAP is recruited (normally <15 Hz). A reduced number of MUAPs (high recruitment frequency) can be seen in neuropathic processes. An increased number of MUAPs (low recruitment frequency), however, can be seen in myopathic disorders or defects of the neuromuscular junction. During maximum contraction, a full interference pattern consisting of overlapping motor units is seen. MUAPs are analyzed in terms of amplitude, duration, number of phases, and stability. The morphology of the MUAPs is affected by the type of needle electrode used, location of the needle within the motor unit territory, age, temperature, and specific muscle being examined. Large, long-duration polyphasic units suggest denervation and reinnervation. Short-duration, small polyphasic units can be seen in myopathic processes. EMG findings in neuropathic and myopathic disorders are summarized in Table 8-2.[1,2]

While performing an EMG/NCV study, several questions must be answered by the examiner.

LOCALIZATION: WHERE IS THE LESION?

EMG/NCV is very useful in localizing the specific anatomic site of a lesion that is causing pain. For example, a complaint of burning feet can be caused by a diffuse peripheral neuropathy (as in diabetes), by a plexus injury after surgery, or by a lumbosacral radiculopathy due to spinal stenosis. Each of these has different findings and can be localized by EMG/NCV. In general, changes in conduction, either a prolonged distal latency or a low velocity, suggest a pathologic lesion between the site of stimulation

TABLE 8–1 Potentials Recorded in Muscle at Rest

Spontaneous Activity	Firing Pattern	Frequency	Waveform	Amplitude	Duration	Significance
Complex repetitive discharge	Regular, abrupt onset and cessation, "motor cycle idling"	5–100 Hz	Polyphasic or serrated, MFAP	100 μV–1 mV		Neurogenic (chronic), myopathic (dystrophy)
Cramp discharge	Increase and subside gradually	(1) <150 Hz (2) 4–15 Hz	MUAP			(1) Ischemic, ↑ Na (2) ↓ Ca, ↓ Mg, ↑ K
End plate noise	Dense and steady, "seashell hissing"	>150 Hz	Monophasic (negative), MEPP	10–20 μV	0.5–1 ms	Normal
End plate spike	Irregular short burst, "sputtering fat in a frying pan"	50–100 Hz	Biphasic (negative–positive) MFAP	100–300 μV	2–4 ms	Decrease in denervated muscle, increase in reinnervated muscle
Fasciculation potential	Spontaneous, sporadic, "typing on cardboard"	0.1–10 Hz	MUAP	>1 mV	>5 ms	Normal, neurogenic (motor neuronopathy), myopathic
Fibrillation potential	Regular, "rain on tin roof," "ticking of clock"	1–50 Hz	Biphasic (positive–negative) MFAP	<1 mV	<5 ms	Neurogenic, NMJ defect, myopathic
Myokymic discharge	Semiregular, "marching soldiers"	(1) 2–60 Hz brief (2) 1–5 Hz continuous	MUAP			Limb (entrapment, radiation), face (MS, brainstem tumor, Bell's palsy)
Myotonic discharge	Wax and wane, "dive bomber"	20–80 Hz	(1) Biphasic (positive–negative) (2) positive MFAP	<1 mV <1 mV	(1) <5 ms (2) 5–20 ms	Myopathic (myotonic syndromes), ↑ K, Schwartz-Jampel
Neuromyotonic discharge	Start and stop abruptly, wane, "pinging"	150–300 Hz	MUAP			Isaac's syndrome, stiff-man syndrome, tetany
Positive sharp wave	Regular	1–50 Hz	Biphasic (positive–negative) MFAP	<1 mV	10–100 ms	Same as fibrillation
Neurotonic discharge	Irregular	30–100 Hz	MUAP		<200 ms	

MFAP, muscle fiber action potential; MUAP, motor unit action potential; MEPP, miniature end plate potential; NMJ, neuromuscular junction.

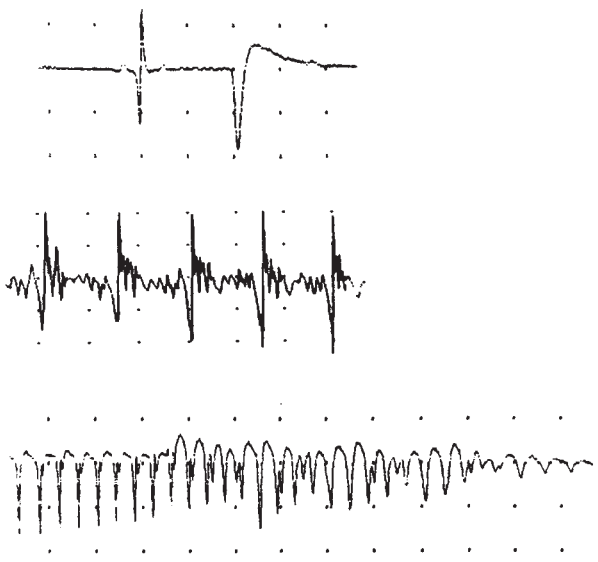

FIGURE 8-3 Spontaneous activities. Fibrillation potential and positive wave (top panel), and complex repetitive discharges (middle panel); time marker 10 ms, amplitude marker 100 μV. Myotonic discharges (bottom panel); time marker 20 ms, amplitude marker 200 μV.

and the recording site. An abnormally small amplitude, however, can occur from an injury anywhere distal to the motor or sensory neuron. A sampling on needle examination of muscles representing different nerves and roots can further localize the site of injury.

Using the example of burning feet, let us examine the differential diagnosis and its EMG/NCV findings. In radiculopathy, motor conduction velocity would be normal, and CMAP amplitude would be reduced if there were axonal degeneration from nerve root compromise. SNAP would be normal because the lesion is proximal to the dorsal root ganglion. (Note that most radiculopathies occur within the spinal canal. The dorsal root ganglion, which is located in the neuroforamina, is distal to most radicular pathologic lesions. The dorsal root ganglion is a bipolar neuron with one axon extending distally to the limb and one extending proximally to the spinal cord.) EMG abnormalities first appear in appropriate paraspinal muscles because of their proximity to the injury site. Abnormalities are next seen in the proximal and then distal muscles within the specific myotomal distribution of the injured nerve root. In a plexus injury, both CMAP and SNAP amplitudes would be decreased if axons were injured. The NCV is usually normal

TABLE 8–2 EMG Findings in Neurogenic and Myopathic Disorders

EMG	Normal	Neurogenic (Axonal)	NMJ Defect	Myopathic
Insertional activity	N	↑	↑	↑
Spontaneous activity	−	+	+	+
MUAP amplitude	0.1–5 mV	↑	↓	↓
Duration	3–15 ms	↑	↓	↓
Phase	<5	↑	↑	↑
Stability	N	N	Variable	N
Recruitment	N	↑	N	↓

MUAP, motor unit action potential; *NMJ*, neuromuscular junction; *N*, normal.

unless stimulation is applied proximal to the lesion. Paraspinal muscles are spared because posterior rami innervate these muscles while the plexus is in the anterior rami distribution. Combined motor and sensory NCV abnormalities are characteristic of most peripheral neuropathies. Needle findings would depend on the severity of motor nerve involvement, and these are usually normal unless the neuropathy is severe. Anatomic localization based on EMG/NCV is summarized in Table 8-3.

PATHOPHYSIOLOGY: IS THE LESION AXONAL OR DEMYELINATING?

Based on the EMG/NCV findings, this distinction can be made with relative ease. If an injury occurs at the cell body or axon, axonal degeneration results. If an injury is directed against the myelin, demyelination ensues. In the majority of peripheral neuropathy, both demyelination and axonal injury will occur, however, characterizing the primary pathological process is important to establish an etiology and to assess the extent of injury. Demyelinating neuropathies can be further divided into segmental (acquired) and uniform (hereditary) types. In the former, nonuniform slowing in individual myelinated nerve fibers results in conduction block and temporal dispersion. In the latter, prolonged latency and slowing of conduction predominate as a result of uniform involvement of all myelinated fibers. Table 8-4 summarizes the EMG/NCV characteristics of demyelinating and axonal injuries.

FIBER TYPE SPECIFICITY: IS THE LESION MOTOR, SENSORY, OR AUTONOMIC?

The NCV tests motor and sensory components separately. Many peripheral nervous system diseases affect both motor and sensory nerves. In a case of distal sensory or motor neuropathies, amplitudes as well as velocities are abnormal. With a dorsal root ganglia lesion or anterior horn cell disease, NCV studies show small amplitude SNAP or CMAP, respectively, and as a rule normal velocity. Routine EMG/NCV studies do not test the integrity of the autonomic nervous system. Autonomic tests will be discussed separately.

DISTRIBUTION: IS THE LESION FOCAL, MULTIFOCAL, OR DIFFUSE?

By determining the distribution of abnormalities, neuropathy, for example, can be further divided into mononeuropathy, multifocal neuropathy, and polyneuropathy. A focal lesion such as carpal tunnel syndrome will result in abnormalities limited to the distal segment of a median nerve. If the same nerve is affected disproportionately in the opposite limb or one nerve is affected more than the other in the same limb, a multifocal disorder is suggested. In a fully developed polyneuropathy, motor and sensory nerves in both upper and lower extremities are affected in equal and symmetrical fashion; in milder cases, however, the abnormalities will be more significant in distal sensory nerves of the lower extremities.

TABLE 8–3 Anatomical Localization Based on EMG and NCV Studies

Lesion	Motor Nerve Conduction	Sensory Nerve Conduction	RNS	EMG
Dorsal root ganglia (sensory neuronopathy)	N	N, ↓ amp	N	N
Anterior horn cell (motor neuronopathy)	N, ↓ amp	N	N/Abn	Abn
Root (radiculopathy)	N, ↓ amp	N	N	Abn
Plexus (plexopathy)	N, ↓ amp	N, ↓ amp	N	Abn
Nerve (neuropathy)	Abn	Abn	N	Abn
NMJ defect	N, ↓ amp	N	Abn	Abn
Muscle (myopathy)	N, ↓ amp	N	N/Abn	Abn

RNS, repetitive nerve stimulation; *NMJ*, neuromuscular junction; *N*, normal; *Abn*, abnormal.

TABLE 8–4 NCV and EMG Characteristics of Demyelinating and Axonal Injuries

	NCV	EMG
Demyelination	1. Prolonged latency, >13% of normal 2. Slow NCV, <70% of normal 3. Conduction block 4. Temporal dispersion	1. Normal insertional activity, no spontaneous activity 2. Reduced recruitment with conduction block 3. Normal MUAP morphology
Axonal injury	1. Normal latency 2. Slow NCV, >70% of normal 3. Small CMAP/SNAP amplitude	1. Increased insertional activity, spontaneous activity 2. Reduced recruitment 3. Large amplitude, long-duration polyphasics with reinnervation 4. Satellite potentials

CMAP, compound muscle action potential; SNAP, sensory nerve action potential; MUAP, motor unit action potential.

CHRONICITY: HOW OLD IS THE INJURY?

Following an axonal injury, the nerve distal to the lesion undergoes Wallerian degeneration. For the first 2 to 3 days, motor conductions distal to a lesion will be normal. Then CMAP amplitude drops progressively, reaching a nadir at about 7 days. SNAP amplitudes distal to a lesion are unaffected for 5 to 6 days but by day 10 to 11, the nadir is reached. After an axonal motor nerve injury, EMG findings will change slowly. Initially, insertional activity is increased. Positive sharp waves and fibrillation potentials may not occur for 2 to 3 weeks following a nerve injury, depending on the length between site of nerve injury and corresponding muscles. The abnormal spontaneous activity can resolve in 3 to 6 months. Therefore needle studies performed less than 2 to 3 weeks after injury, or later than 3 to 6 months after injury, may be normal. Large-amplitude, long-duration polyphasic MUAPs seen in denervation and reinnervation develop 3 to 6 months after an injury. Table 8-5 summarizes the chronology of EMG/NCV findings after axonal injury.

TABLE 8–5 Chronology of NCV and EMG Findings after Axonal Injury

	NCV	EMG
0–1 wk	↓ amp, proximal	↓ recruitment
1–2 wk	↓ amp, proximal and distal	↓ recruitment ↑ insertional activity
2–3 wk	↓ amp, proximal and distal	↓ recruitment ↑ fibrillation potentials
1–3 mo	↑ amp	↓ fibrillation potentials ↓ amp, ↑ duration, ↑ phase
3–6 mo	↑ amp	↑ recruitment ↑ amp, ↑ duration, ↑ phase

SEVERITY AND PROGNOSIS: HOW BAD IS THE INJURY?

The severity of an injury can be determined if EMG/NCV is done in a timely manner. The amplitude difference between the same nerve on affected and unaffected sides gives an idea of extent of injury and potential recovery if they are determined sequentially. A paucity of spontaneous activity in affected muscles 3 weeks after injury indicates an excellent outcome for the return of muscle function. Markedly reduced recruitment of MUAPs indicates severe lesion except for neurapraxia. In general, axonal injury has a worse prognosis than demyelinating disorders.

QUANTITATIVE SENSORY TESTING

The quantitative sensory test (QST) provides a quantitative measure to detect large and small fiber dysfunction. Various stimuli at varying intensities are applied to the skin and a patient is asked to indicate when he or she begins to feel the stimulus. A consensus report defines "sensory detection threshold" as "the smallest stimulus that can be detected at least 50% of the time." By increasing and decreasing stimulus intensity from the predetermined level, "appearance" and "disappearance" thresholds can be determined. Sensory modalities commonly used are vibration and thermal senses—warm, cold, heat pain, and cold pain (Fig. 8-4). The vibration threshold measures large myelinated fiber function, whereas warm, heat pain, and cold pain thresholds reflect the function of unmyelinated C-fibers. The cold threshold measures small myelinated Aδ fiber function.[3]

QST measures not only peripheral nerve fiber function but also central pathway function. Vibratory sense is carried by the dorsal columns and thermal senses via the spinothalamic tract. Normal values depend on methodology, sensory modality tested, and site of test. The sensory detection threshold increases with age; therefore, results should be compared with age-matched reference values. QST can be used to detect subtle sensory changes that may be missed by NCV study. Increased or decreased thermal detection threshold (hypoesthesia or hyperesthesia) and thermal pain threshold (hypoalgesia or hyperalgesia)

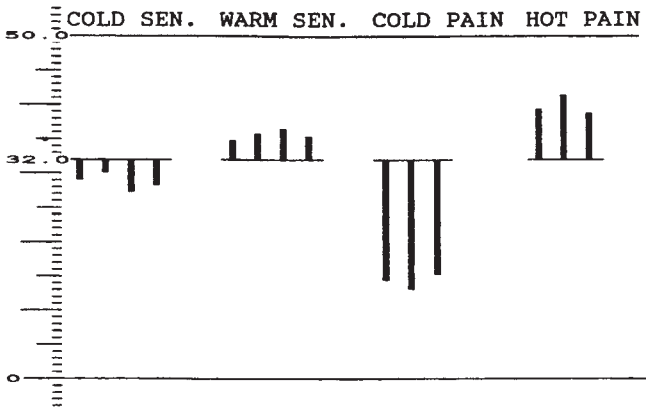

FIGURE 8-4 Example of a thermal QST in a normal subject. Temperature, in degrees Centigrade, on vertical scale. Solid bar represents each trial. Sen, sensation.

have been reported in many painful neuropathies. Cold or heat hyperalgesia is a feature of complex regional pain syndrome. Heat hyperalgesia is common in erythromelalgia, and angry backfiring C-nociceptor (or ABC) syndrome. Cold hypoesthesia, cold hyperalgesia, and cold limb are features of the CCC syndrome, whereas thermal hypoesthesia and hyperalgesia (anesthesia dolorosa) are typical manifestations of postherpetic neuralgia.[3]

QST allows early detection of disease. Sequential testing can be used to monitor disease progression and therapeutic efficacy. However, QST is not objective and relies on patient cooperation. QST does not localize a lesion, as it tests the integrity of the entire sensory pathway from nerve ending to cortex.[3]

SHORT-LATENCY SOMATOSENSORY-EVOKED POTENTIALS

Conventional sensory NCV studies assess a lesion distal to the dorsal root ganglion. SSEPs provide a quantitative measure to study the entire sensory pathway. Typically, a mixed nerve such as median nerve at the wrist or tibial nerve at the ankle is repeatedly stimulated and responses are recorded along the sensory pathway. Those responses are averaged to improve signal-to-noise ratio. Stimulations of the skin within a dermatome or cutaneous nerve such as the superficial radial or sural nerve have more limited value because of the low amplitude response. Submaximal intensity and longer duration of stimulus are required to elicit an optimal response.[4,5]

Stimulations are mediated by group Ia and II sensory afferents, dorsal root ganglion (neuron I), dorsal columns, gracilis and cuneatus nuclei (neuron II), contralateral medial lemniscus, ventroposterolateral nucleus of the thalamus (neuron III), and sensory cortex. Clinically, touch-pressure, position-movement senses are affected with the injury to the dorsal column pathway in both the central and peripheral nervous system. Each identifiable component is labeled according to its polarity (negative or positive) and its mean peak latency (in milliseconds) following stimulation. Useful obligate potentials after median nerve stimulation include EP (Erb's point), N13 (dorsal column of the cervical cord), P14 (caudal medial lemniscus), N18 (thalamus), and N20 (sensory cortex). Identifiable potentials after tibial nerve stimulation are PF (popliteal fossa), LP (lumbar potential), P31 (caudal medial lemniscus), N34 (thalamus), and P37 (sensory cortex) (Fig. 8-5). Knowledge of the generator source of these peaks allows us to localize lesions to parts of the pathway. Age, temperature, limb length, medications, level of attention, and sleep may alter latency and amplitude. Therefore every laboratory has its own normal values. Adult norms are reached at about 8 years of age. Criteria for abnormality include absence of any obligate waves and prolongation of interpeak intervals. For example, absence of N18, N20, or a prolonged P14–N20 interval suggests a lesion between the medulla and sensory cortex. Table 8-6 summarizes some typical SSEP findings and resulting localizations. Absolute latency is a less reliable indicator of abnormality because it varies with limb length. A side-to-side amplitude ratio less than half is considered abnormal by some. Application of SSEPs for a patient with pain is limited to the identification of a potential structural or compressive lesion involving peripheral or central sensory pathway.[4,5]

LASER-EVOKED POTENTIALS AND CONTACT HEAT–EVOKED POTENTIALS

A CO_2 laser can be used to generate pain-related cerebral potentials. The laser stimulator produces radiant heat quickly and activates Aδ and C nociceptors. Twenty to 40 stimuli are delivered at the intervals of 6 to 10 s. The late component, which occurs at approximately 220 to 340 ms following stimulation of the hand, corresponds to Aδ fiber conduction,

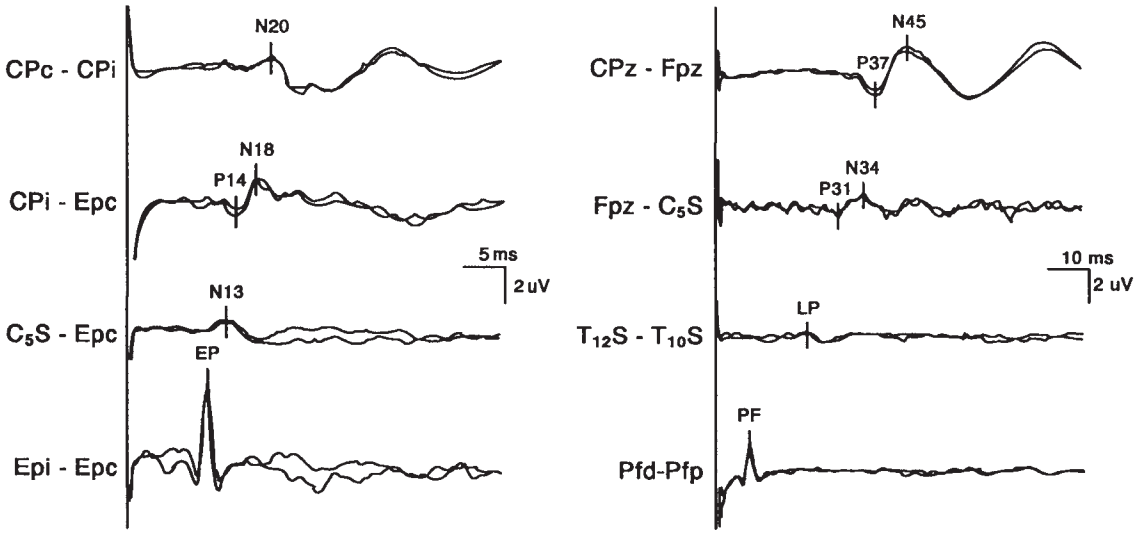

FIGURE 8-5 Median (left) and tibial (right) SSEPs in a normal subject. CPc, contralateral central–parietal; CPi, ipsilateral central–parietal; EPc, contralateral Erb's point; EPi, ipsilateral Erb's point; CS, cervical spine; CPz, midline central–parietal; Fpz, midline frontopolar; TS, thoracic spine; Pfd, popliteal fossa, distal; Pfp, popliteal fossa, proximal; EP, Erb's potential; LP, lumbar potential; PF, popliteal fossa.

TABLE 8–6 Lesion Localization Based on SSEP Findings

SSEPs	Abnormality	Lesion
Median nerve	1. Absent EP P14 N20	Median nerve–brachial plexus Above plexus Above medulla
	2. Prolonged EP–P14 P14–N20	Brachial plexus–medulla Medulla–sensory cortex
Tibial nerve	1. Absent LP P37	Tibial nerve–cauda equina Above lumbar spinal cord
	2. Prolonged LP–P37	Spinal cord–sensory cortex

EP, Erb's potential; *LP,* lumbar potential.

and the ultra-late component at 800 to 1000 ms corresponds to C-fiber; both components are maximum in amplitude (10–50 μV) at the vertex (Cz). LEPs provide an objective measure to assess the function of pain and temperature pathways in patients with neuropathic pain. In a lesion involving the spinothalamic tract including small fiber neuropathy, SSEPs are usually normal but LEPs are abnormal. LEPs are not yet available in most electrophysiologic laboratories because the measure is technically difficult to perform and causes skin burns and pigmentation. However, recent advances in technology enable us to use natural heat, which goes up quickly at the rate of 50°C/s (CHEPs). Latencies and amplitudes are comparable to those of LEPs. CHEPs are easy to perform and cause no side effects. Therefore this testing will eventually become a standard method to assess nociceptive dysfunction.[5,6]

SYMPATHETIC SKIN RESPONSE

The first report of the galvanic skin response appeared in 1890. Since then, various terminology has been introduced on the basis of different stimulating and recording methods (e.g., electrodermal activity, sympathetic skin response [SSR], peripheral autonomic surface potential, psychogalvanic reflex, and sympathogalvanic response [SGR]). A standard method of obtaining SSR is to place a recording electrode on the palmar and plantar surfaces, because these recording sites yield higher amplitudes. A stimulator is placed on either the median or the tibial nerve of the opposite limb, and the stimulus is given randomly at a rate of less than one per minute, and with a stimulus intensity that is sufficient to cause mild pain. A minimum of 5 to 10 responses should be recorded, and SSR responses are obtainable 60% to 100% of the time in normal subjects. Waveforms are usually triphasic, with an initial small negativity followed by a large positive wave, and a subsequent prolonged negative wave (Fig. 8-6). Waveforms can also be monophasic or diphasic with an initial negative or positive peak. Maximal peak-to-peak amplitudes and mean latencies are measured. Amplitude and latency variability can be minimized by reducing stimulus frequency, increasing stimulus intensity, and/or changing stimulus site or mode. Low skin temperature, low level of attention, medication (especially anticholinergics), age, and habituation will also attenuate the response. Normal amplitude is more than 1 mV for the hand, and more than 0.2 mV for the foot. Mean palmar

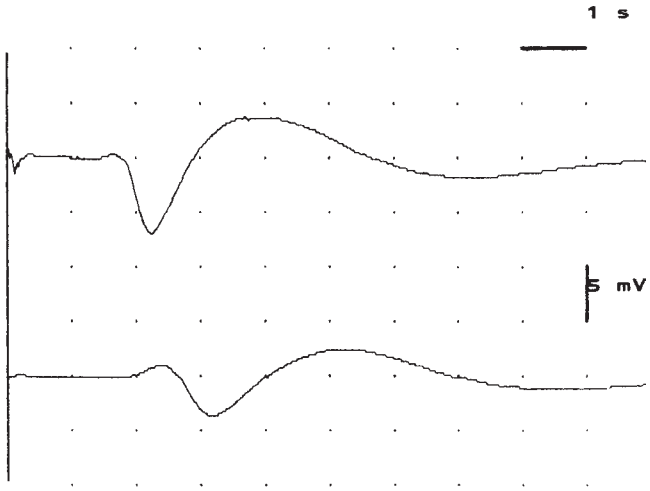

FIGURE 8-6 Normal sympathetic skin response (SSR) recorded simultaneously from the palm of the hand (top) and sole of the foot (bottom) by electrical stimulation.

latency is 1.4 ± 0.1 second and plantar latency is 1.9 ± 0.1 second. The SSR measures change of epidermal resistance due to sweat gland activity. The somatic afferent limb depends on the stimulus type (electrical shock, loud noise, visual threat, deep breathing); with the electrical stimulation, the afferent limb occurs via large myelinated fibers. The efferent limb is a sympathetic pathway, originating in the posterior hypothalamus, descending through the spinal cord to the intermediolateral cell column (T1 to L2), and paravertebral ganglia and then to the sweat gland via small unmyelinated fibers. Therefore it is important to note that neuropathy affecting large myelinated fibers exhibits abnormal SSR when electrical stimulation is used.

Low amplitude or absent response indicates abnormal sympathetic reflex arc, and the lesion can be central or peripheral, preganglionic or postganglionic. A side-to-side amplitude difference of more than 50% is considered to be abnormal by some. In studies of diabetic, uremic, and amyloid neuropathies, the result of SSR correlated well with autonomic symptoms. As a rule, SSR is abnormal in axonal neuropathies. An exception is the demyelinating neuropathy with prominent autonomic features, such as Guillain-Barre syndrome. Some studies have reported abnormal SSR test results in patients with CRPS/RSD and others have not. Immediately following the sympathetic nerve block or sympathectomy, the SSR is absent or reduced in amplitude. The SSR is usually normal in entrapment neuropathy and radiculopathy. SSR evoked by magnetic stimulation in the neck bypasses the afferent limb and directly stimulates postganglionic fibers. This method has less propensity to habituate and therefore less fluctuation of amplitude and latency occurs.

QUANTITATIVE SUDOMOTOR AXON REFLEX TEST AND RESTING SWEAT OUTPUT TEST

This is a sensitive, reproducible, and quantitative method to test sudomotor function. A multicompartment plastic "sweat cell" is tightly secured to the skin. The outer compartment

is filled with acetylcholine solution, and nitrogen gas flows constantly to an inner compartment through an instrument that measures the change of humidity (sudorometer). A direct current is applied and the water content in the inner compartment is continuously measured before, during and after the stimulus. The basis of the test is that the axon terminal of the sweat gland under the outer compartment is activated by acetylcholine iontophoresis; the impulse travel centripetally to a branch point and then distally to the axon terminal under the inner compartment where acetylcholine is released and a sweating response results. Use of the term "axon reflex" should be discouraged, because only the postganglionic sympathetic sudomotor axon is considered to be involved in this setup. With a latency of 1 to 2 min after the induction of the stimulus, sweat output increases rapidly while stimulation continues; then the stimulator is turned off, and sweat output returns to its prestimulus baseline within 5 min (Fig. 8-7). The area under the curve represents the total amount of sweat output expressed in microliter per square centimeter, and the normal value varies depending on the site of testing, gender, and age of the subject. Distal limbs, male, and younger subjects tend to sweat more. Reduced or absent response indicates postganglionic disorder. Normal response does not rule out preganglionic involvement. Excessive and persistent sweating is also considered abnormal. Comparison is made between the two limbs, and an asymmetry of more than 25% is considered to be abnormal.[7]

The RSO test is basically similar to the QSART; a capsule with one chamber is attached to the skin, and the rate of water evaporation is continuously recorded for 5 min. The presence of RSO indicates that the sweat gland is spontaneously activated by the sympathetic fibers.[7]

In a patient with painful diabetic neuropathy, RSO studies show the presence of increased sweat activity, and QSART exhibits short latency, excessive, and persistent sweat patterns, which is evidence of sympathetic overactivity. Sweat test abnormalities correlate well with the symptoms of CRPS/RSD-related pain, for which the pathophysiologic mechanism is uncertain; perhaps a lower firing threshold, or an increased firing frequency due to denervation hypersensitivity of the sudomotor axons may produce excitation of the sweat glands. Recently, the Food and Drug Administration (FDA) approved the Q-Sweat device. This device uses dry air instead of nitrogen gas to measure water content.[7]

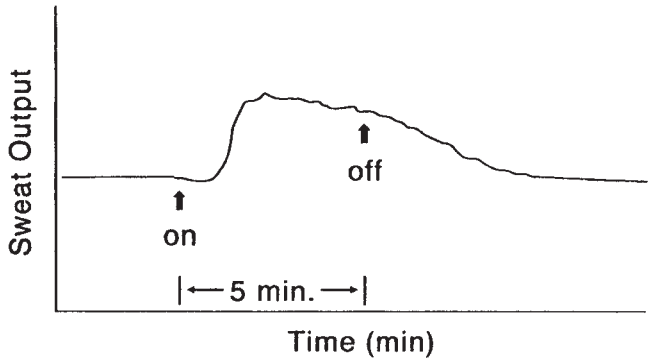

FIGURE 8-7 Example of a normal quantitative sudomotor axon reflex test (QSART). On, off, stimulator on and off.

NOCICEPTIVE REFLEXES

The blink reflex is recorded by electrically stimulating the supraorbital branch of the trigeminal nerve. Ipsilateral R1 (10–13 ms) and bilateral R2 potentials (30–41 ms) are obtained from the orbicularis oculi muscles. The masseter inhibitory reflex is recorded from the masseter muscles bilaterally with stimulation of the mentalis nerve while the muscle is fully activated by clenching teeth. Ongoing EMG activity is interrupted by two silent periods—an early phase with a latency of 10 to 15 ms and a late phase with 40 to 50 ms. These trigeminal reflexes have been reported normal in tic douloureux, but abnormal in facial pain due to neuropathy, multiple sclerosis, and cerebellopontine angle tumor. However, its afferent path is at least in part mediated by non–nociceptive fibers. Flexion reflex or withdrawal reflex is obtained by painful stimulation of a nerve or skin. RIII flexion reflex (80–90 ms) recorded from the short head of biceps femoris by stimulating the sural nerve has been found useful to assess efficacy of pain medications.[6,8]

KEY POINTS

- Electrophysiologic studies are very sensitive indicators of central and peripheral nervous system involvement but do not indicate underlying disease.
- EMG/NCV studies can identify the anatomic site of injury, the type of neurons or fibers involved, the nature of the pathologic alteration, and severity of injury.
- In QST, cold threshold measures Aδ fiber function, whereas warmth, heat pain, and cold pain thresholds reflect the function of C-fibers.
- SSEPs provide a quantitative measure to study the entire sensory pathway, mediated by Type Ia and II sensory afferents.
- LEPs and CHEPs measure the function of Aδ and C-fibers. CHEPs have potential to become a standard neurophysiologic method.
- SSR and QSART have a limited role but are useful for the evaluation of painful diabetic neuropathy or CRPS/RSD.
- Nociceptive reflexes have an extremely limited role.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 9

Anatomy, Imaging, and Common Pain-Generating Degenerative Pathologies of the Spine

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ANATOMY

OSSEOUS SPINAL COLUMN

The spinal column is comprised of 7 cervical, 12 thoracic, 5 lumbar, and 5 fused sacral segments. The terminal portion of the osseous spinal column, the coccygeal segments, varies in number, but typically 4 segments can be visualized. The morphology of the individual vertebrae is quite consistent throughout, with the exception of the first two cervical segments (C1 and C2) and the sacrococcygeal levels.

The C1 level, commonly referred to as the atlas, is comprised of an anterior arch, posterior arch, and paired lateral masses (Fig. 9-1A). The lateral masses articulate with the occipital condyles superiorly and the body of C2 inferiorly (Fig. 9-1B). C1 does not have a vertebral body nor is it separated from adjacent levels by an intervertebral disc. The C2 vertebra, commonly referred to as the axis, has some of the typical features of the remainder of the vertebral segments but is unique in having a superior extension of bone from the vertebral body that articulates with the dorsal margin of the anterior arch of C1: this bony projection is called the odontoid process or dens and allows for head rotation (Fig. 9-1B). Unique to the segments from C3 through C7 are the uncinate processes that arise from the dorsolateral margins of the superior end plates of the vertebral bodies and articulate with the level above (Fig. 9-2).[1]

The typical cervical, thoracic, and lumbar vertebrae consist of an anterior body, paired pedicles, articular pillars and laminae, and a single dorsal midline spinous process (Fig. 9-3). The pedicles attach the body to the posterior neural elements. The articular pillars are comprised of the pars interarticularis and the superior and inferior articular processes. Each level from C3 to L5 has superior and inferior articular processes that serve as the main posterior contact between adjacent levels. The surface of the superior articular process is the inferior facet of the associated zygapophyseal joint, and the surface of the inferior articular process is the superior facet of the joint. The "superior processes" at C1 and C2 and the "inferior process" at C1 are more descriptively referred to as articular surfaces, as they do not have a true morphological extension away from the vertebral segments. The two laminae extend dorsomedially and connect to form the root of the spinous process. The spinous process projects dorsally and serves as an attachment point for the posterior ligamentous structures. The pedicles, articular pillars, and lamina serve to enclose and protect the spinal canal and contents, particularly the spinal cord and nerve roots. Transverse processes vary in size from short in the cervical spine to long in the lumbar spine. In the mid-cervical spine, the transverse processes help to enclose and form the osseous transverse foramina that transmit the vertebral artery and contents. In the thoracic and lumbar spine, the transverse processes serve as anchoring points for the muscles that help to stabilize and protect the spinal column and its contents.

JOINTS

Six specific types of synovial joints exist from the skull base to the lumbosacral junction, including the atlanto-occipital, atlantoaxial, uncovertebral, costovertebral, costotransverse, and zygapophyseal (facet) joints.[2] The atlanto-occipital joint is formed by the bilateral superiorly convex occipital condyles and the bilateral concave superior articular surfaces of the C1 lateral masses (Fig. 9-1B). The main atlantoaxial joint is formed by the inferior articular surfaces of C1 and the superior articular surfaces of C2 (Fig. 9-1B). A true synovial-lined joint also exists between the ventral dens and the dorsal surface of the C1 anterior arch, and the dorsal aspect of the dens and the posterior ligamentous structures. The uncovertebral joints (joints of Luschka) exist only in the cervical spine below C2. The osseous uncinate processes arise from the dorsolateral margin of the superior end plates of the C3–C7 vertebral bodies and articulate with the level above: uncovertebral joints therefore exist from C2–C3 to C6–C7 (Fig. 9-2). The joints of Luschka have features of both cartilaginous and synovial joints and when degenerated can result in foraminal stenosis and even central stenosis.[1,3] As their names imply, the costovertebral and costotransverse joints are articulations between the ribs (costo-) and the vertebral bodies or transverse processes of the thoracic spine (Fig. 9-4).

The facet joints are the most prevalent joint in the spinal column and are formed by the inferior and superior articular processes of adjacent vertebral bodies. The facet surfaces (named relative to the joint space as described below) are covered with articular cartilage that allows for bending motion and offers some protection to shearing forces. The joints are encapsulated by a true synovial lining and loose capsular ligaments.[4] In the cervical spine, there is a thick fibrous capsule laterally under which a small synovial recess may protrude. In the lumbar spine, a thick fibrous capsule is present along the posterior margin of the facet joint. The inferior synovial recess occurs at the caudal extent of this capsule and is the common location for access to the joint space.[5,6] A complete discussion of the innervation of the facet joints is beyond the scope of this

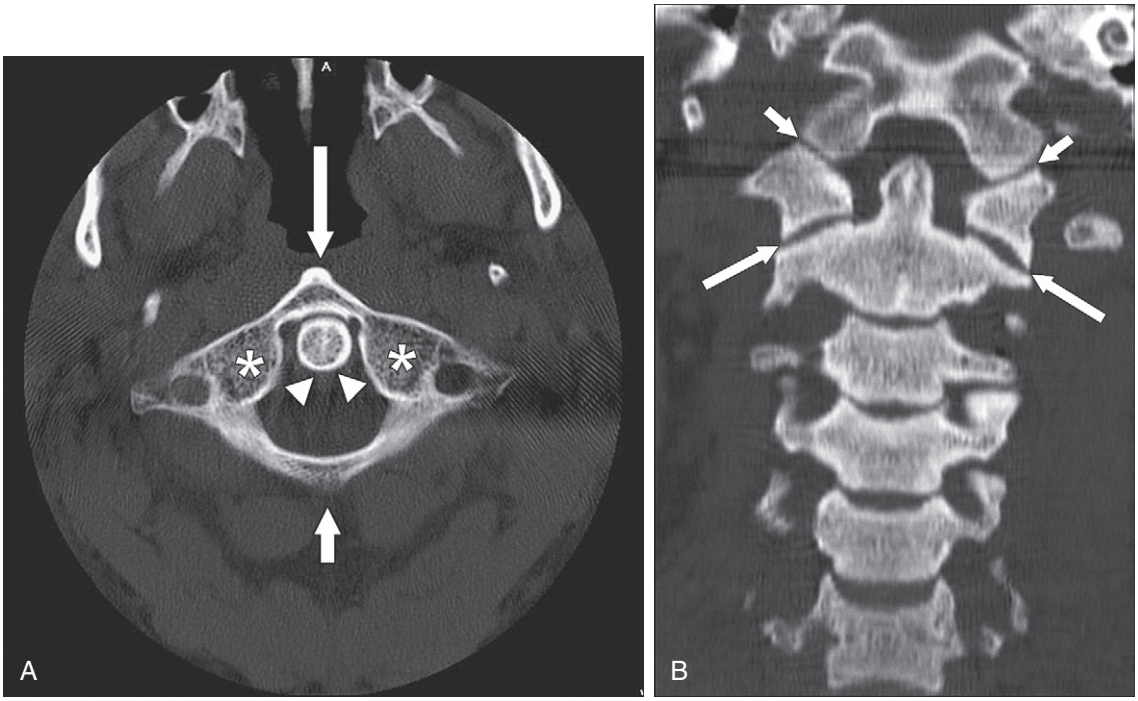

FIGURE 9-1 **A,** Axial CT image through the atlas shows the anterior arch (*long arrow*), posterior arch (*short arrow*), and paired lateral masses (*asterisks*). The tip of the odontoid process (*arrowheads*) articulates with the anterior arch of C1. **B,** Coronal CT reconstruction through the cervical spine demonstrates the articulations between the occipital condyles and the lateral masses of C1 (atlanto-occipital joints, *small arrows*). Also note the atlantoaxial joints (*long arrows*) between the lateral masses of C1 and the body of C2.

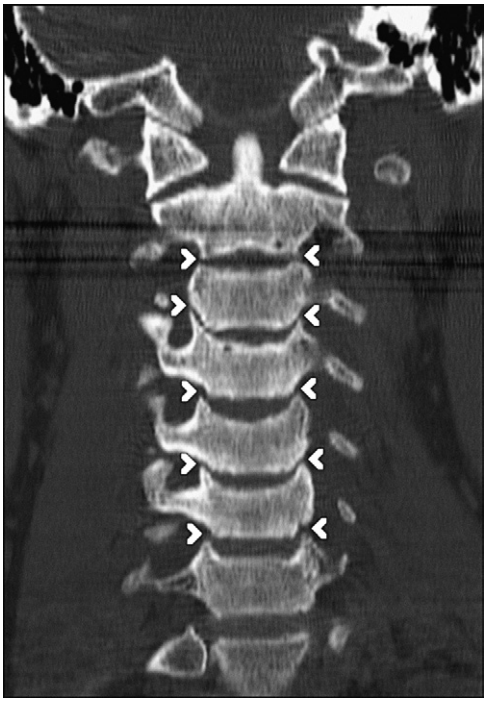

FIGURE 9-2 Coronal CT reconstruction through the cervical spine profiles the uncinate processes and uncovertebral joints (*arrowheads*).

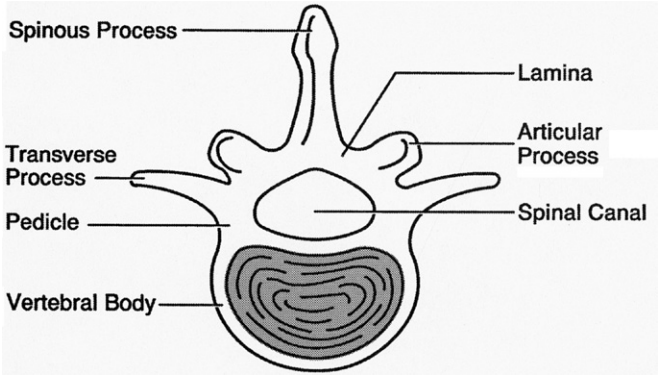

FIGURE 9-3 Axial diagram of a typical vertebral body.

chapter. Generally speaking, the facet joints are dually innervated from paired medial branches of the dorsal primary rami.[7,8] This dual innervation explains why complete denervation of a symptomatic facet joint requires treatment of both medial branches. Knowledge of the different facet joint orientations is important when planning facet joint interventions. The cervical facet joints are obliquely oriented from superior to posterior with a ventral to dorsal angle when viewed in the sagittal plane (Fig. 9-5A). The thoracic facet joints are oriented in the coronal plane limiting access for percutaneous procedures (Fig. 9-5B). The lumbar facet joints have a lunate configuration with the posterior margin oriented in the oblique sagittal plane and the anterior margin oriented in the oblique

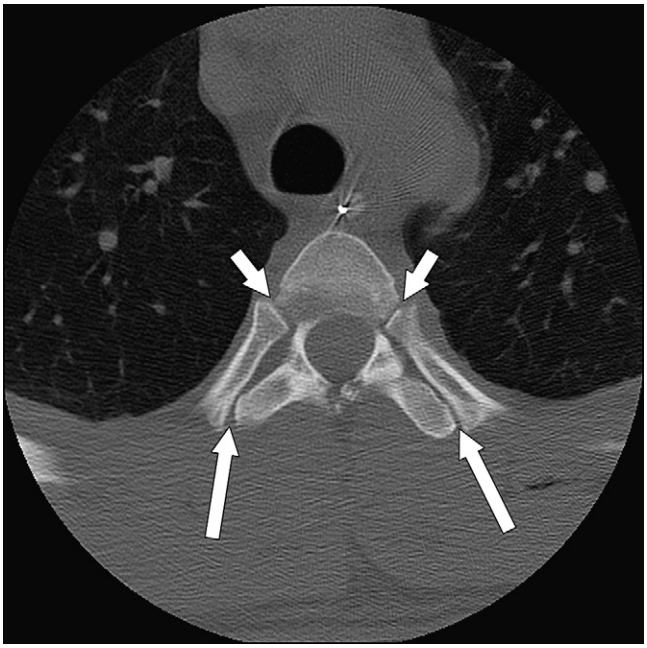

FIGURE 9-4 Axial CT image through the mid-thoracic spine identifies the costotransverse (*long arrows*) and costovertebral joints (*short arrows*).

coronal plane (Fig. 9-5C). Access to the joint under fluoroscopy is accomplished from a shallow oblique sagittal projection.[9]

TRANSVERSE FORAMEN, INTERVERTEBRAL FORAMEN, AND NERVE ROOTS

The transverse foramen, also known as the vertebral foramen or foramen transversarium, occurs in the cervical spine from C1 to C7. The transverse foramina develop when the neural processes posteriorly fuse with the vestigial costal element anteriorly.[10,11] The contents of the transverse foramina include the vertebral artery, vertebral venous plexus, fibers of the sympathetic chain, and fat. Typically round or oval, these foramina vary in size and shape and often reflect the underlying size of the traversing vertebral artery.[12] The vertebral artery typically enters the foramen at C6, but can enter as high as C3. In the sagittal projection, the vertebral artery is a few millimeters ventral to the adjacent exiting nerve root (Fig. 9-6).

In the cervical spine, the intervertebral foramen runs obliquely anterolaterally. It is bounded by the pedicles, uncinate process, vertebral body, and superior articular facet. The exiting cervical nerves are positioned posteroinferiorly in the intervertebral foramina (Fig. 9-6). Small veins connecting the epidural venous plexus and the anterior longitudinal intraspinal venous channel with the perivertebral venous plexus within the transverse foramina traverse the intervertebral foramen (Fig. 9-7).[13] There are eight paired cervical nerve roots, the first exiting the spinal canal between the skull base and C1. Therefore, in the cervical spine, the number of the nerve root passing through the foramen is one greater than the number of the pedicle that it passes beneath. For example, the nerve root passing through the intervertebral foramen at C3–C4 is the C4 nerve root.

The thoracic spine intervertebral foramina are rather constant, bounded by the pedicles, vertebral body, disc, and superior articular process of the vertebra below. The thoracic spinal nerves are more closely associated with the superiorly positioned articular process compared to the cervical spine. Small veins run through the intervertebral foramina as in the cervical spine. The exiting nerve roots are designated by the pedicle under which they immediately course. For example, at the T8–T9 level, the T8 spinal nerve root exits.

Much like the thoracic spine, the lumbar spine intervertebral foramina are bounded by the pedicles, vertebral body, disc, and superior articular process. The spinal nerve roots exit at a 45° angle inferolaterally and are closely associated with the medial and inferior margins of the pedicle under which they exit (Fig. 9-8). The spinal nerve roots are numbered as in the thoracic spine; the numbered root exits below the same numbered pedicle. For example, at the L4–L5 level, the L4 spinal nerve exits.

Throughout the spine, the exiting nerve roots are comprised of a smaller, ventral motor root and a larger, dorsal sensory root. The dorsal root contains a ganglion that can range in size from 5 to 15 mm.[14] This dorsal root ganglion (DRG) occurs in the intervertebral foramen and is most apparent in the lumbar and sacral spine. Small arterial branches from the lumbar arteries supply the DRG and have a fenestrated capillary endothelium. This anatomic configuration results in normal enhancement of the DRG on contrast examinations (Figs. 9-8 and 9-9).[15]

When contemplating a transforaminal or periganglionic intervention in the thoracolumbar region, one must consider the potential complication resulting from damage to the artery of the lumbar enlargement (artery of Adamkiewicz). This artery is the primary supply to the lower two-thirds of the spinal cord and enters the spinal canal via an intervertebral foramen. Although it typically enters on the left from T9–L1, the artery of Adamkiewicz can enter on either side from T5–L4. The artery usually runs in the more superior and ventral aspect of the foramen (Fig. 9-10).[16]

INTERVERTEBRAL DISCS

Intervertebral discs separate the vertebral bodies and contribute a significant proportion (20% to 35%) of the height to the spinal column. The discs are thicker in the cervical and lumbar regions and thicker anteriorly than posteriorly, contributing to the lordotic curvatures of the spine in these regions. The primary function of the disc is to absorb the impact of daily axial loading and confer some flexibility. Discs are composed of three main components: the nucleus pulposus, annulus fibrosis, and the cartilaginous end plate.[17,18] The nucleus pulposus contains type II collagen, hyaluronic acid, and glycosaminoglycans. This composition confers excellent compressive resistance and, when hydrated, has characteristic imaging findings on magnetic resonance imaging (MRI). The annulus fibrosis consists of an outer dense circumferential

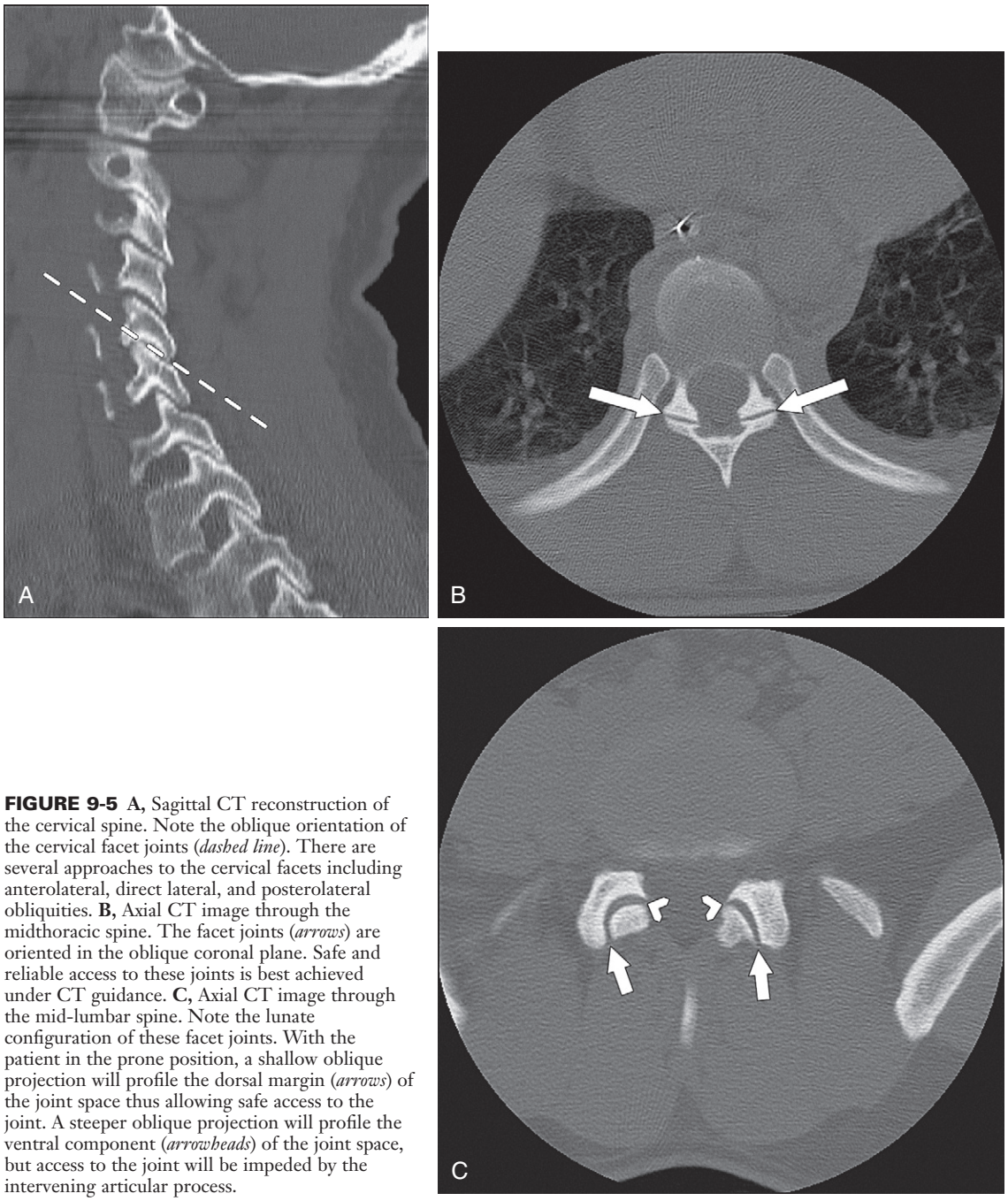

FIGURE 9-5 **A,** Sagittal CT reconstruction of the cervical spine. Note the oblique orientation of the cervical facet joints (*dashed line*). There are several approaches to the cervical facets including anterolateral, direct lateral, and posterolateral obliquities. **B,** Axial CT image through the midthoracic spine. The facet joints (*arrows*) are oriented in the oblique coronal plane. Safe and reliable access to these joints is best achieved under CT guidance. **C,** Axial CT image through the mid-lumbar spine. Note the lunate configuration of these facet joints. With the patient in the prone position, a shallow oblique projection will profile the dorsal margin (*arrows*) of the joint space thus allowing safe access to the joint. A steeper oblique projection will profile the ventral component (*arrowheads*) of the joint space, but access to the joint will be impeded by the intervening articular process.

fibrous band and an inner fibrocartilaginous layer. The outer layer fibers, also known as Sharpey's fibers, insert into the ring apophyses. The cartilaginous end plate is composed of hyaline cartilage that tightly adheres to the vertebral end plate. Vascular supply to the disc is primarily via small nutrient channels through this cartilaginous end plate.[19,20]

LIGAMENTS

Ligaments of the spine provide stability while allowing flexion, extension, and rotation. There are five main ligamentous structures seen throughout the spinal column: anterior longitudinal ligament (ALL), posterior longitudinal ligament (PLL), ligamentum flavum, interspinous ligaments, and the supraspinous ligament. The ALL and PLL run along the anterior and posterior margins of the vertebral bodies, respectively (Fig. 9-11).[21] The ALL adheres to the vertebral body and intervertebral discs. The PLL adheres to the annulus fibrosis of the disc but does not contact the posterior vertebral margin to any significant degree. The ligamentum flavum runs along the length of the spinal canal extending between adjacent laminar segments and defining the dorsolateral margins of the spinal canal. The interspinous ligaments run between adjacent spinous processes, whereas the

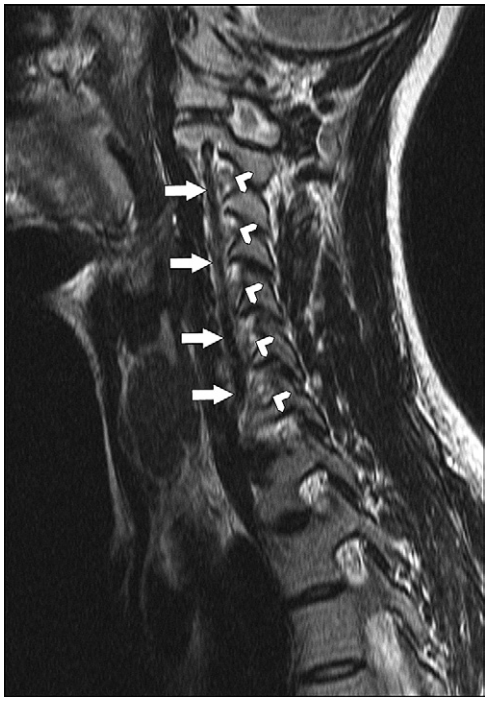

FIGURE 9-6 Parasagittal image through the foramen transversaria. The linear dark flow void (*arrows*) is the vertebral artery. Note the position of the vertebral artery immediately ventral to the exiting spinal nerve roots (*arrowheads*).

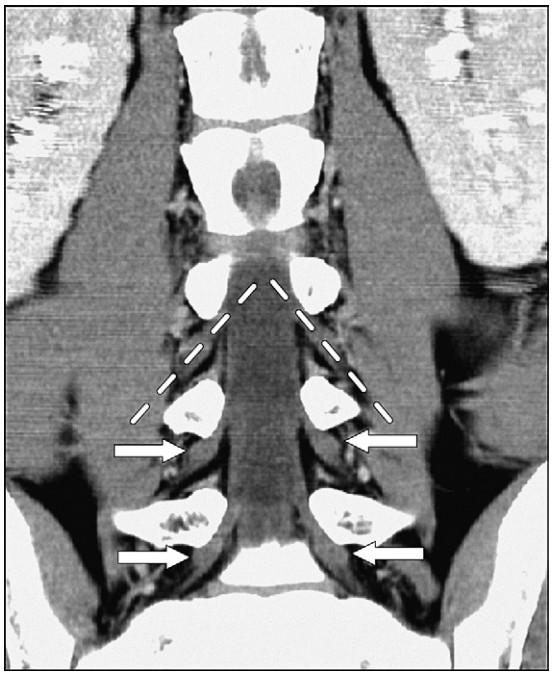

FIGURE 9-8 Coronal CT reconstruction after contrast administration. Note the orientation of the exiting lumbar nerve roots (*dashed lines*) relative to the spinal canal and intervertebral foramina. Enhancement of the dorsal root ganglia (*arrows*) is evident.

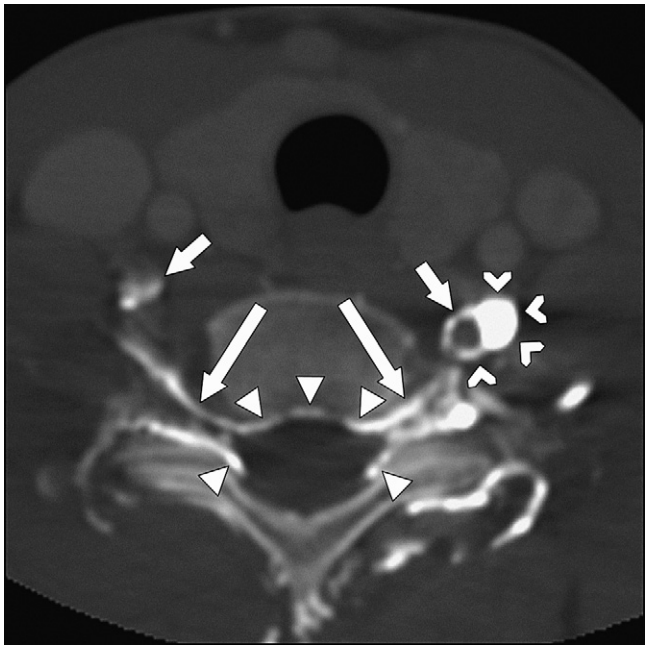

FIGURE 9-7 Axial CT image through the lower cervical spine. Contrast was administered for a neck CT but, as commonly occurs, some contrast filled the venous system in a retrograde fashion. The venous connection between the epidural space (*closed arrowheads*) and the perivertebral venous plexus (*open arrowheads*) via branches through the intervertebral foramina (*long arrows*) are well seen. The vertebral arteries (*short arrows*), not yet within the vertebral foramina, are encircled with venous opacification particularly on the left.

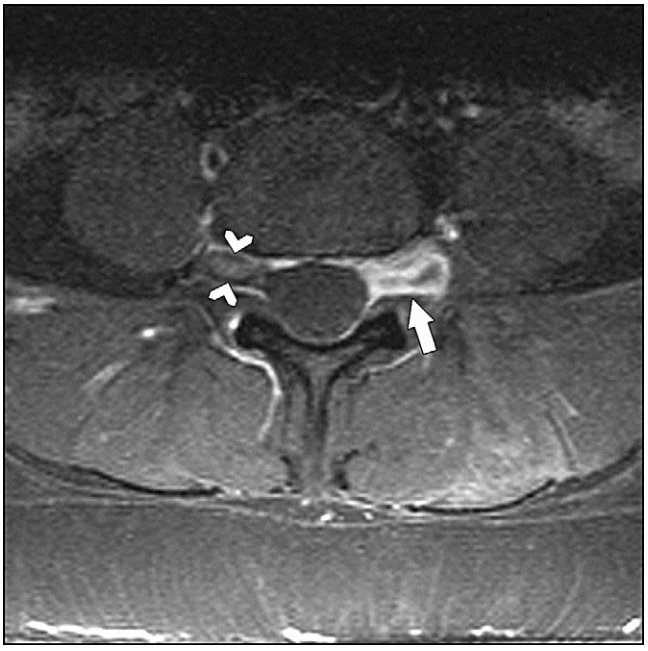

FIGURE 9-9 Axial postgadolinium T1-weighted fat-suppressed MR image. In the left foramen, the oval peripherally enhancing lesion (*arrow*) is a sequestered disc fragment. In the right foramen, normal enhancement of the dorsal root ganglion (*arrowheads*) is identified.

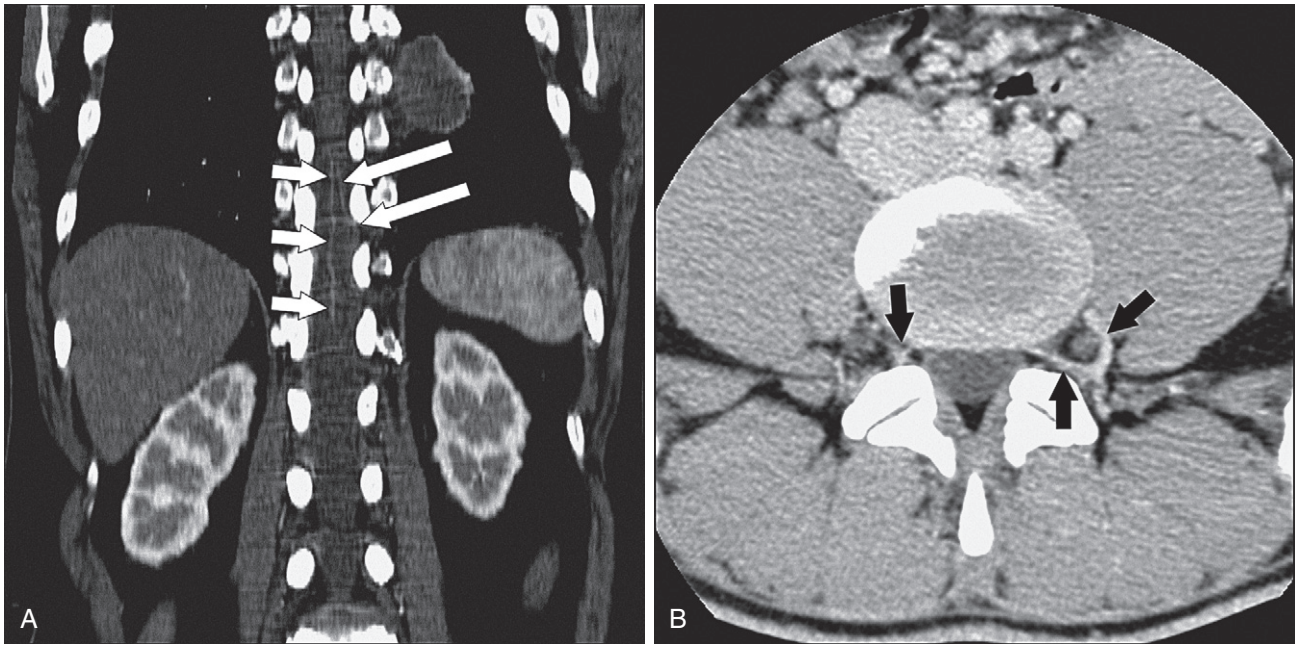

FIGURE 9-10 **A,** Coronal CT reconstruction of a contrast-enhanced aorta study. The high-density linear structure on the surface of the spinal cord is the anterior spinal artery (*short arrows*). The artery of Adamkiewicz (*long arrows*) enters the spinal canal through the left T10–T11 intervertebral foramen. **B,** Axial CT image postcontrast through the mid-lumbar spine demonstrates typical venous structures (*arrows*) within and lateral to the intervertebral foramen.

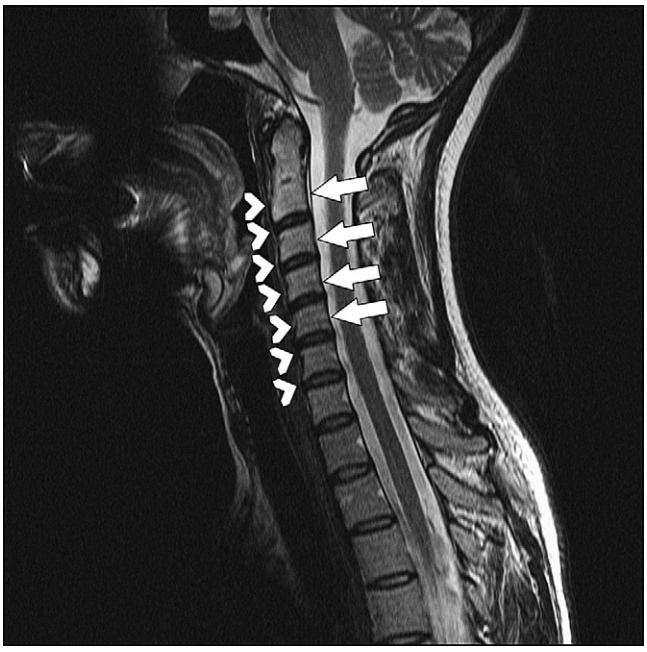

FIGURE 9-11 Sagittal T2-weighted image through the cervical spine. The thin linear hypointense signal paralleling the ventral margins of the vertebral bodies and discs represents the ALL (*arrowheads*). The PLL (*arrows*) has a similar appearance but runs along the dorsal margin of the intervertebral discs.

supraspinous ligament runs along the tips of the spinous processes.

Specialized ligaments are present at the craniocervical junction, including the atlanto-occipital ligament, apical ligament, tectorial membrane, and the cruciate ligaments that form the transverse ligament.[22] These ligaments provide stability and flexibility at the craniocervical junction. Further discussion of these ligaments is beyond the scope of this chapter.

IMAGING OVERVIEW

CONVENTIONAL RADIOGRAPHS (X-RAYS)

Conventional or plain radiographs record differential attenuation of the x-ray beam by tissues based on their differential densities. For example, cortical bone is very dense and completely attenuates the beam. The heart is soft tissue and partially attenuates the beam, and the lung is mostly air, thus attenuating very little of the beam. Conventional radiographs are quick, inexpensive, and easy to perform and have excellent spatial resolution. Important information about the spine can be obtained with conventional radiographs, including alignment, structure, and mineralization. Dynamic, weight-bearing upright flexion and extension views can reveal a stable or unstable spine in chronic and acute scenarios. This is the only modality to date that routinely achieves this type of stress-related imaging. Osseous foraminal stenosis and spondylolysis can be diagnosed with oblique projections. Vertebral fractures and joint dislocations can be detected, although acuity can be difficult to discern. Although conventional radiographs are less optimal than computed tomography (CT) for soft tissue evaluation, degenerative changes of the disc can be identified such as disc dehydration (air in disc) and disc collapse.

Standard frontal (including odontoid view when imaging the cervical spine) and lateral projections are the minimum required for adequate evaluation (Figs. 9-12A–C,

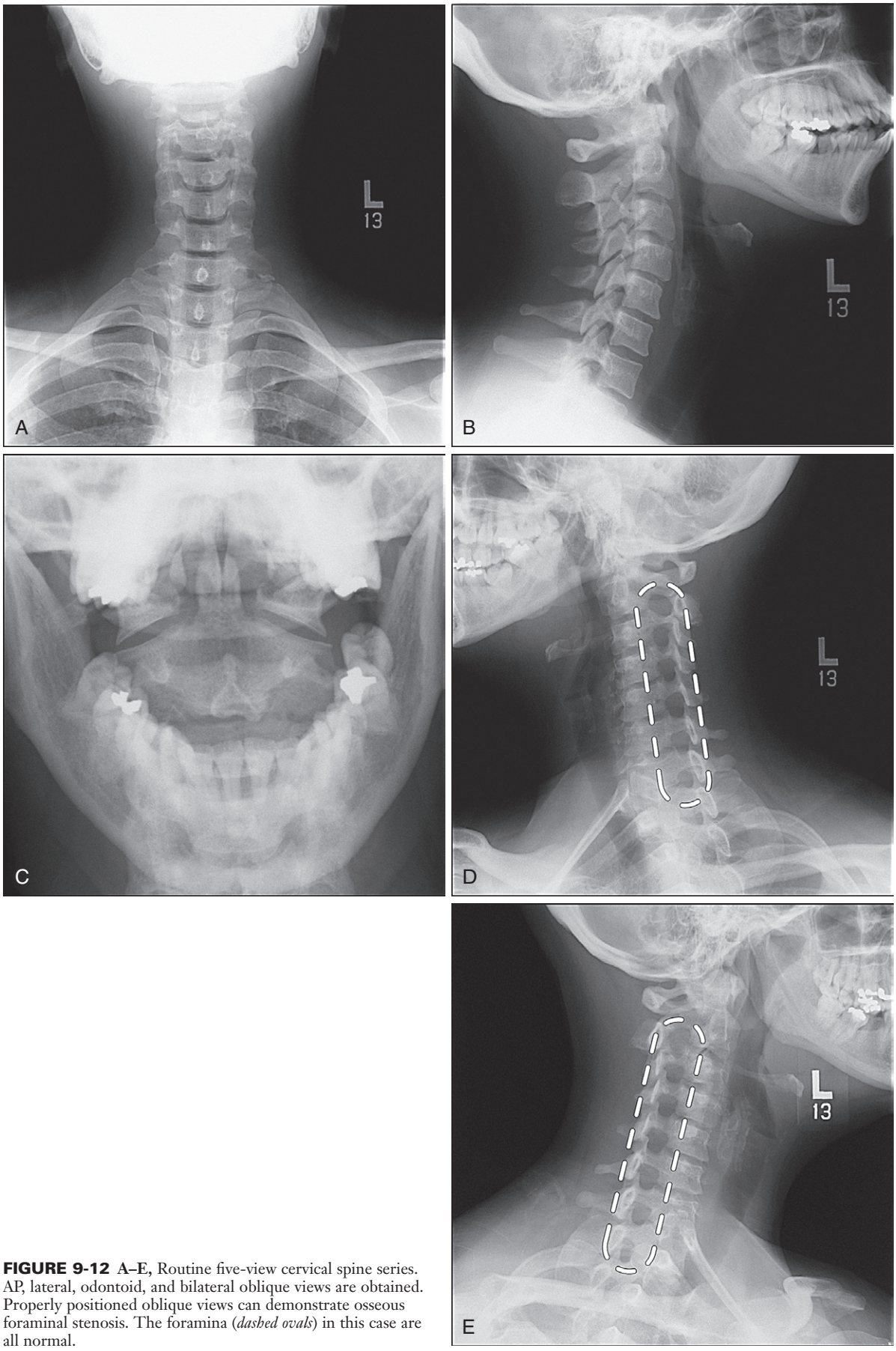

FIGURE 9-12 **A–E,** Routine five-view cervical spine series. AP, lateral, odontoid, and bilateral oblique views are obtained. Properly positioned oblique views can demonstrate osseous foraminal stenosis. The foramina (*dashed ovals*) in this case are all normal.

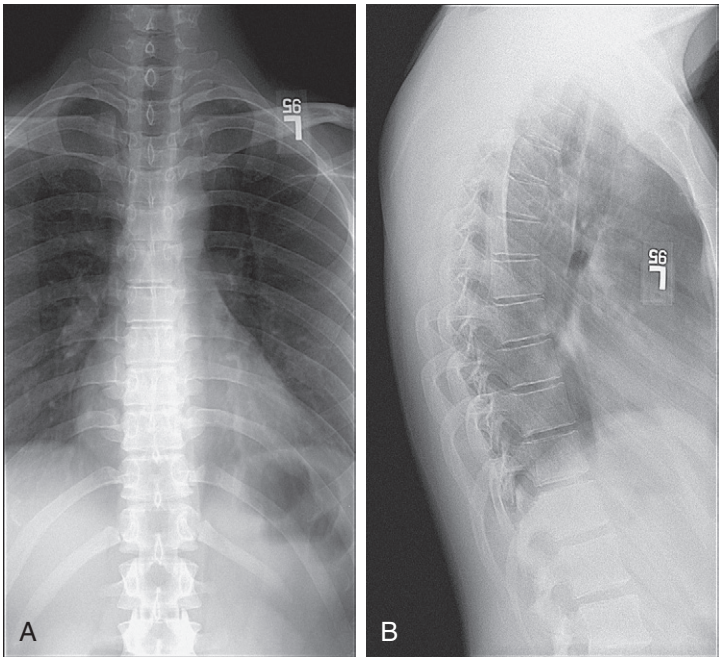

FIGURE 9-13 **A** and **B,** Standard images of the thoracic spine include an AP and lateral view.

13A, B, 14A–C). In the cervical and lumbar regions, oblique projections are helpful in evaluating the facet joints, articular processes, and intervertebral foramina (Figs. 9-12D, E, 14D, E). When spondylolisthesis or spondylolysis is present, flexion and extension views aid in demonstration of abnormal motion. Flexion and extension views may be supplemented by direct real-time observation using fluoroscopy.

Plain films can detect changes related to systemic diseases such as ankylosing spondylitis and diffuse sclerotic/lytic states (Fig. 9-15). Also, there is no good substitute for plain radiographs to evaluate overall alignment abnormalities in patients with extensive kyphoscoliotic deformities.

Conventional radiography is the easiest and most cost-effective method of assessing alignment and structure of the spine in both traumatic and nontraumatic conditions. On lateral projection, three longitudinal curves may be used to evaluate alignment of the vertebrae (Fig. 9-16). The anterior and posterior spinal lines trace the course of the anterior and posterior longitudinal ligaments, respectively. The spinolaminar line traces the course of the ligamentum flavum along the deep surface of the laminae. On frontal projection, a vertical line drawn through the tips of the spinous processes serves as a reference for evaluation of lateral curvature (Fig. 9-17). The relationship of this line and the pedicles will demonstrate rotational malalignment.

Plain radiographs can easily depict hardware failure such as fractures. Even known hardware fractures can be difficult to detect with CT due to beam-hardening artifacts that can obscure large portions of the images.

MYELOGRAPHY AND POSTMYELOGRAPHY CT SCAN

Myelography is the radiographic technique used to evaluate the contents of the spinal canal by the introduction of a nonionic, water-soluble, radiographically dense iodinated contrast material into the spinal subarachnoid space. This contrast material outlines the spinal cord and nerve roots, which appear as filling defects in the radio-dense contrast column on conventional radiographs. Extradural indentations into the contrast column are observed and generally represent disc abnormalities, ligament thickening, or hypertrophic facet degenerative changes. Spinal stenosis can be diagnosed and nerve root impingement can be detected. Redundant thickened nerve roots and arachnoiditis can also be demonstrated (Fig. 9-18). Myelography should always be followed by a postmyelography CT scan to provide better definition of anatomic relationships of the contents of the spinal canal to the surrounding structures.

The use of myelography has decreased significantly due to the invasive nature of the procedure and the availability of other noninvasive imaging tools, including CT and MRI, which provide excellent spatial and contrast resolution. The risks of myelography are directly related to the lumbar puncture (LP) and injection including positional headache, contrast-related seizure, and infection. The most common of these complications is the post-LP positional headache.[23] If this headache does not respond to conservative therapy, an epidural blood patch can be performed for more definitive treatment.[24] Seizures related to intrathecal contrast administration are uncommon, but the seizure threshold does decrease with certain

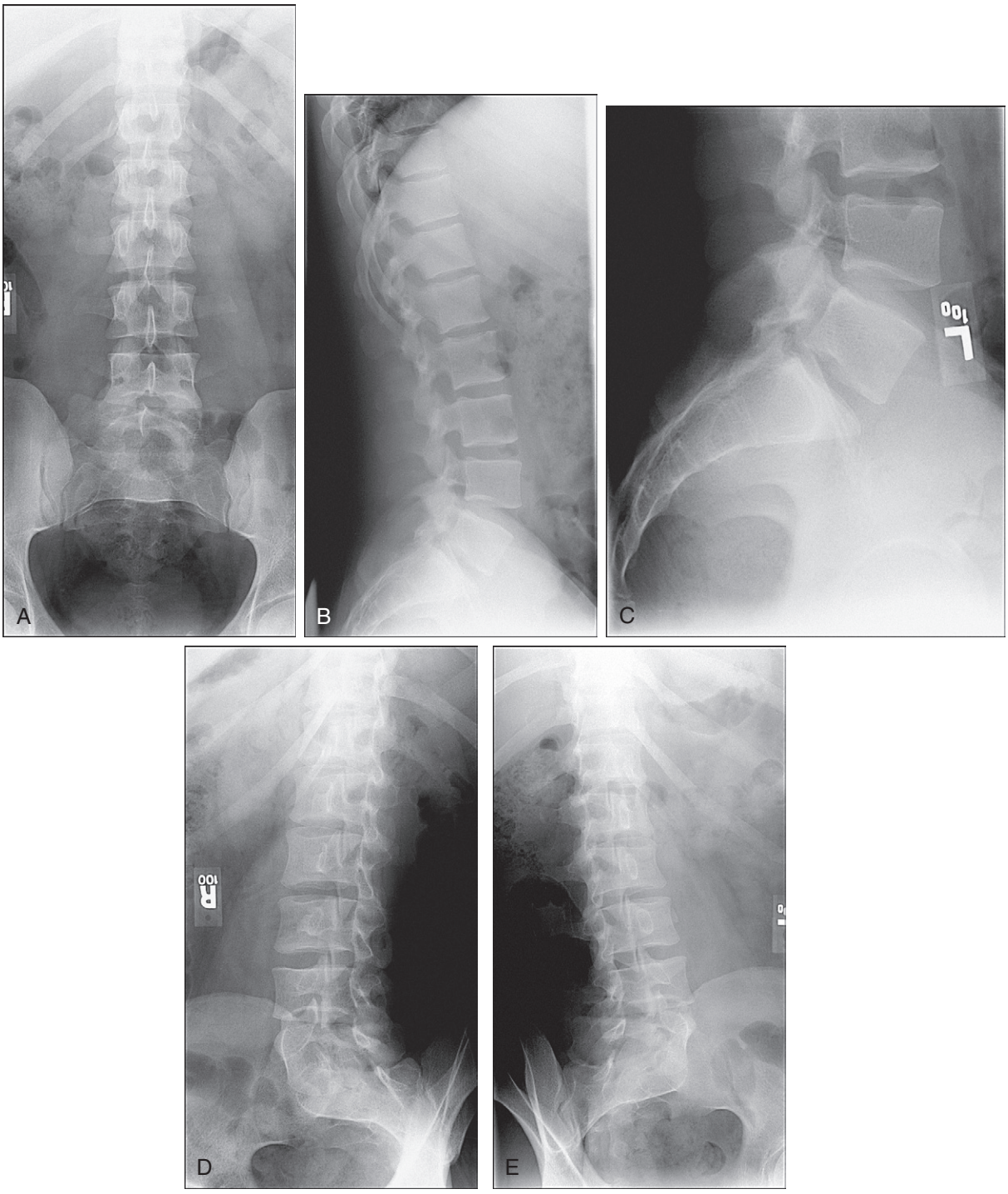

FIGURE 9-14 **A–E,** Routine five-view lumbar spine series. AP, lateral, coned-down view of the lumbosacral junction and bilateral oblique views.

medications including numerous anti-depressants.[25] In general, patients should be screened for specific medications and rescheduled if they are found to be on any seizure threshold–reducing medications. Myelography is now used mainly as a problem-solving tool when CT or MRI examination cannot be performed due to contraindications, are equivocal, or are limited due to artifacts from surgical hardware.

COMPUTER-ASSISTED TOMOGRAPHY (CAT OR CT SCAN)

CT is an x-ray technique that is considerably more sensitive to the differential attenuation of the x-ray beam than plain film radiography. CT provides the best possible definition of osseous structures and has excellent spatial resolution. The newest generation of CT scanners employs

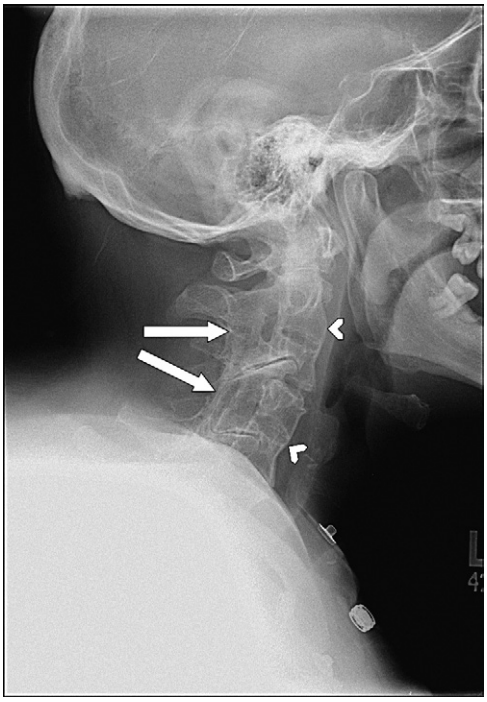

FIGURE 9-15 In this single lateral cervical spine film, the findings consistent with ankylosing spondylitis are easily identified, including facet joint ankylosis (*arrows*) and vertebral body fusion (*arrowheads*).

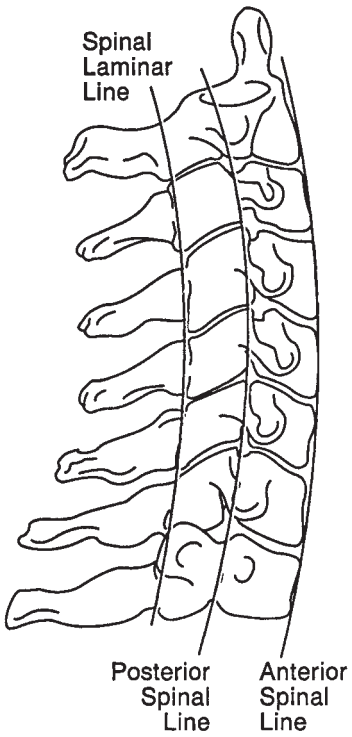

FIGURE 9-16 Lateral diagram of the cervical spine demonstrating the spinal laminar, posterior spinal, and anterior spinal lines.

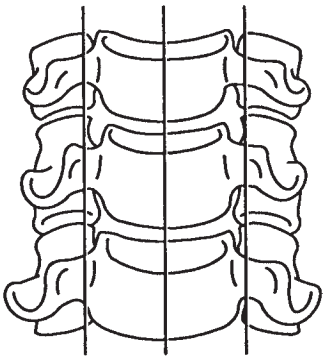

FIGURE 9-17 Frontal diagram of the cervical spine showing normal alignment of the spinous processes.

slip-ring technology (helical acquisition), multidetector systems, high-speed rotation, and dynamic table translation to optimally image the spine. Dose-reduction software now changes the patient dose "on the fly": the current (mA), and therefore the dose, changes in response to the thickness of the individual patient at each slice. Overlapping data sets can be acquired that allow for multiplanar reformatting, and three-dimensional data sets can be acquired for volumetric analysis or volume rendering applications.

As with conventional radiographs, CT imaging is based on differential attenuation of the x-ray beam but can differentiate not only bone from soft tissue but also between different densities of bone and soft tissue structures. Differences in radiographic density of ligament, disc material, and cerebrospinal fluid (CSF) make identification of disc herniations and ligamentous disorders possible using CT (Fig. 9-19). Subtle areas of bone sclerosis or lysis can easily be displayed with CT. Windowing techniques used in the display of CT images allow optimal viewing of image data, depending on the tissue type of interest. The administration of intravenous iodinated contrast material may be valuable in certain circumstances to highlight vascular structures, such as the epidural venous plexus or adjacent arteries.

Artifacts from metallic surgical implants, such as spinal rods, transpedicular screws, laminar wires/hooks, and intervertebral/vertebral body cages can severely limit the diagnostic value of CT images. In these cases, conventional radiographs and myelography may prove to be the best diagnostic imaging modalities. Even this limitation will improve as CT scanners evolve from 4 slices to 16 slices and beyond. The radiation dose from CT can be several times that of plain radiography, depending on technique and protocols. Hence, appropriate care should be exercised in using it in the more sensitive populations, including children, pregnant females, and other young adults.

MAGNETIC RESONANCE IMAGING (MRI)

MRI uses gradient fields and radiofrequency waves to localize and characterize tissues based on the amount and state of the ubiquitously present hydrogen atoms (protons). There is no ionizing radiation employed with MRI,

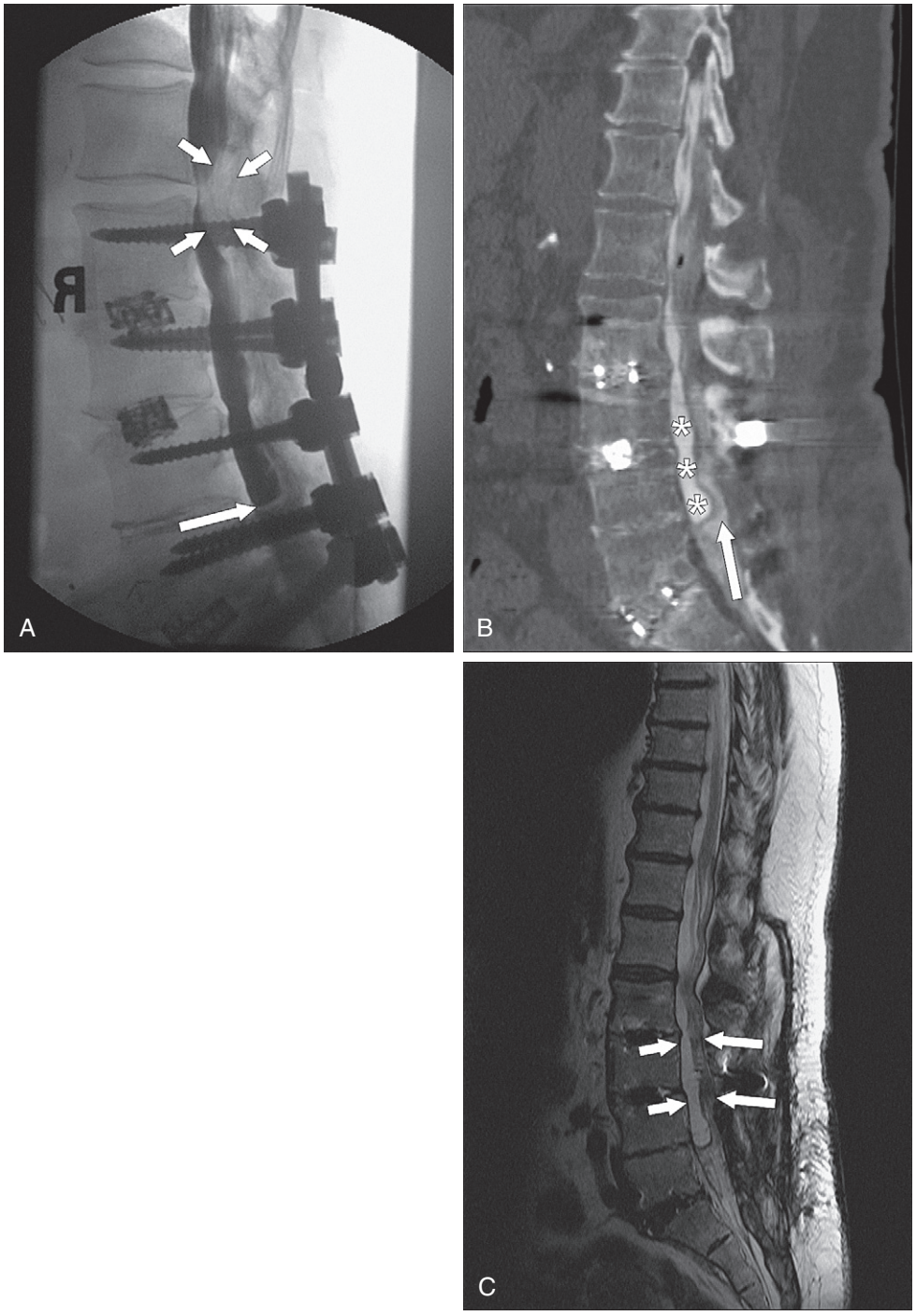

FIGURE 9-18 **A,** This lateral lumbar spine film was obtained after routine myelography. The patient has undergone posterolateral fusion from L2–S1. A waist of contrast column attenuation (*short arrows*) is seen at L1–L2 indicating ligamentum flavum thickening. At the L4–L5 level, the intrathecal contrast is compartmentalized (*long arrow*) suggesting arachnoiditis. **B,** Sagittal CT reconstruction demonstrates a dense ventral subarachnoid collection of contrast (*asterisks*) and a less dense collection dorsally (*arrow*). This appearance is consistent with arachnoiditis. **C,** Sagittal T2-weighted MRI identifies the dorsal position of the nerve roots (*long arrows*) in the thecal sac and the compartmentalization of the CSF spaces (*short arrows*).

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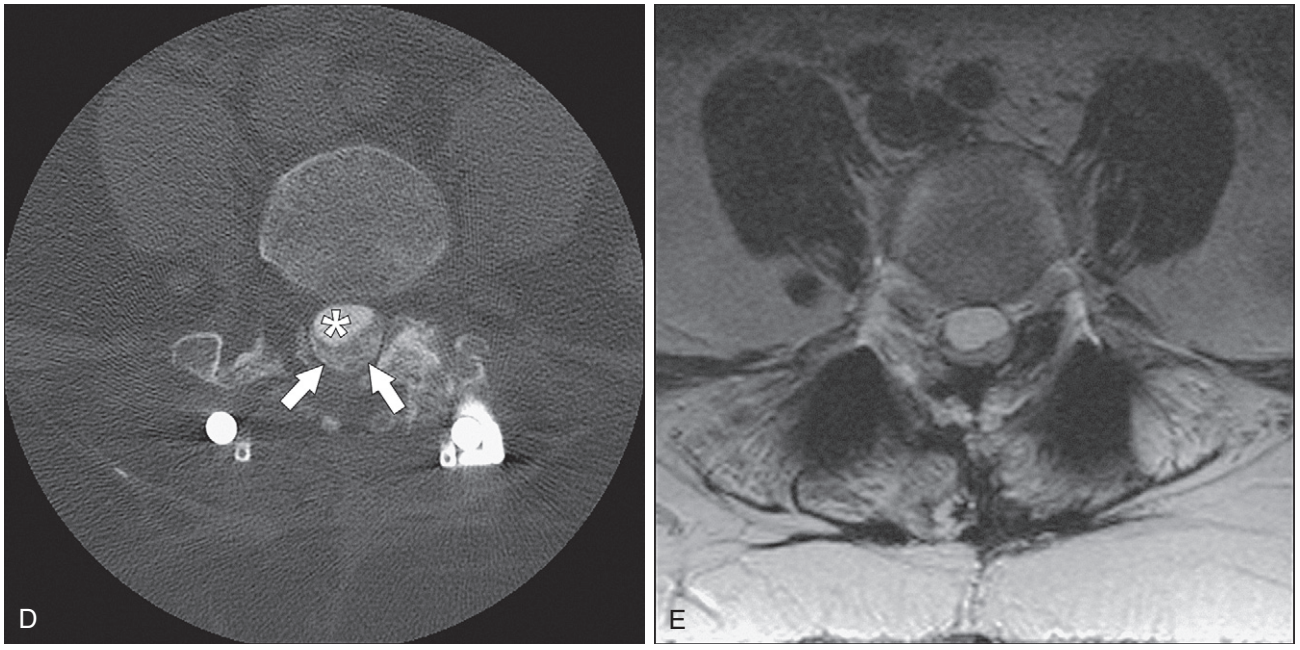

FIGURE 9-18 cont'd D, This axial CT myelographic image shows clumping and peripheral displacement of the spinal nerve roots (*arrows*) with ventral accumulation of contrast (*asterisk*). **E,** Axial T2-weighted MRI was obtained at the same level as the CT image and demonstrates the same findings.

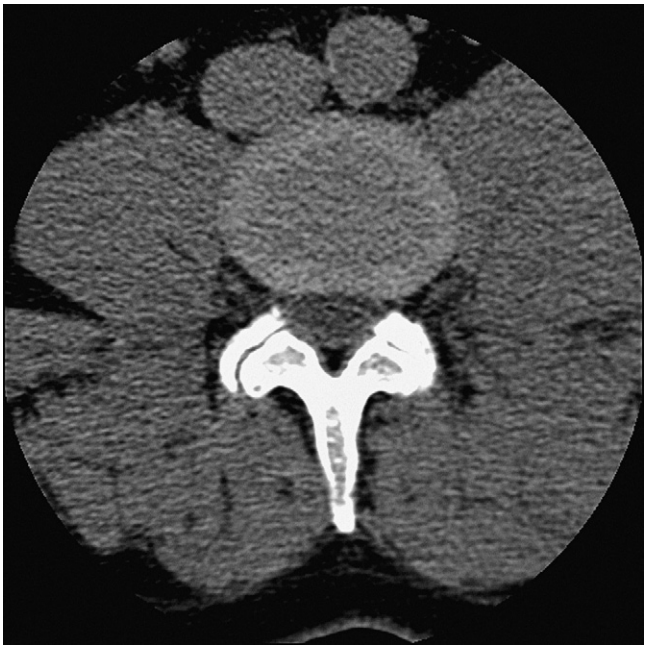

FIGURE 9-19 CT images represent differential attenuation of the x-ray beam by the bones and soft tissues. Fat is low density and is hypodense on CT. CSF is less dense than the ligamenta flava, which are similar in density to the disc and muscles. Cortical bone is generally the densest endogenous structure.

but there are risks including those related to electrical and metal implants and an unknown/unquantified risk to the fetus.[26–30] The very good soft tissue contrast resolution afforded by MRI combined with its multiplanar tomographic capability make it the most versatile and useful diagnostic imaging modality for spinal disorders. It provides a wide field of view with excellent definition of tissue types, such as bone marrow, muscle, ligament, disc material, and nerve roots. MRI allows precise definition of extradural, intradural extramedullary, and intramedullary pathology. Evaluation of medullary bone with MRI is excellent, and many osseous conditions resulting in marrow edema or marrow replacement (e.g., metastatic disease) are well demonstrated. However, demonstration of dense cortical bone, sclerotic lesions, and osteophytes is less precise than by CT.

Standard MRI protocols usually include sagittal and axial images with T1- and T2-weighted sequences. T1 weighting provides excellent anatomical delineation. Generally speaking, high signal intensity on T1 represents fat (such as in fatty bone marrow, subcutaneous fat), whereas low signal intensity represents fluid (such as CSF, bone marrow edema, normal nucleus pulposus) (Fig. 9-20A). T2 weighting makes fat-containing structures less bright than on T1 and makes fluid-containing structures hyperintense (bright) (Fig. 9-20B). Soft tissue structures such as muscles and spinal cord have intermediate signal intensities on T1 and T2 sequences. The STIR (short-tau inversion recovery) sequence is a fat-suppressed, T2-weighted sequence that is extremely sensitive to minute amounts of fluid (Fig. 9-20C). This sequence is particularly useful in detecting edema as can be seen with traumatic injury, malignancy, and infection.[31] Gradient recalled echo (GRE), T2-weighted imaging is exquisitely sensitive to blood products and calcium, and is particularly useful in the setting of spine trauma for evaluating the spinal cord (Fig. 9-20D).[32,33] When evaluating scoliosis, coronal T1- or T2-weighted imaging may be added to better assess the extent of curvature (Fig. 20E).

In the cervical spine, thin-section axial two- or three-dimensional GRE T2 images are used to further evaluate

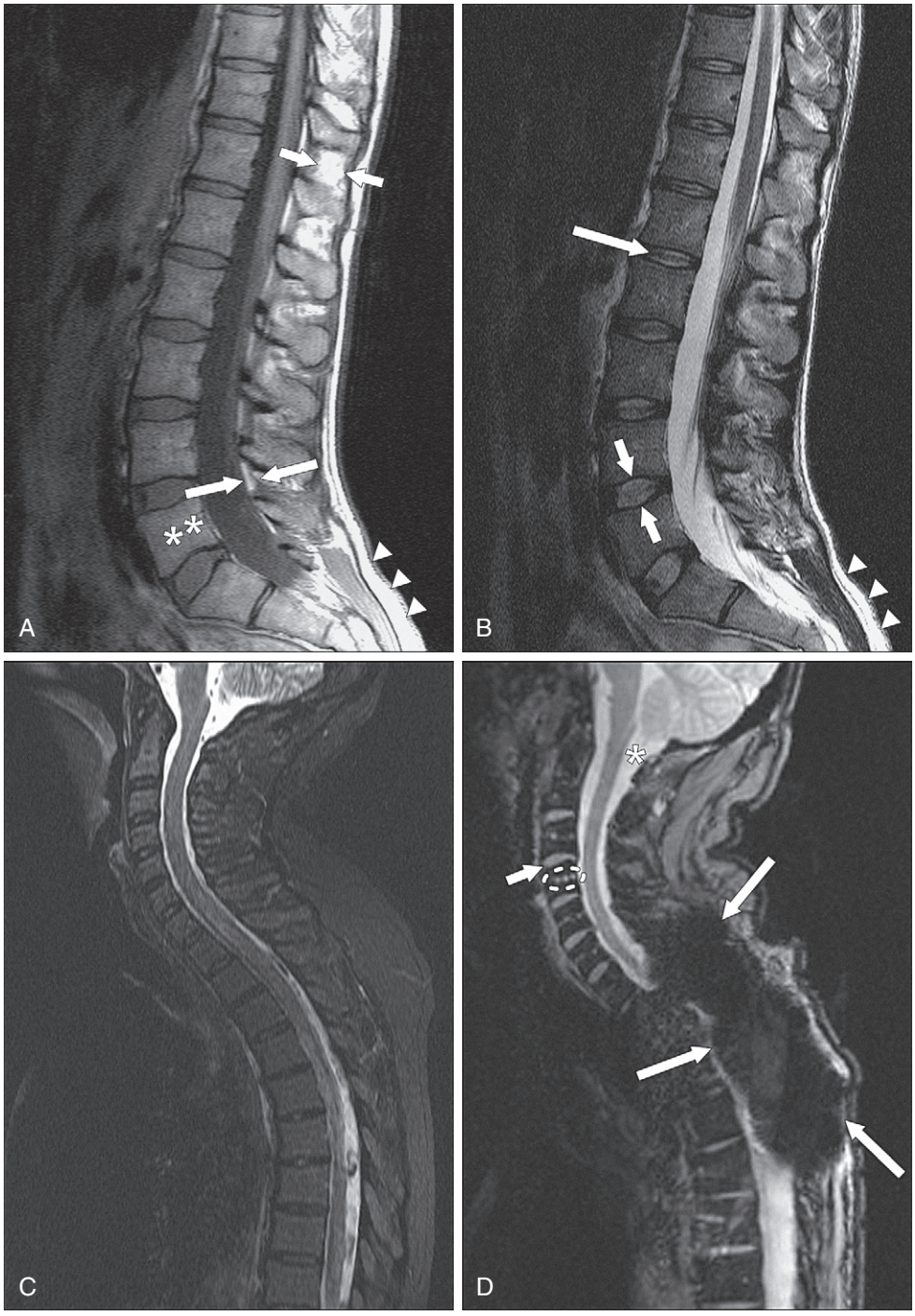

FIGURE 9-20 **A,** T1-weighted sagittal image through the lumbar spine. Fat is hyperintense on T1 images and is seen in the subcutaneous soft tissues (*arrowheads*), interspinous regions (*short arrows*), epidural space (long arrows), and bone marrow (asterisks). The intervertebral discs are mildly hypointense relative to the vertebral marrow. The CSF is hypointense relative to all but cortical bone. **B,** T2-weighted sagittal image. In this sequence, the CSF is the most hyperintense (*white*) structure. Fat remains hyperintense (*arrowheads*) but is less bright than on the T1-weighted sequence. Note the high signal intensity within the intervertebral discs indicating normal disc hydration (*short arrows*). A small, normal hypointense intranuclear cleft is visible in many discs including at L1–L2. **C,** The STIR sequence is a T2-weighted sequence with a fat-suppression technique. The CSF remains hyperintense but the fat has "dropped out" and is now hypointense. Edema is easily depicted in the vertebral bodies or soft tissues using this sequence. **D,** The GRE sequence is a fast T2-weighted sequence that is particularly susceptible to inhomogenities in the magnetic field as are produced by blood, calcium, and metal. In this image the discs (*short arrow*), CSF (*asterisk*), and basivertebral plexi (*dashed oval*) are hyperintense whereas the bone and fascial planes are hypointense. Blooming (*long arrows*) is seen dorsal to C7–T5 due to metallic surgical hardware.

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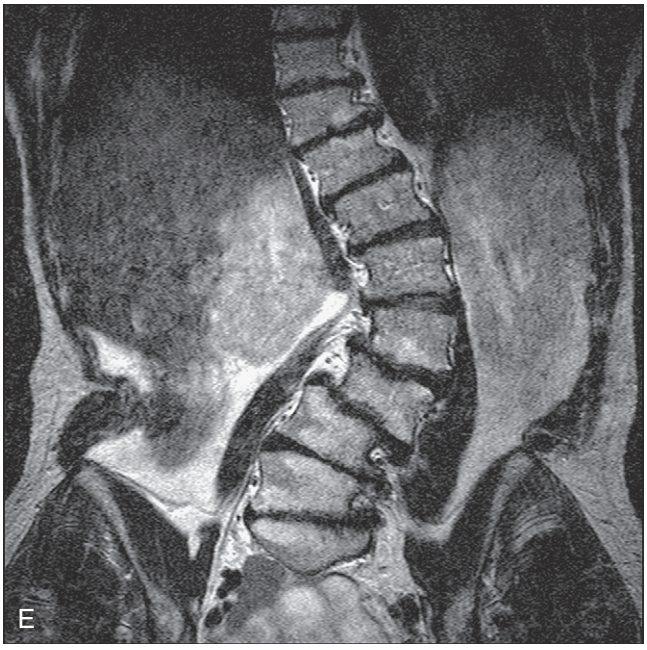

FIGURE 9-20 cont'd E, Any coronal acquisition, in this case a T2-weighted image, will help the interpreter understand the curves involved in kyphoscoliosis.

central canal and intervertebral foraminal stenosis. The degree of stenosis produced by osteophytes may be exaggerated on the GRE T2 sequence because of the sensitivity to susceptibility artifacts. Proton density (intermediate T2) and T2-weighted axial images are used in the lumbar region. Whether using a GRE T2 axial image in the cervical spine or a spin echo T2-weighted axial image in the thoracic or lumbar spine, the effect is the same: a "myelographic" effect is produced with hyperintense CSF within the thecal sac surrounding the intermediate signal intensity of the spinal cord and nerve roots (Fig. 9-21).

When evaluating for infection, multiple sclerosis, intramedullary neoplasm, metastatic disease, or postoperative scarring, sagittal and axial T1-weighted images prior to and following the intravenous administration of gadolinium contrast material are indicated. The addition of fat-suppression techniques can further highlight areas of pathologic enhancement, especially in the bone marrow. The combination of contrast administration and fat suppression will increase diagnostic sensitivity in cases of osteomyelitis/discitis, epidural abscess or tumor, meningitis, leptomeningeal carcinomatosis, and perineural scarring (Fig. 9-22).

Unfortunately, some patients cannot be examined using MRI. The most common problem encountered is claustrophobia. This is often overcome by light/moderate sedation, but sometimes requires the services of an anesthesiologist. Another alternative is the "open-magnet" MRI systems, but the trade-off is lower field strength and therefore poorer spatial resolution, less signal-to-noise, and fewer sequence options.[34] Strict contraindications for MRI relate to the very strong magnetic field required for imaging. Patients with cardiac pacemakers, metallic foreign bodies, and specific metallic surgical implants cannot be evaluated using MRI. Cardiac pacemakers may be disabled or reprogrammed or their leads repositioned by the magnetic field. Metallic foreign bodies or surgical implants, such as cerebral aneurysm clips and heart valves, may be displaced by the magnetic field with catastrophic outcomes. Comprehensive references are available to

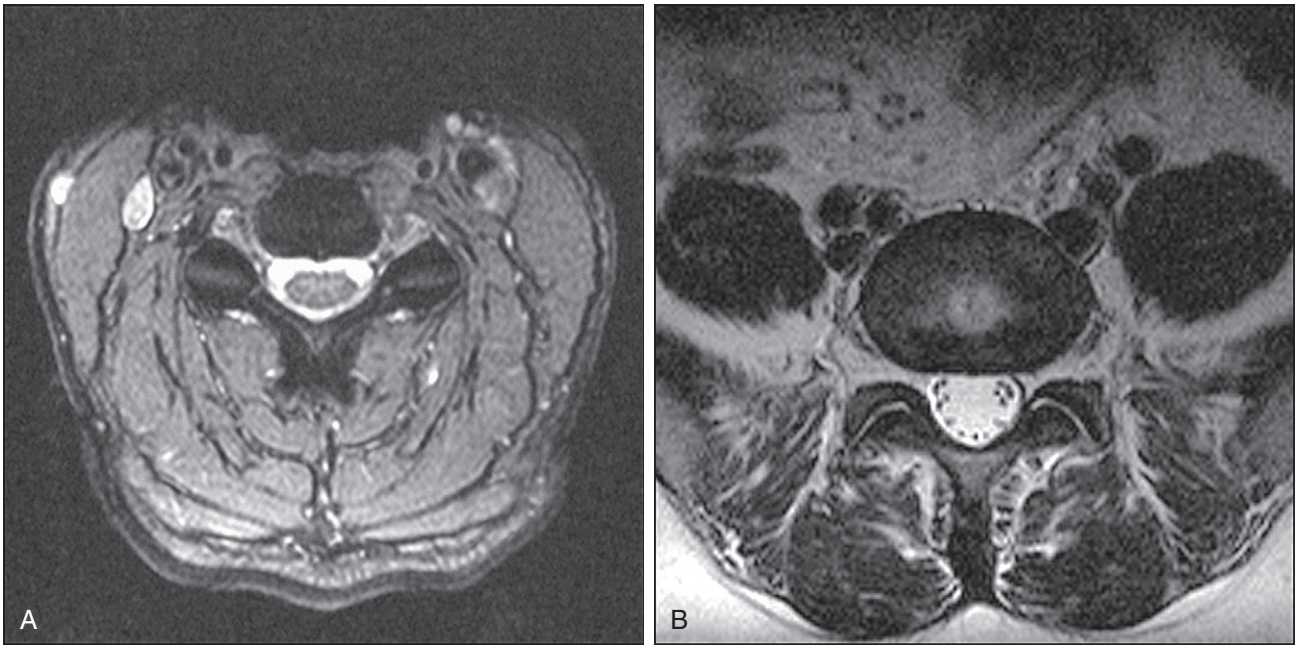

FIGURE 9-21 A, In the cervical spine, the "myelographic effect" is achieved with a T2-weighted GRE sequence. This sequence is less susceptible to pulsation artifact but very sensitive to susceptibility artifact. The latter property can lead to overestimation of foraminal or canal stenosis from osteophytes. **B,** In the lumbar spine, CSF pulsation is dampened and typically not an issue. A conventional or fast spin echo T2-weighted technique is used to achieve the "myelographic effect."

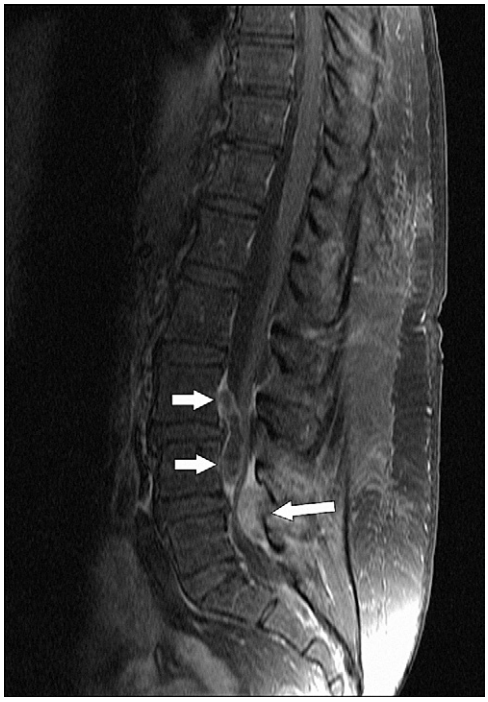

FIGURE 9-22 Sagittal postgadolinium T1-weighted fat saturated image. Inflammatory processes are easily identified such as the large ventral (*short arrows*) and dorsal (*long arrow*) epidural abscess seen here.

determine which implants are safe to be placed into the magnetic field.[35] Metallic implants may also create severe artifact and distort the images significantly, rendering them nondiagnostic.

DEGENERATIVE DISC DISEASE

OVERVIEW

Discogenic pain refers to back pain arising from the disc itself. Degenerative disc disease is a pathologic process, not entirely related to aging, of uncertain etiology that may cause acute or chronic low back pain.[36,37] The conventional radiographic findings in degenerative disc disease include disc space narrowing, vacuum disc, end plate sclerosis, and osteophyte formation (Fig. 9-23A).[38,39] CT scans will identify these same changes but earlier in the course of degeneration (Fig. 9-23B). Due to its excellent soft tissue contrast and multiplanar capabilities, MRI is the modality of choice to evaluate disc degeneration and much effort has been placed into correlating MRI findings with potentially symptomatic levels. In the right hands, a provocative test, discography, can be used to correlate clinical symptoms with the MRI appearance. Although each finding of degenerative disc disease will be discussed separately, the imaging findings are most often seen together when degenerative disc disease is present.

DISC DEHYDRATION AND NARROWING

With T1 weighting, the distinction between hydrated and nonhydrated disc is unapparent and therefore the disc appears homogeneous (Fig. 9-24A). The water content of the intervertebral disc is responsible for the bright signal on T2-weighted MRI (Fig. 9-24B).[40] The tightly packed annular fibers represent the dark T2 signal surrounding the centrally bright nucleus pulposus. Disc hydration, and therefore T2 disc signal, normally decreases with age, but should remain brighter than the signal of bone marrow on T2-weighted sequences. The pathologic process of degenerative disease results in accelerated disc desiccation, which results in a more significant decrease in disc signal, the most severe end of the spectrum of which is complete loss of the signal (Fig. 9-23B–D). Degenerated discs occasionally demonstrate an accumulation of intradiscal gas (nitrogen) that can be detected on plain film, CT, and MRI.[41] On MRI, this "vacuum disc phenomenon" is typically hypointense on T1- and T2-weighted sequences due to lack of protons. Inexplicably, vacuum discs occasionally fill with fluid and can demonstrate high signal intensity on T2-weighted sequences.

Disc height is interpreted relative to other intervertebral levels in the same patient. Individual disc heights can be categorized as either normal or as mildly, moderately, or severely diminished based on percentage loss of disc height compared to a normal level. In a study comparing the disc heights of young versus middle-aged men, it was found that young, healthy men had narrower disc heights compared with middle-aged men.[42] Taken alone, therefore, disc height is not used as an indicator of disc degeneration. The main importance of loss of disc space height is the concomitant decrease in size of the intervertebral foramina and the related potential for nerve root compression.

ANNULAR FISSURE/TEARS

In 1992 Aprill and Bogduk reported a high intensity zone within the midline posterior annulus, discontinuous with the central high signal nucleus pulposus, as a strong predictor of positive discography in patients with low back pain.[43] The linear hyperintense signal on T2-weighted images in the posterior or posterolateral disc represents radial and concentric fissuring of the annular fibers extending from the nucleus to the outer one-third of the annulus.[44] An element of inflammation (granulation tissue) is also thought to contribute to the high intensity zone based on enhancement on postcontrast T1-weighted images. Annular degeneration can be divided into three types including concentric fissuring, transverse tears, and radial tears.[45] Concentric fissuring occurs due to collagen fiber delamination of the annulus fibrosis with deposition of mucoid material.[45,46] This fissuring is high-signal intensity on T2-weighted sequences and parallels the margins of the disc (Fig. 9-25). Transverse tears are small foci of T2 hyperintensity at the junction of Sharpey's fibers with the vertebral body ring apophyses.[45,46] Both concentric fissuring and transverse tears may imply disc degeneration but are not generally symptomatic. Radial tears are full-thickness disruptions of the annulus and represent primary failure of the annulus (Fig. 9-26).[46] The lateral and posterior margins of the outer third of the annulus fibrosis and the PLL are richly innervated by nociceptive nerve endings and therefore disruption is felt to be a source of discogenic back pain.[47] It is this particular feature that supports the notion that radial tears can produce pain, whereas transverse tears and concentric fissures should not.

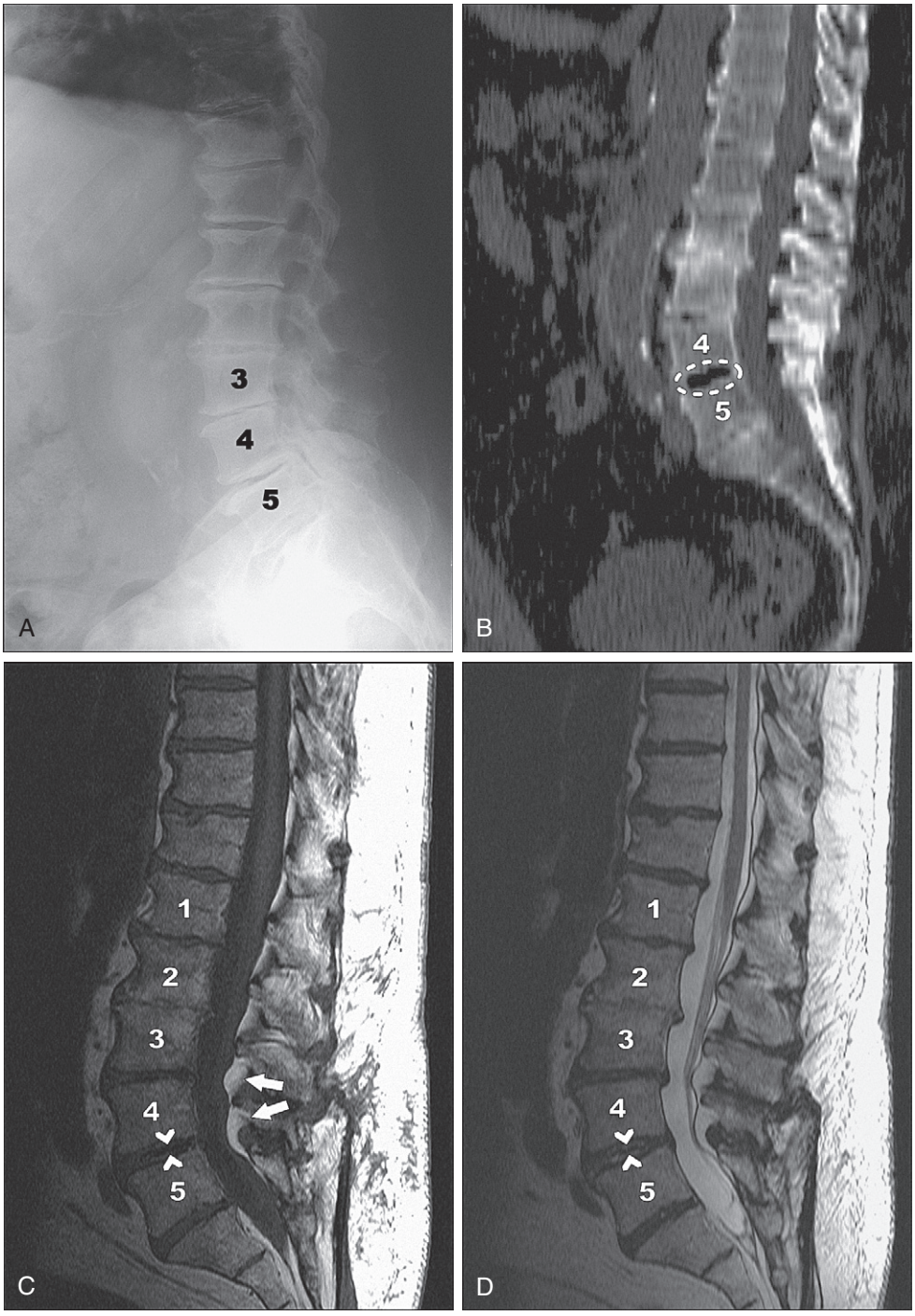

FIGURE 9-23 **A,** The conventional radiographic findings of disc degenerative changes are seen here including loss of disc space height, vacuum disc phenomenon, end plate sclerosis, and osteophyte formation. **B,** This sagittal reconstruction from an abdominal CT scan easily depicts the same changes. A vacuum disc is particularly well seen at L4–L5 (*dashed oval*). **C,** Sagittal T1-weighted image in the same patient shows classic degenerative changes. The vacuum disc at L4–L5 is hypointense (*arrowheads*). The dorsal epidural space (*short arrows*) behind L3–L4 and L4–L5 is large and would be an easy target for epidural steroid injections. **D,** This T2-weighted image shows diffuse disc dessication and complete loss of disc space height at L2–L3. Multiple disc bulges are seen indenting the ventral subarachnoid space at all levels except L5–S1. The linear hypointense signal representing the vacuum disc (*arrowheads*) at L4–L5 is smaller than would be predicted by the CT image.

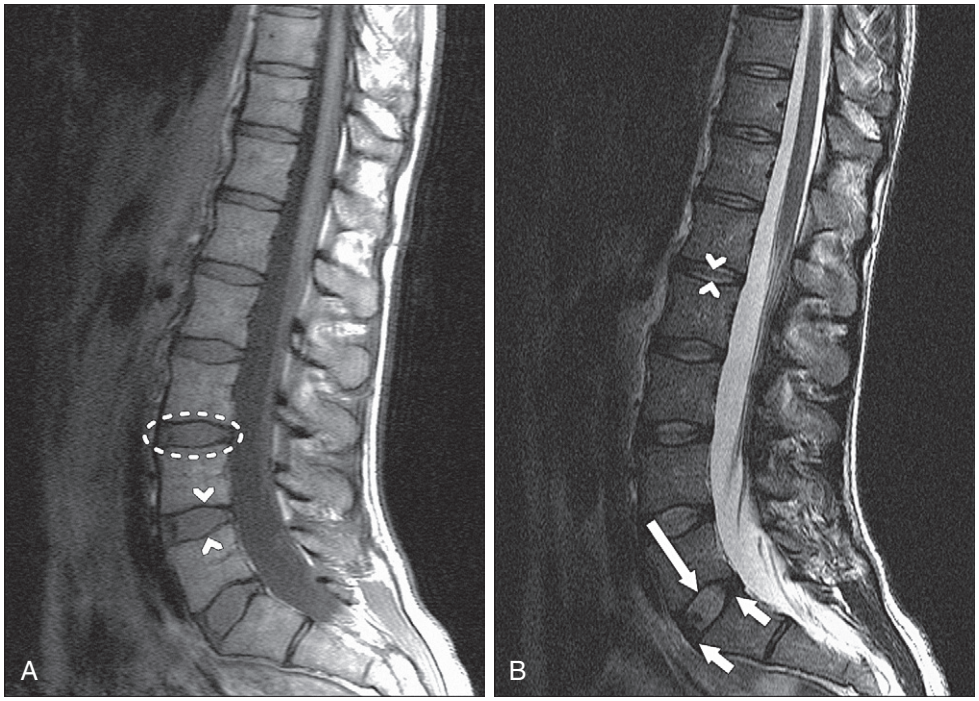

FIGURE 9-24 **A,** On T1-weighted images, the normal intervertebral disc is homogeneously isointense (*dashed oval*). The black signal outlining the superior and inferior margins of the disc (*arrowheads*) represents the cortex of the adjacent vertebral bodies. **B,** In this T2-weighted image, the tightly packed annular fibers are hypointense (*short arrows*). The hydrated nucleus (*long arrow*) is hyperintense except for the central linear intranuclear cleft (*arrowheads*). This intranuclear cleft is a normal finding and should not be misinterpreted as focal desiccation.

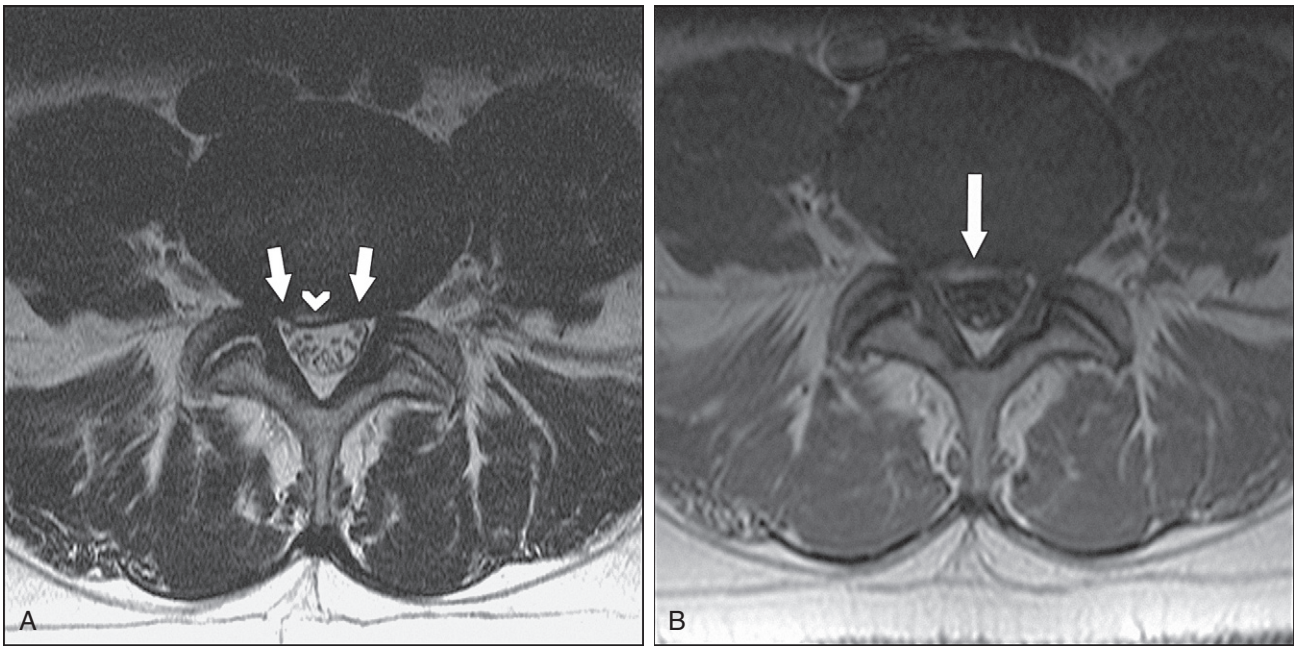

FIGURE 9-25 **A,** Axial T2-weighted image through the L4–5 level. There is a right paracentral protrusion (*short arrows*) that indents the ventral thecal sac. Linear hyperintense signal in the central dorsal annulus (*arrowhead*) parallels the disc margin and represents mucoid deposition within a concentric fissure or tear. **B,** On postgadolinium T1-weighted imaging, annular tears of any type can enhance (*arrow*) as in this case. Enhancement implies nothing other than the likely presence of a reparative process such as granulation tissue.

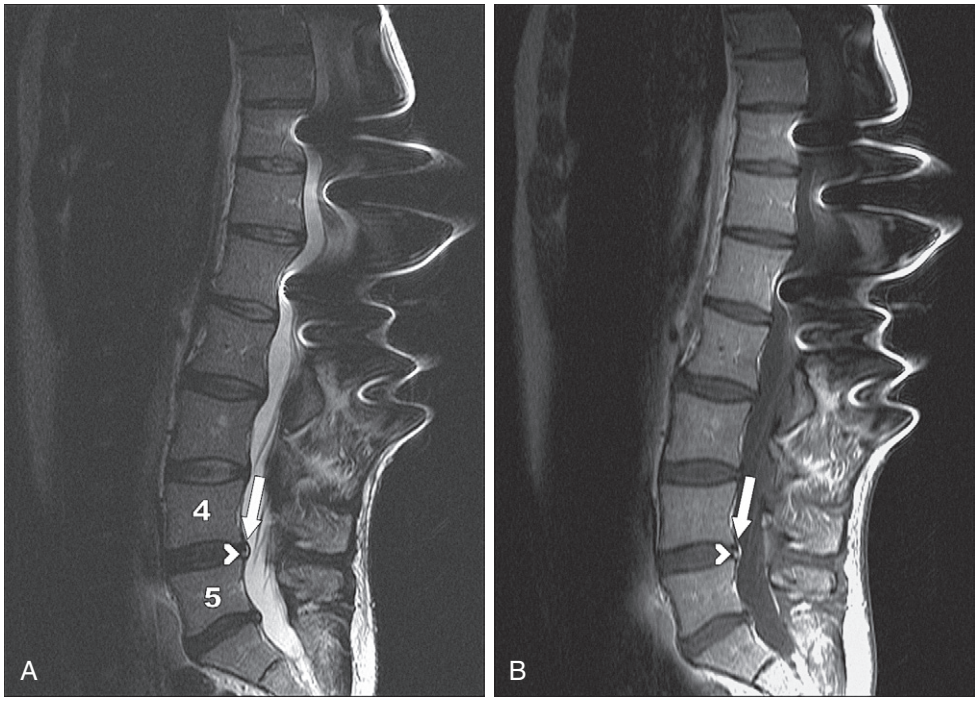

FIGURE 9-26 **A** and **B,** At the L4–5 level, a dorsal concentric annular fissure/tear (*arrow*) and a radial tear (*arrowhead*) are identified. Both of these tears enhance on the postgadolinium T1-weighted sagittal image.

SUBCHONDRAL MARROW CHANGES

Degenerative disease in the vertebral end plates, referred to as Modic-type changes, are classified into three types based on signal characteristics of T1- and T2-weighted signal characteristics.[48] Type I changes refer to low signal in the vertebral end plates on T1- and increased signal on T2-weighted images, representing vascularized marrow (Fig. 9-27A, B). Enhancement of Modic changes, particularly Type I, is not uncommon (Fig. 9-27C).

Type II changes show increased signal intensity on T1- and increased signal or isointensity on T2-weighted images, representing fatty replacement of the bone marrow (Fig. 9-28). Type III changes consist of low signal on both T1- and T2-weighted sequences due to subchondral sclerosis (Fig. 9-29).

It has been suggested that subchondral marrow changes represent chemical inflammation in the vertebral end plates that is a reaction to the diffusion of toxic substances from a degenerated disc.[49,50] Modic changes, therefore, could be a secondary sign of discogenic low back pain. Although Braithwaite et al. found subchondral marrow changes to be very specific, low sensitivity limits the value of Modic changes in detecting the source of a patient's low back pain.[51] One investigator found no relationship between Modic changes and provocative discography.[52]

DISC HERNIATION

OVERVIEW

In an attempt to standardize the reporting of normal and pathologic conditions of the lumbar spine, the North American Spine Society (NASS), the American Society of Neuroradiology (ASNR), and the American Society of Spine Radiology (ASSR) put their efforts together and created recommendations that provide a common nomenclature to promote uniform descriptions of pathological processes affecting the discs.[53]

Due to its superior soft tissue resolution, MRI is the imaging modality of choice to evaluate disc herniations. CT is also useful, but is typically relegated to use as a secondary study either to better delineate bony abnormalities or for patients who cannot undergo or tolerate an MRI examination. CT myelography can be added when contraindications preclude the use of MRI and plain CT is inadequate to define the clinical problem.

DISC CONTOUR

Disc herniation has been defined as a localized displacement of disc material beyond the limits of the intervertebral disc space. A "circumferential bulge" describes disc material bulging out beyond 50% to 100% of the edges of the vertebral body's ring apophysis and is not considered a disc herniation. Localized herniated disc material, that is, disc extending beyond the end plate margin less than 50% of the disc circumference, can be termed "focal" (less than 25%) or "broad-based" (25% to 50%). A focal disc herniation can also occur into adjacent vertebral end plates, commonly referred to as a Schmorl's node (Fig. 9-30).

The terms "protrusion" and "extrusion" describe disc herniations based on the shape of the herniated disc fragment and its relationship to the parent disc margin. A protrusion describes a localized disc herniation that has its base wider than the furthest extent of the apex of

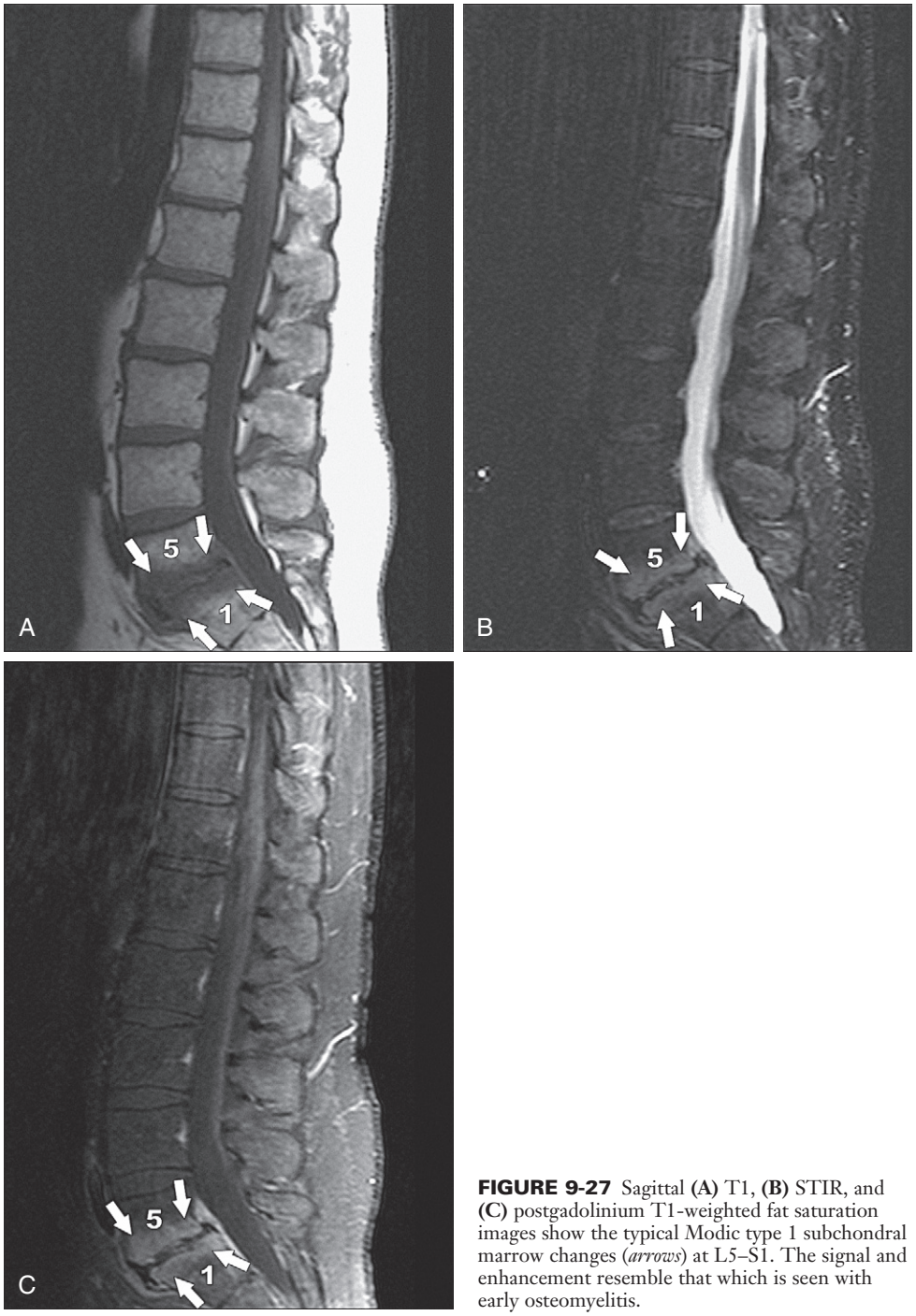

FIGURE 9-27 Sagittal **(A)** T1, **(B)** STIR, and **(C)** postgadolinium T1-weighted fat saturation images show the typical Modic type 1 subchondral marrow changes (*arrows*) at L5–S1. The signal and enhancement resemble that which is seen with early osteomyelitis.

herniated disc material (Fig. 9-31A). An extruded disc is defined by the presence of a herniated disc, where the diameter of the disc fragment from base to apex is wider than the width of the fragment at the base (Fig. 9-31B). A sequestered or free-fragment disc herniation is disc material that has completely separated from the parent disc. Describing disc herniations using these terms is not meant to imply any significance regarding symptom production or the best method of treatment.

Disc migration in the cranial or caudal directions is best evaluated in the sagittal plane. A posterior disc extrusion may be contained by the posterior longitudinal ligament and migrate inferiorly or less commonly, superiorly. Such extrusions may appear on axial imaging as a protrusion but are easily identified as a migrated extrusion on sagittal imaging. Measurements are taken from the posterior margin of the superior or inferior end plate of the vertebral body, to describe the extent of migration for the surgeon. Migrated fragments are usually paramedian, since the attachment of the posterior longitudinal ligament to the posterior vertebral body at midline tends to direct the fragment unilaterally.

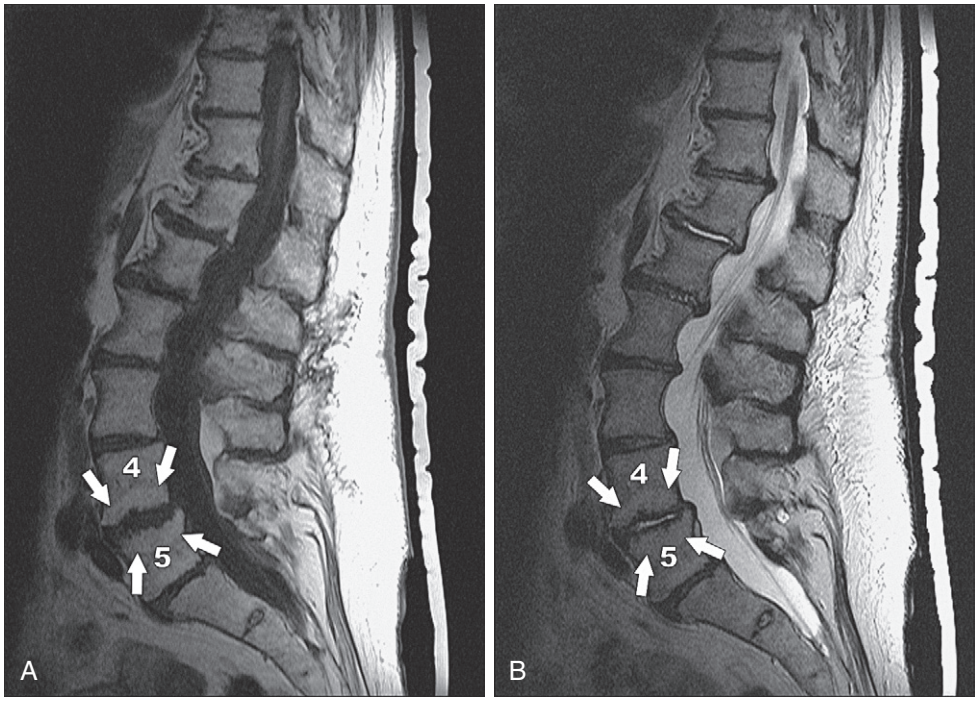

FIGURE 9-28 Sagittal **(A)** T1- and **(B)** T2-weighted images show classic Modic type 2 changes at L4–L5. The hyperintense end plate signal (*arrows*) on both sequences represents focal fatty replacement of bone marrow.

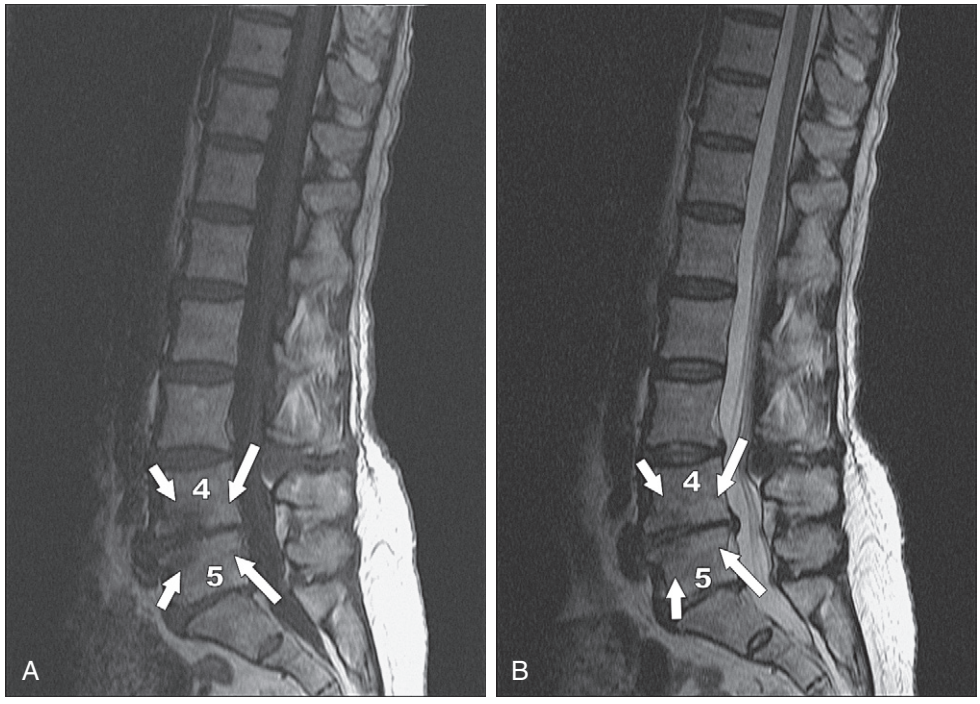

FIGURE 9-29 Sagittal **(A)** T1- and **(B)** T2-weighted images show Modic type 3 changes (*short arrows*) along the ventral half of the L4–L5 end plates. Interestingly, Modic type 2 changes (*long arrows*) are present at the same level along the dorsal margin of the end plates.

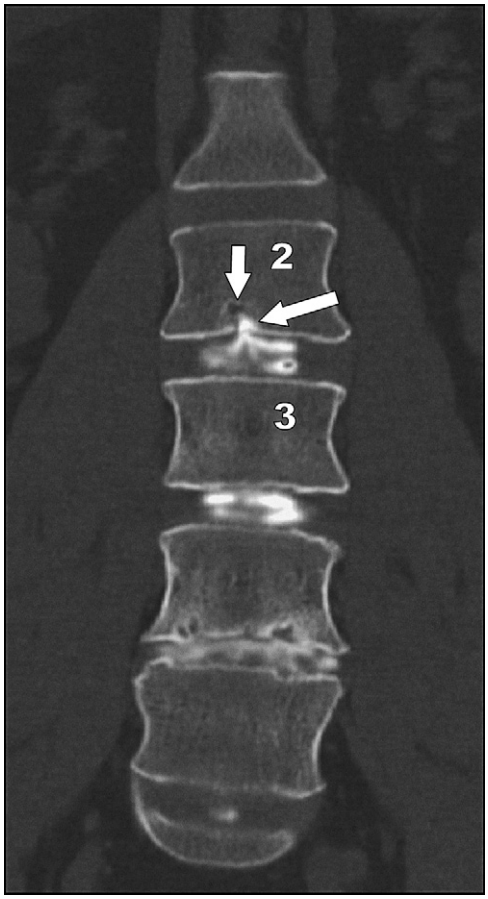

FIGURE 9-30 CT coronal reconstruction after lumbar discography from L2 to L5. There is a Schmorl's node extending through the inferior end plate of L2. A sclerotic margin (*short arrow*) is present. Contrast (*long arrow*) from the L2–L3 discogram is seen extending into the Schmorl's node (intervertebral disc herniation).

DISC HERNIATION POSITION

Using anatomic landmarks to describe the location of a disc herniation provides a precise and consistent classification.[54] An axial image at the level of the disc has four "zones" based on arbitrary sagittal and parasagittal lines drawn through specific anatomic landmarks. The term "central" means the posterior midline aspect of the disc, between the medial aspects of the articular facets. Right and left paracentral/paramedian descriptors can be added if the disc favors one side or the other. The "subarticular" zone is between the medial aspect of the articular process and the medial aspect of the ipsilateral pedicle. The "foraminal" zone is between the parasagittal planes defined by the medial and lateral aspects of the pedicle. Finally, the "extraforaminal" zone is beyond the parasagittal line of the lateral aspect of the pedicle.

Of note, the term "lateral recess" describes the area along the medial border of the pedicle, below the level of the disc and the superior vertebral end plate, and is a part of but does not describe the entire subarticular zone (Fig. 9-32). Strictly speaking, disc herniations that protrude directly posteriorly are not in the lateral recess and can only reach the lateral recess by traveling superiorly or inferiorly from the disc. For example, an L3–L4 disc extrusion that projects inferiorly would enter the lateral recess of L4 and encroach on the L4 nerve root as it descends beneath the L4 pedicle.

On sagittal images, the position of a herniated disc in the craniocaudal direction can be separated into levels based on anatomic landmarks. The suprapedicular level extends from just above the pedicle to the superior end plate. The pedicle level is defined by the superior and inferior edges of the pedicle. The infrapedicular level

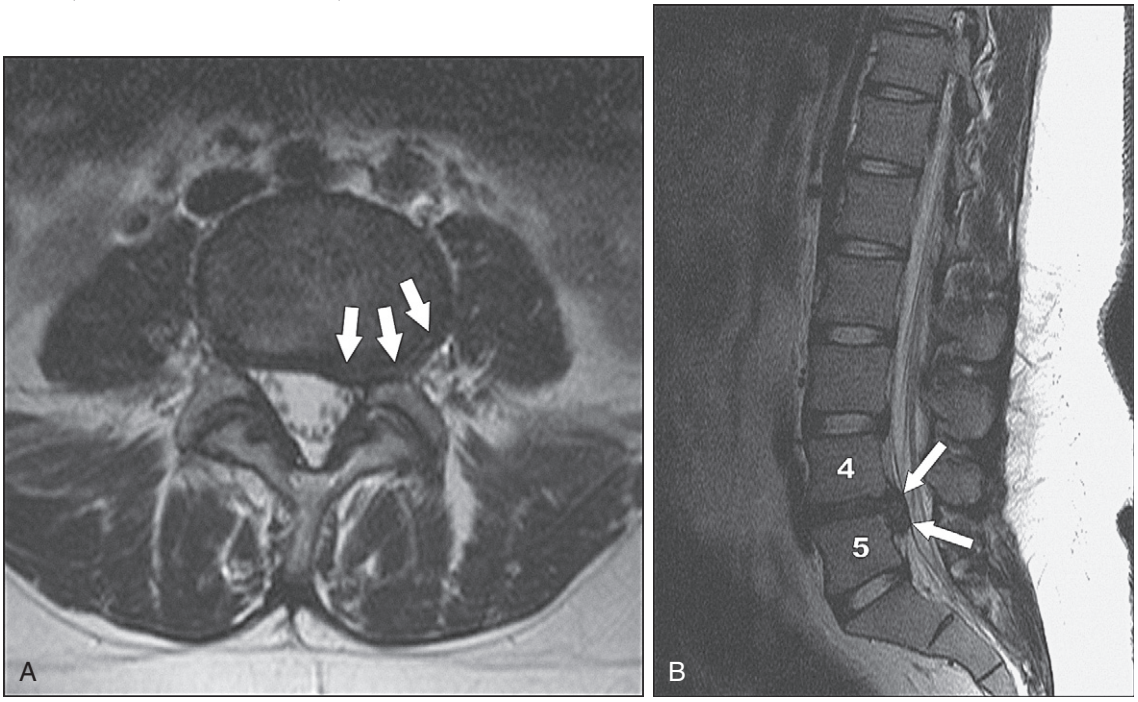

FIGURE 9-31 **A,** Axial T2-weighted MRI demonstrating a broad-based left parasagittal, foraminal, and far lateral herniation (*arrows*). This morphology is consistent with a disc protrusion. **B,** Parasagittal T2-weighted MRI shows a large disc extrusion (*arrows*) at the L4–L5 level. Disc material elevates the PLL and has migrated 6 mm caudal to the parent disc.

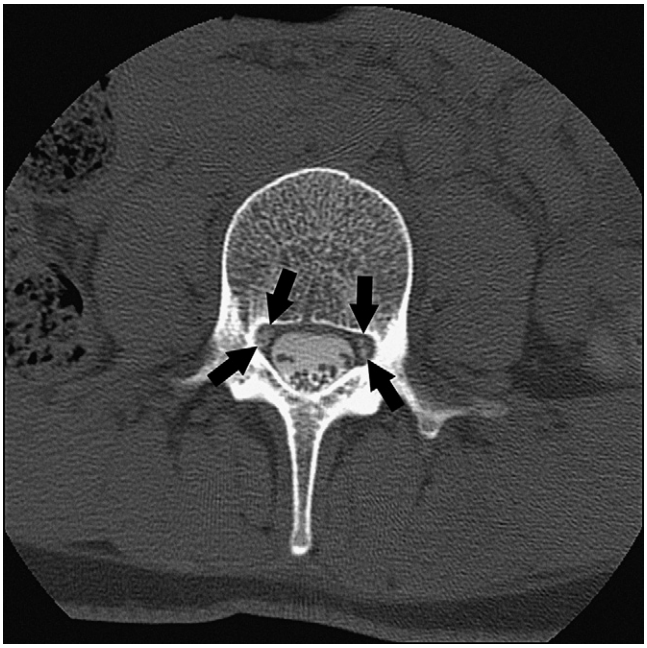

FIGURE 9-32 Axial CT myelogram image in the mid-lumbar spine. The lateral recesses (*arrows*) reside just medial to the medial margin of each pedicle and contain the exiting nerve roots. In this image, the exiting nerve root sleeves are opacified with contrast.

extends from below the inferior edge of the pedicle to the inferior end plate.

Depending on the position of a herniated disc, it can potentially compress adjacent nerve roots. In the cervical spine, a central or paramedian disc herniation will affect the descending nerve roots and not the exiting nerve root at that level. For instance, a right paramedian small disc extrusion at C3–C4 will most likely compress the descending right C5 nerve root. A foraminal disc abnormality will affect the exiting nerve root at that level. For instance, a right foraminal disc extrusion at C3–C4 will likely compress the right C4 nerve root. In the thoracic and lumbar spine, the nerve roots are numbered differently (exiting root is associated with superior level). A right paramedian disc extrusion at T3–T4 or L3–L4 would likely affect the descending right T4 or right L4 nerve roots, respectively. A right foraminal disc extrusion at T3–T4 or L3–L4 would compress the exiting right T3 or L4 nerve roots.

The degree of neural compression can be graded based on the change in the normal round or oval configuration of the spinal cord, nerve root, or root ganglion produced by the herniated disc. Mild compression is defined as 75% to 99% of the normal diameter of the structure being maintained. Similarly, moderate and severe compression is described as 50% to 74% and <50% of the normal diameter, respectively.

FACET JOINT

OVERVIEW

The facet joint is another potential source of low back pain. Considering the numerous potential causes of low back pain, it can be difficult to isolate the facet joint clinically or by imaging as the primary cause of a patient's pain. Facet joint syndrome is a controversial diagnosis referring to focal or referred pain arising from or anatomically correlating with a degenerated facet joint.[55,56]

IMAGING

Facet joint arthropathy includes hypertrophic osteophytic overgrowth, subchondral sclerosis, bone marrow edema, joint space narrowing/widening, joint effusions, and periarticular soft tissue edema.[57] Osteophytosis and subchondral sclerosis are hypointense on T1- and T2-weighted imaging. Bone marrow and periarticular soft tissue edema are hypointense on T1- but hyperintense on T2-weighted sequences (Fig. 9-33A, B). A fat-suppressed T2-weighted sequence is particularly sensitive at detecting marrow or soft tissue edema. The joint space can narrow or, if instability and abnormal motion occur, widen. A small amount of synovial fluid exists in the joint space but effusions are commonly seen, particularly in widened facet joints (Fig. 9-33C). Facet joint arthropathy can result in pain secondary to the intrinsic abnormalities of the bone and joint or can result in extrinsic compression of descending nerve roots in the lateral recess or exiting nerve roots in the intervertebral foramen. Facet joint osteoarthritis can be accurately diagnosed by CT scanning, although the ability to detect bone marrow or periarticular edema is limited. In the cervical spine, subtle sclerotic changes and osteophytes are easily detected on CT, whereas on MRI the changes are either more difficult to detect or are overestimated, particularly on the GRE sequence images. Plain films can detect some facet degenerative changes including sclerosis and hypertrophic overgrowth but are generally the least-sensitive modality.

INTRASPINAL FACET CYSTS

OVERVIEW

Intraspinal facet cysts are fluid-filled, rounded structures with a smooth border that originate from the facet joint. Facet joint arthritic changes and spinal instability are thought to lead to protrusion of articular tissue forming an adjacent cyst.[58,59] The lining of a cyst may contain synovial epithelial cells (synovial cyst) or a fibrous wall surrounding myxoid material (ganglion cyst).[60] Radiologically, both types of cysts appear identical. Treatment and prognosis of synovial and ganglion cysts are the same (decompression) and distinguishing between them is not clinically important. It has been postulated that ganglion cysts represent synovial cysts that have undergone degeneration and lost their communication with the facet joint.[61] For simplicity, the following discussion will refer to all facet-related cysts as synovial cysts.

Synovial cysts are almost invariably discovered adjacent to a degenerated facet joint. They can arise off the dorsal surface of the joint, protruding into the soft tissues but not compressing any neural structures. These cysts can also arise off the ventral surface and protrude into the intervertebral foramen, lateral recess, or lateral spinal canal. Depending on the location, a synovial cyst can compress an exiting nerve root (in the foramen) or a descending nerve root (in the

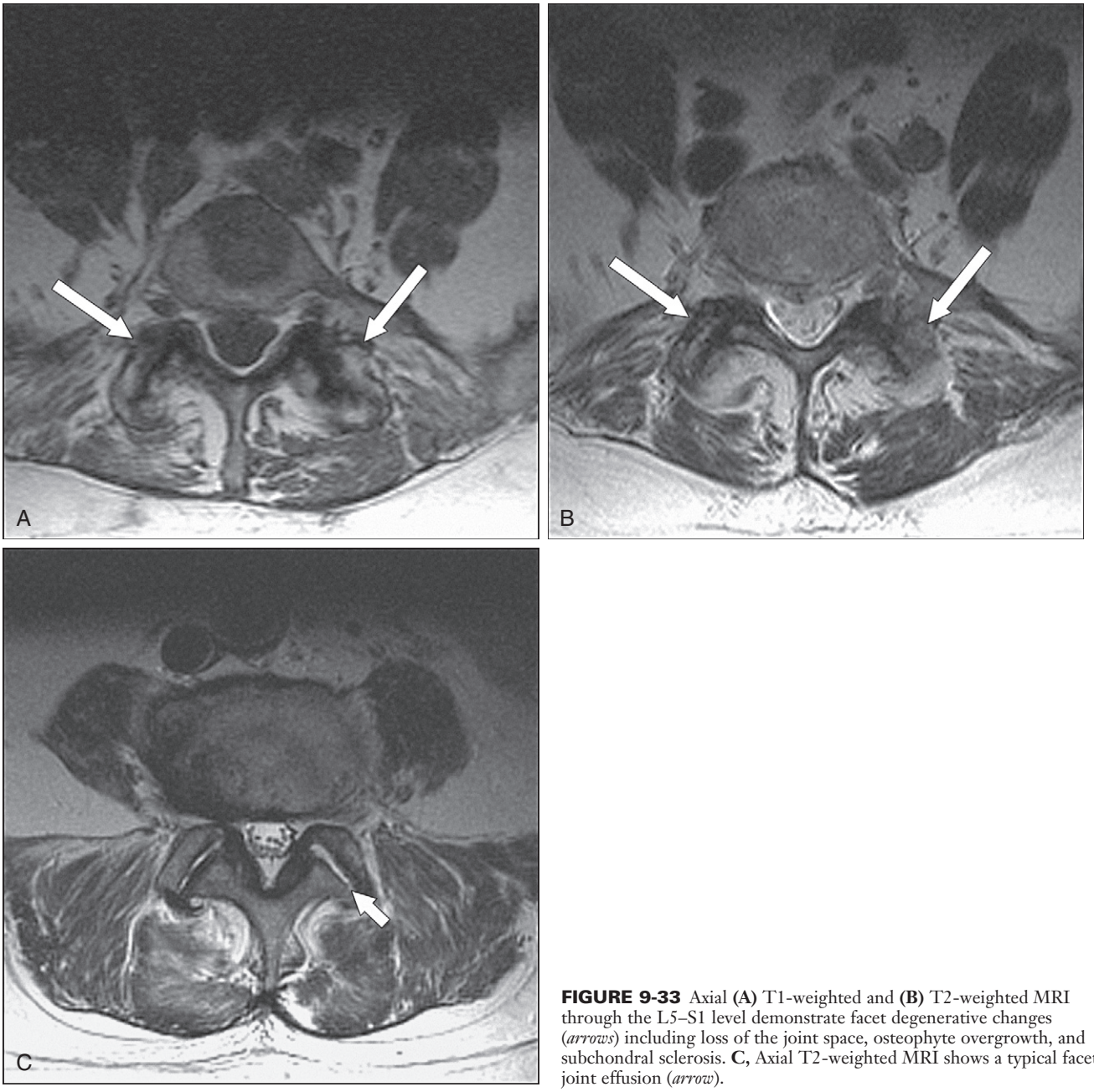

FIGURE 9-33 Axial **(A)** T1-weighted and **(B)** T2-weighted MRI through the L5–S1 level demonstrate facet degenerative changes (*arrows*) including loss of the joint space, osteophyte overgrowth, and subchondral sclerosis. **C,** Axial T2-weighted MRI shows a typical facet joint effusion (*arrow*).

lateral recess or lateral spinal canal). Synovial cysts can also be intrinsically painful because they are often lined with a nociceptive synovial lining.

IMAGING

On CT scan, an uncomplicated synovial cyst is isodense to CSF, located next to a degenerated facet joint and occasionally has a calcified wall (Fig. 9-34A, B).[62] Proteinaceous material or blood within the cyst may be isodense to the adjacent muscle or ligament. CT can also clearly demonstrate gas located within a juxta-articular cystic structure which, when present, almost always represents a synovial cyst. CT myelography may better demonstrate the degree of mass effect or stenosis related to an intraspinal or foraminal synovial cyst, by better defining the spinal subarachnoid space with contrast.

Typical MRI findings for synovial cysts include T1- and T2-prolongation and therefore generally follow CSF signal (Fig. 9-34C, D).[63] Some synovial cysts contain proteinaceous or hemorrhagic material and can also demonstrate T1 hyperintensity. Acute hemorrhage can cause a rapid increase in the size of the cyst and result in acute pain or radiculopathy. The wall of a synovial cyst is typically composed of tough fibrous material and it may be partially or completely calcified. The degree of calcification is

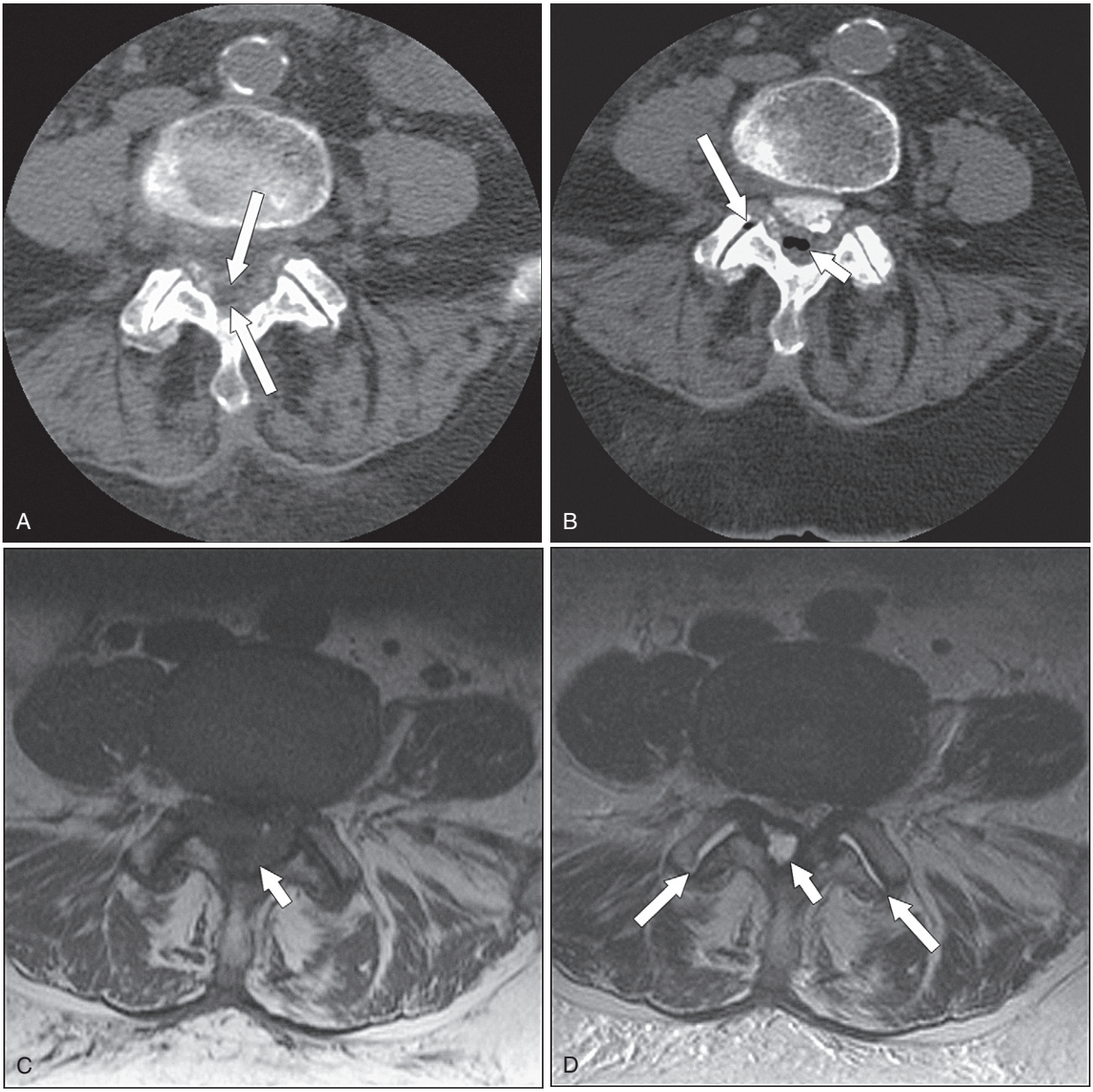

FIGURE 9-34 **A** and **B,** CT imaging of a synovial cyst. The axial noncontrast CT image A shows facet degenerative changes particularly on the patient's right. Ligamentum thickening and calcification are also present. Just deep to the right lamina and partially within the ligamentum flavum, the hypodense synovial cyst (*arrows*) is identified. The patient underwent myelography followed by percutaneous aspiration and steroid injection of the cyst. The postprocedure axial CT image B shows persistent mass effect by the partially calcified cyst. Note the presence of air in the cyst (*short arrow*) and the joint (*long arrow*), which was introduced through the injection and confirms communication between the degenerated facet and the synovial cyst. **C–E,** MRI imaging of a synovial cyst. On T1-weighted imaging **(C),** the cyst (arrow) is almost indistinguishable from ligamentum flavum thickening. The T2-weighted image **(D)** identifies hyperintense fluid within the synovial cyst (*short arrow*) and the joint spaces (*long arrows*), which is consistent with synovial fluid.

Continued

anecdotally predictive of the potential success of percutaneous decompression. Peripheral enhancement of a synovial cyst is common and should not be mistaken as an aggressive feature (Fig. 9-34E).

An important consideration in the differential diagnosis of a juxta-articular cyst is an extruded disc fragment. Recognizing that the lesion is juxta-articular, and is related to a degenerated facet joint, is the key to making the correct diagnosis. Alternatively, a short-term follow-up MRI might show resolution of a disc fragment, but no change in the case of a synovial cyst. Treatment options include conservative management, percutaneous decompression, or surgical removal. Successful outcomes have been reported with all approaches.[64,65]

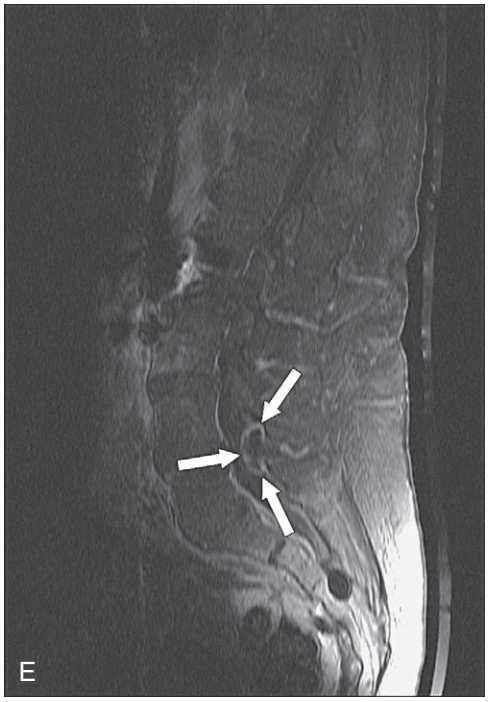

FIGURE 9-34 cont'd Peripheral enhancement (*arrows*) of the synovial cyst wall is common as is demonstrated in the parasagittal postgadolinium T1-weighted fat saturation image **(E)**.

SPINAL STENOSIS

OVERVIEW

CT effectively evaluates spinal stenosis caused by bony abnormalities of the vertebral column and can show a contributing component of a bulging or herniated disc. CT myelography requires a lumbar puncture, but has the added benefit of outlining nerve roots and the contour of the thecal sac particularly as it relates to disc abnormalities and hypertrophic ligaments.

MRI, using axial GRE T2 images in the cervical spine and conventional or fast spin echo T2-weighted images in the thoracic and lumbar spine, provides a noninvasive technique to evaluate the central canal and intervertebral foramen without significant artifact from CSF flow within the canal.

If surgical hardware is present, conventional T2-weighted images are used to minimize susceptibility artifact. In some circumstances, axial T1-weighted sequences can be helpful.

GRADING SPINAL STENOSIS

Although there are various methods to grade spinal stenosis, no single technique has proved reliable in predicting symptoms or favorable surgical outcome. Also, the reliability of grading the severity of lumbar spinal stenosis has been challenged.[66] Consequently, it is difficult to interpret studies examining the efficacy of treatment if there is disagreement on the grading of stenosis.

One grading scheme used by Renfrew in a large spinal imaging practice compares the AP dimension of an abnormal level to an adjacent normal level of the spinal canal in the same patient.[67] The inherent spinal canal diameter is also evaluated to take into account the possibility of a developmentally narrow canal.

Mild, moderate, and severe stenoses are assigned relative to the degree of narrowing (Fig. 9-35). Mild stenosis is defined as 75% to 99% maintenance of the AP dimension of the normal level, while moderate and severe are 50% to 74% and <50%, respectively. Using the AP dimension is not absolute, and stenosis can be up- or down-graded depending on the developmental size of the canal and the amount of space surrounding the nerve roots.

In a similar manner, the intervertebral foramen can be graded. The foramen is evaluated in the AP and craniocaudad dimension. Stenosis in the foramen can be described as craniocaudal, AP, or combined depending on the site of narrowing. Mild foraminal stenosis usually reflects some narrowing of the inferior part of the foramen by a disc bulge or hypertrophic superior articular process. Moderate narrowing implies loss of fat along a portion of the nerve root and some nerve root displacement. Severe foraminal stenosis is used when little to no fat is visible in the foramen and the nerve root is clearly displaced and/or compressed. These changes are most sensitively detected on a sagittal T1-weighted MRI sequence (Fig. 9-36).

SPONDYLOLYSIS AND SPONDYLOLISTHESIS

OVERVIEW

Spondylolysis refers to a discontinuity in the pars intraarticularis of the articular pillar. The etiology is uncertain but felt to be related to chronic microtrauma leading to a stress-type reaction or fracture, particularly in the lumbar spine.[68] Spondylolysis is usually bilateral, most commonly occurring in the lumbar spine at L5. Spondylolysis can occur in the cervical and thoracic spine, albeit rarely, and may be more related to a developmental abnormality as opposed to trauma in these locations (Fig. 9-37). When bilateral pars fractures are present, the vertebral body can slip forward. This is most apparent in the lumbar spine where axial loading and incompetent pars result in spondylolisthesis. Mild and moderate slips generally do not narrow, but paradoxically enlarge, the central canal. Severe spondylolisthesis elongates the spinal canal in the AP direction and narrows the spinal canal in the sagittal plane. All degrees of listhesis tend to result in foraminal stenosis and nerve root compression.

IMAGING

The test of choice to diagnose spondylolysis is CT. Sclerosis and fractures of the pars can be optimally depicted in any plane and the degree of osseous canal or foraminal narrowing can be assessed. MRI can show similar findings although the actual fracture can sometimes be elusive (Fig. 9-38A, B). MRI exquisitely demonstrates the foraminal stenosis and nerve root compression that are invariably present with spondylolysis and spondylolisthesis (Fig. 9-38C). MRI also demonstrates cartilaginous overgrowth in the area of the

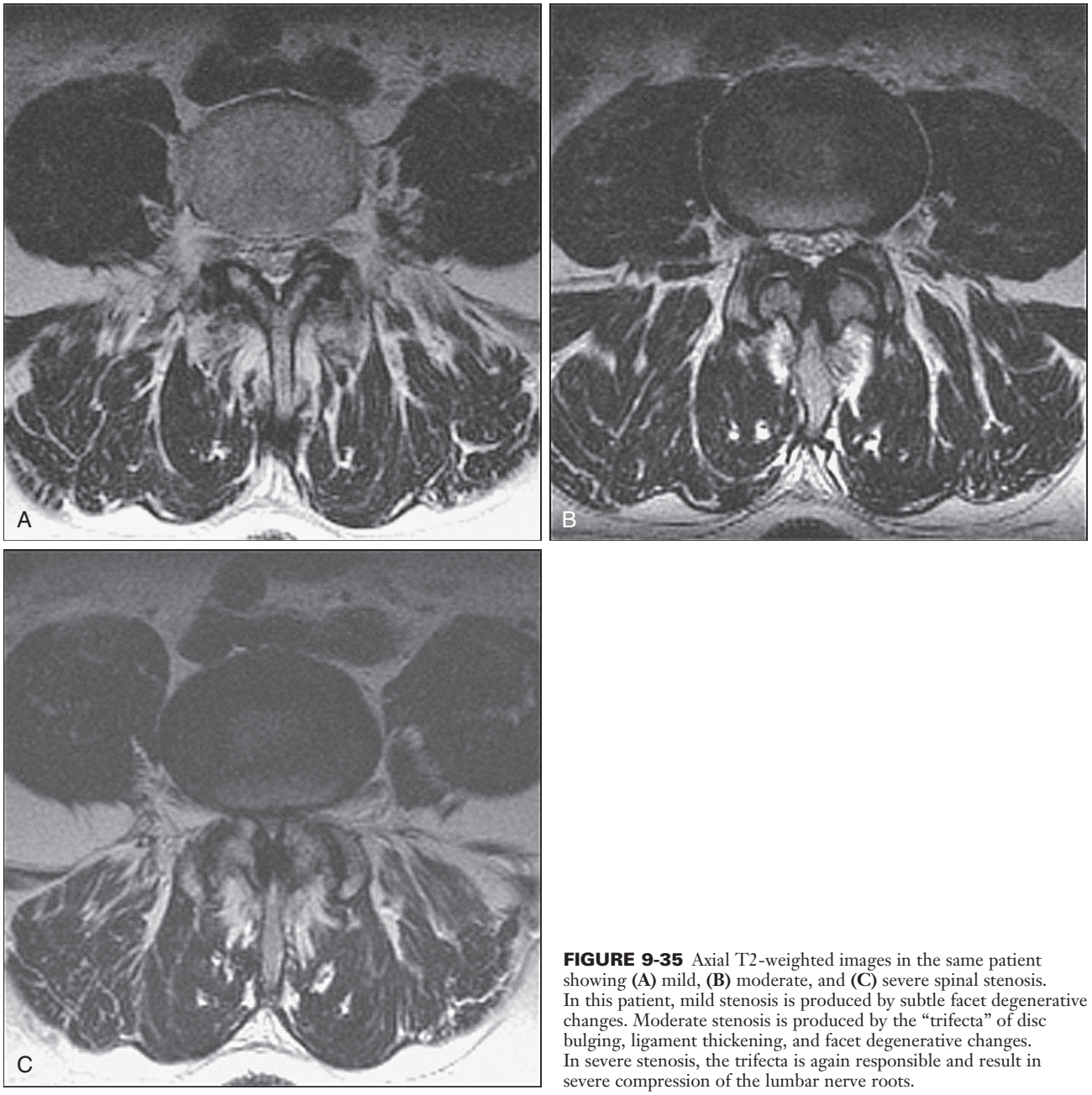

FIGURE 9-35 Axial T2-weighted images in the same patient showing **(A)** mild, **(B)** moderate, and **(C)** severe spinal stenosis. In this patient, mild stenosis is produced by subtle facet degenerative changes. Moderate stenosis is produced by the "trifecta" of disc bulging, ligament thickening, and facet degenerative changes. In severe stenosis, the trifecta is again responsible and result in severe compression of the lumbar nerve roots.

pars fracture that may also contribute to canal and foraminal stenosis. Plain films can easily depict the spondylolisthesis and can demonstrate the pars defect, particularly with an oblique projection. Plain films can be effectively employed to correlate bone detail with an MRI examination, although most imagers prefer CT.

OSTEOPOROTIC COMPRESSION FRACTURES

OVERVIEW

Osteoporotic compression fractures are a major cause of severe back pain in the elderly population, especially women. Benign osteoporotic compression fractures are not always related to a specific trauma and can present with acute onset debilitating back pain, significantly compromising mobility and quality of life. Most compression fractures occur in the mid-thoracic spine and upper lumbar spine, most often affecting the vertebral bodies with the most axial load. Bone pain is generated by irritation of the interosseous and periosteal nociceptive C-fibers, that occur as a result of mechanical deformity, altered axial loading, and inflammation.[69] The vertebral body height decreases, often along the anterior column with an anterior wedge appearance. Bone fragments from the superior or inferior end plates, can retropulse into the spinal canal causing spinal canal stenosis and sometimes spinal cord compression. The amount of decrease in vertebral body height varies from very mild, just along an end plate, to severe with almost complete loss of

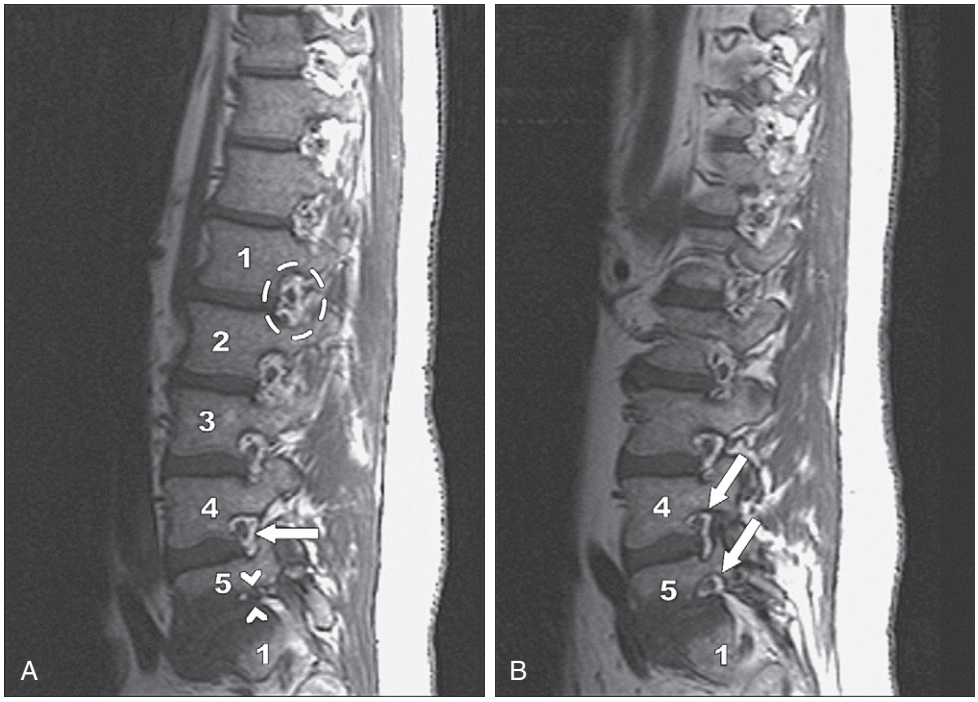

FIGURE 9-36 Parasagittal T1-weighted images show **(A)** mild and severe and **(B)** moderate foraminal stenosis. In **A,** mild stenosis is identified at L4–L5 (*arrow*) and severe stenosis at L5–S1. The severe stenosis is due to loss of disc space height, disc bulging, and osteophyte formation off the vertebral body and superior articular process and results in compression of the exiting nerve root (*arrowheads*). Note the normal appearance on the foramen at L1–L2 (*dashed oval*). In **B,** moderate stenosis is identified at L4–L5 and L5–S1 secondary to similar degenerative changes (*arrows*). Note early encroachment on the exiting L4 nerve root at L4–L5.

vertebral body height. Regardless of the degree of height loss, any acute compression fracture can cause significant pain to the patient. In benign osteoporotic compression fractures, the fracture and edema are usually isolated to the vertebral body and do not extend into the pedicle or posterior elements. Although acute compression deformities can be associated with paravertebral hematomas that can mimic a mass, benign compression deformities are not associated with destructive epidural or paravertebral masses. If there is extension of the edema into the posterior elements or an associated mass, a pathologic compression fracture should be considered. Also, the posterior aspect of the vertebral body is usually straight in benign fractures while pathologic fractures often have a convex border posteriorly.[70]

Cement augmentation with vertebroplasty or kyphoplasty has been a widely used procedure to treat the patient's pain and improve quality of life. Vertebroplasty involves guiding a trocar needle through the pedicle such that the tip is placed in the anterior third of the fractured vertebral body. Once positioned, polymethylmethacrylate (PMMA) is dispersed within the vertebral body. Kyphoplasty uses a similar technique with the addition of balloon inflation within the vertebral body in attempt to restore some of the vertebral body height and create a cavity for cement deposition. Both procedures produce significant and equivalent pain relief with similar risk profiles.[71] Studies have shown, however, that the less expensive vertebroplasty procedure can achieve the same amount of height restoration as kyphoplasty.[71–73] Despite recent controversy of the effectiveness of cement augmentation in pain relief, vertebroplasty and kyphoplasty are widely accepted as a effective treatments for providing immediate pain relief and improved quality of life.[74,75]

IMAGING

Plain radiographs will identify compression deformities on the lateral view, and a radiograph is most often the initial test performed. CT exams do not provide any additional information for diagnosis of fractures, although CT images with reconstructions have excellent resolution of the fracture line within the vertebral body. However, x-rays and CT do not provide information on the acuity of the fracture. MRI images, specifically hyperintensity on the T2-weighted fat suppression sequence and hypointense signal on the T1-weighted image representing the edematous changes, provide the information needed to diagnose acute compression fractures (Fig. 9-39A, B). Fracture lines also can be seen on MRI images as a hypointense band on T1- and T2-weighted images. Chronic healed compression deformities will not show edematous signal change within a compression deformity. Also, acute compression deformities with only minimal loss of vertebral body height, not readily appreciated on plain films, can be seen on an MRI exam due to the edema from the acute fracture.

ACKNOWLEDGMENTS

The authors would like to thank Rita Jarmon and David Botos for help in preparing this chapter.

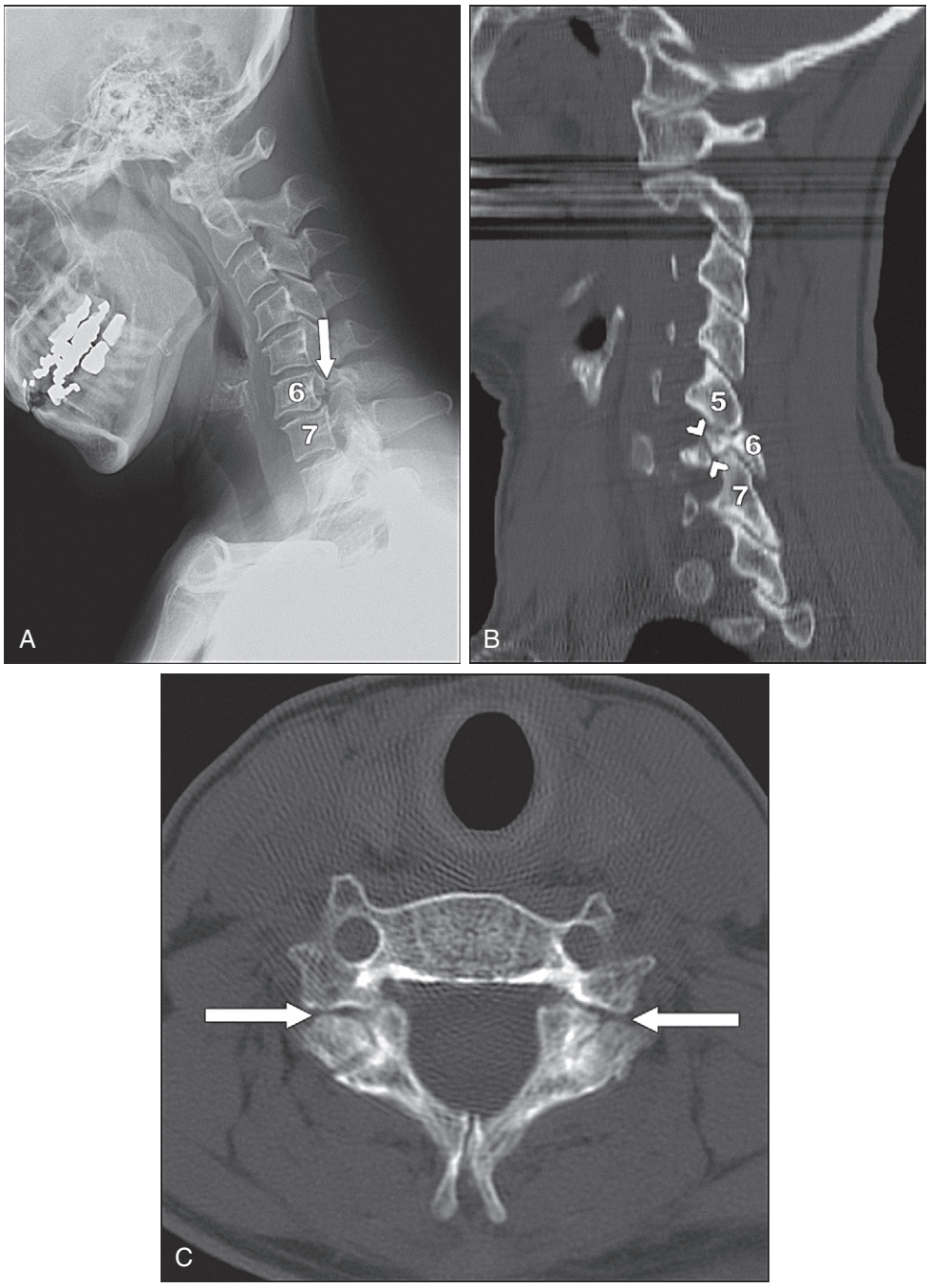

FIGURE 9-37 Developmental cervical spondylolysis on **(A)** lateral plain film, **(B)** sagittal CT reconstruction, and **(C)** axial CT imaging. The plain film reveals a reversed lordosis and anterior subluxation of C6 on C7. Pars deficiencies are suggested (*arrow*). One of the pars fractures is well profiled on the sagittal CT reconstruction (*arrowheads*). The axial CT image demonstrates bilateral pars intra-articularis fractures (*arrows*). The sclerotic margins support a chronic process.

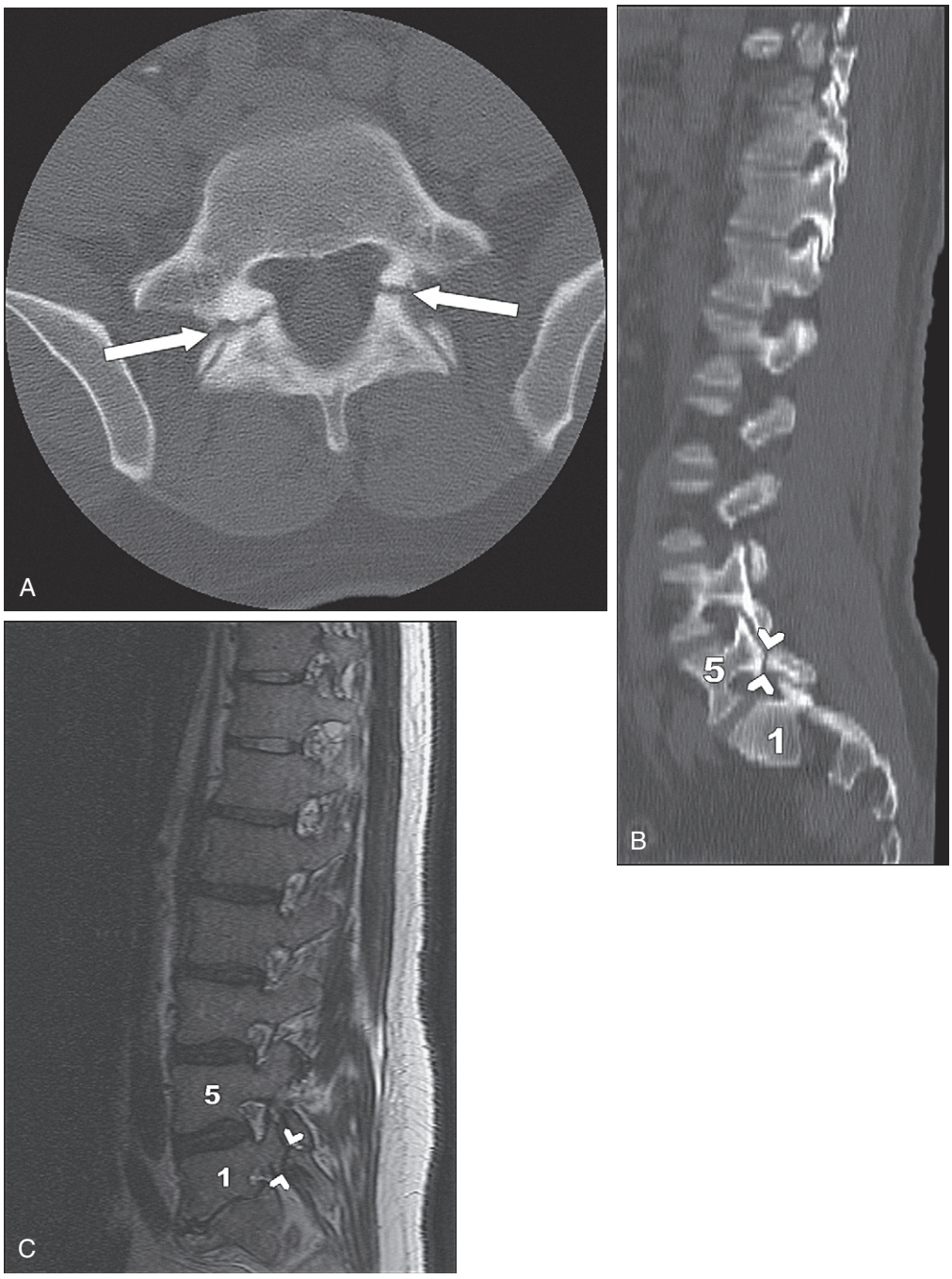

FIGURE 9-38 Developmental lumbar spondylolysis on **(A)** axial CT, **(B)** sagittal CT reconstruction, and **(C)** sagittal T2-weighted MRI. The axial CT image shows the deficient pars intra-articularis (*arrows*) and associated sclerosis. One of the pars defects is easily confirmed on the sagittal CT reconstruction (*arrowheads*) and is identifiable but more subtle on the sagittal MRI (*arrowheads*).

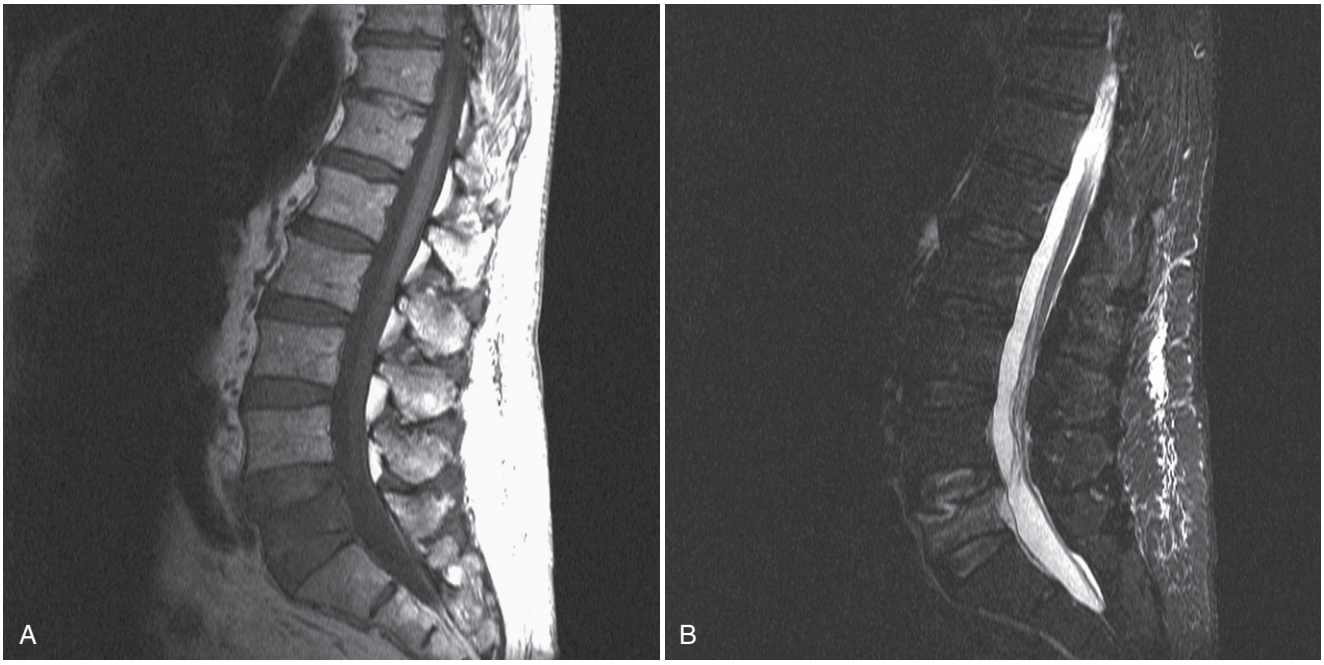

FIGURE 9–39 **(A)** Sagittal T1 and **(B)** stir sequences, showing the classic MR imaging appearance of an osteoporotic compression fracture at L5. The T1-weighted sequence shows abnormal T1-hypointense signal throughout the L5 vertebral body. There is a mild compression deformity of the L5 superior end plate of approximately 20%. There is mild buckling of the posterior cortical margin of L5. The stir sequence (fat suppression T2-weighted image) shows diffuse T2-hyperintensity corresponding to the T1-hypointensity. The marrow signal changes are consistent with edema and relate to inflammation and micromotion of the fractured trabeculae. The curvilinear high T2 signal under the anterior margin of the superior end plate represents fluid within a discrete fracture cleft.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 10

Determination of Disability

David R. Walega, MD

Over 7 million disability assessments are made annually in the United States, many of which are made by physicians in the field of pain medicine. Regardless of training, background, or specialty, physicians are often asked for their expertise regarding disability or impairment in their patients.[1] The process of disability assessment can be fraught with subjective bias and the role of determining disability can pose ethical issues for treating physicians. As "healers," physicians try to maximize the health and functional potential of patients, but in disability assessment, physicians become advocates for patients' financial interests and healthcare resources, which can conflict with the "healer" role. For some physicians, determination of disability causes discomfort or unease. They may feel either prejudiced or overly solicitous in the battle between the disability bureaucracy and advocating for the patient's best interests. Many physicians lack experience or training in the methods of assessing disability, how to perform an independent medical examination, how to assess a patient's ability to return to work, or how to assess what activities a patient is capable of performing. In theory, the determination of disability should be a transparent, unprejudiced, and objective process, and impairments or functional limitations should be correlated with objective evidence for tissue damage, organ dysfunction, or cognitive dysfunction, and this evidence should be reproducible in examination or diagnostic study. Knowledge of basic terminology in disability determination is important to the pain specialist.

Disability is an alteration in one's physical or cognitive capacity to perform a specific task, function, or activity and is highly dependent on individuality and context. Disability is greatly influenced by education, age, and social and cultural factors, as well as vocational opportunities and training. There is no universally accepted method for the assessment of disability. In fact, the definition of disability varies widely among rating agencies and entitlement programs administered through the Social Security Administration (SSA). Disability in this context is typically assessed by an administrative judge, not a physician, and is subjective. In contrast, *impairment* is an objective term that defines the loss or loss of use or derangement of any body part, organ system or organ function, but can also relate to impairments of cognitive or psychological functioning. Impairment may be temporary or permanent, and can be reproducibly measured through testing or physician assessment. *Handicap* is a legal or policy term used to describe a disability. An *impairment rating* or *whole person impairment* is a specific and objective assessment of a patient's impairment, and can be derived by using the American Medical Association's *Guides to the Evaluation of Permanent Impairment*.[2] This rating defines the impact of an impairment on one's ability to perform typical activities of daily living, including self-care, personal hygiene, use of hands, ability to communicate, sensory functioning, sexual function, and ability to travel. The *Guides* are evidence-based consensus estimates defined by more than 120 experts who relate a particular injury, derangement, or loss of function with changes in functionality or activities of daily living. For example, an impairment stemming from small disc herniation that causes moderate leg pain would rate a 5% to 8% impairment of the whole person, while a disc herniation that required decompression and fusion, with residual pain, sensory loss, and electromyography (EMG) abnormalities would render a 25% to 28% rating.[2] Similarly, pathology of the pulmonary or cardiovascular systems can be objectively assessed and rated. Chronic pain syndromes are inherently less verifiable, but can still be assessed with objectivity using this system.[3] Overall, the greater and more impactful the impairment is, the larger the *whole person impairment* percentage will be. Impairment ratings are used in calculating damage awards or other monetary compensation packages. It is important to note that an impairment rating should not be assessed until the patient has reached *maximal medical improvement* (MMI). MMI is the state at which all potential healing, repair, and treatment has been completed, and the impairment is permanent and unlikely to change significantly within the ensuing 1-year period. Again, this is an assessment that should be made by a qualified physician.

DISABILITY PROGRAMS

The SSA is a government agency that administers two federally mandated disability entitlement programs, Title II (Social Security Disability Income) and Title XVI (Supplemental Security Income). The Social Security Act defines disability as "the inability to engage in any substantial gainful activity by reason of a medically determinable physical or mental impairment which can be expected to result in death or has lasted or can be expected to last for a continuous period of not less than 12 months."[4] Disability is entirely based on vocational rather than medical issues, although a medical justification is essential. An adjudicator uses a listing of impairments to determine the severity of the problems identified by a claimant. Multiple impairments are not uncommon, and criteria for disability are fairly strict but at times arbitrary. Information or documentation regarding a claimant's condition is requested of the treating physician and may include office notes, diagnostic test results, narratives, or other specific forms. In contrast, workers' compensation programs are administered by each state, and while the principles of disability assessment are similar, the practice varies from state to state. These programs are meant to provide the injured worker prompt and appropriate medical treatment and restore a worker to his or her pre-injury state and enable the return to work and gainful employment. The worker is provided monetary benefits for lost wages. Four categories of disability are possible—*temporary partial*; *temporary total*; *permanent partial*; *permanent total*—and the work-related injury can be physical or mental. The duration and extent of benefits are determined by the category into which the claimant falls and may include medical expenses, wages, and monetary settlement. A treating physician plays a larger role in coordinating the medical care for the injured worker, as well as assessing impairment and disability. Short- and

long-term disability plans are private insurance policies that provide compensation to those who are disabled by injury or illness, under temporary or permanent conditions. These policies are often a part of an employee benefits package, but can be purchased individually as well. These policies typically do not cover medical expenses. With these private programs, disability is defined as the inability to perform the majority of activities required of a specific occupation. Duration, qualifications for, and restrictions of benefits will vary from policy to policy.

DISABILITY EVALUATIONS

An *independent medical evaluation* (IME) is a comprehensive assessment of a patient by a trained physician. In contrast to most doctor–patient relationships, the evaluating physician for an IME does not provide medical care and does not initiate a therapeutic relationship with the patient undergoing the evaluation. The purpose of the IME is to objectively assess the impact of an injury and subsequent disability on the patient's ability to function in a variety of domains, including self care, work duty, leisure, or recreational activity. The evaluating physician reviews the treatment to date, performs a physical examination, and reviews pertinent diagnostic tests and procedure reports, and then comments on the current clinical status, relevant diagnoses, and whether the patient is at MMI. The IME report should address causation of the injury and the relationship of the injury to the impairment, and any anatomic, physiologic, or psychological impairments should be identified or described, in addition to the permanence of these impairments. *Functional limitations*, defined as a lack of ability to perform an activity within a normal human range as the result of a specific impairment, should be specifically addressed in an IME report. Examples would include an inability to lift more than 25 pounds due to a disc herniation, or an inability to function independently due to an anoxic brain injury. Significant pain behaviors are often identified during the IME, although evidence shows that malingering is present in 1% to 10% of chronic pain patients.[5] The credibility of the patient should be addressed in the IME report. The mechanics of the disability evaluation are found in the *Guides*. Table 10-1 lists the important contents of an IME report.

In contrast to an IME, a *functional capacity evaluation* (FCE) or *work capacity evaluation* (WCE) are measures of a patient's functional ability and are typically performed with a physical therapist or occupational therapist. Tolerances for sitting, standing, walking, bending, reaching, lifting, and climbing are typically assessed, with a specific emphasis on the ability to lift and carry specific weights. The outcome of the evaluations is highly dependent on the patient's motivation and effort, and is inherently subjective to the examiner, especially in chronic pain patients. The WCE often simulates a specific workplace, and is thus easier to perform for sedentary or light-duty jobs as compared to more technical, labor-intensive jobs wherein heavy equipment, tools, or vehicles are needed.

TABLE 10–1 Components of an Independent Medical Evaluation

Narrative history
Current clinical status
Results of physical exam and diagnostic studies
Causation of injury and relationship to job
MMI assessment
Pertinent diagnoses
Impairments and function limitations
Permanence of impairments
Analysis of job tasks
Assessment of patient ability to perform job tasks

MANAGING DISABILITY IN A PAIN PRACTICE

Due to the nature of painful or disabling diseases, pain specialists must often balance disability evaluation and assessment with disability management. An emphasis on proactive management is important, especially with recurrent pain symptoms.[6] Disability and function should be addressed early on in the doctor–patient relationship and continually reassessed when function remains limited. Management should include an assessment of disability risk, patient education, and psychosocial support in addition to a treatment plan that outlines expectations for improvement.[7] Red flags for protracted disability include noncompliance with treatment, poor participation in physical therapy or rehabilitation, refusal or inability to return to work, and noncompliance with weight loss and exercise recommendations.[8] However, an overemphasis on nonorganic signs as a hallmark of malingering, conversion disorder, or impending disability has been called into question.[9] *Disability syndrome* is set of dysfunctional and counterproductive attitudes and beliefs that develop over time as an individual adapts to the role of being a disabled person. The more significant the dysfunction in the patient, the more important the multidisciplinary approach to pain management is necessary. When setting treatment and rehabilitation goals for an established patient, physicians are often more lenient regarding recovery time and return to work after an injury. However, when new patients with longstanding disability issues are evaluated, physicians may be more demanding of a higher level of activity or performance. Catastrophizing, fear avoidance beliefs, and other maladaptive behaviors should be identified and addressed by the pain specialist, as these are predictors of chronic pain and subsequent protracted disability.

KEY POINTS

- Disability is a vaguely defined term that describes the inability to perform specific tasks or functions.
- Impairment is an objective loss of function due to an injury or disease process.
- Pain specialists require an understanding of disability terminology to provide objective ongoing or independent assessments of pain patients with disabilities and impairments.

REFERENCES

Access the reference list online at http://www.expertconsult.com

Pharmacology and Pharmacologic Modalities

CHAPTER 11

Major Opioids in Pain Management

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Opioids remain the "gold standard" for the treatment of moderate to severe pain despite growing analgesic options from other drug groups. Over the past several decades, opioid prescribing for chronic nonmalignant pain (CNMP) has become more widespread, as seen with primary care clinicians dramatically increasing opioid prescribing from 1980 to 2001.[1] Legitimate use of opioids in select and monitored patients with CNMP has been supported by consensus statements developed by national organizations such as the American Pain Society (APS) and American Academy of Pain Medicine (AAPM).[2,3] Yet prescribing remains controversial, with polarized arguments on either side of the debate over their risk and effectiveness in treating CNMP.[3–9]

RATIONALE

Opioids produce reliable analgesia, and their adverse effects (e.g., constipation, nausea and vomiting, sedation, and respiratory suppression) often can be preempted, treated, or reversed. Opioid therapy can be an integral part of a multidisciplinary approach to acute and chronic pain management. An attempt to optimize a patient's pain management may include concurrently combining opioids with nonopioid adjuvant analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen, antidepressants, anticonvulsants, etc.), physical therapy, psychological therapy, and/or injection therapies. Much of the debate concerning the role of chronic opioid therapy (COT) for the management of CNMP, however, has centered on whether opioids should be used as a first-line treatment or whether they should be used at all on a chronic basis. Although a definitive opinion on this important issue is lacking, health-care professionals tend to use opioid therapy as a second-line treatment for CNMP for the following reasons: (1) nonopioid medications, such as NSAIDs and anticonvulsants or tricyclic antidepressants, can be efficacious in treating CNMP secondary to arthritic pain[10] and neuropathic pain,[11] respectively; (2) injection therapies may be effective and obviate the need for opioids; and (3) considering the noteworthy side effects and liability profiles of opioid treatment (see below), the risk-benefit ratio often demands that alternative treatments be implemented before instituting COT.

Although the effectiveness of COT in certain types of CNMP remains controversial, no evidence suggests an absolute contraindication to COT under circumstances in which it is not necessarily the first choice. Animal studies have shown a rightward shift of the opioid dose-response curve in experimental models of pain related to nervous system injury,[12,13] suggesting that higher opioid doses may be required for patients primarily suffering from neuropathic pain or other forms of chronic severe pain. The limiting factor for COT in neuropathic pain treatment may be related to the development of significant side effects associated with the requirement of high opioid dosages rather than to the inherent tolerance found in these pain states. In instances where tolerance is suspected, methadone may offer extra benefits in treating neuropathic pain because of its N-methyl-D-aspartate (NMDA) receptor blocking action that may reduce tolerance to opioids as well as provide analgesia.

In summary, an opioid trial may be considered when alternative analgesics, injection therapies, physical therapy, and psychological therapy have been inadequate, contraindicated, or otherwise exhausted. Although nonopioid drugs may appear to be better and/or safer choices for patients with CNMP, long-term use of such agents may have deleterious or life-threatening effects. Furthermore, drugs such as antidepressants and anticonvulsants have been shown to provide only 50% pain relief for one out of three patients.[14]

GUIDELINES

Since opioids are controlled substances with potential for abuse, their regulation by federal and state agencies is often associated with stigma. One of the major concerns of opioid prescribers is the potential of diversion through fraud, theft, forged prescriptions, or illegal activities of unprincipled health-care professionals. In 1998 the House of Delegates of the Federation of State Medical Boards (FSMB) of the United States established and adopted the Model Guidelines for the Use of Controlled Substances for the Treatment of Pain, which offers clear practice standards for opioid prescribers. These guidelines were subsequently updated in 2004 and converted to a model policy. The policy included the definitions of addiction, pseudoaddiction, tolerance, physical dependence, and substance abuse (Box 11-1).[16] The model policy emphasizes the importance of an evaluation, physical examination, and follow-up to monitor and evaluate for therapeutic efficacy, which includes the patient's functional status. The model

Box 11–1 Definitions

SECTION III: DEFINITIONS

For the purposes of these guidelines, the following terms are defined as follows:

Acute Pain—Acute pain is the normal, predicted physiologic response to a noxious chemical, or thermal or mechanical stimulus, and typically is associated with invasive procedures, trauma, and disease. It is generally time-limited.

Addiction—Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include the following: impaired control over drug use, craving, compulsive use, and continued use despite harm. Physical dependence and tolerance are normal physiological consequences of extended opioid therapy for pain and are not the same as addiction.

Chronic Pain—Chronic pain is a state in which pain persists beyond the usual course of an acute disease or healing of an injury, or that may or may not be associated with an acute or chronic pathologic process that causes continuous or intermittent pain over months or years.

Pain—An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Physical Dependence—Physical dependence is a state of adaptation that is manifested by drug class-specific signs and symptoms that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Physical dependence, by itself, does not equate with addiction.

Pseudoaddiction—The iatrogenic syndrome resulting from the misinterpretation of relief-seeking behaviors as though they are drug-seeking behaviors that are commonly seen with addiction. The relief-seeking behaviors resolve upon institution of effective analgesic therapy.

Substance Abuse—Substance abuse is the use of any substance(s) for non-therapeutic purposes or use of medication for purposes other than those for which it is prescribed.

Tolerance—Tolerance is a physiologic state resulting from regular use of a drug in which an increased dosage is needed to produce a specific effect, or a reduced effect is observed with a constant dose over time. Tolerance may or may not be evident during opioid treatment and does not equate with addiction.

policy also recommends the use of specialty consultations and additional referrals when patients present with complex histories, troubling adverse effects, or lack of progress toward analgesia or improved function. The APS and AAPM have recently published consensus guidelines for rational approaches to prescribing opioids and avoiding potential adverse effects. In these guidelines, information regarding risk assessment tools and websites for obtaining agreement forms for COT were included (Table 11-1).[3,15]

While federal and state law enforcement agencies are the principal regulators of prescription drug abuse, public and congressional outcry over opioid misuse, addiction, and diversion prompted the U.S. Food and Drug Administration (FDA) to get involved. By authority of the FDA Amendments Act (FDAAA) of 2007, the FDA can require drug manufacturers to implement Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits of the drug outweigh the risk. While REMS can include any drug, in 2009 the FDA notified manufacturers of sustained-release opioids (SROs) and long-acting opioids (LAOs) that a "class-wide" opioid-specific REMS would be required to include proposed communication and education materials, a medication guide, elements to ensure safe use, a patient package insert, enrollment forms, and prescriber and patient agreements. Because of their significant abuse potential, the FDA will also require REMS for rapid-onset fentanyl preparations (i.e., Onsolis, Actiq, and Fentora). Currently, the only drugs with an REMS include Embeda (morphine sustained-release/naltrexone), Exalgo (hydromorphone sustained-release), the newest version of OxyContin (oxycodone sustained-release), and Onsolis (a rapid-onset fentanyl buccal soluble film). As of this writing, REMS for the aforementioned have been individually developed by the manufacturers since a class-wide REMS that would apply globally was not available. The impact of REMS on opioid prescribing remains to be seen.

INITIATION OF CHRONIC OPIOID THERAPY

In the absence of comorbid risk factors (e.g., hepatic or renal impairment, age, etc.), there is no direct evidence to support the use of one opioid over the other, to recommend a specific starting dose, or to recommend a specific method of titration.[3] Prescribing opioids for long-term therapy necessitates the consideration of multiple factors. While selection of any SAO (codeine [Tylenol #2, 3, and 4], hydrocodone [Vicodin, Vicoprofen, Lortab, Lorcet, Norco, Hydrocet, and Zydone], morphine, oxycodone [Percocet, Percodan, Endocet, Endodan, Roxicet, Roxicodone, and Tylox], oxymorphone [Opana], or hydromorphone [Dilaudid], SRO (e.g., sustained-release versions of oral morphine

TABLE 11–1 Some Risk Assessment and Monitoring Tools and Websites for Obtaining Consent and Agreement Forms for Chronic Opioid Therapy (COT)

Risk assessment tool	Screener and Opioid Assessment for Patients with Pain (SOAPP)® Version 1.0-14Q
	Opioid Risk Tool (ORT)
	DIRE (Diagnosis, Intractability, Risk, Efficacy) Score: Patient Selection for Chronic Opioid Analgesia
Informed consent form for COT	American Academy of Pain Medicine (http://www.painmed.org/clinical_info/guidelines.html)
COT agreement form	American Academy of Pain Medicine (http://www.painmed.org/clinical_info/guidelines.html)
Monitoring tool	Pain Assessment and Documentation Tool (PADT)
	Current Opioid Misuse Measure (COMM)™

CNMP, chronic nonmalignant pain; COT, chronic opioid therapy.
Source: Chou R, Ganciullo GJ, et al: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain *2009;10:113–130.*

[MS-Contin, Oramorph, Kadian, Avinza, Embeda], oxycodone [OxyContin], oxymorphone [Opana Extended-Release], and hydromorphone [Exalgo]; and fentanyl transdermal patch [Duragesic]), or LAO (e.g., methadone and levorphanol) largely appears to be empirical, a rational approach to prescribing can be aided by a careful review of the patient's medical history. A patient with moderate to severe acute and/or chronic pain who has not improved with nonopioid therapies is a potential candidate for opioid analgesics. Whether or not a patient is opioid naive can help determine if he/she should be started on an SAO versus SRO or LAO. A patient with minimal to no recent opioid exposure should be given a titration trial with a low-dose SAO to establish his/her opioid requirement. The brief half-life of an SAO should minimize its toxic accumulation, and thereby minimize risk of opioid-related side effects. Due to their longer half-life or sustained delivery, SROs and LAOs may accumulate in fixed doses. This feature may make it more difficult to titrate than SAOs on initiation or change of an LAO or SRO regimen. Patients who are opioid naive may require test dosing that is most safely given "as needed." While opioids lack an absolute upper limit to dosing necessary to control a patient's pain, dose escalation may be limited if the selected opioid happens to be one that is compounded with a nonopioid analgesic (NSAID, acetaminophen, or aspirin) that has a known ceiling effect. Thus, combination agents (e.g., codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen, oxycodone/acetaminophen, oxycodone/aspirin, etc.) present a number of drawbacks: (1) in a setting of suboptimal analgesia, attempting to maximize the opioid analgesic may simultaneously raise the nonopioid analgesic above its ceiling dose and into the toxicity range; and (2) patients can develop tolerance to a drug with no ceiling effect while not developing tolerance to the other drug that does have a ceiling effect.

The severity and frequency of the patient's pain should determine whether "as needed" (PRN, pro re nata) versus "around-the-clock" dosing is necessary. For example, in those with acute pain secondary to an injury or surgery, PRN dosing with an SAO may be sufficient if the anticipated healing process is rapid and short. In those with either a slow and prolonged recovery process or persistent chronic pain, an SAO used on a PRN basis can produce a "rollercoaster" effect, whereby patients have pain, take analgesics, experience brief periods of relief, followed by repetition of this cycle when the pain returns. Typical COT aims to avoid perpetuation of this phenomenon by producing stable analgesia that is targeted less at total abolition of pain and more toward augmentation of the patient's function at a tolerable level of pain. Since the usual goal of opioid administration for treatment of chronic pain is to achieve sustained analgesia over regular intervals,[17] SAOs may be given at fixed dosing intervals, just as with an LAO or SRO. Such a strategy permits consistent delivery for reaching steady-state levels and avoids the peak-and-trough effect associated with on-demand dosing. Furthermore, fixed dosing avoids both the reinforcement of pain complaints and behaviors with additional analgesics as well as the precipitation of anxiety.

If a patient responds to the SAO and tolerates its side effects, COT may be best delivered by converting to an equianalgesic LAO or SRO if dosing permits. Benefits of using an LAO or SRO include achievement of safe, effective steady-state levels with regard to fixed dosing intervals[18] and lack of a compounded nonopioid analgesic which may impose a ceiling dose. Intuitively, fixed dosing with SROs or LAOs is thought to provide more sustained levels of analgesia, improved compliance, has less reward-associated reinforcement of potentially dysfunctional cycles where pain and pain medication become a conditioned part of the patient's life, and has a relative decreased risk of addiction or abuse. However, scientific studies have failed to conclusively prove these proposed benefits of SROs and LAOs over SAOs or fixed dosing over PRN dosing.[3] Nonetheless, the use of fixed dosing may prevent delays in delivery that can occur with PRN dosing. While some clinicians advocate the use of only SROs or LAOs for COT, employing conservative fixed dosing combined with PRN dosing of an SAO can also be effective in the management of chronic pain, particularly when there is a need to assess a patient's analgesic threshold. However, consensus in this area of pharmacotherapy also remains elusive at present.

ADMINISTRATION

The convenience of orally administered opioids has made this the preferred route of delivery. Many patients with cancer or acute postoperative pain, however, are unable to tolerate oral ingestion or temporarily are not permitted oral ingestion. Therefore, having multiple means of administering opioids is advantageous.[19] An intravenous (IV) or subcutaneous (SQ) infusion is commonly used in cancer patients, often with around-the-clock dosing for constant effect. Both routes avoid the first-pass effect and can be supplemented by PRN doses for breakthrough pain. The SQ route has several advantages, including faster onset of analgesia compared with most oral preparations (although slower than IV), uncomplicated access in patients with poor venous access, and safer administration compared with the intramuscular route in patients with bleeding disorders or reduced muscle mass.

A variant of the above is patient-controlled analgesia (PCA), most commonly using morphine, hydromorphone, or fentanyl. Widely used for treating postoperative pain, PCA is rapidly finding broader use in treating cancer pain. PCA immediately delivers a preprogrammed IV or SQ dosage of an opioid when the patient activates a button, thereby permitting rapid analgesia without having to wait for a nurse to deliver an IV PRN dose. By placing a maximum limit on the dose and frequency of opioid administered, the physician helps the patient titrate his/her opioid requirement. Because the PCA machine records the patient's individual dosing and frequency parameters, useful information can be obtained about the patient's analgesic requirements, which also simplifies subsequent conversion to a non-PCA opioid regimen.

Alternatives for patients unable to use IV or oral preparations include rectal (suppositories are available containing morphine, hydromorphone, and oxymorphone), sublingual, buccal, intranasal, transdermal, epidural, and intrathecal

routes of administration. Epidural and intrathecal opioids, commonly used in the perioperative, postoperative, obstetrical, and cancer population, make opioids directly available to the opiate receptor-rich neuraxis. These two forms of selective analgesia have the advantage of requiring relatively small quantities of opioids, thereby reducing the risk of central and autonomic complications. Patient-controlled epidural analgesia (PCEA), a new variant of patient-controlled drug delivery systems, administers epidural dosages of opioid, and potentially other drugs, via a similar mechanism such as IV PCA.

TREATMENT ENDPOINTS AND OPIOID SELECTION

Since pain is an untestable hypothesis that can neither be proved nor disproved, using pain relief as the endpoint of opioid therapy is also untestable and subjective. The most feared adverse effect from COT is drug addiction, which manifests as a compulsive use of a drug that causes dysfunction, and the continued use despite the harm related to that dysfunction. Thus, clinicians are advised to focus on functional improvement as an objective endpoint for analgesia that also offers evidence of opioid efficacy that exists in contrast to addiction. The challenge, however, is to develop outcome measures for COT beyond a lower pain score that distinguish function from dysfunction, and that emphasize therapy expectations, goal setting, goal monitoring, and collaboration with the patient's entire treatment team. The two critical issues related to treatment endpoints in COT include defining what outcomes should be expected and followed to demonstrate an effective and safe trial of opioids, and determining when and how opioid therapy should be discontinued (or tapered) if the treatment is either effective or ineffective. Clinical studies in this area are limited.

Markers of opioid benefit in patients treated for CNMP include subjective pain reduction and evidence of improved functional status and quality of life. Determining functional improvement can be accomplished with standardized instruments (SF-36, TOPS, Oswestry, etc.) or through a simple process of ascertaining limitations in function and quality of life prior to treatment and following these endpoints through the course of opioid therapy. The ideal functional assessment model should be simple, brief, individualized, and comprehensive, something that most formalized scales fail to accomplish.

Psychological and social factors, as well as coexistent diseases that may influence pain perception and suffering, can affect the overall assessment of pain.[20–22] Initiation of opioid therapy is unlikely to offer concomitant and proportional improvement in all of these areas. If the psychological amplifiers of pain perception have not been adequately addressed, opioid-induced analgesia may not be maximally effective. Likewise, analgesia and functional improvement resulting from opioid therapy may be discordant with achievements occurring from psychological treatment. Many possible variations in efficacy and functional gain may dictate flexibility in ascertaining treatment endpoints.

Because pain reduction is subjective, it can only serve as a single aspect of adequate COT. Consider, for example, the patient who has a constant pain rated "6 out of 10" ("0" being no pain and "10" being severe pain) with significantly associated disability. While opioid therapy may only decrease the patient's pain from a "6" to a "5," a successful outcome has been achieved if the patient demonstrates improvements in activities of daily living (ADL), ability to participate in physical rehabilitation, and/or ability to return to work. Conversely, an opioid trial can be considered counterproductive if the patient reports increased pain relief without observable functional gains, and possibly even signs of functional loss (daytime sedation, impaired cognition, voluntary unemployment, dysfunctional interpersonal or family relationships, diminished physical activity, or legal difficulties).

While effectiveness of opioid therapy is a primary concern, an equally important part of opioid management relates to deciding when to discontinue opioid therapy if the treatment is deemed to be unsatisfactory. Determination of a treatment failure requires consideration of multiple contributing factors, including (1) underdosing; (2) inappropriate dosing schedule; (3) improper drug delivery route; (4) potentially diminished opioid responsiveness relating to the nature of the pain generator (e.g., neuropathic pain); (5) involvement of unresolved contributors to pain, such as physical, psychological, and social disability; and (6) development of side effects that limit dose escalation. In the face of apparent opioid ineffectiveness from a single agent, opioids as a class may not be problematic as patients can appear resistant to one opioid yet sensitive to another.[23]

The duration of opioid therapy remains a question with no clear consensus amongst practitioners and minimal science to guide the debate. Pharmacological tolerance to opioids can develop during treatment, and may require either escalating the dose to maintain the same level of analgesia or switching to a different opioid. The need to rotate to another opioid is expected to occur in less than 2% to 3% of cases.[24] Although some clinical studies have suggested stabilization of opioid dose requirement following an initial dose increase, it is possible that periodic increases may be warranted during COT. For opioid-tolerant patients, changing from one opioid to another requires knowledge of equianalgesic dosages. Since cross-tolerance between opioids may be incomplete, a patient who has become tolerant to one opioid can respond with effective analgesia to another opioid of less than equianalgesic dose. Management of pain in tolerant patients can be a challenge because typical dosages for the opioid-naive patient do not apply. In such cases, opioids are slowly and incrementally increased until analgesia with tolerable side effects is reached. Analgesia occurring only in conjunction with intolerable side effects indicates that the particular opioid is suboptimal, and there may be a need to change to a different opioid. Analgesia occurring only in combination with sedation after an individual trial of most or all opioids suggests opioid-insensitive pain. Additionally, analgesia may also have more to do with the effects related to sedation rather than direct antinociceptive properties of the drug. As one would expect, side effects without analgesia indicate failure for that particular opioid. In such cases, another opioid may be worth trying, as it may not share this same profile. Clearly, determining the duration of effective opioid therapy must be individualized based on

treatment efficacy balanced with side effects and progression or regression of the underlying disease process. Ultimately, it may be impossible to know how much pain would be present without opioid therapy unless the medication is tapered.

SELECTED OPIOIDS

MEPERIDINE

Although meperidine (Demerol) is a common analgesic, particularly by the intramuscular (IM) route, its primary use in the pain management setting has steadily declined due to potential for neurotoxicity. Meperidine was developed in Nazi Germany as a synthetic opioid with relatively weak μ-opioid receptor agonist properties. Compared to morphine, it is one-tenth as potent and has a slightly more rapid onset and shorter duration of action.[25] At equianalgesic doses, meperidine produces less sedation and pruritus and may be more effective in neuropathic pain.[25] However, it possesses significant cardiac (orthostatic hypotension, and direct myocardial depression),[25] anticholinergic, and local anesthetic properties, which decrease its therapeutic window.[26] Unlike other opioids, epidural or spinal administration of meperidine can produce sensory, motor, and sympathetic blockade.[25] Meperidine does have a beneficial use in the operative setting for treatment of postanesthetic shivering.

Meperidine has a relatively short half-life of 3 hr[26] and prolonged administration (greater than 3 days) is problematic due to the potential for accumulation of its neurotoxic metabolite, normeperidine. Meperidine is demethylated in the liver to normeperidine, which has a half-life of 12 to 16 hr and is well documented to produce central nervous system (CNS) hyperactivity and, ultimately, seizures.[27] Since normeperidine is excreted by the kidneys, its adverse effects are most commonly, although not exclusively, seen in patients with renal impairment. Normeperidine toxicity initially manifests as subtle mood alteration and may progress to potentially naloxone-irreversible tremors, myoclonus, and seizures.[27] Because the hyperexcitability of normeperidine can also occur in patients with normal renal function, chronic administration of meperidine is not recommended. Finally, for patients on monoamine oxidase inhibitors, coadministration of meperidine can have potentially fatal outcomes. Caution may be prudent in coadministering meperidine and any other serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs), tramadol, or methadone.

MORPHINE

Morphine is the prototypical μ-opioid receptor agonist against which all other opioids are compared for equianalgesic potency. It can be given via oral, IV, epidural, or intrathecal routes for perioperative and postoperative pain management. As an SAO, it is available in IR formulations (morphine, MSIR, and Roxanol). As an SRO (MS-Contin, Oramorph-SR, Kadian, Avinza, Embeda), its dosing frequency ranges from every 8 to 24 hr. Unique among currently available SROs is Embeda, which contains both morphine and the opioid receptor antagonist naltrexone. It is the first "abuse-deterrent" opioid formulation on the market, although when taken as directed, the naltrexone remains inert. However, if the medication is crushed for intravenous injection, naltrexone is released to antagonize the effects of morphine. A REMS has been developed by the manufacturer.

With an oral bioavailability of 35% to 75%, morphine's relative hydrophilicity is less than ideal as an analgesic. Because of the delay in transport across the blood-brain barrier, morphine has a slower onset of action compared to other opioids. Conversely, morphine has a relatively longer analgesic effect of 4 to 5 hr relative to its plasma half-life (2 to 3.5 hr), thereby minimizing its accumulation and contributing to its safety.[27] The disproportional duration of analgesia versus plasma half-life is due in part to its low solubility and slower elimination from the brain compartment relative to the plasma concentration.[26] Although morphine's pharmacologic activity is primarily due to the parent compound, morphine's efficacious and toxic effects can also be mitigated or perpetuated by two of its major metabolites: morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G). M3G lacks any μ- and δ-opioid receptor activity and accounts for approximately 50% of morphine's metabolites. It has been shown in animals to cause generalized hyperalgesia, CNS irritability, seizure, myoclonus, and development of tolerance.[28] Whether this explains why neuroexcitatory side effects occur in humans exposed to chronic dosing of morphine has yet to be conclusively proven. Although M3G is devoid of opioid receptor activity, its true mechanism of action remains unknown. Conversely, M6G is a μ- and δ-opioid receptor agonist and accounts for approximately 5% to 15% of morphine's metabolites. M6G has intrinsic opioid agonism and sustains analgesia in addition to side effects. The route of morphine administration may account for variations in concentration of both glucuronide metabolites. Because the intravenous[29] and rectal[30] routes of administration avoid hepatic biotransformation, their glucuronide concentrations are less than with oral administration. Chronic use of oral morphine ultimately results in higher circulating concentrations of the glucuronides (mean ratios of M3G:M6G range from 10:1 to 5:1) than the parent compound.[26] Patients experiencing side effects attributable to M3G and/or M6G may be candidates for rotation to an alternative opioid.

Since morphine's elimination is dependent on hepatic mechanisms, it should be used with caution in cirrhotic patients. However, enterohepatic cycling and extrahepatic metabolism of morphine have also been reported to occur in the gastric and intestinal epithelia.[26] The glucuronides can also undergo deconjugation back to morphine by colonic flora and subsequently reabsorbed.[26] Because morphine metabolites are excreted through the kidneys, the dose should be adjusted in those with renal impairment in order to minimize the risk of adverse side effects associated with the accumulation of glucuronide metabolites. Smith reported that while respiratory depression, sedation, and vomiting due to relatively high concentrations of M6G can be reversed by naloxone, the most concerning adverse effect in patients with compromised renal function is encephalopathy and myoclonus.[28] Peterson et al found the ratio of M6G to morphine correlated with increased blood

urea nitrogen or creatinine levels.[30] Ultimately, morphine's analgesic effects and side effects are likely related to complex interactions between the parent compound and its glucuronide metabolites. Exactly how specific diseases, polypharmacy, and patient age influence ratios of the individual glucuronide metabolites to morphine remains unclear.[26]

OXYCODONE

Oxycodone is a semisynthetic congener of morphine that has been used as an analgesic for over 80 years.[31] As an SAO, it is available in IR preparations as a single agent (oxycodone, OxyIR, or Roxicodone) or compounded with acetaminophen (Percocet, Endocet, or Roxicet) or aspirin (Percodan or Endodan). IR oxycodone has been shown to deliver equivalent analgesia as the SR version (OxyContin).[32] In April 2010, the FDA approved a new ("tamper-resistant") formulation of OxyContin that is more difficult to break, crush, chew, or dissolve for snorting or intravenous injection. Similar to Embeda, a REMS has been developed by the manufacturer. Postmarketing studies, however, will be needed to determine its efficacy in reducing misuse and abuse.

SR oxycodone possesses many of the characteristics of an ideal opioid including no ceiling dose, minimal side effects, absence or minimal active metabolite, easy titration, rapid onset of action, short half-life, long duration of action, and predictable pharmacokinetics.[33] In comparison to SR morphine, it has a prolonged pharmacokinetic profile, which theoretically allows it to be solely administered on an every 12-hr dosing schedule. This, however, reflects a characteristic of the drug delivery system rather than a property of the drug itself. Oxycodone's narrower oral bioavailability (≥50%) than morphine's (15%–64%)[31] can account for variations in dose conversion ratios between the two drugs. Milligram-to-milligram, oxycodone is more potent than morphine and has a shorter onset of analgesia with less plasma variation. Accordingly, oxycodone is associated with fewer side effects (hallucinations, dizziness, and pruritus) than morphine.

While it possesses some intrinsic analgesic properties via activation of the κ-opioid receptors, oxycodone is predominantly a prodrug. It undergoes hepatic metabolism via the cytochrome P450 2D6 enzyme where it is converted into oxymorphone, an active metabolite with μ-opioid agonist properties, and noroxycodone, an inactive metabolite. In the approximately 10% of the population with genetically low levels of the cytochrome P450 2D6 enzyme, lower concentrations of oxymorphone may account for the fact that higher than usual doses of oxycodone may be necessary to obtain pain relief. Analgesic efficacy may also be decreased in those concurrently taking medications that competitively inhibit the P450 2D6 enzyme. Whether the relationship between impaired hepatic metabolism and decreased analgesia has anything to do with lower levels of oxymorphone remains uncertain. Therefore, careful dose titration must be made in those concurrently taking medications with potential interaction such as SSRIs, tricyclic antidepressants (TCAs), or neuroleptics. Finally, because the kidneys excrete oxycodone, the dose should be adjusted in renal dysfunction.

OXYMORPHONE

Oxymorphone is a semi-synthetic opioid that has been available as an IV preparation (Numorphan) since 1959 and then subsequently as a rectal suppository (Numorphan). It was not until 2006 that an oral formulation (Opana Immediate-Release and Extended-Release) was released.[34] Oxymorphone is primarily a μ-opioid receptor agonist that has more affinity for the μ-opioid receptor than morphine and is 10 times as potent as morphine when given intravenously.[34–40] Oxymorphone's affinity for the δ-opioid receptor is greater than morphine, with agonism decreasing tolerance as well as potentiating μ-opioid receptor mediated analgesia.[35] Unlike oxycodone, oxymorphone has little to no affinity for the κ–opioid receptor.[34,35,38,40] Like fentanyl, oxymorphone has less histamine release from mast cells than morphine and is more lipid soluble than morphine and oxycodone.[39] Unlike fentanyl, oxymorphone does not redistribute into fat stores, but rather dissociates slowly from receptors in the central nervous system.[37] The increase in lipophilicity leads to maximum plasma concentrations in 30 min, compared to 1.2 hr for morphine-IR.[34]

Although well absorbed in the GI tract, oxymorphone's bioavailability is only 10% due to extensive first-pass hepatic metabolism. Even though oxymorphone's bioavailability is lower than morphine's (30%) and oxycodone's (50%), oxymorphone's greater lipid solubility facilitates its ability to cross the blood-brain barrier to bind and may account for its rapid onset of analgesia: the time to maximum plasma concentration is shorter for oxymorphone IR (0.5 hr) compared to morphine IR (1.2 hr) and oxycodone IR (1.5 hr).[34–36,39,40] The onset of analgesia for the IR formulation occurs in 30 to 60 min and follows linear pharmacokinetics, allowing for predictable dosing.[34–37,39,40] For the ER formulation, steady-state occurs in three days with every 12-hr dosing.[39]

Oxymorphone is hepatically metabolized and renally excreted. It does require dosing adjustment for hepatic and renal impairment.[36,40] For those with moderate to severe hepatic impairment, oxymorphone is contraindicated.[34] Because moderate to severe renal impairment can result in bioavailabilities as high as 57% to 65%, clinicians should proceed with caution and with a dose reduction.[34] The main metabolite of oxymorphone, oxymorphone-3-glucorinide, has unknown activity and is produced in the liver via uridine diphosphate glucuronosyl transferase enzymes after reduction or conjugation with glucuronic acid.[34–37,39,40] A secondary metabolite, 6-OH-oxymorphone, is formed by reduction by an unknown enzyme and possesses analgesic activity.[34,39] There appears to be minimal interaction with the cytochrome P450 enzyme systems, such that oxymorphone is not metabolized by the CYP2D6 enzyme and does not interact with the CYP2C9 or CYP3A4 enzymes.[39] This can lead to less interpatient variability and fewer drug-drug interactions, which gives oxymorphone a significant advantage over other opioids.[34–37,40] The half-lives for the IR (7–9 hr) and ER (9–11 hr) formulations are approximately two times longer than oxycodone and morphine.[34–37,40] Compared to other strong opioids, oxymorphone has similar efficacy in the treatment of acute, chronic, and cancer pain and a similar side effect profile.[39,40] Since taking this medication with food

can greatly increase the maximum plasma concentration, it is advisable to avoid eating at least 1 hr prior to or 2 hr after taking this medication.[34–37,40] Alcohol should be avoided, as it can produce an almost 300% increase in the plasma concentration.[35,37]

HYDROMORPHONE

Hydromorphone is a hydrogenated ketone analogue of morphine that can be formed by N-demethylation of hydrocodone. It can be given via oral, IV, epidural, or intrathecal routes for perioperative and postoperative pain management. As an oral medication, it is available in an IR formulation (hydromorphone or Dilaudid) and SR formulation (Exalgo), with the latter affording once-daily dosing for chronic pain management. A REMS has been developed by the manufacturer.

Like morphine, hydromorphone is hydrophilic, possesses strong μ-opioid receptor agonist activity, and has a similar duration of analgesic effect (3 to 4 hr). However, side effects of pruritis, sedation, and nausea and vomiting occur less frequently with hydromorphone.[24] Depending on whether it is administered orally or intravenously, hydromorphone's milligram-to-milligram potency is estimated to be five to seven times that of morphine, respectively. Onset of analgesic effect occurs within 30 min when administered orally and 5 min when administered IV.[24] Peak analgesic effect of IV hydromorphone occurs within 8 to 20 min, most likely because its hydrophilicity impairs its ability to cross the blood-brain barrier.[41]

Although it is hydrophilic, it is 10 times as lipid soluble as morphine.[24] This feature, plus its greater milligram-to-milligram potency than morphine, allows equianalgesic doses to be infused subcutaneously but in smaller volumes (10 or 20 mg/ml). Possessing 78% of the bioavailability of IV hydromorphone,[24] SQ administration offers a safe alternative in hospice patients with impaired gastrointestinal (GI) function and requires less maintenance than with an IV site.

Hydromorphone undergoes hepatic biotransformation into its primary metabolite, hydromorphone-3-glucuronide (H3G), with both the parent compound and metabolite being renally excreted. Similar to morphine's M3G metabolite, H3G is an active metabolite that lacks analgesic efficacy but possesses potent neuroexcitatory properties that are 10 times stronger than the parent compound and have been shown to produce neuroexcitation (allodynia, myoclonus, and seizures) when administered directly into the lateral ventricle of rat brains.[26] Because H3G is produced in such small quantities, its effects are negligible except in cases of renal insufficiency where it may accumulate. In those with renal insufficiency hydromorphone is preferable to morphine. Concentrations of H3G are dose dependent and clear with time once hydromorphone is discontinued.

METHADONE

According to the American Heritage Dictionary, the name "methadone" is a derivative merging of the words that describe its chemical structure, 6-dimethylamino-4,4-diphenyl-3-heptanone.[42] When one hears the word *methadone*, many images come to mind. While clinicians trained to expertly use methadone to treat pain may visualize satisfied patients with a better quality of life due to significant pain reduction, patients and many health-care providers can only visualize the former heroin addict using methadone in a drug rehabilitation program. The most recent statistics estimate that in the United States, 268,071 patients are using methadone in opioid treatment programs[43] and nearly 720,000 patients are using methadone to treat chronic pain.[44] Increased prescribing of methadone is likely due to its many attractive features as an analgesic medication: low cost (wholesale price is approximately 5%–7% that of the more expensive proprietary SROs), high bioavailability with absorption and activity within 30 min, multiple receptor affinities, and lack of known metabolites that produce neurotoxicity (e.g., sedation, confusion, hallucinations, and myoclonus). Methadone is well absorbed and has an oral bioavailability (approximately 80%; range 40%–99%) that is approximately threefold that of morphine.[45,46] Its sublingual bioavailability ranges from 34% to 75%, with higher absorption favored by a higher pH of 8.5 in the sublingual space.[47,48] Unfortunately, methadone's pharmacokinetics and pharmacodynamics, exemplified by unpredictable bioavailability and high interindividual variability in steady-state serum levels, can make it a challenge to initiate and titrate, thereby increasing the potential for delayed methadone-related side effects. As methadone use as an analgesic has risen, it has gained attention due to a significant increase in unintentional overdoses and led the FDA to issue a manufacturer's black box warning in 2006. From 1999 to 2005, the number of poisoning deaths in the United States involving methadone increased 468% from 786 deaths in 1999 to 4462 deaths in 2005. A significant number of those deaths, 3701 in 2005, have been classified as unintentional.[49] In a recent study looking at patterns of unintentional pharmaceutical overdoses in West Virginia, 32% of fatal methadone overdoses involved patients with a prescription for methadone.[50]

Methadone, which is structurally unrelated to other opium-derived alkaloids, is available as a hydrochloride powder that can be reconstituted for oral, rectal, or IV administration. It is lipophilic, basic (pK_a = 9.2), and usually exists as a racemic mixture of its two isomers, d-methadone (S-met) and l-methadone (R-Met), both of which have separate modes of action. The d-isomer antagonizes the NMDA receptor and inhibits serotonin and norepinephrine reuptake, while the l-isomer (R-met) possesses the opioid receptor agonist properties. Among opioid receptor subtypes, methadone demonstrates variable affinity. Animal models demonstrate that it has a lower affinity than morphine for the μ-opioid receptor, which may explain why methadone may have fewer μ-opioid receptor-related side effects.[51] Conversely, methadone has a greater affinity than morphine for the δ-opioid receptor.[52] While δ-opioid receptor activity is felt to be crucial to the development of morphine-induced tolerance and dependence, methadone's δ-opioid receptor agonism leads to its desensitization. This feature may partially account for methadone's ability to counteract opioid-induced tolerance and dependence.[53] Aside from acting as

an opioid receptor agonist, methadone also acts as an NMDA receptor antagonist.[54–57] Numerous studies have demonstrated the involvement of the NMDA receptor mechanisms in the development of opioid tolerance[56] and neuropathic pain.[57] Hypothetically, methadone's ability to mitigate opioid-induced tolerance and treat neuropathic pain remains an intriguing concept.

Methadone's lipophilicity most likely accounts for its extensive tissue distribution (mean volume of distribution = 6.7 ml/kg) and slow elimination (mean half-life = 26.8 hr; range = 15 – 55 hr).[46,58] Its delayed clearance (mean 3.1 ml/min/kg) provides the basis for once-daily dosing for methadone maintenance therapy, thereby preventing the onset of opioid withdrawal syndrome for 24 hr or more.[58] Unfortunately, the same does not hold true for analgesia. Furthermore, there is extensive interindividual variation in the relationship between changes in plasma methadone concentration and analgesia.[59] The ability to use methadone for either opioid detoxification or analgesia can be explained by methadone's biphasic elimination phase. The α-elimination phase (distribution phase), which lasts 8 to 12 hr, equates to the period of analgesia that typically does not exceed 6 to 8 hr. Consequently, initial dosing for analgesia may need to be frequent because steady-state kinetics is required for reaching the biphasic profile. The β-elimination phase (clearance), which ranges from 30 to 60 hr, may be sufficient for preventing opioid withdrawal symptoms but is insufficient for providing analgesia. This provides the rationale for prescribing methadone every 24 hr for opioid maintenance therapy and every 6 to 12 hr for analgesia.

Unlike other opioids whose breakdown products contribute to potential neurotoxicity, methadone has no known active metabolites. It undergoes hepatic metabolism, primarily N-demethylation, by the cytochrome P450 (CYP) family of enzymes. As a result, methadone has multiple potential drug interactions that can result from induction, inhibition, or substrate competition at several of the CYP enzymes, including CYP3A4, CYP2D6, and CYP2B6.[60] In the absence of other drugs, CYP3A4 is an autoinducible enzyme, which means methadone can bring about its own metabolism and increase its clearance over time.[51] However, one study found that methadone and its metabolite (2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine) did not change significantly over a 9-month period, indicating that autoinduction by methadone may not occur.[61] In addition to the possibility of drug interactions, gastric pH can affect methadone's degree of absorption. For example, patients who are also taking omeprazole will absorb more methadone.

For most patients, renal excretion of unchanged methadone is insignificant. However, decreases in urinary pH can significantly increase methadone excretion. For example, in patients taking high doses of ascorbic acid with acidic urine, about 34% of an administered dose could be excreted in the urine as unchanged methadone.[62,63] While changes in urinary pH can also influence renal excretion of methadone, it does not accumulate in renal failure and does not appreciably filter during hemodialysis.[64] Thus, the possibility of methadone toxicity is increased in the setting of polypharmacy and/or changes in either gastric or urinary pH. Finally, variability in protein binding, excretion, and equianalgesic potency can further contribute to methadone's potential instability by provoking either overdose or withdrawal symptoms. While signs of toxicity are often clear, signs of decreased analgesia or withdrawal symptoms due to involuntary decreases in free circulating methadone may not be as apparent. Such patients may be erroneously characterized as drug-seeking because they display signs and symptoms of pseudoaddiction, requiring higher doses of methadone.

Methadone's duration of effect is inherently longer acting than other nonmodified or sustained-release opioids. This is especially beneficial for those with impaired GI absorption secondary to "short-gut syndrome" or "dumping syndrome." Unlike the SROs, methadone tablets can be broken in half or chewed. Methadone is also available in an elixir formulation (1 mg/ml or 10 mg/ml), which is advantageous for those with a gastrostomy feeding tube, thus minimizing the risk of clogging the tube by not having to crush a tablet. In addition, the low-concentration elixir theoretically allows for a relatively more careful and precise titration of methadone, which can potentially minimize the risk of delayed-onset toxicity. Ultimately, methadone's pharmacodynamic property as an LAO makes it beneficial for those with impaired GI absorption secondary to "short-gut syndrome" or "dumping syndrome." It is also ideal for those with renal impairment, as it does not accumulate in renal failure and is insignificantly removed during dialysis.

The many attractive features of methadone relate to its pharmacological complexity. The latter, however, can increase the risk of side effects, especially in patients with cardiac issues, those with concomitant illness, or those on multiple medications. As awareness of the proarrhythmic potential—prolongation of QTc interval resulting in torsade de pointes—of methadone has increased, experts have developed consensus guidelines to help clinicians safely prescribe methadone and minimize the risk of cardiotoxicity. The guidelines suggest clinicians inform patients of methadone's risk of pro-arrhythmia, look for cardiac disease history, obtain a baseline EKG followed by periodic monitoring of the QTc interval, and be aware of other factors or medications that might contribute to a QTc prolongation (Table 11-2).[44] Furthermore, uncertainty remains regarding methadone's equianalgesic dosing conversion. A recent review of opioid conversion ratios used with methadone found a relatively strong positive correlation between the previous morphine dose and the final methadone dose and dose ratio, but ratios varied widely.[64] Contrary to logic as it relates to tolerance, methadone appears to have greater potency (milligram-per-milligram) in patients rotating from high dosages of other opioids. Its antagonism of the NMDA receptor may help explain why methadone appears to have increasing potency as a patient's daily morphine-equivalent dose increases when converting from another opioid to methadone.[65] In the opioid-tolerant patient the exact equianalgesic dose for methadone as a conversion from morphine-equivalents is uncertain. Older equianalgesic tables are usually based on studies that included normal controls or opioid-naive patients and, therefore, do not take into account chronic opioid exposure. This tends to lead to excessive dosages.

TABLE 11–2 Consensus Guidelines for Prescribing Methadone

Recommendation 1	Disclosure	Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
Recommendation 2	Clinical History	Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
Recommendation 3	Screening	Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and then a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.
Recommendation 4	Risk Stratification	If the QTc interval is greater than 450 ms but less than 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
Recommendation 5	Drug Interactions	Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

Source: Krantz MJ, Martin J, et al: QTc interval screening in methadone treatment. Ann Intern Med *2009;150:387–395.*

Recently, a panel comprised of experts from the American Academy of Pain Medicine and American Pain Society recommended that a safe starting dose in most opioid-naive adults is 2.5 mg orally every 8 hr with subsequent dose increases no more frequently than weekly.[3] This same panel could not recommend a particular method for converting patients from other opioids to methadone but did suggest that opioid-tolerant patients generally should start at doses no higher than 30 to 40 mg per day, even in patients previously on high doses of other opioids. Converting from methadone to another opioid is even less clear due to insufficient studies available to offer uniform guidelines.[66] Therefore, methadone presents the inexperienced clinician with the challenge of predicting effects, not only in the face of unreliable equianalgesic dosing ratios that may be nondirectional, but also due to fluctuations related to altered hepatic metabolism that can be influenced by drug-drug interactions, protein-binding changes, and altered renal clearance.

BUPRENORPHINE

Buprenorphine is a Schedule III semisynthetic opioid that is a derivative of the morphine alkaloid thebaine. Used primarily as an alternative to methadone maintenance therapy, it is regaining popularity as an analgesic for treating chronic pain, although its use as an analgesic is considered off-label.[67–70] Buprenorphine is available in the sublingual form as Subutex and Suboxone. The main difference between these formulations is that the latter also contains the receptor antagonist naloxone. The ratio of buprenorphine to naloxone is generally 4:1.[69] Though buprenorphine has low abuse potential, the addition of naloxone is intended to cause withdrawal in patients who try to inject this formulation.[67,69,71] For maintenance dosing in addicts, dosing ranges from once daily to as infrequently as three times per week.[67,72]

Buprenorphine has partial agonist activity at μ-opioid receptor and antagonist activity at κ- and δ-opioid receptors. Its unique properties as a partial μ-opioid receptor agonist and κ-opioid receptor antagonist make this drug appealing as an analgesic, especially with regards to its adverse effects. Compared to opioids that have full μ-opioid receptor agonism, partial μ-opioid receptor agonism results in a ceiling effect for respiratory depression and causes less euphoria, the latter creating less craving.[67,69,70,73] The decrease in craving may also be associated with antagonism at the κ-opioid receptor.[67,69,70] Studies also suggest that there may be less tolerance with buprenorphine.[68,72] Buprenorphine's partial agonist activity results in a ceiling dose with a "bell-shaped" dose-response curve, suggesting that buprenophine's analgesic efficacy is limited and paradoxically can result in antagonism at higher doses.[69,70,73] Others, however, have suggested that there is no ceiling effect with regard to analgesia at clinically relevant doses but that the buprenorphine-morphine equivalence at higher doses becomes less predictable.[73,74] Limited spinal analgesia, dysphoria, and psychotomimetic effects are due to its antagonist effects at the κ-receptor.[69] Buprenorphine also acts on opioid receptor like-1 (ORL-1) receptors that may contribute to antihyperalgesia, but it may counteract its antinociceptive effects. One proposed explanation for these opposing effects suggests that binding to ORL-1 receptors in different parts of the body has diverse clinical effects.[68,75]

Buprenorphine is highly lipophilic and is thought to be at least 30 to 40 times more potent than oral morphine.[67–70,72] Buprenorphine was developed in the late 1960s, with IV and sublingual formulations introduced in 1978 and 1981, respectively. In the late 1990s, a transdermal formulation was introduced in Europe.[76–78]

Pharmacodynamically, buprenorphine has a slow onset of action (approximately 90 min) in the sublingual form and relatively long half-life (4 to 5 hr).[79] Its slow dissociation from the μ-opioid receptor may help to explain its prolonged duration of action leading to once-daily dosing in opioid treatment programs.[67,69,70,72,78,80] The slow dissociation from the μ-opioid receptor may also be why cessation of buprenorphine induces only mild withdrawal symptoms.[70,81] Buprenorphine exhibits high affinity for the μ-opioid receptor, which allows for attainment of effective analgesia at low receptor occupancy rates. Because its high affinity for the μ-opioid receptor blocks other opioids from binding, this may necessitate the use of a higher dose of a full μ-opioid receptor agonist if added to a patient's existing buprenorphine regimen.[69] Conversely, introduction of buprenorphine to a patient already taking an alternate opioid may precipitate opioid

withdrawal.[82] Although this appears safe according to certain reports,[70] the general consensus is to start buprenorphine prior to adding a conventional opioid for breakthrough pain.[78] Finally, the high affinity for the receptor means that naloxone may not readily reverse any buprenorphine-induced respiratory depression. The respiratory stimulant doxapram may be more appropriate in this setting.[82,83]

Due to first-pass hepatic metabolism, the bioavailability of buprenorphine is approximately 10% to 15%. However, when taken sublingually it has 60% to 70% of the bioavailability of the intravenous route.[67,69] Buprenorphine is hepatically metabolized primarily via the cytochrome P450 3A4 enzyme into nonactive and active metabolites. The nonactive metabolites (80% to 90%) are the result of glucoronidation, and the active metabolite (norbuprenorphine) results from N-dealkylation.[84,85] Because norbuprenorphine is more potent with regards to respiratory depression,[69] use of buprenorphine needs to be closely monitored in patients with moderate to severe liver dysfunction or those who are on concomitant medications that may induce the CYP 3A4 enzyme. However, buprenorphine appears safe in patients with renal disease, including those patients on dialysis.[69,70,72,78] Overall, the addition of buprenorphine as an alternative opioid offers a distinctive medication with a favorable safety profile when compared with other strong opioid medications.

FENTANYL

Originally formulated as part of a balanced anesthetic for use during surgical procedures, fentanyl continues to be used via the IV, epidural, and intrathecal routes for perioperative and postoperative pain management. Because fentanyl is highly lipophilic, this can present advantages or disadvantages, depending on the desired effect, due to its limited spread along the neuraxis when administered in the epidural or intrathecal space. Fentanyl possesses predominantly μ-opioid receptor agonist properties and little affinity for the κ- and δ-opioid receptors.[86] Compared to morphine, it has an inherently faster onset of action and is 75 to 125 times as potent.[25,27] It is hepatically metabolized by CYP3A4 into the inactive metabolite, norfentanyl.[87] When given intravenously, it has a high first-pass effect and 30- to 60-min duration of analgesia.[86] Its greater degree of potency compared to other opioids allows for the delivery of smaller quantities of the drug measured in micrograms per hour. Although considered short acting, its lipophilicity allows for transdermal application for the management of chronic pain and transmucosal and buccal applications for the management of breakthrough cancer pain.

Transdermal fentanyl (Duragesic patch and other generic patch products) is recommended for use only in opioid-tolerant patients with chronic or cancer pain based on several studies reporting a 20% incidence of hypoventilation when it was used in acute postoperative pain management.[88] In addition to a peel strip that protects the adhesive, the original Duragesic patch consists of four layers: (1) the polyester backing layer is impermeable to drug loss or moisture penetration; (2) the drug reservoir contains fentanyl gelled with hydroxyethyl cellulose and ethanol, the latter of which enhances transdermal absorption of fentanyl; (3) the rate-controlling membrane helps control the rate of drug absorption, whereby 50% of the absorption rate is controlled by the membrane and 50% by the inherent resistance of the skin;[89] and (4) the silicone adhesive layer keeps the patch in place when affixed to the skin. Several newer generic patches use matrix technology that allows for cutting the patch without undermining drug delivery. The patch should be placed on the upper body on a hairless (clipped, not shaved), flat surface of skin free of defects. Once applied to the skin, sustained levels of analgesia can be achieved via fentanyl's continuous transdermal absorption.

Transdermal fentanyl permits 3-day dosing with avoidance of the first-pass effect of the liver, where fentanyl is metabolized primarily by the cytochrome P450 family of enzymes. Because transdermal fentanyl does not pass through the GI tract, it theoretically causes less constipation than oral opioids. Furthermore, not having to depend on the GI tract provides the rationale for prescribing it in those with an inability to tolerate oral medications secondary to chronic nausea and vomiting, in those with impaired GI absorption secondary to "short-gut syndrome" or "dumping syndrome," and in those who are noncompliant with taking oral medications.

Unlike the oral LAOs, dose titration of the patch can sometimes be difficult due to individual variations in transdermal rate absorption, adherence of the patch to the skin due to perspiration (~10%),[89] skin temperature, fat stores, and muscle bulk.[26] Because of the slow and variable rate of absorption after initial patch application or increase in patch dose, it can take 1 to 30 hr (mean value of 13 hr) before therapeutic serum levels are achieved.[90] Therefore, during the first 12 hr patients should be prescribed an SAO or IV PCA to address breakthrough pain and to minimize withdrawal symptoms if rotation is from another opioid, especially since it takes 3 days before steady-state is achieved.[91] The amount of SAO required after steady-state is achieved may also determine if the patch dose needs to be changed, although caution is recommended in making rapid dose adjustments. Conversely, because it takes at least 16 hr before serum fentanyl concentrations drop by 50% after the patch is removed, one would also expect a delay in resolution of analgesia or side effects on removing the patch. Patients should be advised to avoid submerging the patch in hot water, placing a heating pad over the patch, or placing the patch over broken skin, as all of these can influence the rate of drug absorption and attendant side effects. The most common side effects of the transdermal delivery system (<1%) are adhesive related and include erythema, itching, and occasional pustule formation.[48]

Breakthrough pain peaks in 3 to 5 min, lasts an average of 30 min, and occurs 1 to 4 times per day.[92–94] Because onset of analgesia after administration of oral SAOs for breakthrough pain often lags behind the painful episode (30 to 45 min to reach peak effect) due to variable GI absorption and/or first-pass hepatic metabolism,[86,95,96] an alternative formulation of opioids was developed: rapid-onset opioids (ROOs), which are defined by an onset of analgesia of 15 min or less.[97] All four of the available ROOs currently available are fentanyl preparations (oral transmucosal fentanyl citrate [OTFC; brand

name Actiq]; fentanyl buccal tablet [FBT; brand name Fentora]; fentanyl buccal soluble film [FBSF; brand name Onsolis]; and sublingual fentanyl orally disintegrating tablet [sublingual fentanyl ODT; brand name Abstral]), but only OTFC, FBT, and FBSF are available in the United States. Sublingual fentanyl ODT is available in some European countries. All are approved only for breakthrough cancer pain and have the benefit of bypassing first-pass hepatic metabolism. Of the three products available in the United States, all will require an FDA-mandated REMS, although only FBSF currently has one.

OTFC was the first submucosal ROO to come to market. Unlike transdermal fentanyl, OTFC has a rapid onset of analgesia (15 min), short duration of action, and serum half-life of 193 to 386 min.[91] Compared to the intravenous route, it has 47% bioavailability.[87] Rapid absorption occurs via the buccal mucosa combined with slower absorption via the GI tract for the amount swallowed. OTFC yields peak serum concentrations within 20 to 40 min of starting a 15-min application.[98] In a study comparing OTFC to IV morphine in acute postoperative pain both demonstrated a similar onset of analgesia.[99] Absorption is patient-effort dependent; that is, it depends on the patient's application technique. Because OTFC contains sugar and has caused dental carries using OTFC, proper dental hygiene is recommended. FBT was the second submucosal ROO approved for the treatment of breakthrough cancer pain. When placed in the buccal cavity, FBT undergoes an effervescent reaction, theoretically to enhance buccal absorption, and dissolves in an effort independent manner within 30 min.[97,100,101] Advantages of FBT over OTFC include faster median time to maximum peak serum concentration (47 min vs 91 min), greater proportion of transmucosal dose (48% vs 22%), greater early systemic exposure of fentanyl, and lack of sugar.[97,100] Fentanyl buccal soluble film (FBSL; brand name Onsolis) is the most recent submucosal ROO to be approved. The bilayer delivery technology uses a dual-layer polymer film consisting of a mucoadhesive layer that contains the active drug and an inactive layer that facilitates unidirectional flow to prevent diffusion of drug into the oral cavity.[101] Like FBT, application of FBSF is effort independent, produces greater early systemic exposure of fentanyl, and lacks sugar. It requires little saliva to dissolve upon immediately adhering to a moist mucosal membrane, completely dissolves within 15 to 30 min, and has an absolute bioavailability of 71%.[92,101] Sublingual ODT is the only sublingual fentanyl preparation on the market, but it is only available in some parts of Europe. The delivery mechanism consists of a rapidly disintegrating tablet combined with soluble carriers coated with mucoadhesive agents, which enables the quick dissolution of fentanyl to take advantage of the highly permeable sublingual mucosa.[93,94] In one study, first detectable fentanyl plasma levels and peak serum concentrations were noted as early as 8 to 11 min and 40 to 57 min, respectively.[102] Like FBT and FBSF, application of sublingual ODT is effort independent.

Since dosing based on the total daily amount of a fixed opioid regimen is unpredictable, patients taking OTFC, FBT, FBSF, or sublingual ODT should be advised to start at the lowest dose and titrate to effect.[100,103,104] This same dosing strategy is even recommended when converting from one rapid-onset fentanyl preparation to another, as variations in absorption and bioavailability among the three makes them unequal on a microgram-to-microgram basis. Rapid absorption and short duration of effect make all four of the rapid-onset fentanyl preparations ideal analgesics for breakthrough cancer pain, especially in patients with an impaired swallow or GI tract.

SUFENTANIL

Used primarily in the operative setting as an IV or neuraxial analgesic, sufentanil (Sufenta) is a thiamyl analogue of fentanyl. Like fentanyl, sufentanil is lipophilic, predominantly hepatically metabolized by the CYP3A4 isoenzyme, and has a rapid onset with short duration of effect. While the pharmacokinetics and pharmacodynamics of sufentanil and fentanyl are similar, sufentanil has a smaller volume of distribution, greater analgesic potency (IV, five to seven times; epidural or intrathecal, two to five times), shorter half-life (2.7 hr vs 3.1 to 7.9 hr), and more rapid onset of analgesia (IV, 1 to 3 min; epidural or intrathecal, 4 to 10 min) with a shorter duration of effect (IV, 20 to 45 min; epidural or intrathecal, 2 to 4 hr).[25,26] Sufentanil may also produce dose-related skeletal muscle rigidity.

ALFENTANIL

Also used primarily in the operative setting as an IV or neuraxial analgesic, alfentanil (Alfenta) is less lipophilic compared to fentanyl and sufentanil. Its lower lipid solubility means it has a smaller volume of distribution (~25% of that of fentanyl and sufentanil). This, coupled with its short elimination half-life (70 to 111 min) and rapid onset of analgesia (IV, 1 to 2 min; epidural, 5 to 15 min) with a short duration of effect (IV, 10 to 15 min; epidural 4 to 8 hr), makes it ideal in an operative setting due to the lower probability of accumulation with repeated dosing or continuous infusion and its ease of rapid titration.[25,26] Like fentanyl and sufentanil, alfentanil is extensively metabolized in the liver by the CYP3A4 isoenzyme.

REMIFENTANIL

The most potent μ-opioid receptor agonist of the opioids discussed above, remifentanil (Ultiva) is administered IV for the induction and maintenance of anesthesia.[26] More lipophilic than fentanyl, sufentanil, and alfentanil, remifentanil also has a larger volume of distribution, a more rapid distribution and metabolism, a shorter elimination half-life (3 to 10 min), and a more rapid analgesic onset (1 min) with shorter duration of effect (5 to 10 min).[26] Unlike fentanyl, sufentanil, and alfentanil, remifentanil is not metabolized to any appreciable degree by the liver. Instead, its ester side-chain linkage subjects it to rapid degradation by tissue and plasma esterases into an inactive carboxylic acid metabolite that is renally excreted.[26] This confers unique pharmacokinetic and pharmacodynamic parameters that make remifentanil's actions brief and unaffected by renal or hepatic insufficiency. Brisk clearance and lack of accumulation with repeated dosing are advantageous features in an operative setting, but discontinuation of the infusion results in a rapid loss of analgesia.

KEY POINTS

- With an informed and cautious approach, opioids may be safe and effective for treating moderate to severe pain of both malignant and nonmalignant origin.
- Clinicians who choose to offer chronic opioid therapies must formulate rational and individualized regimens according to strategies such as those described by the FSMB and the APS/AAPM consensus guidelines.[3]
- Safe opioid therapy requires a program for continuous and close observation of analgesia and possible adverse effects.
- Subjective reports of pain relief should be corroborated by documentation of objective signs of success, such as improvement in function.
- Experience dictates that improvements in functionality are more frequently encountered when a multidisciplinary treatment plan is employed.

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CHAPTER 12

Opioids Used for Mild to Moderate Pain

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Opioids have a long history of being the standard analgesic used for the management of pain, by which other medications in this category are measured. The treatment strategy for cancer pain developed by the World Health Organization (WHO) provides an overview of the appropriate deployment of various. This process can be conceptualized by following three steps of increasing analgesic potency in response to progression of disease and/or intensification of pain intensity (Fig. 12-1). Mild pain is usually treated with over-the-counter (OTC) analgesics such as aspirin, ibuprofen, or acetaminophen. These agents exert their effect by mitigating the "algogenic soup" that follows tissue injury. For mild to moderate pain, the WHO analgesic ladder advocates the use of short-acting opioids (SAOs) either alone or in conjunction with OTC analgesics. In addition, adjunctive therapy such as acupuncture, transcutaneous electrical nerve stimulation, and/or psychotherapy may be brought into play at this stage. The third step, to relieve moderate to severe pain, entails the use of high-potency SAOs or long-acting opioids (LAOs), either alone or with adjunctive therapy. However, even these more potent opioids may or may not be effective for some forms of pain and there are steps beyond the analgesic ladder that include co-analgesics such anticonvulsants, antidepressants, or interventional pain procedures.

The WHO analgesic ladder for cancer has been adopted for use in chronic nonmalignant pain where SAOs play a vital role. The duration of action of SAOs ranges from 2 to 4 hr, and they are available as single entity medication or in combination with a nonopioid, such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) (Table 12-1). Combination therapy offers drug-sparing effects since a lower dose of each medication is used, avoiding side effects associated with higher doses. However, a potential problem is created by combining an opioid, which can produce tolerance and that has no dose ceiling, with acetaminophen or an NSAID, which may cause toxicity beyond a certain dosage. While patients are often apprehensive about the opioid, they had been relatively unaware of the potential renal or hepatic toxicity from the nonopioid component. Recent warnings from the Food and Drug Administration (FDA) have modified this scenario. Data from the FDA Adverse Event Reporting System (2005) showed that 60% of acetaminophen-related fatalities involved the use of an acetaminophen/opioid combination. Although an FDA advisory committee voted in favor of eliminating prescription acetaminophen/opioid combination products, to date the FDA has not followed this recommendation. However, this federal agency is considering other measures to reduce the risk of unintentional liver failure due to acetaminophen toxicity.[1–3]

When opioids are administered with aspirin, acetaminophen, or ibuprofen, these medications are referred to as "weak opioids." This is a misnomer referring to the limit to which they can be prescribed due to the restrictive dosing of the nonopioid component. When administered without the co-analgesic and in sufficient quantities, so-called "weak opioids" can be as potent as morphine. Table 12-1 compares dosages of these analgesics to the prototype opioid, morphine 10 mg IV. The rationale for combination products, however, is straightforward: their efficacy outweighs the disadvantage of limited dosing. One randomized, controlled trial[4] compared the analgesic efficacy and safety of the oxycodone 10 mg/acetaminophen 325-mg formulation to a 20-mg dose of controlled-release (CR) oxycodone for the treatment of acute pain following oral surgery illustrates this point. The combination treatment of oxycodone/acetaminophen was superior to CR oxycodone in outcome measures of pain intensity and pain relief. The combination treatment also provided a faster onset and 24% reduction in the number of patients reporting treatment-related adverse events. Thus, the "opioid-sparing" effect was significant and resulted in fewer side effects leading to better compliance.[5] A similar scenario exists for codeine in combination with acetaminophen and hydrocodone with ibuprofen added.[6] Similarly, combination products of codeine have been found to be more effective than the single agent.[7]

This chapter reviews the use of SAOs and provides the reader with a practical approach to employing these medications in clinical practice. It also briefly mentions their nonmedical use and the problem of prescription opioid overdose, both growing national epidemics.

SPECIFIC SHORT-ACTING OPIOIDS

OXYCODONE

Oxycodone is a semisynthetic opioid processed from thebaine, an organic chemical found in opium. It is one of the most popular opioids in the United States. The popularity of oxycodone is in some part due to its suitability for oral administration due to high bioavailability (60%); oxycodone is 1.5 to 2 times more as potent as morphine. Unfortunately, this property may also be responsible for its abuse. The first report that oxycodone, sold under the brand name Eukodal, produced a "striking euphoria" responsible for addictive behavior was published in Germany in the 1920s. Even though oxycodone was subsequently placed in the more restricted Schedule II controlled substance category in the United States (Table 12-2), its abuse has been a recurrent problem with law enforcement authorities. An increased number of prescriptions written for oxycodone (and hydrocodone) between 1995 and 2004 were associated with similar increases in nonmedical use and the number of emergency department visits during this time period.[8] Similarly, the opioid most highly associated with questionable activity

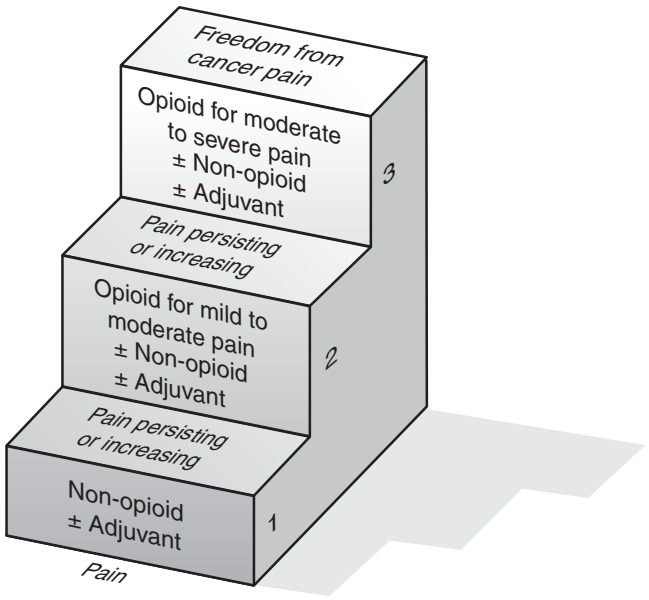

FIGURE 12-1 World Health Organization Analgesic Ladder

was oxycodone in a study based upon Schedule II data from a prescription monitoring program.[9] But it has been mainly the sustained-release formulation of oxycodone that has driven the renewed interest in the abuse potential of opioids. Abusers would crush the long-acting matrix preparation and either inhale the powder or inject dissolved drug into their veins. Inasmuch as the rate of drug delivery to the central nervous system is believed to be an important factor in the reinforcing strength of any drug, this was a very effective (but highly dangerous) method for addictive behavior. The development of extended-release opioid medications that are difficult to convert into more rapid-acting forms, that is, "abuse-deterrent formulations," was in direct response in order to discourage this type of activity.[10,11]

HYDROCODONE

Hydrocodone is an opium derivative and is Schedule III when in combination with acetaminophen or ibuprofen and Schedule II when used as a single entity product. It has been rumored that arguments were levied against putting this medication and codeine into the Schedule II category because this would have restricted their use as antitussives. But hydrocodone abuse potential is similar to that seen with the Schedule II oxycodone.[8] Hydrocodone and oxycodone combination products produced similar opiate-like effects and psychomotor impairment, in non–drug-abusing volunteers.[12] Similarly, volunteers with sporadic prescription opioid abuse had similar responses to these two opioids (i.e., increased ratings of drug liking, physiologic effects including miosis, and modest respiratory depression) that were generally dose related.[13]

The abuse potential of the two aforementioned SAOs has had a dramatic societal impact. In the 1999–2006 period, the number of poisoning deaths increased dramatically in the United States from approximately 20,000 to 37,000, largely because of overdose mortality involving prescription opioids.[14] This increase occurred at a time when there was a fourfold increase in the use of prescription opioids nationwide. Methadone, oxycodone, and hydrocodone were involved in 64.0%, 22.9%, and 13.9% of deaths, respectively.[14] Although methadone accounted for the largest association with accidental poisoning, oxycodone and hydrocodone shared the spotlight. The high prevalence of a substance abuse history and lack of prescriptions in one cohort of decedents in West Virginia

TABLE 12–1 SAO Conversion Dosing, Metabolism, and Comments

Generic Name	Morphine Equivalent Conversion[41] Factor per Milligram of Opioid	Metabolism	Comments
Codeine	0.15	Codeine is metabolized to its primary active compounds morphine and codeine-6-glucuronide. The half-life of codeine in plasma is 2.5 to 4 hr.	Most widely employed naturally occurring opioid; has strong antitussive effects.
Hydrocodone	1.0	Hydrocodone is metabolized by the liver into several metabolites, and has a serum half-life of 3.8 hr.	Many products combining hydrocodone and nonopioid analgesics available; has strong antitussive effects.
Oxycodone	1.5	Unlike morphine and hydromorphone, oxycodone is metabolized by the cytochrome P450 enzyme system in the liver, making it vulnerable to drug interactions.	High abuse potential; many products combining oxycodone and nonopioid analgesics available.
Propoxyphene	0.23	Peak plasma concentrations of propoxyphene are reached in 2 to 2.5 hr. Metabolized by the liver to norpropoxyphene, an active metabolite with a propensity to accumulate.	Not more effective than APAP alone; neurotoxic metabolite.
Tapentadol	0.15*	Reaches maximum serum concentrations within about 90 min and has an elimination half-life of approximately 4 hr. Meaningful pain relief within 1.5–2 hr.	Avoid in patients taking SSRIs, SNRIs, MAOIs, or triptans.
Tramadol	0.10	Metabolized in the liver to its active metabolite, O-demethyl tramadol, which is excreted by the kidneys. Elimination half-life of approximately 5 hr.	Avoid in patients at risk for seizures; avoid in patients taking SSRIs.

** Tapentadol was not studied by Korff.[41]*

TABLE 12–2 Federal Controlled Substance Schedules

	Description of Criteria	Examples
Schedule I	Have no currently accepted medical use and high potential for abuse, addiction, or physical dependence	Heroin, lysergic acid, marijuana, mescaline, methaqualone
Schedule II	Have accepted medical use and high potential for abuse, addiction, or physical dependence	Morphine, hydromorphone, methadone, oxycodone, cocaine, amphetamine, methlphenidate
Schedule III	Have accepted medical use and potential for abuse, addiction, or physical dependence less than drugs in Schedules I and II.	Opioids combined with non-narcotic drugs (e.g., hydrocodone/acetaminophen, codeine combination), dronabinol, anabolic steroids, benzphetamine
Schedule IV	Have accepted medical use and potential for abuse, addiction, or physical dependence less than drugs in Schedules I–III.	Benzodiazepines, chloral hydrate, dextropropoxyphene, phenobarbital, fenfluramine
Schedule V	Have accepted medical use and potential for abuse, addiction, or physical dependence less than drugs in Schedules I–IV.	Diphenoxylate in combination with atropine (antidiarrheals), antitussives with limited amounts of narcotics (e.g., codeine)

Source: Modified from Fujimoto D: Regulatory issues in pain management. Clin Geriatr Med *2001;17:537–551.*

suggest that most of the deaths are related to substance abuse.[15] To mitigate this problem, providers are advised to use state prescription-drug monitoring programs to monitor the use of controlled substances by their patients.

CODEINE

Codeine is an opioid metabolized to active analgesic compounds, including morphine. This opioid is frequently administered in combination with acetaminophen, butalbital, and caffeine intended for the treatment of headache and commonly employed as an antitussive. Codeine is the dominating opioid in several European countries. In examining Norway's prescription database, a majority (58%) of patients received codeine only once, most likely for acute pain, whereas a small minority (0.5%) had a prescription pattern indicating problematic opioid use.[16] There is no readily discernible reason for the absence of substantial abuse potential for this SAO.

TRAMADOL

Tramadol has several mechanisms of activity including agonist activity at the mu opioid receptor as well as inhibition of the reuptake of norepinephrine and serotonin. It was initially thought to lack abuse potential. However, aberrant behavior has subsequently been reported in several patients and it remains to be seen whether it will remain an unscheduled drug. It has been studied in moderate to severe pain associated with osteoarthritis,[17] fibromyalgia,[18] low back pain,[19] and diabetic neuropathy.[20–23] The analgesia produced may be suboptimal necessitating rational polypharmacy with co-analgesics, psychological approaches, and physical therapy. As the case with hydrocodone and codeine, tramadol has found a niche in the pediatric population. Tramadol 1 to 2 mg/kg is an effective oral agent in the postoperative period in children ready to be transitioned from patient-controlled analgesia.[23] Commonly reported adverse events with tramadol included nausea, dizziness, somnolence, and headache. More problematic is the association of seizure activity, albeit occurring in less than 1% of users. This risk is increased by a history of alcohol abuse, stroke, head injury, or renal compromise. Furthermore, patients receiving serotonin selective reuptake inhibitors should avoid taking tramadol due to the risk of producing the serotonin syndrome.

TAPENTADOL

Tapentadol is a centrally acting analgesic with dual mechanisms of action: μ-opioid receptor: agonist activity and norepinephrine reuptake inhibition. An immediate release formulation of tapentadol was approved for relief of moderate to severe acute pain by the FDA in November 2008. Tapentadol is included in this discussion of opioids used for mild to moderate pain because it may have a ceiling dose. Currently, it is not recommended to exceed more than 700 mg/day of tapentadol on the first day of therapy and no more than 600 mg/day on subsequent days with most patients taking 50 to 100 mg every 4 to 6 hr as needed for pain. Tapentadol is a Schedule II controlled substance with abuse potential similar to other potent opioid analgesics. During clinical trials, immediate release tapentadol 100 mg provided analgesic efficacy equivalent to that produced by 15 mg of immediate release oxycodone. Tapentadol can cause nausea, vomiting, constipation, dizziness, and somnolence. Nonetheless, the incidence of side effects associated with tapentadol appears to be slightly less than that seen with equianalgesic doses of oxycodone.[24–28]

PROPOXYPHENE

Propoxyphene hydrochloride is an odorless, white crystalline powder with a bitter taste that is freely soluble in water. Although propoxyphene is no stronger than acetaminophen, it remains a relatively popular analgesic with increased interest spurred by the finding that the d-isomer, dextropropoxyphene, is a noncompetitive NMDA receptor antagonist.[29] Thus, it may have extra-opioid effects with some potential theoretical benefit in cases of neuropathic pain.

The most frequently reported adverse effects are dizziness, sedation, nausea, and vomiting. However, there are more serious potential problems including seizures, cardiac dysrhythmias, and even heart block if taken in excessive amounts, either accidentally or because of suicidal intent. Concomitant use of alcohol, sedatives, tranquilizers, muscle relaxants, or antidepressants is a risk factor for accidental overdose,

TABLE 12–3 Combinations of Weak Opioids and Acetaminophen Elixirs

Generic Name	Brand Name	Formulation	Dose
Codeine	Tylenol with Codeine #3	Elixir (120 mg acetaminophen/12 mg per 5 ml)	0.8–1.0 mg/kg every 4 hr by mouth based on codeine
Hydrocodone	Lortab	Elixir (167 mg acetaminophen/2.5 mg per 5 ml)	Start at 0.1 mg/kg every 3 or 4 hr based on hydrocodone

particularly in the elderly.[30–32] Because of these risks, the FDA recently required manufacturers of propoxyphene containing products to strengthen the warning label to address these issues. Manufacturers of propoxyphene-containing products have also been required to develop a medication guide that must be provided with each prescription or refill.[33,34]

SPECIAL CONSIDERATIONS

NSAIDs VERSUS SHORT-ACTING OPIOIDS FOR ACUTE AND POSTOPERATIVE PAIN

NSAIDs should be considered possible first-line agents for most acute injuries and minor surgical procedures. Since the COX-2 inhibitors have not been shown to have greater analgesic potency than standard NSAIDs, the specific NSAID should be chosen on the basis of cost, availability, and individual risk for potential side effects. In postoperative pain management, the basis for using nonopioid analgesic adjuvants is to reduce opioid consumption and lessen opioid-related adverse effects. For instance, perioperative strategies employed to prevent or limit the duration of ileus include modification of pain management strategies to limit opioid administration by including NSAIDs.[35] But the literature on this subject has been contaminated. In February 2009, a major case of scientific misconduct was discovered. Pain researcher Scott Reuben, who had published 21 papers over a period of 15 years, was alleged to have fabricated data. Suddenly many advances in postoperative pain management, which had been assumed to be factual, seemed now open to reexamination. However, carefully performed systematic reviews proved robust against the impact of Reuben's misconduct.[36]

There are several scenarios in which opioids may be preferable. As NSAIDs cause platelet dysfunction, use in a patient with a low platelet count is relatively contraindicated. Likewise, the patient with a low threshold for bronchospasm may do better perioperatively with an opioid. Women may want to avoid NSAIDs during pregnancy as these medications may increase the risk of miscarriage. NSAIDs as a group tend to exacerbate reflux esophagitis and peptic ulcer. Individuals prone to these conditions may be better off with opioids. At risk also are patients with congestive heart failure, intrinsic renal disease, liver failure with ascites, and those receiving diuretics. Opioid analgesics might be advantageous in these scenarios, although they too must be used with caution because most are excreted by the kidneys and metabolized by the liver.

The use of various analgesic medications in the pediatric population for acute and postoperative pain follows a stepwise approach similar to the WHO's analgesic ladder. When analgesia is poorly controlled with acetaminophen, salicylates, or an NSAID, a weak opioid (e.g., codeine, oxycodone, tramadol, or hydrocodone) can be added to bring about additional pain relief. There are special elixirs of these medications that make them more palatable in this age group (Table 12-3). There are special precautions that are necessary in this age group because of the propensity to produce excessive sedation and respiratory depression. These problems are extremely uncommon except with excessive dosing or the presence of an underlying medical condition that predisposes the patient to the central respiratory depressant effects of opioids. This is particularly true in younger infants. Hepatic and renal dysfunction make opioids potentially hazardous, as do a history of apnea and the use of concomitant sedative medications.

USE OF SHORT-ACTING OPIOIDS IN NONMALIGNANT PAIN

Short-acting opioids are often used during the initial titration period in chronic pain and in patients whose pain occurs episodically and only a few times per day. After an appropriate amount of medication has provided an optimal balance between pain relief and side effects, the patient may be converted to an equivalent dose of an LAO, although some patients prefer to remain on the SAO for the control of continuous pain and breakthrough pain.[37] LAOs are believed to be preferable for chronic pain because they provide less variation in blood levels and possibly promote a lower propensity for the development of abusive behaviors. However, the basis for this preference in chronic pain patients is controversial.[38,39] Nonetheless, its validity is suggested by finding a preponderance of emergency room visits for toxicity to originate from SAOs.[40]

CONCLUSION

There is a definite role for the use of SAOs in the management of mild to moderate pain in acute, chronic, and cancer pain. Anti-inflammatory medications are being touted as an alternative to SAOs in acute pain conditions, including that incurred during the postoperative period. There are many variables that go into the decision of whether to use these nonopioids and, at present, it is not clear if SAOs will retain their preeminence for the treatment of mild to moderate acute pain. There are individual issues among the SAOs that mandate comparisons and warrant individualization of therapy in many instances. In general, the WHO analgesic ladder provides a basis upon which to model therapy for all types of painful conditions.

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CHAPTER 13

Risk Stratification and Management of Opioids

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Opioid treatment of chronic pain has evolved in recent years to encompass risk management in key domains. Knowledge regarding misuse and addiction has increased, and agreement is nearly universal that patients should be assessed for risk, stratified according to risk category, and monitored closely as treatment progresses. Additional risks of opioid treatment have been underappreciated and include endocrine deficiencies, sleep-disordered breathing, and opioid-induced hyperalgesia. The evidence base continues to evolve, and further research is needed into the clinical implications of chronic opioid therapy as applicable to every risk domain.

ASSESSING FOR RISK OF MISUSE OR ADDICTION

"Universal precautions," assumes all patients are at some risk for opioid misuse or addiction; therefore, minimal prevention measures are applied that include initial assessment, an opioid treatment agreement, informed consent, regular urine drug tests (UDTs), regular reassessment of treatment goals, and thorough documentation.[1] Patients are evaluated for the presence of opioid-related risk factors that include personal[2] or family history of substance misuse, young age, history of sexual abuse, mental disease,[3] social patterns of drug use, psychological stress,[4] poor social support, polysubstance misuse,[5] cigarette dependency, and repeated rehabilitations for substance misuse.[6]

Several tools are available to assess patients for risk of opioid misuse before beginning opioid therapy for pain. Three such tools are endorsed in a guideline for the use of opioids in the treatment of chronic noncancer pain approved jointly by the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM).[7] The Screener and Opioid Assessment for Patients with Pain, Version 1 (SOAPP 1.0), is a 14-item, self-administered questionnaire that examines such predictors as history of substance misuse, sexual abuse, mood disorders, impulsivity, legal problems, and chaotic social environment (Tables 13-1 and 13-2).[8] (A 24-item revised SOAPP designed to be less liable to deception than the original SOAPP is also available.)[9] The Opioid Risk Tool (ORT), is a five-item, self-report questionnaire, which provides a gender-specific score, and can be completed in less than 5 min (Tables 13-3 and 13-4). It assesses for personal and family history of substance misuse; age; history of preadolescent sexual abuse; and the presence of certain mental disorders, and has successfully identified which patients are at lowest and highest risk. Both the SOAPP and the ORT stratify patients into risk categories to be monitored accordingly. A third tool for initial assessment, the Diagnosis, Intractability, Risk, Efficacy (DIRE), incorporates risk factors for substance misuse in addition to characteristics regarding the patient's pain (Table 13-4).[10] Rather than assigning a patient a risk category, the DIRE purports to determine whether the patient is a good candidate for long-term opioid therapy. A comparison study found the SOAPP to be the most sensitive of the three tools at detecting high-risk patients, followed by the ORT and then the DIRE.[11]

Choice of which tool to use will be influenced by several factors of the clinical environment, the most significant of which is likely to be the time available. In addition to the three aforementioned initial screening tools, the APS/AAPM guideline cites the Current Opioid Misuse Measure (COMM) to help identify opioid misuse among patients currently being treated with opioids.[12] Information on the SOAPP and the COMM is available at http://www.painedu.org/index.asp. Once a patient's risk category is determined, whether high, moderate, or low, the patient is monitored at a level commensurate to the degree of risk (Table 13-5).[13] At each clinic visit, the patient should be reassessed for the 4As: analgesia, activities of daily living, adverse effects, and aberrant drug-taking behaviors.[14] It is important to set treatment goals in collaboration with the patient and to document progress in the medical record as part of a periodic review.

Complete pain relief may not be possible, and much depends on the specific priorities of the patient. For example, one patient may desire as much pain relief as possible, while another patient's priority may be to avoid feeling sedated. Functional goals such as returning to work or performing other daily activities should be discussed. Reassess patients periodically to determine whether the goals are being met. If not, a different treatment approach should be considered, which may include discontinuing opioids. UDTs, when incorporated into a comprehensive monitoring plan, can help check for compliance with opioid therapy but should not replace clinical judgment. Most patients should be tested at baseline, and then tested randomly as therapy progresses in keeping with the selected monitoring level. Signs of aberrant behavior should trigger a UDT. Two main types of UDT are available. Initial screening, usually a radioactive or enzyme-mediated immunoassay test, can show whether substances are present but typically cannot isolate specific opioids. Confirmation testing generally requires a gas chromatography/mass spectrometry (GC/MS), which can detect actual molecular structures of specific drugs and their metabolites. Initial testing may be done in the office, but confirmation testing is most often handled by a laboratory.

Clinicians should interpret UDTs with caution, as several factors, including the rate of drug metabolism, can impact test results. One cannot tell from viewing test results exactly how much drug was taken or when. However, used in conjunction with other monitoring measures, UDTs can help indicate whether illicit or unauthorized prescriptions are present, and whether the patient is actually taking the prescribed medication. The clinician should document and

TABLE 13–1 Screener and Opioid Assessment for Patients with Pain (SOAPP-R), Version 1.0

Name _____ Date _____

The following are some questions given to all patients at the Pain Management Center who are on or being considered for opioids for their pain. Please answer each question as honestly as possible. This information is for our records and will remain confidential. Your answers alone will not determine your treatment. Thank you.

Please answer the questions below using the following scale:

0 = Never, 1= Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often

1. How often do you have mood swings?	0	1	2	3	4
2. How often do you smoke a cigarette within an hour after you wake up?	0	1	2	3	4
3. How often have any of your family members, including parents and grandparents, had a problem with alcohol or drugs?	0	1	2	3	4
4. How often have any of your close friends had a problem with alcohol or drugs?	0	1	2	3	4
5. How often have others suggested that you have a drug or alcohol problem?	0	1	2	3	4
6. How often have you attended an AA or NA meeting?	0	1	2	3	4
7. How often have you taken medication other than the way that it was prescribed?	0	1	2	3	4
8. How often have you been treated for an alcohol or drug problem?	0	1	2	3	4
9. How often have your medications been lost or stolen?	0	1	2	3	4
10. How often have others expressed concern over your use of medication?	0	1	2	3	4
11. How often have you felt a craving for medication?	0	1	2	3	4
12. How often have you been asked to give a urine screen for substance abuse?	0	1	2	3	4
13. How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past five years?	0	1	2	3	4
14. How often, in your lifetime, have you had legal problems or been arrested?	0	1	2	3	4

Please include any additional information you wish about the above answers. Thank you.

Source: Butler SF, Budman SH, Fernandez K, et al: Validation of a screener and opioid assessment measure for patients with chronic pain. Pain *112:65–75, 2004.*

TABLE 13–2 Scoring Instructions for the Screener and Opioid Assessment for Patients with Pain (SOAPP-R), Version 1.0

To score the SOAPP V.1-14Q, simply add the ratings of all the questions. A score of 7 or higher is considered positive.

Sum of Questions	SOAPP Indication
≥ = 7	+
<7	–

What does the cutoff score mean?

For any screening test, the results depend on what cutoff score is chosen. A score that is good at detecting patients at risk will necessarily include a number of patients that are not really at risk. A score that is good at identifying those at low risk will, in turn, miss a number of patients at risk. A screening measure like the SOAPP generally endeavors to minimize the chances of missing high-risk patients. This means that patients who are truly at low risk may still get a score above the cutoff. The table below presents several statistics that describe how effective the SOAPP is at different cutoff values. These values suggest that the SOAPP is a sensitive test. This confirms that the SOAPP is better at identifying who is at high risk than identifying who is at low risk. Clinically, a score of 7 or higher will identify 91% of those who actually turn out to be at high risk. The negative predictive value for a cutoff score of 7 is 0.90, which means that most people who have a negative OAPP are like at low risk. Finally, the positive likelihood ratio suggests that a positive SOAPP score (at a cutoff of 7) is nearly three times (2.94 times) as likely to come from someone who is actually at high risk (note that, of these statistics, the likelihood ratio is least affected by prevalence rates). All this implies that by using a cutoff score of 7 will ensure that the provider is least likely to miss someone who is really at high risk. However, one should remember that a low SOAPP score suggests that the patient is really at low risk, while a high SOAPP score will contain a larger percentage of false positives (about 30%), while at the same time retaining a large percentage of true positives (about 30%), while at the same time retaining a large percentage of true positives. This could be improved, so that a positive score has a lower false positive rate, but only at the risk of missing more of those who actually do show aberrant behavior.

SOAPP Cutoff Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
Score ≥7	0.91	0.69	0.71	0.90	2.94	0.13
Score ≥8	0.86	0.73	0.75	0.86	3.19	0.19
Score ≥9	0.77	0.80	0.77	0.80	3.90	0.28

Source: Butler SF, Budman SH, Fernandez K, et al: Validation of a screener and opioid assessment measure for patients with chronic pain. Pain *112:65–75, 2004.*

TABLE 13–3 Opioid Risk Tool©

Item	Mark Each Box That Applies	Item Score If Female	Item Score If Male
1. Family history of substance abuse:			
• Alcohol	[ ]	1	3
• Illegal drugs	[ ]	2	3
• Prescription drugs	[ ]	4	4
2. Personal history of substance abuse:			
• Alcohol	[ ]	3	3
• Illegal drugs	[ ]	4	4
• Prescription drugs	[ ]	5	5
3. Age (mark box if 16 to 45)	[ ]	1	1
4. History of preadolescent sexual abuse	[ ]	3	0
5. Psychological disease			
• Attention deficit disorder, obsessive-compulsive disorder, bipolar, schizophrenia	[ ]	2	2
• Depression	[ ]	1	1
Total		____	____

Total score risk categories: low risk, 0 to 3; moderate risk, 4 to 7; high risk: ≥8.

Source: Webster LR, Webster RM: Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med *6:432–442, 2005.*

TABLE 13–4 Diagnosis, Intractability, Risk, Efficacy (DIRE) Score

For each factor, rate the patient's score from 1 to 3 based on the explanations in the right-hand column.

Diagnosis	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, nonspecific back pain. 2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain. 3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.
Intractability	1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process. 2 = Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers prevent (insurance, transportation, medical illness). 3 = Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.
Risk	(R = Total of P + C + R + S below)
Psychological	1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues. 2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder. 3 = Good communication with clinic. No significant personality dysfunction or mental illness.
Chemical health	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse. 2 = Chemical coper (uses medications to cope with stress) or history of chemical dependency in remission. 3 = No chemical dependency history. Not drug-focused or chemically reliant.
Reliability	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through. 2 = Occasional difficulties with compliance, but generally reliable. 3 = Highly reliable patient with meds, appointments, and treatment.
Social support	1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles. 2 = Reduction in some relationships and life roles. 3 = Supportive family/close relationships. Involved in work or school and no social isolation.
Efficacy score	1 = Poor function or minimal pain relief despite moderate to high doses. 2 = Moderate benefit with function improved in a number of ways (or insufficient information—hasn't tried opioid yet or very low doses or too short of a trial). 3 = Good improvement in pain and function and quality of life with stable doses over time.

Total score = D + I + R + E

Score 7–13: Not a suitable candidate for long-term opioid analgesia

Score 14–21: Good candidate for long-term opioid analgesia

Source: Belgrade MJ, Schamber CD, Lindgren BR: The DIRE score: predicting outcomes of opioid prescribing for chronic pain. J Pain *7:671–681, 2006.*

TABLE 13–5 Match Monitoring to Patient's Risk of Opioid Misuse

Low Risk (Routine)	Moderate Risk	High Risk
Pain assessment	Biweekly visits	Weekly visits
Substance misuse assessment	Biweekly prescriptions	Weekly prescriptions (on attendance)
Informed consent	Regular prescription database check	Quarterly prescription database check
Signed treatment agreement	Verification via family members/friends	Friend/family member controls medication
Regular follow-up visits, prescriptions	Random UDT	UDT: scheduled and random
Initial prescription database check	Question comorbid disease	Consider blood screens
Medical reports	Consider psych/pain specialist evaluation	Psych/addiction specialist evaluation
Initial UDT	Consider medication counts	Consider pain specialist evaluation
No specialist consult required	Consider limiting RO analgesics	Limit RO analgesics
Med type, unrestricted		Consider limiting SAO
Document 4As		
Document patient-physician interactions		

UDT, urine drug test; 4As, analgesia, activities of daily living, adverse effects, aberrant drug-related behaviors; RO, rapid onset; SAO, short-acting opioids.
Source: Webster LR, Dove B: Avoiding opioid abuse while managing pain: a guide for practitioners, *North Branch, MN, 2007, Sunrise River Press.*

address with the patient any aberrant behaviors that arise during the course of opioid therapy and should intensify monitoring measures accordingly. Intensified levels of monitoring may involve limiting the amount or types of medication prescribed, requiring frequent physician visits and UDTs, bringing in specialists to co-manage the patient, and appointing a third party to dispense medication to the patient.

Prescription monitoring programs, now operational in 34 states, are used for investigating illegal practices and can sometimes be used by physicians—depending on state law—to track whether patients are getting opioids from more than one provider.[15] The programs provide a valuable monitoring tool and must only be used in the course of professional practice, never for personal purposes. Think also about the possible motivations underlying opioid misuse. Some patients overuse medication in an attempt to escape unrelieved pain. Other patients are trying to self-treat a mental health problem, such as depression or anxiety. Still others are seeking euphoria, driven by addiction or recreational use. The more a clinician understands what drives a patient to misuse opioids, the more readily he or she can tailor effective interventions. It should not be assumed that a low-risk patient will never misuse opioids or that a high-risk patient always will. It is also important to remember that stressors such as increased pain, disease progression, and difficulties with family, job, or finances can cause a patient to change categories over time. Benefits of opioid therapy may include pain relief, increased function, and heightened quality of life. The clinician should re-weigh the risk-benefit profile at frequent intervals to ensure treatment is not being harmed by a substance use disorder, medical or psychiatric comorbidity, or social stressor that makes compliance with opioid therapy difficult or impossible for the patient.

UNDERAPPRECIATED RISKS OF OPIOID TREATMENT

ENDOCRINE DEFICIENCIES

The impact of opioids on the endocrine system has not been well addressed clinically. It is apparent from research that long-term consumption of opioids contributes to hormone deficiencies, in particular those that produce adverse sexual side effects.[16–20] These effects may include decreased libido and muscle mass, erectile dysfunction, fatigue, depression, hot flashes, menstrual irregularities, weight gain, and osteoporosis. Given the potential for such effects to reduce quality of life, lower pain thresholds, and increase anxiety and depression, they require timely monitoring and interventions.

A literature review examining the impact of chronic opioid therapy on the endocrine system found extensive hypogonadism in men and women primarily due to central suppression of hypothalamic secretion of gonadotropin-releasing hormone (GnRH).[16] Men taking sustained-release opioids for pain have demonstrated significantly lower levels of testosterone, luteinizing hormone (LH), and other hormones than nonopioid controls.[17] Lower-than-normal testosterone levels and sexual desire have been documented in opioid-consuming male cancer survivors.[18] Women taking chronic opioids also sustain inhibition of sex hormones: Opioid-consuming women compared to nonopioid controls demonstrated lower values of testosterone, estradiol, dehydroepiandrosterone sulfate, LH, and follicle-stimulating hormone (FSH).[19] Similar effects on hormone levels are found with intrathecal administration of opioids. In one study, 23 of 24 men and 22 of 32 women receiving intrathecal opioids had decreased libido, and all opioid-receiving premenopausal women developed menstrual irregularities.[20]

Patients taking opioids for chronic pain should be screened for symptoms associated with abnormalities of sex hormones, and those on high-dose opioids (≥100-mg morphine equivalent) should be tested for serum hormone levels. Recommended lab tests include those for total testosterone, free testosterone, estradiol, LH, and FSH. Hypogonadism is typically diagnosed at less than 300 ng/dL total (bound and free) testosterone.[16]

As a first treatment choice, Katz and Mazer recommend opioid rotation or opioid reduction accompanied by nonpharmacologic treatments for pain.[16] If these measures are unsuccessful, hormone replacement therapy may be considered as follows:

- Testosterone: gel, cream, buccal, transdermal
- Estrogen
- Dehydroepiandrosterone (DHEA), prasteron (INN) (50 to 100 mg/day)
- Thyroxine
- Growth hormone
- Hydrocortisone

Testosterone replacement therapy may be delivered via intramuscular injection or with a transdermal delivery method. For females, consider an oral contraceptive with an androgenic progestin component. The risks and benefits of sex hormone supplementation should be monitored clinically for side effects and via lab tests that include prostate-specific antigen (PSA) in males, complete blood count, and lipid profile.

It should also be noted that poor cortisol and decreased growth hormone secretion have been documented with opioid therapy.[20] Fatigue, muscle weakness, and cognitive disturbances are symptoms of growth hormone deficiency. The clinical significance of these findings has not yet been elucidated.[16]

SLEEP-DISORDERED BREATHING

Recent research has associated sleep-disordered breathing with opioid consumption.[21–23] In one study, 75% of patients with chronic pain who were taking opioids, methadone in particular, had obstructive and central sleep apneas.[21] A significant additive effect was observed with concomitant benzodiazepine administration on methadone-related sleep apnea. In another study, 30% of patients undergoing methadone maintenance treatment had central sleep apnea, which is uncommon in the general population.[22]

The extent to which all opioids are implicated in sleep-disordered breathing bears closer examination. A study of 60 patients taking chronic opioids that included morphine, hydrocodone, oxycodone, and fentanyl as well as methadone, found a dose-dependent relationship between chronic opioid use and the development of what the investigators termed "a peculiar pattern of respiration," consisting of central sleep apneas and ataxic breathing.[23] Complicating risk factors for apnea such as benzodiazepine use, chronic pain, and high body mass index (BMI) (an apparent factor for obstructive but not central sleep apnea) need to be better researched and understood.

Screening and therapeutic options may vary considerably and, at present, the success rate is unpredictable. Regardless, because sleep-disordered breathing appears to be common among opioid-treated pain patients, early detection and interventions along with increased monitoring of patient response are called for.

Data suggest sleep studies are advisable for patients taking methadone more than 40 mg per day and other opioids at approximately 100 to 150 mg morphine equivalent per day.[24] Other risk factors such as concomitant benzodiazepine use or high BMI mean that a patient should be considered for a sleep study at lower opioid doses. For example, it is advisable to obtain a polysomnograph for an obese patient with severe pain before prescribing opioids. Pending those results, or if polysomnography is not possible, the clinician should avoid prescribing opioids at night and should not prescribe benzodiazepines as a sleep aid. Alternatively, tricyclic antidepressants, anticonvulsants, and atypical antipsychotics could be used off-label to facilitate sleep. Sleep studies may be performed via polysomnography or in the home. Home studies, although they lack an electroencephalogram (EEG), are inexpensive and may prove adequate for many patients, particularly for the purpose of ongoing monitoring. Acceptance of home sleep studies as clinically useful faced some initial resistance and reimbursement issues, but Medicare and most insurance companies now approve them.

Table 13-6 shows the current risk stratification strategy used at Lifetree Pain Clinic (e.g., patients considered at highest risk are those on around-the-clock opioids whose central apnea index [CAI] shows five or more events per hour). Checking for adherence with medical direction regarding opioid therapy is vital to the treatment strategy. Patients with sleep apnea must be adherent, and clinicians should impress patients with that necessity.

Often the best treatment is unclear; therefore, it may be necessary to consult with a sleep expert. At the Lifetree clinic, about half of patients diagnosed with central apneas have responded to oxygen alone, while in some cases, continuous positive airway pressure (CPAP) alone has worsened central apneas. If follow-up monitoring checks reveal no increase in safety, opioid dose may need to be lowered and alternative therapies incorporated. Treatment options need to be informed by further research and require individualization.

If, for whatever reason, methadone is chosen for pain, it must be initiated at a low dose and titrated slowly because of its long half-life and lack of cross-tolerance to other opioids.[25] The following conservative prescribing guidelines are recommended for initiating or converting to methadone[25]:

- Do not use conversion tables to determine the initial dose. Consider the patient to be opioid-naive for initiating methadone, regardless of prior opioid dose.
- Start with a ceiling dose of no more than 20 mg/day (10 mg/day for elderly or infirm patients).
- Adjust other medications down slowly while concurrently titrating methadone up slowly.
- Adjust doses no more often than weekly to allow steady-state blood levels of methadone to develop and for the maximum respiratory-depressant effects to become clear.
- The starting dose and speed of methadone titration may need to be adjusted downward if patients are taking concomitant benzodiazepines.

The optimal treatment of opioid-related, sleep-disordered breathing may change with new research. Clinicians who prescribe opioids should be vigilant and treat sleep apnea when it occurs. The challenge is to monitor and adjust medications for maximum safety and pain management.

TABLE 13–6 Risk Stratification after Sleep Study Screening

Level 3 (highest risk)	Around-the-clock opioids with CAI ≥ 5 events/hr
	Around-the-clock opioids with AHI ≥ 30 events/hr
Level 2 (moderate risk)	Around-the-clock opioids with AHI ≥ 5 events/hr
Level 1 (lowest risk)	Patients with AHI < 5 events/hr

AHI apnea=hypopnea index; CAI, central apnea index.

Source: Webster LR: Examining the relationship between long-term opioid therapy and sleep-disordered breathing. Pract Pain Manage *8:56–62, 2008.*

OPIOID-INDUCED HYPERALGESIA

Sometimes administration of opioids appears to make a patient's pain worse. Opioid-induced hyperalgesia (OIH) is best described as a paradoxical response in which sensitivity to painful stimuli increases following opioid administration to treat pain.[26] The mechanism or mechanisms must be better understood, but neuroplastic changes in the peripheral and central nervous systems that lead to sensitization of pronociceptive pathways are thought to be to blame.[26–27] Confusion is possible at the clinical level between OIH and tolerance, which appear to develop together[28] and which may look similar in terms of patient response. However, tolerance, a neurophysiologic adaptation of decreased analgesic effectiveness in response to desensitization of antinociceptive pathways,[27] may be overcome by increasing doses. In contrast, OIH is characterized by lessened analgesic effectiveness coupled with an enhanced sensitivity to pain in which increasing doses may worsen pain. OIH is also a hallmark of opioid withdrawal.[29]

OIH has been demonstrated in animal models,[27–30] and research suggesting that OIH occurs in humans has principally centered on patients in methadone maintenance programs, patients undergoing surgery, and healthy volunteers.[27] Research involving patients treated with chronic opioid therapy has been limited. One preliminary prospective study of six subjects with chronic nonmalignant low-back pain found all patients became hyperalgesic using the cold pressor test, as well as tolerant after 1 month of oral morphine therapy.[31] The testing of the pain tolerance threshold was a facet of the research designed to distinguish tolerance from OIH at the experimental level.

In contrast to experimental models, it may be more difficult to differentiate clinically whether an exaggerated pain response in patients on chronic opioid therapy is due to tolerance or whether the opioid itself is inducing the pain. Most patients on chronic opioid therapy will, over time, require less stimulus to produce a given pain response; however, the response is not proof that the opioid induced the pain. In general, OIH may be suspected when opioids become ineffective in the absence of disease progression, especially if diffuse allodynia unassociated with the previous pain complaint is present.[26]

To assess for the presence of OIH, other possible causes for failure of opioid analgesia must be ruled out as follows[32]:

- Worsening pain pathology
- Opioid tolerance
- Physical withdrawal
- Inadequate analgesia
- Addiction

Means to minimize OIH or possibly to resolve it, include the following[32]:

- The lowest clinically effective opioid dose
- Adjuvant medications to enhance opioid sparing
- Long-acting opioids
- Opioid rotation[33]
- Opioids that incorporate low-dose opioid antagonists[34,35]

Research is unclear regarding optimal opioid doses to avoid OIH, and individual genetic factors, no doubt, contribute. At present, good clinical advice would be to avoid peaks and valleys or periods of opioid withdrawal during opioid administration. Interest in agonist-antagonist combinations is increasing. For example, two randomized clinical trials found significant chronic pain relief along with lessened physical withdrawal in patients taking oxycodone combined with low-dose naltrexone compared with oxycodone alone [34,35]; however, further research is needed to confirm the consistency of these results. What additional literature exists on the resolution of OIH indicates that blockade of NMDA receptors may reduce or reverse OIH,[36] and that methadone may be useful in attenuating OIH, if only at high doses.[33]

CONCLUSION

Opioid analgesia is life enhancing for many who otherwise would live with chronic pain. However, opioids come with significant risks and will prove more harmful than helpful for some patients. Warning signs to look for include no benefit from opioids despite dose adjustments, side-effect management, and/or opioid rotation; poor tolerance at analgesic doses; persistent adherence problems despite appropriate limits and monitoring; or the presence of a complicating comorbid condition that renders opioid therapy ineffective or harmful.[37] For patients who do not realize adequate benefit from opioid therapy and pending additional research into the impact of long-term opioid administration, humane tapering and alternative pain therapies may provide the best option.

KEY POINTS

- The risk-benefit profile of long-term opioids should be carefully weighed in regard to risks for misuse or addiction, endocrine deficiencies, medical comorbidities such as sleep-disordered breathing, and the development of heightened pain sensitivity.
- Every clinician who provides opioids should be familiar with risk factors for opioid misuse or addiction, screen patients accordingly, and set a level of clinical monitoring and reassessment appropriate to the degree of risk, which may change over time.
- Patients with symptoms of sex hormone deficiency and those on high-dose opioids should receive timely interventions and monitoring that may include opioid rotation, opioid reduction, or hormone replacement therapy.
- A link to sleep apnea has been found with methadone that appears to worsen when tranquilizers are added. Additional results indicate a need for caution when using all opioids, not just methadone.
- Heightened pain sensitivity—or OIH—is possible with opioid therapy and should be suspected if inadequate analgesia pairs with unexplained escalation of pain. Resolution of OIH may involve opioid rotation or other measures up to tapering from opioids.
- Further research is required to elucidate the clinical implications of chronic opioid therapy.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 14

Legal and Regulatory Issues in Pain Management

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Access to effective pain treatment requiring prescription opioid analgesics remains inequitable, resulting in a high prevalence of unrelieved pain in the United States. This situation stems from a variety of clinical and patient issues, including characteristics of the health-care system and health-care professionals.[1–7] In recent years, however, issues concerning pain management have increasingly been raised concerning public policy and law. Restrictive federal and state policies relating to drug control and health-care practice (referred to as "regulatory barriers") can impede pain management, determined by the extent that practitioners know of and adhere to such policies. Addressing these barriers involves an understanding of the convergence of pain medicine and the law—both in terms of laws and policies affecting pain management and of litigation involving pain management.

LAWS AND POLICIES AFFECTING PAIN MANAGEMENT

Legislative bodies typically create laws (i.e., statutes) that are broad and general, and depend on the relevant regulatory agency to interpret and implement the laws. For medicine, the legislature grants authority to the state medical board to operationalize and uphold its laws through regulation. Such professional boards generally have updated their pain management policies in reaction to changing professional standards. Alternatively, pain-related laws have not kept pace with advances in medical and scientific understanding. This has particular implications for treating pain with opioids, where relevant legislation can have extensive detail and not reflect current medical standards. Although clinicians generally do not receive training in legal and regulatory issues related to opioid prescribing, and are not familiar with the federal and state laws that govern their practice, they are increasingly being called on to have knowledge of these policies.[8]

FEDERAL CONTROLLED SUBSTANCES LAWS

Controlled substances laws govern the distribution of prescription medications that have an abuse liability (i.e., that fulfill the potential to produce psychological or physical dependence), establishing a closed distribution system to minimize their abuse, trafficking, and diversion. The federal Controlled Substances Act (CSA)[9] is the principal drug control law in the United States. The CSA prohibits the nonmedical use of controlled substances and establishes criminal penalties for their illicit possession, manufacture, and distribution, while at the same time recognizing that they have a useful and legitimate medical purpose, that they are necessary for public health, and that their medical availability must be ensured. "Controlled substances" status of any medication is not intended to diminish its medical usefulness or create the perception that practitioners should avoid its use when appropriate. The legislative history, as well as language contained in the CSA itself (and its related regulations called the Code of Federal Regulations [CFR]), makes it clear that efforts to prevent drug abuse and diversion should not interfere with legitimate medical practice and appropriate patient care.[10] This position conforms to a longstanding medico-legal principle, referred to as "balance" and established by the *Single Convention on Narcotic Drugs of 1961*.[11]

The CSA specifies five classification schedules for controlled substances, each carrying different penalties for unlawful uses. Both a drug's medical usefulness and abuse liability form the basis for the decision to assign it to a particular schedule.[12] Schedule I controlled substances (e.g., heroin, LSD, and marijuana) have no currently accepted medical use, no accepted safety for use under medical supervision, and a high potential for abuse, and are available only for scientific research. Drugs that have an approved medical use are placed in Schedules II through V according to potential for abuse (Box 14-1). Under federal law, the Drug Enforcement Administration (DEA) is the primary federal agency responsible for enforcing the CSA and, thus, has regulatory authority over controlled substances in every schedule.

Licensed practitioners must be registered with the DEA to prescribe, dispense, and administer controlled substances,[13] which must be used only for legitimate medical purposes and in the usual course of professional practice.[14] Prescriptions for Schedule II medications must be written and may not be refilled,[15] while five refills are permitted for drugs in Schedules III and IV.[16] Federal law allows oral or faxed (but not electronic) transmission of prescriptions for Schedule II controlled substances in medical emergencies under specific circumstances.[17] It also is possible under federal law to partially dispense and fax (but not transmit orally or electronically) prescriptions under certain circumstances.[18] Importantly, the DEA recently revised the CFR to provide practitioners with the option of writing prescriptions for controlled substances electronically.[19]

Despite these requirements, numerous additional provisions demonstrate that federal drug control laws are not intended to interfere with medical practice or limit the availability of controlled medications for patient care.

Ensuring Medication Availability: The CSA authorizes the DEA to establish production quotas for a number of opioids and other controlled substances as a means to curtail diversion resulting from excessive unused supplies.[20]

Box 14–1 Controlled Substances Schedules for Opioid Analgesics

Schedule II drugs have the highest potential for abuse, and include such opioids as codeine, fentanyl, hydromorphone, meperidine, methadone, morphine, and oxycodone.

Schedule III drugs have a lower abuse potential than Schedule II drugs, and include opioids such as dihydrocodeine and hydrocodone- or codeine-combinations with aspirin or acetaminophen.

Schedule IV drugs have a lower abuse potential relative to drugs in Schedule III, and include opioids such as dextropropoxyphene, propoxyphene, and pentazocine.

Schedule V drugs have a low abuse potential compared to drugs in Schedule IV and include compounds or preparations containing limited quantities of opioids such as codeine or opium, which may be used for over-the-counter preparations to treat cough or diarrhea, respectively.

Such quotas, however, are intended to maintain sufficient supplies for accommodating all medical and scientific needs.[21]

Medical Practice Is Not Regulated: The authorization to regulate medical practice belongs to the states and underlies the medical practice acts that are designed to protect the public health and safety.[22] Thus, the CSA provides no authority for the DEA to define or regulate medical practice.[9] The DEA's enforcement authority is intended to relate to clinicians involved in unlawful distribution of controlled substances that is outside legitimate health-care practice (i.e., behaviors that are clearly criminal).

Treating Addiction versus Treating Pain: Under the CSA it is unlawful to prescribe opioids (i.e., methadone and buprenorphine) to treat addiction, which requires separate registration by the federal government as an opioid treatment program (OTP) for the purpose of maintenance or detoxification of opioid addiction.[23] However, methadone, a Schedule II medication approved for the purpose of addiction treatment, also can be prescribed as an analgesic according to the same laws for prescribing any other Schedule II opioid; the same holds true for buprenorphine and other Schedule III opioids. In addition, it continues to be permitted under federal law to use opioids to treat pain in patients even when they have a history of substance use or current addictive disease. Critically, determining the legitimacy of a particular prescribing practice must be based on the purpose of the prescribing and not the type of patient being treated.

Treating Intractable Pain: DEA regulations clearly state that practitioners who use opioids to treat intractable pain over an extended period are considered to be acting within the course of professional practice.[24] Such a provision further supports the necessity of making clinical and legal determinations founded on the purpose of prescribing.

Off-Label Use: Once a medication is approved, a physician can prescribe and a pharmacist can dispense that medication for "off-label" uses (i.e., uses not included in the approved labeling), if there is a recognized medical basis for those uses.[25,26] Federal law does not restrict a physician's prescribing either to recommended doses or to labeled indications.[27] Off-label medication use simply reflects physicians' lawful ability to prescribe for a medical purpose and in the interest of the patient according to their best knowledge and judgment.[28]

Prescription Amount and Duration: Federal laws do not set limits on the amount or duration of medication that a practitioner can prescribe, administer, or dispense at one time. Importantly, the DEA clarified that this standard did not change when the CFR was recently amended to allow practitioners to issue multiple prescriptions of a Schedule II controlled substance, each issued on the same date and filled sequentially (called a "prescription series").[29] With the CFR amendment, the DEA's stated intent was to permit health-care professionals to better manage chronic pain in stable patients while exercising improved control over potential medication abuse and diversion, which is consistent with the principle of balance.[30]

STATE CONTROLLED SUBSTANCES AND HEALTH-CARE LAWS

Both federal and state laws regulate the prescribing, dispensing, and administering of controlled substances. In addition, states are solely responsible for regulating health-care practice, including medical, pharmacy, and nursing practice, and such regulatory policies can be used to address concerns that professionals hold about investigation or sanction for prescribing pain medications. State drug control laws, however, are generally not as balanced as federal law.[31] For example, such state laws generally do not reflect the federal law's recognition that controlled medications are important to public health.[32] Some state laws also consign greater restrictions than do federal laws regarding the prescribing and dispensing of opioids, which ultimately can interfere with medical decision making that should be based both on the expertise of the practitioner and individual patient needs, rather than on excessive governmental conditions. The messages and requirements contained in state policies that govern health-care practice, including opioid prescribing, are known to contribute to inadequate pain management.[33,34] As a result, achieving more balanced state policy is a necessary part of a multifaceted plan to improve pain and symptom management while stemming prescription medication abuse and diversion.[35]

EVALUATING THE QUALITY OF STATE PAIN POLICY

A criteria-based policy research methodology recently was developed to evaluate and promote balanced state drug control and health-care regulatory policies related to pain management, palliative care, and end-of-life care. Balanced state policies do not create barriers to appropriate health-care practice and patient care and will support pain treatment, including the use of controlled substances, as an essential part of quality medical practice. The evaluation uses 16 criteria from two categories: (1) positive provisions—policy language that can *enhance* pain relief, and (2) negative provisions—language that can *impede* pain relief. The report containing a complete description of the criteria, the evaluation methodology, and the

identified policy language from all states (including the District of Columbia) that satisfies each criterion has been collected by the Pain & Policy Studies Group.[36] State policy evaluations were conducted in 2000, 2003, and 2006–2008, but the 2008 evaluation provides the findings presented in Table 14-1.

Overall, policy language that promotes appropriate pain management and that can enhance patient access to effective pain care is common in policies from state regulatory agencies, rather than from legislative drug control statutes.[31] A state's drug control laws are considered unbalanced when they lack these positive messages, because they focus disproportionately on the abuse potential of opioids while failing to recognize their public health and medical benefits when used appropriately. In addition, some state policies, which were adopted to prevent drug abuse and substandard prescribing practices, create additional requirements that unduly restrict health-care decision making, do not conform to and even conflict with current standards of professional practice, and place excessive burdens on patients.

GRADING THE QUALITY OF STATE PAIN POLICY

Findings from each criteria-based evaluation of state pain policy also serve as the basis for a methodology to quantify a state's policy based on its quality, creating a single metric that can then be used to compare all states and track policy change over time. Each state now has been assigned a grade (ranging from A to F) for 2000, 2003, 2006, 2007, and 2008. A higher grade means that a state's policies has many positives and few negatives and is, therefore, more balanced and consistent with modern medicine. An A is achieved only if a state has a high number of positive provisions and no instances of restrictive or ambiguous language. A lower grade is associated with the presence of provisions that contradict current medical knowledge, are inconsistent with policy guidance recommendations from authoritative sources, or fail to communicate the appropriate messages about pain management to professionals, patients, and the public. An F results when a state has many negative provisions and no positive language.

TABLE 14–1 Frequency of Criteria Fulfilled During 2008 Evaluation of State* Pain Policies

Positive Provisions: Criteria that Identify Policy Language with the Potential to Enhance Pain Management
1. Controlled substances are recognized as necessary for the public health (in 4 states)
2. Pain management is recognized as part of general medical practice (in 46 states)
3. Medical use of opioids is recognized as legitimate professional practice (in 51 states)
4. Pain management is encouraged (in 39 states)
5. Practitioners' concerns about regulatory scrutiny are addressed (in 40 states)
6. Prescription amount alone is recognized as insufficient to determine the legitimacy of prescribing (in 34 states)
7. Physical dependence or analgesic tolerance are *not* confused with "addiction" (in 37 states)
8. Other provisions that may enhance pain management
Category A: Issues related to health-care professionals (in 48 states)
Category B: Issues related to patients (in 23 states)
Category C: Regulatory or policy issues (in 49 states)
Negative Provisions: Criteria that Identify Policy Language with the Potential to Impede Pain Management
9. Opioids are considered a treatment of last resort (in 6 states)
10. Medical use of opioids is implied to be outside legitimate professional practice (in 10 states)
11. Physical dependence or analgesic tolerance are confused with "addiction" (in 16 states)
12. Medical decisions are restricted
Category A: Restrictions based on patient characteristics (in 8 states)
Category B: Mandated consultation (in 8 states)
Category C: Restrictions regarding quantity prescribed or dispensed (in 8 states)
Category D: Undue prescription limitations (in 5 states)
13. Length of prescription validity is restricted (in 4 states)
14. Practitioners are subject to additional prescription requirements (in 6 states)
15. Other provisions that may impede pain management (in 4 states)
16. Provisions that are ambiguous
Category A: Arbitrary standards for legitimate prescribing (in 15 states)
Category B: Unclear intent leading to possible misinterpretation (in 20 states)
Category C: Conflicting (or inconsistent) policies or provisions (in 8 states)

Source: Pain & Policy Studies Group: Achieving Balance in State Pain Policy: A Progress Report Card, ed 4. Madison. WI: University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, 2008.
** Includes the District of Columbia.*

The grades, and the methodology used to calculate the grades, are contained in a recent report by the Pain & Policy Studies Group.[37] In the aggregate, the last decade was a time of notable improvement in the quality of many states' drug control and professional practice policies. No states' grade decreased over the entire 8-year evaluation timeframe; by and large, states have avoided adopting new policies that could impede pain management and the medical use of controlled substances. Generally, this substantial policy change has contributed to an abundance of positive messages about effective pain treatment, including statements to reduce licensees' concerns about regulatory scrutiny when prescribing opioids.

Much of the improvement in the quality of state pain policies results from individual health-care regulatory boards taking advantage of policy templates by the Federation of State Medical Boards to promote consistency in state medical board policy.[38,39] These templates encourage safe and effective pain relief, perpetuate the message that pain management and the appropriate use of controlled substances is an accepted part of professional practice, and reassure clinicians that they have nothing to fear from their licensing agency if reasonable professional practices are followed when using controlled substances for patient care. In addition, health-care regulatory boards (e.g., medical, osteopathic, pharmacy, and nursing) in some states have worked together to adopt joint guidelines for pain management, palliative care, and end-of-life care.[36] Such policies tend to emphasize the value of a multidisciplinary approach to treating pain, recognize that the goal of pain treatment should include improvements in patient functioning and quality of life, and ensure that a broader variety of health-care practitioners should not fear disciplinary action from their licensing board.

Given this notable regulatory progress, most states now can achieve greater balance in their pain policies only through efforts to remove long-outdated restrictive or ambiguous language from law, some of which has been present for over 30 years. This is especially the case with drug control laws that contain outdated definitions of "drug-dependent person" (or "addict") that are based on the concept of physical dependence and developing a withdrawal syndrome. Such definitions should be abrogated because they can legally classify as an addict any patient who is taking an opioid to treat pain.[40] Repeal from law of archaic restrictive language has received less attention compared to the work of professional licensing boards to adopt positive policy.[37] Although states must be allowed to vary in their approaches to public policy, the creation of undue restrictions is not obligatory in laws designed to control drug diversion or regulate professional practice. Avoiding such language ensures that patient care decisions requiring medical judgment are not inappropriately limited by governmental laws.

THE IMPORTANCE OF PRACTITIONERS IN IMPROVING STATE POLICY

Inadequately treated pain is a multifactorial phenomenon and, as such, focusing solely on changing state policy is likely insufficient to guarantee patient access to appropriate pain relief and symptom control. Addressing this single factor, however, remains a necessary activity to attain a supportive professional practice and regulatory environment for the safe and effective treatment of pain. Since the late 1990s, there has been an evolution in how the pain management field characterizes unbalanced policy, from being a "condition" that is unavoidable and intractable to a "problem" that can be solved.[41] Achieving balanced state policies covering pain-related issues requires a strategic approach, often beginning simply by determining the types of policies in need of improvement. For example, improving statutory law requires legislative activity, whereas changing regulatory policy involves engaging with the relevant health-care administrative agency such as the medical, pharmacy, or nursing board. Health-care practitioners increasingly have assumed a leadership role in collaborating with legislators or members of administrative agencies to construct state policy that avoids undue restrictions, recognizes the professional obligation to treat pain, and promotes effective patient pain care. This activity has been successful when practitioners have acted alone, in conjunction with a state pain initiative or other organization, or as a member of a legislatively created advisory committee.

LITIGATION INVOLVING PAIN MANAGEMENT

The provision of pain management by health-care professionals has been the subject of litigation in all four domains of the law: administrative proceedings, civil litigation, criminal litigation, and constitutional challenges. Cases have arisen in both state and federal tribunals. We will consider the general nature and trends of proceedings in each of these domains, with brief mention of particular cases. Readers are encouraged to directly access the referenced cases for more details on those of particular interest.

ADMINISTRATIVE PROCEEDINGS

The most influential and frequently discussed proceedings are those of state medical licensing boards. Until very recently, medical boards generally were viewed by physicians as hostile to the prescribing of opioid analgesics except for patients in an advanced stage of terminal illness.[42] The phenomenon of opiophobia and the pervasive myths and misinformation concerning opioid analgesics were as prevalent among members of medical boards as in the medical profession generally as well as the general public.[43] Prior to 1999, there was no record of a state medical board initiating any disciplinary proceeding against a physician for failure to provide adequate pain relief to a patient, yet proceedings for excessive or otherwise inappropriate prescribing of opioids was common. This state of affairs was particularly curious as the data confirmed that in fact undertreated pain had reached epidemic proportions by the latter part of the 20th century and lamentably continues unabated.[44]

A case that demonstrates the attitudes of state medical boards toward opioid prescribing, particularly regarding chronic noncancer pain, was *Hoover v. Agency for Health Care Administration*, a disciplinary action by the Florida medical licensing board. Dr. Katherine Hoover was a

board-certified internist who cared for a number of patients with serious chronic pain problems that were effectively manageable only with opioids. The board singled out seven of her patients as the basis of disciplinary proceedings. The hearing officer in the case ruled in favor of Dr. Hoover, finding that the board's "experts" (two physicians who did not treat chronic pain patients and who had only reviewed pharmacy computer printouts) failed to establish that her prescribing for these patients was excessive. Nevertheless, the board imposed sanctions against Dr. Hoover, which she appealed. The Court of Appeals reversed the board's disciplinary action stating: "[T]he board has once again engaged in the uniformly rejected practice of overzealously supplanting a hearing officer's valid findings of fact regarding a doctor's prescription practices with its own opinion in a case founded on a woefully inadequate quantum of evidence."[45]

In 1999, the Oregon Board of Medical Examiners became the first state board to actually discipline a physician for inadequate management of pain. Dr. Paul Bilder, a pulmonary specialist, was found to have failed to properly manage the pain or severe symptom distress of six seriously ill or dying patients over a period of 5 years.[46] Despite a formal reprimand, a requirement to complete the board's Physician Education Renewal Program, and a 10-year probation, Dr. Bilder was the subject of board discipline 2 years later for further instances of undertreating pain.[47]

Largely through the efforts of the Federation's Model Guidelines (1998) and Model Policy (2004) on opioid prescribing, a majority of state medical boards are now on record emphasizing the need for physicians to incorporate sound pain management practices into their patient care.[48] However, the gulf between policy and practice persists.

CIVIL LITIGATION

As with administrative proceedings regarding pain management practices, the civil litigation climate has changed markedly in the last two decades. Before 1990, there were no civil actions solely or primarily grounded on an alleged failure of a health-care institution or professional to provide effective pain relief. In the next decade, several cases revealed that in fact undertreated pain could be shown to be substandard patient care. The first such case was successfully litigated in North Carolina in 1991, when a skilled nursing facility (SNF) was subjected to a multimillion-dollar–damage jury verdict because one of its nurses had deliberately deprived an elderly patient dying of metastatic prostate cancer of the strong pain relievers previously prescribed by a community physician. This conduct was deemed to be so egregious that millions of dollars of punitive damages were assessed in addition to compensatory damages.[49]

Ten years later, a California jury determined that a physician had perpetrated elder abuse when he failed to adequately manage the pain of a hospitalized patient who was within weeks of death from lung cancer. Again, damages in excess of a million dollars were awarded to the deceased patient's family, and the jury came within one vote of also assessing punitive damages.[50] The case was particularly significant for several reasons. First, as an elder abuse claim, the plaintiff's burden of proof was the much more challenging "clear and convincing evidence" standard rather than the "preponderance of the evidence" standard generally applicable in medical malpractice claims. Second, the jury found liability not for a mere departure from the standard of acceptable care, but rather for a gross departure or reckless disregard for the patient's well-being. They did so despite testimony by defense experts that the defendant's treatment was consistent with the usual custom and practice among physicians. What may have enabled the jury to find the custom and practice itself to be deficient was the admission into evidence of the Agency for Health Care Policy and Research Clinical Practice Guidelines for the Management of Cancer Pain.[51] The therapy recommended in these guidelines was in stark contrast to that provided by the defendant physician. It should be noted that the family initiated the litigation only after their complaint against the physician filed with the Medical Board of California failed to result in any disciplinary action against the physician, even though the Board's own expert reported that the pain management provided was inadequate.

The third case also involved an elderly cancer patient, this one suffering from mesothelioma. The allegations in the suit brought by his widow and daughter were that at both a local community hospital and the SNF to which he was subsequently transferred, his pain management was woefully inadequate, resulting in weeks of unnecessary suffering before he died.[52] Because this case was in California, as was the previous one just noted, all defendants elected to settle with the plaintiffs prior to trial. Also, state regulatory agencies took disciplinary action against the SNF and the physician responsible for the patient's care.[53]

The reaction of the medical profession generally to these trends toward holding health-care professionals and institutions responsible for the effective management of pain has been quite mixed. Proponents of the proposition that good pain management is an essential element of quality patient care argue that such changes in approach are long overdue. Critics argue that they place clinicians between a rock and hard place, still very much vulnerable to punitive measures for "overprescribing," yet now also at risk for administrative sanction and civil liability for undertreating pain. A more balanced and nuanced perspective would be that it was always an anomalous and untenable situation that there could be overprescribing but never underprescribing, or that all other aspects of patient care were governed by a minimally acceptable standard of care, except for the management of pain sometimes requiring opioids.

CRIMINAL LITIGATION

Criminal prosecutions of physicians at either the state or federal level are relatively rare, and generally reserved for egregious departures from acceptable care.[54] Those concerning pain management usually involve allegations that excessive prescribing of opioids either lead to a patient's untimely death and therefore constituted homicide, or that the prescriptions had no legitimate medical purpose

and therefore violated provisions of the federal CSA. These cases vary significantly based on their underlying facts, but the following are illustrative of the two general types.

In 1994, the attorney general of Kansas filed a two-count indictment against small-town Kansas physician L. Stanley Naramore relating to his care of two terminally ill patients. One of these patients, Ruth Leach, will be our focus. She was dying of advanced breast cancer metastatic to bones, lungs, and brain. Dr. Naramore was charged and convicted of her attempted murder based on the doses of Versed and fentanyl that he prescribed to control her pain when she was in the hospital, and his plan to subsequently administer morphine. Shortly after explaining the need to ensure her comfort, he was told by the patient's son that he would be held accountable for the patient's death, whereupon he withdrew as her physician. Mrs. Leach was subsequently transferred to another hospital where she died several days later of her cancer. At the criminal trial the state's expert witnesses testified that the types and doses of pain medications prescribed Dr. Naramore were excessive and would have shortly thereafter resulted in respiratory failure. Dr. Naramore's expert witnesses testified that his plan for controlling Ruth Leach's pain was well within the standard of acceptable care given her pain and distress and her impending death from cancer.

Perhaps the most significant aspect of the Naramore prosecution was the disposition of the conviction on appeal.[55] The Kansas Court of Appeals noted that the transcript of this trial looked very much like the typical "battle of the expert witnesses" that characterizes medical malpractice cases. While in such civil actions a jury has substantial discretion as to what evidence it finds persuasive, in a criminal prosecution the jury must find beyond a reasonable doubt that all elements of the offense charged have been proven. The court concluded that on the record before it, no reasonable jury could have found that beyond a reasonable doubt Dr. Naramore intended to kill Ruth Leach rather than to control her pain and symptom distress as she was dying of her underlying disease. The case should stand not only as reassurance to physicians caring for dying patients, but also as a cautionary tale for prosecutors that if the defendant can provide competent, credible expert testimony in support of the appropriateness of the care provided, the state's burden of proof cannot be met and in the reasonable exercise of prosecutorial discretion no charges should be filed.

Federal prosecutions for violations of the CSA have often involved physicians caring for large numbers of patients with chronic noncancer pain. A typical, and closely followed case, was *United States v. Hurwitz*. Dr. William Hurwitz operated a pain medicine practice in McLean, Virginia; patients from 39 states came to his practice seeking opioids to manage their chronic pain conditions. He was indicted in 2004 by a federal grand jury on 62 counts, including drug trafficking resulting in death and serious bodily injury and health-care fraud, among others. The prosecution claimed that Dr. Hurwitz knew, or in the exercise of sound clinical judgment should have known, that many of the persons to whom he prescribed opioids were either addicts or sought drugs for misuse or diversion. He was subsequently convicted of 50 counts. On appeal, the 4th Circuit Court of Appeals reversed the convictions and remanded the case for a new trial on the grounds that he had not been allowed to argue to the jury that his prescribing had been a good faith exercise of clinical judgment.[56] When retried, Dr. Hurwitz was convicted of 16 counts and sentenced to 57 months in prison.

There is a legitimately concerning element that is common to many of these prosecutions. The government and its expert witnesses have been able to persuade juries that there are only two types of situations and a clear line of demarcation separates them. The first constitutes adherence to the standard of care for prescribing opioids. The second is a material departure from the standard of care that takes the physician's action outside the bounds of medical practice and renders the prescribing physician nothing more than a drug dealer with a medical degree. In fact, whether one is prescribing opioids for chronic pain or practicing any other form of medicine, there are many levels of care, only one of which can be properly characterized as "outside the bounds of medicine." At the pinnacle of the hierarchy of practice would be "best practices," such as consistently following nationally recognized clinical practice guidelines. Below that would be the usual custom and practice or acceptable care, which may or may not track the guidelines. Further down would come isolated instances in which a practitioner's care falls below the standard of care and may give rise to a malpractice claim or minor action by a state medical board. Below this would be serious or repeated departures from acceptable practice, which might not only lead to multiple adverse medical malpractice verdicts but also suspension or revocation of medical licensure. The final category would be practices so far removed from the standard of care as to be characterized as "outside the bounds of medicine." Unless and until drug regulators, prosecutors, and juries come to recognize these distinctions, there will continue to be a profound chilling effect on prescribing practices from high-profile and successful prosecutions like that of William Hurwitz.

CONSTITUTIONAL CASES

The cases involving pain management that involve constitutional interpretation have, for the most part, concerned the phenomenon of prohibitions on or attempts to regulate the practice of providing a lethal prescription at the request of a terminally ill patient. In 1997, the U.S. Supreme Court ruled unanimously that there is neither a constitutional right to nor a constitutional prohibition of what was then characterized as "physician-assisted suicide." Thus, the matter was left to "the laboratory of the states" as one of the justices phrased it.[57] In the early years of the President George W. Bush's administration, Attorney General John Ashcroft sought to nullify the Oregon Death with Dignity Act, which legalized and regulated the provision of lethal prescriptions for terminally ill patients. He insisted that such prescriptions violated the CSA since there was no legitimate medical purpose to support them. The case took many years to litigate, and by the time it reached the Supreme Court,

Ashcroft had been succeeded by Alberto Gonzales. In 2006, the Supreme Court ruled (by a 6–3 vote) that the Attorney General had exceeded his authority when he issued an interpretive ruling that such prescriptions violated the CSA and could therefore be the basis of physician sanction.[58] The reasoning of the majority was that regulation of the medical profession has been traditionally a matter of state law, and nothing in the language or history of the CSA supported the Attorney General's position.

CONCLUSION

In the past two decades pain management has taken on a visibility and sense of priority heretofore unprecedented. Considerable progress in the policy environment has been made, and is likely to continue given the increased appreciation, resources, and activity for this topic. Awareness and use of the policy information and policy change actions mentioned in this section not only can contribute to further improvement in laws and regulatory policies across the United States, but also can lead to health-care professionals having more thorough knowledge about the requirements and restrictions contained in the policies governing their practice. In addition, the extent that regulatory agencies officially recognize the legitimacy of effective pain management using controlled substances, coupled with an increased practitioner understanding of the messages from their states' statutes, regulations, and other health-care policies, has a great potential to reduce concerns about scrutiny for such practice and to enhance compliance. We have entered a period when newly adopted state drug control laws and regulations and health-care regulatory board policies are establishing few significant barriers to appropriate and effective prescribing of controlled substances for pain relief. As this occurs, the challenge then becomes revoking already-instituted impediments, as well as ensuring that the enhancements in policy that we currently are witnessing are sustained.

Health-care institutions and professionals are now on notice that pain management must be a priority in patient care. However, law and public policy also require that the prescribing of opioids for pain control must reflect recognition that these medications pose a risk of abuse and diversion, so they must be prescribed responsibly and in the exercise of sound clinical judgment and oversight of patient adherence to the pain management plan of care. Despite some exceptions, adverse legal actions against health-care professionals have involved extreme cases, leaving most practitioners without major risk.[59]

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 15

Psychopharmacology for Pain Medicine

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A large percentage of patients with chronic pain disorders have coexisting, or comorbid, psychiatric conditions, which are the most prevalent comorbidities in patients with chronic pain. Compared to patients with little or no psychiatric comorbidity, these patients have a worse pain and disability outcome, regardless of treatment, be it medications, nerve blocks, or physical therapy.[1–3] This is particularly true in patients with chronic low back pain.[4] Patients with pain and psychiatric comorbidity are commonly referred to pain medicine clinics and frequently present on psychoactive medications. Many of these medications, such as antidepressants and anticonvulsants, also have analgesic properties, and are a mainstay of the drug armamentarium of the pain physician. Consequently, it behooves the astute pain practitioner to be familiar with the psychiatric comorbidities of patients with chronic pain and to understand how to use psychoactive medications to treat both pain and/or psychopathology. Psychotherapeutic modalities, such as cognitive behavioral therapy, relaxation training, or biofeedback, play an important role in the treatment of both psychiatric and chronic painful illness, and in some cases are the preferred method of treatment. However, this chapter focuses on the use of medications as they pertain to treating patients with pain and psychiatric comorbidity. As with many of the medications used in pain medicine, psychoactive medications with reported analgesic properties do not always have a Food and Drug Administration (FDA) indication for this purpose, but can legally be prescribed for off-label use.

EPIDEMIOLOGY

Over two decades of studies of U.S. pain clinic populations have shown that 60% to 80% of these patients have psychiatric illnesses by DSM criteria.[5–7] Estimates are lower in persons with pain in primary care, institutional, and community settings, but regardless of setting, given the prevalence of persistent pain in adults, estimated at 20% to 45%, pain-psychiatric comorbidity constitutes an important public health problem.[8,9] Patients with psychiatric illness report greater pain intensity, more pain-related disability, and a larger affective component to their pain.[3,10,11] The majority of patients with psychiatric comorbidity developed their psychiatric illness after the onset of chronic pain. Major depression alone affects 30% to 50% of all pain clinic patients, followed by anxiety disorders, personality disorders, somatoform disorders, and substance use disorders.[5,12,13] Virtually all psychiatric conditions can be treated with variable improvement, and the majority of patients provided with appropriate treatment significantly improve. Of the disorders that most frequently affect patients with chronic pain, major depression and anxiety disorders are the most common and have the best response to medications, and so their treatment is the focus of this chapter. Regardless of the specific psychopathology, however, improvement in psychiatric illness results in diminished pain levels, greater acceptance of the chronicity of pain, improved functionality, and an improved quality of life. Although this chapter focuses on psychopharmacologic treatment, it is important to note that, in general, combined pharmacologic and psychotherapeutic treatments are more effective in treating depression and anxiety than pharmacologic treatment alone. Psychotherapeutic treatments (e.g., cognitive behavioral therapies, relaxation and biofeedback, interpersonal therapies, group therapies, etc.) are covered in other chapters in this book.

PSYCHIATRIC NOSOLOGY

Mental health practitioners use the *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* or the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) as an aid in making psychiatric diagnoses.[14] While these manuals elegantly outline the suggested criteria for psychiatric diagnosis, they are not very good at highlighting which symptoms are more or less important in making a diagnosis. While the criteria have high reliability, that is, two psychiatrists applying the criteria to the assessment of the same patient will very often come up with the same diagnosis, the criteria do not all have equally high validity. That is, there is no universal agreement that the symptoms listed under diagnostic criteria for a particular condition are the best description of that illness.[15] In this light, and in an attempt to demystify psychiatric diagnosis for the pain physician, the following descriptions of psychopathology will emphasize the hallmark features of each illness.

MAJOR DEPRESSION AND SUBTHRESHOLD DEPRESSION

According to the DSM-IV, major depressive disorder (MDD) requires two key features: depressed mood and loss of interest or pleasure in most activities (anhedonia) for at least 2 weeks. The lifetime risk of MDD is 7% to 12% in men and from 20% to 25% in women.[16] But, the risk of major depression in patients with pain is at least twice as high. As the most prevalent of the psychiatric comorbidities, major depression can be distinguished from situational depression (also termed "demoralization" or an "adjustment disorder with depressed mood") by the triad of persistently low mood, self-attitude changes, and changes in vital sense, all lasting at least 2 weeks.[15] Low mood manifests itself by emotions of "feeling blue," down, or depressed. Anhedonia, or the inability to experience pleasure, is a key reflection of low mood. A diminished self-attitude is seen in thoughts of guilt or thinking that one is a bad person. Changes in vital sense refer to

changes in sleep, appetite, or energy levels. Patients with major depression often feel that their thinking is slow or fuzzy and have difficulty concentrating. Depressed patients may feel anxious, have panic attacks, or post-traumatic stress disorder (PTSD) symptoms, which if they occur in the presence of significant depression symptoms are consistent with a MDD, not a separate anxiety disorder. Depressive symptoms may present as Beck's triad, with patients feeling hopeless, hapless, and helpless. They see the future as bleak, they feel they cannot help themselves, and no one can help them.[17] Suicidal thoughts reflect the severity of depressive symptoms. Untreated or undertreated major depression has a lifetime risk of death through completion of suicide of 10% to 15%.[18] Major depression is a serious complication of persistent pain, and if not treated effectively, it will reduce the effectiveness of all pain treatments. Even low levels of depression ("subthreshold depression") may worsen the physical impairment associated with chronic pain conditions and should also be treated.[10]

TREATMENT

Antidepressants can take up to 2 to 4 weeks for an initial response, but all can take 4 to 8 weeks for full clinical improvement after a typical dose is reached, and remission may take longer. This can be particularly the case for depressed patients who also suffer from comorbid pain. Patients should remain on them for 6 to 12 months for the treatment of an initial depressive episode, and 5 years for the treatment of a recurrent depressive episode. Regardless of the medication chosen, approximately 60% of patients will respond (have at least a 50% improvement) to the initial antidepressant prescribed. At least 80% of patients will respond to at least one medication, either with or without an augmentation agent, such as lithium, an anticonvulsant, or another antidepressant.[19] There is some evidence that pain patients with major depression have increased treatment resistance, particularly when their pain is not effectively managed.[8] Older adults tend to respond at lower doses of antidepressants, and dose titration should occur more slowly in this group because of their heightened sensitivity to side effects and toxicity.[20] A good rule of thumb in starting antidepressants in any age group is to begin with 25% to 50% of the standard initial treatment dose for a week, and then advance gradually over the next 2 to 3 weeks to the treatment dose. This minimizes side effects and increases treatment compliance.

Often, patients with chronic pain are on multiple medications that can potentiate the side effects of antidepressants, such as headache, nausea, constipation, or sedation, so "starting low and going slow" is even more important in this population. Typically, in the initial treating period, re-evaluations are done every 2 to 4 weeks, with dose adjustments if indicated. Monoamine oxidase inhibitors (MAOIs), such as phenelzine, which are rarely prescribed anymore, should not be prescribed with other antidepressants concurrently. Because of the inherent risks of these medications, they should be used only by experienced psychopharmacologists.[21]

Cognitive behavioral therapy (CBT) in conjunction with antidepressant therapy is the most efficacious treatment for major depression. Cognitive behavioral therapy examines negative and destructive thoughts that arise in conjunction with low moods, helping patients to see the unrealistic and maladaptive qualities of thoughts and behaviors.[22]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

Since the introduction of fluoxetine (Prozac) in 1987, many SSRIs have been introduced. They have an immediate effect on the blockade of the presynaptic serotonin reuptake pump in the central nervous system (CNS), which has been shown in animals to increase the duration of serotonin in the synaptic cleft, increasing the effects of neurotransmission.[23] The antidepressant efficacy of SSRIs and their low side effect profiles have made them the most widely prescribed class of antidepressants.

However, the SSRIs have few independent pain properties. Pain patients whose depression responds to an SSRI may have diminished pain that is attributable to improvements in the affective components of their pain, but there is little evidence supporting independent analgesic activity of SSRIs. While a few case reports have shown improvements in diabetic neuropathic pain on SSRIs, double-blind, placebo-controlled clinical trials that exclude patients with depression have not consistently demonstrated analgesic benefit.[24–28]

In deciding to prescribe an SSRI, care must be taken in reviewing all other medications a patient is taking, as well as reviewing the overall general medical condition of the patient, as all SSRIs have been associated with easy bruising/bleeding[29] and osteoporosis.[30,31] SSRIs can lead to serotonin syndrome when given with other medications including SNRIs, TCA, MAOIs, triptans (e.g., sumatriptan), and antiemetics (e.g., ondansetron, metoclopramide). Moreover, a serotonin syndrome can be precipitated by a combination of SSRIs and multiple analgesics, including tramadol, meperidine, fentanyl, and pentazocine. The use of SSRIs in combination with tramadol can lower the seizure threshold, and caution should be taken if combining these drugs.[32] No additional laboratory workup is required in starting SSRIs, and dose titration is based on clinical response and side effects. Fluoxetine tends to be more activating and is prescribed in the morning, while paroxetine with its anticholinergic effect of activating muscarinic receptors, is more sedating and has greater anxiolytic properties. Paroxetine has a relatively shorter half-life than most SSRIs and is often associated with withdrawal symptoms upon discontinuation. Sertraline and citalopram tend to be less sedating than paroxetine and are generally prescribed to be taken in the morning.[21]

Patients should begin on one-half of the usual dose for a week (see Table 15-1) and then to the standard dose, to minimize the side effects of nausea, diarrhea, tremor, and headache. Some patients can experience sedation or overstimulation. Approximately 75% to 80% of patients on SSRIs can experience sexual side effects, such as decreased libido, impotence, ejaculatory disturbances, or anorgasmia. This can be particularly the case in elderly patients who may already have diminished libido due to possible comorbid pain and depression. Rare side effects include dystonia, akathisia, palpitations, a lowered

TABLE 15–1 Selective Serotonin Reuptake Inhibitors (SSRIs)

Drug	Usual Start Dose	Average Dose	Maximum Dose
Citalopram (Celexa)	10 mg qd	20–40 mg qd	60 mg/day
Fluoxetine (Prozac)	10 mg qd	20–40 mg qd	80 mg/day
Fluvoxamine (Luvox)	25 mg qd	50–100 mg bid	300 mg/day
Paroxetine (Paxil)	5–10 mg qd	20–40 mg qd	60 mg/day
Sertraline (Zoloft)	25 mg qd	50–150 mg qd	200 mg/day

seizure threshold, serotonin syndrome, or syndrome of inappropriate antidiuretic hormone (SIADH).[33]

SSRIs are metabolized by hepatic oxidation, and their use may alter the serum levels of other hepatically metabolized drugs. SSRIs induce and/or inhibit various cytochrome P450 enzymes. Most significantly, they can increase levels of tricyclic antidepressants and benzodiazepines.[34] They may also affect levels of carbamazepine, lithium, antipsychotics, and commonly used analgesics, such as methadone, oxycodone, and fentanyl.[35] Fluoxetine, paroxetine, and to a lesser extent fluvoxamine are inhibitors of cytochrome 2D6; fluoxetine and fluvoxamine also interfere with cytochrome 3A4.[16] There is also evidence that sertraline at doses greater than 100 mg may inhibit these enzymes,[36] and thus may increase the circulating metabolites of certain opioids. Citalopram and escitalopram have less effect on CYP450 enzyme activity. If taken in an overdose, SSRIs are rarely, if ever, lethal. In discontinuing SSRIs, they should be tapered down slowly to avoid a withdrawal syndrome, which has the same symptoms as initiation of SSRIs (headache, nausea, diarrhea, or myalgias).

TRICYCLIC ANTIDEPRESSANTS (TCAs)

TCAs are one of the oldest classes of antidepressants and they act by inhibiting both serotonergic and noradrenergic reuptake. This lengthens the time serotonin and norepinephrine remain in the synaptic cleft, enhancing their neurotransmission.[37] The analgesic properties of TCAs are independent of their treatment effects on depression, thus making them a good choice for treating depression in the patient with chronic pain, particularly if cost is a factor.

All TCAs are equally effective for the treatment of depression, and the choice of a particular one is determined by side effects. The magnitude of anticholinergic and antihistaminic effects is the largest determinant. Amitriptyline and imipramine are more sedating, with more weight gain and orthostatic hypotension. Other anticholinergic side effects include dry mouth, constipation, blurred vision, urinary retention, sexual side effects, excessive sweating, and confusion or delirium. TCAs also decrease the seizure threshold. Desipramine and nortriptyline have fewer anticholinergic side effects, and of all of the TCAs, desipramine has the fewest anticholinergic side effects. Serum plasma levels can be monitored for TCAs, and this is particularly important for desipramine, imipramine, and nortriptyline, which have the best correlation of blood levels to therapeutic antidepressant response.[20] The therapeutic blood level for nortriptyline ranges from 50 to 150 ng/ml, and is 75 to 225 ng/ml for both desipramine and imipramine, as desipramine is simply the desmethyl metabolite of imipramine.[16]

Prior to initiating treatment patients should have laboratory screening of electrolytes, BUN, creatinine, and LFTs. TCAs also have quinidine-like properties, are potentially proarrhythmic, and can prolong the QTC interval. All patients aged over 40 years or with any history of cardiac disease should have a baseline EKG, with particular attention to the QTC interval, checking that it is less than 450 ms.[37] TCAs are strongly protein-bound (85% to 95%) and undergo first-pass hepatic metabolism. Subsequent stages involve demethylation, oxidation, and glucuronide conjugation. Amitriptyline is demethylated to nortriptyline, and imipramine is demethylated to desipramine. Hepatic clearance involves the P450 enzyme system, and so drugs such as SSRIs, cimetidine, and methylphenidate increase TCA plasma levels. SSRIs and TCAs should not be prescribed at the same time unless plasma levels are carefully monitored. Phenobarbital, carbamazepine, and cigarette smoking induce the P450 enzyme system, and thus decrease serum TCA levels.[34]

As with SSRIs, to minimize side effects and increase adherence initiation of TCAs should begin at lower doses (usually 25 mg for a week) than the target doses for antidepressant effect (typically 75–150 mg; see Table 15-2). The elderly are more sensitive to their side effects, and many psychiatrists begin at doses of 10 to 20 mg in this age group.[20] With diminished or altered metabolism of TCAs, as well as the multiple medications older patients are frequently taking, they are more prone to develop toxic serum levels, and monitoring should be more frequent. There is a withdrawal syndrome with abrupt discontinuation of TCAs, characterized by fever, sweating, headaches, nausea, dizziness, or akathisia. Unlike the SSRIs, overdose can be lethal. TCA overdose is a leading cause of drug-related overdose and death. Three to five times the therapeutic dose is potentially lethal, so this narrow therapeutic range must be respected, and blood levels serially done. Toxicity results from anticholinergic and proarrhythmic effects, such as seizures, coma, and QTC widening.[38]

Also, unlike the SSRIs, TCAs have independent analgesic properties. A series of studies by Max and others have illustrated the analgesic properties of TCAs, which are independent of its effects on improving depression.[39,40] TCAs have been shown to be modestly effective for diabetic neuropathy pain, chronic regional pain syndrome, chronic headache, poststroke pain, and radicular pain.[19,39–43] Additionally, TCAs are useful as preemptive analgesics, being opioid-sparing in the postoperative period.[44] While the initial studies were done with amitriptyline and

TABLE 15–2 Tricyclic Antidepressants (TCAs)

Drug	Usual Start Dose	Average Dose	Maximum Dose
Amitriptyline (Elavil)	10–25 mg qd	75–150 mg qd	300 mg/day
Amoxapine (Asendin)	25 mg bid	75–200 mg bid	600 mg/day
Clomipramine (Anafranil)	25 mg qd	150–250 mg qd	250 mg/day
Desipramine (Norpramin)	10–25 mg qd	75–150 mg qd	300 mg qd
Doxepin (Sinequan)	10–25 mg qd	75–150 mg qd	300 mg qd
Nortriptyline (Pamelor)	10–25 mg qd	75–150 mg qd	200 mg qd
Protriptyline (Vivactil)	5 mg qd	10 mg tid	60 mg/day

desipramine, subsequent studies have confirmed that the other TCAs have equivalent analgesic properties. Of note, the typical doses for the analgesic benefit of TCAs (25 to 75 mg) are lower than the typical doses for antidepressant effect (75 to 150 mg). However, many patients are referred to the pain specialist after a failed trial of TCAs at lower doses. And yet there is a dose-response relationship for analgesia. So even if one is using a TCA solely for pain relief, patients may benefit with a dose in the antidepressant range, in conjunction with blood level monitoring.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

The nontricyclic SNRIs are a newer group of antidepressants that, like the TCAs, act by inhibiting serotonin and norepinephrine reuptake. This appears to be one of the mechanisms accounting both for the higher rates of depression remission and the analgesic efficacy associated with TCAs and SNRIs as compared with SSRIs.[28,45] Venlafaxine, duloxetine, and, most recently, milnacipran are the main drugs in this category and have significantly less alpha-1, cholinergic, or histamine inhibition. In the United States, milnacipran (Savella®) is FDA approved for the treatment of fibromyalgia but not depression, and thus will not be discussed in detail. However, in Europe milnacipran has an established use for both chronic pain and depression. Lesser alpha-1, cholinergic, or histamine inhibition in this class of drugs results in fewer side effects than the tricyclics, with equivalent antidepressant and potentially equal analgesic benefits. Placebo-controlled studies have demonstrated modest efficacy in neuropathic pain for both venlafaxine[45,46] and duloxetine.[47] A numbers-needed-to-treat analysis suggested superior analgesic properties of TCAs (particularly amitriptyline), which may be due to their properties of NMDA antagonism and sodium channel blockade, in addition to their combined serotonin and norepinephrine reuptake inhibition.[45]

Venlafaxine is given in two or three divided daily doses (even with extended-release formulations), beginning at 37.5 mg/day for a week and then slowly increased to as high as 375 mg/day (Table 15-3). A typical dose is 150 to 225 mg/day. Generally, patients are escalated over a month to 75 mg/day, and then depending on clinical response, the dose is adjusted.

No laboratory studies are needed prior to starting venlafaxine, but caution should be taken in patients with hypertension. Particularly at doses over 150 mg/day, venlafaxine may increase systolic blood pressure by 10 mm or more. This is likely due to the onset of norepinephrine reuptake inhibition, which occurs at higher doses of venlafaxine[45] that appear to be needed for analgesic efficacy in neuropathic pain, unlike tricyclics that may be effective at lower than antidepressant doses. Other side effects include nausea, somnolence, dry mouth, dizziness, nervousness, constipation, anorexia, or sexual dysfunction. Venlafaxine may affect hepatic metabolism of other medications, but it is a weak inhibitor of the CYP system.[36]

Structurally, venlafaxine is similar to tramadol, and in mice venlafaxine demonstrates opioid-mediated analgesia that is reversed by naloxone. Both controlled studies and case reports indicate that venlafaxine has analgesic properties independent of its antidepressant effects in a variety of neuropathic conditions.[48–51] Many patients are unable to tolerate the side effects of tricyclics, so venlafaxine and duloxetine are promising agents in patients with major depression and chronic pain.

Duloxetine (Cymbalta) is an SNRI approved for use in the United States for diabetic peripheral neuropathic pain, fibromyalgia, major depression, and generalized anxiety disorder. It is the only major psychotropic drug approved in the United States for both pain and psychiatric

TABLE 15–3 Miscellaneous Antidepressants

Drug	Usual Start Dose	Average Dose	Maximum Dose
Bupropion (Wellbutrin)	75 mg bid	100–150 mg bid	600 mg qd
Duloxetine (Cymbalta)	30 mg qd	60 mg qd	120 mg
Mirtazapine (Remeron)	15 mg qhs	30–45 mg qd	60 mg qd
Nefazodone (Serzone)	100 mg bid	150–300 mg bid	600 mg/day
Trazodone (Desyrel)	50 mg qhs	150–250 mg bid	600 mg/day
Venlafaxine (Effexor)	37.5 mg qd	75–112.5 mg bid	375 mg/day

conditions, and thus it is the treatment of choice for patients with neuropathic pain and psychiatric comorbidity. Typical starting dose is 30 mg at dinnertime for a week and then increasing to 60 mg at dinnertime. Dosing in the evening tends to mitigate the side effects of nausea and tiredness. Other side effects include dry mouth, dizziness, constipation, or sexual dysfunction. Dosing in the elderly should begin lower, such as 20 mg/day, due to increased side effects and less tolerability.[52] The maximum dose that has been studied is 120 mg/day. Most of the studies show no significant benefit above doses of 60 mg/day, but there is a range of individual responses and some patients will preferentially respond at the higher dose. Duloxetine is a moderate inhibitor of the CYP2D6 liver enzyme, and thus may increase TCA and antipsychotic levels.[36] No laboratory tests are needed prior to prescribing duloxetine. It should not be prescribed to patients with renal or liver insufficiency.

OTHER ANTIDEPRESSANTS

Bupropion is a noradrenergic and dopaminergic reuptake pump inhibitor, prolonging the time norepinephrine and dopamine remain in the synaptic cleft.[23] Unlike many of the other antidepressants it has significant psychostimulant properties. It is used in the treatment of depression, ADHD, and smoking cessation, at doses up to 600 mg/day (Table 15-3). Two studies have shown that bupropion has independent analgesic effects in a variety of neuropathic conditions.[53] Anecdotal reports have also indicated that bupropion is effective in alleviating the sedative effects of opioids. Consequently, bupropion has an important use in pain medicine. Enthusiasm is dampened, however, by a randomized controlled trial (RCT) in 44 patients with chronic low back pain showing no significant pain improvement.[54]

Treatment should start at 75 to 100 mg in the morning to avoid insomnia that may occur if the drug is started at night. After 5 days, this dose is advanced to the average treatment dose of 100 to 150 mg bid, even for sustained-release preparations. At these doses there is a very slight decrease in seizure threshold. Doses from 450 to 600 mg/day may cause seizures in 4% of patients, so these doses should be avoided.[55] Bupropion should not be prescribed to patients with seizures, eating disorders, or those taking MAOIs. Caution is needed in coprescribing bupropion with tramadol since the lowering of seizure threshold is most likely additive. Side effects include nervousness, headache, irritability, and insomnia.

Mirtazapine is an antidepressant with antagonism of serotonin and central presynaptic alpha2-adrenergic receptors, stimulating serotonin and norepinephrine release. This serves to potentiate serotonergic and noradrenergic transmission, while having no anticholinergic effects.[34] It is thought to preferentially augment serotonergic transmission and have an antihistaminic effect at lower doses, 15 to 30 mg/day. At higher doses, 45 to 60 mg/day, it augments more noradrenergic transmission (Table 15-3). As a result, at lower doses it is more sedating and has antianxiety effects, with the side effect of weight gain. At higher doses it is more activating and can provoke anxiety symptoms. Agranulocytosis and neurotropenia can rarely occur with this medication, at an incidence of 0.3%.[21] One case report and an open-label study indicate that there may be analgesic benefits to mirtazapine, but improvements in depression were not adequately controlled.[56,57]

Trazodone is a serotonin-2 antagonist/reuptake inhibitor (SARI), and is used for major depression and insomnia. The sedative qualities of trazodone are so great that few patients are able to get to high enough of a dose to be in the effective antidepressant range. Trazodone is most often prescribed for insomnia that accompanies depressive, anxious, or pain symptoms and is the preferred treatment for insomnia for many pain physicians.[19] Typical dosing for sleep is 25 to 100 mg at bedtime (Table 15-3). For depression, dosing for trazodone and nefazodone is 50 to 600 mg/day in two divided doses. A rare but serious side effect of trazodone is priapism, occurring in 1 in 1000 to 1 in 10,000 cases.[58] Side effects common to both medications are sedation, dizziness, dry mouth, orthostatic hypotension, constipation, and headache. Studies have shown that trazodone has few analgesic properties. No such studies have been done with nefazodone, but one would not expect a different result.

ANXIETY DISORDERS

Anxiety disorders are a broad spectrum of disorders, including generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and PTSD. There is a high prevalence rate of anxiety disorders in chronic pain clinic populations, with 30% to 60% of patients having anxiety at pathological levels.[2,6,8] Generalized anxiety disorder is the most frequent anxiety disorder affecting pain patients.

Anxiety is a broad concept with many dimensions. Anxiety can be an enduring personality trait that at times becomes excessive. It can be a symptom among a constellation of symptoms as part of another disorder, such as major depression. Or, it may be an episodic disorder, provoked by stressful and taxing challenges, such as chronic pain. Anxiety also has a biological component and is responsive to medications.[5] It is difficult to determine when anxiety is pathological, but one guideline is when anxiety interferes with normal functioning. There is both trait anxiety and situational anxiety. Trait anxiety is excessive worry and concern, often about routine matters. The amount of worry and anxiety is out of proportion to the likelihood of the negative consequences occurring, and the patient has great difficulty controlling worry.

Patients' situational anxiety is often anxiety about pain and its negative consequences. Patients may be conditioned to be excessively fearful that activities will cause uncontrollable pain, causing avoidance of those activities, which in some patients can be extreme, almost phobic. Also, pain may activate thoughts that patients are seriously ill.[59] Pain-specific anxiety as well as generalized anxiety amplify pain perception and pain complaints through several biopsychosocial mechanisms, including sympathetic arousal with noradrenergically mediated lowering of nociceptive threshold, increased firing of ectopically active pain neurons, excessive cognitive focus on pain symptoms, and poor coping skills. Patients with pathologic anxiety are often restless, fatigued and irritable and have poor concentration.

They may have muscle tension and sleep disturbances. Their mood is often low, but not at the severity level found in MDD.[19]

TREATMENT

Overall, cognitive behavioral therapy demonstrates the best treatment outcomes for anxiety disorders. Significant improvements are further obtained with relaxation therapy, meditation, and biofeedback.[60] Antidepressants are effective, but generally at higher doses than what is typically prescribed for depression. Anxiolytics, such as benzodiazepines and buspirone, are most useful in the initial treatment stages to stabilize a disorder. However, the side effects and physiologic dependency associated with benzodiazepines in particular make them a poor choice for long-term treatment.

ANTIDEPRESSANTS

As in depression treatment, it may take 4 to 8 weeks after the patient is on the target dose to see improvement. To improve compliance, escalation of doses must be done very slowly, because anxious patients are poorly tolerant of side effects. Antidepressants are useful in diminishing the overall level of anxiety and preventing anxiety or panic attacks, but they have no role in treating acute anxiety. Both the SSRIs and SNRIs are effective agents among antidepressants. Paroxetine tends to have greater antianxiety effects, but all of the SSRIs have good anxiolytic properties.[61] Effective doses for SSRIs are higher than those for depression, typically 60 to 80 mg/day.[62]

Of the TCAs, clomipramine is the most effective, with particular usefulness in obsessive compulsive disorder. Nefazodone has antianxiety effects, as does venlafaxine at higher doses. Mirtazapine has anxiolytic properties at the lower, more sedating doses, and higher doses of 45 to 60 mg can worsen anxiety with its activating qualities.[63] Similarly, while there are reports that bupropion is effective in depressions with anxious features, its stimulating effects make it less attractive as a primary antianxiety agent.

SNRIs, specifically venlafaxine and duloxetine, have also demonstrated efficacy in generalized anxiety, and have an FDA indication for treatment of generalized anxiety disorder.[64]

BENZODIAZEPINES (BZDs), BUSPIRONE

These medications are useful in the treatment of acute anxiety, panic attacks, and the stabilization of generalized anxiety. Occasionally, anxiety cannot be stabilized with antidepressants and patients remain on BZDs in the long term. BZDs bind to the BZD component of the gamma-aminobutyric acid (GABA) receptor, an inhibitory neurotransmitter. They depress the CNS at the levels of the limbic system, brainstem reticular formation, and cortex.[23] While they are widely prescribed by pain practitioners, studies indicate that they have few independent analgesic properties. However, these medications are also used as muscle relaxants and to treat pain associated with muscular spasticity. Issues of tolerance often limit their long-term use for anxiety or muscle pain.

Acute anxiety or panic attacks can be treated with short-acting BZDs, such as lorazepam 0.5 to 2 mg q6hr, prn, which has a rapid onset of action (10 to 15 min) and a half-life of 10 to 20 hr.[34] Table 15-4 lists these features of many BZDs. Caution should be taken in prescribing short half-life drugs, such as alprazolam. While it has a rapid onset of action, it typically lasts only 2 to 3 hr and many patients have significant rebound anxiety, resulting in a rollercoaster of peaks and valleys of anxiety during the day.

Buspirone is also an effective anxiolytic. It acts as a serotonin agonist. It is especially useful in treating patients with a history of substance abuse who may abuse BZDs. It has no addictive properties, and does not impair psychomotor or cognitive functions. It is started at 5 mg tid and can be advanced as high as 10 mg tid.[37] Unlike the short-acting BZDs that deliver anxiolysis with the first dose, buspirone requires 1 to 4 weeks of administration for antianxiety benefits to appear. Patients can experience headache, dizziness, paresthesias, and GI upset.

Clonazepam 0.25 to 1 mg tid, a long-acting BZD, is often used in conjunction with a short-acting agent or an antidepressant to stabilize persistent anxiety or prevent acute

TABLE 15–4 Benzodiazepines (BZDs)

Drug	Onset	Half-Life (hr)
Alprazolam (Xanax)	Intermediate	6–20
Chlordiazepoxide (Librium)	Intermediate	30–100
Clonazepam (Klonopin)	Intermediate	18–50
Clorazepate (Tranxene)	Rapid	30–100
Diazepam (Valium)	Rapid	30–100
Estazolam (ProSom)	Intermediate	10–24
Flurazepam (Dalmane)	Rapid-intermediate	50–160
Lorazepam (Ativan)	Intermediate	10–20
Midazolam (Versed)	Rapid	2–3
Oxazepam (Serax)	Intermediate-slow	8–12
Temazepam (Restoril)	Intermediate	8–20
Triazolam (Halcion)	Intermediate	1.5–5

anxiety attacks. Diazepam, which also has psychoactive metabolites lasting several days, and flurazepam, are other agents with long half-lives.

The side effects of BZDs limit their use as long-term agents. Acutely, all of the BZDs can cause profound sedation, confusion, or respiratory depression, and can be fatal in overdose. Caution is taken in prescribing these medications concurrently with opioids, which can compound the risk of these side effects. Rarely but with more frequency in the elderly, BZDs can be disinhibiting agents, and can lead patients to become agitated. All of the BZDs have physiologic-dependence potential depending on the dose and duration of treatment. All of them can cause physical and psychological dependence, and often require long tapering schedules from 1 to 3 months to minimize withdrawal symptoms.[19] Abrupt discontinuation of BZDs can cause insomnia, anxiety, delirium, psychosis, or seizures. Recent evidence indicates that long-term prescription of BZDs adversely affects short- and long-term memory, as well as learning abilities.[65] Furthermore, given that CBT with coping skills training is one of the most effective treatments for anxiety disorders, anxiolytics can undermine this treatment because it may reinforce the notion that only a pill can solve a patient's anxiety problems, decreasing their self-efficacy for anxiety control.

MOOD STABILIZERS AND ANTIEPILEPTICS

Mood stabilizers are agents that possess both antimanic and antidepressant properties. Some of these medications are antiepileptic drugs. In psychiatry, they are most frequently prescribed for bipolar disorder. There is no evidence that bipolar disorder occurs at a higher frequency in patients with chronic pain.[2] This class of medications is often used to treat patients with chronic neuropathic pain, trigeminal neuralgia, and headache. Some of the medications in this class are lithium, valproic acid (Depakote is the longer-acting brand name formulation), carbamazepine (Tegretol®), and lamotrigine (Lamictal®). While many of the other anticonvulsants have antimanic properties if prescribed either as a sole agent or in combination with other agents, they have little, if any, antidepressant effects of their own, and thus are not true mood stabilizers. The other anticonvulsants are useful as secondary or tertiary agents in bipolar disorder, or as augmentation agents in the treatment of major depression. The anticonvulsants are frequently prescribed in pain medicine and are documented analgesics for a variety of conditions, most often neuropathic pain and headache prophylaxis. Their use is covered in more detail in other chapters of this text.

LITHIUM

Lithium is the most commonly prescribed mood stabilizer for bipolar disorder and is the only one demonstrating a clear decrease in suicide attempts for those taking it.[66] It is also used as an augmentation agent for MDD, administered in conjunction with antidepressants to which a patient has had a partial response. With mixed results, lithium has been used as prophylaxis for chronic daily headaches and cluster headaches. Lithium has a narrow therapeutic range for both benefit and toxicity, thus obtaining serum levels is important. Lethal overdoses can involve as little ingestion of 4 to 5 times the daily dose. Lithium has effects on the thyroid and kidney, and their function must be monitored. These difficulties in using lithium and its sparse analgesic benefits make it less useful to the pain practitioner. Typically, patients with chronic pain on lithium are followed by a psychiatrist.

VALPROIC ACID

Depakote is the brand name of long-acting valproic acid, with a duration of action of 8 to 12 hr. It has both antimanic and antidepressant effects, although with less anti depressant effect than lithium. It is also useful as an augmentation agent in depression. Depakote can also be used for the treatment of impulsivity and aggression. Valproic acid has an established use in migraine prophylaxis, and neurologists have extensive experience with it in seizure treatment. Starting dose is 250 mg/day and a typical dose used in pain medicine is 250 mg tid, while doses used in treatment of bipolar disorder are higher, 500 to 1000 mg tid.[34] Serum levels are monitored for therapeutic and toxicity ranges. Prior to initiating treatment, CBC and liver function tests are done. Anemia and neurotropenia are rare side effects of valproic acid, but thrombocytopenia is more common. Platelet levels should be checked at least 2 weeks after the start of treatment and 2 weeks after reaching a therapeutic dose. Fortunately, platelet levels quickly rise after discontinuation of valproic acid. Sedation, dizziness, and hepatitis are other side effects. Hepatotoxicity/hepatic failure and pancreatitis are also rare but serious potential side effects. As a result, this medication is contraindicated in patients with hepatic disease. This medication should not be given to pregnant women, as it is associated with neural tube defects.

LAMICTAL

Lamotrigine, or Lamictal, as it is known by its trade name, is an antiepileptic medication very commonly prescribed for seizure control by neurologists and for mood stabilization by psychiatrists. It is often prescribed for bipolar patients with prominent depressive symptomatology and it appears to be more effective in preventing depression than mania.[16] Its mechanism for treating bipolar disorder is not known. Lamictal has been reported to reduce neuropathic pain in case reports,[67] but two RCTs in a variety of neuropathic pain conditions showed no effect.[68,69] Lamotrigine does have an established use as a preventive agent in headache management, and a recent systematic review concludes that it is efficacious in reducing the frequency of migraines.[70] Although generally well tolerated, rash may occur in up to 10% of individuals and Steven-Johnson syndrome, also known as toxic epidermal necrolysis, has been reported in 0.08% of individuals.[16] The rash appears to be related, in part, to the starting dose and the rate of increase. As a result, this medication is often started 25 mg daily for 2 weeks, then 50 mg daily for 2 weeks, 100 mg daily for 1 week, and then 200 mg daily for most patients.

CARBAMAZEPINE

Carbamazepine, also know as Tegretol, is an anticonvulsant used to treat partial seizures and generalized seizures. Carbamazepine is a well-established mood stabilizer and is also the first-line treatment for trigeminal neuralgia and other neuropathic pain disorders with a lancinating quality.[16] This medication is usually started at doses between 200 and 400 mg daily in divided doses with a therapeutic dose range of 750 to 2500 mg daily in divided doses. Caution must be exercised when using this medication as it has serious side effects including rash, agranulocytosis, and aplastic anemia necessitating regular lab monitoring. Carbamazepine also interacts with other medications through the induction of liver enzymes, including the induction of its own metabolism.

NEUROLEPTICS

Also termed "antipsychotics," neuroleptics have been available for almost 50 years. They are used to treat any psychotic process, the hallmark illness being schizophrenia, and psychotic symptoms in depression, mania, or delirium are also indications for their use. Both the typical and newer-generation atypical neuroleptics have independent analgesic properties, and are effective analgesics for nociceptive and neuropathic conditions.[71] Historically, the serious side effects of Parkinsonism and tardive dyskinesia have limited their use in pain medicine (particularly for the older generation of antipsychotics such haloperidol (Haldol®) or fluphenazine (Prolixin®). More often, neuroleptics are used in inpatient settings where other analgesic agents have produced delirium.

However, based on a recent review of the literature, there is evidence that demonstrates a role for antipsychotics in treating many different types of pain including cancer pain and chronic non cancer pain, such as fibromyalgia, chronic headache, low back pain, musculoskeletal pain, chronic pain in older patients, chronic facial pain, and diabetic neuropathy.[72] The mechanism of antipsychotic pain relief has not been clearly delineated. It may be that antidopaminergic properties play a role in analgesia, whereas the serotoninergic antagonism may also be important for pain relief.[73] Antipsychotic antagonism of alpha2-adrenoceptors may also mediate analgesia.[74]

TYPICAL NEUROLEPTICS

Typical neuroleptics (Table 15-5) act as antipsychotics through their antagonism of dopamine receptors, particularly the D2 receptors. They also have actions on histaminic, cholinergic, and alpha-1 adrenergic receptors. Haloperidol is the prototypical agent in this class, with a molecular structure similar to morphine. All of the typical neuroleptics have varying degrees of anticholinergic side effects: dry mouth, dizziness, sedation, weight gain, constipation, or blurred vision. They are also plagued by varying degrees of extrapyramidal effects: tremor, dystonia, akathisia, and, most seriously, tardive dyskinesia, which is permanent. All of these agents very slightly lower the seizure threshold and may elevate serum glucose levels. Cardiovascular effects include hypotension, tachycardia, nonspecific EKG changes (including torsades de pointes), and, exceedingly rare, sudden cardiac death.[34]

ATYPICAL NEUROLEPTICS

The first atypical neuroleptic was clozapine, which is used in treatment-refractory schizophrenia. Subsequently, several other agents have been released in this class: risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone (Table 15-6). The atypicals have a lesser degree of dopamine D2 receptor antagonism and a greater degree of D4 receptor antagonism than the typical neuroleptics.[55] Additionally, they have some degree of serotonin-2 receptor blocking. This mixed receptor profile results in far fewer extrapyramidal, anticholinergic, and cardiac side effects. However, virtually all the side effects of the typical agents can occur with atypical neuroleptics. Caution should be used in prescribing this class for patients with diabetes. Emerging evidence indicates that the atypicals, particularly olanzapine, lower glucose tolerance and can elevate serum glucose levels.[75] Overall, since the atypicals are better tolerated than typical neuroleptics, they are quickly becoming the first-line treatment for psychotic symptoms. Both classes are equally as effective for the "positive symptoms" of psychosis: hallucinations and delusions. However, the atypicals are more effective for the "negative symptoms:" flat affect, poor motivation, and social withdrawal. Additionally, these agents are increasingly used as augmentation agents for treatment-resistant depression or

TABLE 15–5 Selected Typical Neuroleptics

Drug	Usual Dose	Maximum Dose
Fluphenazine (Prolixin)	5–10 mg bid-tid	40 mg/day
Haloperidol (Haldol)	2–5 mg bid-tid	100 mg/day
Perphenazine (Trilafon)	8–16 mg bid-tid	64 mg/day
Thiothixene (Navane)	5–10 mg tid	60 mg/day
Trifluoperazine (Stelazine)	5–10 mg bid	40 mg/day
Loxapine (Loxitane)	20–50 mg bid-tid	250 mg/day
Chlorpromazine (Thorazine)	10–50 mg bid-qid	2000 mg/day
Thioridazine (Mellaril)	100–200 mg bid-qid	800 mg/day

TABLE 15–6 Atypical Neuroleptics

Drug	Usual Dose	Maximum Dose
(Aripiprazole) Abilify	5 mg qd	30 mg qd
(Clozaril) Clozapine	100–300 mg qd-bid	900 mg/day
(Zyprexa) Olanzapine	5–15 mg qd	20 mg/day
(Seroquel) Quetiapine	50–150 mg bid-tid	800 mg/day
(Risperdal) Risperidone	2–4 mg qd-bid	16 mg/day
(Geodon) Ziprasidone	20–40 mg bid	160 mg/day

anxiety, and may be very useful in helping patients disabled by pain and comorbid agitated depression control their anger.[19,76]

The use of atypical neuroleptics in pain medicine will continue to grow. Case reports and retrospective studies indicate that they may be effective as a secondary or tertiary agents for migraine and chronic daily headache prophylaxis.[74] They have been effective as abortive agents for cluster headache.[74] A small study showed analgesic benefit in those with cancer pain.[77] In mice, studies of risperidone demonstrate an opioid-mediated analgesia to thermal pain.[78] In one animal pain model, the strong antinociceptive effect of risperidone was attributed to its selective opioid antagonist via m1, m2, and kappa1 opioids, and delta-opioid systems.[73] Olanzapine (Zyprexa®) has been shown to provide pain relief from alpha2-adrenoceptors, opioid, and serotonergic receptor activity.[73] The dosage range for the analgesic benefit of atypicals is yet unclear.

Whether an atypical or typical is prescribed, in starting a neuroleptic patients must be warned about the side effects, especially the risks of tardive dyskinesia, which is permanent if it occurs. In prescribing a neuroleptic for a nonpsychotic patient, initial dose should be very low with a slow escalation, since these patients are neuroleptic-naive and are very prone to its side effects.

CONCLUSION

Some 60% to 80% of patients with chronic pain attending pain clinics have significant psychiatric pathology. This comorbidity worsens their pain and disability, and this mental distress is an independent source of suffering, further reducing quality of life. The boom in psychotherapeutic medications over the past 25 years, combined with more effective psychotherapies, has resulted in significantly improved treatment. Many of these medications have analgesic benefits independent of their treatment effects on depression, anxiety, or psychosis. The antidepressants, anticonvulsants, and antipsychotics are the most notable for their pain properties. The improved treatment results for psychopathology and the emergence of additional analgesics is a boon to pain medicine practice.

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CHAPTER 16

Membrane Stabilizers

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The treatment of neuropathic pain presents a distinct challenge for health-care practitioners. A wide range of conditions resulting in chronic neuropathic pain include, but are not limited to, diabetic polyneuropathy, postherpetic neuralgia, central neuropathic pain, traumatic/surgical nerve injury, incomplete spinal cord injury, trigeminal neuralgia, multiple sclerosis, radiculopathy, complex regional pain syndrome (CRPS), and HIV-associated peripheral neuropathy. Defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system, neuropathic pain is often described as burning, lancinating, or tingling in nature.

Neuropathic pain is the unfortunate consequence of detrimental changes that occur after tissue injury.[1] Pathologic changes after injury result in plasticity or alterations in the way peripheral nerve fibers respond to and deliver input to the central nervous system (CNS). The source of neuropathic pain may be related to damage of a peripheral nerve, with or without associated autonomic changes or CNS dysfunction. Examples of these changes include prolonged central sensitization, damage to neuronal inhibitory functions, and alteration of the effects of pain on the sympathetic nervous system. When abnormal neural activity persists beyond the expected duration of healing, the pain sensation becomes chronic in nature, and persists without ongoing disease.

Following tissue injury, the threshold of A-δ and C-fiber activation decreases, and an augmented response to a given stimulus occurs. In addition, alterations in ion channels located at the site of injury take place. Sodium and calcium channels play a fundamental role in the propagation of hyperexcitability in central and peripheral neurons.[2] After nerve injury, the number of ion channels accumulates in excess, and leads to ectopic, spontaneous firing of sensory nerves and dorsal root ganglion cell bodies. The result of neuronal membrane hyperexcitability is the chronic perception of pain.

Research into the physiologic source and pharmacologic management of neuropathic pain has led to the study of sodium- and calcium-channel blockade.[3,4] The pathology leading to epilepsy was extrapolated and studied as a possible source for the development of neuropathic pain in patients. Membrane stabilizers include agents typically used for the treatment of epileptic foci in the brain. As a result of this inferential leap, these agents have been used in patients with neuropathic pain. There are multiple classes of medications that fall under the membrane stabilizer classification, including sodium-channel blocking agents (antiepileptics, anticonvulsants, local anesthetics, tricyclic antidepressants, and antiarrhythmics) and calcium-channel blocking agents (Table 16-1).

When evaluating the effectiveness of medications for neuropathic pain, outcome measures most commonly include changes in the average daily pain score by a 10-cm (100-mm) visual analog scale (VAS) and on an 11-point Likert scale (0, no pain; 10, worst possible pain) numeric rating scale (NRS); patient-reported pain relief of 30% or greater (moderate benefit); patient-reported pain relief of 50% or greater (substantial benefit). "Numbers needed to treat" (NNT) is used to allow a comparisons among different drugs and diseases in order to better judge the efficacy of an agent more precisely.[5,6] The NNT is the number of patients treated with a particular drug in order to obtain one patient with a defined degree of relief. Usually, the parameter, NNT > 50% pain relief, is used because it is easily understood, and seems to be related to relevant clinical effect.[5] The "numbers needed to harm" (NNH) is the number needed to treat with a certain drug before a patient can experience a significant side effect. The NNH of several drugs for pain management is not yet known. The drugs with a low NNT/NNH ratio are superior to the drugs with high NNT/NNH ratio.

SODIUM-CHANNEL BLOCKERS

These agents include the antiepileptic/anticonvulsants, local anesthetics, tricyclic antidepressants, and antiarrhythmics. As a group, they inhibit the development and propagation of ectopic discharges. The primary agents used for neuropathic pain are antiepileptics/anticonvulsants and local anesthetics. Gabapentin and pregabalin, also anticonvulsants, are discussed separately under calcium channel antagonists, as their mechanism of action differs from other agents that are typically used for epilepsy and convulsions.

Sodium-channel blockers are used for primary therapy or adjunctive treatment for processes such as trigeminal neuralgia, CRPS, diabetic neuropathy, radicular extremity pain, chemotherapy-induced peripheral neuropathy, and postherpetic neuralgia. When using these agents, as with all membrane stabilizers, it is crucial to be knowledgeable of the proper dosages, toxicities, and their effects when coadministered with other drugs. As a general rule, the dose should be titrated to patient comfort within safety standards.

ANTICONVULSANTS

PHENYTOIN (DILANTIN)

The initial dosage of phenytoin is 100 mg BID to TID (Table 16-2). It is primarily used for the treatment of diabetic neuropathy; however, due to the mixed results of its efficacy and high side effect and medication interaction profile, it has fallen into disuse. Phenytoin provides pain relief by blocking sodium channels, thereby preventing the release of excitatory glutamate and inhibiting ectopic discharges.

Studies have been performed in trials regarding the efficacy of phenytoin for diabetic neuropathy, with conflicting

TABLE 16–1 Commonly Used Membrane Stabilizers: Mechanisms of Action and Common Side Effects

Membrane Stabilizer	Mechanism	Side Effects
Carbamazepine	Na channel blockade	Sedation, dizziness, gait abnormalities, hematologic changes
Oxcarbazepine	Na channel blockade	Hyponatremia, somnolence, dizziness
Phenytoin	Na channel blockade	Sedation, motor disturbances
Lamotrigine	Stabilize slow Na channel; suppress release of glutamate from presynaptic neurons	Rash, dizziness, somnolence
Gabapentin/pregabalin	Binds to alpha-2-delta subunit of voltage-gated Ca channel	Dizziness, sedation
Valproic acid	Na channel blockade; increase GABA	Somnolence, dizziness, gastrointestinal upset
Topiramate	Na channel blockade; potentiate GABA inhibition	Sedation, kidney stones, glaucoma
Mexiletine	Na channel blockade	Nausea, blurred vision
Lidocaine cream/TD	Na channel blockade	Skin irritation

TABLE 16–2 Dosing Recommendations for Neuropathic Pain

Membrane Stabilizer	Initial Dosage	Titration	Maximum Dosage
Carbamazepine	100–200 mg twice daily	Increase by 200-mg increments gradually	1200 mg daily
Oxcarbazepine	600 mg twice daily	Increase by 300 mg daily	1200–1800 mg every 3 days
Phenytoin	100 mg twice to 3 times daily		
Lamotrigine	25–50 mg at bedtime	Increase by 50 mg every 1–2 weeks	300 mg–500 mg daily
Gabapentin*	100–300 mg at bedtime	Increase by 100–300 mg 3 times daily every 1–7 days, as tolerated	3600 mg (1200 3 times daily)
Pregabalin*	50 mg 3 times daily or 75 mg twice daily	Increase to 300 mg daily after 3–7 days, then by 150 mg/day every 3–7 days as tolerated	600 mg daily (200 mg 3 times daily or 300 mg twice daily)
Valproic acid	250 mg twice daily	Increase by 250 mg weekly	500 mg twice daily
Topiramate	50 mg daily at bedtime		1500 mg twice daily
Mexiletine	150 mg daily	Increase to 300 mg in 3 days, and then to 600 mg	10 mg/kg daily
Lidocaine cream	2%, 5%, 10%		
Lidocaine patch (Lidoderm)	5%		12–18 hr on/6–12 hr off

** Reduce if patient has impaired renal function.*

results.[7] Therefore, this agent should not be considered first-line therapy for neuropathic pain. Intravenous phenytoin has been investigated in the pain management setting. Doses of this agent at 15 mg/kg have provided relief of acute pain when administered over a 2-hour period. Side effects include slowing of mentation and somnolence, with nystagmus and ataxia seen in some patients. Among the epileptic drugs, unique to phenytoin is the development of facial alterations, including gum hyperplasia and a coarsening of facial features. Fosphenytoin, an intravenously administered pro-drug that converts to phenytoin, is used by some to avoid a long dosing interval or initial burning at the injection site.

Phenytoin activates the cytochrome P450 enzyme system in the liver, and, hence, careful assessment of co-therapy is warranted. For example, phenytoin decreases the efficacy of methadone, fentanyl, tramadol, mexiletine, lamotrigine, and carbamazepine. As a result, dosages of these medications should be adjusted accordingly. Co-administration with antidepressants and valproic acid could lead to increased blood concentration of phenytoin, lowering the subsequent doses required for effect in patients. The role of phenytoin in the treatment of neuropathic pain is considered to be the therapy of last resort.

CARBAMAZEPINE (TEGRETOL)

The initial dosage of carbamazepine is 100 to 200 mg BID, titrated to effect, with typical dose ranges of 300 to 1200 mg/day, administered in two divided doses. Common maintenance doses are 600 to 800 mg. The chemical structure of this compound is similar to that of the tricyclic antidepressants, although the mechanism of action for analgesia is quite different. This agent is thought to inhibit pain via peripheral and central mechanisms. Carbamazepine selectively blocks active fibers, having no effect on normally functioning A-δ and C-fiber nociceptors. Major uses of the drug include primary therapy for trigeminal neuralgia (tic doloreux), thalamic-mediated post-stroke pain, postherpetic neuralgia, and diabetic

neuropathy. Drowsiness, dizziness, and nausea and vomiting are common side effects, and can often be limited by slow titration. Carbamazepine is associated with very deleterious side effects, including pancytopenia (necessitating a complete blood count and monitoring while on this therapy), Stevens Johnson syndrome, and toxic epidermal necrolysis.

Carbamazepine is considered to be the pharmacologic treatment of choice for trigeminal neuralgia, a sharp severe facial pain in one or more of the distributions supplied by the trigeminal nerve.[8] While the pathology of this process has not fully been determined, the majority of cases are believed to be caused by compression of the trigeminal nerve at the pontine origin of the nerve by an aberrant loop of an artery or vein.

With a NNT of <2, carbamazepine is the most studied treatment for trigeminal neuralgia, and many studies have highlighted its usefulness.[8] One study noted the effect of carbamazepine in 70 patients with trigeminal neuralgia, and demonstrated a 68% decrease of pain episodes and a 58% decrease in the severity of pain. Research from other studies noted a verbal response by patients of "excellent" or "good" upon initiation of therapy for 2 weeks.[9] Additionally, the positive effect of carbamazepine on trigeminal neuralgias has been tested by crossover, placebo, and controlled double-blinded studies[10]; yet, even with these positive results, trigeminal neuralgia is a disease process that, in many patients, is difficult to completely treat, often requiring multiple agents.

Carbamazepine has also been investigated for use in pain states caused by diabetes mellitus. Its application in animals resulted in a decrease in hyperalgesia to various stimuli. This agent has been shown to be more beneficial than placebo in the human diabetic patient population.[7] Carbamazepine therapy, when compared with a nortriptyline/fluphenazine combination in patients with painful diabetic neuropathy, was found to be equally effective, with fewer side effects.

Patients on carbamazepine therapy should have blood tests done every 2 to 4 months, as there is an increased risk of developing agranulocytosis and aplastic anemia with this agent. Studies noted that the NNH for severe adverse effects was 24, and for minor adverse effects, such as sedation, was 3.[8]

OXCARBAZEPINE (TRILEPTAL)

Oxcarbazepine, the keto-analog of carbamazepine, was developed to preserve carbamazepine's membrane-stabilizing effects while minimizing minor adverse effects, such as sedation and serious, life-threatening reactions. A major advantage of oxcarbazepine is that monitoring of drug plasma levels and hematologic profiles is generally not necessary. Similar to carbamazepine, oxcarbazepine blocks sodium channels; it does not affect gamma-aminobutyric acid (GABA) receptors.

Significant hyponatremia (sodium <125 mmol/L) may develop during treatment with oxcarbazepine. This typically occurs during the first 3 months, with normalization of sodium levels within a few days of discontinuing the drug. Monitoring of sodium levels should be performed when instituting oxcarbazepine therapy. Frequently reported adverse effects of oxcarbazepine include dizziness, somnolence, and nausea and vomiting, which are generally well tolerated.

In a randomized, placebo-controlled trial over 16 weeks, oxcarbazepine was evaluated in patients with painful diabetic neuropathy.[11] Patients were treated with 300 mg and titrated to a maximum dose of 1800 mg/day. Oxcarbazepine-treated patients reported less pain on a VAS, global improvement, and less sleep disturbances due to pain.

The superior side-effect profile of oxcarbazepine compared to carbamazepine has led to its increased use. In several countries, oxcarbazepine is now the drug of choice for trigeminal neuralgia. While a case series reported its efficacy in the treatment of neuropathic pain, prospective, randomized controlled studies are lacking at this time.

VALPROIC ACID (DEPAKOTE)

This drug acts at the GABA-A receptor. There are conflicting reports in the literature as to the efficacy of this drug in neuropathic pain, although studies demonstrated that this agent was effective in migraine therapy at dosages of 800 mg/day for a period of 8 weeks.[9] Side effects include gastrointestinal upset, somnolence, and dizziness. The exact role of this agent in the armamentarium of the pain practitioner is yet to be elucidated.[6]

LAMOTRIGINE (LAMICTAL)

The initial dosage is 25 to 50 mg at bedtime, and can be increased to 50 mg twice daily after 2 weeks. Subsequently, it may be increased by 50 mg increments every 1 to 2 weeks as tolerated, to a dose of 300 to 500 mg/day in two divided doses. Upon discontinuation, drug administration should be slowly tapered over a 2-week time period. Like other agents discussed, lamotrigine is an agent that blocks sodium channels in actively firing nerves. It has no effect on sensation in the native, normally functioning nervous system. Unique to lamotrigine is the fact that, in addition to acting as a sodium-channel blocker, the drug prevents release of an excitatory transmitter involved in pain propagation: glutamate.

A major use for lamotrigine is in trigeminal neuralgia. While carbamazepine has been advocated as the first-line therapy for trigeminal neuralgia, it is not always effective in these patients. Lamotrigine has been investigated in this patient model for use as a coadministered drug, and as a substitute for carbamazepine.[12] Twenty-one trigeminal neuralgia patients, who received no benefit from carbamazepine therapy, were treated with lamotrigine.[7] In a group of 7 men and 14 women, 14 of the patients noted significant to complete relief of their symptoms after the institution of lamotrigine therapy, and the remaining 7 patients had no benefit. The use of lamotrigine may, therefore, be indicated in carbamazepine-resistant trigeminal neuralgia. This positive result has also been seen in follow-up with a group of 15 patients with trigeminal neuralgia receiving lamotrigine therapy. In this review,[13] 73% of patients were free of their painful symptoms at the conclusion of the study. Subsequent interval follow-up revealed a continued positive result, with no change in pain scores reported by

patients. As a result of these studies, lamotrigine may have a role in prevention of trigeminal neuralgia in susceptible patients.

Lamotrigine has also been evaluated in the diabetic neuropathy population. Patients suffering from diabetic neuropathy may receive benefit from lamotrigine therapy. In two replicate randomized, double-blind, placebo-controlled trials, a total of 360 patients were treated with lamotrigine. In patients receiving 400 mg, a reduction in pain-intensity score versus placebo was observed in one of the two studies. Doses of 200 mg and 300 mg did not demonstrate any benefit.[14] A group of 15 patients with diabetes-induced (types I and II were combined) peripheral neuropathy were treated in an open study. They were tested with brush and cold stimuli for allodynia and pinprick for hyperalgesia. Upon completion of the study, patients were tested and reported improvement of pain in all settings, and their relief persisted as noted during the subsequent 6-month interval follow-up.

In one randomized controlled trial (RCT), lamotrigine (300 mg/day) was found to significantly reduce pain in distal sensory polyneuropathy (DSP), but not in antiretroviral toxic neuropathy (ATN) associated with HIV disease.[15] HIV-associated neuropathy is believed to be on the rise, concomitant with the increase in the number of patients who become diagnosed with the virus. Patients with distal sensory peripheral neuropathy associated with HIV infection were subjected to a placebo-controlled, randomized, double-blind study to identify the benefit of lamotrigine therapy. While both placebo-treated patients and patients receiving lamotrigine had a decrease in pain, the rate of decrease was more rapid in the lamotrigine group. Patients administered antiretrovirals and lamotrigine, however, were noted to have slower pain relief than those maintained on lamotrigine without the antiretroviral agents. In a subsequent larger trial, it was found to be effective for both DSP and ATN HIV-related pain.[16] The effect of lamotrigine as an adjunctive therapy was also studied in 220 patients with a variety of neuropathic pain conditions uncontrolled by monotherapy.[17] This randomized, double-blind, placebo-controlled study evaluated the efficacy and tolerability of lamotrigine in addition to gabapentin, a tricyclic antidepressant, and a nonopioid analgesic. The study patients suffered from diabetic peripheral neuropathy, postherpetic neuralgia, traumatic/surgical nerve injury, incomplete spinal cord injury, trigeminal neuralgia, multiple sclerosis, or HIV-associated peripheral neuropathy. Lamotrigine was generally well tolerated, but did not demonstrate effective pain relief as evaluated by pain score or use of rescue medication.

A rash is the most common side effect seen in patients. This rash is more likely to develop in pediatric patients, especially when lamotrigine is combined with valproic acid. Stevens-Johnson syndrome has occurred in rare cases. Prescribing physicians should also be aware that when lamotrigine is combined with the CYP450 inhibitor, valproate, the initial dose should be reduced to 12.5 mg daily, and titration should be done cautiously. Additionally, when combined with anticonvulsants that induce hepatic enzymes, such as phenytoin and carbamazepine, the efficacy of lamotrigine may be diminished and a higher dose required for symptomatic improvement.

TOPIRAMATE (TOPAMAX)

The initial dose is 50 mg at bedtime, increasing to an upper limit of 200 mg BID. Studies have demonstrated that pain relief begins to occur at doses of 200 mg/day. In addition to affecting sodium channels and calcium channels, topiramate enhances the action of the GABA (inhibitory) neurotransmitter, and inhibits the AMPA-type glutamate (excitatory) receptor.

Topiramate has been assessed for use in patients with diabetic neuropathy. A 14-week, double-blind study showed that topiramate therapy had more efficacy than placebo in relieving the pain sensed by patients with diabetic neuropathy. A review[7] of other double-blind studies had not corroborated these results, however. In a double-blind, randomized, crossover trial, 50 to 400 mg of topiramate were assessed in patients with chronic, lumbar radicular pain, resulting in an improved global pain relief score, but leg pain was not reduced.[18] The study was limited by frequent side effects and a high dropout rate. The exact role of topiramate is yet to be determined, and, thus, may be best reserved as an adjunct for pain management with other membrane stabilizer agents. Case reports in the literature have also highlighted the use of this agent for additional forms of neuropathic pain, including postherpetic neuralgia, intercostal neuralgia, and CRPS. The primary side effect seen with topiramate is sedation. Other unique consequences of this agent include the potential for development of kidney stones and ocular glaucoma, as topiramate is an inhibitor of the enzyme, carbonic anhydrase.[10] Weight loss associated with topiramate may be a benefit for some and problematic for others.

LEVETIRACETAM (KEPPRA)

Levetiracetam is structurally unrelated to other antiepileptic agents and its mechanism of action has yet to be determined. A starting dose for levetiracetam is 500 mg twice daily, and may be increased to a recommended 3000 mg/day in divided doses. Dosages up to 5000 mg/day have been assessed in the treatment of neuropathic pain.[19] Linear pharmacokinetics allow for predictable effects as the dosage is increased. Levetiracetam is not metabolized by the cytochrome P450 system, and, thus, does not have significant drug interactions.[20] Levetiracetam was found to be ineffective in the treatment of neuropathic pain secondary to a spinal cord injury[21] and postmastectomy pain.[22] Adverse effects include asthenia, dizziness, somnolence, and headache.

LOCAL ANESTHETICS

Local anesthetics are used in neuropathic pain states to block the aberrant firing of abnormal nerves, although they also block normally conducting (non-nociceptive) nerves. As a group, they are effective in the treatment of postherpetic neuralgia, trigeminal neuralgia, radiculopathies, and peripheral neuropathies.

LIDOCAINE

The typical dose is 1 to 5 mg/kg IV. Side effects include dizziness, blurred vision, and seizure, typically presenting at a plasma level of 10 mg/ml.[10] Given that lidocaine is an antiarrhythmic, bradycardia and cardiac depression (present at 20 to 25 mg/ml plasma concentration) are potential risks of this agent; therefore, obtaining electrocardiography studies is indicated for long-term or high-dosage use of lidocaine. A formulation of 5% lidocaine is available in transdermal application, which has proven of benefit to patients with various types of neuropathic pain, including postherpetic neuralgia, post-thoracotomy pain, intercostal neuralgia, and meralgia parasthetica.[23]

The eutectic mixture of local anesthetics (EMLA)—comprised of prilocaine and lidocaine—has also been advocated for use as a topical local anesthetic. This agent is sometimes used as an adjunct for venipuncture in the pediatric population; care must be taken with the amount of EMLA cream given to patients to avoid toxicity. Prilocaine is readily metabolized to o-toluidine, which can lead to methemoglobinemia. However, if dosages of prilocaine are kept below 600 mg, clinical methemoglobinemia is less likely to develop.

MEXILETINE

The standard starting dose is 75 to 150 mg/day, with a target of 300 to 450 mg/day. This agent is an antiarrhythmic, and, for pain relief, can be considered an oral analog of lidocaine. Pain physicians may provide IV lidocaine for pain management, with monitoring of dose and effect. On obtaining a dose of intravenously administered drug, this may be readily converted to oral mexiletine.

Mexiletine can be used for diabetic neuropathy, thalamic stroke pain, spasticity, and myotonia, although its effects are minimal.[24] Common side effects, including somnolence, irritability, blurred vision, and nausea and vomiting, severely limit the utility of this medication. Patients are also at risk for developing blood dyscrasias, and should have blood tests on a regular basis.

CALCIUM-CHANNEL BLOCKERS

Recommended first-line treatment agents of neuropathic pain include the calcium-channel blockers.[25] There are six different types found in nervous tissue: L, N, P, Q, R, and T. Calcium-channel blockers used for treatment of neuropathic pain bind to the alpha2-delta subunit of L-type voltage-gated calcium channels, and result in decreased release of glutamate, norepinephrine, and substance P.[26,27] While structurally derived from the inhibitory neurotransmitter, GABA, neither gabapentin nor pregabalin bind to or have activity at the GABA receptor. They also have no effect on uptake or metabolism of GABA.

GABAPENTIN (NEURONTIN)

The standard initial dose is 100 to 300 mg daily; with a gradual increase to a maximum of 3600 mg/day in TID divided doses. To minimize adverse effects, the initial dose is often given at bedtime. After 2 to 5 days, the dose is increased to 300 mg twice daily, and after another 2 to 5 days to 300 mg 3 times daily thereafter. Subsequently, the dose can be increased by 300 to 600 mg every other week as tolerated until an effective dosage is obtained or the maximum daily dose is reached. The main dose-limiting side effects are fatigue, somnolence, and dizziness, which are often attenuated by gradual dose titration. Although gabapentin has few drug interactions, dosage reduction is necessary in patients with renal insufficiency. Introduced in 1994, gabapentin is now available in generic form, which may make it a more cost-effective option. However, starting dosages of gabapentin often do not provide immediate pain relief, and slow titration requirements may result in adequate therapeutic pain relief taking up to 2 months.

Gabapentin has many uses for patients suffering from multiple pain conditions. Studies have been performed on patients being treated for postherpetic neuralgia, CRPS, painful diabetic neuropathy, and other forms of neuropathic pain.[28,29] Gabapentin has been assessed in postherpetic neuralgia pain through double-blind studies. Patients with postherpetic neuralgia being maintained on opioids and/or tricyclic antidepressants (TCAs) were identified and divided into two groups: 113 received gabapentin and 116 received placebo therapy, in addition to their current background pain regimen. For an 8-week period, patients were maintained on their respective therapies, with increased titration of the drug to a maximum dose of 3600 mg/day, achieved in 4 weeks. Results indicated that the gabapentin patients had a decrease in their VAS for pain of nearly 2 points, compared to a decrease of only 0.5 in the placebo-treated patients. Along with a decrease in pain, patients also reported improvement in their SF-36 (quality of life) scores, noting improved functionality, feeling better, and more restful sleep at night.

The effect of gabapentin on the neuropathic pain of diabetes has also been evaluated.[28] A randomized, double-blind, placebo-controlled trial that pooled patients from multiple centers, showed a decrease of 2.5 on the VAS for patients receiving gabapentin up to 3600 mg/day versus a decrease of 1.4 for patients in the control group.[28] As with the postherpetic neuralgia study, patients also had an increase in their SF-36 scores, more restful sleep at night, and an overall improvement in functioning.

Gabapentin has also been studied in patients with lumbar spinal stenosis. In a pilot study, both patient groups received the standard care, including physical therapy, lumbosacral bracing, and nonsteroidal anti-inflammatory drugs (NSAIDs).[30] The treatment group also received gabapentin, 900 to 2400 mg, in divided TID. After 4 months, patients who received gabapentin reported improvement in pain scores, increased walking distance, and decreased sensory and motor deficits. Given these results, it appears that gabapentin can be indicated as adjunctive therapy for symptomatic spinal stenosis.

In a double-blind, randomized, placebo-controlled, 8-week trial, patients included those with CRPS, postherpetic neuralgia, radiculopathy, postlaminectomy syndrome, post-stroke syndrome, phantom limb pain, and other neuropathic pain syndromes. Gabapentin was initially started at 900 mg/day for 3 days, and then increased to a maximum

of 2400 mg/day at the end of week 5. The conclusion of the study showed that gabapentin reduced pain and improved some quality of life measures in these patients.[31] Gabapentin has also been found to be effective in reducing the pain associated with multiple sclerosis, specifically paroxysmal pain with a throbbing, pricking, and cramping quality rather than the dull, aching pain experienced by multiple sclerosis patients.[32] Finally, gabapentin appears to improve the analgesic efficacy of opioids in patients with neuropathic cancer pain.[33]

Studies of gabapentin in postamputation pain and phantom limb pain have been less effective than in other neuropathic pain states. Nikolajsen and colleagues[34] administered gabapentin to patients following limb amputation, and found no effect on postamputation or phantom limb pain. In a small cohort–control study, gabapentin was found to be effective in the treatment of chemotherapy-induced, painful peripheral neuropathy.[35] However, an earlier, larger RCT found no benefit to gabapentin therapy for the same condition.[36]

In an extremely important and well-performed trial, combination therapy of gabapentin and the tricyclic antidepressant, nortriptyline, was found to be highly effective in the treatment of neuropathic pain resulting from diabetes and varicella zoster.[37] Although this study was not designed to show synergism between these two medications, the results are highly suggestive of a synergistic analgesic effect. Patients achieved greater pain relief on a combination of low dosages of gabapentin (600 mg po TID) and nortriptyline (50 mg po QHS) than with either medication given alone at high doses. Importantly, patients on combination therapy received good analgesia without the significant side effects suffered by those on monotherapy. This trial, supported by the Canadian Institutes of Health, is a rare study in that the investigators had no influence from pharmaceutical companies, and two inexpensive generic medications were studied.

PREGABALIN (LYRICA)

Initial pregabalin dosing is 150 mg/day, given in two or three divided doses, or 75 mg given at bedtime in elderly patients. Upward dose titration can be completed after 3 to 7 days to 300 mg/day, and subsequently increased to a maximum dose of 600 mg/day within 2 weeks of initiation. Similar to gabapentin, pregabalin dosing must be decreased in patients with reduced kidney function. Pregabalin advantages over gabapentin include a more rapid onset of pain relief, linear pharmacokinetics with low intersubject variability,[38] fewer dose-related side effects allowing for faster dosage upward titrations, and twice daily versus 3 times daily dosing. Additionally, maximum benefit often occurs after 2 weeks of treatment at target doses of 300 to 600 mg/day compared with up to 2 months in gabapentin-treated patients.

Pregabalin is an alpha2-delta ligand structurally related to gabapentin. It similarly binds to calcium channels and modulates calcium influx into hyperexcited neurons, leading to its antinociceptive and antiseizure effects.[26] While it is structurally derived from the inhibitory neurotransmitter GABA, it does not bind to GABA or benzodiazepine receptors. Pregabalin is approved for the treatment of peripheral and central neuropathic pain, including postherpetic neuralgia and painful diabetic neuropathy.

In patients with postherpetic neuralgia, a trial was conducted in 370 patients, evaluating doses of 150, 300, or 600 mg/day versus placebo.[39] The RCT demonstrated reduced mean pain scores and improvement in sleep interference. Patients responded at all dosages, with the greatest response noted with 600 mg/day. Patients responded as early as the first week, and beneficial effects were sustained throughout the 13-week study duration. Adverse effects were generally mild to moderate, and 13% of patients withdrew from the study, most commonly due to dizziness or somnolence.

In a randomized, double-blind study, the effects of pregabalin on neuropathic pain from diabetic neuropathy were evaluated.[40] A total of 395 patients were randomized to receive 150, 300, or 600 mg/day. In patients who received 600 mg/day, 46% reported greater than 50% improvement of pain scores from baseline, and the NNT to achieve this response was 6.3. Pregabalin also improved pain-related sleep interference, and overall was well tolerated with a NNH of 10.3 in patients treated with 600 mg/day.

In patients with central neuropathic pain from spinal cord injury, pregabalin was evaluated in a 12-week multicenter study.[41] A total of 137 patients were randomized to either a flexible-dose regimen of 150 to 600 mg/day or placebo, and were allowed to continue an existing stable pain regimen. Pregabalin was found to be significantly more effective in relieving central neuropathic pain than the placebo.

Pregabalin has also been studied for use in patients with refractory neuropathic pain.[42] A 15-month, open-label study was conducted in 81 patients with postherpetic neuralgia and diabetic neuropathy refractory to treatment, including gabapentin, a TCA, and a third medication (e.g., other anticonvulsant, opioid, SSRI, tramadol). Patients took 150 to 600 mg/day for 3-month intervals, and then had a 3- to 28-day "drug holiday." As evaluated by the VAS, patients had a clinically meaningful and sustained pain intensity reduction during the treatment cycle, with return of pain during "drug holidays." In patients with unsatisfactory response to other medications, pregabalin may be considered as an adjunctive therapy.

The advantage of pregabalin is its early response and favorable side-effect profile. Most common adverse effects include somnolence and dizziness, and are noted more frequently with higher doses. When discontinuing pregabalin, it should be gradually tapered down over at least 1 week to minimize symptoms, including insomnia, nausea, headache, and diarrhea.

ZONISAMIDE (ZONEGRAN)

The initial dose is 100 mg QD for 2 weeks, increasing by 200 mg/week, for a target of 600 mg/day. This agent acts by blocking T-type calcium channels and sodium channels; its action also increases GABA release. It has uses in various types of neuropathic pain.

An open-label, dose-titration study resulted in minimal change in VAS scores after 8 weeks of therapy.[43] Similar results were seen in a randomized, double-blind, placebo-controlled, pilot study in patients with painful peripheral neuropathy.[43] Side effects include ataxia, decreased appetite, rash, and renal calculi (due to the carbonic anhydrase inhibitor effect). In children, there is an increased risk of oligohydrosis and susceptibility to hyperthermia. The exact role of zonisamide in the management of patients with neuropathic pain is yet to be elucidated, and further research is needed.

ZICONOTIDE (PRIALT)

Ziconotide is a ω-conopeptide (previously known as SNX-111) that is administered intrathecally due to its peptidic structure. It is derived from the venom of a marine snail (genus *Conus*). Ziconotide blocks calcium influx into N-type calcium channels that are present in the dorsal horn lamina of the spinal cord, thus preventing the afferent conduction of nerve signals.[44] Administration occurred via an intrathecal infusion pump, and dosing should be started low, at a recommended dose of 2.4 μg/day (0.1 μg/hr). Due to a lag time, it should be titrated up slowly, at intervals of no more than two to three times per week, to a recommended maximum of 19.2 μg/day.[44] Ziconotide does not cause tolerance, dependence, or respiratory depression, and adverse effects primarily involve the CNS, including dizziness, ataxia, confusion, and headache.

Ziconotide has been evaluated in randomized, double-blind, placebo-controlled trials for severe, chronic, treatment-refractory pain in both malignant and nonmalignant patients.[45] Patients experienced a significant improvement in mean pain score and global pain relief. The response rate was higher in patients receiving a maximum of 21.8 μg/day; however, pain relief was accompanied by a high incidence of adverse effects, and resulted in frequent interruptions of the trial. A slow titration schedule with a lower maximum infusion rate was associated with significantly lower drop-out rates, but also resulted in a more modest treatment effect. At the conclusion of one trial, nearly 90% of patients elected to continue receiving ziconotide. Rare, but serious adverse effects include hallucinations; thus, ziconotide is not recommended for use in patients with a history of psychosis. Creatinine kinase (CK) elevations were noted in some studies to be related to ziconotide. The etiology remains unclear, and CK levels should be monitored periodically.

The role of ziconotide for chronic pain management has yet to be fully elucidated. Currently, ziconotide is approved for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of or refractory to other treatments, including intrathecal opiates.

NIMODIPINE (NIMOTOP)

Nimodipine has been shown to decrease the dose of morphine for cancer pain in 9 of 14 patients.[46] In a colorectal surgery population, concomitant calcium-channel blocker therapy did not decrease opioid requirements.[47] Nimodipine taken concurrently with antiretroviral medications demonstrated a trend towards improvement, and/or the stabilization of HIV-associated neuropathy when compared to placebo.[48]

MAGNESIUM

Research has recently been performed evaluating the antagonists of the N-methyl-d-aspartate (NMDA) receptor, including the membrane-stabilizing effect of magnesium. In a study of seven patients with postherpetic neuralgia, the intravenous infusion of 30 mg/kg of magnesium sulfate over 30 min was found to be more effective in relieving the pain when compared to an intravenous infusion of saline.[49]

KEY POINTS

- In neuropathic pain, there is altered processing and changes in central modulation. These include pathologic activity in injured nerves (resulting in hyperexcitability, spontaneous and evoked pain), loss of C-fibers, sprouting of the large fibers in the outer laminas of the dorsal horn where the nociceptive-specific neurons are located (resulting in allodynia), and increased activity in the sympathetic nervous system.
- Some of the molecular changes in neuropathic pain include the accumulation and novel expression of sodium channels in peripheral nerves; increased activity of glutamate receptor subpopulations, especially the NMDA receptor; reduction of GABA inhibition; and changes in the penetration of calcium into the cells.
- The mechanisms of action of the membrane stabilizers include blockade of the sodium channel, suppression of the release of glutamate or blockade of glutamate activity, increase in GABA content, and binding to the alpha-2-delta subunit of GABA (see Table 16-1).
- The most common side effect of lamotrigine is the development of a rash. This is usually seen in pediatric patients and upon rapid titration of drug dosage.
- The most common side effect of oxcarbazepine is hyponatremia.
- Gabapentin is an effective drug in neuropathic pain, specifically postherpetic neuralgia and painful diabetic neuropathy. It is well tolerated, and its common side effects include dizziness and sedation.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 17

Nonopioid Analgesics: NSAIDs, COX-2 Inhibitors, and Acetaminophen

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used analgesic medications in the world because of their ability to reduce pain and inflammation.[1–3] The NSAIDs are structurally diverse, but all have antipyretic, anti-inflammatory and analgesic or antihyperalgesic properties. The salicylates (aspirin-like medications) have been used to treat pain conditions for thousands of years, with Ebers Papyrus recommending the application of a decoction of the dried leaves of myrtle to the abdomen and back to expel rheumatic pains from the womb; and Hippocrates recommending the juices of the poplar tree to treat eye diseases and those of willowbark to relieve the pain of childbirth and to reduce fever.[4] NSAIDs are among the oldest, most successful drugs known to modern medicine in treatment of fever, pain, and inflammation.

More than 100 million prescriptions for NSAIDS are written by clinicians in the United States each year and more than 30 million Americans use prescription or over-the-counter (OTC) NSAIDs regularly.[5,6] This class of medications contains compounds that are often chemically diverse but are grouped together based on their therapeutic actions. Many of the NSAIDs used today are available as OTC products, with more than 14 million patients using NSAIDs for relief of symptoms associated with arthritis alone.[7] Today, NSAIDs are the most widely prescribed drugs in the world with sales in the United States alone of nearly $5 billion.[3]

From the introduction of aspirin in 1899 to the newest class of NSAIDs, the coxibs, NSAIDs have a long history of clinical use. They have even demonstrated clear clinical utility in such severe pain states as osteoarthritis, rheumatoid arthritis, and metastatic spread of cancer to bone, usually supplementing rather than replacing the role of opioids.[8,9] Although often labeled as an NSAID, acetaminophen has important differences, such as its weak anti-inflammatory effects and its generally poor ability to inhibit cyclooxygenase (COX) in the presence of high concentrations of peroxides, as are found at sites of inflammation.[10,11] Unlike NSAIDs, acetaminophen does not have an adverse effects on platelet function[12] or gastric mucosa.[11]

MECHANISM OF ACTION

The mechanism of action of NSAIDs is inhibition of prostaglandin production from arachidonic acid by either reversible or irreversible acetylation of the cyclooxygenase (COX) (Fig. 17-1). COX is present in at least two isoforms (COX-1 and COX-2) and is dispersed throughout the body. The COX-1 isoform is constitutive, causing hemostasis, platelet aggregation, and the production of prostacyclin, which is gastric mucosal protective. The inhibition of the COX-1 isoform may be responsible for the adverse effects related to the nonselective NSAIDs.[13] It is the COX-2 isoform that is induced by proinflammatory stimuli and cytokines causing fever, inflammation, and pain, and thus the target for antipyresis, anti-inflammation, and analgesia by NSAIDs.[4] COX-1 is necessary for normal functions and is found in most cell types. COX-1 mediates the production of prostaglandins that are essential in the homeostatic processes in the stomach (gastric protection), lung, and kidney, and platelet aggregation. COX-2 is generally considered to be an inducible enzyme, provoking pathologic processes such as fever, pain, and inflammation. COX-2, despite being the inducible isoform, is expressed under normal conditions in a number of tissues, which probably include brain, testis, and kidney. In inflammatory states, COX-2 becomes expressed in macrophages and other cells propagating the inflammatory process.[14] The pain associated with inflammation and prostaglandin production results from the production of prostanoids in the inflamed body tissues that sensitize nerve endings and leads to the sensation of pain.[15]

Originally thought of as possessing solely peripheral inhibition of prostaglandin production, more recent research indicates that NSAIDs have peripheral and central mechanisms of action.[2,16,17] Peripherally, prostaglandins contribute to hyperalgesia by sensitizing nociceptive sensory nerve endings to other mediators (such as histamine and bradykinin) and by sensitizing nociceptors to respond to non-nociceptive stimuli (e.g., touch).[16,18] Peripheral inflammation induces a substantial increase in COX-2,[19] and prostaglandin synthase expression in the central nervous system (CNS). Centrally, prostaglandins are recognized to have direct actions at the level of the spinal cord enhancing nociception, notably the terminals of sensory neurons in the dorsal horn.[20] Both COX-1 and COX-2 are expressed constitutively in dorsal root ganglia and spinal dorsal and ventral gray matter but inhibition of COX-2 and not COX-1 reduces hyperalgesia.[21] Additionally, the proinflammatory cytokine interleukin-1beta (IL-1β) plays a major role in inducing COX-2 in local inflammatory cells by activating the transcription factor NF-κB. In the CNS IL-1β causes increased production of COX-2 and PGE_2, producing hyperalgesia, but this is not the result of neural activity arising from the sensory fibers innervating the inflamed tissue or of systemic IL-1β in the plasma.[22] Peripheral inflammation possibly produces other signal molecules that enter the circulation, crossing the blood–brain barrier, and act to elevate IL-lβ, leading to COX-2 expression in neurons and non-neuronal cells in many different areas of the spinal cord.[22,23] At present, evidence suggests that in humans during surgery interleukin 6 (IL-6) triggers the formation of PGE_2 in the CNS, which in turn causes increased production of COX-2 and PGE_2.[24]

There appear to be two forms of input from peripheral inflamed tissue to the CNS. The first is mediated by

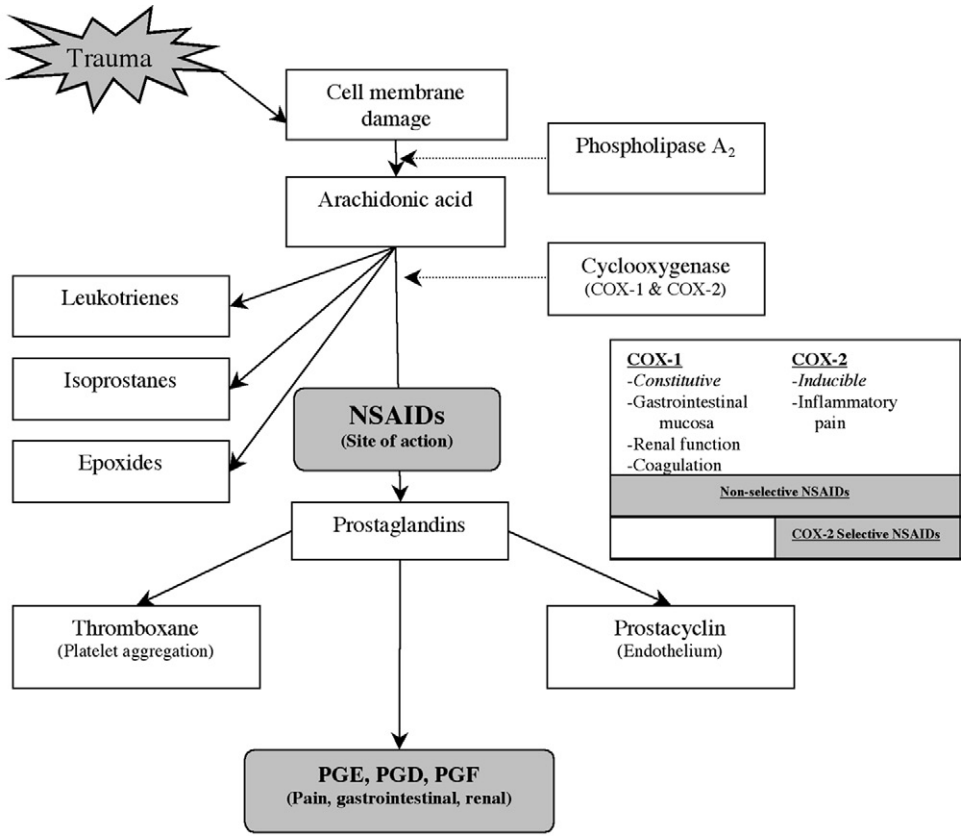

FIGURE 17-1 Site of action of NSAIDs.

electrical activity in sensitized nerve fibers innervating the inflamed area, which signals the location of the inflamed tissue as well as the onset, duration, and nature of any stimuli applied to this tissue.[21] This input is sensitive to peripherally acting COX-2 inhibitors and to neural blockade with local anesthetics.[25] The second is a humoral signal originating from the inflamed tissue, which acts to produce a widespread induction of COX-2 in the CNS.[24]

PHARMACOKINETICS

NSAIDs are most often administered enterally, but intravenous, intramuscular, rectal, and topical preparations are available. NSAIDs are highly bound to plasma proteins, specifically to albumin (>90%), and therefore only a small portion of the circulating drug in plasma exists in the unbound (pharmacologically active) form. The volume of distribution of NSAIDs is low, ranging from 0.1 to 0.3 L/kg, suggesting minimal tissue binding.[25] Most NSAIDs are weak acids with pK_a less than 6, and since weak acids will be 99% ionized two pH units above their pK_a, these anti-inflammatory medications are present in the body mostly in the ionized form. In contrast, the coxibs are nonacidic, which may play a role in the favorable tolerability profile.

ABSORPTION

As previously stated, most NSAIDs are administered enterally and their pH profile facilitates absorption via the stomach, and the large surface area of the small intestine produces a major absorptive site for orally administered NSAIDs. Most of the NSAIDs are rapidly and completely absorbed from the gastrointestinal (GI) tract, with peak concentrations occurring within 1 to 4 hr. The presence of food tends to delay absorption without affecting peak concentration.[10] Most NSAIDs are not available in parenteral forms in the United States. Only three have been approved for parenteral administration: ketorolac, propacetamol, and ibuprofen. Parenteral administration may have the advantage of decreased direct local toxicity in the GI tract, but parenteral ketorolac tromethamine, for example, does not decrease the risk of adverse events associated with COX-1 inhibition. Topical NSAIDs possess the advantage of providing local action without systemic adverse effects. These medications, such as diclofenac epolamine transdermal patch (Flector®) and diclofenac sodium gel (Voltaren®), are formulated to traverse the skin to reach the adjacent joints and muscles and exert therapeutic activity, and may offer some advantage in terms of decreased adverse events.

DISTRIBUTION

The majority of NSAIDs are weakly acidic, highly bound to plasma proteins (albumin), and lipophilic. The relatively low pH of most NSAIDs, in part, determines the distribution because they are ionized at physiologic pHs. In areas with acidic extracellular pH values, NSAIDs may accumulate (inflamed tissue, GI tract, kidneys).[26] Additionally, the unbound drug is generally considered responsible for pharmacologic effects, and the apparent volume of distribution (Vd/F), determined after oral administration, is usually 0.1 to 0.3 L/kg, which approximates plasma volume.[26] This high protein binding places only a small portion in the active unbound form. However, some NSAIDs (i.e., ibuprofen,

naproxen, salicylate) have activity that is concentration dependent because their plasma concentration approaches that of plasma albumin and the Vd/F increases with dose.[26] The high protein binding of the NSAIDs has particular relevance in the state of hypoalbuminemia or decrease albumin concentrations (e.g., elderly, malnourished). A greater fraction of unbound NSAIDs are present in the plasma, which may enhance efficacy but also increase toxicity. NSAIDs compete for binding sites with other highly plasma protein–bound drugs such as warfarin; thus the possibility of bleeding may be increased with concomitant use of these medications.

ELIMINATION

The major metabolic pathway for elimination of NSAIDs is hepatic oxidation or conjugation. The half-lives of NSAIDs vary, as active metabolites may be present or the metabolite is the active form when liberated from the prodrug. Also, the elimination of the NSAIDs may determine the dosing frequency, as NSAID plasma elimination half-lives vary widely from 0.25 to 70 hr.[26] Renal excretion of unmetabolized drug is a minor elimination pathway for most NSAIDs accounting for less than 10% of the administered dose.

SPECIFIC MEDICATIONS

There are multiple NSAIDs available in the United States and even more available outside of the United States. Table 17-1 provides information on chemical class, pharmacologic data, and therapeutic dosages.

SALICYLATES

Aspirin

Acetylsalicylic acid (ASA) is the most widely use analgesic, antipyretic, and anti-inflammatory agent in the world and remains the standard for which all other NSAIDs are compared. Aspirin is comprised of the active compounds acetic acid and salicylic acid, forming acetylsalicylic acid. Aspirin inhibits the biosynthesis of prostaglandins by means of an irreversible acetylation and consequent inactivation of COX; thus, aspirin inactivates COX permanently. This is an important distinction among the NSAIDs because aspirin's duration action is related to the turnover rate of cyclooxygenases in various target tissues. The duration of action of other NSAIDs, which competitively inhibit the active sites of the COX enzymes, relates more directly to the time course of drug disposition.[27] Because platelets are devoid of the ability to produce additional cyclooxygenase, thromboxane synthesis is arrested.

PROPIONIC ACID

Naproxen

Naproxen is a nonprescription nonsteroidal anti-inflammatory drug; a newly formulated controlled-release tablet is available (Naprelan®). It is fully absorbed after enteral administration and has a half-life of 14 hr. Peak concentrations in plasma occur within 4 to 6 hr. The half-life is approximately 14 hr, but steady-state serum levels require more than 48 hr. Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels, naproxen is more than 99% albumin-bound. Naproxen is extensively metabolized to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Most of the drug is excreted in the urine, primarily as unchanged naproxen. Naproxen has been used for the treatment of arthritis and other inflammatory diseases. Metabolites of naproxen are excreted almost entirely in the urine. About 30% of the drug undergoes 6-demethylation, and most of this metabolite, as well as naproxen itself, is excreted as glucuronide or other conjugates.

Ibuprofen

Ibuprofen is one of the most widely used NSAIDs after ASA and *N*-acetyl-*p*-aminophenol (APAP) in OTC use for the relief of symptoms of acute pain, fever, and inflammation. Ibuprofen is rapidly absorbed from the upper GI tract, with peak plasma levels achieved about 1 to 2 hr after administration. It is highly bound to plasma proteins with an estimated volume of distribution of 0.14 L/kg, and is primarily hepatically metabolized (90%) with less than 10% excreted unchanged in the urine and bile. A short plasma half-life (2 ± 0.5 hr) and lack of active metabolites, OTC availability, and low toxicity potential support use in febrile and mild to moderate pain conditions.[27a] Ibuprofen at a dose of 1200 to 2400 mg/day has a predominantly analgesic effect for mild to moderate pain conditions, with dosage of 3200 mg/day recommended only under continued care of clinical professionals. Even at anti-inflammatory doses of more than 1600 mg per day, renal side effects are almost exclusively encountered in patients with low intravascular volume and low cardiac output, particularly in the elderly.[28] The effectiveness of ibuprofen has been demonstrated in the treatment of headache and migraine, menstrual pain, and acute postoperative pain.[29–31] In addition to the enteral formulation of ibuprofen, the Food and Drug Administration (FDA) approved a parenteral formulation in 2009. In a multicenter, randomized, double-blind, placebo-controlled trial, Caldolor® has been studied in postoperative patients (single-site orthopedic or abdominal surgery) with results indicating significant reductions in median morphine use utilizing 800 mg IV q6h (by 22% vs. placebo; $p = 0.030$) and rest pain and incident pain.[32]

Ketoprofen

The pharmacologic properties of ketoprofen are similar to other proprionic acid derivatives, although formulations differ in their release characteristics. The optically pure (S)-enantiomer (dexketoprofen) is rapidly reabsorbed from the GI tract, having a rapid onset of effects. Additionally, capsules release the drug in the stomach, whereas capsule pellets (extended release) are designed to resist dissolution in the low pH of gastric fluid, but release the drug at a controlled rate in the higher pH environment of the small intestine. Peak plasma levels are achieved about 1 to 2 hr after oral administration for the capsules and the 6 to 7 hr

TABLE 17–1 Chemical Characteristics and Dosage of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Acetaminophen

Medication (Generic) Name	Proprietary (Trade) Name	Half-life (hr)	Percent Protein Bound (%)	Usual 24-Hr Adult Dose Range	Adult Daily Dose and Frequency	Dosage Schedule	Comments
Salicylates							
Aspirin	Multiple	2–3	~90	2/4–6 g	600–1500 mg	QID	Irreversible inhibitor of cyclooxygenase, caution when used with anticoagulants, associated with Reye's syndrome in children
Buffered/ enteric aspirin	Bayer, Bufferin, Ecotrin, multiple others			2.4–6 g	600–1500 mg QID		
Propionic Acid Derivatives							
Naproxen	Naprosyn, others	14	99	750 mg–1 g	250, 375, 500 mg	BID	
Naproxen sodium	Aleve, Anaprox	14	99	550–1100 mg	275–550 mg	BID	
Ibuprofen	Motrin, Advil, others	6	99	1.2–2.4 g (pain)	200–800 mg	QID	Available without prescription; parenteral formulation
				2.4–3/2 g (inflammation)	3200 mg		
Parenteral ibuprofen	Caldolor	~2	99	3.2 g	400–800 mg 50–75 mg	Every 6 hr	
Ketoprofen	Orudis	2–4	99	225 mg	50–75 mg	TID	
Oxaprozin	Daypro	40–60	99	1.2 g	1.2 g	Once daily	
Acetic Acid Derivatives							
Diclofenac	Voltaren	1–2	99	150–200 mg	50 mg, 75 mg	BID–QID	Accumulates in synovial fluid; multiple formulations
Diclofenac/ misoprostol	Arthrotec	1–2	99	150–200 mg; *misoprostol should not exceed 800 mcg*	50 mg/ 200 mcg; 75 mg/ 200 mcg	BID–QID	Gastroprotective
Diclofenac gel	Voltaren Gel (1%)		99	32 g	2–4 g	QID	Decreased systemic absorption
Diclofenac Patch	Flector Patch (1.3%)	12	99	360 mg	1 patch (180 mg)	BID	Decreased systemic absorption
Etodolac	Lodine	7	99	400–1200 mg	200–300 mg	BID, TID, QID	15–20 mg/kg/24 hr
Indomethacin	Indocin, Indocin SR, multiple others	~4	90	<200 mg	25–50 mg, SR: 75 mg; rarely >150 mg	BID	Limited use because of high side effect profile in elderly
Ketorolac	Toradol	5–6	99	Oral not >60 mg/day; parenteral 30–60 mg, then 15–30 mg	Oral: 10 mg; Q6H not >5 days total	QID	Limited use duration (<5 days); may precipitate renal failure in elderly or hypovolemic patients; efficacious in treating postoperative pain
Nabumetone	Relafen	20–24	99	1.0–1.5 g	500–750 mg	BID	Gastroprotective prodrug that is converted into the active molecule
Anthranilic Acid Derivatives							
Mefenamic acid	Ponstel	3–4	99	1.0–4.0 g	250 mg	QID	
Oxicam							
Meloxicam	Mobic	15–20	99	7.5–15 mg	7.5 mg (OA); 15 mg (RA)	Once daily	COX–2 selectivity at 7.5-mg dose

Continued

TABLE 17–1 Chemical Characteristics and Dosage of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Acetaminophen—cont'd

Medication (Generic) Name	Proprietary (Trade) Name	Half-life (hr)	Percent Protein Bound (%)	Usual 24-Hr Adult Dose Range	Adult Daily Dose and Frequency	Dosage Schedule	Comments
Coxibs (COX-2 Selective NSAIDs)							
Celecoxib	Celebrex	6–12	97	200 mg	100–200 mg 400 mg, acute pain	Once daily or BID	Gastroprotective
Etoricoxib	Arcoxia	20–26	92	60–90 mg; 120 mg (<8 days)	90 mg	Once daily	
Aniline Derivatives							
Acetaminophen	Tylenol, others	2–3	20–50	2–4 g	325–650 mg; 650 mg–1 g	Q4H; QID	Hepatotoxicity, in many medication combinations; therefore, patient education is needed

after administration of the capsule pellets. Ketoprofen has high plasma protein binding (98%–99%) and an estimated volume of distribution of 0.11 L/kg. Ketoprofen is conjugated with glucuronic acid in the liver, and the conjugate is excreted in the urine. The glucuronic acid moiety can be converted back to the parent compound. Thus, the metabolite serves as a potential reservoir for the parent drug, and this may be important in persons with renal insufficiency. The extended-release ketoprofen is not recommended for the treatment of acute pain because of release characteristics. Individual patients may show a better response to 300 mg daily as compared to 200 mg, although in well-controlled clinical trials patients on 300 mg did not show greater mean effectiveness. The usual starting dose of ketoprofen is 50 or 75 mg with immediate release capsules every 6 to 8 hr or 200 mg with extended release capsules once daily. The maximum dose is 300 mg daily of immediate-release capsules or 200 mg daily of extended-release capsules. Ketoprofen has shown statistical superiority over acetaminophen on the time-effect curves for pain relief and pain intensity difference in the treatment of moderate or severe postoperative pain and acute low back pain.[33–35]

Oxaprozin

In contrast to the other proprionic acid derivatives, oxaprozin peak plasma levels are not achieved until 3 to 6 hr after an oral dose, and its half-life of 40 to 60 hr allows for once-daily administration.[36] Peak plasma concentration occurs at about 1.5 hr after administration. Oxaprozin is highly bound to plasma proteins and has an estimated volume of distribution of 0.15 L/kg. Oxaprozin is primarily metabolized by the liver, and 65% of the dose is excreted into the urine and 35% in the feces as metabolites. Oxaprozin diffuses readily into inflamed synovial tissues after oral administration and is capable of inhibiting both anandamide hydrolase in neurons and NF-κB activation in inflammatory cells, which are crucial for synthesis of proinflammatory and histotoxic mediators in inflamed joints.[37–39]

ACETIC ACID

Diclofenac

Diclofenac has COX-2 selectivity and the selective inhibitor of COX-2 lumiracoxib is an analog of diclofenac. Its potency against COX-2 is substantially greater than that of indomethacin, naproxen, or several other NSAIDs and is similar to celecoxib.[10] Diclofenac is rapidly absorbed after oral administration, but in substantial first-pass metabolism only about 50% of diclofenac is available systemically. After oral administration, peak serum concentrations are attained within 2 to 3 hr. Diclofenac is highly bound to plasma proteins and has an estimated volume of distribution of 0.12 L/kg. Diclofenac is excreted primarily in the urine (65%), and as bile conjugates (35%). Diclofenac is available in two enteral formulations, diclofenac sodium and diclofenac potassium. Diclofenac potassium is formulated to be released and absorbed in the stomach. Diclofenac sodium, usually distributed in enteric-coated tablets, resists dissolution in low pH gastric environments, releasing instead in the duodenum.[40] Hepatotoxicity via elevated transaminases may occur, and transaminases should be measured during therapy with diclofenac. Other formulations of diclofenac include topical gels (Voltaren® Gel) and transdermal patches (Flector® Patch). Additionally, diclofenac is available in a parenteral formulation for infusion (Voltarol® ampules), and more recently a formulation for intravenous bolus has been developed (diclofenac sodium injection [DIC075V; Dyloject®]). Uniquely, diclofenac accumulates in synovial fluid after oral administration,[41] which may explain why its duration of therapeutic effect is considerably longer than the plasma half-life of 1 to 2 hr. Oral preparations have been shown to provide significant analgesia in the postoperative period for adults experiencing moderate or severe pain following a surgical procedure.[42]

The transdermal application of diclofenac has also shown efficacy in the treatment of musculoskeletal disorders such as ankle sprains, epicondylitis, and knee osteoarthritis.[43,44] The advantage of the transdermal formulation

is the lack of appreciable systemic absorption (6% [158 times lower] of the systemic exposure from enteral diclofenac sodium), and accumulation of the medication at the site of application, thereby providing local pain relief. In comparison to enteral delivery, topical application of diclofenac provides analgesia by peripheral activity and not central mediation.

Etodolac

Etodolac has some degree of COX-2 selectivity, conferring less gastric irritation compared with other NSAIDs.[45] The analgesic effect of full doses of etodolac is longer than that of aspirin, lasting up to 8 hr. After oral administration, peak serum concentrations of 16 and 25 mg/L are attained within 2 hr of administering 200 and 400 mg, respectively. Etodolac is highly bound to plasma proteins and has an estimated volume of distribution of 0.4 L/kg. Etodolac is excreted primarily in the urine, and 60% of a dose is recovered within 24 hr. More than 60% of the metabolites are hydroxylated with glucuronic conjugation. The half-life of etodolac is approximately 7 hr in healthy subjects. When compared with other NSAIDs, etodolac doses of 300 and 400 mg daily have tended to be more effective than aspirin of 3 to 4 g daily and was similar in efficacy to sulindac at 400 mg daily.[10] Clinical doses of 200 to 300 mg twice a day for the relief of low back or shoulder pain have been equated to analgesia with naproxen 500 mg twice a day.[46] In postsurgical pain, etodolac 100 to 200 mg was approximately equivalent to aspirin 650 mg in providing pain relief, although etodolac had a longer duration of action.[47]

Indomethacin

This is a nonselective COX inhibitor introduced in 1963, but has fallen out of favor with the advent of safer alternatives. Indomethacin is a more potent inhibitor of the cyclooxygenases than aspirin, but patient intolerance generally limits its use to short-term dosing. Oral indomethacin has excellent bioavailability. Peak concentrations occur 1 to 2 hr after dosing. Indomethacin is 90% bound to plasma proteins and tissues. The concentration of the drug in the cerebrospinal fluid is low, but its concentration in synovial fluid is equal to that in plasma within 5 hr of administration.[10] Complaints associated with GI irritation are common, including diarrhea, and ulcerative lesions are a contraindication to indomethacin use. Intravenous indomethacin has FDA approval for closure of persistent patent ductus arteriosus but its side effect profile limits other uses.

Ketorolac

Ketorolac tromethamine is a NSAID with activity at COX-1 and COX-2 enzymes, which block prostaglandin production. After oral administration, peak serum concentrations are attained within 1 to 2 hr. Ketorolac is highly bound to plasma proteins and has an estimated volume of distribution of 0.28 L/kg. Ketorolac is excreted primarily in the urine and has a half-life of approximately 5 to 6 hr in healthy subjects. Administration of ketorolac is available for enteral, ophthalmic, and parenteral delivery, and is only one of two parenteral NSAIDs currently available in the United States (see ibuprofen). Intranasal routes have been studied with 31.5 mg of nasal solution in postoperative patients.[48] The intranasal route was shown to significantly reduce morphine consumption, but at present intranasal ketorolac is not readily available. Ketorolac has been used to treat mild to severe pain following major surgical procedures, including general abdominal surgery, gynecologic surgery, orthopedic surgery, and dentistry. Multiple studies have investigated the analgesic potency of ketorolac, and in animal models the analgesic potency has be estimated to be between 180 to 800 times that of aspirin.[49,50] When compared to morphine, ketorolac 30 mg intramuscular (IM) has been shown to be equivalent to 12 mg morphine IM and 100 mg meperidine IM.[51] It has been observed that the mean values for total body clearance were decreased by about 50% in patients with renal impairment compared with healthy control subjects,[52] and may precipitate or exacerbate renal failure in hypovolemic elderly patients and especially those with underlying renal dysfunction. Therefore, ketorolac is recommended for limited use (3–5 days).

Nabumetone

Nabumetone is a prodrug that undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), which has some degree of COX-2 selectivity conferring less gastric irritation compared with other NSAIDs.[53] Nabumetone is highly bound to plasma proteins and has an estimated volume of distribution of 0.68 L/kg. Nabumetone is excreted primarily in the urine and has a half-life of approximately 20 to 24 hr in healthy subjects, thereby enabling single daily dosing. When compared with other NSAIDs, nabumetone has tended to show efficacy[54] and tolerability in the treatment of arthritis.[55,56]

ANTHRANILIC ACID

Mefenamic Acid

Mefenamic acid not only blocks prostaglandin synthesis but also the tissue response to prostaglandins. Peak serum concentrations are attained within 2 to 4 hr and the half-life is 3 to 4 hr. Mefenamic acid is highly bound to plasma proteins and is excreted primarily in the urine. Mefenamic acid has been associated with severe pancytopenia and many other side effects. Hence, therapy is not to occur for more than 1 week.[57]

OXICAM

Meloxicam

The enolic acid derivative shows nonselectivity, except for meloxicam which shows relative COX-2 selectivity. For example, meloxicam shows dose-dependent COX selectivity, where 7.5 mg is more selective for COX-2 and at 15 mg meloxicam becomes less selective.[58] After oral administration, peak serum concentrations are attained within 5 to 10 hr after administration. Meloxicam is highly bound to plasma proteins and has an estimated half-life of approximately 15 to 20 hr in healthy subjects.

COX-2 INHIBITORS

COX-2 inhibitors (celecoxib, rofecoxib, and valdecoxib) were approved for use in the United States and Europe, but both rofecoxib and valdecoxib have now been withdrawn from the market due to their adverse event profile. Recently, parecoxib and etoricoxib have been approved in Europe but still await approval in the United States. The newest drug in the class, lumiracoxib, is under consideration for approval in Europe and the United States. Upon administration, most of the coxibs are distributed widely throughout the body, with celecoxib possessing an increased lipophilicity, enabling transport into the CNS. Lumiracoxib is more acidic than the others, which may favor its accumulation at sites of inflammation. Despite these subtle differences, all of the coxibs achieve sufficient brain concentrations to have a central analgesic effect,[59] and all reduce prostaglandin formation in inflamed joints. The estimated half-lives of these medications vary (2 to 6 hr for lumiracoxib, 6 to 12 hr for celecoxib and valdecoxib, and 20 to 26 hr for etoricoxib). Likewise the relative degree of selectivity for COX-2 inhibition is lumiracoxib = etoricoxib > valdecoxib = rofecoxib >> celecoxib.[10]

Celecoxib

Currently, celecoxib is the only selective COX-2 inhibitor available in the United States. After oral administration, peak serum concentrations are attained 2 to 3 hr after administration. Celecoxib is highly bound to plasma proteins, is excreted primarily by hepatic metabolism, and has a half-life of approximately 11 hr in healthy subjects. Celecoxib does not interfere with platelet aggregation; thus, perioperative administration can be conducted as part of a multimodal analgesic regimen without increased risk of bleeding. Additionally, NSAID-induced GI complications are one of the most common drug-related serious adverse events, but celecoxib preferentially inhibits the inducible COX-2 isoform and not the constitutive COX-1 isoform, thus conferring some gastroprotective effect.

The efficacy and tolerability of celecoxib have been examined in multiple studies. Celecoxib has demonstrated effectiveness in both placebo and active-control (or comparator) clinical trials in patients with osteoarthritis, rheumatoid arthritis, and postoperative pain.[60–62]

Etoricoxib

Etoricoxib is a second-generation, highly selective cyclooxygenase 2 (COX-2) inhibitor with anti-inflammatory and analgesic properties.[63] It shows dose-dependent inhibition of COX-2 across the therapeutic dose range, without inhibition of COX-1; does not inhibit gastric prostaglandin synthesis; and has no effect on platelet function.[64] Etoricoxib shows 106-fold selectivity for COX-2 over COX-1,[65] compared with 7.6-fold selectivity observed with celecoxib.[64,65] Etoricoxib was first introduced clinically as a medication in 2002 by Merck & Co and is now available in at least 62 countries throughout the world, but still awaits approval in the United States. Other second-generation coxibs include parecoxib and lumiracoxib, but neither has obtained FDA approval.

ACETAMINOPHEN

Acetaminophen (paracetamol [APAP]) is an analgesic and antipyretic medication that produces its analgesic effect by inhibiting central prostaglandin synthesis with minimal inhibition of peripheral prostaglandin synthesis.[10,11] After oral administration, peak serum concentrations are attained within 0.5 to 3 hr. A small portion of acetaminophen is bound to plasma proteins (10%–50%) and has an estimated volume of distribution of 0.95 L/kg. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. The half-life of acetaminophen is approximately 2 to 3 hr in healthy subjects. As previously stated, acetaminophen and NSAIDs have important differences such as acetaminophen's weak anti-inflammatory effects and its generally poor ability to inhibit COX in the presence of high concentrations of peroxides as are found at sites of inflammation.[10,11] Compared to NSAIDs, acetaminophen does not have an adverse effect on platelet function[12] or the gastric mucosa.[11] It is absorbed rapidly, with peak plasma levels seen within 30 min to 1 hr, and is metabolized in the liver by conjugation and hydroxylation to inactive metabolites, with a duration of action of 4 to 6 hr.[66,67] Paracetamol is perhaps the safest and most cost-effective nonopioid analgesic when it is administered in analgesic doses.[68] In elderly persons, paracetamol is recommended as first-line therapy for pain.[69] The American Geriatrics Society advocates 4 g as the total daily dose in elderly persons, with the exceptions of patients with hepatic insufficiency or history of alcohol abuse for whom a maximum dose reduction of 50% to 75% is recommended.[70] Paracetamol is available in parenteral form as propacetamol; 1 g of propacetamol provides 0.5 g of paracetamol after hydrolysis.[71] Propacetamol is widely used in many countries other than the United States, and has been shown to reduce opioid consumption by about 35% to 45%[72] in postoperative pain studies[72,73] including after cardiac surgery.[74]

EFFICACY

A useful method of assessing the efficacy of medications, the "number needed to treat" (NNT), evaluates the efficacy of active treatment compared to placebo (Table 17-2). Clinically, the NNT measures how many patients need to receive a certain treatment in order for one patient to derive a clear benefit. In pain studies, this translates into the number of patients needed to treat with a certain drug in order for one patient to achieve at least a 50% decrease in pain intensity. This value is calculated by 1/([goal achieved active group/total active] – [goal achieved placebo group/total placebo]); the 95% confidence interval (CI) of NNT can be obtained by taking the reciprocal value of the 95% CI for absolute risk reduction.

SAFETY, TOXICITY, AND ADVERSE EFFECTS

Although NSAIDs are the most widely used OTC medications, with a long history of use, research, and medication advancements, NSAIDs remain as a source of adverse effects. NSAIDs not only share therapeutic

TABLE 17–2 Comparative Analgesic Efficacy

Analgesic and Dose (mg)	Number of Patients in Comparison	Percent with at Least 50% Pain Relief	NNT	Lower Confidence Interval	Higher Confidence Interval
Etoricoxib 180/240	248	77	1.5	1.3	1.7
Etoricoxib 120	500	70	1.6	1.5	1.8
Diclofenac 100	545	69	1.8	1.6	2.1
Celecoxib 400	298	52	2.1	1.8	2.5
Acetaminophen 1000 + codeine 60	197	57	2.2	1.7	2.9
Rofecoxib 50	675	54	2.3	2.0	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Ibuprofen 400	5456	55	2.5	2.4	2.7
Oxycodone IR 10 + acetaminophen 650	315	66	2.6	2.0	3.5
Diclofenac 25	502	53	2.6	2.2	3.3
Ketorolac 10	790	50	2.6	2.3	3.1
Naproxen 400/440	197	51	2.7	2.1	4.0
Piroxicam 20	280	63	2.7	2.1	3.8
Lumiracoxib 400	370	48	2.7	2.2	3.5
Naproxen 500/550	784	52	2.7	2.3	3.3
Diclofenac 50	1296	57	2.7	2.4	3.1
Ibuprofen 200	3248	48	2.7	2.5	2.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (intramuscular)	946	50	2.9	2.6	3.6
Naproxen 200/220	202	45	3.4	2.4	5.8
Ketorolac 30 (intramuscular)	359	53	3.4	2.5	4.9
Acetaminophen 500	561	61	3.5	2.2	13.3
Celecoxib 200	805	40	3.5	2.9	4.4
Ibuprofen 100	495	36	3.7	2.9	4.9
Acetaminophen 1000	2759	46	3.8	3.4	4.4
Acetaminophen 600/650 + codeine 60	1123	42	4.2	3.4	5.3
Aspirin 600/650	5061	38	4.4	4.0	4.9
Acetaminophen 600/650	1886	38	4.6	3.9	5.5
Ibuprofen 50	316	32	4.7	3.3	8.0
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2
Aspirin 650 + codeine 60	598	25	5.3	4.1	7.4
Acetaminophen 300 + codeine 30	379	26	5.7	4.0	9.8
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0
Placebo	>10,000	18	N/A	N/A	N/A

Source: Adapted from Bondolier (http://www.medicine.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html)

actions but also similar adverse effects, including GI ulceration and bleeding, disturbance of platelet function, sodium and water retention, nephrotoxicity, and hypersensitivity reactions.[75] In fact, in 1995 the FDA requested that all prescription medications containing NSAIDs provide warning of "potential serious adverse cardiovascular events and the serious and potentially life-threatening GI adverse events associated with the use of this class of drugs." The adverse effects range from minor (e.g., nausea, gastric irritation, dizziness) to major (e.g., allergic reaction, GI, renal and coagulation derangements, and delay in bone healing) in acute use. Chronic use of these medications may increase minor or major adverse effects. The three most common adverse drug reactions to NSAIDs are GI, dermatologic, and neuropsychiatric, the last one oddly not being age related.[57,76] However, most clinically significant complications involve the GI, renal, hematologic, and hepatic organ systems.[57]

GASTROINTESTINAL

Gastrointestinal bleeding is one of the most frequently reported significant complications of NSAID use. The effects of NSAIDs on gastric mucosa has been estimated to occur in 30% to 40% of users.[77] NSAIDs affect the GI tract with symptoms of gastric distress alone and through actual damage with ulceration. Dyspepsia has been shown

to have an annual prevalence with NSAID use of about 15%.[57] An estimated 7000 deaths and 70,000 hospitalizations per year in the United States are attributed to NSAID users. Among rheumatoid arthritis patients, an estimated 20,000 hospitalizations and 2600 deaths per year are related to NSAID GI toxicity.[57,78] Evidence of the association between NSAIDs and gastropathy accrued in the 1970s with the increased use of endoscopy and the introduction of several new NSAIDs.[57,79]

The risk of developing GI complications with the continued and long-term use of NSAIDs is now well recognized. Likewise, risk factors have been identified for the development of NSAID-induced gastropathy. Risk factors include history of GI complications, high-dose or multiple NSAIDs, advanced age, concomitant corticosteroid use, and alcohol use.[80] Administration of GI-protective agents (e.g., misoprostol, H_2-receptor antagonist, and proton pump inhibitors) may attenuate the complications associated with long-term NSAID use. Other strategies include the use of selective COX-2 inhibitors such as celecoxib, which are less ulcerogenic in the GI tract as compared with nonselective NSAIDs.

RENAL

NSAIDs can decrease renal function and cause renal failure. Renal impairment has been reported to occur in as many as 18% of patients using ibuprofen, whereas acute renal failure has been shown to occur in about 6% of patients using NSAIDs.[57,81,82] The proposed mechanism is reduction in prostaglandin production leading to increased reduced renal blood flow with subsequent medullary ischemia may result from NSAID use in susceptible individuals.[82] Acute renal failure may occur with any COX-2–selective or nonselective NSAID.[83] The relative risk for acute renal failure has been reported for the following: selective COX-2 inhibitors and nonselective NSAIDs to be relative risk, 2.31; 95% CI, 1.73–3.08.[83] The risk factors for NSAID-induced renal toxicity include chronic NSAID use, high-dose or multiple NSAIDs, volume depletion, congestive heart failure, vascular disease, hyperreninemia, shock, sepsis, systemic lupus erythematous, hepatic disease, sodium depletion, nephrotic syndrome, diuresis, concomitant drug therapy (diuretics, ACE inhibitors, beta blockers, potassium supplements), and advanced age.[84]

HEPATIC

Hepatotoxicity seems to be a rare complication of most NSAIDs.[85] Hepatic-related side effects of NSAIDs have been reported to occur in 3% of patients receiving the drugs.[86] The mechanism by which almost all NSAIDs produce hepatoxicity seems to be immunologic or metabolic, with dose-related toxicity being seen in aspirin and acetaminophen.[57] In contrast, paracetamol has a recognized potential for hepatotoxicity, believed to be responsible for at least 42% of acute liver failure cases observed, and has become the most common cause of acute liver failure in the United States.[87] Most of these cases were due to intentional or unintentional overdose with 79% reporting taking the analgesic specifically for pain, and 38% were taking two different preparations of the drug simultaneously.[87] Acetaminophen is almost entirely metabolized in the liver, and the minor metabolites are responsible for the hepatotoxicity seen in overdoses.[88] Mechanisms of acetaminophen hepatotoxicity include depletion of hepatocyte glutathione, accumulation of the toxic metabolite NAPQI, mitochondrial dysfunction, and alteration of innate immunity.[89] Risk factors include concomitant depression, chronic pain, alcohol or narcotic use, and/or using several preparationssimultaneously.[87] The lowest dose of acetaminophen to cause hepatotoxicity is believed to be between 125 and 150 mg/kg.[90,91] The threshold dose to cause hepatotoxicity is 10 to 15 g of acetaminophen for adults and 150 mg/kg for children.[90,92] The most recognized dosing limit is 4 g/24 hr in healthy adult patients. Clinicians should continually inquire about medication usage, as many patients are not aware that prescription narcotic-acetaminophen combinations contain acetaminophen, and unintentionally combine these medications with OTC acetaminophen.

CARDIOVASCULAR

The inhibition of cyclooxygenase reduces the production of thromboxane and prostacyclin. Thromboxane functions as a vasoconstrictor, and facilitates platelet aggregation. Thromboxane A_2 (TXA_2), produced by activated platelets, has prothrombotic properties, stimulating activation of new platelets as well as increasing platelet aggregation. Endothelial-derived prostacyclin (PGI_2) functions in concert with thromboxane, primarily inhibiting platelet activation, thus preventing the formation of hemostatic plug. Nonselective NSAIDs inhibit both the COX-1 and COX-2, thereby reducing production of thromboxane and prostacyclin. The nucleated endothelial cells are able to regenerate prostacyclin, but the anucleated platelets are incapable of regenerating this enzyme. The imbalance of thromboxane and prostacyclin may lead to a thrombogenic situation. Low-dose aspirin (81 mg/day) has been advocated as a platelet aggregation inhibitor, thereby reducing thrombotic events related to platelet aggregation. Aspirin at larger doses 1.5 to 2 g/day has been described to result in a paradoxical thrombogenic effect.[2,93] The analgesic effects of aspirin are usually at higher doses, possibly negating the antithrombotic effects of aspirin. Celecoxib is an anti-inflammatory agent that primarily inhibits COX-2, an inducible enzyme not expressed in platelets, and thus does not interfere with platelet aggregation. Alternatively the selectivity in COX-2 inhibition has led to increased thrombotic events and rofecoxib and valdecoxib have now been withdrawn from the market due to their adverse event profile. A systematic review and meta-analysis assessing the risks of serious cardiovascular events with selective COX-2 inhibitors and nonselective NSAIDs indicates that rofecoxib was associated with a significant dose-related risk (relative risk, 2.19 [>25 mg daily]) of serious cardiovascular events during the first month of treatment, although celecoxib was not associated with an elevated risk. Among the nonselective NSAIDs, diclofenac had the highest risk (relative risk, 1.40), compared with ibuprofen (relative risk, 1.07) and piroxicam (relative risk, 1.06) and naproxen (relative risk, 0.97).[94]

CONCLUSION

NSAIDs are useful analgesics for many pain states, especially those involving inflammation. Acetaminophen provides comparable analgesic effects but lacks clinically useful anti-inflammatory activity. Development continues of COX-2 selective inhibitors to attenuate the GI and hematologic side effects of traditional NSAIDs. However, the very selectivity of the coxib may hamper their use in selected patients. NSAIDs have tremendous benefit in pain states with inflammation, but side effects may limit their use. Alternatively, acetaminophen has analgesic effects and lacks anti-inflammatory activity, but possesses minimal side effects when taken appropriately. Overall, NSAIDs have similar pharmacokinetic characteristics: they are rapidly and extensively absorbed after oral administration, tissue distribution is very limited (due to high protein binding), and they are metabolized extensively in the liver with little dependence on renal elimination. Therefore, the choice of NSAID may be determined by its efficacy and side effect profile.

KEY POINTS

- NSAIDs are antihyperalgesic compounds with anti-inflammatory activity determined by their ability to decrease prostaglandin formation through inhibition of COX following tissue injury.
- There are two major isoforms of COX. COX-1 is largely constitutive and is responsible for the production of prostaglandins involved in homeostatic processes in the stomach (gastric protection), lung, and kidney, and in platelet aggregation. COX-2 is an inducible form created in the presence of inflammation, and is largely responsible for the production of prostaglandins involved in pain and inflammation. Selective COX-2 inhibitors are capable of producing the same antihyperalgesic effect of the nonselective NSAIDs but without effects on platelet function and gastropathy.
- Initiation of NSAIDs or APAP should occur with patient education of side effects and should be prescribed with the lowest effective dose and for the shortest duration.
- Combination medications (opioid/APAP or opioid/NSAID) should occur with patient education of the contents of the combination medication.
- Transdermal preparation may be a safe alternative to enteral or parenteral medication in certain patient populations.
- Concomitant use of nonselective NSAID and minidose ASA may reduce the efficacy of minidose ASA.
- The NSAIDs are extremely effective as part of a multimodal perioperative analgesic regimen. Selective COX-2 inhibitors provide an additional advantage in the perioperative period of not affecting the platelet coagulation profile.
- NSAIDs or paracetamol should not be prescribed in high-risk patients.
- GI-protective medications may be a viable option in patients whom a COX-2 selective medication is not available, or patients at very high risk, such as those with a previous GI event.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 18

Myofascial Pain

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Myofascial pain disorders are a heterogeneous group of clinical entities that share features that originate from soft tissue pain with resultant regional symptomatology. Common examples of myofascial pain disorders include episodic tension-type headache, myofascial pain syndrome, temporomandibular disorder, muscle cramps, and low back pain.

MECHANISMS OF MUSCLE PAIN

Muscle pain is thought to occur by two main mechanisms: peripheral and central. Peripheral factors include trauma, dysregulated deep-tissue microcirculation,[1] and altered muscular metabolism and mitochondrial function.[2] Mechanical, thermal, or chemical stimulation can lead to activation of intramuscular group III and group IV nociceptors, which in turn give rise to an inflammatory cascade mediated by immune cells, leading to further recruitment of inflammatory cells and propagation of local inflammation and sensitization. Pain transmission occurs along Aδ and C-fibers into the inner lamina of the spinal cord, where complex changes occur, leading to sensitization and chronic pain.

Continuous nociceptive input via these pathways can lead to central sensitization of higher-order neurons, resulting in enhanced sensitivity to painful stimuli via excitatory glutamate and aspartate-related neurotransmitter release (hyperalgesia),[3,4] reduced thresholds to nonpainful stimuli (allodynia), and increased receptive fields, causing referred pain.[5]

Supraspinal mechanisms can also contribute to chronic muscular pain states. These include decreased cerebral activity, hippocampal suppression, and possibly impaired stress responses.[6] Once central sensitization occurs, pain becomes autonomous from sensory input from the affected muscle(s).

PAINFUL CONDITIONS WITH MYOFASCIAL INVOLVEMENT

TENSION-TYPE HEADACHE

The International Headache Society classifies tension-type headaches (TTHs) as infrequent episodic (<12 days/yr), frequent episodic (12 to fewer than 180 days/yr), and chronic (≥180 days/yr). Pathophysiologic mechanisms responsible for TTH can be divided into peripheral and central causes. Peripheral mechanisms are demonstrated by increased tenderness of pericranial myofascial tissue compared to a healthy population,[7,8] as well as increased electromyographic and algometric pressure recordings. Continuous nociceptive input can lead to central sensitization, thereby converting episodic TTH into chronic headaches.[9] It has been shown that frequent TTH causes patients to suffer from nociceptive hypersensitivity to various stimuli at both cephalic and extracephalic sites.[10–12] Seventy percent of patients with tension headaches suffer from muscle tightness and tenderness, indicative of peripheral pain mechanisms, with the percentage even higher in individuals suffering episodic headaches.[13] Other studies support roles for increased nitric oxide production, NMDA receptor activation,[14] and neurogenic inflammation of the trigeminovascular system.[15] Central pain processing appears to be relatively normal in patients with infrequent episodic headaches, where peripheral pain mechanisms probably play a larger role.[16]

TEMPOROMANDIBULAR DISORDER

Temporomandibular disorder (TMD) is a broad term used to describe conditions arising in the jaw joint, muscles of mastication, and associated craniofacial structures.[17] These conditions most commonly include pain, dysfunction, arthritis, and internal derangement.[18] The International Headache Society designates TMD as a subtype of secondary headaches, and the American Academy of Orofacial Pain subclassifies it into articular and masticatory muscle disorders. TMD is more prevalent in females than males, and mostly affects adults aged 20 to 50 years. Young patients may be more likely to suffer from myogenous TMD.[19] Electromyographic recordings have demonstrated altered muscular contraction,[20] as well as increased muscular tone in patients with TMD.[21] Not surprisingly, electromyographic biofeedback has shown efficacy in TMD.[22] Other evidence suggests that small muscles, such as those involved in mastication, may be more prone to hyperalgesia than larger muscles.[23]

MYOFASCIAL PAIN SYNDROME

Despite the lack of specific objective criteria for the diagnosis of myofascial pain syndrome (MPS), the work of Travell and Simons characterizes MPS by the presence of loci of hypersensitivity within a tender, taut, palpable band of muscle called a trigger point (TP). TPs are characterized by referred pain on palpation and elicitation of a local twitch response (LTR) with application of mechanical pressure; yet in spite of these conventionally accepted criteria, studies have shown weak inter-rater reliability in the identification of TP.[24,25]

Trigger points can be classified into active TPs or latent TPs. Active TPs are described as pain in a motor locus associated with spontaneous electrical activity,[26] whereas the more common latent TPs do not cause spontaneous pain, but can be triggered by factors such as mechanical stressors, dysfunctional postures, changes in weather, and either excessive immobility or the exaggerated use of muscles.[19] It has been suggested that a positive feedback cycle involving disproportionate acetylcholine release, sarcomere shortening, and increased concentrations of

sensitizing substances leads to the formation of a TP circuit, which upon connection with other spinal dorsal horn neuronal pathways, activates latent TPs to become an active TP.[27] Some studies have shown that latent TPs are present in the shoulder-girdle muscles of half of asymptomatic young adults and in 5% to 45% of lumbogluteal muscles. Other hypotheses suggest that hyperactive muscle spindles and end plates, focal dystonia, and/or psychological morbidity may play a role in the formation of TPs.

LOW BACK PAIN

Low back pain (LBP) is a significant public health problem with a lifetime prevalence rate ranging between 50% and 80%.[28] Spine structures serve many functions, including protecting the spinal cord, maintaining posture and truncal stability, and acting as a steadying force for movement of the extremities. Skeletal and ligamentous structures serve as a protective foundation from which attached muscles provide functional motor control, flexibility, and movement coordination. Lumbar muscle function is well-known to play an important role in LBP. Correct neuromuscular control and lumbar muscle proprioceptive feedback is essential in preventing LBP and sustaining postural stability.[29] Weakness in the core muscles (lumbo-pelvic-hip complex), unbalanced gait mechanics, or dysfunctional muscular proprioception can lead to tears, strains, sprains, or spasm within the paraspinal musculature. Multiple studies show electromyographic evidence of increased paraspinal muscle tone in patients suffering from chronic LBP,[30–32] and muscle spasm may be superimposed on primary injuries such as acute disc herniation. However, attributing LBP to solely myofascial pathology requires excluding other causes. Among the three layers of lumbar paraspinal musculature, only the most superficial is palpable. Additional support for muscular dysfunction as the cause of LBP comes from controlled trials demonstrating efficacy for botulinum toxin and a variety of muscle relaxants,[33] as well as the proven effectiveness of neuromuscular re-education and lumbar stabilization.[34]

MUSCLE CRAMPS

True muscle cramps are painful involuntary skeletal muscle contractions associated with electrical activity.[35] EMG studies show fast rates of repetitive firing of motor units[36,37] in affected muscles. True muscle cramps, which by definition occur in the absence of fluid or electrolyte imbalance, have diverse etiologies. They are more commonly found in patients with well-developed muscles, in the third trimester of pregnancy, and in metabolic disorders such as cirrhosis and renal disease.[38] Other causes of muscle cramps include medications, lower motor neuron disease, hypothyroidism, and hereditary disorders.[35] The precise origin of cramps is the subject of debate, but there is evidence that abnormal discharges come from both central origins and peripheral motor neurons.[39] Arguments in favor of a peripheral origin include the variable electromyographic morphology of fasciculations,[40] the fact that cramps can be induced by repetitive peripheral nerve stimulation,[37] and their high-frequency discharge rates (>150 Hz). Painful cramps can often be terminated by stretching the cramped muscle.

TREATMENT

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants (TCAs)—amitriptyline, nortriptyline, desipramine, and imipramine—provide analgesia independent of their antidepressive effects by multiple mechanisms, which include norepinephrine and serotonin reuptake inhibition in inhibitory descending pathways (Table 18-1). Among the two, serotonergic reuptake inhibition may be less important in analgesia, although combined serotonin–norepinephrine reuptake inhibitors are generally better analgesics than selective norepinephrine reuptake inhibitors. The former point may explain the comparative decreased efficacy of selective serotonin reuptake inhibitors (SSRIs). Other active mechanisms include blockade of peripheral neural sodium channels, muscarinic and nicotinic acetylcholine receptors, alpha adrenergic receptors, NMDA receptors, substance P release, and to a lesser extent, dopamine receptors.[41]

Multiple studies have shown TCAs to be effective in reducing the frequency and intensity of TTHs[42–44] and facial pain/TMD.[45–47] The typical doses of amitriptyline in these studies ranged between 20 to 100 mg, which is considerably lower than that required to treat depression. Yet, even at these low doses, their use is limited secondary to myriad side effects, which include dry mouth, constipation, fluid retention, weight gain, difficulty concentrating, and cardiotoxicity.

Multiple systematic reviews have concluded TCAs to be effective at reducing the frequency and intensity of TTH (Table 18-2).[19,41] Of note, a double-blind, placebo-controlled, three-way crossover study in TTH

TABLE 18–1 Differences in Mechanisms of Action of TCAs

Drug	Serotonin	Norepinephrine	Dopamine	Sedative	Antimuscarinic
Amitriptyline	+++	+	—	+++	+++
Nortriptyline	+++	++	—	++	++
Desipramine	—	+++	—	+	+
Imipramine	+++	++	—	++	++

TABLE 18–2 Tricyclic Antidepressants

Drug	Trade Name	Mechanism of Action	Typical Dose Range, mg/day	Pharmacology	Evidence for Efficacy	Common Adverse Side Effects
Amitriptyline	Elavil, Endep	Inhibits NE and 5HT reuptake, muscarinic acetylcholine receptor antagonist, H1 receptor antagonist, α1 adrenergic receptor antagonist, blocks Na+ channels	10–150 in evening/bedtime dosing; starting dose 25–75 mg oral; starting dose in elderly 10–25 mg (oral)	Liver metabolism and urine excretion primarily and feces; half-life 10–26 hr	Strong—tension headacheModerate—facial pain with myofascial component and TMD	Dry mouth, constipation, fluid retention, weight gain, difficulty concentrating, and cardiotoxicity
Nortriptyline	Pamelor	Inhibits NE and 5HT reuptake, muscarinic acetylcholine receptor antagonist, blocks Na+ channels	25–150 in evening/bedtime dosing; starting dose 25–50 mg (oral)	Liver metabolism, urine excretion primarily and feces; half-life 18–44 hr	Moderate—chronic tension-type headache	Drowsiness, dizziness, nausea, vomiting, insomnia, sweating, dry mouth, tachycardia, pruritus, weight gain, constipation
Imipramine	Tofranil	Inhibits NE and 5HT reuptake, M2 muscarinic acetylcholine receptor antagonist, histamine H1 receptors antagonist, blocks Na+ channels, enhances dopaminergic activity	25–150, 0.2–3 mg/kg, starting dose 0.2–0.4 mg/kg (oral)	Liver metabolism, urine excretion primarily and bile/feces; half-life 11–25 hr	Moderate—tension-type headache	Drowsiness, dizziness, nausea, vomiting, headache, insomnia, sweating, confusion,dry mouth, tachycardia, constipation
Desipramine	Norpramin	Inhibits NE reuptake, muscarinic acetylcholine receptor antagonist, blocks Na+ channels	25–150; starting dose 25–75 mg daily (oral)	Liver metabolism, urine excretion primarily; half-life 12–27 hr	Weak—tension-type headache	Drowsiness, dizziness, nausea, vomiting, blurry vision, diaphoresis, confusion,dry mouth, tachycardia, constipation

5HT, 5-hydroxytryptamine (serotonin); NH, norepinephrine.

found significant reductions in scalp tenderness and headache intensity with intermediate doses of amitriptyline (75 mg/day) compared with the serotonin-specific reuptake inhibitor citalopram and placebo.[44] For TMD, the evidence appears more modest, with two randomized control trials (RCTs) demonstrating efficacy of amitriptyline and a sulfur-containing analog of amitriptyline, dothiepin. One double-blind, RCT assessing the efficacy of dothiepin in chronic atypical facial pain and arthromyalgia found 71% of the 93 patients in the treatment group became pain-free after 9 weeks versus 47% in the placebo group.[45] Sixty-eight (81%) of the 84 patients who elected to continue treatment with dothiepin were pain-free at their 1-year follow-up. A subsequent study found significantly reduced pain intensity in patients with chronic facial pain who received amitriptyline compared with placebo.[46] No dose-response relationship measuring analgesia between low-dose (≤30 mg) and high-dose (≤150 mg) amitriptyline was deemed significant.[46]

ANTICONVULSANTS AND CALCIUM CHANNEL ANTAGONISTS

Pregabalin and gabapentin, an analog of GABA, exert their analgesic effects by acting on the α_2-δ_1 subunit of cellular calcium channels and blocking neurotransmitter release. Their binding to calcium channels results in suppression of abnormal neuronal discharges and an increased threshold for nerve activation. Although generally well-tolerated, the most common side effects of gabapentin and pregabalin include dizziness, sedation, lightheadedness, somnolence, and weight gain.

Gabapentin and pregabalin are first-line agents for the treatment of neuropathic pain, but have also demonstrated effectiveness in conditions characterized by muscle pathology (Table 18-3). A randomized, placebo-controlled study conducted in 133 patients with chronic daily headache, which often involves increased muscle tone,[48,49] demonstrated a modest improvement in the

TABLE 18–3 Calcium Channel Antagonists

Drug	Trade Name	Mechanism of Action	Typical Dose Range, mg/day	Pharmacology	Evidence for Efficacy	Common Adverse Side Effects
Gabapentin	Neurontin	Binds α_2-δ_1 subunit of calcium channels blocking neurotransmitter release	300–3600 in TID dosing; starting dose 100 daily or TID (oral)	Urine excretion; half-life 5–7 hr	Strong—neuropathic pain Moderate—spasticity in patients with multiple sclerosis and spinal cord injury, fibromyalgia Weak—chronic daily headache, myofascial pain, low back pain, muscle cramps	Dizziness, sedation, lightheadedness, somnolence, nausea, vomiting, weight gain
Pregabalin	Lyrica	Binds α_2-δ_1 subunit of calcium channels blocking neurotransmitter release	50–450 in BID or TID dosing; starting 50 mg BID (oral)	Negligible metabolism; urine excretion (90%); half-life 6.3 hr	Strong—neuropathic pain, fibromyalgia	Dizziness, somnolence, ataxia, weight gain, peripheral edema, headache, dry mouth, blurred vision

severity and frequency of headaches in gabapentin-treated patients compared to controls. This and other studies have led some experts to recommend gabapentin as a first-line treatment for headache prophylaxis. Placebo-controlled studies have also shown benefit for gabapentin in reducing spasticity in patients with multiple sclerosis and spinal cord injury[50,51] and for chronic masticatory myalgia.[52]

Weaker evidence supports use of gabapentinoids for other myofascial pain disorders. A retrospective review of gabapentin treatment in patients with neuropathic pain, myofascial pain, and chronic LBP found significant decreases in pain scores in both the neuropathic pain and myofascial groups, but not for LBP.[53] In an open-label study evaluating gabapentin in patients with muscle cramps associated with a variety of different medical conditions, Serrao et al[54] noted a significant reduction in muscle cramps at the first 2-week follow-up visit after gabapentin treatment. Cramps had resolved in all patients by 3 mo, lasting for the 6-mo treatment period.

Other membrane stabilizers have been studied in muscle pain. Both placebo-controlled[55] and open-label[56] studies evaluating sodium valproate, an anticonvulsant that acts via a variety of mechanisms including the blockade of T-type calcium and sodium channels, and facilitation of GABA, have shown benefit in TTH and chronic daily headaches. An earlier randomized, placebo-controlled trial also found phenytoin pretreatment to be an effective means of reducing succinylcholine-induced postoperative myalgias.[57]

SKELETAL MUSCLE RELAXANTS

Skeletal muscle relaxants such as cyclobenzaprine (Flexeril), chlorzoxazone (Paraflex), carisoprodol (Soma), methocarbamol (Robaxin, Robaxisal), tizanidine (Zanaflex), and baclofen (Lioresal) are believed to exert their mechanism of action primarily within the brain and in some cases spinal motor neurons. Cyclobenzaprine, structurally related to first-generation tricyclic antidepressants, inhibits the reuptake of norepinephrine in the locus coeruleus and inhibits descending serotonergic pathways in the spinal cord. The latter effect may have an inhibitory effect on alpha motor neurons in the spinal cord, resulting in decreased firing and a reduction in mono- and polysynaptic spinal reflexes. Tizanidine acts as a weak agonist at alpha-2 adrenergic receptors, and enhances presynaptic inhibition at spinal motor neurons. Carisoprodol, a precursor of the sedative-hypnotic meprobamate, is believed to produce muscle relaxation by blocking interneuronal activity in the descending reticular formation and spinal cord. Baclofen activates GABA-B receptors in the brain and reduces the release of excitatory neurotransmitters in both the brain and spinal cord. Baclofen also acts by inhibiting the release of substance P in the spinal cord.

Numerous studies conducted over many years have evaluated various skeletal muscle relaxants in conditions associated with muscle pain (Table 18-4). Three separate randomized trials evaluating cyclobenzaprine in patients with cervical and lumbar spinal muscle spasm demonstrated efficacy in short-term follow-up.[58–60] In two of these studies,[59,60] cyclobenzaprine was superior to diazepam. A meta-analysis review found that cyclobenzaprine is more effective than placebo for LBP associated with muscle spasm, especially in the first 4 days of treatment.[61] Another randomized, placebo-controlled trial found cyclobenzaprine to be more effective than both placebo and clonazepam in patients with TMD.[62]

In a double-blind, placebo-controlled trial evaluating carisoprodol treatment in TMD, no difference was found between treatment and control groups.[63] Yet in a more recent multicenter, randomized, double-blind, placebo-controlled, parallel-group study, carisoprodol was found to provide significant pain relief in patients with acute, painful muscle spasm of the lower back when compared to placebo.[64] Another double-blind, placebo-controlled trial reported a significant improvement in subjective feedback in TMD treated with meprobamate.[65]

TABLE 18–4 Skeletal Muscle Relaxants

Drug	Trade Name	Mechanism of Action	Typical Dose Range, mg/day	Pharmacology	Evidence for Efficacy	Common Adverse Side Effects
Cyclobenzaprine	Flexeril	Exact mechanism unknown, likely primary action on brain stem (central-acting)	5–30 in divided doses; starting 5 mg daily (oral)	Liver metabolism and urine excretion primarily; half-life 18 hr	Strong—cervical and lumbar spinal pain, muscle spasm Moderate—TMD with myofascial pain	Dry mouth, drowsiness, headache, diarrhea, constipation, dizziness, nausea, confusion
Chlorzoxazone	Paraflex, Parafon Forte	Exact mechanism unknown, likely inhibits polysynaptic reflex pathways in spinal cord (central-acting)	750–3000; starting 250 mg TID (oral)	Liver metabolism and urine excretion; half-life 1.1 hr	Moderate—acute musculoskeletal pain, back pain, acute lumbosacral muscle strain	Drowsiness, dizziness, headache, lightheadedness, hepatotoxicity, GI upset, malaise, paradoxical CNS stimulation
Carisoprodol	Soma	Exact mechanism unknown, likely interneuronal inhibition in spinal cord and descending reticular activating system (central-acting)	1050–1400; starting 250–350 mg QID (oral)	Liver metabolism and urine excretion; half-life 2.4 hr	Moderate—acute musculoskeletal pain, not for spasticity Weak—TMD	Drowsiness, dizziness, headache, ataxia, insomnia, confusion, tremor, irritability
Methocarbamol	Robaxin	Exact mechanism unknown (central-acting)	3000–8000; starting 750 mg Q6H (oral)	Liver metabolism and urine excretion; half-life 1–2 hr	Moderate—nocturnal leg cramps, acute muscle spasm	Dizziness, drowsiness, lightheadedness, nausea, rash, headache, somnolence, hypotension
Tizanidine	Zanaflex, Sirdalud	Binds to α2-adrenergic receptors, reducing presynaptic neurotransmitter release (central-acting)	2–36; starting 2 mg (oral)	Liver metabolism and urine excretion (60%) and feces (20%); half-life 2.5 hr	Moderate—spasticity, paravetebral muscle spasm Weak—TTH	Dry mouth, somnolence, asthenia, headache, dizziness, hallucinations, hypotension, constipation
Baclofen	Kemstro, Lioresal	Binds to GABA-B receptors, inhibiting neurotransmitter release (central-acting)	15–80; starting 5 mg TID (oral)	Liver metabolism (15%) and urine excretion (70–80%) and feces; half-life 5.5 hr	Strong—spasticity of spinal cord origin Moderate—cervical dystonia, upper motor neuron disease, stiff-person syndrome, acute back pain	Drowsiness, nausea, weakness, somnolence, dizziness, confusion, ataxia, constipation, headache, hypotension, weight gain

Two randomized, double-blind studies performed in patients with acute lumbar and cervical paravertebral muscle spasm found that tizanidine provided comparable pain relief to diazepam, but was associated with increased spinal mobility.[66,67] Another placebo-controlled study found tizanidine to be effective for patients with painful muscle spasm following lumbar disk surgery.[68] Studies determining efficacy of tizanidine for treating TTH have yielded conflicting results, with some,[69,70] but not all,[71] demonstrating efficacy.

There is robust evidence supporting the use of intrathecal baclofen in spinal cord injury (SCI) related–spasticity.[72–74] With regard to oral agents for spasticity associated with multiple sclerosis, several controlled studies have shown benefit for oral baclofen.[75] For tizanidine, most, but not all studies have demonstrated efficacy.[75] In comparative-effectiveness studies between oral baclofen and tizanidine, the results have been mixed.

BENZODIAZEPINES

Benzodiazepines enhance presynaptic inhibition in the spinal cord by targeting inhibitory neurotransmitter receptors that are directly activated by GABA. Benzodiazepine receptor binding facilitates GABA A receptor binding, increasing the influx of negatively charged chloride ions across the

cell membrane. The increased membrane conductance leads to hyperpolarization of Ia afferent terminals at neuronal synapses. These changes in membrane polarization lead to inhibition of normal neuronal transmission and reduced motor neuron output. Common side effects include dizziness, somnolence, confusion, memory loss, ataxia, sedation, and physical dependence with sustained use. Psychological effects include paradoxical anxiety, depression, paranoia, and irritability.

Clinical studies have shown conflicting results regarding the use of benzodiazepines such as diazepam (Valium), clonazepam (Klonopin), alprazolam (Xanax), and midazolam (Versed) in TMD and TTH. The evidence for their effectiveness in muscle spasm is moderate, but their significant adverse effect profile and possible inferiority when compared to traditional muscle relaxants preclude routine use (Table 18-5).

Several systematic reviews[76–78] have concluded that benzodiazepines serve a beneficial role in managing TMD. Specifically, clinical trials have demonstrated the efficacy of long-term use of agents such as diazepam and clonazepam in TMD.[79–81] One such randomized, placebo-controlled study showed diazepam to be more effective in treating chronic myofascial orofacial pain when compared with ibuprofen or placebo.[82] Among short-acting benzodiazepines, midazolam and triazolam have been studied. The former was found to exhibit antinociceptive properties in both animal and human studies involving induced facial pain.[83,84] In a 4-day placebo-controlled trial, the latter was noted to improve sleep but not reduce pain or nocturnal masticatory muscle activity in patients with TMD.[85]

In other studies, benzodiazepines have shown varying degrees of efficacy in relieving TTH. A randomized, double-blind, placebo-controlled crossover study comparing alprazolam to placebo in the treatment of chronic tension headache demonstrated that alprazolam reduced the intensity but not the frequency of headaches.[86] This effect may be related to the fact that alprazolam, in contrast to other benzodiazepines, possesses some antidepressant activity. Several placebo-controlled studies have found diazepam to be effective in muscle contraction headaches.[87,88] In a double-blind, placebo-controlled study comparing frontalis electromyographic biofeedback, diazepam, placebo pills, and sham electromyographic biofeedback in patients with chronic muscle tension headaches, both treatment groups were found to be superior to placebo, although only diazepam reached statistical significance.[89] Interestingly, the biofeedback patients experienced a persistent reduction in the frequency and intensity of headaches at 4-week follow-up, while headaches returned to baseline in the diazepam group.

TABLE 18–5 Benzodiazepines

Drug	Trade Name	Mechanism of Action	Typical Dose Range, mg/day	Pharmacology	Evidence for Efficacy	Common Adverse Side Effects
Diazepam	Valium	Increases inhibitory GABA transmission	2–40; starting dose 2 mg PRN or BID–QID (oral, IM, IV)	Liver metabolism and urine excretion; half-life 30–60 hr	Strong—spasticity of spinal cord origin Moderate—chronic orofacial muscle pain, tension-type headache Weak—TMD	Drowsiness, dizziness, ataxia, headache, nausea, somnolence, tremor, sedation
Clonazepam	Klonopin	Increases inhibitory GABA transmission	0.5–4; starting 0.25 mg BID (oral)	Liver metabolism and urine excretion; half-life 20-50 hr	Moderate—TMD with myofascial pain, nocturnal muscle spasms	Drowsiness, ataxia, confusion, diarrhea, constipation, dry mouth, fatigue, headache, tremor, dysuria, hypotension
Alprazolam	Xanax	Increases inhibitory GABA transmission	0.75–4; starting 0.25 mg TID (oral)	Liver metabolism and urine excretion; half-life 11.2 hr, (elderly) 16.3 hr, (alcoholic liver disease) 19.7 hr	Moderate—TTH	Lightheadedness, dry mouth, nausea, headache, vomiting, constipation, depression, insomnia, rigidity, hypotension, ataxia, tachycardia
Lorazepam	Ativan	Increases inhibitory GABA transmission	1–10; starting dose 2–3 mg/day; divided BID–TID; starting dose 1–2 mg/day divided BID–TID in elderly (oral, IM, IV)	Liver metabolism and urine excretion; half-life 14 hr		Sedation, dizziness, weakness, hypotension, respiratory depression, hypoventilation, local injection site reaction, weakness, unsteadiness

Several studies have compared diazepam to conventional muscle relaxants for cervical and lumbar paravertebral muscle spasm with conflicting results.[59,60,66,67] In two studies comparing cyclobenzaprine to diazepam, one found cyclobenzaprine to be superior to diazepam, which in turn was better than placebo,[60] while the other found no meaningful differences between treatment groups.[59] For the two studies comparing diazepam to tizanidine, both found better range of motion in the lumbar spine in the tizanidine group, but no differences in pain, functional capacity, or self-assessment.[66,67]

CONCLUSION

Myofascial pain is a common, yet underappreciated condition that can occur in isolation, or as a result of biomechanical alterations that accompany primary disorders. In view of the heterogeneity of myofascial pain, multiple mechanisms may exist in different patients, or even within a single patient. This poses serious challenges to pharmacologic management. There are many different medication classes that have been demonstrated to be effective for muscle disorders, with perhaps the strongest evidence supporting tricyclic antidepressants and muscle relaxants. But the effect size is modest for pharmacotherapy, which underscores the need for a multimodal approach that emphasizes an individually structured exercise program, psychotherapy if indicated, complementary and alternative medicine, and functional restoration. More studies comparing different medications and treatment approaches are needed to identify which patients will respond best to various treatments, and to develop more effective preventive measures.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 19

Pharmacology for the Interventional Pain Physician

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A comprehensive understanding of drugs used by the interventional pain physician is essential for safe and effective patient care. This chapter will review the clinical pharmacology and potential side effects of drugs most commonly used in interventional pain therapy. The drug categories reviewed include radiographic contrast agents, local anesthetics, corticosteroids, and topical antiseptics.

Regardless of one's familiarity with a category of medication, a review of each drug's most current product information is well advised. This information is located within published manufacturer information on the medication's package insert, and can often be found within a current *Physicians' Desk Reference*.[1] It should also be stressed that there are inherent risks associated with any drug. As such, drugs should be administered only when there is a clinical indication and when the prospects of patient benefit outweigh the risks involved. Additionally, drugs should be administered in the smallest dose that will reliably produce the desired effect. Increasing the total dose or volume should never be used to compensate for inadequate injection technique.

RADIOGRAPHIC CONTRAST AGENTS

Iodinated contrast agents provide greater attenuation of x-ray radiation, relative to tissue and bone, reducing the amount of radiation reaching the detector (fluoroscopic intensifier). This allows contrast to be easily visualized on x-ray images. Iodinated contrast media (ICM) in image-guided procedures is utilized to define the anticipated spread and location of the injectate. This improves safety by avoiding injection of drugs into unintended locations such as intravascular or intrathecal spaces.

CHEMICAL PROPERTIES

All currently available ICM are based on variations of the 2, 4, 6 tri-iodinated benzene ring.[2] They are classified on the basis of their chemical structure, osmolality, iodine content, and ionization. The iodine content is responsible for x-ray attenuation and the concentration in mg iodine/ml is used to express the strength of the attenuation of a particular agent. Clinically used agents have between 180 to 400 mg/ml of iodine. The chemical composition of contrast media is in four different forms: ionic monomers, ionic dimers, nonionic monomers, and nonionic dimers (Fig. 19-1). Ionization of ICM is produced by substitutions on the benzene ring at the 1, 3, and 5 positions to produce water solubility and physiologic pH. Solubility of the nonionic contrast media is due to substitution with hydrophilic side chains such as hydroxyl or amide groups.

PHARMACOLOGY

Hyperosmolality greatly increases the hemodynamic and toxic effects of these agents and is obviously increased with ionic ICM agents due to their dissociation in solution. The concentration of iodine necessary to obtain radiographic attenuation dictates the number of particles in solution (osmolality) needed for a particular agent to be effective. The first agents developed were ionic monomers and often 5 to 8 times the physiologic osmolality of 300 mOsm/kg water. This created the potential for osmotoxic reactions including pain on injection, hemolysis, endothelial damage (capillary leak and edema), vasodilation (flushing, warmth, hypotension, and cardiovascular collapse), hypervolemia, and direct cardiodepressive effects. These reactions may not be problematic for the small amount of contrast used by the pain interventionist, however, ionic ICM are strictly contraindicated for all applications involving the central nervous system (CNS) and may cause severe or fatal neurotoxic reactions following intrathecal administration.[3]

Non-ionic ICM are the agents of choice for interventional pain procedures due to their lower osmolality and toxicity. The commercially available agents are listed in Table 19-1. ICM are hydrophilic and demonstrate low protein binding. After intravascular injection there is rapid distribution into the extracellular space and the fall in plasma concentration is rapid. Elimination is by glomerular filtration without reabsorption and there is virtually no metabolism. In patients with normal renal function the elimination half-life is approximately 2 hr, and with renal impairment excretion can last for weeks.[4,5]

ADVERSE REACTIONS

These agents are relatively safe with 70 million injections per year worldwide and 15 million per year in the United States alone.[6,7] Minor reactions requiring no or limited treatment are reported in 3% to 12% of all recipients.[8] Severe reactions manifesting with anaphylactic or anaphylactoid symptoms of severe bronchospasm, laryngeal edema, angioedema, pulmonary edema, hypotension, convulsions, cardiac dysrhythmias, or arrest occur with an incidence of 0.2% to 0.06% for high osmolar agents and at 5 times lower incidence for low osmolar agents.[2,8]

Adverse reactions to ICM can be classified as idiosyncratic or immediate and delayed. The immediate reactions are generally the most severe and consist in this setting of anaphylactoid type reactions of varying severity. These reactions are generally independent of dose and unpredictable, and usually occur within 1 hr of administration. There is increased risk in patients with a prior reaction to ICM, and with underlying disease including asthmatics,

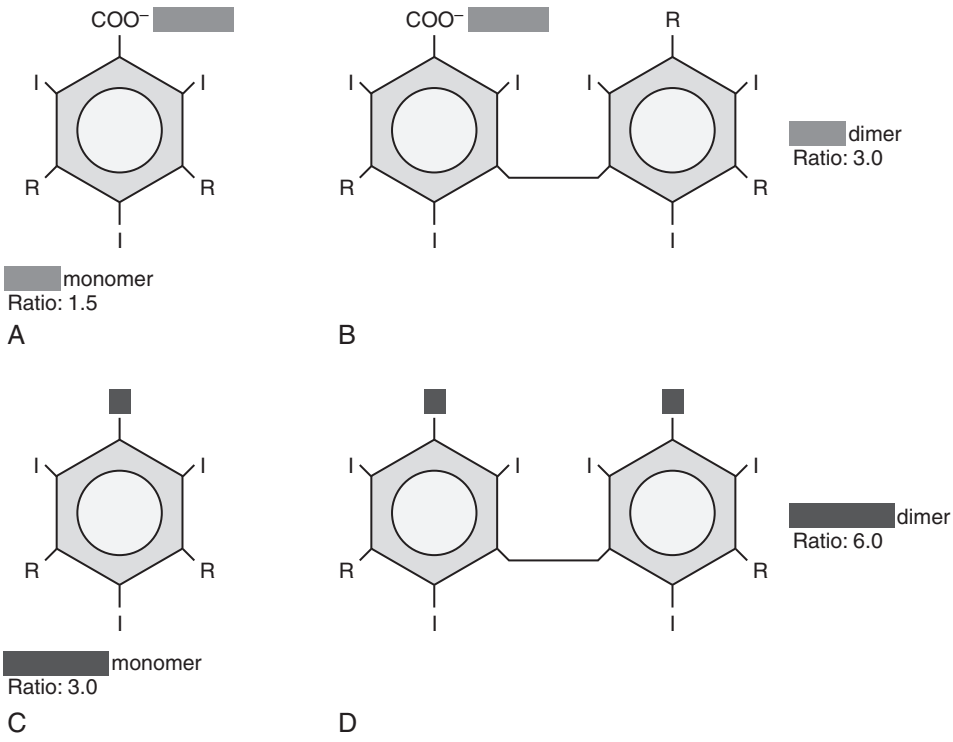

FIGURE 19-1 Classification of contrast agents. **A,** Ionic high-osmolality monomers. **B,** Ionic low-osmolality dimers. **C,** nonionic low-osmolality monomers. **D,** Nonionic iso-osmolar dimers.

TABLE 19–1 Commercially Available Monomeric and Dimeric X-ray Contrast Media

Generic Name	Trade Name*
Monomeric Contrast Media	
Ionic Monomers	
Meglumine iothalamate	Conray
Meglumine ioxithalamate	Telebrix
Sodium amidotrizoate	Urografin, Hypaque
Nonionic Monomers	
Iohexol	Omnipaque
Iopentol	Imagopaque
Ioxitol	Ixilan
Iomeprol	Iomeron
Ioversol	Optiray
Iopromide	Ultravist
Iobitridol	Xenetix
Iopamidol	Iopamiro
Dimeric Contrast Media	
Ionic Dimer	
Ioxaglate	Hexabrix
Nonionic Dimers	
Iotrolan	Isovist
Iodixanol	Visipaque

** The use of trade names is for product identification purposes only and does not imply endorsement.*

Source: Christiansen C: X-ray contrast media—an overview. Toxicology *209:185–187, 2005, with permission from Lippincott Williams & Wilkins.*

history of atopy, and advanced heart disease.[8] If suspected these reactions need to be treated with antihistamines, epinephrine, corticosteroids, and full cardiopulmonary resuscitation as needed.[9] Delayed reactions are composed of chemotoxic reactions and cutaneous manifestations of delayed hypersensitivity. The chemotoxic reactions include contrast mediated nephrotoxicity, decreased cardiac contractility, and neurotoxicity, all of which are dose dependent and should be rare in this setting with use of nonionized agents. The delayed allergy-like skin reactions are twice as frequent for nonionic dimers as for nonionic monomers.[2,10]

PREVENTION STRATEGIES FOR ADVERSE REACTIONS

For the pain interventionist who uses only small quantities of ICM during image-guided procedures, the primary aim is to prevent the idiosyncratic and potentially severe anaphylactoid reactions. The first step is to understand the risk factors, including a previous reaction to ICM, and take a history to elucidate the type of reaction the patient experienced. The history should also include the type of agent and whether it was an ionic or nonionic agent. There are treatment protocols for antihistamine and corticosteroid prophylaxis against anaphylactic and anaphylactoid reactions, including oxygen, intravenous fluids, antihistamines (H_1 and H_2blockers), adrenergic drugs (epinephrine), and corticosteroids. However, there is agreement of efficacy only in patients receiving ionic ICM.[7,10,11] Ionic ICM have 4 times the incidence of these reactions compared to nonionic agents. No studies have demonstrated a decreased

incidence of reaction in patients with a previous reaction to nonionized ICM. Prophylaxis may be of value but must be weighed against the potential risks of treatment in a specific patient.

Although not generally recommended as a fluoroscopic contrast agent, some practitioners find the use of gadolinium-containing contrast agents beneficial as an alternative in high-risk patients. However, there is an upper limit to safe dosage of gadolinium (0.3 mmol/kg body weight) and caution and reduced dosage have to be taken in patients with moderate to severe renal dysfunction due to its association with development of nephrogenic systemic fibrosis. Gadolinium has approximately the same x-ray attenuation as iodine at 70 kV.[12] Commercial preparations contain either 0.5 mmole/ml or 1.0 mmole/ml gadolinium, with a 0.5-mmole/ml gadolinium solution (e.g., Omniscan) producing slightly less than half the x-ray attenuation of a 180 mg/ml iodine (1.19 mmole/ml iodine) contrast preparation. Consideration of potentially decreased efficacy and dose limitation needs to be weighed in particular situations to determine if use of this alternative ICM will be of benefit.

LOCAL ANESTHETICS

Local anesthetics, in clinically appropriate concentrations, block neural conduction in a reversible manner by blocking sodium channels located on internal neuronal membranes. This results in inhibition of sodium permeability necessary for action potential propagation. It is the reversibility of action that creates significant utility in diagnostic and therapeutic procedures. Local anesthetics (LAs) may abolish sensation in various parts of the body by topical application, injection in the vicinity of peripheral nerves, or administration within the epidural or subarachnoid space.

CHEMICAL COMPOSITION AND CLASSIFICATION

Local anesthetics are composed of an acyl or aromatic group connected to an alkyl tertiary amine group by either an ester or amide bond. The classification of LAs into esters or amides is based on this bond, which determines metabolic pathways. For the amino-ester LAs, there is relatively rapid breakdown by plasma cholinesterase to a common metabolite, para-amino-benzoic acid (PABA) with the exception of cocaine, which has an alternate metabolic pathway. Amino-amide LAs are metabolized by the cytochrome P450 system and conjugation as a route to elimination.

Akyl substitutions on a LA increase the lipid solubility. The potency of LAs have been shown to be directly related to lipophilicity and is often expressed as the octanol:water partition coefficient.

All LAs are weak acids as quaternary amines and are positively charged. As tertiary amines they are weak bases and uncharged. They must be in their lipophilic base form to access their site of action on the Na+ channel. The pKa of the LA and pH at the site of injection (usually physiologic pH of 7.4 but can be locally altered, such as in areas of infection) influence the amount of LA in base form and the speed of block onset. The addition of bicarbonate to a solution to increase the pH and speed of onset can be done to epinephrine-containing LAs that are adjusted to an acidic pH for stability in commercial preparations. In general, the lower the pKa of the LA the faster its the onset. Other factors influencing the speed of onset include the concentration and amount of LA used and the anatomic location of injection or application.

LAs prevent generation and conduction of the nerve impulse by blocking voltage gated Na+ channels within the cell membrane. This reduces or prevents the transient increase in Na+ permeability needed for depolarization and propagation of a nerve impulse. Not all nerve fibers are equally sensitive to block. A differential sensitivity to block is seen when the concentration of an LA is sufficient to block some nerve fiber types but not others. Clinically, small unmyelinated C-fibers, autonomic fibers, and small myelinated Aδ delta fibers (pain and temperature) are more sensitive than larger myelinated Aγ, Aβ, and Aα fibers (motor, proprioception, touch, and pressure.) This differential sensitivity is of significant use in accomplishing pain or autonomic blockade without necessarily effecting motor block. LAs exhibit differences in their ability to provide differential sensitivity and bupivacaine has been used for this capability since its introduction in 1963. More recently, ropivacaine, is stated to be more motor sparing than bupivacaine and less cardiotoxicity at equipotent doses.[13–15] Interestingly, nearly the opposite differential sensitivity is seen with vitro nerve studies. The reason for this is not known but is thought to be due to phase block, which is the phenomenon that nerves that are frequently firing are more easily blocked, and anatomic considerations in nerve bundles.

A frequent consideration in the selection of a local anesthetic is the duration of action. There are multiple factors that determine duration of action. Increased lipid solubility of a particular agent generally increases its duration of action. As previously stated, the rate of metabolism can be a factor (e.g., amino-ester LAs). Generally, the speed of uptake and/or elimination from the site of deposition, which is also dependent on tissue perfusion, influences the duration of action. Perfusion of course is dependent on anatomic location (parauterine > intercostal > epidural > peripheral nerve >intrathecal), and sometimes is purposely manipulated by the addition of vasoconstrictors to decrease perfusion and uptake and thus prolong block.

Mixtures of LAs to produce quick onset and/or a prolonged duration have been intermittently advocated. The results of this practice are varied and controversial and depend on the location of utilization and the particular LAs used. There is some evidence to suggest that peripheral nerve block with bupivacaine/lidocaine or ropivacaine/lidocaine vs bupivacaine or ropivacaine alone provides a quicker onset but shorter duration of action.[16] Studies on epidural use suggest no significant difference when used in combination in terms of speed of onset or change in duration of action.[17,18] Benefits in terms of reduced toxicity have not been elucidated. Toxicity is presumed to be additive when considering the maximum doses of more than one agent (Table 19-2).

The important properties of LAs including potency, speed of onset, duration of action, differential block, and toxicity are dependent on the physiochemical properties of an LA as well as the manner in which it is used. At this time the most frequently used include lidocaine, bupivacaine, and ropivacaine.

TABLE 19–2 Infiltration Anesthesia

Drug	Plain Solution			Epinephrine-Containing Solution	
	Concentration (%)	*Max Dose (mg)*	*Duration (min)*	*Max Dose (mg)*	*Duration (min)*
Short Duration					
Procaine	1–2	500	20–30	600	30–45
Chloroprocaine	1–2	800	15–30	1000	30
Moderate Duration					
Lidocaine	0.5–1	300	30–60	500	120
Mepivacaine	0.5–1	300	45–90	500	120
Prilocaine	0.5–1	350	30–90	550	120
Long Duration					
Bupivacaine	0.25–0.5	175	120–240	200	180–240
Ropivacaine	0.2–0.5	200	120–240	250	180–240

ADVERSE REACTIONS

The most common adverse reactions are autonomic responses or anticipatory reactions to medical procedures. These include tachycardia, sweating, hypotension, and syncope. They are characteristically short-lived with resolution in minutes requiring no treatment or can be treated with muscarinic blockers or ephedrine.

Another common reaction is the response to vasoconstrictor additives, usually epinephrine, which is either inadvertently injected intravascular or rapidly absorbed. Symptomatically this produces tachycardia, hypertension, and anxiety or feelings of doom. If injected peri- or intra-arterial it can produce distal ischemia from arterial spasm. This can produce serious complications from organ ischemia.

LAs can cause local and systemic toxicity. LAs used in highly concentrated solutions may be neurotoxic. Local toxicity can also occur with intraneural injections even with normal concentrations. Systemic toxicity is estimated to occur with an incidence of 7 to 20/10,000 for peripheral nerve blocks and 4/10,000 for epidural blocks.[19,20] Toxic levels usually occur due to excessive dose, intravascular injection, or other reasons for unanticipated rapid absorption, predisposing medical conditions (e.g., seizure disorder), or difficulties with metabolism or elimination. Usually systemic toxicity results first in the CNS and then has cardiovascular effects but this obviously depends on the rate of increase in blood concentration as well as the individual patient's comorbidities. CNS symptoms consist of metallic taste, perioral numbness, dizziness, muscle twitching, and ultimately generalized seizures. Toxic cardiovascular effects include arrhythmias, cardiac depression, vasodilation, hypotension, and cardiac arrest/collapse. The potent lipophilic LAs are more cardiotoxic and resuscitation is known to be difficult using usual resuscitation efforts and medications.[14] The use of 20% intralipid has been shown to be effective for resuscitation from bupivacaine-induced cardiac toxicity.[19,21] The mechanism is uncertain but believed to be by extraction of the lipophilic LAs. There is evidence that it is more effective for bupivacaine and levobupivacaine than ropivacaine, which is less lipophilic.[21,22] A published regimen consists of 20% intralipid with a bolus of 1.2 to 2.0 ml/kg followed by infusion of 0.25 to 0.5 ml/kg. However, the optimal dose has not been established.[19]

Allergic reactions to LAs are relatively rare, constituting less than 1% of adverse reactions.[23,24] The vast majority of these are due to PABA from amino-ester LAs. Because it is a common metabolite of this class there is near-complete cross-reactivity of allergy within this class of LA. Amino-amide LAs are exceedingly rare causes of allergic reactions and because of their varying metabolic products, they do not have predictable allergic cross-reactivity. Paraben preservatives are structurally very similar to PABA and can show allergic cross-reactivity to amino-ester LAs. The commonest allergic reactions are delayed (24 hrs to a week) minor cutaneous rashes. These are generally self-limited and treated with antihistamines and topical corticosteroids. Of note is the possibility of allergic cross-reactivity to bisulfite preservatives in patients with known food allergies and paraben preservatives in patients with sulfa antibiotic allergy.

Intrathecal administration of LAs or spinal anesthesia can cause dense and widespread block. A high level or complete spinal block will result in respiratory compromise by diaphragmatic and accessory muscle paralysis and in total sympathectomy. Immediate resuscitation can be required, including respiratory and cardiovascular support. Intrathecal administration of some LAs (lidocaine, chloroprocaine) and additives (metabisulfite) are suspected of causing toxic effects ranging from transient neurologic symptoms (TNS) to adhesive arachnoiditis and permanent neurologic injury. There is significant controversy around the toxic effects of intrathecal local anesthetics and additives regarding etiology and incidence of the reported complications.[25]

CORTICOSTEROIDS

Naturally occurring corticosteroids are classified into three functional groups: mineralocorticoids, glucocorticoids, and adrenal androgens. Glucocorticoids, originally named for their role in glucose metabolism, are the corticosteroid most commonly used for interventional pain procedures.

Several therapeutic mechanisms of action for corticosteroids have been proposed. These actions include anti-inflammatory effects, direct neural membrane stabilization, as well as modulation of peripheral nociceptor neurons and spinal cord dorsal horn cells.

The anti-inflammatory effects of glucocorticoids are attributable to their inhibition of inflammatory mediator production at both the local tissue and systemic immune response levels. With any type of tissue trauma there is a release of inflammatory mediators including arachidonic acid and its metabolites (prostaglandins, leukotrienes), various cytokines (IL-1, IL-6, TNF-α), and other acute phase reactants.[26]

Corticosteroids injected in the area of injury may inhibit the production of local inflammatory mediators. Other mechanisms of action for injected corticosteroids include reduced spontaneous ectopic discharge rates seen following nerve injury, including in neuromas.[27] Reversible inhibition of nociceptive C-fiber transmission, but not A-B fiber transmission, has been shown following corticosteroid application.[28] Similar effects were confirmed using methylprednisolone on a peripheral mononeuropathy nerve injury animal model.[29] These studies confirm that locally applied corticosteroids suppress afferent ectopic discharges at the site of nerve injury, supporting a direct membrane stabilizing effect. Lastly, glucocorticoid receptor sites have been located on noradrenergic and 5-hydroxytryptamine neurons within the dorsal horn substantia gelatinosa—known pathways of pain transmission.[30,31] This suggests that corticosteroids may modulate nociceptive input from peripheral nociceptors by a direct action on the spinal cord.

Chemical modifications to the parent four-ringed hydrocortisone molecule have allowed for synthetic glucocorticoids with a vast array of anti-inflammatory potencies, mineralocorticoid activities, durations of action, solubility, and metabolic transformation.

As a general rule, the anti-inflammatory efficacy and duration of activity are greater with less soluble corticosteroid preparations. Although the type of corticosteroid selected by interventional pain specialists is frequently based upon its duration of action (biological half-life) and anti-inflammatory potency, steroid particulate size relative to a red blood cell and aggregation is emerging as a major determinant of corticosteroid selection (Table 19-3).[32]

Serious adverse events have been increasingly reported in patients undergoing transforaminal epidural injections with particulate corticosteroid solutions. An inadvertent injection of a steroid particulate into the artery of Adamkiewicz during thoracic or lumbar transforaminal epidural steroid injection could result in spinal cord ischemia leading to profound lower extremity motor deficits, even paraplegia.

Another complication of cervical level transforaminal steroid injection is infarction of the spinal cord or brain following injection of a particulate corticosteroid into a radicular artery or vertebral artery. Similar but lower rates of infarction have been reported with lumbar transforaminal injection or particulate corticosteroid. Anecdotally, no serious adverse event has been reported following injection of a nonparticulate steroid.

Following systemic absorption, the vast majority of corticosteroid is reversibly bound to two plasma proteins: corticosteroid-binding globulin and albumin. Note that only the unbound fraction of corticosteroid is responsible for its cellular-mediated anti-inflammatory effects. The protein-bound corticosteroid undergoes sequential oxidative-reduction reactions yielding inactive compounds. This is followed by hepatic-mediated conjugation (sulfate or glucuronide), resulting in water-soluble metabolites that are renally excreted.

The majority of corticosteroids-related systemic adverse reactions are usually mild and transient when the drug is administered as an intermittent injection-type therapy (as opposed to chronic daily use) (Table 19-4). Several other purported adverse reactions have been reported following corticosteroid injection. Sterile meningitis and arachnoiditis have been reported following intrathecal injection of methylprednisolone, although these may possibly be related to the polyethylene additive of the preparation.[33] Brief euphoric or manic reactions have been reported following high-dose conticosteroid therapy.[34,35] Although rare, analphylactoid reactions have been reported following intravenous, intramuscular, and soft-tissue conrticosteroid injections.[36–38] The "succinate" salts of hydrocortisone and methylprednisolone have been most implicated; with absence of any allergic-type reaction following administration of

TABLE 19–3 Pharmacologic Properties of Common Glucocorticoids Used in Spine Injections

Agent	Biological Half-Life (hr)	Anti-Inflammatory Potency	Salt-Retaining Potency	Particulate Size (Aggregation)
Hydrocortisone	8–12	1	1	
Hydrocortone				
Triamcinolone	12–36	5	0	<RBC size to 13× (extensive, densely packed)
Kenalog40				
Methylprednisolone	12–36	5	0.5	<RBC size (few, densely packed)
Depo-Medrol				
Dexamethasone	36–72	25	0	<RBC size (none)
DecadronPhosphate				
Betamethasone	36–72	25	0	Varied size (extensive, densely packed)
Celestone, Soluspan				

RBC, red blood cell.

TABLE 19–4 Potential Adverse Systemic Reactions Associated with Corticosteroids

1. Fluid retention
2. Elevated blood pressure
3. Hyperglycemia
4. Generalized erythema/facial flushing
5. Menstrual irregularities
6. Gastritis/peptic ulcer disease
7. Hypothalamic-pituitary-adrenal axis suppression
8. Cushing's syndrome
9. Bone demineralization
10. Steroid myopathy
11. Allergic reaction

acetate or phosphate salts of the same corticosteroid. Any type of anaphylactic reaction should be treated promptly and aggressively with supportive therapies (i.e., airway, breathing, circulation, supplemental oxygen), including advanced cardiac life support guidelines when indicated.

The selection and administration of any drug by the interventional pain physician must be based on a comprehensive understanding of the safety profile of the drug, pharmacologic and chemical properties of the drug, and the patient's previous experience with the drug.

SKIN ANTISEPTIC AGENTS

The vast majority of interventional pain procedures are performed through percutaneous needle placement. At a minimum, the skin at the surgical site should be cleaned and prepped with an antimicrobial agent to reduce the risk of postoperative infection. No antimicrobial agent alone is effective in killing all microbes (bacteria, viruses, spores) on the skin. As such, the goal of preoperative skin preparation is to reduce the resident microbial count to subpathogenic levels in a short period of time and with the least amount of skin irritation.

The most common skin preparation agents in clinical use include products containing iodophors and chlorhexidine gluconate. Additionally, agents are further classified as either aqueous-based or alcohol-based solutions. Aqueous-based iodophors, such as povidone-iodine, can be safely used on mucous membrane surfaces. Alcohol-based solutions offer a quicker onset and often more sustained antimicrobial activity. All have the potential for skin irritation with prolonged contact; therefore, it is advisable to remove the residual antiseptic preparation at the end of the procedure and evaluate the patient's skin condition prior to discharge. The ideal preoperative skin antiseptic agent should significantly reduce microbial counts on intact skin; be broad spectrum; be fast acting; have a persistent effect lasting for hours; and be nonirritating to the skin. Table 19-5 reviews common skin-preparation antiseptic agents.

Infections associated with percutaneous interventional pain procedures are relatively rare. However, percutaneous injection-related infections not only involve skin and subcutaneous tissues, but also the targeted neuraxial structures leading to potentially devastating conditions such as epidural abscess, discitis, osteomyelitis, and meningitis. The treatment of these infections may involve hospitalization, prolonged antibiotic therapy, and surgery. Therefore, adherence to comprehensive infection-control practices for preoperative skin antisepsis is necessary regardless of the setting in which the pain procedure is performed.[39,40] These practices are adaptable to all clinical settings including hospital operating rooms, ambulatory surgery centers, radiology suites, and physician offices. Nevertheless, a recent study of infection control practices in ambulatory surgical centers revealed that lapses in infection control were common.[41]

Infection control involves much more than the selection of the skin antiseptic agent. Physicians performing interventional pain procedures must adhere to all infection-control practices, including meticulous hand washing, skin preparation, instrument sterilization, strict aseptic technique, and timely antibiotic prophylaxis when indicated.

REFERENCES

Access the reference list online at http://www.expertconsult.com

TABLE 19–5 Activity and Clinical Considerations of Common Skin Antiseptic Agents

	Alcohol	Povidone-Iodine	Chlorhexidine Gluconate	Chlorhexidine Gluconate with Alcohol
Mechanism of action	Denatures proteins	Oxidation/substitution with free iodine	Disrupts cell membranes	Disrupts cell membranes and denatures proteins
Gram-positive bacteria	Excellent	Excellent	Excellent	Excellent
Gram-negative bacteria	Excellent	Good	Good	Excellent
Viruses	Good	Good	Good	Good
Speed of action	Excellent	Moderate	Moderate	Excellent
Residual activity	None	Minimal	Excellent	Excellent
Use on mucous membranes	No	Yes	With caution	No
Cautions	Flammable. Optimum concentration 60–90%.	Maximum effectiveness after it has dried. Inactivated by blood. Shellfish allergies are not a contraindication.	Avoid direct contact with cornea, nerves and meninges.	Flammable. Avoid direct contact with cornea, nerves, and meninges.

Source: Modified from Schaefer MK, Jhung M, Dahl M, et al: Infection control assessment of ambulatory surgical centers. JAMA *303:2273–2279, 2010.*

Therapeutic interventions

CHAPTER 20

Diagnostic Nerve Blocks

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Diagnostic nerve blocks provide important clinical information when interpreted in light of the problem-oriented pain history and comprehensive neurological physical examination. Many causes of the etiology of a painful syndrome are not readily apparent, even when competent and experienced clinicians have evaluated the patient, reviewed the diagnostic radiologic information, as well as results of laboratory and psychological testing. It therefore behooves the prudent practitioner to have a fundamental appreciation of the applicability of diagnostic nerve blocks, particularly when considering whether a given patient is a candidate for therapeutic nerve blocks, radiofrequency lesioning, or neurolytic blocks. Since pain is a totally subjective phenomenon, what is needed to identify the neural pathway subserving it is some sort of objective diagnostic test. Differential neural blockade provides a discrete and reproducible endpoint in well-selected individuals for whom a clear-cut diagnosis of pain mechanisms may not be readily apparent. A description of the classic approach to differential nerve blocks follows.

CLASSIC DIFFERENTIAL NERVE BLOCKS

Differential neural blockade may provide the essential information necessary for verifying a particular diagnosis or delineating a treatment plan of management. This technique is premised upon the concept of selective blockade of one neurologic modality without blocking the others, and is divided into two clinical approaches. The basis for the anatomic approach is the actual anatomic separation of somatic and sympathetic nervous system fibers, so that an injection of local anesthetic solution blocks one modality without affecting the others. The basis for the pharmacologic approach relies on the difference in sensitivities of the various types of nerve fibers to local anesthetics, so that an injection of local anesthetic solutions in different concentrations may selectively block different types of fibers. While the techniques of differential neural blockade are appealing based on their simplicity, the techniques are controversial largely because of the changing state of knowledge regarding factors determining nerve conduction and nerve blockade by local anesthetics as well as our evolving appreciation of the complexities of chronic pain.[1–3]

The foundation for differential neural blockade is nerve fiber length and fiber diameter. Nerve fiber length determines relative susceptibilities of a given fiber to local anesthetic concentrations, and nerve fiber diameter determines the modalities subserved by the fiber (Table 20-1).

There are four subclasses of A fibers: Aα, Aβ, Aγ, and Aδ. A-alpha fibers subserve motor function and proprioception. A-beta fibers subserve touch and pressure. A-gamma fibers subserve muscle spindle tone. A-delta fibers subserve sharp pain and temperature sensations. B-fibers are thin myelinated, preganglionic autonomic nerves; and the unmyelinated C-fibers subserve dull pain and temperature. C-fibers are thinner than the myelinated A- and B-fibers and have a lower conduction velocity than the others (Table 20-1). The simplest example of the pharmacologic approach with the most discrete end points is the differential spinal block. A differential spinal block attempts to block separately sympathetic, sensory, and motor systems for the subsequent determination of the etiology of an individual's lower abdominal or lower extremity pain mechanism. The ability to perform and interpret results of the examination are contingent on the ability to perform lumbar puncture and standard subarachnoid anesthesia, including the requisite monitoring of vital signs associated with such block. After obtaining informed and written consent, an intravenous catheter is secured and a crystalloid infusion is begun as for any subarachnoid block. A full complement of noninvasive hemodynamic monitors is applied and baseline vital signs are recorded. In the *conventional differential spinal block*, four solutions are prepared and labeled A, B, C, and D. Solution A contains no local anesthetic (placebo); solution B contains 0.25% procaine; solution C contains 0.5% procaine; and solution D contains 5.0% procaine. These solutions are injected sequentially (obviously this is labor and time intensive as the effects of each solution must completely dissipate prior to injecting the subsequent solution in sequence) through a 25- to 27-gauge pencil-point spinal needle, which has been introduced in standard fashion at the L2–L3 or L3–L4 interspace. There are four basic interpretations of the differential spinal block (Table 20-2) as follows:

Psychogenic pain. If the injection of the placebo solution (solution A) relieves the patient's pain, the pain is tentatively classified as psychogenic, depending on duration of analgesia. For prolonged or permanent pain relief, the pain is probably truly psychogenic, whereas if the pain relief is temporary, the response is likely a placebo reaction.

TABLE 20–1 Classification of Nerves by Fiber Size and Relation of Fiber Size to Function and Sensitivity to Local Anesthetics*

Group/Subgroup	Diameter (μm)	Conduction Velocity (m/s)	Modalities Subserved	Sensitivity to Local Anesthetics (%)†
A (myelinated)				
A-alpha	15–20	8–120	Large motor, proprioception	1.0
A-beta	8–15	30–70	Small motor, touch, pressure	↓
A-gamma	4–8	30–70	Muscle spindle, reflex	↓
A-δ	3–4	10–30	Pain, temperature	0.5
B (myelinated)	3–4	10–15	Preganglionic autonomic	0.25
C (unmyelinated)	1–2	1–2	Pain, temperature	0.5

*Subarachnoid procaine.
†Vertical arrows indicate intermediate values, in descending order.

TABLE 20–2 Interpretation of Classic Differential Spinal Block

Solution Injected	Intended Blockade	Pain Relief	Interpretation
Saline	None	If yes	Placebo responder or psychogenic mechanism
0.25% procaine	Sympathetic	If yes	Sympathetic mechanism
0.5% procaine	Sensory	If yes	Somatic mechanism
5% procaine	Motor	If none	Central mechanism*

*A central mechanism may be due to a CNS lesion above the level of block; true psychogenic pain; malingering; or encephalization (original peripheral pain mechanism becomes self-sustaining at central level).
Source: Data from Winnie and Candido.[1–3]

Sympathetic pain. If the patient does not obtain relief following the placebo injection, but experiences relief from 0.25% procaine (solution B), the mechanism subserving the patient's pain is likely mediated by the sympathetic nervous system. This presumes that there are clinical signs of complete sympathetic block (increased skin temperature; psychogalvanic reflex response, sweat chloride test, etc.) and no detectable sensory changes.

Somatic pain. If the patient does not obtain relief following the injection of placebo or 0.25% procaine, but 0.5% procaine provides significant relief, this typically indicates that the pain is subserved by Aδ fibers and/or C-fibers, and is therefore classified as somatic. The caveat, of course, is that the patient did exhibit signs of sympathetic nervous system blockade following the injection of 0.25% procaine, and that the pain relief from 0.5% procaine is accompanied by analgesia or anesthesia in the areas of concern. This is important because of the variability in C_m for B-fibers that is known to exist. If the patient has an elevated C_m for B-fibers, pain relief from 0.5% procaine might be due to a sympathetic block rather than a sensory block.

Central pain. If the injections of solutions A, B, and C fail to resolve the patient's pain, 5% procaine (solution D) is then injected to block all modalities, including motor function. If solution D does relieve the pain, the mechanism is still considered to be somatic, and it is presumed that the patient has an elevated C_m for Aδ and C-fibers. However, if there is no relief following the injection of the 5% solution, the pain is classified as central in origin, with the four possible subclassifications as noted in Table 20-2.

The *modified differential spinal block* was developed to overcome the disadvantages inherent in the conventional differential block and is, in essence, an observational process that is the reverse of the classic approach. In the modified block, only solutions A and D are injected through the spinal needle. If the patient obtains no or only partial relief following the injection of solution A (placebo), then 2 ml of 5% procaine (solution D) are injected through the spinal needle. The needle is then removed, and the patient is placed supine. The modified differential block is less labor intensive than the classic approach and has proven to be as efficacious as the former in the clinical setting. The proposed interpretation of the modified differential spinal is as follows:

- If the patient's pain is relieved after injection of solution A, the interpretation is the same as in the conventional differential spinal technique.
- If the patient does not obtain relief following the injection of solution D (5% procaine), the diagnosis is considered to be the same as in the conventional approach whereby the patient fails to get relief following injection of all solutions (A through D).
- If the patient obtains complete pain relief after injection of solution D, the pain is considered to be somatic and/or sympathetic in nature. At this point the regression of blockade becomes important, as 5% procaine blocks motor, sensory, and sympathetic fibers. Therefore, the patient is queried as to the return of his or her pain concomitant with the regression of, first, motor block, followed by sensory block regression, and, ultimately, by sympathetic block regression.

- If the pain returns when the patient again appreciates a pinprick as sharp (recovery from analgesia), the mechanism is considered to be somatic (subserved by Aδ fibers and/or C-fibers).
- If the pain relief persists for a prolonged period after recovery from analgesia, the mechanism is considered to be mediated by the sympathetic nervous system (mediated by B-fibers).

The *differential epidural block* was developed by Raj[4] in an effort to circumvent the possibility of producing post–lumbar puncture headache from the differential spinal block and to allow for better assessment of *incident pain* if a catheter is placed. The basis for the procedure is identical to that of the differential spinal block, with the technique relying on placement of a standard 18- or 20-gauge Tuohy-type epidural needle into the epidural space at L2–L3 or L3–L4 as described above for the differential spinal block. Four solutions are sequentially injected, with solution A still indicating a placebo (typically normal saline solution), and solution B containing 0.5% lidocaine, presumed to be the mean sympathetic blocking concentration of lidocaine in the epidural space. Solution C is 1% lidocaine, presumed to be the mean sensory blocking concentration of lidocaine, and solution D is 2% lidocaine, a concentration intended to block all modalities (sympathetic, sensory and motor). The sequence of injections is identical to that proposed for the conventional differential spinal block, with the same patient observations being made following the injection of each of the solutions in sequence.

There are two shortcomings of the technique, as proposed by Raj, however. First, because of the delay in onset of blockade of each modality using the epidural approach (as compared with subarachnoid administration of local anesthetic), a significantly longer period would be required between injections, thus increasing the time-intensive nature of the procedure. In a busy, outpatient contemporary pain management center, this might prove to be prohibitive. Second, if local anesthetics occasionally fail to give discrete end points when administered in the subarachnoid space, they do so even more frequently when administered epidurally, therefore tending to further "muddy the waters" in assessing the response of patients to each subsequent injection. Again, however, the technique may be modified as for differential spinal block so that only two solutions, A and D, may be administered sequentially as above for differential spinal block.

The *anatomic approach to differential block* is the other modality described. The utility of the technique is that, unlike differential spinal block (and to a lesser extent differential epidural block), painful conditions affecting any body region may be addressed (including but not limited to the lower abdomen and lower extremities). The anatomic approach relies on three injections: a placebo, a sympathetic nerve block, and a somatic sensory and motor block. The sympathetic block is carried out at a site where the sympathetic fibers are anatomically separate from sensory and motor fibers, and can thus be blocked independently of one another. The various sympathetic and somatic block procedures vary depending on the painful area to be evaluated (Table 20-3). Whereas the anatomic approach certainly has applicability for head and neck and upper extremity pain, the differential epidural approach may be preferred for thoracic pain to minimize the likelihood of pneumothorax resulting from thoracic paravertebral blocks used in the anatomic approach.

As an example of a modified anatomic approach to differential block for the patient with upper extremity pain, a differential brachial plexus block approach might be chosen. Two sequential injections are made into the perivascular compartment at the interscalene (for shoulder pain), infraclavicular (for pain between the shoulder and the wrist), or axillary level (for pain in the lower forearm to the fingers). One injection consists of normal saline solution; the other consists of 2% chloroprocaine. The same observations are made as for differential spinal block. If the patient obtains pain relief following the injection of saline, the pain is considered to be of "psychogenic" origin, with the same considerations applying as previously mentioned. If pain disappears following the chloroprocaine injection, the pain is considered to be either sympathetic or somatic. The pain is considered to be somatic if it returns once the sensory block dissipates; but if pain relief persists after the sensory block dissipates, it is considered to have a sympathetic nervous system origin. If the patient continues to experience pain, even in the face of complete sensory and motor block, the pain is considered to be central, with the same considerations as previously mentioned for differential spinal block.

LIMITATIONS OF DIFFERENTIAL BLOCKS

Despite the seemingly objective nature of differential neural blockade as a means of confirming a diagnosis when a patient's pain is obvious, as well as its role in establishing a

TABLE 20–3 Anatomic Differential Block: Procedural Sequence

Site of Pain	Block Performed First after Placebo	Sympathetic Block	Somatic Block
Head	Sympathetic	Stellate ganglion	Trigeminal I, II, III; C2; occipital nerve
Neck	Sympathetic	Stellate ganglion	Cervical plexus or specific nerve
Arm	Sympathetic	Stellate ganglion	Brachial plexus or specific nerve
Chest	Somatic	Thoracic sympathetic	Intercostal nerve or paravertebral somatic
Abdomen	Somatic	Celiac plexus	Intercostal nerve or paravertebral somatic
Pelvis	Somatic	Hypogastric plexus	Paravertebral somatic or intercostal nerve
Leg	Sympathetic	Lumbar sympathetic	Lumbosacral plexus or specific nerve

Source: Data from Winnie and Candido.[1–3]

TABLE 20–4 Diagnostic Blocks: Limitations

Potential limitations due to altered primary afferent nerve activity:
Receptor sensitization by tissue factors
Spontaneous discharge from dorsal root ganglion (DRG) proximal to injury
Propagation of antidromic activity distal to site of nerve injury
Sympathetic influences on receptor sensitization, inflammation, or neuroma firing
Potential limitations due to altered spinal processing:
Peripheral nerve block alters balance of large fiber and C-fiber input to dorsal horn
Spinal block of superficial fibers of descending inhibitory system
Acute activation of descending inhibitory tracts by stress of nerve block procedure
Presence of conditioned descending stimulatory modulation, which may persist
Pain dependent on converging inputs from two sources, not both apparent
Potential limitations due to central plasticity:
Unpredictable response to block of conditioning afferent input with central sensitization
Block of afferents may normalize dorsal horn responsiveness, leading to prolonged relief
Block of adjacent uninjured nerve may relieve pain in its area if altered central processing
Block of injured nerve may not relieve deafferentation pain if there is DRG receptive field expansion
Potential limitations due to local anesthetic effects:
Relief after sympathetic block may be due to subtle undetected somatic block
Intended profound somatic blocks typically less than complete neural block
Differential pharmacologic block by local anesthetics is unpredictable, with varying degrees of overlapping partial block of each sensory modality
Systemic effects of absorbed local anesthetics on neuropathic pain

DRG, dorsal root ganglion.
Source: Data from Hogan and Abram.[6]

diagnosis when there appears to be no demonstrable cause, some difference of professional opinion exists regarding its ultimate utility.[5,6] Some authors argue that the use of a nerve block to identify a nerve pathway that is the source of an individual's ongoing pain assumes three potentially false premises: (1) pathology causing pain is located in an exact peripheral location and impulses from this site travel via a unique and consistent neural route, (2) injection of a local anesthetic totally and selectively abolishes sensory function of intended nerves, and (3) relief of pain following local anesthetic block is due solely to block of the target neural pathway. These assumptions are limited by certain complexities of the anatomy, physiology, and psychology of pain perception, and the effect of local anesthetics on impulse conduction (Table 20-4). The resultant potential limitations of diagnostic blocks have been reviewed by Hogan and Abram,[6] and examples are provided below and in Table 20-4.

A peripheral nerve block performed proximal to the site of an injury may not interrupt pain due to spontaneous discharge from dorsal root ganglion (DRG) cells. However, a nerve block distal to the site of nerve injury may interrupt propagated antidromic C-fiber activity that maintains peripheral receptor sensitization. Selective sympathetic block may produce multiple indirect effects: interrupting receptor sensitization, peripheral inflammation, or neuroma firing. Spinal block may interrupt superficial fibers of the descending inhibitory system. Stress-induced analgesia may occur during a diagnostic block procedure due to activation of descending inhibitory spinal tracts. Blocking one limb of converging inputs may relieve pain but fail to identify a major underlying pain source. The response to diagnostic block may be unpredictable in the presence of central sensitization; and block of an adjacent uninjured nerve may relieve allodynia in its distribution. Relief after sympathetic block may be due to subtle somatic block that is not clinically obvious. A typically less than complete local anesthetic neural block may produce an apparently negative diagnostic somatic block. Differential pharmacologic block by local anesthetic is unpredictable and may not be reliably produced, and less reliably reproduced between independent observers. Neuropathic pain may be relieved by systemic effects of absorbed local anesthetics. The reader is referred to the review by Hogan and Abram[6] for additional details.

ROLE OF DIAGNOSTIC BLOCKS

Boas and Cousins have listed seven aspects of a patient's pain that may be profitably investigated using nerve blocks.[7] These are the foundation for the following discussion (Table 20-5).

ANATOMIC LOCATION OF PAIN SOURCE

Direct injection of local anesthetics into tender superficial or deep tissues may clearly delineate the source of pain. Examples include nerve entrapment syndromes including radiculopathies, post-traumatic neuroma formation, myofascial trigger points, and focal muscle spasm. Prompt, complete pain relief on at least two separate occasions may confirm the diagnosis (double-diagnostic blocks), although said pain relief does not guarantee that myofascial pain is the principle cause. Other confounding factors include the possibility of placebo effects and systemic uptake of local anesthetics, as well as the spread to adjacent nerves/structures.

TABLE 20–5 Diagnostic Nerve Blocks: Questions To Be Addressed

1. Anatomic location and source of pain
2. Visceral versus somatic origin of trunk pain
3. Sympathetic versus somatic origin of peripheral pain
4. Identify referred pain syndromes
5. Segmental levels of nociceptive input
6. Painful muscle spasm versus fixed contracture deformity
7. Diagnosis of central pain states

Source: Data from Boas and Cousins.[7]

Facet joint diagnostic blockade is probably most accurately performed by medial branch nerve block. The greatest specificity for a positive response to a facet denervation procedure is achieved when the diagnosis is established via highly controlled anesthetic blocks.[8] The gold standard used here is the subsequent carefully recorded short- to longer-term response to a facet denervation procedure.

With sciatica the sensitivity of selective nerve root block is very high, with only a moderate level of specificity being demonstrated.[8] Additionally, diagnostic selective nerve root injections may be a useful tool in the diagnosis of radicular pain in atypical presentations, particularly when diagnostic imaging and clinical examinations do not correlate.[9,10] However, North et al. found that the specificity and sensitivity of nerve root blocks are very low (9%–42% sensitivities) specific to the diagnosis of "sciatica."[11] Selective nerve root block was most helpful as a negative predictor for the presence of nerve root compression if the block result was negative. Pain relief with blockade of a spinal nerve cannot distinguish between pathology of the proximal nerve in the intervertebral foramen or pain transmitted from distal sites by that nerve.[6] The same group (North et al[11]) found the strongest association between the relief of sciatica and relief by medial branch posterior ramus (facet) blocks.

The diagnosis of third occipital nerve headache after whiplash injury in cases where there is no distinguishing feature on history or physical examination is typically made by local anesthetic C2–C3 facet joint blocks.[12] The false-positive rate, however, of anesthetic blocks of the medial branches of the cervical dorsal rami in the diagnosis of cervical zygapophysial joint pain is high (27%; 95% confidence interval, 15%–38%). This seriously detracts from the specificity of the block.[13] Some evidence exists that local anesthetic peripheral nerve blocks may provide useful diagnostic information in cases of peripheral mononeuropathy.[14] However, pain relief following paravertebral spinal nerve injection does not predict success by neuroablative surgery, either by dorsal rhizotomy or dorsal root ganglionectomy.[6]

VISCERAL VERSUS SOMATIC TRUNK PAIN

The origin of pain in the chest, abdomen, or pelvis may be evaluated by diagnostic blocks. A somatic source may be confirmed by injections into costochondral tissue, truncal muscles, or intercostal nerves. Persistent postoperative truncal wound pain may also be evaluated by muscle and neuroma infiltration. Rectus abdominis muscle entrapment of cutaneous nerves may also be isolated. If it can be established that pain is visceral in origin, treatment may be directed towards exploration of abdominal or pelvic organs, or towards denervation of visceral structures, if an untreatable malignancy is encountered. Celiac plexus block, hypogastric plexus block, intercostal nerve block, or local infiltration techniques have all been employed in the diagnosis of painful states involving the viscera and the trunk.[15] However, given the relatively large volume of local anesthetic employed for blocks such as that of the celiac plexus, systemic local anesthetic effects and local spread in the abdomen to adjacent structures cannot be dismissed with any certainty, even when using advanced techniques of image guidance including computed tomography (CT) scans and ultrasound-assistance to perform the blocks.

SYMPATHETIC VERSUS SOMATIC PERIPHERAL PAIN

When sympathetic nerve activity is suspected to play an important role in a patient with chronic pain, sympathetic blocks may help confirm the diagnosis. Diagnostic sympathetic blocks should be performed at anatomic sites separate from somatic nerve fibers. These include the cervicothoracic and lumbar sympathetic chain. Confirmation of pain relief and complete sympathetic block on two occasions with different local anesthetics may establish the presence of a sympathetically maintained pain state. Failure to obtain relief is consistent with sympathetically independent pain (SIP). This distinction is descriptive of a pattern of response with potential therapeutic implications; however, it does not indicate a separate disease process. Somatic nerve blocks may assist in the diagnosis of specific musculoskeletal or neuropathic pain syndromes, as described previously.

REFERRED PAIN STATES

Somatic–somatic pain states may be identified if injection of the original pain site simultaneously relieves pain in the referral zone. This phenomenon can be seen when medial branch blocks for facet syndrome relieve distal buttock and thigh pain, or when injection of active trigger points for myofascial pain provides relief of distant somatic referred pain.

SEGMENTAL LEVELS OF NOCICEPTIVE INPUT

Determining the spinal segments associated with somatic or visceral pain, coupled with knowledge of the segmental innervation of body tissues, may indirectly aid in locating the bodily structures involved. Either paravertebral somatic or intercostal nerves may be progressively blocked until all pain is relieved. Repeated blocks with fluoroscopic or ultrasound guidance are essential to making an accurate diagnosis.

CENTRAL PAIN STATES

Central pain arises from the brain or spinal cord. It may occur after a central lesion or as a result of abnormal central modulation of nociceptive and non-nociceptive input. Examples include thalamic syndrome after cerebrovascular accident and traumatic spinal cord injury. The classic response seen with a central pain state is inadequate analgesia after multiple peripheral blocks. Inadequate pain relief is expected after epidural anesthesia to a segmental level that supplies the painful area, as well as poor analgesia with systemic or intraspinal opioids. However, temporary relief of central pain has occurred following diagnostic spinal anesthesia, such as relief of lower but not upper extremity pain in a patient with hemiplegia after a cerebral infarction.[16] Neuropathic pain associated with lesions of the peripheral nervous system may also be associated with altered central processing of nociception. This pain is often relieved with spinal or plexus anesthesia, and it may have a partial response to opioid analgesics.[17,18] Both central and peripheral neuropathic pain may be relieved by intravenous local anesthetic administration.[19,20]

Psychogenic pain has been given an important place in the interpretation of differential blocks. Failure to relieve pain with complete sensory and motor block of the segmental levels associated with the painful area suggests the presence of supraspinal mechanisms. It does not in and of itself allow the specific diagnosis of either central pain or a psychogenic pain syndrome. Temporary pain relief after a placebo block is a common phenomenon, which allows only for the diagnosis of placebo responder. Observations of unusual responses, such as prolonged dramatic analgesia after a placebo injection or the presence of excessive pain behaviors, may correlate with the clinical impression formed during the initial history and physical examination.

PROGNOSTIC BLOCKS

Local anesthetic blocks may be used to evaluate patients with cancer pain as potential candidates for neurolytic blocks, such as celiac plexus block for the visceral pain of pancreatic cancer.[21] Opioid or local anesthetic injections help predict the response to an implanted apparatus for intraspinal drug administration in similar patients with cancer pain. A single block or repeated local anesthetic blocks may be used before a contemplated neurodestructive procedure is undertaken. Failure to obtain adequate analgesia will prevent an unnecessary operation or intervention. Once initial postblock analgesia is achieved, the patient can experience the extent of pain relief and the presence of any unpleasant side effects, such as numbness and dysesthesias, prior to accepting a neurodestructive procedure. However, positive prognostic blocks do not reliably predict long-lasting analgesia, without deafferentation pain, after neurodestructive procedures in patients with chronic nonmalignant pain.[22,23]

ADDITIONAL TECHNIQUES OF DIAGNOSTIC BLOCK

SACROILIAC JOINT INJECTIONS

That the sacroiliac joint may be a source of low back pain is rarely disputed; what is disputed is the value of performing diagnostic nerve blocks to verify clinical suspicion of the joint being involved as a factor in the etiology of the patient's symptoms.[24] Unfortunately, intra-articular spread of local anesthetic is necessary to achieve efficacy, and this is rarely achieved without adjacent spread of the injectate to nontargeted tissues and nerves, including the second, third, and fourth sacral nerves (roots of the pudendal nerve). Pain relief following injection may be related to infiltration of the sacroiliac joint ligament or sacrospinalis muscle, thus giving the incorrect impression that the joint is the source of the pain. Groin pain seems to be a distinguishing characteristic of patients who respond favorably to sacroiliac joint injection.[25] Unfortunately, no historical or physical examination findings demonstrate sufficient specificity to allow for reliable clinical diagnosis of sacroiliac joint pain; and there is no gold standard, verifying the presence of this diagnosis, to which the results of sacroiliac joint injection can be compared.[8]

INTERVERTEBRAL DISC INJECTIONS

Pain may arise from the annulus of the intervertebral disc, and discography may be a useful technique for determining the internal structure of the disc. Identifying a particular disc as the source of a patient's pain is difficult due to overlap in innervations and due to similar pain arising from facet pathology. Although provocation discography with evaluation of induced pain can discern physiologically abnormal and sensitive discs, this does not establish whether the test identifies the source of the patient's pain.[6] One report implies that the diagnostic accuracy in predicting surgical outcomes following discography was 91% at cervical levels, and 82% for lumbar levels.[26] A study of 182 significantly painful disc levels in 111 patients wherein intradiscal lidocaine was injected was correlated with contrast leakage by CT scan or fluoroscopy. In leaking discs (55% of total), there was a 74% incidence of complete, or near-complete, resolution of pain following the injection of lidocaine, implying that painful intervertebral discs that exhibit discogenic leakage tend to be highly responsive to local anesthetic administration, while nonleaking discs tend not to improve. This observation has implications with respect to treatment and to targeting the origin of a given individual's low back pain.[27] Additionally, severely painful discs (as identified using lidocaine injection intradiscally) demonstrate complex annular derangements with both

radial defects and/or degenerative changes present, alone or in combination as evaluated by CT scan.[28] Other authors have corroborated these findings using retrospective reviews of data collected wherein 28 patients underwent provocation and analgesic discography with balloon-tipped intradiscal catheters placed for the purpose of administering local anesthetics. Eighty percent of painful intervertebral discs, as detected by provocation discography, were sufficiently anesthetized to produce a 50% or greater reduction in pain during the analgesic phase.[29] In prospective and randomized fashion, 42 patients with severe low back pain at either L4–L5 or L5–S1 underwent provocation discography using either radiocontrast (1.5 ml) or else bupivacaine 0.5% (0.75 ml). Anterior interbody fusion was performed in individuals demonstrating a positive response to provocation discography. Rates of improvement in VAS pain scores, as well as for Oswestry Disability Index were superior following the bupivacaine provocation discography procedures than after the standard contrast studies.[30] Discography is most accurate and beneficial when the diagnosis of discogenic pain is highly probable, based on sequential analysis of the history, physical examination, and imaging studies.[8] It appears from these recent studies using intradiscal provocation with local anesthetics that this may provide an enhancement in the diagnostic information and predictive value yielded by this examination procedure.

SELECTIVE SYMPATHETIC BLOCKADE

Lumbar sympathectomy may be performed to relieve lower extremity ischemic pain due to advanced peripheral vascular disease. This therapeutic intervention may be preceded by a prognostic lumbar sympathetic nerve block (LSNB) using a local anesthetic agent. The presence of an acceptable increase in skin temperature following LSNB further supports performance of a therapeutic lumbar sympathectomy (by radiofrequency lesion or by neurolytic blockade) designed to increase blood flow to the ischemic extremity. The role of the efferent sympathetic nervous system in persistent pain states is often unclear. Particularly in patients who have received the diagnoses of complex regional pain syndrome (CRPS), reflex sympathetic dystrophy, or sympathetically maintained pain, there often is a dearth of diagnostic evidence to support the clinical findings. Because of this, historically, sympathetic blocks have been utilized to provide diagnostic insight and to guide therapy. The purpose of diagnostic sympathetic block is to selectively interrupt sympathetic nervous system control of vasculature, while leaving somatic pathways unchallenged. The intended end point, complete sympathetic block in an extremity, has proven to be an elusive goal. One means of improving on the predictive value of accurately determining successful LSNB is to utilize a sympathetic skin response (SSR).[31] In a prospective study of 70 LSNBs performed in 13 patients with CRPS of the foot, SSR was monitored in both feet prior to and following bupivacaine administration. CT scan use confirmed appropriate needle placement for each block. There was an 83% success rate of LSNB using this approach, with the SSR demonstrating an accuracy of prediction of clinical success in 95%; with a sensitivity of 92% and a specificity of 94% at 7 min after the local anesthetic injection.[31] In a pediatric population (ages 10 to 18 years) in double-blind, placebo-controlled crossover fashion, 23 patients with suspected CRPS of the lower extremity underwent lumbar sympathetic catheter placement and injection versus IV lidocaine administration. The LSNB provided superior pain relief, reduction of mean pain intensity of allodynia to brush, and reduction of pinprick temporal summation, compared to IV lidocaine. There was no appreciable beneficial effect provided by the IV lidocaine administration.[32] This implies that LSNBs do, indeed, provide a mechanistic explanation of why the sympathetic nervous system may modulate pain in cases of abnormal sympathetic nervous system activity (i.e., CRPS with sympathetically mediated pain).

Stellate ganglion blockade (SGB) may fail to produce sympathetic denervation of the upper extremity due to the multiple sites of sympathetic nerve activity that bypass the ganglion. Production of Horner's syndrome is no guarantee that sympathetic flow to the hand has been interrupted.[33,34] Also, at lumbar levels there are multiple pathways of sympathetic fibers including collateral chains and crossover connections that may allow persistent sympathetic innervation to reach the lower extremities, hence minimizing the validity of selective lumbar sympathetic nerve blocks in effecting a diagnosis. Unfortunately, the degree of sympathetic nervous system dysfunction does not correlate with the response of pain to sympathetic blockade, nor does the response correlate with serum norepinephrine levels.[35–37] Therefore, although clinicians continue to employ sympathetic blocks for diagnosis and treatment of many diverse painful states, the evidence does not support their use diagnostically except in selected studies.[32] Skin perfusion does increase on the ipsilateral hand following SGB as measured by laser Doppler fluxmetric hand perfusion studies, however, and does so in a manner inversely related to the duration of symptoms of CRPS.[38] This implies that although the use of these blocks for diagnostic purposes may be somewhat controversial, there is a rationale for using them as a treatment modality in established cases of CRPS.

INTRAVENOUS REGIONAL SYMPATHETIC BLOCK

Intravenous regional blocks (IVR) using bretylium and guanethidine have been administered to patients with suspected sympathetically mediated pain syndromes. Both agents inhibit release of norepinephrine from nerve terminals, and guanethidine depletes tissues of it. Regional sympathetic block follows these procedures, and the patient's response during the post-block period may indicate the extent to which the pain is mediated by the sympathetic nervous system. Since there is a high correlation between relief of pain following IV phentolamine and IVR guanethidine, it is likely that each agent is producing analgesia by a sympatholytic mechanism.[39] Unfortunately, there is no indication that a given patient who responds favorably to IVR sympatholysis will have a long-term beneficial effect following either a series of blocks or from systemically administered antisympathetics.

LOCAL ANESTHETIC INFUSIONS

Intravenous lidocaine hydrochloride has been used in the diagnosis of neuropathic pain states. Patients who respond favorably to IV lidocaine infusions may be placed on oral congeners of lidocaine, notably mexiletine or tocainide for prolonged management. Studies suggest that there is selective peripheral and central analgesia produced by intravenous lidocaine in neuropathic pain states.[40] While at least four studies document the analgesic effect of oral mexiletine in individuals who responded favorably to IV lidocaine,[41–44] there is one randomized and controlled study that indicates the ability of IV lidocaine to diagnose predictably potential responders to oral mexiletine.[45] This is in light of data that suggest that both lidocaine and mexiletine suppress the excitability of dorsal horn neurons by blocking Na+ and K+ channels, as well as persistent sodium currents in sensory axons of individuals suffering from neuropathic pain syndromes.[46,47] Clinically, however, mexiletine has not proven to be as effective as opioids in managing some types of neuropathic pain, including that due to amputation.[48]

INTRAVENOUS PHENTOLAMINE

Phentolamine, an α-adrenergic blocking agent, has been administered intravenously in an attempt to determine if a patient's pain is sympathetically mediated. Response to IV phentolamine should indicate patients who might expect positive response to systemic or transdermal sympatholytic agents. Unfortunately, phentolamine has demonstrated local anesthetic properties, possibly biasing the analgesia that results from its use.[49,50] Additionally, the role of α-receptors in sympathetically mediated pain is poorly quantified.[51] Other reports suggest that phentolamine response may not differ appreciably from placebo response.[52,53] Considered alone, the phentolamine test is not very specific or sensitive (for diagnosing sympathetically mediated pain).[6] Indeed, a recent review noted that the phentolamine infusion test rationale was based on lack of standardization, wide variations in outcome measures, and methodologic flaws.[54] However, phentolamine was not unique among agents used as prognosticators when administered by infusion for chronic pain states. The authors also noted similar findings for tests conducted using lidocaine, ketamine, and opioids, drawing into question the continued promotion of such tests in the diagnostic phase of determining pain mechanisms and potential courses of treatment.[54]

PREREQUISITES FOR OPTIMAL DIAGNOSTIC BLOCK

The physician must make a complete evaluation of the patient prior to undertaking any diagnostic nerve block. A comprehensive history should include a pain diary, a history of the present pain, and all previous diagnostic workup and therapy information. A complete neurological and general physical examination including a functional evaluation should be undertaken. Results of diagnostic studies and psychological evaluations are reviewed. A physician who is knowledgeable about pain syndromes and diagnostic procedures must then determine if a diagnostic block is indicated and document the specific goal to be achieved with the selected procedure. Communication with the patient is necessary to obtain informed consent, ensuring that the true goals and limitations of the block are understood. The patient must be monitored for any major regional anesthesia or conduction block.

The following modifications to regional anesthesia procedures may improve the reliability of diagnostic nerve block:

- Limit the use of preprocedure sedatives and analgesics to ensure that the patient remains communicative at all times.
- Limit the volumes of local anesthetics to minimize the likelihood of spread to adjacent, unwanted sites.
- Make liberal use of radiography including fluoroscopy, CT scans, contrast material, ultrasonography, and plain film x-rays to improve accuracy.
- Employ a peripheral nerve stimulator with a variable output to locate target nerves precisely for plexus and peripheral nerve block.
- Repeat positive blocks with a local anesthetic of different duration, if the first block is successful, in an attempt to correlate the duration of pain relief to that of the expected duration of the local anesthetic.
- Maintain detailed observations and records of the effects of the diagnostic block.
- Record the patient's pain scores at rest and with function, as well as vital signs, sensory and motor examination findings, signs of sympathetic nervous system function, and the presence of pain behaviors both before and after the diagnostic block.
- Ask the patient to maintain records of neurologic symptoms, degree of pain relief, pain scores, activity levels, and analgesic intake following discharge.

INTERPRETATION OF BLOCK RESULTS

It is important to understand the limitations of diagnostic blocks. They are not intended to be therapeutic, and they have little diagnostic value unless considered within the framework of all other information obtained about the patient. Careful observation of the patient's response to blockade must be made and recorded. The extent of motor, sensory, and sympathetic block must be assessed by neurologic testing and correlated with the degree of pain relief and functional improvement over time. Conclusions about various aspects of the patient's pain may then be made, considering all of the information mentioned previously.

PITFALLS IN EVALUATING RESULTS

Pain relief due to an unintended action of a block can be classified as a false-positive response. False-positive results may occur due to a placebo response, systemic effects of local anesthetics, spread of agent to adjacent tissues or nerves, unreliable patient report of block effects, and temporary alterations in central processing due to lack of normal afferent input.[7] Placebo response occurs in about 30% of patients and should always be considered after a positive

diagnostic block. A report of differential spinal block for chronic pain has noted this response in just less than 20% of patients.[55] The presence of a placebo response has no reliable diagnostic significance. Confirmatory facet blocks with different local anesthetics have documented a false-positive rate for uncontrolled blocks in 27% to 38% of patients.[13,56] Systemic effects of local anesthetics may be expected to influence neuropathic pain states, particularly after use of large doses.[57] Distal block of afferent sensory input to the spinal cord may temporarily relieve pain due to a proximal or central lesion.[16–18,58] This implies that normal sensory input is activating a sensitized central neuronal pathway, and it is temporarily interrupted by the diagnostic block.

False-negative responses may occur when a block fails to relieve pain. This may result from an incomplete block, the presence of alternative pain pathways, unappreciated referred pain syndromes, unreliable patient report of block effects, and diagnostic testing performed at inappropriate times.[7] Blocks may be incomplete due to deficiencies in technique, particularly when reduced volumes of local anesthetics are used to achieve selective block. Failure to select all the pertinent neural pathways may result in apparent failure, particularly for painful joints that have multiple, overlapping innervations. Failure to document complete block of desired target nerve fibers in the expected location will also lead to apparent failure. It is not unusual for sympathetic or somatic blocks to be less than complete. Referred somatic pain phenomena may lead to failure to block the correct source of somatic pain initially. For example, back and leg pain may be due to lumbar disc herniation or degeneration, or to piriformis muscle syndrome, facet joint disease, sacroiliac joint dysfunction, ligamentous strain or tear, or myofascial pain, requiring radically different diagnostic somatic blocks to be performed. Diagnostic blocks should not be performed unless the patient is experiencing significant pain; the extent of pain relief should be evaluated when the maximum local anesthetic effect has been achieved.

Diagnostic nerve blocks can be useful aids in the workup and management of chronic pain states, particularly when the specific diagnosis remains in doubt following an exhaustive clinical evaluation. However, as stated by Hogan and Abram, these blocks are informative only in proportion to the care with which they are performed and the thoroughness with which the response is evaluated, and the findings should be interpreted cautiously.[6]

KEY POINTS

- Pain relief after local anesthetic blockade does not reliably predict successful neurodestructive surgery, that is, long-lasting analgesia without deafferentation pain.
- Prognostic local anesthetic blocks may be used to evaluate patients for neurolytic block. A negative response to blockade may be extremely valuable in preventing an unnecessary neurodestructive procedure.
- Relief of neuropathic pain with intravenous lidocaine appears to predict potential responders to oral mexiletine therapy.
- Placebo response occurs frequently and should be considered after a positive diagnostic block.
- After an initial positive block, confirmatory medial branch blocks with a different local anesthetic demonstrate a 27% to 38% false-positive rate.
- It is not unusual for sympathetic or somatic nerve blocks to be less than complete. This should be considered after a negative diagnostic block.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 21

Neurosurgical Procedures for Treatment of Intractable Pain

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The destruction of the nervous system is an irreversible technique to control otherwise intractable pain. However, prior to the development of effective augmentative techniques, such as intrathecal drug delivery and neurostimulation (both peripheral and central), these were the mainstay of neurosurgical pain treatment. Options exist for lesioning the brain and brainstem, cranial nerves, spinal cord, and peripheral nerves. While the rise of these newer therapies has pushed aside many ablative procedures, several still remain valuable components of the neurosurgical armamentarium.

GENERAL COMMENTS

The interruption of peripheral or central nervous system (CNS) pathways carrying pain has always seemed the most direct and logical manner to solve the problem of medically intractable pain, whether benign or malignant in origin. The targets for these interventions are myriad, beginning with peripheral nerves and ganglia and extending to the ascending spinothalamic tract and central aspects of the spinal cord, as well as the trigeminothalamic tract (Figs. 21-1 and 21-2). Supratentorial structures such as the thalamus and cingulate gyrus have also been destroyed in the quest for pain control. Unfortunately, the results of these interventions have not been as straightforward as the theories behind their employ, once again demonstrating that the physiology underlying the development and maintenance of chronic pain is more complex than we understand.

Several methods have been used to lesion the nervous system. The easiest is simply avulsion/resection of a peripheral nerve or cranial nerve branch. Thermocoagulation (TC) or radiofrequency (RF) lesioning has been most often used in the CNS, including the creation of ganglionic, spinal cord, and intracerebral lesions. Cryoablation found some favor in the 20th century, but is rarely used today.

Patients selected for these procedures should have chronic pain that has failed to adequately respond to multiple other conservative nonsurgical treatments. These may include rehabilitation, oral medications (anti-inflammatories, opioids, anticonvulsants, antidepressants), and injections. Given the advances in neurostimulation and intrathecal drug delivery, it is also reasonable to conduct a trial of these therapies prior to considering ablative procedures. This is true both for patients with pain due to late-stage malignancies (due to their higher medical risk in undergoing surgery) and those with pain from nonmalignant causes (due to the risk of permanent neurologic morbidity from the procedures).

Once the patient is selected, it is just as important to carefully select the correct ablative procedure, considering both the etiology of the pain and its location within the nervous system, so as to maximize the chance of achieving pain relief. For instance, central neuropathic pain will not likely respond well to a peripheral neurectomy or dorsal root ganglion lesion.

This chapter reviews the published experience with several neuroablative procedures, beginning with those that are still most commonly in use. Certain procedures (such as trigeminal ganglionic lesions and spinal facet denervation) are covered elsewhere in this book.

DORSAL ROOT ENTRY ZONE LESIONS/CAUDALIS DORSAL ROOT ENTRY ZONE

The dorsal horn of the spinal cord serves as both a relay center and an integration site for sensory signaling. First performed by Sindou[1] in 1972 (via coagulation) and then Nashold and Ostdahl[2] in 1974 (via RF energy), lesioning of the dorsal root entry zone (DREZ) was seen as a way to remove the portions of the CNS that had already undergone central sensitization in response to a peripheral lesion, such as malignancy or nerve injury. The lesions are intended to injure Lissauer's tract and preserve fibers subserving proprioception and certain aspects of touch that travel in the dorsal rootlets to the dorsal columns. It continues to have clinical application primarily for the treatment of pain due to traumatic brachial plexus root avulsions.

PROCEDURE

Intradural exposure of the intended anatomic levels is accomplished, followed by microsurgical dissection of the dorsal rootlets to free them from each other. After identifying the correct anatomic levels, either by electrical stimulation or the presence of avulsed rootlets, lesions are created on the inferolateral aspect of the rootlet entry zone. The small lightly or unmyelinated fibers that carry pain signals to the dorsal horn enter from the lateral aspect of the DREZ while the medial side contains primarily those fibers destined for the dorsal columns. Lesions are created either by coagulating and opening the pia on the lateral aspect of the dorsal rootlets followed by microbipolar coagulation of the DREZ (Sindou's method) or by using a DREZ RF needle (0.25-mm diameter) to make 1-mm–spaced lesions at 75°C for 15 s. Laser[3] and ultrasonically[4] created lesions have also been described.

For the treatment of facial pain, the lesions may be made in the trigeminal nucleus caudalis. This is essentially a cranial continuation of the dorsal horn, extending from the brainstem down into the upper cervical spinal cord,

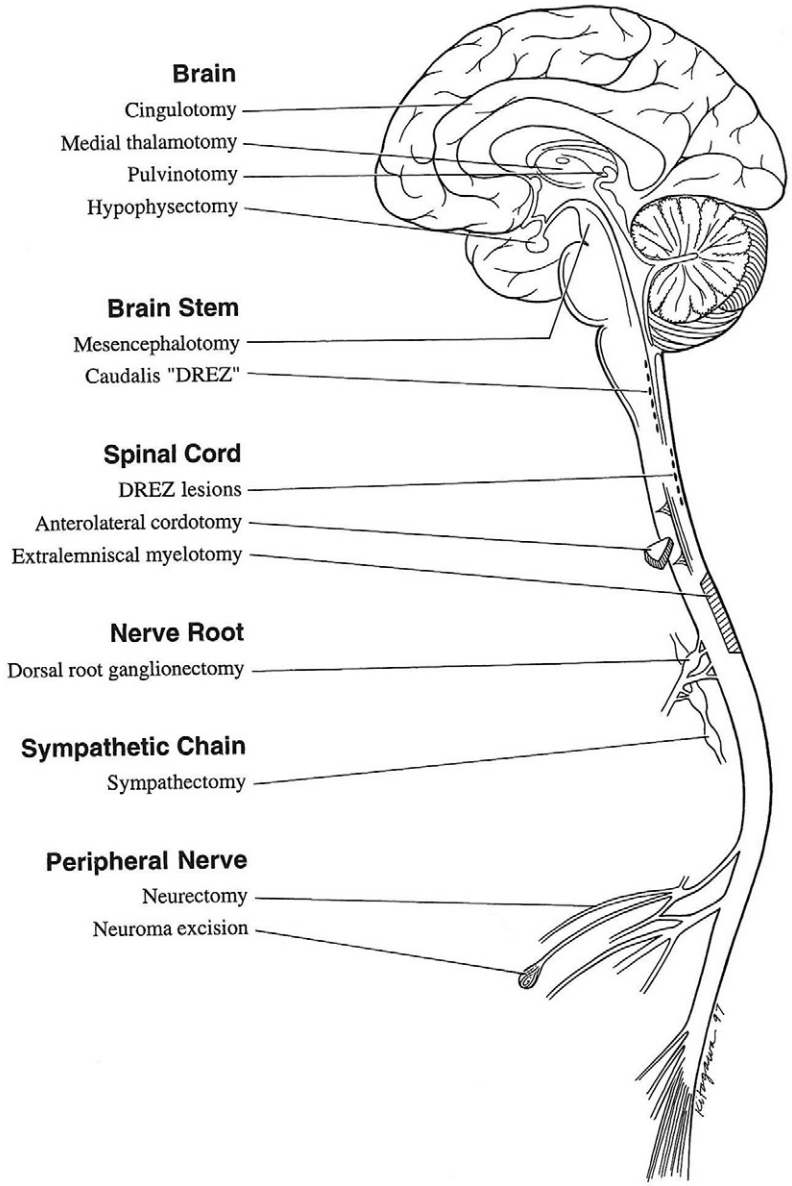


FIGURE 21-1 Schematic diagram of various neuroablative procedures available for treatment of intractable pain. *From Burchiel K, editor:* Surgical Management of Pain, *New York, Thieme, 2002, p. 635*

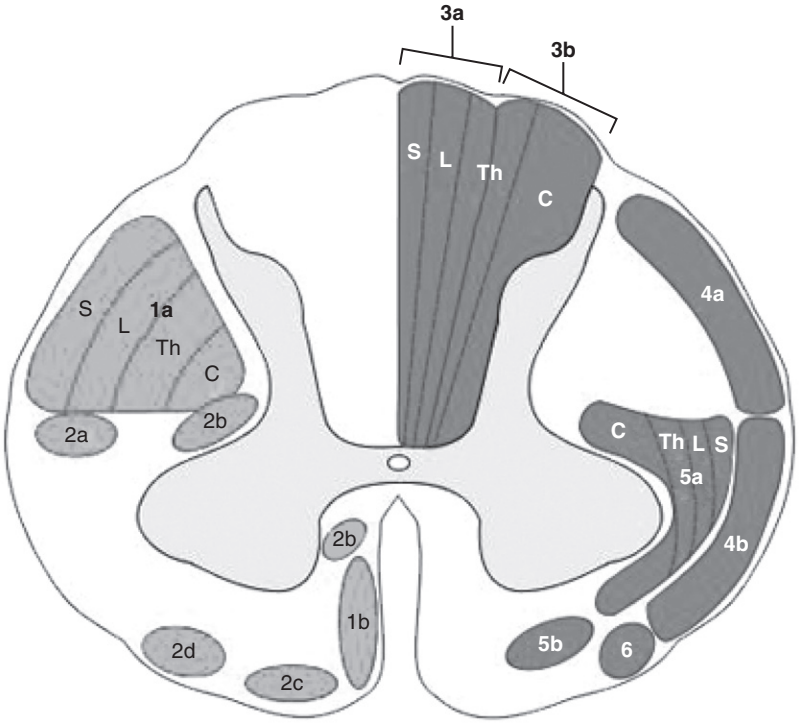
and receives much of the nociceptive signaling from the trigeminal system. As pioneered by Bernard,[5] these lesions are made from the upper rootlets of C2 to a point just above the obex. In the nucleus caudalis, cells receiving input from the first division are located in a more ventrolateral position while cells receiving input from the third division are located in a more dorsomedial position. Moreover, the third division is only represented in the more cranial aspect of the nucleus while the first division has a much broader extent.

Great care must be exercised in targeting DREZ lesions due to the presence of the corticospinal tract just laterally to the dorsal horn. Moreover, the size and angulation of the DREZ and dorsal horn vary depending on the spinal level, being much thinner in the thoracic region. Moreover, the inherently tenuous vascular supply to the spinal cord must not be disrupted. Motor complications range from 0% to 69%.[6]

RESULTS

Larger series show reasonable rates of pain control. Dreval et al.[4] published results of 124 patients with brachial plexus avulsion pain followed a mean of 47.5 months after DREZ and reported an 87% rate of good pain control. Most series for this indication note good pain relief in a majority of patients (usually between 50% and 80% of the cohort). The limited series of results of DREZ lesioning for phantom limb pain show less favorable outcomes (14%–67% good pain relief). This is similar for pain due to spinal cord injury and truncal postherpetic pain.[6]

Initially, the caudalis DREZ procedure was plagued by a high incidence of postoperative ataxia (up to 90%) due to the location of the nucleus caudalis deep in the spinocerebellar tract. Nashold et al.[7] developed new angled, insulated RF needles specifically for this procedure that protected this pathway from damage during



Motor and decending (efferent) pathways (left, medium grey)

1. Pyramid Tracts
1a. Lateral corticospinal tract
1b. Anterior corticospinal tract
2. Extrapyramidal Tracts
2a. Rubrospinal tract
2b. Reticulospinal tract
2c. Vestbulospinal tract
2d. Olivospinal tract

Somatotopy Abbreviations:
S: Sacral, **L**: Lumbar
Th: Thoracic, **C**: Cervical

Sensory and ascending (afferent) pathways (right, dark grey)

3. Dorsal Column Medial Lemniscus System
3a. Gracile fasciculus
3b. Cuneate fasciculus
4. Spinocerebellar Tracts
4a. Posterior spinocerebellar tract
4b. Anterior spinocerebellar tract
5. Anterolateral System
5a. Lateral spinothalamic tract
5b. Anterior spinothalamic tract

6. Spino-olivary fibers

FIGURE 21-2 Diagram depicting the ascending and descending tracts of the spinal cord.

lesioning of the nucleus caudalis, reducing the ataxia complication rate down to 39%. As opposed to spinal DREZ, the best indication for caudalis DREZ is postherpetic facial pain (71% excellent to good relief in the Duke series[8]).

PERIPHERAL NEURECTOMY/ GANGLIONECTOMY

Resection of a peripheral nerve found its most significant use in the treatment of trigeminal neuralgia[9–12] and peripheral neuromas.[13,14] While it is not often used for the former indication, it remains a mainstay of treatment for the latter.

NEURECTOMY PROCEDURE

Avulsion of the peripheral branches of V1 (supraorbital and supratrochlear nerves) was often used in the treatment of trigeminal neuralgia in this region so as to selectively cause cutaneous anesthesia and spare the corneal anesthesia that often results from RF trigeminal ganglionolysis that includes V1. This has also been applied to the V2 and V3 branches in those patients deemed inappropriate candidates for other procedures for relief of trigeminal pain.

Supraorbital neurectomy is most commonly performed via an incision through the eyebrow while infraorbital neurectomy uses an approach to the maxilla via the gingivolabial margin. Once the nerve is located, it is wound around a small instrument and avulsed.

RESULTS

In the series by Grantham et al.,[15] the average duration of pain relief from these procedures was 33.6 months. Oturai et al.[16] compared RF coagulation and neurectomy, and found that only 51% of patients undergoing neurectomy were pain-free postoperatively and 78% had pain recurrence, compared to a pain-free rate of 83% of the RF cohort with only 49% pain recurrence.

Neurectomy has also been used for orbital pain,[17] thoracic pain,[18] shoulder pain,[19] and pelvic pain.[20–22] It is sometimes applied as a treatment for postoperative neuropathic pain that afflicts 5% to 8% of people undergoing hernia repair.[23] Among the 26 patients with postherniorraphy pain reported by Zacest et al.,[24] 19 had significant pain improvement after ilioinguinal neurectomy, but 13 had later pain recurrence. Others[25] have also reported results indicating that the long-term results for this procedure are not durable. Publications that do report better pain relief from this procedure are either small series[26] or more limited in their follow-up time.[27]

GANGLIONECTOMY PROCEDURE

Ganglionectomy is intended to avoid the issue of peripheral nerve regeneration, which may follow peripheral RF ablation or avulsion. While selecting patients who will benefit most from the procedure is still a challenge, most investigators agree that diagnostic anesthetic nerve blocks of the prospective target root should produce significant temporary pain relief.

The dorsal root ganglion contains the cell bodies of the sensory neurons whose central projections enter the dorsal horn of the spinal cord. The ganglion itself lies in the lateral aspect of the neural foramen, distal to the termination of the subarachnoid space in the nerve root sleeve. It may be exposed by resection of the lateral portion of the facet joint and inferior aspect of the lamina of the superior vertebral segment overlying the target root. Opening the root sleeve exposes the ganglion, which can be separated from the underlying ventral root and resected.

The C2 ganglion has been resected as a therapy for intractable occipital neuralgia. In this procedure, the ganglion is located ventral to the copious venous plexus in between the laminae of C1 and C2. The inferior aspect of the C1 lamina must sometimes be removed to gain access to the ganglion.

RESULTS

Results from ganglionectomy have been highly variable. In Taub's[28] large series of 61 patients who underwent ganglionectomy for persistent radicular pain following lumbar surgery, 59% of patients achieved good pain relief. Strait and Hunter[29] reported that 66% of his patients who had both the L5 and S1 ganglia resected for this same indication were pain-free. However, of the 37 patients in Wetzel's[30] series followed at least 2 years after ganglionectomy, only 19% of patients had durable pain relief from the procedure. North et al.[31] published even more disappointing results, with only 1 of the 13 patients reporting greater than 50% pain relief at 5.5 years postoperatively. There was little effect on medication intake and minimal functional improvement in the cohort.

Despite these issues, ganglionectomy may yet have a role to play. Young[32] and Arbit et al.[33] published series of patients treated with ganglionectomy for cancer pain. In the latter series, 13 of 14 patients had excellent or good results following thoracic ganglion resection for malignant chest wall pain. However, the median follow-up was only 22 weeks (longest 45 weeks), which may provide one explanation for the greater utility of the procedure in cancer pain.

Acar et al.[34] found that the procedure may also be useful for treatment of intractable occipital neuralgia in patients who received good temporary relief from selective C2 and C3 blocks. At final follow-up (mean 42.5 mo), 60% of patients reported either excellent or moderate pain relief. In Lozano's[35] series, 80% of patients with neuropathic occipital pain or a traumatic etiology reported an excellent or good response to the procedure. Not surprisingly, those individuals who had undergone a prior peripheral neurectomy or RF ablation procedure did not obtain additional pain relief from the procedure.

SYMPATHECTOMY

Currently, the most common indication for sympathectomy is palmar hyperhidrosis. However, for many decades, interruption of the sympathetic chain has been performed for a variety of pain syndromes, such as complex regional pain syndrome (I and II) and angina pectoris, as well as painful vasospastic disorders such as syndrome X and Raynaud's syndrome. Often these conditions are characterized by pain that does not conform to traditional peripheral nerve or dermatomal innervation patterns and whose intensity is out of proportion to the inciting event and/or imaging findings. Vascular and dystrophic changes often accompany the pain.

Roberts[36] proposed the term *sympathetically mediated pain* to describe the phenomenon of pain abolition due to cessation (temporary or permanent) of sympathetic transmission. However, there is still a dearth of concrete understanding of the exact mechanisms by which the sympathetic nervous system either generates or maintains neuropathic pain syndromes despite significant research in this area.[37] In determining a patient's candidacy for sympathectomy, a determination must be made as to the relative contributions of sympathetically mediated pain (SMP) and sympathetically independent pain (SIP) to the overall level of pain. Most commonly this is determined by observing the clinical response to local anesthetic sympathetic blocks. Intravenous phentolamine (α_2, adrenergic blockade) and guanethidine Bier block (adrenergic depletion) may also be used to this end. Sympathectomy is offered to those patients with appropriate pain syndromes who have failed other therapies and have demonstrated substantial temporary relief from these injections.

PROCEDURE

Surgical sympathectomy may be performed via several routes, depending on the region of the chain to be disrupted. Thoracic sympathectomy is most commonly performed by resecting the T2 and T3 ganglia for the treatment of upper extremity pain. This region is approached either anteriorly via a small thoracotomy or, most typically, via thoracosopic approaches. In the thoracoscopic procedure, ports are placed after deflating the ipsilateral lung. After elevating or opening the pleura, the sympathetic chain is identified on the paramedial posterior thoracic wall. The chain is coagulated and sectioned above and

below the intended ganglia and the specimen is removed. Pneumothorax is evacuated with a small red rubber catheter or chest tube prior to closing. It is rare to leave a chest tube following a thoracoscopic sympathectomy. The chain may also be approached posteriorly, via costotransversectomies at T2 and T3. The pleura is dissected away from the underside of the rib heads and transverse processes prior to their resection. The chain is located over the pleura near the lateral vertebral body. This is clipped/coagulated and resected. A similar approach may be conducted in the lower thoracic region for relief of neuropathic visceral pain (such as chronic pancreatitis) that has responded temporarily to splanchnic blockade. For this purpose, the ganglia from T9 to T12 are resected, along with the splanchnic nerves. This most frequently is performed as a bilateral procedure.

Lumbar sympathectomy is perfomed for relief of pain in the lower extremities. Typically the ganglia at L2 and L3 are resected. This may be approached via an open, muscle splitting retroperitoneal approach through a flank incision, sweeping the peritoneal sac away from the vena cava or aorta (depending on the side of symptoms). The chain is found at the junction of vertebral body and psoas muscle.

Wilkinson[38] has pioneered RF thoracic sympathectomy. This involves fluoroscopically placing RF needle electrodes at the levels of the T2 and T3 sympathetic ganglia. The ganglion is located near the dorsal half of the vertebral body near the craniocaudal midpoint of the vertebral body. Multiple lesions are created in the craniocaudal direction to ensure appropriate lesioning. Intraprocedural monitoring of limb termperature may be used to determine the procedural endpoint. A 2°C rise in temperature in the ipsilateral limb is considered significant. Complications from thoracic procedures include pneumothorax, Horner's syndrome, vascular injury, and intercostal neuralgia. Lumbar sympathectomy carries the risk of ejaculation problems in men. Rarely patients may experience "postsympathectomy neuralgia," a constant, aching pain in the proximal portion of the targeted limb. This is almost always self-limited to several months.

RESULTS

Series of patients undergoing thoracic sympathectomy for pain have reported rates of 65% to 100% at achieving significant pain relief, at least initially.[39–42] Success rates for lumbar sympathectomy are similar.[43,44]

Wilkinson[45] performed 37 RF sympathectomies for pain in 27 patients (3 bilateral). Eight were diagnosed with CRPS and 14 with causalgia. Useful pain relief was initially noted in 93% of targeted regions, but this declined to 69% at the 1-year follow-up. In his entire series of 110 patients undergoing RF sympathectomy for a variety of indications, there were 6 symptomatic pneumothoraces. Two patients developed persistent Horner's syndrome and 7 patients had transient intercostal neuralgia.

CORDOTOMY

The none-too-subtle premise of cordotomy is the interruption of the spinothalamic and spinoreticular pathways in the anterolateral quadrant of the cord carrying pain inputs to the brain from the periphery. These lesions are intended to preserve fine touch and proprioceptive tracts. Within the spinothalamic tract, the sacral fibers are located more dorsolaterally and the cervical fibers more ventromedially. Moreover, at any spinal level, axons composing the spinothalamic tract are primarily projections from cells located in the contralateral cord beginning two or three spinal segments below the specific level. Therefore, a lesion should produce pain relief beginning two or three dermatomes below the level of the lesion. Caution must be taken in lesioning the upper cervical cord, however, due to respiratory fibers of the reticulospinal tract lying medial to the spinothalamic tract. For this reason, bilateral upper cervical cordotomy is often not performed and patients with tenuous respiratory function are often considered unsuitable candidates. This procedure has found most utility in the treatment of refractory malignant pain. While open cordotomy was first performed by Spiller in 1912, Mullan[46–48] pioneered the percutaneous approach, which enabled even medically fragile patients with advanced malignancies to undergo the procedure.

PROCEDURE

In the open procedure, intradural exposure is first accomplished, followed by sectioning of the dentate ligament at the appropriate level. Grasping the free end of the dentate ligament allows the surgeon to gently rotate the cord away from the operative side and expose the ventral cord. A cordotomy hook with a 45-degree angle is inserted into the anterolateral quadrant and may be taken to the medial pia before sweeping ventrally. Care is taken to not violate the medial pia and risk injury to the anterior spinal vessels.

Percutaneous cordotomy is often performed in the upper cervical (C1–C2) region to treat hemibody malignant pain. This may be done using either CT or fluoroscopic guidance combined with contrast myelography. Following dural puncture from a lateral approach, contrast is instilled into the CSF, allowing identification of the dentate ligament and definition of the ventral hemicord. A stimulating/lesioning electrode is advanced through the needle and impedance mapping is used to signal entry into the cord. Pial penetration is heralded by an increase in the impedance from around 300 ohms to over 500 ohms. Patients may also report pain with this maneuver. Low frequency electrical stimulation is used to obtain a motor threshold for approximation of the distance to corticospinal tract. High frequency stimulation should produce contralateral sensations covering the painful region. Serial RF lesions are then created until the area of pinprick analgesia encompasses the patient's area of pain.

RESULTS

The majority of the outcomes literature regarding cordotomy deals with percutaneous procedures. Sindou et al.[49] culled 2022 patients from the literature and personal experience who underwent cordotomy for malignant pain and reported a 75% success rate at 6 months and 40% at 1 year. Tasker[50] noted that he could complete the procedure with a single lesion 95.5% of the time with 94.4% of patients achieving an adequate result, dropping to 84% at the

last follow-up. The most common complications are ataxia or paresis due to collateral lesioning of the nearby spinocerebellar and corticospinal tracts, respectively. This is transient in a significant percentage of patients (2.9%–100%) but permanent in a minority (1%–20%). Severe respiratory failure was noted in 0.5% to 27% of patients, and some[51] have advocated an anterior transdiscal approach in the lower cervical region as a method of avoiding this complication. Unfortunately, one particularly devastating complication is the late onset of new pain following cordotomy. Of Nagaro's[52] series of 45 patients who underwent cordotomy, 33 experienced this problem. In 28 patients, the new pain was in the mirror-image location of the original pain and could often be abolished by blockade of the nerves subserving the original pain. This type of pain has been reported as affecting 1% to 16% of patients in various series. Bowsher[53] suggested that this was due to destruction of pathways providing unilateral inhibition of nociceptive cells with naturally bilateral receptive fields.

Regarding surgical cordotomy, Cowie and Hitchock's[54] report of 56 patients listed a 95% immediate pain-free result, which diminished to 55% at 1-year follow-up. For patients with nonmalignant pain, the success rate was 85% initially, but only 35% at 1 year and 20% at 3 years. Two patients died from respiratory failure.

COMMISSURAL MYELOTOMY

Commisural myelotomy involves severing the fibers of the spinothalamic tract where they cross the spinal cord in the anterior commissure. It is expected that interrupting the flow of nociceptive information in this fashion will produce analgesia at the spinal level of the myelotomy and just below. However, more extensive areas of pain relief are often noted following this procedure. It has been frequently noted that the pattern of postmyelotomy pain relief cannot be predicted on the basis of the traditional maps of the spinal tracts. The exact mechanism behind this phenomenon is not known, but likely involves the existence of extralemniscal nociceptive pathways. Given that myelotomy does produce some damage to the dorsal columns, even in the most talented of hands, and that the dorsal columns already carry multimodality sensory information, this is a leading contender for the location of this collateral pathway.[55–57] Myelotomy is considered primarily for patients with intractable pain in the lower body and pelvis.

PROCEDURE

The spinal cord is exposed over the spinal neural level (rather than the bony spinal segment) corresponding to the pain. A small probe is inserted just lateral to the fibrous septum in the dorsal midline between the posterior columns. Traditionally, this is then used to carefully section the midline crossing fibers until the anterior cleft of the cord is noted, taking care not to injure the ventrally located anterior spinal artery and other epidural veins. For lower body and pelvic pain, the cord is often exposed via a T9 laminectomy.

Nauta et al.[58] and others have reduced the exposure and depth of dissection required for this procedure. In their technique, which may be perfomed either openly or stereotactically,[59] a single punctate lesion is made in the dorsal midline of the cord. Given the theory that pain relief from this procedure is due to the lesioning of a dorsal column nociceptive pathway, some surgeons[60] perform bilateral lesions of the paramedian dorsal colums without sectioning of the deeper midline crossing fibers.

RESULTS

Given that the patient population considered eligible for this procedure is rather small (and smaller still in the era of neurostimulation), extant series are all rather small. Most patients are suffering from intractable malignant pain and have a limited life expectancy following the procedure. In Hirschberg's[57] series of eight patients, survival ranged from 3 to 11 months following myelotomy and all had significant pain relief up until death. One patient experienced new leg weakness following the procedure. Nauta's[58] group of six patients who underwent punctate midline myelotomy had similar results. However, in Kim's[61] cohort of eight patients undergoing high thoracic myelotomy for visceral pain from gastric cancer, three developed new pain at other sites (with relief of the preoperative pain) and one developed proprioceptive deficits and paresthesias. Across the published series, the outcomes from punctate and traditional techniques do not differ much.

INTRACEREBRAL LESIONS

Moving the site of lesioning cranially is often intended to accomplish one of several well-defined goals: capture pain involving the face, head, and neck that cannot be treated with spinal ablative lesions, treat a wider area of the body, treat the affective nature of pain, or reduce hormonal drivers of malignancy.

MIDBRAIN TRACTOTOMY

First performed in 1938 by Dogliotti and then reported in 1942 by Walker, lesioning of the spinothalamic tract in the midbrain is intended to produce hemibody analgesia in patients with intractable pain that involves the head and neck.[62] Unfortunately, its utility has been severely hampered by disturbing postoperative dysesthesias and other complications, such as auditory disturbances due to the approach through the colliculus. Moreover, the technical difficulty of the exposure was also a hindrance. Wycis and Spiegel[63] described a stereotactic, rather than open, technique for the procedure. This and other series[64,65] report over 150 patients undergoing the procedure. Pain relief was highly variable and complications plentiful. The most common complications were dysesthesias (15%–40%), gaze palsy, and hemiparesis. Attempts to minimize complication and improve pain relief included moving the lesion more cranially to avoid the auditory and visual problems inherent in lesioning the brainstem near the colliculi. Colombo[66] noted that the disturbing dysesthesias are often associated with abolition of the SSEP signals, indicating unintended lesioning of the medial lemniscal fibers in addition to the spinothalamic fibers. Intraoperative stimulation may help identify the spinothalamic fibers from the

lemniscal fibers by the painful sensations evoked by stimulating the former and the more vibratory or pleasant sensations from stimulating the latter tract. Lesioning includes not only the spinothalamic tract proper but often also a second lesion just medial to the first that includes the periaqueductal gray matter.

THALAMOTOMY

The thalamus serves as the main deep relay nucleus for most motor and sensory functions. Several thalamic nuclei have been targeted, either singly or in isolation, to achieve pain control, including the medial/intralaminar thalamus, ventrocaudal (Vc) nucleus and pulvinar. Cells in the Vc nucleus subserving anesthetic body regions have a higher likelihood of exhibiting an abnormal bursting firing pattern as compared to those Vc cells subserving areas of normal sensation.[67] In the medial thalamus, the central lateral (CL) and centromedian/parafascicular complex (CM/Pf) are most commonly lesioned due to their large input from the spinothalamic tract and diffuse cortical projections.[37] These nuclei are more difficult to identify due to the lack of specific somatotopic physiologic responses evoked with intraoperative stimulation, unlike what is observed when targeting the Vc nucleus. Of 913 patients undergoing medial thalamotomy for pain reported in the literature, 73% had some initial pain relief with a recurrence rate of approximately 25%. Lesioning other nuclei in addition to the medial thalamus did not appear to increase the chance of clinical success.[68] Stimulation of the Vc thalamus produces a paresthetic sensation akin to that of spinal cord stimulation. This is frequently evoked as part of the medial-lateral targeting process during surgery to implant thalamic stimulating electrodes in the ventral intermediate (Vim) nucleus for tremor control. Several groups have reported that stimulation of the CM and Pf nuclei may be associated with unpleasant and even painful sensations.[69]

Lesioning the medial thalamic complex (CL or CM/Pf) does not produce sensory deficits. The largest series have been published by Jeanmonod et al.[70] Their initial paper described 69 patients who underwent CL thalamotomy. Two-thirds of these patients achieved at least 50% pain relief. This group later expanded the series to 85 patients, 52% of which experienced greater than 50% pain relief with a mean follow-up of 3 years.[68] One-third of patients had no pain relief. Interestingly, patients with only constant pain (without superimposed paroxysms) were more likely to fail the procedure. Young et al.[71] performed radiosurgical medial thalamotomy for intractable pain in 19 patients (24 lesions). After a mean of 12 months, 4 patients were pain free and 5 others had greater than 50% pain relief. However, in both the series of Urabe and Tsubokawa[72] as well as that of Sugita et al.,[73] approximately 15% of patients had significant postoperative confusion.

Mark and colleagues[74,75] reported results of Vc thalamotomy in 28 pateints. Eighteen obtained good pain relief. They defined several patterns of postoperative neurologic changes. Those patients with "VPL sensory syndrome" exhibited significant hypesthesia but little pain relief. Those with intralaminar or Pf nucleus syndrome had good pain relief without significant sensory changes. Tasker[76] reviewed the literature on Vc thalamotomy for pain and noted significant complications in 32% of patients and only a similar percentage with good pain relief. Postoperative dysesthesias were common. He stated that lesioning this target is not very useful for eliminating burning pain and recommended a trial of neurostimulation in this region rather than lesioning.

Lesions in the pulvinar, located posterior to the CM/Pf complex, have also been created for the treatment of intractable pain. These lesions produce pain relief in a minority of patients and appear to be better for relief of oncologic pain and less so for those with neuropathic pain of nonmalignant origin. As has been noted with other ablative procedures for pain, the clincal benefit tends to substantially fade with time.[77]

HYPOPHYSECTOMY

This procedure was a logical extension of the work by Huggins[78] and others that demonstrated that hormonal deprivation slowed the growth of prostate and breast cancers. Luft and Olivecrona's series[79] of 12 patients was the first demonstration of the utility of pituitary ablation for control of prostate and breast cancer with relief of severe pain in one patient. Thompson et al.[80] reported results of 47 patients undergoing the procedure for prostate cancer. Interestingly, 60% had significant initial pain relief, while only 14% had oncologic control. However, only 16% maintained this pain relief at 1 year postoperatively. Among the 203 breast cancer patients undergoing hypophysectomy in Fracchia's[81] series, 90% had initial pain relief and 101 were still alive and pain free 1 year later. Other series[82] show similar dramatic initial results that often are lost as the cancer progresses. No significant series of the use of this technique for pain have been published in over 20 years.

The pituitary gland may be ablated via either a standard craniotomy or a less invasive transphenoidal approach. The gland is destroyed either via direct resection, instillation of alcohol into the sella, RF, cryotherapy, or interstitial brachytherapy. Stereotactic radiosurgery may also be considered, but the variable time to onset of clinical effect with this technique may limit its utility in patients with a limited life expectancy and urgent problems. The complications of panhypopituitarism produced by this technique are not surprising.

CINGULOTOMY

Lesions of the anterior cingulate gyrus target the affective components of pain, rather than the pain transmission itself. Freeman and Watts[83] anecdotally noted that some patients undergoing prefrontal lobotomy for psychiatric indications also experienced significant pain relief. Autopsy studies revealed involvement of the cingulate gyrus. The procedure typically involves bilateral stereotactically placed RF or radiosurgical lesions in the bilateral anterior cingulate gyrus. Foltz and White[84] published the first series of 12 patients undergoing stereotactic (as opposed to open) cingulotomy for pain. Of the 16 patients reported, 4 of 11 with bilateral lesions had an excellent result and 5 of 11 had a fair result. Most reported series are retrospective analyses of small

cohorts.[85–91] The largest series is that of Ballantine et al.,[92] who reported results on 133 patients undergoing cingulotomy for pain relief. Pain relief was initially obtained by 20 of the 35 patients with malignant pain, but this waned significantly over several months. However, 62% of patients with failed back surgery syndrome obtained significant durable pain relief. Grouping together multiple series, the procedure shows a modest benefit, with slight majorities of patients with malignant (52%) and benign (53%) etiologies obtaining useful pain relief.[93]

CONCLUSION

While not commonly used, certain ablative neurosurgical techniques continue to have a role in the management of medically intractable pain. Moreover, they all have a role to play in our understanding of the pathophysiology behind the generation and maintenance of chronic pain states. With the rise in neurostimulation as a treatment for many types of neuropathic pain, there is concern that some of these valuable treatments will be lost forever. Neurosurgeons and other physicians who treat chronic pain must continue to be educated in these procedures to ensure that they continue to be available for carefully selected patient populations.

KEY POINTS

- Ablative techniques have been used for many decades to control intractable pain. While they continue to have some well-defined indications, they have largely been replaced by neurostimulation procedures.
- The results of ablative procedures for pain tend to be highly variable, with a substantial proportion of patients obtaining relief early and then experiencing recurrence of pain.
- Ablative procedures such as cordotomy may be useful in treating pain of malignant origin, given the limited life expectancy of these patients.
- Spinal dorsal root entry zone (DREZ) lesions may be useful in treating neuropathic pain due to brachial plexus root avulsion, if a trial of neurostimulation has failed.
- The physiology underlying the development and maintenance of neuropathic pain, and the mechanism of action/loss of effect of an ablative neurosurgical procedure for pain, remain to be fully elucidated.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 22

Physical Medicine and Rehabilitation Approaches to Pain Management

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Physical medicine and rehabilitation practitioners use a comprehensive approach to assess and manage acute and chronic pain conditions. The treatment they provide is guided by understanding the cause of pain, related musculoskeletal impairment, compensatory biomechanical patterns, duration of pain, functional deficits, and related psychosocial factors. Therapeutic programs often include medication and exercise for flexibility, strength, and fitness, and may use passive modalities, injections, interventional treatments and cognitive and behavioral interventions. Treatment programs for acute pain focus on addressing the pain generator, using temporary relative rest if indicated, and education for stretching, strengthening, fitness, and proper biomechanics. Programs for chronic pain also include exercise regimens, but often require behavioral and psychological interventions, and direct treatment of the pain generator itself is rarely effective. Physical medicine approaches often include the various techniques and methods provided by physical therapy. Physical therapy includes therapeutic exercise, functional training in home and work activities, manual therapy, prescription and application of devices, and passive modalities. The goals of pain treatment programs vary considerably between patients, but the cornerstones are self-efficacy, return of functional capacity, and acceptable analgesia.

The purpose of this chapter is to briefly review commonly used physical modalities and therapeutic exercise, discuss the basics of a rehabilitation program for pain, and to introduce the concept of comprehensive interdisciplinary pain management.

OVERVIEW OF MODALITIES

Modalities are methods used by therapists to exchange energy with tissues with the goal of creating a therapeutic response. Passive modalities may include the application of heat, cold, sound waves, electricity, and electromagnetic waves to effect changes in tissue structures such as muscle, fascia, ligament, tendon, capsule, and nerve. Modalities are an adjunctive treatment included as part of a rehabilitation program, rarely used in isolation. Modalities are most useful when treating acute pain where the specific underlying musculoskeletal abnormalities can be matched with an appropriate intervention. The long-term use of modalities is discouraged, since they may reinforce passive coping behavior.

HEAT AND COLD

Therapeutic heat transfer occurs by one or a combination of mechanisms: *radiation*, *conduction*, *convection*, *conversion*, and *evaporation*. *Radiation* is the transfer of heat through thermal radiation at the surface. *Conduction* is heat exchange through direct contact. *Convection* is characterized by transfer of thermal energy through movement in a fluid medium, although the therapeutic energy exchange still occurs through conduction. *Conversion* occurs when a different type of energy is converted to heat energy. *Evaporation* results in loss of heat when a liquid on a surface undergoes a phase transition into a gas. These mechanisms may be used alone or in combination to transfer heat to or from tissues, resulting in physiologic changes. Of these mechanisms, only conversion can be used to transfer heat to structures deeper than several centimeters beneath the surface. Remaining mechanisms are able to provide only superficial exchange of thermal energy. Conduction, convection, and evaporation are the ways that cold can be applied.

Applying heat causes improved elasticity of soft tissue as well as increased blood flow, metabolic activity, enzymatic activity, oxygen demand, and capillary permeability. Nerve conduction velocity increases with application of heat. The heated tissues become more supple, and there are increases in healing cells and nutrients and decreases in metabolic waste. However, heat can also increase edema and bleeding. There is some evidence from animal models that heat improves chronic inflammatory conditions, but may aggravate acute inflammation. The target temperature for these modalities is generally accepted to be 40° to 45° C, and the thermal pain threshold is normally about 45° C. Using the patient's pain response to a modality can prevent excessive temperatures, as long as the sensorium is intact. Box 22-1 summarizes the indications for heat modalities used for musculoskeletal pain management. Box 22-2 lists general contraindications and precautions for the use of therapeutic heat.

Superficial heat causes the greatest increase in temperature at the surface of the skin, with less heat penetrating to the deep tissues: about 1° C at a depth of 2 to 3 cm. It is often applied using hydrocollator packs, a variety of fluid baths, and infrared lamps. Hydrocollator packs are heated to 74.5° C. Several layers of towels are used to prevent burning of the skin and minimize loss of heat to the air. Immersion of body parts in water around 40° C is another way to apply superficial heat that allows for therapy

Box 22–1 Indications for Therapeutic Heat

Muscle spasm
Pain
Contracture
Hematoma resolution
Hyperemia
Increase collagen extensibility
Accelerate metabolic processes

Box 22–2 Contraindications for Therapeutic Heat

Acute inflammation
Hemorrhage or bleeding disorders
Decreased sensation
Poor thermal regulation
Malignancy
Edema
Peripheral vascular disease
Ischemia
Atrophic skin or scarred skin
Inability to respond to pain

Box 22–3 Common Uses for Therapeutic Ultrasound

Contractures
Tendonitis
Degenerative arthritis
Subacute trauma

Box 22–4 Precautions for Ultrasound

Malignancy
Open epiphysis
Pacemaker
Laminectomy site
Radiculopathy
Near brain, eyes, or reproductive organs
Pregnant or menstruating uterus
Heat precautions in general
Caution around arthroplasties, methyacrylate, or high-density polyethylene

Box 22–5 Indications for Cryotherapy

Acute trauma
Edema
Hemorrhage
Analgesia
Pain
Muscle spasm
Spasticity
Reduction of metabolic activity

Box 22–6 Precautions and Contraindications for Cryotherapy

Ischemia
Raynaud's disease or phenomenon
Cold intolerance
Insensitivity
Inability to report pain

activities to take place during heating. Paraffin baths are typically used for peripheral limbs, especially the hands and arms. Temperatures around 53° C are used because paraffin transfers less heat than water does. Infrared lamps can provide similar warming to tissues if angle of incidence and distance are optimized. Superficial heat leads to mild analgesia and a sense of relaxation but the mechanisms remain unclear.

Ultrasound waves, shortwaves, and microwaves can safely penetrate deep into tissues before the energy they carry is converted to thermal energy. Ultrasound diathermy (to distinguish from diagnostic ultrasound) is the only method commonly used at this time. It can easily heat the bone-muscle interface up to 45° C, even in deep structures such as the hip. Ultrasound generators convert electrical energy into vibratory energy through the piezoelectric properties of a crystal transducer. When ultrasound vibrations are directed into tissue, they generate heat based on the water and protein content of the tissue, and in areas of transition between tissue densities, such as at the interface between bone and muscle. Tissues that heat poorly due to high water concentration are fat and skin, and tissues that heat well due to high protein concentration are ligament, tendon, muscle, bone, and nerve, with bone and nerve heating the most. Ultrasound is safe for use near metal implants because the heat energy is rapidly conducted away, but caution must be used near prosthetic cements, which do not release heat as easily. Ultrasound may also cause gaseous cavitation and acoustic streaming effects that do not transmit thermal energy, but may increase tissue pressures and cellular metabolism, and disrupt cell membranes. Duration of treatment is 5 to 10 min and is based on the size of the treatment area. Although ultrasound diathermy has superior deep-heating capability, it does not produce the same degree of analgesia or relaxation as superficial heat modalities. Ultrasound may be used to help deliver analgesics and anti-inflammatories across the skin in a process called phonophoresis. Box 22-3 lists some common uses and Box 22-4 lists precautions for ultrasound.

Applying cold through conduction, convection, or evaporation results in loss of heat from tissues; this results in vasoconstriction followed by vasodilation, decreased local metabolic activity, decreased enzymatic activity, and decreased oxygen demand. Tissues and muscles become stiffer, nerve conduction slows, and muscle spindle and Golgi tendon organ activity decreases. Muscle isometric strength increases and rate of muscle fatigue decreases. Cold also results in analgesia and relaxation. Boxes 22-5 and 22-6 summarize general indications and contraindications for cryotherapy.

Cold is often used during the first 48 hr after an acute musculoskeletal injury to decrease inflammation, edema, and pain. Cold application should not exceed 30 min and should not be placed directly over superficial nerves to prevent neurapraxia. Cold is normally applied in ice packs at –12° C with towels layered over to protect the skin. As with the application of superficial heat, the surface of the skin is affected first and most, but after 20 min, tissues 2 cm deep are cooled by about 5° C. Cold water (5 to 13° C) immersion can be used but is generally poorly tolerated, although muscle temperatures can decrease by about 6 degrees after 30 min of immersion. Vapocoolant spray is used for cutaneous anesthesia, and is used by some

practitioners in conjunction with passive stretching to treat myofascial pain. Evaporation of the spray induces cutaneous cooling, with postulated cutaneosomatic reflex effects at the muscle spindle level.

Cold and heat can be used together in contrast baths with alternating warm and cold immersion to cause cyclic vasodilation and vasoconstriction, with beneficial effects hypothesized for pain from rheumatologic and neuropathic conditions.

Thermal modalities should be used in conjunction with exercises for motion and flexibility. The effects of most of these treatments on functional outcomes and range of motion are minimal when used alone.[1,2]

ELECTRICITY

Iontophoresis is the process by which various drugs (i.e., corticosteroids, lidocaine) are introduced into a joint or around periligamentous or tendinous structures via electrical current. Iontophoresis uses electromigration and electro-osmosis to increase permeation of charged and neutral compounds. The medicine is applied to the electrode with the same charge, and then the electrical field is set up on the skin surface to push the medicine away from the electrode and toward the target tissue. Topical delivery minimizes systemic side effects and bypasses hepatic metabolism.[1] Iontophoresis is non-invasive, painless, and avoids potential side effects and adverse reactions of oral medications or injection therapies (i.e., increasing risk for bleeding, intravenous catheter infiltration, and pump malfunction). Penetration may be particularly intense at sweat glands and areas of skin breakdown. Iontophoresis is commonly used with overuse conditions such as epicondylitis and plantar fasciitis.[3,4]

Electrical fields are also used in transcutaneous electric nerve stimulation (TENS) to directly affect pain transmission. Suggested mechanisms of pain relief include modulation of the gating mechanisms at the dorsal horn system to decrease pain transmission to the brain and stimulation of endogenous neurotransmitters and opioids. Cutaneous nerve fibers are stimulated using surface electrodes emitting a mild electrical current. The stimulation can vary by type of current, amplitude, pulse width, and frequency. Duration of the treatment and length of each treatment can vary widely, with some protocols calling for continuous treatment. High-frequency low-intensity stimulation patterns are better tolerated and result in immediate analgesia, while low-frequency, high-intensity patterns cause more discomfort and result in longer-lasting analgesia. Interferential current therapy (ICT) uses electrical current like TENS, but combines two different high-frequency pulses so that their interference pattern creates a low-frequency stimulation. The high-frequency stimulation penetrates skin better than low-frequency stimulation, but the treatment results in the longer-lasting effects of low-frequency stimulation.[1,5]

OVERVIEW OF A COMPREHENSIVE REHABILITATION PROGRAM

An individualized therapeutic program aims to correct soft tissue inflexibilities and improve muscle strength deficits and imbalances, endurance, and power to the appropriate muscle groups. Consideration is given to the joints above and below the injured area that are linked together and referred to as the "kinetic chain." The program should also include patient education about posture, body mechanics, and proprioception. A patient's return to activity should be monitored in a supervised setting so that any residual problems can be addressed.

A comprehensive rehabilitation program consists of acute, recovery, and maintenance phases (Table 22-1). During the acute phase, education about how to protect the injured tissue is important. A review of proper body mechanics and activities of daily living should be completed. Relative rest is important because excessive immobilization results in decreased muscle strength, endurance, and flexibility. Modalities can be used judiciously for symptom control and reduction in swelling. Medications may be used to facilitate the rehabilitation program by decreasing pain and inflammation. Manual therapy techniques may help modify pain by assisting in early controlled motion of the injured tissue. Mechanoreceptor activation can assist in modifying muscle tone and pain. Therapeutic exercise should begin during the acute phase. Once acute inflammation and pain have been addressed, the program focuses on the subacute or recovery phase. Goals of this phase include achievement of full or optimal range of motion with limited or no pain, regaining appropriate strength, balance, and proprioception. Manual techniques should focus on improving soft tissue extensibility that helps promote proper alignment of collagen fibers during healing and remodeling. These techniques may include massage, fascial stretching, traction, and joint mobilization. Myofascial release improves elasticity and motion by applying pressure in shear forces directed by fascial planes, and assists with pain control. Mobilization is also used to facilitate motion at specific joints or joint segments. These techniques may facilitate a patient's progress but again should not be relied upon solely because protracted passive treatment places the patient in a dependent role.

A flexibility program is devised to achieve proper balance and allow the patient to achieve a neutral position, the least painful and best posture. While maintaining the posture, exercises progress from static to dynamic. Challenges to the neutral posture are afterward incorporated by gravity and then by a therapist or assistive device. Activity-specific retraining is initiated first by breaking the motion into components. Training for each component is completed before reassembling the entire motion. Cardiovascular training should be maintained adapting the method to the specific injury. Aquatic training should be considered if a nonweight-bearing activity is necessary.

TABLE 22–1 Comprehensive Rehabilitation Program

Phases	Theraphy Focus
Acute	Education, relative rest, pain control
Recovery	Full or optimal range of motion, strenght, balance, proprioception
Maintenance	Return to work and sport specific activity, aerobic conditioning

The final or maintenance phase is devised as the patient returns to the work or sport-specific activity to promote continued fitness as well as to prevent reinjury. Education about ergonomics and equipment or adaptive devices should be complete. The patient should be able to perform a home exercise program independently and know how to solve problems that may occur during this last stage of recovery.

THERAPEUTIC EXERCISE

There are three main types of therapeutic exercise: exercises that improve flexibility, muscle strength, and aerobic capacity. A rehabilitation program to manage musculoskeletal pain and dysfunction will address all of these areas. Education about proper biomechanics and ergonomics customized to specific work or sport activities will also be an important part of the individualized rehabilitation program.

When implementing an exercise program, the specific adaptation to imposed demand (SAID) principle should be applied. The principle states that the body responds to given demands with specific and predictable adaptations. Stronger muscles develop with strength training. Oxidative capacities of skeletal muscles increase with aerobic training. Pliability of connective tissue increases with flexibility exercises.

FLEXIBILITY EXERCISES

Maintaining or regaining muscle flexibility and range of motion is an important part of a rehabilitation program. Connective tissue stretches with a small amount of force and returns to its original length when the force is removed. When the muscle fibers are straightened, more force is required to apply a stretch. Furthermore, if connective tissues are stretched to a certain length and maintained, the tension within the tissue decreases. For best results, stretching should be maintained for 30 s with the patient perceiving a pulling sensation rather than pain. Warming an area before stretching improves the elongation of the collagen fibers. Rapid or bouncing stretches promote tissue recoil and a sustained stretch is not achieved. The risk of excessive loading and injury also occurs with bouncing. If too much force is applied with stretching, the patient will experience muscle soreness for more than 24 hr. Joint laxity may result from excessive stretching during healing of tendons and ligaments. With adherence to an appropriately applied stretching program, flexibility should improve within 1 to 2 months.

STRENGTH TRAINING

Muscle strengthening is a well-accepted part of any rehabilitation program. The practitioner must have a complete understanding of functional anatomy so that the appropriate balance between agonist and antagonist muscle groups is achieved. The amount of resistance to be applied is determined by the muscle's capability, and should be assessed for each individual. Improvements in strength observed during the first 2 weeks of resistance training are related to neuromuscular reeducation and more efficient recruitment of muscles. Later gains are due to hypertrophy of muscle fibers and result in increased cross-sectional area. Training is most effective when exercises focus on different muscle groups in rotating sessions. Initially, one to three sets of 8 to 12 repetitions 3 to 5 times per week is recommended. Resistance should not be increased by more than 10% per week. If progress is not made, the practitioner should evaluate the technique and training intensity, and also consider neurogenic weakness.

AEROBIC FITNESS

The patient must maintain cardiovascular fitness during rehabilitation. If the injury or dysfunction prohibits weight bearing, a non–weight-bearing aerobic activity needs to be implemented. To improve aerobic capacity, the oxidative metabolism of the muscle must be stressed. Oxygen consumption (VO_2) increases in proportion to the intensity of the exercise. VO_2 max, the highest level of oxygen consumption achieved during exercise, is the best indicator of aerobic fitness. Intensity of exercise is the difficulty level of the exercise and is usually used in reference to maximal effort. This is typically at 40% to 85% of VO_2 max for aerobic training. The duration for aerobic training is usually greater than 15 min of continuous exercise. Frequency for aerobic training is usually 3 to 6 times per week. When prescribing an exercise program, remember that if activity level is reduced beyond 1 week, aerobic conditioning decreases. Intensity, duration, and frequency parameters must be adjusted in the deconditioned patient. Increases of 10% to 20% of VO_2 max can be noted within 8 to 12 weeks of training. If improvements are not observed, there may be inadequate frequency, intensity, or duration of training.

TREATMENT INTERVENTIONS SPECIFIC TO SPINE-RELATED CONDITIONS

Treatment approaches for spine-related conditions include flexion-based therapy, stabilization exercises, mechanical diagnosis and treatment (MDT), neurodynamic therapy, and various manual therapy and soft tissue approaches, as well as activity and therapeutic exercise as described above. Stabilization exercise training is the most common technique used, and emphasizes not only strengthening muscles but motor relearning of inhibited muscles. Patients are advanced from training in isometric and eccentric strengthening of core muscle groups to include Swiss ball and other dynamic multiplanar exercises, and finally gradual return to work- and sport-specific activities. Stabilization exercises reduce the recurrence of low back pain from spondylolysis and spondylolisthesis.[6] Stabilization exercises prevent recurrence and improve pain and function of nonspecific chronic low back pain, but do not reduce pain or disability in acute low back pain.[7,8]

Continuation of normal activity seems to be the best approach for acute low back pain.[9] Exercise programs provided after the resolution of acute low back pain can help reduce the recurrence rate and lengthen the time to recurrence.[10]

More specific exercise programs based on mechanical assessment may add more specificity to the exercise treatment program. MDT or "McKenzie" therapy is based on diagnosing and treatment directed by a therapist where pain is relieved or changed in pattern with repeated movement, that is, centralizing symptoms—symptoms in distal extremity (arm or leg) moving to a more proximal area along the spine. Most, but not all, patients who "centralize" do so with extension-based movements; others may respond to side bending of the spine or flexion of the spine. This treatment approach may be more appropriate for acute discogenic-related pain conditions.[11] Neurodynamic therapy is based on the premise that irritated nerve structures or chronic tension on cervical, lumbar, or peripheral nerves cause ongoing pain and dysfunction. Therapy focuses on decreasing tension on the neural structures by decreasing tension in the perineural tissues (i.e., soft tissue, muscle) and decreasing pain.

INTERDISCIPLINARY COMPREHENSIVE PAIN MANAGEMENT

Patients failing to progress in the acute, subacute, and maintenance program may need referral to a more comprehensive interdisciplinary, functional restoration rehabilitation–based program. Patients may continue to report ongoing pain and reduced physical and psychological functioning. Progress may also be impeded by disturbed sleep, affective distress (i.e., depression, anger, anxiety), fear of movement and reinjury, and deconditioning. In these cases, treatment of chronic pain may not only be focused on removing an underlying organic disease, but on the reduction of disability through modification of environmental contingencies and cognitive processes. Behavioral interventions, including cognitive behavioral therapy, relaxation training (i.e., deep breathing, progressive muscle relaxation), and education, are key components in interdisciplinary programs.

Comprehensive interdisciplinary rehabilitation pain treatment programs typically involve a number of health care providers including rehabilitation specialists; physical, occupational, and therapeutic recreational therapists; pain psychologists; biofeedback specialists; and nursing and vocational counselors. This interdisciplinary approach relies heavily on a coordination of services fostered by ongoing communication between team health care provider members with a goal of improving patient function at home and/or in the workplace, fostering independence, and improving psychosocial functioning (Box 22-7). Typical programs may last 7 to 8 hr per day for 3 to 4 weeks.[12] At the completion of the program, patients are encouraged to continue utilizing pain management techniques as they return to previous levels of sport, work, and/or community function. An extensive review of the behavioral treatment for chronic low back pain has shown that it can be an effective treatment for chronic low back pain.[13–15] Systematic reviews support the efficacy of multi- and inter-disciplinary treatment for chronic pain conditions.[16–18] Recent guidelines published by the American Pain Society for the treatment of low back pain support the use of interdisciplinary treatment, when available, for patients with non-specific low back pain, and as a treatment option that should be discussed for patients considering single-level laminectomy for lumbar disc herniation.[19]

Box 22–7 Staff Composition of an Interdisciplinary Pain Management Team

Physiatrist/pain medicine specialist
Nurse educator
Pain psychologist
Physical therapist
Occupational therapist
Vocational counselor
Biofeedback therapist
Therapeutic recreational therapist

In addition, early pharmacologic interventions should include trials of antidepressant medications for depressed mood and medications to help improve disturbed sleep. Lower-dose tricyclic and tricyclic-like antidepressants may help augment serotonin levels in the brain and improve the quality of sleep. Targeted analgesia may also involve a number of medications from a number of pharmacologic classes including anti-inflammatories, antiepileptics, muscle relaxants, and, in carefully selected patients, opioid medications.

KEY POINTS

- Pain management is the first step in restoration of function. Functional improvement is not always synonymous with alleviation of pain.
- Physical modalities (ultrasound, hot packs, etc.) may be of benefit in acute pain situations. Chronic use of these interventions should be discouraged.
- Exercise treatment is a helpful adjunct in treating patients with all types of pain disorders. Exercise programs should include flexibility, muscle strengthening, and aerobic exercise.
- Referral for comprehensive multidisciplinary and interdisciplinary treatment may be necessary for those patients failing to progress in the acute, subacute, and maintenance-based programs.
- The treatment of chronic pain may shift focus from removing an underlying organic disease to reducing disability through modification of environmental factors and cognitive processes.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 23

ACUPUNCTURE

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Acupuncture (*Jin jiu*) is an essential component of traditional Chinese medicine (TCM). The term "acupuncture" comes from the Greek words *acus* (needle) and *punctura* (puncture). Scientific evidence has demonstrated physiologic effects of acupuncture (AP) and electroacupuncture (EA) stimulation over the last four decades. AP consists of mechanical stimulation via needle insertion and thermal input by moxibustion. AP on the body surface is known as external therapy in contrast to internal therapy by intake of medication.

HISTORY AND THEORIES

Acupuncture can be traced back over 3000 years ago in China. The first written medical text on acupuncture was in the *Huang Di Nei Jing* (*The Yellow Emperor's Internal Classic*), written by Chi Po around 200 BC. AP was well publicized in the Western world thanks to *New York Times* writer James Reston's article in 1971. He described the firsthand experience of AP with an emergency appendectomy and perioperative care while accompanying President Nixon on a visit to China.

Taoist philosophy underlay the hypothetical framework of AP. *Tao* (way) was described by Lao-tse in the Tao Te Ching around 500 BC that assumed nature is constantly changing. Tao is the source of all creation and acts through two opposing but balancing forces: the yin and the yang. *Yin* implies dark, cold, rest, passivity, inward, decrease, wet, and female. *Yang* means bright, hot, activity, outward, increase, dry, and male. People exist within the tensions created by these two forces in a dynamic interaction with nature. Illness occurs when yin and yang fall out of balance and harmony. AP restores the balance by promoting yin and yang energy within organ systems.[1]

The concept of *qi* (vital energy) is fundamental to the practice of classic AP. Qi is the energy that flows through different "meridians" or channels that connect the internal body with the external environment. There are different types of qi that serve functions such as hereditary, protective, and nourishing energy. The network of meridians runs around the body while each meridian is associated with an organ system. There are 12 paired principal, 2 unpaired, and 8 extra meridians. Obstruction of qi may result in the disequilibrium of yin and yang that may manifest as pain or illness. The meridians emerge at the surface of body via acupuncture points (acupoints) where external stimulation may modulate the qi.

There are six pathologic factors that cause disease, including wind, cold, heat, dampness, dryness, and fire in TCM. The four steps in assessing a patient's symptoms are observation; listening and smelling; palpation; history-taking. The goal is to assess balance of yin and yang, and to gain insight into other symptoms. There are eight diagnostic principles for symptom classification including yin or yang, external or internal, cold or hot, and deficiency or excess.[2]

TECHNIQUE

No consensus exists about which technique of needle insertion in AP is most favorable or efficacious. Positions of patients may include prone or supine to allow adequate access for treatment and optimal comfort. A lateral decubitus or sitting position may also work. The skin is wiped with an alcohol pad and stretched prior to needle insertion to minimize discomfort. Tubular guides can assist needle insertion. The usual angle of insertion is perpendicular or oblique. Horizontal insertion is often used over face and chest.

There are more than 361 established *acupoints* that distribute along meridians. Acupoints are sites of low skin resistance and accessible for stimulation. An acupoint is identified by its meridian, a Chinese name and number. Acupoints are located through anatomic landmarks such as bony structures, muscles, and external features. The *cun*, a defined unit of measurement to locate acupoints via specific landmarks, is the distance between the joint creases of interphalangeal joints of a patient's flexed middle finger or equivalent to the width of patient's thumb.

The selection of acupoints may follow various schools of AP. Tender or trigger points are used as local acupoints. Distal points are selected according to involved meridians. The insertion of the needle is usually accompanied by "deqi" (obtaining qi) described as soreness, heaviness, and numbness around the site. There is feedback as if surrounding tissue is grabbing and holding the needle that confirms accurate placement. The disposable stainless steel needle consists of a body or shaft with a handle. Common sizes are 30 to 32 gauge with lengths ranging from 20 to 125 mm. Manipulation of needle depends on either an excess or deficiency state of the qi. AP stimulation can be accomplished manually or with EA stimulators. Moxa (a Chinese herb) or a heat lamp may be applied over needles. Patients need to avoid strenuous activities because generalized fatigue occurs at the beginning of AP.

SCIENTIFIC EVIDENCE AND MECHANISM OF ACUPUNCTURE

There are three domains of evidence in AP and EA that will delineate the modulation of pain in clinical practice.[3]

NEUROHUMORAL DATA

Animal studies of AP cannot be extrapolated to humans due to complex delineation between AP and stress-induced analgesia (SIA). Exposures to a variety of stressors induce subsequent analgesia. The SIA may be either nonopioid or opioid in nature (reversed by opiate antagonists and cross-tolerant with morphine). Maier and colleagues reported that 30 min of intermittent foot shock and 60 to 80 tail

shocks generate opioid SIA, while 3 min of continuous foot shock and 5 to 40 tail shocks produce nonopioid SIA.[4]

Pomeranz proposed that AP appears to cause release of various endorphins and monoamine neurotransmitters in both the peripheral nervous system and central nervous system (CNS). AP activates sensory nerve fibers in muscles and sends signals to the spinal cord. This activates other centers in the midbrain and hypothalamic–pituitary axis that cause the release of neuropeptides. Enkephalin and dynorphin are released at the level of the spinal cord and may block afferent pathways. Enkephalin produced at midbrain may stimulate the inhibitory raphe descending system and release monoamines serotonin and norepinephrine. These neurotransmitters may further block pain transmission in the spinal cord. Beta-endorphin released from the hypothalamic–pituitary axis may result in analgesia through both the systemic circulation and cerebrospinal fluid.[5]

Han demonstrated that EA of 2 Hz accelerates the release of enkephalin, beta-endorphin, and endomorphin; while EA of 100 Hz selectively increases the release of dynorphin. A combination of the two frequencies produced simultaneous release of all four opioid peptides resulting in maximal therapeutic effects.[6]

The popularity of the gate-control theory of pain by Melzack and Wall led to electrical stimulation therapies and the development of the transcutaneous electrical nerve stimulation unit (TENS). Electrical stimulation has been frequently employed for needle stimulation in AP and related techniques.[7]

NEUROIMAGING DATA

Updates in biophysiologic and imaging techniques offer enhanced evaluation of the sequential events following AP-induced stimulation. Functional MRI (fMRI) is a noninvasive technique that depends on differences in the relative concentration of oxygenated to deoxygenated hemoglobin within the brain in response to stimuli.

Functional MRI studies at *Hegu* (LI4) and *Zusanli* (ST36) indicated that the limbic system may play an important role for AP effects. Fang et al. conducted a clinical study on 10 healthy adults during manual AP at *Taichong* (LV3), *Xingjian* (LV2), *Neiting* (ST44), and a sham point on the dorsum of left foot. The results provided additional evidence that AP modulates the limbic-paralimbic-neocortical network. Fang and colleagues hypothesized that AP mediates analgesia, anxiolysis, and other therapeutic effects via an intrinsic neural circuit that plays a central role in the affective and cognitive dimensions of pain as well as in the regulation and integration of emotion and memory processing and autonomic, endocrine, immunologic, and sensorimotor functions.[8]

AP stimulation elicits deqi, a composite of unique sensations that is essential for clinical efficacy according to TCM. Manual acupuncture was performed in randomized order during fMRI in 42 acupuncture-naive, healthy adult volunteers. The most significant differences in deqi sensations between AP and tactile stimulation control were observed with aching, soreness, pressure and dull pain. Hui and colleagues provided scientific data on the characteristics of deqi response in AP and its association with distinct nerve fibers.[9]

NEUROMODULATION DATA

Basic and clinical studies have revealed that AP and related techniques trigger a sequence of events that may involve activation of c-fos within the CNS in addition to the release of neurotransmitters and endogenous opioid substances.[10]

In order to apply appropriate AP stimulation, diverse needle manipulation techniques are required. These manipulations are performed in many ways, such as twirling the needle or varying the insertion angle. Kim et al. designed a study to evaluate the antinociceptive effect of these manipulations to acupoint ST36 on formalin-induced pain in rats. Animals were divided into four groups and levels of pain were measured. Several pain-related gene expressions were investigated in the spinal cord using reverse transcriptase-polymerase, chain-reaction analysis. Needle manipulation suppressed the mRNA expression of pain-related genes such as Fos, opioid receptor-like 1, tachykinin 1, tachykinin receptor 1, mu-opioid receptor, and 5-hydroxytryptamine receptor 2A. Kim and colleagues proposed that needle manipulation enhanced analgesia by suppression of the transcription of pain-related genes.[11]

INDICATIONS

Acupuncture and related percutaneous neuromodulation therapies have been used to treat both acute and chronic pain. Wang and colleagues[12] critically examined prospective randomized controlled trials (RCTs) and suggested that AP and stimulation were effective in the short-term management of low back pain (LBP), neck pain, and osteoarthritis of the knee. However, short-term treatment with AP did not result in long-term benefits. The efficacy of AP for dental pain, colonoscopy pain, and intraoperative analgesia are inconclusive. Studies describing the use of AP during labor supported efficacy only during the early stages. The effects of AP on postoperative pain were inconclusive, depending on the timing of intervention and level of consciousness.[12]

ADVERSE EFFECTS, COMPLICATIONS, AND MEDICAL CONSENT

Witt and colleagues[13] conducted a prospective study of patients who received AP for knee or hip osteoarthritis pain, LBP, neck pain or headache, allergic rhinitis, asthma, or dysmenorrhea. A total of 229,230 patients received an average of 10 AP treatments. About 8.6% of patients reported at least one adverse effect and 2.2% reported one that required treatment. Common adverse effects were bleeding or hematoma (6.1%), pain (1.7%), and vegetative symptoms (0.7%). Two patients experienced a pneumothorax and the longest duration of a side effect was 180 days. A new medical consent form was developed based on ethical and legal aspects that consist of five modules: introduction to AP and moxibustion, risks of AP treatment, conditions that can increase the risk, doctor's statement, and consent. Witt and colleagues concluded that AP is a relatively safe treatment, and the new consent form could support both patients and professionals.[13]

White summarized the range and frequencies of significant adverse events associated with AP.[14] The most common were

pneumothorax and injury to the CNS. Over 60% of cases in AP-related infection had contracted hepatitis B, and the second most important AP-related infection was localized in the external ear due to auricular AP. There were miscellaneous events of seizures and drowsiness judged severe enough to cause traffic hazards. There were 12 primary reports of deaths. According to 12 prospective studies that surveyed more than a million treatments, the risk of a serious adverse event with AP is estimated to be 0.05 per 10,000 (0.0005%) treatments, and 0.55 per 10,000 (0.0055%) individual patients. White concluded that risk of serious events occurring in connection with AP is lower than in conventional medical treatments. The range of adverse events was broad and some events such as trauma and infection may be preventable.[14]

PRECAUTIONS AND RELATIVE CONTRAINDICATIONS

Pregnancy is a relative contraindication due to potential induction of premature labor. Bleeding diathesis and anticoagulant therapy may result in bleeding and hematoma formation. Steroids should be discontinued prior to therapy if possible due to attenuation of AP effects. Heavy meals and alcohol prior to AP is imprudent due to risk of vasovagal symptoms. Caution should be exercised when performing AP over the thoracic region in compromised patients. Care should be taken to avoid electromagnetic interference associated with EA and pacemakers.

CLINICAL DATA

Clinical research on AP has had a number of limitations including incomplete understanding of mechanisms, ineffective blinding of participants, unclear adequacy of regimen, difficulty in identification of suitable sham or placebo as controls, and the use of standardized treatment regimens rather than the individualized approach of AP in the real world. AP is most likely to benefit patients with back pain, neck pain, tension headache, migraine, and knee osteoarthritis (OA). Promising but less definitive data support acupuncture in shoulder pain, fibromyalgia, postoperative pain, and temporomandibular joint pain. AP has not been proven to improve pain from rheumatoid arthritis.[15]

HEADACHE

Linde and colleagues[16] studied all randomized trials with a postrandomization observation period of at least 8 weeks that compared the clinical effects of AP intervention with a control (treatment of acute headaches only or routine care), and a sham AP intervention or another intervention in patients with episodic or chronic tension-type headache. Eleven trials with 2317 participants met the inclusion criteria. Linde et al concluded that acupuncture could be a valuable nonpharmacologic tool in patients with frequent episodic or chronic tension-type headaches.[16]

Linde et al[17] also reviewed 22 trials with 4419 participants meeting the inclusion criteria. AP was associated with slightly better outcomes and fewer adverse effects than prophylactic drug treatment in these trials of migraine. They reported consistent evidence that AP provides additional benefit to treatment of acute migraine attacks only or to routine care. Linde and colleagues suggested that AP is at least as effective as or more effective than prophylactic drug treatment, and has fewer adverse effects for patients with migraine headaches.[17]

Li and colleagues[18] enrolled 175 patients with migraines and randomized them into three groups. Significant decreases in VAS scores from baseline were observed in the fourth hour after treatment when VAS was measured in patients who received either verum (or real acupuncture, that is, a needle intervention intended to have a specific therapeutic effect) or sham AP. Verum AP is more effective than sham AP, based on either Chinese or Western nonacupoints in reducing discomfort of acute migraine. Verum AP is effective in relieving pain and preventing migraine relapse or aggravation.[18]

NECK PAIN

Trinh and colleagues reviewed 10 trials that studied AP for chronic neck pain and concluded that there is moderate evidence that AP relieves neck pain better than some inactive treatments, sham treatments, and wait-list controls at short-term follow-up. For chronic neck disorders with radicular symptoms, there was moderate evidence that AP was more effective than a wait-list control. There was limited evidence that AP was more effective than massage.[19]

Fu and colleagues reviewed 14 studies in a systematic and meta-analysis review. In particular, the meta-analysis based on the primary outcome of short-term pain reduction found that AP was more effective than the control in the treatment of neck pain. AP was significantly more effective than sham AP for pain relief. These researchers conducted a quantitative meta-analysis and confirmed the short-term effectiveness and efficacy of AP in the treatment of neck pain.[20]

LOW BACK PAIN

Sherman and colleagues performed a secondary analysis of data for 638 participants in clinical trial comparing different types of AP to usual care to identify baseline characteristics that predicted responses to individualized, standardized, or simulated AP treatments. They identified significant predictors of improvement in back function and symptoms after AP were higher baseline levels of dysfunctions, receipt of an AP treatment, and nonuse of opioids. They found little evidence for the existence of subgroups of patients with LBP that would be especially likely to benefit from AP. Those persons with chronic LBP and more severe baseline dysfunction had the most short-term benefit.[21]

Yuan et al. published a systemic review of 23 trials ($n = 6359$) and reported that there is moderate evidence that AP is more effective than no treatment, and strong evidence of no significant difference between verum and sham AP for short-term pain relief. There is strong evidence that AP can be a useful supplement to certain forms of conventional therapy for nonspecific LBP. However, the effectiveness of AP compared with other forms of conventional therapies still requires further investigation.[22]

Inoue and colleagues conducted a RCT in 26 patients with LBP randomly allocated to either an AP group or a local anaesthetic injection group. They reported that both

injection and AP relieved pain but AP was superior for immediate and sustained effects. They suggested that AP is a useful treatment for LBP. The difference in the effects between AP and local anesthetic injection may be attributable to differences in the mechanisms of pain suppression.[23]

CONVENTIONAL TRANSCUTANEOUS VERSUS ACUPUNCTURE-LIKE TENS

Lower frequency stimulation is used (4 Hz) to achieve deqi as high frequency causes muscle spasms at intensity needed to produce the aching sensation. For conventional TENS, high frequency is used (50–200 Hz) for the optimum presynaptic inhibition through the Gate mechanism, but deqi is not achieved because muscle spasms prohibit the use of sufficient intensity to recruit type III nerves. AP-like TENS is superior to conventional TENS because it produces prolonged analgesia and thus does not have to be used continuously. One 30-min treatment session a day (or twice a week) is sufficient therapy using AP-like TENS for chronic pain.[24]

PERCUTANEOUS ELECTRICAL NERVE STIMULATION (PENS)

Hamza et al.[25] designed an RCT study to evaluate the effect of differing durations of electrical stimulation on the analgesic response to percutaneous electrical nerve stimulation (PENS) in 75 consenting patients with LBP. All patients received PENS for four different time intervals (0, 15, 30, and 45 min) in a random sequence over the course of 11-week study period. All active PENS treatments were administered using alternating frequencies of 15 and 30 Hz three times per week for 2 consecutive weeks. In contrast to the sham treatment, the health status survey short form revealed that electrical stimulation for 15 to 45 min three times per week for 2 weeks improved patient function. Hamza et al. recommended 30 minutes is the optimal duration of electrical stimulation with PENS therapy.[25]

Ghoname and colleagues[26] compared the effectiveness of PENS with TENS and flexion-extension exercise therapies in patients with LBP. They enrolled 29 men and 31 women with LBP secondary to degenerative disc disease. Ninety-one percent of the patients reported that PENS was the most effective in decreasing the LBP compared with the other three modalities. The PENS was significantly more effective in physical activity, quality of sleep, and sense of well-being. Ghoname et al reported that PENS was more effective than TENS or exercise therapy in providing short-term pain relief and improved physical function in LBP.[26]

OSTEOARTHRITIS

Joint OA is a major cause of pain and functional limitation. Few treatments are safe and effective in managing the pain and symptoms. AP has been proposed as a useful nonpharmacologic treatment for OA. Selfe and Taylor summarized 10 RCTs involving 1456 participants and provided updated evidence that acupuncture or EA was an effective treatment for pain and physical dysfunction associated with knee OA.[27]

Ahsin et al.[28] compared plasma beta-endorphin and cortisol levels with self-assessment scores of intensity of pain before and after 10 days of EA treatment in patients suffering from chronic pain as a result of knee OA. There were 40 patients of both genders with primary knee OA recruited into a single-blinded, sham-controlled study. Ahsin and colleagues concluded that EA resulted in an improvement in pain, stiffness, and disability. Of clinical importance is that improvements in objective measures of pain and stress/pain associated biomarkers were shown to be greater than those of a sham treatment. Ahsin et al. demonstrated that acupuncture resulted in physiologic changes with a significant rise in plasma beta-endorphin and a significant fall in plasma cortisol beyond placebo effects.[28]

Manheimer and colleagues[29] studied 16 trials involving 3498 patients with knee OA (12), hip OA (3), and hip and/or knee OA (1). AP used as an adjuvant to the exercise-based physiotherapy program did not result in greater improvement than the exercise program alone. These researchers concluded that sham-controlled trials show statistically significant benefits; however, these benefits are small and probably due at least partially to placebo effects from incomplete blinding. Waiting list–controlled trials revealed statistically significant and relevant benefits, which may be due to expectation or placebo effects.[29]

POSTOPERATIVE PAIN

Wu and colleagues[30] recruited 60 women who had spinal anesthesia during cesarean section and were randomly assigned to the control, AP, and EA groups. After the operation, the subjects received either AP or EA on bilateral acupoints, *San Yin Jiao* (Sp6), and patient-controlled analgesia (PCA). The first time of requesting morphine, the frequency of PCA demands in 24 hr, and the doses of PCA used were recorded. The results revealed that the AP and EA groups could delay the time of requesting morphine up to 10 to 11 min when compared with the control group. The total dose of PCA used within the first 24 hr was 30% less in the AP and EA groups when compared with the control group, which was statistically significant. However, there was no significant difference between the AP and EA groups. Wu et al. showed that the application of AP or EA could definitely delay the time of requesting any pain medication after cesarean section and decrease the requirement of PCA within the first 24 hr.[30]

MYOFASCIAL PAIN AND TRIGGER POINT

Melzack et al. reported a remarkably high degree (71%) of correlation between trigger points and acupuncture points for pain on the basis of two criteria: spatial distribution and the associated pain pattern. This close correlation suggests that trigger points and acupuncture points for pain, although discovered independently and labeled differently, represent the same phenomenon and can be explained in terms of the same underlying neural mechanisms.[31] Dorsher updated the studies and confirmed the conceptual comparison of trigger points to classical acupoints in pain and clinical correspondence was likely 95% or higher. Although separated by 2000 years temporally, the acupuncture and myofascial pain traditions have fundamental clinical similarities in the treatment of pain disorders.[32]

Dorsher examined whether myofascial referred pain data can provide independent physiologic evidence of AP meridians. Trigger point regions were subdivided from prior validated trigger point region–classical acupoint correspondence results into subsets according to the 12 AP organs of their anatomically corresponding acupoints. For all 12 subsets of trigger point regions, their summed referred pain patterns accurately predicted the distributions of corresponding AP meridians, particularly in the extremities. Dorsher demonstrated that myofascial referred pain data may provide the physiologic evidence of AP meridians.[33]

DIFFERENT BACKGROUNDS IN ACUPUNCTURE PROVIDERS

Kalauokalani and colleagues[34] collected descriptive data comparing physician and nonphysician acupuncturists. Physicians use a mixture of styles including French energetic and neuroanatomic approaches for needle placement. In contrast, most nonphysician licensed acupuncturists use the TCM approach. There was a high correlation between physician and nonphysician acupuncturists regarding acupoint selection for LBP despite differences in predominant styles of AP. In addition to AP needling, physicians also use other medical treatments; whereas nonphysicians employ various TCM treatments as adjuncts to AP. Further research is necessary to determine the impact of different AP credentials and styles on LBP treatment outcomes and cost-effectiveness.[34]

FUTURE DIRECTION: UPDATES SINCE THE NATIONAL INSTITUTES OF HEALTH CONSENSUS STATEMENT

The National Institutes of Health (NIH) organized a conference of experts to evaluate the available literature in 1997. While designing studies to evaluate efficacy remain a challenge, AP was widely practiced in the United States for treatment of postoperative- and chemotherapy-related nausea and vomiting and dental pain. Other promising results have been seen in headache, LBP, asthma, menstrual cramps, fibromyalgia, and myofascial pain.[35]

The Society for Acupuncture Research (SAR) hosted an international conference in November 2007 for the 10th anniversary of the landmark NIH Conference on AP in 1997. More than 300 acupuncture researchers, practitioners, students, funding agency personnel, and health policy analysts from 20 countries attended. The conference concluded that mechanistic models for AP effects have focused on the effects of AP needle stimulation on the nervous system, muscles, and connective tissue. Future iterative testing, expanding, and merging of non-mutually exclusive mechanistic models could potentially lead to a better understanding of the physiology of manual and electrical acupuncture.[36]

The researchers in the German trials concluded that AP is effective in chronic pain, although exact selection of acupoints may play only a limited role. The placebo aspect of AP was inconclusive due to design flaws of available studies. Although AP did not show a benefit in treating knee OA or LBP when compared to the sham group, AP was better than a wait-list control and standard of care. AP may work well in stand-alone clinics for chronic cancer-related pain. Further establishment of convincing benefit will integrate AP into acute treatment in more comprehensive oncology programs.[37]

CONCLUSION

Although the actual incidence of adverse effects has yet to be identified, AP appears to cause low rates of adverse effects or complications. Despite current data regarding its efficacy, AP appears to provide only temporary benefits. AP continues to play an important role as an adjunct to integrative pain management. Most of the current literature on AP consists of anecdotal and biased information from case reports to clinical studies with suboptimal designs to assess efficacy. There is an enormous demand for RCTs to explore integration of AP to acute and chronic pain management. Ideally, translational studies on acupuncture are based on advances in bench research.

KEY POINTS

- AP and related techniques trigger a sequence of events that involves the release of endogenous opioid-like substances, monoamine neurotransmitters (e.g., serotonin and norepinephrine), expression of c-fos in CNS, and potential reversal of neuroplasticity in animal models.
- EA of 2 Hz accelerates the release of enkephalin, beta-endorphin, and endomorphin, while EA of 100 Hz selectively increases the release of dynorphin.
- PENS and AP-like TENS may present potential application in both acute and chronic pain management.
- Current data regarding the clinical efficacy of AP and related techniques has provided only short-term benefits in chronic pain management.
- AP is most likely to provide benefit in patients with LBP, neck pain, tension headache, migraine, and OA of the knee.
- Promising but less definitive data supports AP for myofascial pain, fibromyalgia, postoperative pain, dental pain, shoulder pain, and temporomandibular joint pain.
- AP and related techniques may be considered for premenstrual syndrome, dysmenorrhea, pregnancy-related conditions, and early stages of labor.
- There is insufficient evidence for AP effectiveness for pain management in the areas of neurologic conditions, mental health, functional bowel disorders, and rheumatoid arthritis.
- Nausea, pallor, dizziness, and syncope are vasovagal responses to AP. Drowsiness and generalized fatigue are common, especially in the beginning.
- Bleeding, hematoma, and needle discomfort may occur in AP; pneumothorax could be a serious complication requiring vigilant and timely treatment.
- There is no current standard of care in frequency, number, or optimal duration of AP treatment to determine success or failure in pain management.

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CHAPTER 24

Psychological Interventions for Chronic Pain

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Cognitive, affective, and social factors have long been recognized as influencing the experience of pain. Beecher[1] observed that the personal meaning of pain was an important determinant of the pain complaints he observed in soldiers wounded in World War II. Later, the work of Melzack and Wall[2] on the "gate-control" theory of pain stimulated much interest in the multidimensional and subjective aspects of the pain experience. The pioneering work of Fordyce and colleagues[3] detailed the role social and environmental factors play in the way an individual expresses pain behaviorally. These historical developments supported by research data influenced the definition of pain promulgated by the International Society for the Study of Pain, which includes both sensory and emotional factors in the experience of pain.[4] The literature in the role of psychological factors in the experience of pain was summarized in Turk, Meichenbaum, and Genest's seminal work that detailed the application of cognitive-behavioral interventions in the management of chronic pain.[5]

The wide acceptance of psychological interventions as a treatment modality is based on two complementary lines of research. First, early studies of laboratory pain demonstrated the role of psychological factors in determinng the level of reported pain and pain thresholds. Second, the psychotherapy literature demonstrated the positive impact that psychological interventions can have on many areas of functioning and quality of life. The benefit of psychological treatments among individuals with chronic pain is particularly clear for anxiety and depression, which are two emotional states shown to influence the experience of pain.

This chapter provides an overview of psychological interventions utilized for chronic pain, focusing primarily on the interventions that have been empirically tested through the use of clinical trials. Targets for psychological treatment include (1) reducing pain and pain-related disability; (2) treating comorbid mood disturbances, particularly depression; (3) increasing perceptions of control and self-efficacy; (4) increasing health behaviors, such as appropriate medication use, exercise/activation, sleep habits; and (5) addressing pain-related psychosocial factors, such as the impact of pain on family functioning and work life. This chapter provides pratitioners with an overview of the evidence-based psychological interventions for the management of chronic pain. Specialized training is necessary to developing competency in applying these strategies.

BEHAVIORAL INTERVENTIONS

Learning theory, incorporating the principles of operant conditioning (e.g., reinforcement and punishment), provides the theoretical basis for behavioral interventions in persons with chronic pain.[3] In the case of acute pain, environmental and interpersonal contingencies have limited time to shape the pain experience. However, in the case of chronic pain the prolonged nature of the experience provides substantial opportunities for pain behaviors to be reinforced and maintained. Many of the behavioral techniques used in pain management are adapted from the strategies used extensively in managing anxiety, depression, and health behaviors.

OPERANT INTERVENTIONS

In an operant model of pain, the primary focus of intervention is the behavior of the patient. These behaviors can include either verbal expressions of pain (e.g., complaints of pain or requests for medication), gross motor movements that are indicators of pain (e.g., grimacing or limping), or avoidance of potential pain-generating activities. These observable behaviors are subject to the principles of operant conditioning, which state that a given behavior is highly influenced by the consequences of that behavior. Reinforcing consequences increase the likelihood that a behavior will occur in the future and neutral or punishing consequences decrease the likelihood that a behavior will occur. For example, when a patient grimaces and a loved one responds by expressing concern, grimacing may occur more frequently in the future when that loved one is present. In this case, the social attention in the form of concern reinforces the grimace. Alternatively, pain can serve as punishment for engaging in an activity. If an individual experiences pain during or following standing or walking, this is likely to decrease the frequency of these activities.

The goal of operant interventions is to decrease learned pain behavior and replace these maladaptive responses that are assocaited with the sick role with more adaptive behaviors.[3] Operant interventions ideally occur in an environment where there is the opportunity to control the social consequences of pain behaviors and shape new more adaptive behaviors. Historically, most operant pain programs are based on inpatient units where this level of control is possible; however, operant conditioning interventions can be incorporated into outpatient treatment as well. "As needed" pain medication prescriptions are changed to fixed time intervals in order to remove the contingent relationship between complaints of pain (i.e., the pain behavior) and pain relief (i.e., the reinforcer). Pain complaints are largely ignored and more adaptive behaviors, including attending physical therapy and increasing activity level, are socially rewarded (i.e., reinforced).

Pacing and behavioral activation are important components of operant behavioral pain management programs. When individuals push their activity level to the point of

pain exacerbation, they are more likely to decrease their activity over time. Operant programs designed to avoid this negative pattern have three components:

1. Establish a baseline. A specific target behavior is identified, such as sitting at a desk. A baseline is established by measuring for several days the amount of time the individual can sit at the desk before exacerbation of back pain—for instance, an average 30 min.
2. Time-contingent activity is begun. Rather than having the individual sit until the pain is intolerable and then stop, an initial goal is set at 70% to 80% of the baseline level, such as 20 to 24 min. The individual would start by sitting no more than 20 min, thus avoiding the punishment of pain exacerbation and obtaining the social reinforcement associated with success.
3. The level of the behavior is gradually increased, usually no more than 5% per week with patients instructed to use time, not pain, as an indicator for stopping the activity. Over a period of weeks, the individual would increase the comfortable duration of sitting to perhaps 60 min without shifting positions or standing up.

This process of gradually increasing the nature, frequency, or duration of a behavior is called "shaping." The goal of such an intervention is to increase the adaptive behavior while managing the consequences, which include removing any punishment (e.g., pain) and introducing reinforcement (e.g., experience of success, social attention). The involvement of the significant other or family in treatment is desirable, so they can be taught the principles for shaping behavior. Further, inclusion of others (i.e., family, friends, caregivers) in treatment can facilitate generalization of treatment gains from the inpatient setting to the home environment.

RELAXATION INTERVENTIONS

An extensive literature documents the benefits of developing a relaxation response, particularly in the areas of anxiety and stress management. The goal for most relaxation techniques is nondirected relaxation accomplished through two common components: first, repetitive focus on a word, body sensation, or muscle activity; and second, a passive attitude toward thoughts unrelated to the attentional focus.[5,6] Common methods used for teaching relaxation include systematically tensing and relaxing specific muscle groups (e.g., progressive muscle relaxation), focusing on breathing and enhancing diaphragmatic breathing, and using guided imagery. A psychophysiologic model of pain, which has received some empirical support,[7] suggests that stress or pain leads to subtle increases in muscle tension, which can exacerbate pain at the site of an injury. A primary goal of relaxation training is to break the cycle between pain and muscle tension. Expert panels[6] and meta-analyses[8] summarized empirical support for the use of these techniques in pain management and recommended the broad integration of relaxation techniques with biomedical interventions for pain management.

BIOFEEDBACK

Biofeedback provides the individual with detailed information about a physiologic process that is typically not within the individual's awareness. Through this detailed feedback, the individual can learn voluntary control over usually involuntary processes. Biofeedback for pain management usually entails providing feedback about muscle tension, typically using electromyographic (EMG) feedback from the site of the pain or a standard location such as the frontalis muscles, or feedback about skin temperature, typically using thermistors attached to the fingers. Empirical support for the efficacy of biofeedback for pain management exists for several specific painful conditions, including Raynaud's phenomenon, tension and migraine headaches, vulvar vestibulitis, and low back pain. Although widely used in the field of pain medicine, particularly in conjunction with relaxation training, the empirical support for its specific efficacy beyond the general effects of relaxation strategies has not been widely demonstrated except in the treatment of headaches.[6] For patients who have difficulty recognizing the physiologic changes that may accompany pain or stress, biofeedback may be useful in assisting them in recognizing these changes. Further, patients who are drawn to technology, or conceptualize their pain experience as a primarily physical phenomenon, may prefer a biofeedback approach to relaxation training.

COGNITIVE-BEHAVIORAL INTERVENTIONS

The demonstration that cognitive and emotional factors influence the experience of pain has encouraged the application of cognitive-behavioral theory (CBT) and treatment to the management of chronic pain.[5] These interventions typically include components of the behavioral model, particularly relaxation training, and some components of operant conditioning. However, an emphasis is also placed on cognitive factors, such as attitudes and beliefs that underlie maladaptive emotional and behavioral responses to pain.[9] Expert panels[6] and meta-analyses[8] have found good evidence for the use of cognitive-behavioral interventions for chronic pain management.[8,10] The strongest support is in the treatment of individuals with low back pain, rheumatoid arthritis, and osteoarthritis pain.[10] CBT has been shown to have a positive impact on pain intensity, pain-related interference, health-related quality of life, and depression among individuals with chronic pain.[8]

COPING SKILLS TRAINING

Patients engage in a range of coping responses to manage pain and related stressors. Some coping responses (e.g., activity avoidance) are associated with increased distress and suffering, while other coping responses (e.g., problem solving)[5] are linked to better emotional and physical functioning. Specific coping skills are highly adaptive and effective for individuals with chronic pain, often including some of the strategies outlined above, particularly relaxation and pacing of activity level. Primary goals of coping skills training are to increase perceptions of pain as a controllable experience and decreasing the use of maladaptive coping

strategies. In this approach, the emphasis is on skill development and refinement. In the case of skill development, a new skill is introduced and patients are encouraged to develop and refine the skill during low pain periods before attempting to implement the coping skill during an actual period of pain exacerbation. The skill is shaped over time, so that the skill is gradually applied to increasingly challenging (i.e., painful) episodes as the individual becomes more proficient in that skill. A similar approach is taken to the application of many pain coping skills, including cognitive or behavioral distraction, relaxation, pacing of activities, and the appropriate use of social support. Attention is paid to factors that increase or decrease pain and these factors guide the application of pain coping skills.

COGNITIVE RESTRUCTURING

Cognitive restructuring focuses on the role of cognitive factors, such as attitudes, thoughts, and beliefs, in determining emotional and behavioral responses to pain. These interventions challenge negative self-talk, such as catastrophizing (e.g., "I can't stand the pain anymore"), and replace these self-statements with more positive statements that reduce negative affect, emphasize control, and encourage adaptive coping (e.g., "This is a challenge that I have faced before and I can handle it this time."). Catastrophizing is a particularly maladaptive response to pain that has been shown to correlate with depression and disability.[9] In the context of treatment, patients are frequently asked to monitor their thoughts about their pain, or pain-related situations, identify negative thoughts, and generate more accurate, adaptive thoughts to replace the negative thoughts. The emphasis is on balanced thinking, not necessarily positive thinking. This self-monitoring process is supplemented with more in-depth discussions of the underlying attitudes and beliefs contributing to the negative thoughts.

HYPNOSIS

Hypnosis is another tool used for pain management that targets beliefs and attitudes about pain and aids in having more control over the pain experience. Hypnosis for pain management usually begins with an induction consisting of suggestions for focused attention and relaxation. This is usually followed by specific suggestions to alter how the pain is viewed or experienced.[11] Often, the treatment includes posthypnotic suggestions that the benefits experienced during the session—decreased pain intensity—will last after the session or that the individual will experience increased comfort when engaging in specific behavior such as taking a deep breath or touching the painful site. The goal when working with people with chronic pain is to teach them self-hypnosis so they can use the skill to reduce pain and discomfort outside of the treatment session. Hypnosis has been most widely applied and studied with pain due to cancer, and expert panels concluded that the use of hypnosis reduces chronic pain due to malignancies.[6] There are also data supporting its efficacy in treating pain due to irritable bowel syndrome, temporomandibular joint disorders, and tension headaches. Meta-analyses indicate that hypnosis can lead to significant reductions in pain that are similar to those experienced with the relaxation techniques described above. It is not clear whether hypnosis is effective beyond what is seen in these treatments.[11]

SELF-MANAGEMENT AND PEER SUPPORT

Self-management (SM) group interventions, based on the principles of CBT, have gained widespread application with chronic conditions marked by pain, distress, and functional impairment. Key elements in self-management include developing knowledge about the health condition, self-monitoring progress, acquiring relevant skills, and problem solving.[12] SM interventions have improved outcomes in many conditions, including rheumatologic diseases,[13] fibromyalgia,[14] and depression.[15] Because SM interventions are often provided in a group setting, they incorporate social support and peer interaction that may facilitate behavior change and maintain treatment gains. SM interventions can be provided by professionals, laypersons, or peers. More recently SM interventions using Internet and telecommunication technologies demonstrated improvements in pain and health distress and reduced health care utilization in persons with chronic low back pain.[16] SM interventions are best conceptualized as one component of a multidisciplinary pain treatment plan.

MULTIDISCIPLINARY TREATMENT

There is significant evidence to support the use of multidisciplinary approaches that include psychological intervention, compared to single-discipline or unimodal approaches, particularly when the focus is on improving long-term outcomes of mood, daily functioning, return to work, health care utilization, and quality of life.[10,17] The use of a multidisciplinary approach may also extend initial treatment gains over several years.[10] While psychological intervention is an integral component of multidisciplinary pain management, it may be particularly important to target individuals whose psychological and behavioral characteristics may prevent them from benefitting from other aspects of the treatment plan. Individuals who are highly distressed, see their pain as uncontrollable, have highly negative life events, perceive themselves to be disabled, and have low readiness to engage in self-management are all at high risk to respond poorly to treatment.[18]

Attention to psychosocial health is a responsibility shared by all members of the multidisciplinary pain team beginning with the patient and family and including clinicians who are not formally identified as mental health providers. Early detection and referral for potential problems is a primary responsibility of physicians and other providers who are likely to encounter patients early in their pain career, as there is evidence that early intervention for psychological issues enhances outcome.[19] Physicians who are managing chronic pain patients need to have an established relationship with a psychologist who has pain expertise. Referral to a specific provider, along with an explanation to the patient that places the referral within the biopsychosocial model of pain and indicates how the psychologist may be helpful to the patient will facilitate follow-through.

INPATIENT VERSUS OUTPATIENT CARE

While there are data to support the utility of multidisciplinary treatment for chronic pain,[17] data to guide the clinician in determining whether the patient requires admission to an inpatient pain program are sparse. The decision to pursue admission to an inpatient program is based on clinical assessment of the patient and his or her environmental circumstances. Inpatient chronic pain programs offer the advantage of increased medical attention, close monitoring of positive and negative health behaviors, and a structured treatment setting. Inpatient admission maybe appropriate for patients with nonmalignant pain of 6 months or more and (1) who require detoxification, (2) have major functional disabilities, (3) need intensive and extensive psychological or behavioral therapy, (4) need temporary removal from a detrimental home situation to refocus their lives away from the pain, and (5) have failed conventional methods of treatment. As part of admission planning both medical and psychological evaluations should be completed on an outpatient basis.

SUMMARY

A number of psychological interventions have been empirically demonstrated to reduce pain and suffering in patients with a wide variety of chronic pain syndromes. A typical course of treatment usually includes many of the behavioral and cognitive approaches detailed here and the specific approaches utilized are tailored to the needs of the patient. These interventions are usually part of a multidisciplinary approach and are provided in conjunction with other pain interventions (e.g., medication, physical therapy). Although many patients with chronic pain may benefit from psychological intervention, certain subpopulations—those who are highly distressed, see their pain as uncontrollable, have highly negative life events, perceive themselves to be disabled, have low readiness to engage in self-management, and have problematic medication use (dose escalation, misuse, or underuse)—are likely to need psychological intervention to maximize treatment gains. As research develops, there will be a growing emphasis on matching psychological pain interventions with patient characteristics.[20] Based on existing literature, certain pain disorders (e.g., headaches) may be highly responsive to specific psychological interventions such as biofeedback, and these treatments should be considered a standard part of medical management. For individuals who are not suitable candidates for some medical or pharmacological treatment (e.g., chronic opioid therapy for the recovering substance abuser), psychological treatment may be considered an essential first-line treatment option. Modern pain theory, and the existing evidence base, indicate that psychological intervention should be a routine part of chronic pain management rather than a treatment of last resort.

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CHAPTER 25

Substance Use Disorders and Detoxification

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SUBSTANCE USE AND CHRONIC PAIN

The prevalence of substance use disorders in patients with chronic pain is higher than in the general population.[1] Over the past two decades, opioid analgesic prescriptions have increased to patients with chronic nonmalignant pain.[2-3] In a study of primary care outpatients with chronic non-cancer pain who received at least 6 months of opioid prescriptions during 1 year, behaviors consistent with opioid abuse were recorded in approximately 25% of patients.[4] Almost 90% of patients attending a clinic specializing in pain management were taking medications and 70% were prescribed opioid analgesics.[5] In a review of substance dependence or addiction in patients with chronic pain, the prevalence ranged from 3% to 19% in high-quality studies.[6,7] Another more recent review found that addiction in patients with chronic non-cancer-related pain ranged from 0% to 50% of patients.[8] Specifically for opioid use disorders, one study showed that the frequency of opioid use disorders was four times higher in patients receiving opioid therapy compared with general population samples (3.8% vs. 0.9%). In contrast, two studies found the prevalence of chronic pain in patients who received methadone maintenance therapy for the treatment of opioid dependence ranged from 55.3% to 61.3%.[9,10]

Determining the presence of a substance use disorder usually involves the problem of how to evaluate the patient with chronic pain who is prescribed controlled substances with abuse potential.[11] Individuals with substance use disorders are more often initiated and continued on opioid therapy for non-cancer pain than others. Rates of opioid use were four times higher for those with substance use disorders than those without substance use disorders, and were seven to eight times higher for the subset with an opioid dependence diagnosis. Those with substance use disorders were much more likely to receive higher doses, more days' supply, and more potent Schedule II drugs.[12] Other studies of opioid therapy have found that patients who developed problems with their medication all had a history of substance abuse.[13] Inaccurate and underreporting of medication use by patients complicates assessment.[14] However, in patients with chronic pain who developed new substance use disorders, the medications prescribed by their physicians were commonly involved.[15] A prospective survey of chronic pain patients abusing prescription opioids showed 91% purchased prescription opioids through illegitimate sources.[16]

Comorbid psychiatric disorders also play a role in the complexity of treating patients with chronic pain. Psychiatric disorders are associated with increased physical symptoms, aberrant drug behaviors and linked to increased opioid use.[17-19] For example, pain arising from chronic medical disorders are rated as more severe in the presence of major depression.[20] A prospective trial of 6349 participants showed that common psychiatric disorders, such as depression, anxiety, and drug abuse disorders, predict initiation and ongoing regular use of opioids in patients with chronic pain.[21]

The causes and onset of substance use disorders have been difficult to characterize in relationship to chronic pain. During the first 5 years after the onset of chronic pain, patients are at increased risk for developing new substance use disorders and additional physical injuries.[22] This risk is highest in patients with a history of substance abuse or dependence, childhood physical or sexual abuse, and psychiatric comorbidity.[23] Chronic pain is associated with long-term substance use after detoxification. Therefore addressing and treating patients for their chronic pain could improve their long-term outcome.[24] In a study of chronic low back pain patients, 34% had a substance use disorder, yet in 77% of cases the abuse was present before the onset of their chronic pain.[25] The mechanisms of relapse into substance abuse are not well understood and probably involve multiple factors; however, a cycle of pain followed by relief after taking medications is a classic example of operant reinforcement of future medication use that eventually becomes abuse. Careful monitoring of patients is essential to prevent this complication of the treatment of chronic pain. Research in patients with substance abuse has demonstrated abnormalities in pain perception and tolerance. An increased sensitivity to pain and the reinforcing effects of relieving pain with substance use suggest a different mechanism for the development of substance abuse in patients with chronic pain.

Patients with substance use disorders have increased rates of chronic pain and are at the greatest risk for undertreatment with appropriate medications and subsequent self-medication with illicit drugs.[26] Almost a quarter of patients admitted to inpatient residential substance abuse treatment and over a third of patients in methadone maintenance treatment programs reported severe chronic pain, with almost half of the inpatients and two-thirds of the methadone maintenance patients suffering pain-related interference in functioning.[26] In another study of methadone maintenance therapy, patients with pain were more likely to overuse both prescribed and nonprescribed medications.[9] Higher doses of methadone have been used in these patients with chronic pain, compared to patients without chronic pain and on methadone maintenance.[9,10] Patients with substance abuse and back pain were less likely to complete a substance abuse treatment program compared to those without pain.[27] Ethical principles such as beneficence, quality of life, and autonomy can provide particularly useful guidance for the use of chronic opioid therapy, recognizing that benefits should be optimized in a context of risk management.[28]

RISKS OF PHARMACOLOGIC TREATMENT FOR CHRONIC PAIN

OPIOIDS

Opioids are effective in the treatment of chronic nonmalignant pain, as demonstrated in randomized placebo-controlled trials, in reducing pain, pain-related disability, depression, insomnia, and physical dysfunction.[29] Since chronic pain is an independent risk factor for substance use after detoxification, treating the patient's pain may improve long-term outcome.[24] A recent review of the guidelines for neuropathic pain treatment suggests opioids as second-line medications. They may be considered first-line agents in certain circumstances (i.e., acute neuropathic pain, during titration periods with a first-line agent and episodic exacerbations of neuropathic pain).[30] Most experts agree that opioids with slow onset of action and longer duration of action are preferred to minimize the initial euphoria and interdose withdrawal symptoms. Extended-release oral medications and transdermal routes of administration decrease these qualities of opioids. A constant rather than intermittent, "as needed" schedule should be followed, keeping the time between dosages and the individual dose amounts consistent. Opioid dependence is mediated by the actions and interactions of opioid receptors.[31] Mesolimbic dopaminergic projections to the nucleus accumbens have been implicated in the development of psychological dependence. In contrast, physical dependence on opioids is probably due to noradrenergic activity in the locus ceruleus.

However, the treatment of nonmalignant chronic pain with opioids remains a subject of considerable debate with fears of regulatory pressure, medication abuse, and the development of tolerance, creating a reluctance to prescribe opioids and, subsequently, their underutilization. Fortunately, the prescribing of long-term opioids for the treatment of chronic nonmalignant pain syndromes has increased despite dramatic coverage by the public press of the various forms of abuse of these medications.[32] Chronic pain conditions may facilitate the development of tolerance to opioid analgesia.[33] The loss of analgesia over time can have many causes and should be carefully evaluated to determine its etiology. It is most likely due to disease progression or other changes in the patient's condition such as the development of delirium. While tolerance does occur and several mechanisms have been described, it is relatively rare in clinical practice.[34,35] The incidence of analgesic tolerance is lower with more potent opioids such as fentanyl, presumably because these agents are more receptor-specific and fewer receptors are needed to produce an analgesic effect. Tolerance to different opioid effects emerges at different rates, with constipation the most likely to persist, suggesting receptor-related differences.

Predicting which patients are at risk for developing an addiction to opioids has been studied. Demographic factors have not been consistent. Strong predictors include personal history of illicit drug use and alcohol abuse.[36-39] Self-reported craving has also been shown to be a possible risk factor.[40] Interestingly, one study showed that there was no relationship between pain scores and opioid misuse.[38] Comorbid psychiatric and chronic pain disorders put patients at risk for opioid addiction.[17-19] One prospective trial showed worse functional outcomes at 1 year for patients with disabling spinal disorders who were prescribed opioids.[41]

BENZODIAZEPINES

Benzodiazepines such as diazepam and clonazepam are commonly prescribed for insomnia and anxiety in patients with chronic pain, but no studies have demonstrated any benefit for these target symptoms.[42,43] Only a limited number of chronic pain conditions such as trigeminal neuralgia, tension headache, and temporomandibular disorders were found to improve with benzodiazepines.[44] Clonazepam has been reported to provide long-term relief of the episodic lancinating variety of phantom limb pain.[45] A recent extensive review failed to conclude that benzodiazepines significantly improved spasticity following spinal cord injury and no evidence was found to support the analgesic efficacy of barbiturates.[46,47] Benzodiazepines have been used for the detoxification of patients with chronic pain from sedative/hypnotic medications and were superior to barbiturates for minimizing symptoms of withdrawal.[48] Higher levels of withdrawal symptoms during detoxification predicted relapse to future use of benzodiazepines.[49]

Benzodiazepines also cause cognitive impairment as demonstrated by abnormalities on neuropsychological testing and EEG.[50,51] In patients with chronic pain use of benzodiazepines and not opioids was associated with decreased activity levels, higher rates of healthcare visits, increased domestic instability, depression, and more disability days.[52] Combining benzodiazepines with opioids may cause additional problems. In methadone-related mortality, almost 75% of deaths were attributable to a combination of drug effects and benzodiazepines were present in 74% of the deceased.[53,54] Benzodiazepines have been associated with exacerbation of pain and interference with opioid analgesia, which is mediated by the serotonergic system.[55-57] Benzodiazepines also increase the rate of developing tolerance to opioids.[58]

DIAGNOSIS OF SUBSTANCE USE DISORDERS

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association defines both substance abuse and dependence as maladaptive (behavioral) patterns of substance use leading to clinically significant impairment or distress. Substance abuse must be accompanied by any of the following: interpersonal problems, legal problems, failure to fulfill major role obligations, and recurrent substance use in hazardous situations. Substance dependence is distinguished from abuse by more than simply a continuum of severity. In contrast to abuse, substance dependence is manifested by tolerance, withdrawal, using the substance in larger amounts or over a longer period than was intended, persistent desire or unsuccessful efforts to decrease or control substance use, spending large amounts of time in activities necessary to obtain the substance, the giving up or reduction of important activities because of substance use, and continued substance use despite knowledge of having physical or psychological problems caused or exacerbated by the substance. Making the

distinct diagnosis of dependence is important because it reliably predicts more severe medical sequelae, poorer treatment outcomes, higher relapse rates, and worse overall prognosis.

Recent efforts have attempted to standardize diagnostic criteria and definitions for problematic behaviors of medication use and substance use disorders across professional disciplines (Table 25-1).[59] The core criteria for a substance use disorder in patients with chronic pain include the loss of control in the use of the medication, excessive preoccupation with the medication despite adequate analgesia, and adverse consequences associated with the use of the medication.[60] Items from the Prescription Drug Use Questionnaire that best predicted the presence of addiction in a sample of patients with problematic medication use were (1) the patients believing they were addicted, (2) increasing analgesic dose/frequency, and (3) a preferred route of administration. The diagnosis of addiction in the patient with chronic pain must demonstrate certain drug-taking behaviors that interfere with the successful fulfillment of life activities. Access to opioids may not be a specific problem because a physician has been prescribing them. If addiction is present, however, the patient may fear that opioid access will be limited and therefore try to conceal any problematic use of the medication. The presence of maladaptive behaviors is emphasized to diagnose addiction because physical dependence and tolerance should be recognized as normal physiologic phenomena.

Increased function and opioid analgesia without side effects, not the avoidance of high doses of opioids, are the goals of treatment.[32]

The evaluation of a patient suspected of misusing medications should be thorough and include an assessment of the pain syndrome as well as other medical disorders, patterns of medication use, social and family factors, patient and family history of substance abuse, and a psychiatric history. Reliance on medications that provide pain relief can result in a number of stereotyped patient behaviors that are often mistaken for addiction. Persistent pain can lead to increased focus on opioid medications. Patients may take extraordinary measures to ensure an adequate medication supply even in the absence of addiction. This may be manifested as frequent requests for higher medication doses and larger quantities of medication or seeking medication from additional sources. Patients understandably fear the reemergence of pain and withdrawal symptoms if they run out of medication. Drug-seeking behavior may be the result of an anxious patient trying to maintain a previous level of pain control. In this situation the patient's actions define pseudoaddiction that results from therapeutic dependence and current or potential undertreatment but not addiction.[61,62] These behaviors resolve once adequate opioid therapy is prescribed.

In patients with higher risk of addiction, prevention begins with a treatment contract to clarify the conditions under which treatment with opioids will be provided. Elements of a contract emphasize a single physician being responsible for the prescription of the medication, and, in advance, describe for the patient all the conditions under which continued use of opioids would be inappropriate. Under optimal circumstances opioid contracts attempt to improve compliance by distributing information and utilizing a mutually designed, agreed-upon treatment plan that includes consequences for aberrant behaviors and incorporates the primary care physician to form a "trilateral" agreement with patient and pain specialist.[63,64] When there is concern that a patient will have difficulty taking medications as directed, a policy of prescribing small quantities of medications, performing random pill counts, and not refilling lost supplies should be explicitly discussed and then followed. External sources of information such as urine toxicology testing, interviews with partners and family members, data from prescription monitoring programs, and review of medical records can improve detection of substance use disorders.[65] Patients who denied using illicit substances that were detected on urine toxicology were more likely to be younger, receiving worker's compensation benefits, and have a previous diagnosis of polysubstance abuse.

The occurrence of any aberrant medication-related behaviors should prompt evaluation for addiction. Even when the diagnosis of a substance use disorder is suspected in patients taking opioids for chronic pain, behaviors such as stealing or forging prescriptions are relatively uncommon.[66] These more serious aberrant behaviors consistent with addiction also include selling medications, losing prescriptions, using oral medications intravenously, concurrent abuse of alcohol or illicit drugs, repeated noncompliance with the prescribed use of medications, and deterioration in the patient's ability to function in family, social, or occupational roles. Concerns by family or friends about the patient's pattern of medication use, an appearance suggesting intoxication, or the patient having other difficulties with functional abilities require in-depth evaluation. Any unwillingness to discuss the possibility of addiction or changes in chronic opioid therapy requires discussion about the patient's worries and possible aberrant behaviors, including medication misuse.

TABLE 25–1 Definitions Approved by American Society of Addiction Medicine

Abuse	Harmful use of a specific psychoactive substance
Addiction	Continued use of a specific psychoactive substance despite physical, psychological, or social harm
Misuse	Any use of a prescription drug that varies from accepted medical practice
Physical dependence	Physiologic state of adaptation to a dependence-specific psychoactive substance characterized by the emergence of a withdrawal syndrome during abstinence that may be relieved in total or in part by readministration of the substance
Psychological dependence	Subjective sense of need for a specific-dependence psychoactive substance, either for its positive effects or to avoid negative effects associated with its abstinence

TREATMENT OF SUBSTANCE USE DISORDERS IN PATIENTS WITH CHRONIC PAIN

In general, an active substance use disorder is a relative contraindication to chronic opioid therapy. However, treatment with opioids can be accomplished successfully if

the clinical benefits are deemed to outweigh the risks. The treatment of this extraordinary subset of patients with chronic pain will always require considerably more effort and frustration on the part of the physician. A strict treatment structure with therapeutic goals, landmarks to document progress, and contingencies for noncompliance should be made explicit and agreed upon by the patient and all the providers of health care. The first step for the patient is acknowledging that a problem with medication use exists. The next step for the clinician is to stop the patient's behavior of misusing medications. Then, sustaining factors must be assessed and addressed. These interventions include treating other medical diseases and psychiatric disorders, managing personality vulnerabilities, meeting situational challenges and life stressors, and providing support and understanding. Finally, the habit of taking the medication inappropriately must be extinguished.

The patient should be actively participating in an addictions treatment program that will reinforce taking the medication as prescribed and examine the possible reasons for any inappropriate use. Relapse is common and patients with addiction require ongoing monitoring even if the prescription of opioids has ceased. Traditional outpatient drug treatment or 12-step programs can provide support for recovery. Relapse prevention should rely on family members or sponsors to assist the patient in getting prompt attention before further deterioration occurs. If relapse is detected, the precipitating incident should be examined and strategies to avoid another relapse should be implemented. Although the misuse of medications is unacceptable, complete abstinence is not always the most appropriate or optimal treatment of patients with chronic pain. Restoration of function should be the primary treatment goal and may improve with adequate, judicious, and appropriate use of medications.[67]

LONG-TERM OPIOID THERAPY

The long-term opioid therapy remains controversial and may be complicated by many adverse outcomes.[68,69] Outcomes from trials have been inconclusive, although one meta-analysis did show that opioids improved pain relief when compared to naproxen and nortriptyline, but not any significant improvement in function.[70,71] A total approach to the patient including a history of substance abuse, psychosocial comorbidities, and aberrant drug-related behaviors must be considered in an evaluation. Only if these potential risks can be minimized or treated should chronic opioid treatment be considered.[32] Although a risk of addiction exists in all patients, a recent review and meta-analyses showed that only a small percentage of patients (0.05%) with no previous substance abuse problems developed an addiction when treated with long-term opioids.[71] Close monitoring and random drug screening may serve as a deterrent for substance abuse in this population.[6] Regardless, each patient requires a careful risk-benefit analysis when starting long-term opioid therapy.

WHY IS DETOXIFICATION NECESSARY?

Detoxification does not imply that a patient has been given the diagnosis of substance use disorder such as addiction, abuse, or misuse of medications. Detoxification is simply the process of withdrawing a person from a specific psychoactive substance in a safe and effective manner. Although addiction may necessitate detoxification in order to begin drug rehabilitation treatment, there are many reasons that patients must undergo detoxification. Because long-term treatment will have resulted in physiologic dependence, discontinuation or substantial dose reduction requires gradual tapering of the medication. In the treatment of chronic nonmalignant pain, the ongoing assessment of a therapeutic trial of medications such as opioids may result in the conclusion that the risk-benefit ratio is no longer acceptable (Table 25-2). A carefully planned and monitored detoxification will avoid a withdrawal syndrome in the patient who has become physiologically dependent on medications such as opioids or benzodiazepines.

TABLE 25–2 Indications for Detoxification

Intolerable side effects
Inadequate response or benefit
Aberrant drug-related behaviors
Noncompliance
Loss of control of medication use
Preoccupation with the medication
Continued use despite adverse consequences
Refractory comorbid psychiatric illness
Lack of functional improvement or impairment in role responsibilities

OPIOID DETOXIFICATION

Although physiologic opioid dependence can be demonstrated experimentally within 7 days, most patients will not experience withdrawal symptoms unless they have continuously taken opioids for at least several weeks. Patients with a history of physiologic opioid dependence, opioid withdrawal, or any other drug withdrawal will generally be more likely to experience opioid withdrawal after shorter periods of treatment. Regardless of the total daily dose, once physiologic dependence is established, abrupt discontinuation of opioids will precipitate acute withdrawal. Even a reduction in dose can precipitate withdrawal to a lesser degree. Patients taking opioid analgesics on a variable schedule are at higher risk for experiencing intermittent withdrawal. Even a long overnight dosing hiatus from short–half-life opioids can cause significant withdrawal symptoms. Exacerbations of pain or intermittent withdrawal symptoms relieved by taking medications are highly reinforcing and a common factor in the failure of detoxification. Patients with these experiences will require longer tapering schedules and more support to overcome this conditioned habit.

The essential element for successful opioid detoxification is the gradual tapering of the dose of medication. Opioid withdrawal is generally not dangerous except with patients at risk from increased sympathetic tone (e.g., increased intracranial pressure or unstable angina). However, opioid withdrawal is very uncomfortable and distressing to patients. Patients with pain are often particularly miserable during opioid withdrawal because of

the phenomenon of rebound pain. Increases in pain can occur even if the analgesic effects of opioid therapy had not been appreciable. Although it is generally not possible to avoid discomfort completely, the goal of detoxification is to ameliorate withdrawal as much as is clinically practical. Explaining the treatment plan to patients before the detoxification begins is critical. In particular, patients should know to expect worsening of pain and should have a few concrete short-term goals to focus on, such as the improvement in withdrawal symptoms, increasing functional abilities, or an alternative analgesic trial when withdrawal has resolved. The projected length of a taper is typically a balance between the expected severity of withdrawal symptoms (increased with faster tapers) and their expected duration (shorter with faster tapers).

SETTING

The inpatient setting offers more intensive monitoring, supervision, and other support that generally allows for a faster taper schedule. Indications for inpatient detoxification include the failure of outpatient detoxification attempts, medically unstable patients, comorbid psychiatric illness, unreliable or noncompliant patients, and complicated pharmacologic regimens requiring taper of more than one medication or illicit drug. Usually opioid detoxification can be accomplished in the outpatient setting. Outpatient detoxification should be planned with a careful inventory of support and monitoring systems. Patients should plan not only for discomfort but also temporary emotional lability and reduction in function. Compensatory planning might include warning family and work supervisors, planning for a decrease in workload on the job, and even taking vacation or sick leave days. Extensive support with frequent monitoring substantially increases the likelihood of a successful taper.

Higher success rates have been reported for patients with better therapeutic relationships or formal treatment programs that have included a period of stabilization on long–half-life opioids and then proceed with a taper slowly over a period of months. Office visits should occur at least weekly but daily contact with the patient proves a major advantage for ensuring success. Most contact with the patient does not have to involve the physician and often can be done over the telephone. A nursing visit to check vital signs and assess the severity of withdrawal can provide enormous help to the patient. This should include allowing the patient to express discomfort and frustration but then focus on the treatment plan and the patient's progress. Formal checklists of signs and symptoms such as the Subjective Opioid Withdrawal Scale (SOWS) and the Objective Opioid Withdrawal Scale (OOWS) allow for the objective rating of withdrawal and documentation of the patient's condition over time (Table 25-3).[72] Adjustment to the treatment plan is then based on several sources of information and not just the patient's complaints.

TABLE 25–3 Opioid Withdrawal Rating Scales

Objective Opiate Withdrawal Scale (OOWS)
Score 1 point for each sign that is present during a 10-minute observation period.
___ Yawning (≥1 yawn per observation period)
___ Rhinorrhea (≥3 sniffs per observation period)
___ Piloerection (gooseflesh: observe patient's arm)
___ Perspiration
___ Lacrimation
___ Mydriasis
___ Tremors (hands)
___ Hot and cold flashes (shivering or huddling for warmth)
___ Restlessness (frequent shifts of position)
___ Vomiting
___ Muscle twitches
___ Abdominal cramps (holding stomach)
___ Anxiety (from mild fidgeting to severe trembling or panic)
Total score ___ (*maximum severity* = 13)
Subjective Opiate Withdrawal Scale (SOWS)
Patients should rate each symptom statement on a scale of 0-4: 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely.
___ I feel anxious.
___ I feel like yawning.
___ I am perspiring.
___ My eyes are tearing.
___ My nose is running.
___ I have goose flesh.
___ I am shaking.
___ I have hot flashes.
___ I have cold flashes.
___ My bones and muscles ache.
___ I feel restless.
___ I feel nauseous.
___ I feel like vomiting.
___ My muscles twitch.
___ I have cramps in my stomach.
___ I feel like taking [name of opioid] now.
Total score ____ (*maximum severity* = 64)

AGENTS

The primary principle for detoxification is that medication should not be prescribed by a "cookbook" approach but through ongoing patient evaluation and subsequent dosage titration. The simplest strategy institutes a taper of the agent that the patient is currently using. This may be a short–half-life agent but offers the advantages of using an agent already familiar to the patient, simplifies an anxiety-filled process, and avoids the imperfect calculation of dosage equivalence and incomplete cross-tolerance. Short–half-life agents possess the disadvantage of pharmacokinetics that may not allow a smooth taper. Serum levels will fluctuate more with increasing dosing intervals. Patients will usually experience mild withdrawal within 4 to 8 hr of a dosage reduction. The severity of withdrawal will usually peak with a short–half-life agent at 8 to 36 hr; however, it can occur as late as 72 hr. When using these agents, certain procedures can minimize the risks of severe withdrawal symptoms (Table 25-4).

TABLE 25–4 Short–Half-Life Opioid Taper

Determine the total daily dosage being used by the patient.
Adopt a fixed interval schedule with equal doses every 4–6 hr for 48 hr.
Increase the prescribed dose until the patient has no opioid withdrawal symptoms for 48 hr.
Taper the amount of each dose without lengthening the interval between doses.
Taper the total daily dose approximately 10% every 3–7 days.
Slowing the taper may be accomplished by: (1) increasing the number of days at a given total dose; (2) decreasing a single dose amount while keeping the remaining doses the same; (3) increasing the time between doses only if the smallest individual dose has been reached.

TABLE 25–6 Buprenorphine Taper

Test for the precipitation of acute withdrawal symptoms by giving an initial dose of 0.1 mg SQ/IM or 1.0 mg SL.
Determine the total daily dose of the prescribed agent being taken by the patient.
Estimate the equivalent total daily dose of buprenorphine (0.2 mg SQ/IM = morphine 10 mg PO).
Adopt a fixed interval schedule with equal doses every 8–12 hr.
Titrate the dosage until the patient has no withdrawal symptoms for 24–72 hr.
Taper the dose and interval to 0.1 mg SQ/IM or 1.0 mg PO QD.
Discontinue the medication when the patient experiences no or tolerable withdrawal symptoms.

The preferable pharmacologic strategy is to choose a long–half-life pure opioid agonist such as methadone, sustained-release morphine or oxycodone, and transdermal fentanyl patches (Table 25-5). This strategy has the primary advantage of more consistent opioid serum levels with less chance of intermittent withdrawal between doses. With a long–half-life agent, the onset of withdrawal symptoms should be expected at 12 to 24 hr, although 24 to 48 hr is the usually reported time course. The severity will usually peak at 36 to 96 hr but can occur up to 1 week later. Substitution, which is often not exact, may require some initial titration to achieve dosing equivalence. An initial test dose of the agent can be given to determine the total dose needed. Switching from short– to long–half-life opioids in anticipation of detoxification may serendipitously prove an effective analgesic strategy. Side effects, intermittent withdrawal, and rebound pain may all improve such that detoxification may not be needed. Equianalgesic tables should only serve as a general guideline to estimate equivalent opioid doses. Clinical judgment should be used and individual patient characteristics considered when applying any table, because there is variance between equivalence charts.[73]

A third detoxification strategy uses the partial agonist/antagonist opioids. The agent most commonly used in this category is buprenorphine or the buprenorphine-naloxone combination called suboxone (Table 25-6). The buprenorphine-naloxone combination comes in a 4:1 ratio, respectively. The naloxone component prevents abuse of the medication, especially in an intravenous form.[74] The use of partial agonist/antagonists is designed to reduce the severity of withdrawal and cause less reinforcing drug effects. As a result, the taper should be easier and more successful. There is also less risk of respiratory depression, which is an infrequent consequence of overestimating the dosing equivalence with pure agonist substitution. When using partial agonist/antagonists such as buprenorphine, it is important to give a small test dose under supervision because of the rare precipitation of withdrawal symptoms secondary to the partial antagonist effect. If patients tolerate the test dose, then the titration of dose equivalence substitution can proceed. Buprenorphine-naloxone is effective for outpatient or inpatient detoxification, and improved outcomes when compared to clonidine for detoxification.[74-79] Evidence has not clearly supported buprenorphine is a superior detoxification agent when compared to methadone.[80] In fact, one Cochrane review failed to find a difference between any of the detoxification agents.[81] However, a recent extensive review suggests that buprenorphine may be the most effective detoxification treatment.[78] Buprenorphine-naloxone has been shown to be safe and well tolerated.[74-79]

TABLE 25–5 Long–Half-Life Opioid Taper

Determine the total daily dose of the prescribed agent being taken by the patient.
Estimate by conversion the equivalent total daily dose of the long–half-life opioid.
Adopt a fixed interval schedule with equal doses every 6–8 hr for 48 hr.
Increase the prescribed dose of long–half-life opioid until the patient has no withdrawal symptoms for 3–5 days.
Taper the amount of each dose unless the patient can tolerate an interval schedule of dosing every 8–12 hr.
Taper the total daily dose approximately 10% every 3–7 days.
Increase the number of days at a given total daily dose to slow the taper.

ADJUNCTIVE AGENTS

Several nonopioid pharmacologic agents are commonly used as adjunctive agents to provide patients additional relief from withdrawal symptoms (Table 25-7). Clonidine, an alpha-2-adrenergic agonist that decreases adrenergic activity, is the most commonly prescribed. Clonidine can

TABLE 25–7 Adjunctive Agents for Symptoms of Opioid Withdrawal

Symptom	Agent Type	Agent
Diarrhea	Bismuth products	Pepto-Bismol®
Rhinorrhea	Antihistamines	Diphenhydramine, loratadine
Muscle aches	Muscle relaxants	Methocarbamol
Abdominal cramps	Anticholinergics	Dicyclomine HCl
Insomnia	Antihistamines	Diphenhydramine
	Antidepressants	Trazodone, doxepin

help relieve many of the autonomic symptoms of opioid withdrawal, such as nausea, cramps, sweating, tachycardia, and hypertension, which result from the loss of opioid suppression of the locus ceruleus during the withdrawal syndrome.[82] Other adjunctive agents include nonsteroidal anti-inflammatory drugs for muscle aches, Pepto-Bismol® for diarrhea, dicyclomine for abdominal cramps, and antihistamines for insomnia and restlessness.

SCHEDULE

Unless patients are involved with dangerous aberrant drug-taking behaviors, there is generally no urgency to shorten the duration of opioid detoxification. The longer a patient has been taking opioids, the more difficulty they are likely to have with withdrawal. The taper will then require more time to be completed. Other factors that tend to increase the difficulty and length of a taper are medical comorbidity and complexity, older age, female gender, and detoxification from multiple agents simultaneously. Detoxification is more difficult in the last stages of a taper, and it should be anticipated that decreases in the dose of opioids would need to be more gradual during this time. If a taper becomes more complicated, the schedule should be extended by decreasing the dosage reductions or lengthening the intervals between reductions. As long as patients are demonstrating ongoing progress, there is generally no reason not to extend an opioid taper over several weeks or even months. Progress can be demonstrated by simple compliance with taper instructions, not using other illicit substances, improvement in side effects of opioids, and maintenance of function.

FOLLOW-UP

The process of detoxification does not end with the completion of the opioid taper. Patients can have lingering subacute withdrawal symptoms for weeks. In rare circumstances they can last for months. Insomnia and rebound pain are the most common symptoms. After the taper, patients who had difficulty with aberrant drug-taking behaviors continue to need increased levels of monitoring and supervision in their treatments because the risk of relapse is high. Patients without a history of addiction and aberrant drug-taking behaviors do not require specialized substance abuse treatment. These patients should be reassured that they do not have an addiction or the diagnosis of substance abuse/dependence. However, any detoxification precipitated by the diagnosis of addiction or medication misuse should have further evaluation and treatment. Referral to an addiction specialist is usually a helpful first step. Furthermore, active ongoing participation in the treatment prescribed for addiction should be a condition of continued pain treatment. For these patients, the prevention of relapse requires a long-term outpatient program of substance abuse rehabilitation.

BENZODIAZEPINE DETOXIFICATION

The technique of a benzodiazepine taper follows the same general principles of an opioid taper.[83] If patients have been using benzodiazepines only intermittently, there is generally no need for a taper. However, anyone who has been using benzodiazepines continuously for more than 2 weeks should be tapered to avoid the unpleasant experience of mild withdrawal and the risk of unexpected major withdrawal symptoms. The higher the total daily dose and the longer the duration of use, the higher the risk of significant and potentially dangerous withdrawal with abrupt cessation. The general features of benzodiazepine withdrawal are similar to those of opioid withdrawal with hyperarousal and hypersympathetic states. However, in its more specific features, the withdrawal syndrome is more like the one observed with alcohol (Table 25-8). Similarly, benzodiazepine withdrawal is much more dangerous than opioid withdrawal and includes the potential for seizures, hallucinations, hyperthermia, and delirium tremens. Like alcohol withdrawal, when untreated, severe benzodiazepine withdrawal has a high rate of morbidity and mortality.

The two main techniques for detoxification include a taper of the agent a patient has been taking and the substitution of an equivalent dose of a long–half-life agent such as diazepam or clonazepam. Another strategy for benzodiazepine detoxification utilizes phenobarbital substitution, especially in cases of complex detoxification from multiple agents such as opioids, sedative-hypnotics, and alcohol. The phenobarbital dose should be determined by a series of test doses and subsequent observation to determine the level of tolerance. It is important to note that infrequently the "second-generation" benzodiazepines (clonazepam, alprazolam, oxazepam, triazolam) are not fully cross-tolerant with each other or with the more traditional agents. A patient may require higher doses than expected

TABLE 25–8 Signs and Symptoms of Sedative-Hypnotic Withdrawal

Hyperarousal	**Psychiatric**
Agitation	Depersonalization
Anxiety	Depression
Hyperactivity	Hyperventilation
Insomnia	Malaise
Fever	Paranoid delusions
	Visual hallucinations
Neurological	**Gastrointestinal**
Ataxia	Abdominal pain
Fasciculation/myoclonic jerks	Constipation
Formication	Diarrhea
Headache	Nausea
Myalgia	Vomiting
Paresthesias/dysesthesias	Anorexia
Pruritus	**Cardiovascular**
Tinnitus	Chest pain
Tremor	Flushing
Seizures	Palpitations
Delirium	Hypertension
Genitourinary	Orthostatic hypotension
Incontinence	Tachycardia
Loss of libido	Diaphoresis
Urinary urgency, frequency	

to avoid significant withdrawal symptoms when taking these medications. Benzodiazepine tapers will generally require more time than opioid tapers with less frequent dose reductions. A taper of 6 weeks or more, especially with long–half-life agents, is not unusual.

CONCLUSION

Patients with chronic pain are at increased risk of substance use disorders. However, it is crucial to appreciate that there are many causes for aberrant medication-related behaviors. Misuse of medication is a clinical problem that can be the result of dependence but is more likely to be the result of inadequate analgesia. This can be due to undertreatment with opioids and other analgesics, disease progression, or tolerance to medications. Eventually, instead of consulting their physician, the patient may simply take more medication. Without the proper instructions, they will often take it inappropriately. If the patient does have an addiction, they will be preoccupied with the medication, have lost control of its use, and continue taking it regardless of the negative consequences they are now suffering. This patient requires specialized evaluation and treatment in addition to the management of their chronic pain syndrome. If careful planning and common principles are applied, detoxification will facilitate the transition from ineffective or problematic treatments to other potentially more effective treatments for pain. Treatment may include drug rehabilitation but it should not be prescribed for every patient undergoing detoxification. By avoiding unpleasant or dangerous withdrawal syndromes and providing the patient with the reinforcement that all treatments should result in benefits that outweigh their risks, the therapeutic relationship will be strengthened and the chances for successful treatment optimized.

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Access the reference list online at http://www.expertconsult.com

Perioperative Pain Management

CHAPTER 26

Pain Management in the Emergency Department

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The complaint of pain is the most common symptom presenting to the emergency department (ED).[1,2] The causes of pain encompass the entire range of human diseases, including psychological illness. The assessment of the severity of pain is subjective, and what appears to be the same problem or injury can affect each individual very differently. Several systems have been developed to quantify the degree of pain, but all rely on patients' perception of their pain.[3,4] Practitioners must bring all their clinical acumen into play to make an appropriate decision regarding the need for and class of analgesic to use in a given circumstance.

Pain can be divided into two major categories, acute and chronic. Acute pain serves a physiologic function in that it is a warning to the patient that something is wrong, and sends the patient for help or prevents the patient from doing further harm by limiting activity. The bulk of this chapter will be devoted to the discussion of the management of acute pain in the ED. The transition point from acute to chronic pain has been variably defined, ranging from as little as 4 to 6 weeks up to 6 months of pain.[5]

CHRONIC PAIN

Chronic pain serves no useful function to the patient. Patients with chronic pain can be divided into four general groups. These groups are patients with chronic pain secondary to underlying diseases such as cancer, sickle cell disease, and AIDS; patients with known pain syndromes such as tic douloureux and migraine headache; chronic pain patients without an identifiable cause; and finally, the group of patients who uses the complaint of chronic pain to obtain drugs or for other personal gains.

Each of these groups of patients requires a different management approach. Cancer patients with new pain or with acute worsening of their previous pain should be evaluated for a new complication and their pain aggressively managed with opiates.[6] Patients with known pain syndromes and without objective cause for their pain require an aggressive team approach, and if they are patients within your institution, prearranged therapeutic plans should be in place for when they appear in the ED. This is particularly helpful for those patients with sickle cell disease and frequent pain crises. The final group is a subset of pain patients who tests the patience and professionalism of emergency physicians and nurses. The majority of these patients are seeking narcotics. The diagnosis of malingering must be a diagnosis of exclusion, and cannot be made on the first visit by a patient to the ED. An appropriate workup for the patient's complaint should be done, and often needs to be repeated two or three times before the diagnosis of malingering is made. If malingering is suspected, the patient should be referred to the outpatient pain and psychiatric services for further evaluation and treatment. Each time these patients appear in the ED, the emergency physician should perform at least a basic history and physical examination, but can refuse to give further narcotics. Another approach is to use such agents as butorphanol (Stadol), which has good analgesic activity but gives little euphoria. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be offered, but these patients will often refuse them or state that they cannot take them. There are no hard-and-fast rules as to how to handle this type of patient. All physicians can do is maintain their professional ethics and practice, and do their best by referring the patient to the appropriate outpatient services.

ACUTE PAIN

Pain is a combination of physical, chemical, and psychological factors. There is no current method to directly measure the degree of pain that a given patient is experiencing from a given injury. However, if a patient presents to the ED with a complaint of pain, an attempt should be made to quantify the patient's perception of the degree of pain. A patient's verbal report is the only way to reliably obtain a patient's evaluation of the pain. Several tools have been developed to grade a given patient's pain and the response to treatment (Table 26-1). Pain scales should be incorporated as part of the triage process, and should be located on the record where the vitals are recorded. The severity of pain index should be recorded during the initial assessment process, and early and effective management of pain should be ensured.[7] After treatment, the assessment should be repeated as needed. All too often this does not occur.[8]

Numerous studies have documented inadequate use of analgesic agents in the ED.[9,10] This is particularly true in the pediatric population.[11] Many patients do not receive any pain medications while in the ED, even though their primary presenting complaint was pain.[9,12] In addition to

TABLE 26–1 Pain Assessment Tools

Clinical Tool	Grading Pain	When Used
Verbal quantitative scale	0 to 10 (None to worst possible)	Routine evaluation
Visual analog device	[_____] None to worst. Patient places a mark on the line	Routine evaluation
Global satisfaction question	Are you satisfied with your pain relief? Yes/No	Useful for confusing patients
Pediatric pain scales		
Observer generated	Facial expressions, crying	Neonate to age 3 and some 3–6
Draw a picture of your pain	Estimate location, intensity, and character	Over age 6 and some 3–6
Faces scale		Over age 6 and some 3–6
Pain thermometer	Like visual scale for adults	Over age 6 and some 3–6

no analgesia, there are a number of therapeutic errors that may result in the inadequate use of analgesics in the ED. These include prescribing the wrong agent; inappropriate dosage and dosing intervals or route of administration; improper use of adjunct agents; and concern for medically induced addiction to narcotics.

Failure to give analgesics is an issue that must be addressed by education of nursing staff and physicians.[13] The goal should be adequate pain relief for all patients. Emphasis of the importance of pain control to the patient is key in this process of changing practice habits. Patient satisfaction may be directly related to adequate pain control.[14,15] In addition, the early control of acute pain appears to reduce the incidence of chronic pain syndromes, and may improve the patient's outcome.[16] Finally, health-care providers have taken an oath to reduce or prevent pain and suffering.

Correction of the inappropriate usage of analgesics also requires a great deal of physician reeducation, and frequently major changes in practice habits must be instituted. Severe pain generally requires the use of parenteral opioids. In the acute situation, an IV line should be established, and the dosage titrated for the individual patient. The amount required of a given opiate for adequate pain relief can vary widely from patient to patient. For example, the effective level for morphine has been reported to be as much as eight times greater from one patient to another. The IM route should be avoided, as it is painful and the onset of action is variable. If an IV cannot be obtained, the subcutaneous route offers an excellent alternative. In addition there are newer agents that can be given by the sublingual or nasal route. Fentanyl is available in sucker form, which has great applicability in the pediatric population. Sufentanil and butorphanol, both potent opioids, are effective when given via the nasal mucosa. Once the route and dosage are determined, the analgesic should be given at frequent enough intervals to prevent the return of pain.

There is little role for adjunct agents in the management of acute pain in the ED. The exception is the clinical circumstance of persistent nausea and vomiting following the use of opioids, or in patients with pain who also have nausea and vomiting. The practice of using an adjunct to reduce the opioid dose simply is not valid and exposes the patient to another set of side effects. This practice should be abandoned.

The risk of addiction to the opioids with medical use must be a concern for physicians, especially when treating patients with chronic pain. However, in the acute patient there seems to be little evidence for undue concern. Of 11,892 inpatients who received opioids while in the hospital, only 4 became addicted without a prior history of substance abuse.[17]

SPECIFIC PROBLEMS

ABDOMINAL PAIN

For years the conventional teaching was to avoid the use of opioids for abdominal pain until a definitive decision had been made regarding surgery. This was sound and necessary practice prior to the development of modern diagnostic tools, such as CT scanning. Simply put, this practice is outdated. From the published literature on this subject, there has not been a significant increase in management errors demonstrated nor is there evidence for major morbidity or mortality associated with the early use of opiates in the treatment of abdominal pain.[18–22] The goal in patients with abdominal pain is not to achieve pain-free status, but rather to substantially reduce the severity of the pain. Opioids given by the IV route allow for careful titration of these agents. The patient should be kept responsive enough to allow for subsequent examinations. Close observation of the patient's course is mandatory, especially in patients with ulcerative colitis because of the added risk of toxic megacolon. NSAIDs can be effective adjunct therapy when treating biliary or renal colic.

HEADACHE

The complaint of headache is commonly seen in the ED.[23] Many of these patients have a known history of a specific type of headache such as migraine or vascular headaches. There are many causes of headache, and a minority of these patients may require extensive workups, including CT scanning, MRI, and lumbar puncture, to rule out a life threatening cause of headache. By far the majority of patients presenting to the ED with the complaint of headache will need only pain relief and follow-up.[24] A useful reference to assist the emergency physician to sort through this complaint is the *Classification and Diagnostic Criteria for Headache Disorders*, 2nd edition, published by The International Headache Society in 2004.[25] This handbook provides an organized approach to the diagnosis and management of the various types of headache and facial pain.

Migraine

Every year in the United States, over 1 million patients per year present to EDs with the complaint of migraine. If the patient does not have a clear and reproducible history of migraines, this diagnosis should be made with caution, and a headache workup needs to be done. If the prodromal symptoms, pattern of pain, and associated symptoms are similar to past attacks, the workup may be limited to a history and physical examination unless there is coexisting illness. Most of these patients have had failure of their usual medications to control pain prior to arrival at the ED. Therapy to relieve the pain is indicated. In mild to moderate migraine, acetaminophen or nonsteroidal agents are often effective. In more severe and persistent migraine, such agents as sumatriptan given subcutaneously or by nasal spray, or prochlorperazine or chlorpromazine by the IV route, may be required to both relieve the pain and to counteract nausea and vomiting.[26,27] Sumatriptan is contraindicated in patients with known coronary artery disease, hypertension, pregnancy, and peripheral vascular disease. The other two agents may be associated with hypotension, sedation, and dystonic reactions, and an anticholinergic drug should be added if these agents are given in high doses. Patients receiving chlorpromazine or similar agents should receive a 500-cc bolus of saline prior to the drug being given to help avoid hypotension. When added to standard acute migraine therapy, 10 to 25 mg of dexamethasone given IM or IV appears to reduce the incidence of recurrent migraine over the next 24 to 72 hr.[28] Opioids should only be given for patients who do not get relief by other means, or in those who are unable to receive other agents.[29] Dihydroergotamine is contraindicated in vascular disease, in the elderly, if the patient is on MAO inhibitors, and if sumatriptan has already been used. This agent is especially useful for patients with a refractory attack of migraine, and if used, the patient should first receive an antiemetic.

Cluster Headache

Cluster headaches are seen much less commonly in the ED, and emergency physicians are often less comfortable with management of this clinical problem. If the patient is having a typical pattern of headache, there is little indication for extensive workup and treatment should be initiated to control the pain. In many cases, sumatriptan will abort the attack. Frequently, the patient with this problem has already used this medication, and is in need of pain control. High-flow oxygen will often end the attack. If these attempts fail, dihydroergotamine given by the IV route is effective. Numerous other agents have been used, but if the above fails, neurological consultation should be considered to assist in managing this problem.

Subarachnoid Hemorrhage

Without a high index of suspicion, the emergency physician may not recognize this entity. Subarachnoid hemorrhage (SAH) has a high morbidity and mortality rate, exceeding 50%. Many of these patients will expire before they can get to medical care. Patients with SAH often deteriorate rapidly, and early diagnosis is mandatory to maximize the chances for a good outcome. The current approach is to rapidly obtain a CT to look for blood, and if this is negative, to do a lumbar puncture. CT cannot be relied on alone, as approximately 10% of acute SAH will not show blood on CT. This percentage is based on results from the earlier generations of CT scanners, and is probably much less today. A large, multicenter study is needed to determine the routine use of LP in the presence of a negative CT scan. However, it is clear that the percentage of false negatives may exceed 50% by 1 week after the acute headache.[30]

In many cases, patients describe the headache as if their head is exploding, or that the top of their head felt as if it was going to come off. These patients will frequently state that this is or was the worst headache of their life. Even if the patient has none of the other features of a SAH, these complaints should not be ignored. A patient giving this type of history should have the workup for SAH. After the practitioner decides on a course, pain relief can be given. Nonsteroidals are contraindicated in the treatment of patients with suspected SAH because of their anticoagulation properties. Opioids are safe and effective, but should be titrated to prevent excessive sedation.

Tension Headache

This is the most common cause of headache in the ED, and is frequently associated with other medical and psychological problems. Tension headaches are also the most general and difficult to categorize. To a great extent, this is a diagnosis of exclusion, and should only be given if the practitioner is satisfied that a more serious problem is not causing the headache. This may require imaging studies. Tension headaches often have a general pattern, in that the patient complains of a band-like pressure around the head and associated neck stiffness. Other symptoms are usually absent, and if present are mild. Pain relief can usually be achieved with acetaminophen or nonsteroidals. If there is associated anxiety, mild tranquilizers may help to prevent recurrence.

Other Causes of Headache

There are numerous other disease processes that are either the direct cause of or are associated with the complaint of headache. An in-depth discussion of these is beyond the scope of this chapter. In many of these conditions, associated neurologic symptoms will make the complaint of headache secondary. If the headache is related to a space-occupying lesion in the brain, opioids in careful doses are very useful to relieve the patient's suffering. The patient requires rapid consultation with the appropriate specialty. For headaches associated with underlying medical diseases, such as hypertension, the treatment of the underlying problem will often relieve the headache with minimum need for analgesia. Suffice it to say, the emergency physician must use judgment when prescribing pain medications for the headache patient. Underlying causes for the headache should not be masked by the aggressive use of analgesics. However, patients should not be denied some relief of their discomfort. Careful selection of the agent used, appropriate titration of the dosage of the agent, and proper delivery route of the drug can go a long way towards

achieving these therapeutic goals without overly confusing the clinical picture.

CHEST PAIN

Chest pain is a frequent complaint in the ED. The causes of chest pain are myriad, and the emergency physician must make rapid clinical decisions if the pain is secondary to a life-threatening disease.[31] The three most common serious diseases presenting with chest pain are myocardial ischemia and infarction, pulmonary embolism, and dissection of the thoracic aorta. Clinical pathways, particularly for myocardial ischemia, are well established. Part of these pathways is the use of morphine for the reduction of pain and anxiety. A major role of this agent is in those patients whose pain is not fully relieved by nitrates and beta-blockers. Doses should be given IV, and titrated to achieve pain relief without respiratory depression. The clinician must carefully monitor the patient to avoid hypotension. Aortic dissection commonly requires an opioid to relieve the severe pain experienced by patients with this condition. Pulmonary embolism seldom requires heavy analgesia, and good pain relief can usually be obtained with NSAIDs. Opioids are safe and effective, if required.

Most of the remaining causes of chest pain are either inflammatory, such as pericarditis, or due to musculoskeletal problems. The majority of these patients will respond well to NSAIDs or to acetaminophen. Adjunct therapy of heat or cold, massage therapy, and physical therapy may be indicated in follow up. A commonly occurring condition where NSAIDs should be avoided is in those patients with gastroesophageal reflux disorder (GERD). Acetaminophen may be used, but primary treatment with antacids and histamine blockers should be initiated.

MUSCULOSKELETAL PAIN

All people experience a variety of aches and pains secondary to contusions, minor arthritis, and soft tissue sprains and strains. By far the majority of these individuals treat themselves at home with a host of over-the-counter (OTC) medications of varying degrees of efficacy, and other adjunctive measures. The OTC drugs most frequently used today are ibuprofen and acetaminophen. If these patients present to the ED, the types and doses of the drugs taken by the patient need to be obtained in order for the emergency physician to give appropriate treatment and to avoid overdosing the patient. Icing sprains and contusions and appropriate splinting and rest of the injured extremity is mandated in the acute period, but these adjunct therapies are often overlooked during long waits in the waiting room. This group of patients comprises the largest single source of complaints regarding failure of staff to control pain.

Although there has been little research to support the use of muscle relaxants, they do appear to have a role in acute musculoskeletal injury when there is associated severe muscle spasm. Commonly used agents are orphenadrine citrate, methocarbamol, and the benzodiazepines. These agents cannot be a substitute for adequate analgesia. Oral opioids may be required in the management of severe musculoskeletal pain, especially when these patients are discharged. Acetaminophen with codeine has been used for years, but in reality codeine is a poor analgesic and has not been demonstrated to be more effective than NSAIDs or acetaminophen alone. Other oral opioids are effective in the management of severe pain, but physicians are often reluctant to prescribe them on an outpatient basis because of the fear of causing addiction. Included in this group are hydrocodone, oxycodone, and oral meperidine. These agents should be used if the pain is severe, and are generally safe to prescribe for short-term use. All of these agents do have a relatively high potential for abuse, and they should be prescribed with discretion and in limited amounts.

Patients with obvious fractures should be seen ASAP, and early immobilization be obtained. This prevents further soft tissue injury and will reduce the pain. Opioids often are required to control the pain, and the safest and most effective method is titration of these agents by the IV route. Patients given IV opioids need to be monitored for respiratory depression, hypotension, and excessive euphoria. If patients require extended "road trips" to radiology for multiple x-rays or CT scanning, they should be accompanied by medical personnel to both monitor their vital signs and to give additional analgesia if required.

PAIN MANAGEMENT IN PEDIATRICS

It has been well demonstrated that the pediatric population is often overlooked for adequate analgesia.[11] Children over the age of 5 can usually tell you where it hurts, and how much. Pediatric scales have been developed and are a useful adjunct for pain assessment (Table 26-1). Pediatric patients are often overlooked in a busy department because the bulk of their complaints are not life or limb threatening, and they do not openly complain. Their parents may attribute their child's fussiness to being tired and hungry, or to being frightened from being in the ED. The same attention and assessment for pain is mandated in the pediatric population, and appropriate doses of analgesics should be given. The same agents that are effective in adults are effective in children when used in proper dosage and if administered by the appropriate route.

ANALGESIA DURING PROCEDURES

The use of "OK, OK" anesthesia has little role in the practice of emergency medicine. This is a time-honored but brutal practice that has been used for everything from reduction of small joints to using force to restrain children for repair of small lacerations. Although it is impossible to do any procedure without some pain and discomfort, every attempt should be made to keep these to a minimum.[32] Adequate sedation prior to performing the procedure helps to reduce the anxiety and fear associated with procedures and reduces the memory of the event. Also it produces muscle relaxation, an important effect for major joint reduction. Numerous regimens have been developed to provide sedation, amnesia, muscle relaxation, and analgesia. The emergency physician needs to have an excellent knowledge of one or two of these regimes, and to know what side effects to expect. Patients must be monitored carefully, and specific procedures to

TABLE 26–2 Recommendations of American College of Emergency Physicians Clinical Policies Committee

1. Personnel involved in the administration of agents to and monitoring of procedural sedation and analgesia patients must understand the drugs given, have the ability to properly monitor the patient, and the necessary skills to intervene to manage the potential complications. An excellent approach is to have one support person present in addition to the provider.
2. The patient should receive a history of past or present illnesses and allergies, and limited physical aimed at vital signs, airway, and cardiovascular status. Recent ingestion of food is not a contraindication.
3. Initial consent to treatment is adequate, but separate consent may be obtained.
4. Advanced life support equipment and oxygen should be available. In addition, antagonists (naloxone for opiates, flumazenil for benzodiazepines) need to be present. An IV line should be obtained.
5. Patient monitoring must include frequent vital signs. Constantly monitoring pulse oximetry and cardiac monitoring are excellent options, but may not be mandatory in every circumstance. The patient's appearance and response to verbal stimuli should be watched during and after the procedure.
6. Drugs should be administered slowly and titrated to desired effect.
7. The patient should be monitored carefully during the postprocedure period. Discharge occurs when the patient responds appropriately, the vital signs are stable and back to normal for the patient, respiratory function is normal, pain has been addressed, minimal nausea, and new symptoms are handled. Patients should be back to baseline before discharge or discharged to a responsible third party.

ensure that this occurs need to be in place. The American College of Emergency Physicians has published guidelines to assist in developing the approach to safe use of procedural sedation and analgesia (PSA), also known as conscious sedation[33] (Table 26-2). The American Society of Anesthesiologists also recommends a period of fasting of 6 hr for solids and 2 hr for liquids prior to PSA.[34] To date, there has been no evidence that PSA as performed in the ED requires prolonged fasting, and prior ingestion of food is not a contraindication. If ingestion of food or liquids has occurred recently, the degree of sedation should be minimized by carefully titration of the agent(s) used to obtain PSA.

SPECIFIC AGENTS

FENTANYL AND MIDAZOLAM

This combination is widely used for PSA in both adults and children. Fentanyl is a short-acting opioid with high potency and minimal cardiovascular effects.[35] This agent has a rapid onset of action, usually within 2 min, and the duration of action is 30 to 40 min. Serum half-life is approximately 90 min. This combination of rapid onset, high potency, and short half-life makes fentanyl an excellent agent for most ED procedures. The usual required dose is between 2 and 3 μg/kg by slow IV push given in increments of 0.5 to 1 μg/kg every 2 min to a max of 5 μg/kg for both adults and children. The total amount of the agent required is dependent on the individual's response. Because of its high potency, safety, and relatively short half-life, fentanyl is very easy to titrate by using multiple small doses to achieve the desired effect. Fentanyl can induce severe respiratory depression, especially when used with other agents such as midazolam. This side effect is dose related, and usually appears within 5 min of administration of the agent. The doses used for PSA in the ED have not been reported to cause muscular and glottic rigidity or chest rigidity, which has been well documented when the agent is used in general anesthetic doses of over 50 μg/kg. This reaction can be reversed by either naloxone or succinylcholine. Seizures have not been documented when using fentanyl for ED PSA. General pruritus is not present with the use of fentanyl as occurs with many opioids, as it does not cause histamine release, and nausea is usually minimal when compared to other opioid analgesics. Fentanyl can also be administered orally in the form of a lollipop, making it useful in children if the IV route is not possible or required. The dose is usually 10 to 15 μg/kg, and onset of action is between 12 to 30 min. It is not feasible to fully titrate the dosage administered when fentanyl is given by the oral route. Nausea and vomiting are more common, but major side effects of seizures and chest rigidity have not been reported.

Midazolam is so frequently used in combination with fentanyl that these two agents should be considered together. The usual dose is 0.02 to 0.1 mg/kg for adults and 0.05 to 0.15 mg/kg for children. Midazolam also has a rapid onset of action of 1 to 3 min and a relatively short half-life of 30 to 60 min. When given IV, the drug is easily titrated to achieve the desired response. Midazolam provides excellent sedation, a beneficial hypnotic effect, muscle relaxation, amnesia, and antiseizure activity. The major side effect is respiratory depression, which is dose related and is more pronounced in the presence of other central nervous system depressants such as alcohol. The elderly and patients with chronic lung, liver, or renal disease are more sensitive to this agent. In general, cardiovascular side effects are not seen at sedative dosages. If other agents, such as fentanyl, are used in combination with midazolam, hypotension may occur. This will usually respond to a bolus of saline solution. Occasionally children will have paradoxical agitation when midazolam is used. If the IV route is not available, midazolam may be administered by rectal suppository, orally, and by nasal insufflation. This alternative can be useful to sedate children before simple therapeutic or diagnostic procedures. A specific regimen for the use of the combination of fentanyl and midazolam has been developed and appears to be safe and effective.[36] This recommendation is midazolam 0.02 mg/kg IV and fentanyl 0.5 mcg/kg IV. Repeat one or both agents as needed every 2 min.

KETAMINE

Ketamine has had extensive use in PSA and is especially useful and safe in the pediatric population.[37] It is a derivative of phencyclidine, a notorious street drug. When ketamine is used, dissociation of the limbic and thalamoneocortical systems occurs, and essentially the patient is unable to perceive pain. It does not produce muscle relaxation, and if this is required for the procedure another agent such as midazolam must be added. Hypertension may occur with the use of ketamine, especially in adults. The presence of cardiovascular disease, traumatic head injury, eye injury, glaucoma, and hyperthyroidism is a relative contraindications for this agent. In the past, emergence phenomena such as hallucinations and nightmares have been reported to be as high as 50% in the adult population, but newer literature suggests a much lower level of less than 20%.[38] Fortunately, most of these reactions are usually mild. The drug should be avoided in patients with a history of personality disorders. Both of these complications are much less common in the pediatric population. Laryngospasm is a serious complication in children, especially in those less than 3 months old, and it should not be used in this age group. Laryngospasm rarely occurs in children older than 3 months. Ketamine can be given by all routes of administration, including IM. The IV route is the easiest to titrate, and the dose required is 1 to 2 mg/kg by the IV route. Onset of action is within 1 min of IV infusion, and the duration of action is only 15 min. In adults, prolonged procedures require a constant infusion of ketamine at the rate of 1 to 2 mg/kg/hr, while in children repeated small doses of 0.05 to 0.1/kg are given as required. This agent is an excellent first-line agent in the pediatric population, and is a good alternative to opioids in adults allergic to opioids, and for patients at risk of hypotension and respiratory problems.

ETOMIDATE

Etomidate is an ultra–short-acting non-barbiturate hypnotic imidazole with minimal cardiovascular effects. It is administered at 0.1 to 0.15 mg/kg IV over 30 to 60 sec and redosed every 3 to 5 min. Its onset of action is almost immediate and effect lasts 5 to 15 min. One side effect is myoclonus, which may occasionally interfere with an intended procedure. Adrenal suppression may also occur with even one dose, so this agent should be avoided in septic and multitrauma patients. Injection pain is common and may be avoided by cannulating a large vein or applying a tourniquet proximally and injecting 0.5 mg/kg lidocaine IV 30 to 120 sec prior to the etomidate injection. Etomidate provides no analgesia. It is often suggested as a first-line agent for healthy patients requiring PSA.[39]

PROPOFOL

Propofol is a unique ultra–short-acting anesthetic agent unrelated to any other anesthetic class.[40] It is administered by slow injection of an initial loading dose of 0.5 to 1 mg/kg IV followed by 0.5 mg/kg IV every 3 to 5 min as needed. Anesthesia occurs within 40 sec and lasts 6 min. Propofol is not recommended for children less than 3 years old. Absolute contraindications include hypersensitivity to egg lecithin and soybean oil. Propofol can induce transient hypotension so should be used with caution in patients with hypovolemia, hypotension, or poor cardiac function. Like etomidate, propofol injection may be painful and can be prevented by similar techniques mentioned above. Propofol provides no analgesia. It is considered a first-line agent for PSA in young healthy patients.

OTHER AGENTS

Numerous agents have been used to provide PSA. These include nitrous oxide and methohexital. These agents appear to be safe and effective, but have side effects and appear to offer no advantage over the agents previously discussed. In the past, chloral hydrate was used extensively in children, but this agent has little indication today because of its delayed onset of action and prolonged duration. The use of the combination of meperidine, promethazine, and chlorpromazine, known as DPT, should be dropped because of the numerous side effects that are seen with this mixture.

LOCAL ANESTHETICS

These remain a mainstay of anesthesia in the ED. The so-called caine drugs are divided into two classes, the esters and the amides, and the various agents have different times of onset and duration (Table 26-3). The most commonly used in the ED are lidocaine, bupivacaine, and mepivacaine, all of which are amides. If a patient has a history of allergy to these agents, almost invariably it will be to the ester class. Allergic reactions to the amides are exceedingly rare, and they can typically be safely used. Pain during administration is the norm. Efforts should be made to reduce this discomfort. These include using as small a needle as possible, warming the solution to be injected, slow injection of the agent, injecting through the wound edges rather than through skin, and use of topical anesthetics prior to administration. Buffering the injected solution with sodium bicarbonate has been advocated.[41]

TABLE 26–3 Common Local Anesthetics

Agent (Trade Names)	Type of Agent	Use, Onset, and Duration
Lidocaine (Xylocaine, Dilocaine, Ultracaine)	Amide	Blocks, infiltration. Onset rapid. Duration 90–200 min
Tetracaine (Pontocaine)	Ester	Spinal, topical, eye. Onset slow. Duration 180–600 min
Mepivacaine (Carbocaine)	Amide	Epidurals, blocks, infiltration. Onset very rapid. Duration 120–240 min
Bupivacaine (Marcaine)	Amide	Blocks. Onset intermediate. Duration 180–600 min
Procaine (Novocaine, Neocaine)	Ester	Blocks, infiltrations. Onset slow. Duration 60–90 min

The amount of bicarbonate solution suggested for lidocaine is 1 cc of bicarbonate per 10 cc of lidocaine solution. All of these agents may produce central nervous system and cardiovascular toxicity if blood concentrations are too high. The potential toxic effects of these agents include seizures and ventricular fibrillation. These tragedies can be avoided by calculating total doses before use and by careful administration of the agent.

Topical anesthesia has been used for years especially in ENT and dental practice. Cocaine is an excellent topical agent for such things as nosebleed because of its additional vasoconstrictor effect. A 50/50 mixture of topical tetracaine and adrenaline solutions will produce similar results. The major application for topical anesthetics is in treating lacerations in small children. The two agents used most frequently are the combination of lidocaine, epinephrine, and tetracaine in solution, and EMLA, a eutetic mixture of local anesthetic agents. This compound comes in cream form and the active ingredients are lidocaine and prilocaine. The cream is applied directly to the laceration under an occlusive dressing without pain to the child. Within 30 to 60 min complete anesthesia can be obtained which will last up to 5 hr. Depth of penetration is limited, and for deep wounds additional injection may be required. There are theoretical concerns about the effect of this combination on wound healing, but these concerns have largely been refuted. This agent has been a real boon to the management of lacerations in the pediatric population, and has markedly reduced the need to tie them down as was done in the past.

KEY POINTS

- Pain is the most common complaint seen in the emergency department. The emergency physician must ensure that patients in pain are treated with appropriate analgesics as soon as is feasible.
- With modern diagnostic modalities, such as CT scanning, there is no reason to withhold pain medications for patients with abdominal pain. The goal is to reduce the pain for patients while they are undergoing diagnostic evaluation. Oversedation should be avoided to enable reliable physical examinations by consultants.
- Procedural sedation and analgesia, that is, conscious sedation, is an integral part of the practice of emergency medicine. The emergency physician must know several of the various regimens well, and anticipate each of these regimens potential side effects and complications. Protocols for the appropriate monitoring of these patients need to be in place.
- Drug seeking is a problem in every ED. However, a patient's complaint should not be attributed to this without adequate diagnostic evaluation. Drug-seeking behavior is a diagnosis of exclusion.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 27

Preemptive Analgesia

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The primary goal of the perioperative physician is to provide sufficient analgesia during a surgical procedure so that it can be performed at the highest surgical standard with the least possible impact on the patient. This objective includes the prevention of intraoperative pain, as well as short (acute) and long-term (chronic/persistent) postoperative pain. Over the past 30 years, many strategies have been employed toward this end; unfortunately, the early results were very disappointing, and later studies yielded mixed results. The failures can be attributed to a multitude of factors, including the study design of clinical trials, an incomplete understanding of the basic neurophysiology of the surgical injury, the semantics of the terminology used to describe the phenomenon, and understanding the concept of what constitutes postoperative pain.

TERMINOLOGY

Preemptive analgesia: Preemptive analgesia is an analgesic (antinociceptive) treatment that prevents the transmission of noxious afferent input to the central nervous system and/or development of altered processing of the afferent input that amplifies postoperative pain. A number of the trials that produced disappointing results in preventing postoperative pain can be traced to an oversimplification or a literal interpretation of preemptive analgesia. Instead of preventing the ongoing noxious input from the periphery that originated with the surgical incision and continued throughout the postoperative recovery period, physicians sought to prevent the noxious input associated with the surgical incision alone. This strategy disregards the consequent, nociceptive stimulus that continues during the healing process.

Preventive analgesia: Preventive analgesia is an antinociceptive treatment encompassing the entire period of high-intensity noxious stimuli produced by the peripheral nervous system that can alter peripheral or central sensory processing. This includes at least two phases: the primary phase during which the noxious stimuli is related to the surgical injury itself; and the secondary phase during which the ongoing noxious stimuli is produced by the release of chemicals, including inflammatory mediators from damaged tissue (Fig. 27-1). The secondary phase can begin during the intraoperative period and extend long into the postoperative recovery period. The duration of the postoperative recovery period depends on many factors, including the type of surgical operation performed, and the immunologic and nutritional status of the patient, as well as the associated medical comorbidities. The importance of addressing the two phases of the injury is borne out in the basic science literature.

During the past three decades, many advances have been made toward understanding the pathophysiology of nociceptive pathways. Both physicians and basic science researchers have become more knowledgeable about the nociceptive mediators that act in the periphery and activate the primary nociceptive afferent, as well as those that act centrally at the level of the spinal cord and supraspinally. One important finding is that tissue injury resulting from a noxious stimulus produces changes in the peripheral afferent and in the spinal cord, which leads to prolonged excitability. This hypersensitive state can persist for days to months, and contributes to acute and chronic postsurgical pain, a process referred to as *peripheral and central sensitization* (see Chapter 2 for details).

PATHOPHYSIOLOGY OF PREEMPTIVE AND PREVENTIVE ANALGESIA

Sensitization can occur in both the peripheral and central nervous systems following a surgical injury. The relative contribution of each component is a matter of debate. However, following tissue injury, a multitude of inflammatory mediators are released and activate the peripheral nociceptive afferent. The continued activation of these afferents enhances the patient's response to further stimuli. The inflammatory mediators can activate and increase the sensitivity of the nociceptors, thereby changing the nociceptive threshold of the afferent. Persistent activation can also lead to alterations in the neurophysiologic properties of the primary afferent itself. Peripheral sensitization refers to the summation of these processes.

There are a number of events that occur on the cellular level that are responsible for peripheral hypersensitization. Transient receptor potential vanilloid (TRPV) receptors on small C-fibers are nonselective cation channels. TRPV receptors are known to play an important role in peripheral sensitization and, thus, are prime targets for novel analgesics. They are activated by repeated heat stimulation or exposure to acidic environments found in healing tissues, which results in a painful burning sensation.[1] Inflammatory mediators, such as prostaglandin E2, serotonin, bradykinin, epinephrine, adenosine triphosphate, interleukin-1β, interleukin-6, tumor necrosis factor, chemokines, and nerve growth factor, also sensitize TRPV receptors. The release of these mediators also increases the magnitude of Na^+ current in sensory neuron-specific channels.[2] The activation of TRPV and these Na^+ channels begin a vicious circle that culminates in increased pain. Both sensory neuron-specific sodium channels and TRPV receptors can be phosphorylated by intracellular kinases (protein kinase C or tyrosine kinase), thereby potentiating the release of excitatory amino acids and peptides from sensory afferents and accentuating the pain. The inflammatory activation of TRPV receptors and sensory neuron-specific sodium channels results in vasodilatation and edema. The neurogenic inflammation is mediated by a calcitonin gene-related peptide, substance P, and neurokinin A, and can further sensitize the nociceptive afferents, leading to allodynia or hyperalgesia.[3,4]

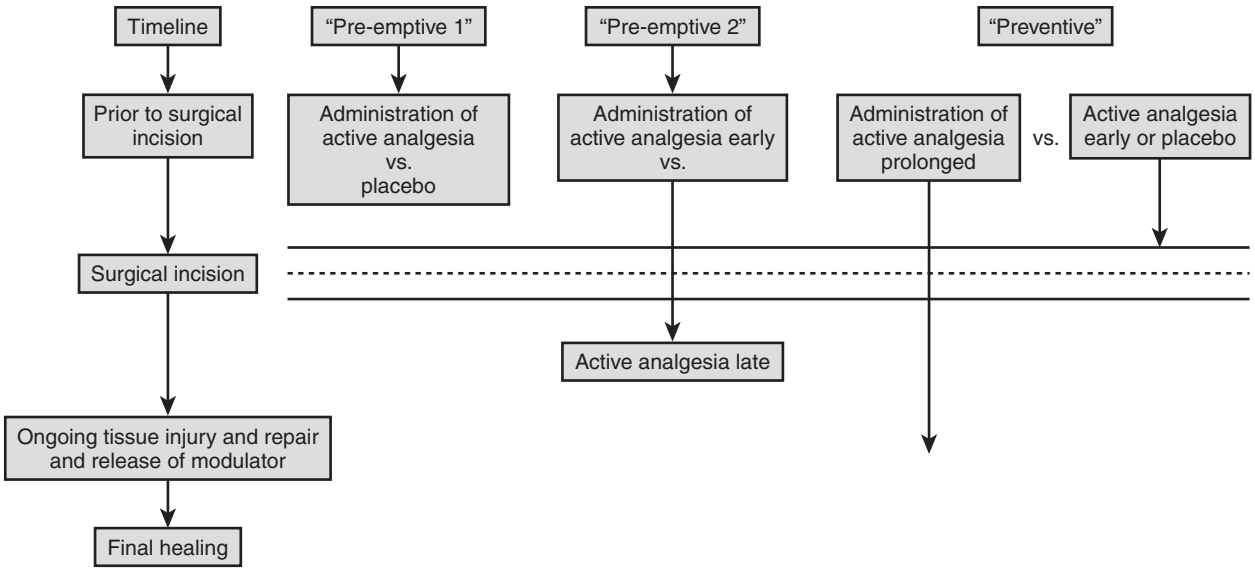

FIGURE 27-1 Timeline of surgical injury and recovery on the y-axis and timeline of perioperative analgesic interventions on the x-axis. Representation of research study design differences of "pre-emptive" versus "preventive" analgesia.

Hypersensitivity and alterations also take place in the central nervous system, the spinal cord, and supraspinal structures as a result of a surgical injury. Following a tissue injury, such as an incision through the skin fascia and muscle, a subset of Aδ- and C-fibers becomes spontaneously active,[5] and barrages the second-order neurons in the spinal cord. In turn, these neurons release excitatory neurotransmitters, which increase the amplitude of the spinal cord neuron response and lower the response threshold for further stimuli. Therefore, the response of the dorsal horn neurons to a particular stimulus—be it noxious (hyperalgesia) and/or innocuous (allodynia)—is altered, and perception of the painful stimulus is increased in intensity as well as duration. The injury also results in alterations of dorsal horn neurons. These neurons react to non-noxious stimuli as if they were noxious (allodynia) and to noxious stimuli (hyperalgesia) with an exaggerated response, but they also begin to respond to stimuli outside their original receptive field (secondary sites). There is evidence that C-fiber input from an injury also causes formation of anatomic connections at the spinal cord level between neurons that respond to Aβ-fiber transmission and neurons that respond to Aδ- and C-fiber transmission. Animal studies have shown that Aβ-fibers from injured tissue begin to produce and release substance P, normally found in C-fibers, and contribute to pain sensitivity.[6] Central sensitization has two temporally distinct phases. An early phase of hypersensitivity is triggered by changes in glutamate receptor phosphorylation and ion channel properties. The second phase (longer lasting) involves transcriptional changes that result in formation of new proteins responsible for prolonged pain hypersensitivity.[7]

The development of central and/or peripheral sensitization after traumatic injury or surgical incision can result in amplification of pain, or pain greater than the magnitude anticipated postoperatively. Therefore, preventing the establishment of altered central processing by analgesic treatment may, in the short term, reduce postprocedural or traumatic pain and accelerate recovery. In the long term, the benefits may include a reduction in chronic pain and improvement in the patient's quality of recovery and life satisfaction. Theoretically, providing analgesia in order to block the initial barrage of afferent produced by the surgical incision can result in a reduction of pain from minor or short-duration surgical procedures. However, surgical procedures that produce substantial tissue injury resulting in the release of inflammatory mediators and peripheral or central sensitization will require analgesic techniques that are in effect throughout the period of injury and recovery. Crile[8] first discussed this concept at the turn of the century. Woolf[9] established the neurophysiologic basis of central sensitization after injury in a series of animal experiments, and Wall,[10] in an editorial, suggested preinjury analgesia for the reduction of postinjury pain.

PREEMPTIVE AND PREVENTIVE ANALGESIA IN CLINICAL INVESTIGATIONS

The clinical definition of preemptive analgesia is one of the major controversies in perioperative pain medicine, and contributes to the confusion regarding its clinical relevance. Confining the definition of preemptive analgesia to only the immediate preoperative or early intraoperative (preincisional) period may not be clinically relevant or appropriate because the inflammatory response may last well into the postoperative period and continue to maintain peripheral sensitization. Although experimental studies convincingly confirm the concept of preemptive analgesia in decreasing postinjury pain, the findings of clinical trials of preemptive analgesia are mixed.[11–13]

Three types of methodologic approaches have investigated preemptive and preventive analgesia (see Fig. 27-1). The first approach (preemptive) involves a comparison between specific preoperative therapies in one group of patients with an untreated control group. The second type of study (preemptive) compares the efficacy of a specific

therapy when given preoperatively versus postoperatively. The third type of methodology (preventive) involves comparing the effects of continuous analgesic therapy when administered throughout the perioperative period versus administration in the preoperative period only, or when no treatment is provided.

Moniche and colleagues[11] performed a systematic review (1983–2000) of 80 randomized controlled clinical trials of preemptive analgesia for acute or chronic postoperative pain, which included only trials with identical, or nearly identical, analgesic regimens initiated before versus after surgical incision. This author concluded that, statistically, improvement in postoperative pain relief during or at certain time points occurred in 24 of the 80 trials (3761 patients). The trials were stratified according to the type of drug: nonsteroidal anti-inflammatory drugs (NSAIDs), intravenous opioids, parenteral NMDA receptor antagonists, epidural analgesia (single dose or continuous), caudal analgesia, and peripheral local anesthetics. Postoperative effectiveness was evaluated through quantitative analysis for pain relief using pain scores, time to first analgesic request, and consumption of supplementary analgesics between the preemptive and postsurgical group. For the quantitative analysis, the average pain scores within the first 24 hr postoperatively were chosen. Overall, evidence for preemptive analgesia was minimal; however, individual medications and techniques were found to be beneficial in the subgroup analysis. No benefit was noted in the preemptive group treated with NSAIDs, intravenous opioids, intravenous ketamine, peripheral local anesthetics, and caudal analgesia for postoperative pain relief. However, a NMDA receptor antagonist, dextromethorphan, did demonstrate a preemptive effect. Single-dose epidural studies showed some benefit, although in most of the trials, improvements were insignificant. The administration of continuous epidural infusion produced statistically improved pain scores, but did not support that preemptive analgesia was of greater benefit than applying the analgesic technique after the onset of surgery.

A more recent meta-analysis, using more stringent inclusion criteria from the Cochrane Collaboration, found a pronounced preemptive effect with epidural analgesia, local anesthetic wound infiltration, and systemic NSAID administration, but had mixed results for opioids or systemic NMDA receptor antagonists (Table 27-1).[13] This was followed by a randomized controlled study, in

TABLE 27–1 Perioperative Analgesic Interventions—Best Time to Apply Intervention

Drug	Citation	Effect	Lower	Upper	N Total	P Value
Epidural analgesia	Aida (1999)	0.72	–0.28	1.16	88	0.00
Epidural analgesia	Aida (2000)	0.74	–0.21	1.28	60	0.00
Epidural analgesia	Dahl (1992)	–0.25	–0.98	0.47	32	0.47
Epidural analgesia	Dahl (1994)	–0.60	–0.1.34	0.14	32	0.09
Epidural analgesia	Esmaoglu (2001)	0.00	–0.64	0.64	40	1.00
Epidural analgesia	Holthusen (1994)	–0.35	–0.1.19	0.49	25	0.38
Epidural analgesia	Katz (1994)	0.96	–0.29	1.62	42	0.00
Epidural analgesia	Katz (2000)	0.38	–0.79	0.04	94	0.07
Epidural analgesia	Kundra (1997)	0.73	–0.05	1.50	30	0.05
Epidural analgesia	Kundra (1998)	0.51	–0.02	1.04	60	0.05
Epidural analgesia	Obata (1999)	0.47	–0.01	0.96	70	0.05
Epidural analgesia	Richards (1998)	–0.22	–0.79	0.35	50	0.44
Epidural analgesia	Wong (1997)	0.73	–0.05	1.50	30	0.05
Epidural analgesia	**(13)**	**0.25**	**0.10**	**0.41**	**653**	**0.00**
Local anesthetics	Altintas (2000)	–0.57	–1.15	0.02	49	0.05
Local anesthetics	Dahl (1993)	0.63	–0.04	1.21	50	0.03
Local anesthetics	Fischer (2000)	0.47	–0.01	0.96	70	0.05
Local anesthetics	Gill (2001)	–0.43	–1.14	0.28	34	0.21
Local anesthetics	Hanlon (2000)	–0.30	–0.76	0.17	74	0.20
Local anesthetics	Ke (1998)	0.64	–0.03	1.30	39	0.05
Local anesthetics	Kissin (2001)	0.73	–0.05	1.50	30	0.05
Local anesthetics	Molliex (1996)	–0.38	–0.98	0.23	45	0.21
Local anesthetics	Orntoft (1994)	–0.32	–1.18	0.53	24	0.42
Local anesthetics	Pasqualucc (1996)	0.68	0.15	1.21	60	0.01
Local anesthetics	Turner (1994)	–0.09	–0.61	0.43	60	0.72
Local anesthetics	**(11)**	**0.10**	**–0.07**	**0.27**	**535**	**0.26**
NMDA antagonists	Chia (1999)	–0.42	–0.94	0.11	60	0.11
NMDA antagonists	Dahl (2000)	–0.46	–0.98	0.07	60	0.06
NMDA antagonists	Helmy (2001)	0.63	–0.03	1.28	40	0.05

TABLE 27–1 Perioperative Analgesic Interventions—Best Time to Apply Intervention—cont'd

Drug	Citation	Effect	Lower	Upper	N Total	P Value
NMDA antagonists	Mathisen (1999)	–0.10	–0.74	0.54	40	0.76
NMDA antagonists	Menigaux (2000)	–0.19	–0.94	0.58	30	0.60
NMDA antagonists	Rogers (1995)	–0.22	–0.57	0.13	128	0.21
NMDA antagonists	Wu (1999)	1.39	–0.81	1.97	60	0.00
NMDA antagonists	**(7)**	**0.00**	**–0.19**	**0.20**	**418**	**0.97**
NSAIDs	Buggy (1994)	–0.17	–0.81	0.47	40	0.58
NSAIDs	Colbert (1998)	0.54	–0.07	1.00	77	0.02
NSAIDs	Fletcher (1995)	0.70	–0.04	1.36	40	0.03
NSAIDs	Hanlon (1996)	0.63	–0.03	1.28	40	0.05
NSAIDs	Nagatsuka (2000)	0.00	–0.44	0.44	82	1.00
NSAIDs	Nelson (1993)	–0.19	–0.63	0.44	41	0.53
NSAIDs	Norman (2001)	0.67	–0.07	1.27	48	0.02
NSAIDs	Ong (2003)	0.79	0.25	1.33	60	0.00
NSAIDs	Reuben (2002)	0.92	0.25	1.60	40	0.00
NSAIDs	Romsing (1998)	–0.38	–1.06	0.29	37	0.24
NSAIDs	Sisk (1989)	–0.92	–1.60	–0.25	40	0.01
NSAIDs	Sisk (1990)	–0.80	–1.29	–0.31	72	0.00
NSAIDs	**(12)**	**0.14**	**–0.02**	**0.30**	**617**	**0.09**
Systemic opioids	Doyle (1998)	0.73	–0.05	1.5	30	0.05
Systemic opioids	Fassoulaki (1995)	–0.05	–0.75	0.65	34	0.88
Systemic opioids	Mansfield (1994)	–0.08	–0.60	0.44	60	0.76
Systemic opioids	Millar (1998)	–0.09	–0.60	0.43	60	0.74
Systemic opioids	Richmond (1993)	–0.93	–1.50	–0.36	60	0.00
Systemic opioids	Sarantopoulos (1996)	–0.30	–0.95	0.34	40	0.34
Systemic opioids	Wilson (1994)	–0.63	–1.28	0.03	40	0.05
Systemic opioids	**(7)**	**–0.24**	**–0.46**	**–0.01**	**324**	**0.04**

Source: From Ong CK, Lirk P, Seymour RA, et al: The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg *100:757–773, 2005.*
**Squares to the left of the centerline represent a study in which the findings favor post-treatment; those to the right favor pretreatment of preemptive analgesia.*

which the use of perioperative parecoxib in lumbar spine surgery was shown to reduce postoperative opioid consumption, lower pain scores, and increase patient satisfaction with their analgesic regimen.[14] However, a meta-analysis of randomized controlled trials using perioperative NSAIDs or COX 2 inhibitors demonstrated a reduction in postoperative pain scores with nonselective NSAIDs, but not with COX 2 inhibitors.[15] COX 2 inhibitors were found to reduce postoperative morphine consumption, but were also associated with an increased risk of renal failure (number required to harm of 73). Additionally, in the trials that used ketamine and COX 2 inhibitors, no significant difference was noted; however, three trials that used intravenous or intramuscular dextromethorphan and COX 2 inhibitors had a reduction in either pain intensity or supplemental analgesic use in the postoperative period.

Despite the findings of Ong and colleagues,[13] the use of the NMDA antagonist, ketamine, has increased in recent years. Its major benefit is probably related to its modulation of opioid-induced hyperalgesia. A decrease in opioid-induced hyperalgesia has been associated with lower postoperative pain scores and opioid consumption.[16,17] Interestingly, in the setting of anesthetics in which no opioids were administered, the preoperative bolus administration of ketamine alone provided no postoperative benefit.[18]

One class of oral medications that appears to have a potential for inducing preemptive[19] and preventive[20] analgesia consists of the gabapentinoids, gabapentin and pregabalin. As of June 2010, approximately 35 trials had tested the hypothesis of preemptive or preventive analgesia induced by gabapentin, and 15 trials used pregabalin. The results for a preemptive effect of single-dose gabapentin have been overwhelmingly positive,[19] and involve a wide range of surgical procedures, including those performed by otolaryngology, gynecologic, general, orthopedic, and orthopedic spine surgeons in both adults and pediatrics. Gabapentin has also been shown to possess preventive and postoperative analgesic effects.[21] In trials that reported no significant difference with the addition of gabapentin, a common factor was the use of other preemptive strategies, such as concomitant peripheral nerve blockade or other adjuvant analgesics,[22] or examination of outcome measures involving referred pain, such as shoulder pain related to thoracotomy.[23] Two conclusions can be drawn from these results. Gabapentin does provide a preemptive analgesic effect when compared to placebo preemptive treatment, and is only of benefit for treating pain at the site of the surgical injury

itself, and not the areas of referred pain. Pregabalin, a medication structurally similar to gabapentin that acts on the same molecular target, has also been found to provide preemptive and preventive analgesia in a wide range of surgical procedures, including hysterectomy, lumbar discectomy, knee arthroplasty, hip arthroplasty, gastrectomy, and cholecystectomy. Similar to gabapentin, pregabalin, when combined with other adjuvant analgesic modalities, provides minimal additional benefit.[24] Although gabapentin and pregabalin have few side effects, their use preoperatively can impact the anesthetic plan, as they have consistently been shown to cause postoperative sedation or drowsiness in randomized controlled trials; and one trial that investigated the use of gabapentin for neurosurgery resulted in prolonged endotracheal intubation.[25] Therefore, it is important that the anesthesiologist adjust the quantity of commonly administered sedatives and/or general anesthetics given to the patient preoperatively or intraoperatively.

The combination of experimental data and positive clinical trials strongly suggests that preventive analgesia is a clinically relevant phenomenon. In a systematic review of clinical trials examining preemptive or preventive analgesic approaches, Katz and McCartney[26] reported an analgesic benefit of preventive analgesia, with no such benefit when using a preemptive strategy. Maximal clinical benefit is observed when there is complete blockade of noxious stimuli, with extension of the blockade into the postoperative period. Recent preclinical and clinical studies provide substantial evidence that central sensitization and persistent pain after surgical incision is predominantly maintained by the incoming barrage of sensitized peripheral pain fibers throughout the perioperative period[27] and extending into the postsurgical recovery period. By preventing central sensitization and its prolongation by peripheral input, preventive analgesia, along with intensive multimodal analgesic interventions, could, theoretically, reduce acute postprocedure pain/hyperalgesia and chronic pain after surgery or trauma.[28]

CONCEPTUAL CHALLENGES OF PREEMPTIVE AND PREVENTIVE ANALGESIA

The surgical incision does not produce a single, one-time noxious stimulus, but a continuous barrage of C-fiber and Aδ-fiber input to the spinal cord. Hence, a single, preincisional analgesic intervention is not likely to block this assault throughout the postsurgical recovery period, thereby allowing nociceptive information to reach the spinal cord and resulting in hypersensitization. Likewise, the inflammatory processes incited by the surgical incision also produce central sensitization for a prolonged period following surgery. The difficulty is in predicting the *duration* of the noxious inflammatory state. Clearly, surgical technique, patient characteristics, and other factors play a role in this phenomenon, making comparative studies difficult.

Confounding the issue of the efficacy of preemptive and preventive anesthesia is the diversity of single intervention versus continuous intervention used in these studies. First, failure of the medical literature, including the many reviews and meta-analyses, appears to lie in *not* investigating the efficacy of each technique in its own study. Second, many studies included the use of premedications or intraoperative analgesic adjuvants, as well as nitrous oxide, all of which have a well-known analgesic effect that could have made it difficult to detect significant differences between the control and experimental groups.

Third, the lack of strong evidence supporting preemptive analgesia in clinical studies may be related to the fact that no completely objective standard exists to measure pain. Pain severity measured by visual analogue and numeric rating scales, as well as amount of opioid consumption, is often used in clinical trials as measures of outcome. Pain rating scales, though self-reported, are highly reliable, and can be used systematically as indices of pain. Opioid consumption is, indeed, a reflection of pain intensity, but it is not a reliable index, as it is profoundly influenced by various psychological factors, including anxiety level, mood, and expectation of recovery.

A fourth reason that preemptive analgesia is not an obvious phenomenon in clinical trials may be that it is extremely difficult to completely block noxious input from reaching the spinal cord despite the analgesic technique used. Researchers have used plasma cortisol levels as a determinant of the stress response to determine if complete neural blockade occurs during surgery. Kehlet and colleagues[29] showed that only a block extending from T4 to S5 prevented a rise in cortisol levels following lower abdominal surgery.

Finally, suboptimal results in these studies may be related to the lack of comprehensive analysis of subgroups involving medication, method of delivery, *and* type of surgical procedure performed. Although it has been common practice to consider surgical interventions as a homogenous injury, there is growing evidence that preemptive approaches to analgesia may need to be procedure-specific.[30] This approach to subgroup analysis, though appropriate, will require the generation of substantially more data to evaluate the efficacy of each medication regimen for each specific surgical intervention.

FUTURE CONSIDERATIONS

Other questions that require further investigation in order to completely treat postsurgical pain include: What are the components that make up postsurgical pain? What are their respective contributions to that postsurgical pain? Surgical injury, including the lacerating and crushing of nociceptive afferents is of foremost importance in this regard, followed by the inflammatory response. The secondary effects of the injury, including peripheral and central sensitization, are important components. However, one component that has not been clearly elucidated is the most commonly administered and intraoperative analgesic—the opioid. Chronic opioid therapy is associated with decreased pain thresholds and, hence, requires increased use of analgesics[31]; intraoperative opioids have been associated with postoperative hyperalgesia.[16] This begs the question: Is the preemptive or preventive effect of nonopioid adjuvant analgesics the result of true intrinsic preemptive properties of the intervention, or is it the product of substituting one analgesic without hyperalgesic side effects for one with these side effects? In one study,

ketamine was shown to decrease postoperative opioid use following intraoperative opioid administration; this outcome was interpreted to mean that ketamine reduced the opioid-induced hyperalgesia[16]; however, the same result could also be interpreted as a preemptive or preventive effect.

CONCLUSION

The management of postoperative pain has improved tremendously with the development of intravenous patient-controlled analgesia and the greater use of peripheral nerve and epidural catheters to deliver local anesthetics. Nevertheless, the more logical approach remains to block the development of pain before it is produced; this is the theoretical promise of preemptive or preventive analgesia. Unfortunately, the optimal medication or delivery technique has not yet been identified. Neuroplasticity is a well-recognized phenomenon, although is not yet fully understood. As we develop a better understanding of this process through more research, additional studies investigating the effects of preemptive analgesia will continue. It is a commonly held belief that completely blocking the afferent input, combined with a multimodal approach, may be most effective. This may very well be true, but, however logical, the data do not fully back up this premise. The two medications that are most consistently preemptive or preventive are the gabapentinoids that do not completely block the nociceptive afferent barrage accompanying a surgical injury. It is because of the potential of preemptive analgesia to revolutionize the field of pain medicine that, despite inconsistent data, it continues to be an area of great interest and exploration.

KEY POINTS

- Postoperative pain results from peripheral and central sensitization.
- The NMDA receptor responds to glutamate, an excitatory amino acid.
- The concept of preemptive analgesia is the perception that therapies can be applied prior to a noxious event in order to prevent or reduce the magnitude and duration of postinjury pain and/or the development of chronic pain.
- The concept of preventive analgesia is using antinociceptive treatment to cover the entire period of high-intensity noxious stimuli from the periphery to alter peripheral or central sensory processing. The primary phase is that during which noxious stimuli are related to the surgical injury, and the secondary phase is that during which ongoing noxious stimuli are related to the release of chemicals, including inflammatory mediators from damaged tissue. The secondary phase can begin intraoperatively and continue long into the postoperative recovery period.
- Although several experimental studies support the concept of preemptive and preventive analgesia, human clinical studies have demonstrated inconsistent and controversial results.
- Therapies that have been tested in preemptive trials include NSAIDs, intravenous opioids, intravenous ketamine, peripheral local anesthetics, caudal and epidural analgesia, dextromethorphan, gabapentin, and pregabalin.
- Preemptive analgesia is not an obvious phenomenon in clinical trials because of the central sensitization that is induced by inflammatory processes. Consequently, the preemptive effect could be negated in the immediate postoperative period secondary to inflammation, and, thus, the preventive approach is preferred.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 28

Perioperative Nonopioid Infusions for Postoperative Pain Management

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Opioids are the most commonly used medications for perioperative pain control. Oral nonopioids such as the anticonvulsants have been used to decrease postoperative pain. Recent studies evaluated the efficacy of nonopioids, such as ketamine, lidocaine, and naloxone, as perioperative infusions to decrease postoperative pain and limit the opioid requirements of patients after surgery. Other drugs such as esmolol and dexmedetomidine have also been investigated but these drugs have rarely been employed for perioperative pain management. In this chapter, the results of the studies on infusions of ketamine, lidocaine, and naloxone will be summarized, and recommendations on their clinical applicability as part of perioperative pain management will be made.

INTRAVENOUS KETAMINE INFUSION

Ketamine is a noncompetitive N-methyl-D-aspartate glutamate receptor antagonist and a sodium channel blocker.[1,2] The drug is available as racemic ketamine, which contains the S(+) and R(–) stereoisomers. The S(+) ketamine has four times greater affinity for the NMDA receptor than the R(–) ketamine. Ketamine has a half-life of 80 to 180 min. Its metabolite norketamine has a longer half-life and is one-third as potent as the parent compound.[3]

Early studies showed ketamine to have analgesic properties at low doses.[4–8] The drug also has many ideal qualities as an analgesic. It does not depress the laryngeal protective reflexes,[9] does not suppress cardiovascular function in the presence of an intact nervous system,[10] causes less depression of ventilation compared to opioids,[11] and may stimulate respiration.[12] Ketamine has been used in subanesthetic doses as an analgesic.[7] The analgesic effects of ketamine occurs at plasma concentrations of 100 to 150 $ng.ml^{-1}$.[13] The undesirable characteristics of ketamine include postoperative malaise,[14] accumulation of metabolites,[15] development of tolerance,[16] cardiovascular excitation, and the occurrence of psychotomimetic side effects.[17,18]

Most of the randomized controlled clinical studies on perioperative IV ketamine showed some beneficial effect. In a study in patients who underwent cervical and lumbar spine surgery, ketamine (1 mg/kg bolus) followed by 83 $mcg.kg^{-1}.hr^{-1}$ resulted in lower pain scores, less analgesic requirements, and better satisfaction than patients who had saline infusion or those who had lower dose of ketamine infusion (same bolus but with an infusion rate of 42 $mcg.kg^{-1}.hr^{-1}$).[19] The same salutary effects were seen in patients who had major abdominal surgery. Perioperative ketamine infusion (0.5 mg/kg bolus followed by 2 $mcg.kg^{-1}.min^{-1}$) for 48 hr after surgery resulted in lower morphine consumption than patients who had saline infusion or those who had the same infusion given intraoperatively.[20] The pain scores were noted to be lower in the ketamine infusion group compared to the control group. To better look at the effect of timing of the ketamine bolus and the ketamine infusion, Bilgin et al.[21] compared ketamine bolus followed by an infusion with ketamine bolus alone either before surgical incision or at wound closure. The patients underwent gynecologic laparotomy. The investigators noted that the patients who had the ketamine bolus and infusion had lower pain scores and lower morphine consumption.

The addition of ketamine infusion (bolus of 0.3 mg/kg at induction and an infusion of 0.1 $mg.kg^{-1}.hr^{-1}$ for 48 hr) to a tramadol infusion (3 mg/kg at induction followed by 0.2 $mg.kg^{-1}.hr^{-1}$ for 48 hr) resulted in less pain and lower morphine requirements compared to patients who had the tramadol infusion alone.[22]

No beneficial effect of the ketamine infusion was noted when the general anesthetic consisted of total intravenous anesthesia with remifentanil and propofol infusion.[23] The absence of beneficial effect may be related to the generous use of opioids intraoperatively.

The role of perioperative IV ketamine infusion in preventing post-amputation pain has been studied.[24] Ketamine 0.5 $mg.kg^{-1}$ bolus followed by an infusion of 0.5 $mg.kg^{-1}.h^{-1}$ for 72 hr was not effective in reducing morphine consumption or in decreasing the incidence of stump allodynia. At the 6-month follow-up, the incidence of phantom pain and stump pain was 47% for both phantom and stump pain in the ketamine group compared to 71% and 35% in the control (saline) group, respectively. There was no statistical difference in incidences between groups and the investigators concluded that IV ketamine did not significantly reduce acute central sensitization or the incidence and severity of postamputation pain.[24]

A ketamine infusion appears to have a salutary effect on epidural analgesia. The addition of a ketamine infusion to epidural analgesia in patients who underwent surgery for rectal adenocarcinoma resulted in less patient-controlled anesthesia (PCA) morphine requirements and reduced area of hyperalgesia.[25] Interestingly, the patients also had less residual pain until the sixth postoperative month. The same investigators repeated their results in patients who underwent colon resection.[26] Another group of investigators noted the beneficial effect of adding low-dose IV ketamine (0.05 $mg.kg^{-1}.hr^{-1}$, approximately 3 mg/hr) to epidural analgesia after thoracotomy.[27] In this study, the patients who had the ketamine infusion had less pain and took less medications at 3 months after the surgery. Unfortunately, this salutary effect of ketamine in preventing chronic pain after surgery was not confirmed in another study.[28] The ketamine infusion (1 $mg.kg^{-1}$ at induction, 1 $mg.kg^{-1}.h^{-1}$ during surgery, then 1 $mg.kg^{-1}$ for 24 hr) improved immediate postoperative pain but did not

affect the intake of analgesic; in addition, the neuropathic pain scores were the same at 4 months after the surgery.[28]

Most of the studies showed no increased side effects. Zakine et al.[20] did not see any incidence of delusions, nightmares, or sleep or psychiatric disorders in their study. Webb et al.,[22] on the other hand, noted a higher incidence of hallucinations in the ketamine–tramadol infusions group. Psychomotor, sleep disturbance, and trail-making performance were, however, similar.

Several review articles noted the large variations in clinical settings, small number of patients studies, different ketamine regimens, and different routes of administration in the clinical studies on IV ketamine infusion.[29–33] In summary, most of the randomized and controlled studies showed some beneficial effects of a low-dose ketamine infusion. It also appears to improve the efficacy of epidural analgesia. It does not seem to have any effect when the anesthetic technique is total IV anesthesia where moderate amounts of intraoperative opioid are used. IV ketamine may find its use as an adjunct in opioid-tolerant patients, or in patients with a higher incidence of chronic postsurgical pain such as thoracotomy, inguinal herniorraphies, limb amputation procedures, or even mastectomies.

INTRAVENOUS LIDOCAINE INFUSION

Lidocaine has peripheral and central effects suitable for the relief of pain. Lidocaine inhibits leukocyte migration and metabolic activation,[34] and decreases albumin extravasation in animal models of chemical peritonitis.[35] Centrally, it has been shown to modify the neuronal responses in the dorsal horn[36] and selectively suppress synaptic spinal transmission by decreasing C-fiber–evoked activity in the spinal cord.[37] Local anesthetic infusions have been used in the treatment of neuropathic pain[38,39] and pain from burns.[40]

Several studies showed the beneficial effects of intravenous lidocaine in abdominal surgery. In a randomized, double-blind, placebo-controlled study, Cassuto et al.[41] showed the analgesic efficacy of a low-dose lidocaine infusion in patients who underwent cholecystectomy. After an intravenous bolus of 100 mg of lidocaine, they infused lidocaine at 2 mg/min, starting at 30 min before the surgery, and continued for 24 hr after the surgery. Compared to the group who had saline infusions, the patients who had the lidocaine infusions had significantly lower pain scores during the first day of surgery and required significantly less meperidine during the first 2 postoperative days.[41] Whole blood levels of lidocaine were between 1 and 2 mcg/ml. Other randomized, controlled studies showed the technique to result in lower postoperative pain scores, less opioid consumption, faster return of bowel function, and reduced hospital stay.[42–44] Groudine et al.[42] compared lidocaine versus saline in patients who had radical retropubic prostatectomy. In the lidocaine group, the patients had 1.5 mg/kg bolus of lidocaine before induction, and an intraoperative infusion of either 3 mg/min or 2 mg/min (for patients <70 kg) that was continued until 1 hr postoperatively. Although the analgesic consumption between the patients in the two groups was the same, the patients who had the lidocaine infusion had a lower Visual Analog Score (VAS), a shorter return of bowel movement (62 ± 13 hr vs. 74 ± 16 hr), and a shorter hospital stay (4 vs. 5 days). The same beneficial effect was noted after major abdominal surgery. Koppert et al.[43] gave a 1.5-mg/kg bolus over 10 min, followed by 1.5 mg.kg.hr 30 min before surgical incision and continued up to 1 hr after the end of surgery. The control group had saline bolus followed by saline infusion. The lidocaine infusion group had lower VAS, less morphine usage (130 vs. 159 mg) over a 72-hr period, and had bowel movements sooner.[43] It is interesting to note that the opioid-sparing effect was most pronounced on the third postoperative day, prompting the investigators to theorize that the lidocaine infusion may have a true preventive analgesic effect. Another study done in patients who had laparoscopic cholecystectomy showed the same benefits.[44] In this study, the patients were given a lidocaine bolus injection of 1.5 mg/kg at the induction of anesthesia followed by a continuous infusion of 2 mg.kg.hr intraoperatively and 1.33 mg.kg.hr postoperatively for 24 hr. The control group had saline bolus injections followed by a saline infusion. The times to first flatus (17 vs. 28 hr), defecation (28 vs. 51 hr), and hospital discharge (2 vs. 3 days) were significantly shorter in the patients who had the lidocaine infusion. The lidocaine infusion also significantly reduced opioid consumption and postoperative pain and fatigue scores.

Two studies in patients who had abdominal surgery not only looked at pain relief but the effect of the lidocaine infusion on markers of inflammation and immune response. A randomized study in patients who underwent transabdominal surgery showed less severe postoperative pain in the first 8 hr after surgery, at rest, and during coughing.[45] There was no difference in pain scores for the 12 to 72 hr after surgery between the IV lidocaine and IV saline. In this study, the authors noted less ex vivo production of IL-1ra and IL-6 and better maintenance of the lymphocyte proliferation response to phytohemagglutinin-M in the intravenous saline group. Another study did not notice improved pain scores but showed other salutary effects when lidocaine infusion was employed in patients undergoing colorectal surgery. Herroeder et al.[46] gave an IV bolus of lidocaine (1.5 mg/kg) followed by a continuous infusion of 2 mg/min until 4 hr postoperatively. Although the pain ratings were the same compared to a saline control group, the return of bowel function was accelerated and the length of hospital stay was shortened by 1 day. The authors also noted significant attenuation of the plasma levels of IL-6, IL-8, complement C3a, and IL-1ra, as well as expression of CD11b, P-selectin, and platelet-leukocyte aggregates. The findings showed the ability of IV lidocaine to modify the anti-inflammatory activity, which modulates surgery-induced response.

The combination of dextromethorphan, 40 mg IM, and IV lidocaine, 3 $mg.kg^{-1}.hr^{-1}$ was shown to result in better pain relief and faster recovery of bowel function when compared with chlorpheniramine and IV saline, chlorpheniramine and IV lidocaine, or dextromethorphan and IV saline.[47]

The beneficial effects of IV lidocaine infusion were not duplicated in patients who had a total hip replacement or coronary artery bypass graft surgery. In a randomized, double-blind, placebo-controlled study, Martin et al.[48] gave

1.5 mg/kg lidocaine bolus over 10 min at 30 min before surgical incision followed by an infusion of 1.5 mg.kg.hr until 1 hr after the end of the surgery. There was no difference between the two groups in terms of postoperative pain scores, opioid consumption (17 vs. 15 mg morphine over 24 hr), and hip flexion. Neither was the low-dose lidocaine infusion effective in reducing the supplemental fentanyl, midazolam, or propanolol postoperative requirements in patients who underwent coronary artery bypass.[49] Also, the lidocaine infusion did not reduce the time to extubation, ICU stay, or hospital length of stay. Note that there is only one study in total hip or in CABG surgery, and it is too soon to conclude that a lidocaine infusion is not effective in these type of surgeries. Whether the higher incidence of neuropathic pain after these surgeries is a factor is not yet known at this time.

When the lidocaine infusion (1.5 mg/kg bolus followed by an infusion of 2 $mg.kg^{-1}.hr^{-1}$) was used in patients undergoing ambulatory surgery, it was noted that the infusion resulted in less intraoperative opioid use and less pain scores.[50] However, there were no differences in the time to discharge or in the incidences of postoperative nausea and vomiting. Whether this lack of salutary effect was due to the different kinds of surgeries or to the minimal suppression of the inflammatory process that accompanied the surgeries is not known.[51]

IV lidocaine infusion appears not to be as effective as perioperative epidural analgesia. Compared to thoracic epidural analgesia, IV lidocaine was inferior in terms of pain relief and attenuation of cytokine "surge" in patients who underwent colonic surgery. In a beautifully done randomized blinded study, Kuo et al.[52] showed that thoracic epidural analgesia resulted in better pain relief, lower opioid consumption, earlier return of bowel function, and lesser production of cytokines than IV lidocaine during the 72-hr observation study period. The patients who had the IV lidocaine experienced better pain relief and less cytokine release than the control (saline) group.

A less rigorous unblinded study compared the IV lidocaine infusion with epidural analgesia in patients who had open colon resection.[53] The IV lidocaine group had infusions of 1 to 2 mg/min (1 mg/min in <70-kg patients and 2 mg/min in >70-kg patients), while the epidural analgesia group had 10 ml/hr of 0.125% bupivacaine and hydromorphone of 6 mcg/ml. The infusions were started within 1 hr of the end of surgery and continued until return of bowel function or by day 5. There were no statistical differences in the average pain scores (VAS of 2.2 in the epidural group vs. 3.1 in the IV lidocaine group) and a trend towards greater opioid consumption in the IV lidocaine group. The return of bowel function or the length of hospital stay was not statistically different between the groups.[53] Although the study was randomized, it was not blinded. It should also be noted that two chronic pain patients in the IV lidocaine group were excluded and an epidural had to be subsequently placed in one of the patients for "further pain treatment."[53]

A meta-analysis of eight trials noted improved rehabilitation and shortened hospital stay when a lidocaine infusion was used.[54] The improved rehabilitation was supported by decreased postoperative pain at 24 hr after surgery, lower incidence of nausea and vomiting, and shorter duration of ileus. The ability of IV lidocaine to shorten the duration of paralytic ileus has been shown not only clinically, such as first passage of gas and feces, but also through radiopaque markers and serial abdominal radiographs.[55]

The beneficial effects of a perioperative lidocaine infusion in abdominal surgery may be related to its ability to suppress inflammatory processes secondary to the surgery.[45,46,51,52] IV lidocaine has been shown to attenuate the increased levels of proinflammatory cytokines,[45,46,52] which induce peripheral and central nervous system sensitization leading to hyperalgesia.[56] The lack of beneficial effect of IV lidocaine infusion may not be evident when the surgical trauma is minimal[51] as in ambulatory surgery[50] or in surgeries where there is a moderate component of neuropathic pain such as in total hip surgery[48] or in thoracic surgery.[49]

The efficacy of perioperative IV ketamine and lidocaine infusions is shown in Table 28-1. It can be seen that

TABLE 28–1 Efficacy of Perioperative Ketamine and Lidocaine Intravenous Infusions

	Ketamine	Lidocaine
Bolus dose	0.5–1 mg/kg	100 mg–1.5 mg/kg
Usual infusion dose	40–100 $mg.kg^{-1}.hr^{-1}$	2–3 mg/min (2 mg/min for patients <70 kg)
Infusion dose with epidural analgesia	0.05 (approximately 3 mg/hr) –0.25 $mg.kg^{-1}.hr^{-1}$	
Efficacy		
Abdominal surgery	Beneficial	Beneficial
Pelvic: gynecologic, urologic	Beneficial	Beneficial
Spine surgery	Beneficial	
Total hip replacement		Not beneficial
Coronary artery bypass surgery		Not beneficial
Total intravenous anesthesia	No additional benefit	
Concomitant PCEA	Additional benefit	
Compared to PCEA		Blinded study[52] showed less efficacy, while a randomized, unblinded study showed nonstatistically significant pain scores and a trend toward greater opioid consumption in the IV lidocaine group[53]

PCEA, patient-controlled epidural anesthesia.

infusion of either drug is beneficial in abdominal surgery. Ketamine infusion is effective in spine surgery but showed no added benefit when the technique of general anesthesia is total IV anesthesia. Lidocaine infusion appears to have no benefit in patients who undergo total hip replacement or coronary artery bypass surgery. A nicely done randomized blinded study showed less efficacy of IV lidocaine infusion when compared to epidural analgesia.

INTRAVENOUS NALOXONE INFUSION

The use of naloxone, a pure μ-receptor antagonist, with morphine to decrease the incidence of side effects is intuitive. However, its use comes with the possibility of reversing the analgesia from the opioid.[57] Naloxone infusion has been utilized to decrease the incidence of nausea, vomiting, respiratory depression, and urinary retention after epidural[58,59] and intrathecal opioids.[60,61] Studies showed that a naloxone intravenous infusion at 10 $mcg.kg^{-1}.hr^{-1}$ reduced the duration and quality of analgesia from epidural morphine[58] or fentanyl.[59] A study in patients who had hip surgery under spinal analgesia with bupivacaine and morphine showed that naloxone IV infusion at less than 1 $mcg.kg^{-1}.hr^{-1}$ was associated with inferior analgesia.[60] Another study showed that the infusion of naloxone at 1 $mcg.kg^{-1}.hr^{-1}$ attenuated the pain relief in the patients who had intrathecal morphine after lumbar laminectomy.[61] A retrospective study in patients who had radical prostatectomy and were given 0.8 to 1.7 mg intrathecal morphine showed the IV infusion of naloxone at 5 mcg.kg.hr provided excellent analgesia with infrequent and minor side effects.[62] Unfortunately, the study was retrospective and without a control group.[62]

The efficacy of a naloxone infusion in decreasing the incidence of side effects from neuraxial opioids led Gan et al.[63] in investigating the effect of naloxone infusion on PCA morphine. In a randomized, controlled, double-blind study, Gan et al.[63] assigned 60 patients who underwent hysterectomy into three groups: PCA morphine, 1 mg/ml, with saline infusion; PCA morphine with low-dose naloxone infusion (0.25 $mcg.kg^{-1}.hr^{-1}$); and c) PCA morphine with high dose naloxone infusion (1 $mcg.kg^{-1}.hr^{-1}$). The authors noted that both naloxone doses were equally effective in reducing the incidence of nausea and vomiting and pruritus compared with placebo. There was no difference in the verbal rating scores for pain among the three groups; the cumulative morphine usage was significantly lower in the low-dose group (42.3 ± 24.1 mg) compared with the placebo (59.1 ± 27.4 mg) or the high-dose group (64.7 ± 33 mg). There was no incidence in the respiratory depression and no difference in sedation scores, respiratory rate, hemodynamic parameters, or antiemetic use among the three groups.[63]

The ability of low doses of naloxone to improve postoperative analgesia is secondary to its dose-dependent effect on pain in animals and humans. Woolf[64] noted that small doses of naloxone produced analgesia in rats while large doses resulted in hyperalgesia. Levine et al.[65] noted that naloxone initially produced analgesia in a dose-dependent manner and then caused hyperalgesia. Other investigators noted this biphasic or dual modulatory effect of naloxone.[66–69] The mechanisms of analgesic effect of naloxone maybe related to the release of endorphins or displacement of endorphins from receptor sites not pertinent to analgesia.[63] Potentiation of the activity of opioid receptors is another possibility although this upregulation phenomenon has been demonstrated after prolonged naloxone infusion (7 days) and in animals.[70,71] At higher doses, naloxone blocks the action of the released or displaced endorphin at the postsynaptic receptor.

There seems to be no added efficacy when naloxone is administered via IV PCA.[72–74] The lack of added benefit maybe due to the different pharmacokinetics of the drug when given intermittently or as an infusion. Naloxone has an alpha half-life of 4 min and a beta half-life of 55 to 60 min,[75,76] and a continuous infusion of the drug may have resulted in a constant plasma levels resulting in a more consistent effect.

In summary, it appears that the present indication for IV naloxone infusion is to control the side effects of neuraxial opioids. Only the study by Gan et al.[63] showed the efficacy of a low-dose naloxone infusion in reducing opioid consumption. Its increased clinical use for postoperative analgesia should await additional controlled studies.

LOCAL ANESTHETIC WOUND INFUSIONS

Some surgeons infiltrate the surgical incision with local anesthetics at the end of the operation. Such practice only results in transient relief since the effect of the local anesthetic does not last long. For the effect to last longer, surgeons infuse the wound with local anesthetics after the surgery. There have been several studies which showed that wound infusions can reduce postoperative pain, diminish opioid intake and opioid-related side effects, and increase patient satisfaction. These wound infusions have been employed in painful procedures such as thoracic, cardiac, breast augmentation, abdominal, gynecologic, cesarean section, and spinal surgeries.

Studies showed the beneficial effects of local anesthetic wound infusions after thoracic operations. A continuous local anesthetic infusion of bupivacaine 0.5% at 4 ml/hr for 48 hr has been shown to be beneficial after cardiac surgery[77] (Table 28-2). In this study, two catheters were placed at the median sternotomy site, one in the subfascial plane and the other in the subcutaneous tissue. The wound infusion significantly reduced pain scores and PCA morphine use, and improved patient satisfaction.[77] In addition, the time to ambulation and duration of hospital stay were less. It is interesting to note that 0.25% bupivacaine infusion was no different from a saline infusion. When compared to either a single-shot epidural morphine or a continuous thoracic epidural infusion of bupivacaine, alone or in combination with fentanyl or morphine, a continuous infusion of 0.25% bupivacaine after thoracotomy resulted in significantly lower pain scores and lower opioid usage for 4 postoperative days.[78] The infusion rate was 2 to 4 ml/hr for 72 hr. In this study, a catheter was placed at the level of the pericostal sutures adjacent to the intercostal nerve bundle and another catheter placed

TABLE 28–2 Results of Studies on Efficacy of Local Anesthetic Wound Infusions

Study, Reference #	Infusion	Surgery	Results*/Comments
Fredman et al.,[81] R, DB, PC	Bupivacaine 0.25%, 9 ml/hr	Laparotomy	No benefit, catheter placed in SC layer
Cheong et al.,[82] R, C	Bupivacaine 0.5%, 2 ml/hr	Laparotomy	VAS same with less morphine use compared to IV PCA; catheter placed in SC layer
Baig et al.,[83] R, DB, PC	Bupivacaine 0.5%, 4 ml/hr	Laparotomy	VAS same, less narcotic use; catheter placed in SC layer
Beaussier et al.,[84] R, DB, PC	Ropivacaine 0.2%, 10 ml/hr	Colorectal surgery	Significant benefit, catheter placed preperitonally
Fredman et al.,[86] R, DB, PC	Ropivacaine 0.2%, 10 ml/hr	Cesarean section	Significant benefit, catheter placed above fascia
Zohar et al.,[87] R, DB, PC	Bupivacaine 0.25%, 9 ml/hr	Abdominal hysterectomy	Significant benefit, catheter placed above fascia
Kristensen et al.,[88] R, DB, PC	Bupivacaine 0.25%, 15 ml q 4hr	Hysterectomy	No benefit, catheter placed between muscle layer and peritoneum
Bianconi et al.,[89] R, DB, PC	Ropivacaine 0.25%, 5 ml/hr	Spine fusion	Significant benefit, catheter placed SC
Singh et al.,[90] and[91] R, DB, PC	Bupivacaine 0.5%, 2 ml/hr	Spinal arthrodesis	Significant benefit in immediate postoperative period, decreased graft site pain at 4 yr; catheter placed at outer table of iliac bone graft site
Blumenthal et al.,[92] R, DB, PC	Ropivacaine 0.2%, 5 ml/hr	Bankart procedure	Significant benefit in immediate postoperative period, less pain at iliac crest graft site at 3 mo; catheter placed at iliac crest site, interscalene catheter also used
White et al.,[77] R, DB, PC	Bupivacaine 0.5%, 4 ml/hr	Cardiac surgery	Significant benefit, one catheter placed in subfascial plane and another in SC tissue
Rawal.,[80] R, C	Ropivacaine, 0.25% or 0.5%, 10 ml boluses for VAS > 3	Breast augmentation surgery	Significantly better than oral medications; catheter placed SC
Wheatley et al.,[78] Retrospective	Bupivacaine 0.25%, 2–4 ml/hr	Thoracotomy	Intercostal nerve catheter infusion more than PCEA
Luketich et al.,[79] R, C	Bupivacaine 0.25%, 1 ml/10 kg/hr	Thoracotomy	Comparative efficacy of intercostal nerve catheter infusion with PCEA

C, controlled; DB, double blind; PC, placebo-controlled; PCA, patient-controlled anesthesia; PCEA, patient-controlled epidural anesthesia; R, randomized; SC, subcutaneous; VAS, Visual Analog Score.
**See text for details of study and results.*

above the fascia in the subcutaneous tissue. A big drawback in this study was that it was retrospective in nature.[78] A randomized study showed equivalent pain control between an intercostal-nerve catheter infusion and a thoracic epidural infusion of bupivacaine and morphine.[79] In this study, an intercostal nerve catheter was placed posteriorly at the eight intercostal space and tunneled vertically, below the parietal pleura, to the third intercostal space. The intercostal nerve infusion of 0.25% bupivacaine was at 1 ml.10 kg.hr (7 ml/hr for a 70-kg patient) for 72 hr. In addition, the patients had PCA with morphine. As stated, the two groups were similar in terms of pain scores, mean ICU days, and hospital days. The epidural analgesia had its drawbacks in that the epidural group had increased narcotic requirements and an increased number of urinary catheter days.[79] While two of the three studies are intercostal nerve infusions and not really wound infusions,[78,79] the study by White et al.[77] showed that wound infusion can be an effective regimen after thoracotomy. The same beneficial effect was shown after breast augmentation surgery.[80] A patient-controlled subcutaneous infusion of ropivacaine, either 0.25% or 0.5%, at 10-ml boluses for a VAS greater than 3 was shown to provide lower pain scores, less analgesic usage, less nausea and vomiting, and better global analgesia.

The effect of wound infusion after abdominal surgery appears to depend on where the wound catheter is placed (Table 28-2). A study showed no benefit of 0.25% bupivacaine after abdominal surgery.[81] Another study showed similar pain scores with less morphine usage when compared to IV PCA.[82] A third study showed no difference in pain scores, less morphine requirements (34 mg vs. 60 mg), and earlier ambulation.[83] However, the length of hospital stay or time to first bowel movement was the same when compared to a saline infusion.[83] In these three studies where the effect of the local anesthetic wound infusion was nil or not dramatic,[81–83] the catheters were placed subcutaneously and not subfascially. Subcutaneous placement restricts the blockade of parietal nociceptive inputs to the superficial layer of the abdominal wall, while subfascial placements block the fascia and peritoneum, which are richly innervated tissues.[84] The superior efficacy of catheters placed in the subfascial region, compared to placement in the subcutaneous tissues, was shown by a group of investigators.[85] The benefit of a preperitoneal administration of 0.2% ropivacaine at 10 ml/hr for 48 hr was shown after colorectal surgery. The infusion significantly reduced morphine consumption for 72 hr, improved pain relief at rest and while coughing, improved sleep quality, and reduced time to recovery of bowel function and duration of hospital stay.[84]

After cesarean section, local anesthetic wound infusions result in significantly lower pain scores after coughing, fewer patients receiving rescue opioid medications, and more patients describing their analgesia as good or excellent[86] (Table 28-2). In this study, the wound catheter was placed above the fascia and an infusion of 10 ml of 0.2% ropivacaine was initiated by the patient once every hour. The same beneficial effect of a local anesthetic wound infusion was noted in patients who had abdominal hysterectomy with bilateral salpingo-oophorectomy.[87] In this study, a catheter was placed above the superficial abdominal fascia and 0.25% bupivacaine was delivered via a patient-controlled device programmed to deliver 9 ml; the lockout interval was 60 min. The patients who had the wound infusion received less rescue analgesia, had less nausea and vomiting, and had better patient satisfaction. Interestingly, a randomized study showed the lack of beneficial effect when the catheter was placed between the muscle layer and the peritoneum.[88] The preperitoneal bupivacaine infusion (15 ml, 2.5 mg/ml, every 4 hr for 48 hr) did not improve analgesia at rest, during coughing, or during mobilization compared to saline.[88]

The beneficial effects of a local anesthetic wound infusion were also noted after orthopedic surgeries (Table 28-2). After spine fusion surgery, 40 ml of 0.5% ropivacaine was infiltrated into the wound followed by a subcutaneous infusion of 0.2% at 5 ml/hr over 55 hr after spine fusion surgery. The patients who had the ropivacaine infusion had significantly lower pain scores, less postoperative blood loss, and shorter hospital stay than the patients who had a saline infusion.[89] In patients who had posterior spinal arthrodesis, 0.5% bupivacaine was infused, at a rate of 2 ml/hr for 48 hr, through a catheter that was placed adjacent to the outer table of the harvested iliac crest bone graft site. The initial perioperative results showed decreased narcotic use and lower pain scores.[90] Long-term follow-up showed significantly decreased pain scores at the graft site and increased patient satisfaction at 4 years.[91] In addition, no patient experienced chronic iliac crest dysesthesias (0 of 9) compared to 7 of 10 patients in the saline group.[91] The same beneficial effect was noted after a Bankart repair, better pain relief for 48 hr after surgery and at 3 months after surgery was noted after a ropivacaine infusion through an iliac crest catheter.[92] Other studies, although nonrandomized, showed the same lower postoperative pain scores and earlier return to daily activities in patients who had a local anesthetic infused at the graft site.[93,94]

The plasma levels of the local anesthetic were noted to be below toxic levels whether 0.25% or 0.5% bupivacaine was infused at 4 ml/hr for 48 hr[77] or ropivacaine 0.2% was infused at 10 ml/hr.[88] In a study that looked into the pharmacokinetics of the local anesthetic, the injection of 200 mg of 0.5% ropivacaine followed by an infusion of 0.2% at 5 ml/hr for 55 hr resulted in peak total plasma concentration at 24 hr to be within safe limits and no local anesthetic side effects were observed.[89] None of the studies noted complications from the procedure including wound infection. A risk from the technique is direct tissue toxicity such as myotoxicity,[95] but this possibility from subcutaneous, subfascial, or preperitoneal local anesthetic infusions is rare.

A qualitative and quantitative review of the literature on local anesthetic wound infusions concluded that the available data consistently showed improved analgesia across a range of procedures, a very low technical failure rate, and zero reported toxicity.[96] Patient compliance is acceptable and wound infection rates have not increased. Future studies should focus on the optimal concentration and volume of the local anesthetic, the optimal site of placement of the wound catheter, a more detailed assessment of the dynamic analgesia and side effects from the technique, and comparison of wound infusions with other analgesic techniques such as neuraxial anesthesia and continuous peripheral nerve blocks.[97]

KEY POINTS

- Most of the randomized studies on perioperative intravenous (IV) ketamine infusion showed beneficial effects. The surgeries studied included abdominal, gynecologic, or spine surgery.
- Ketamine IV infusion appears not to be beneficial when total IV anesthesia is the technique of intraoperative anesthesia.
- The addition of a ketamine infusion in patients who had patient-controlled epidural analgesia resulted in less opioid requirement and probably a lower incidence of chronic pain after surgery.
- Most of the studies on perioperative IV lidocaine infusion showed salutary effects especially in abdominal surgery. The infusion appears to be less effective in total hip surgery and coronary artery bypass surgery. Whether this is due to a higher incidence of neuropathic pain in these surgeries is not known.
- The efficacy of perioperative IV lidocaine infusion may be related to the degree of trauma, it may not be as effective when the surgical trauma is greater.
- Perioperative IV lidocaine infusion appears to be less effective than epidural analgesia. While one study showed IV lidocaine infusion to be as effective as epidural analgesia, that study was not blinded.
- The present use of perioperative IV naloxone infusion is in controlling the side effects of neuraxial opioids.
- A local anesthetic wound infusion is an effective and simple technique to decrease postoperative pain. Side effects are minimal and blood levels of the local anesthetic after 48 to 55 hr of infusion are below toxic levels.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 29

Patient-Controlled Analgesia

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Patient-controlled analgesia (PCA) has become a standard technique in the clinical treatment of pain, allowing patients to self-administer predetermined doses of analgesic medication. PCA systems also record patient usage information such as total number of demands and drug delivery during the previous 1- and 24-hr periods. This information can help optimize drug delivery based on the pattern of use of the individual patient.

Current PCA models usually contain the following basic variables: initial loading dose, demand (bolus) dose, lockout interval, basal continuous infusions, and 1- to 4-hr maximal dose limits. The demand dose is the amount of analgesic the patient receives after activation of the pump. Newer devices allow for entries in units of micrograms, milligrams, and milliliters, thereby reducing the potential for programming errors when using drugs other than morphine. Optimization of efficacy and safety depends on the selection of a demand dose large enough to provide sufficient analgesia but small enough to minimize side effects. A lockout interval is the time during which there will be no drug delivery, even if the patient pushes the demand button. Theoretically, use of a lockout interval that is less than the time to peak effect of the drug may result in inadvertent overdosage due to stacking of analgesic doses. However, lockout intervals between 5 and 10 min appear optimal regardless of the opioid used.[1,2]

SAFETY AND EFFICACY OF PCA

ADVANTAGES OF PCA

Patient-controlled analgesia is extremely popular for many reasons. Patients like the security of knowing they can achieve pain relief quickly and easily without involving a nurse, not having to wait for pain relief, and not having intramuscular (IM) or subcutaneous injections.[3,4] Because of the ease with which each demand dose can be given, small boluses can be given frequently. When used properly, the ability of patients to titrate analgesics to their needs can theoretically generate a steady plasma level of analgesia and avoid the peaks and troughs associated with bolus dosing on a 3- to 4-hr basis. PCA may avoid subtherapeutic opioid concentration troughs, which can be associated with unpleasant recovery secondary to guarding, poor chest expansion, and reluctance to mobilize. PCA may also help avoid excessive peak plasma concentrations, with associated respiratory depression and sedation.[5] Although two meta-analyses demonstrated that PCA was associated with higher patient satisfaction and greater analgesic efficacy (compared with IM opioids), there was no difference in adverse effects.[6,7] Recent comparisons of PCA with conventional methods of opioid analgesia have produced contradictory results. Some show significantly better analgesia with PCA and others report no difference.[2] Furthermore, recent studies also report similar incidences of nausea and vomiting, sedation, pruritus, and bowel function, suggesting that the differences in total opioid dosages between PCA and conventional approaches may be relatively unimportant.[8-10] Given the continuing popularity of PCA, these results are somewhat surprising. It appears that good results can be obtained regardless of analgesic technique, if analgesia can truly be given on demand with appropriate doses and medication intervals. In many circumstances, PCA is the best way to achieve these goals.

Safe use of PCA requires that the patient controls the analgesic delivery. Increasing plasma concentrations of opioid usually cause sedation prior to causing clinically significant respiratory depression. Sedation usually impairs the ability of the patient to activate the PCA. Both nursing personnel and the patient's family members must understand this concept, so that only the patient pushes the demand button. Ideally, patients, nurses, and family members should receive education about PCA use. Not every patient is a good candidate for PCA; patients must be cooperative, must comprehend the concept, and must be able to push the PCA button. PCA may not be appropriate for very young children, or for patients with certain mental or physical limitations. Nurse-controlled analgesia (NCA) may be used if the patient's age, developmental level, or muscle strength interact with the ability to use the PCA device. NCA is a safe and effective method of analgesic administration in the pediatric intensive care unit (ICU) setting.[11] Finally, because of pharmacokinetic and pharmacodynamic variability among patients, conventional PCA settings may need to be adjusted for the individual.[5]

DISADVANTAGES OF PCA

Disadvantages of PCA can constrain its use and effectiveness. The most frequent negative perceptions relate to inadequate analgesia and/or presence of side effects, but some patients also report not trusting the PCA pump, or fearing overdose or addiction.[12,13] Chumbley et al. reported 22% of patients feared addiction and 30% feared overdose,[12] much higher than the 4% and 11%, respectively, reported by Kluger and Owen.[13] However, 43% of patients in the former study did not receive preoperative education about PCA, whereas all patients in the latter study received education about pain management and PCA prior to surgery.

Oversedation with PCA can occur as a result of repeated excessive use (patient misunderstanding of the analgesic goal), mistaking the PCA handset for the nurse call button, and family, visitor, or unauthorized nurse-activated demand boluses.[14] Operator errors can cause oversedation via programming of incorrect bolus dose size, incorrect concentrations, incorrect background infusions, and/or unintended background infusions. Incorrect procedures may lead to use of the wrong syringe or analgesic mixture.

Standardization of protocols and drug concentrations within an institution may reduce the chance of program errors.[15,16] Suboptimal interface design may pose a safety problem with PCA. An alternative user interface for a PCA machine has been designed with a human factors approach (taking into account human capabilities and limitations), with the goal of making the task of interfacing with the machine more transparent. This promoted ease of use and significantly reduced both programming times and rates of programming errors.[17]

Mechanical malfunctions of a PCA pump can occur, with inadvertent excessive medication delivery.[18,19] Despite this, the safety of PCA is supported by meta-analysis. There is no significant difference in the frequency or severity of oversedation and respiratory depression with PCA than with conventional intramuscular or intravenous dosing.[6]

IMPORTANCE OF ACUTE PAIN SERVICE

Implementation of an acute pain service (APS), which often consists of a team of physicians and nurses that are well educated about PCA, may also promote PCA safety and efficacy. Comparison of PCA managed by an APS versus PCA managed by the surgical staff indicated that patients with APS-supervised PCA had significantly fewer side effects, used more opioid, were more likely to have adjustments made to the PCA dose in response to inadequate analgesia or side effects, and were more likely to be ordered oral opioid analgesia rather than IM opioids after PCA.[20] This suggests that an APS is more likely to tailor the PCA to suit individual patients. Some of the benefits ascribed to PCA may be due to an association between PCA use and supervision of the analgesic regimen by concerned and knowledgeable clinicians.

TYPES OF PCAs

INTRAVENOUS PCAs

Many opioids have been used effectively for IV PCA. Opioids that are pure μ-receptor agonists tend to be the first choice for IV PCA.[21] The ideal opioid for IV PCA would have a rapid onset of action, high efficacy, and intermediate duration of action without significant accumulation of drug or metabolites over time.[5] Morphine, hydromorphone, and fentanyl most closely fulfill these criteria and are widely used for opioid-based IV PCA. On the other hand, meperidine metabolites can accumulate, suggesting that meperidine may not be a good first choice for IV PCA. All opioids have a similar spectrum of adverse effects, although qualitative differences are detectable. The patient's clinical history and hospital protocols tend to influence the choice of opioid selected for IV PCA. There are few prominent differences in pain scores and incidence of adverse effects between different opioids.[21-23] Consequently, patients are satisfied with PCA regardless of the opioid used. The typical dosing, lockout interval, and basal infusion parameters are indicated in Table 29-1.

TABLE 29–1 Sample Bolus Doses and Lockout Intervals for Opioid IV PCA

Drug	Bolus (mg)	Lockout Interval (min)
Fentanyl	0.015–0.05	3–10
Hydromorphone	0.1–0.5	5–15
Meperidine	5–15	5–15
Morphine	0.5–3	5–20
Oxymorphone	0.2–0.8	5–15
Remifentanil (labor)	0.5μg/kg	2
Sufentanil	0.003-0.015	3–10

For safety reasons, a continuous background infusion with IV PCA should only rarely be prescribed for spontaneously breathing opioid-naïve patients.[24,25] Continuous infusions pose increased risk for respiratory depression.[26-28] If a patient becomes sedated, continuing delivery of opioid at a basal rate may cause respiratory depression. Continuous opioid infusion in association with PCA may provide a more constant plasma opioid levels and improve analgesia.[25] However, other investigators found that addition of a basal infusion rate did not reduce pain, fatigue, or anxiety,[24,29] and also failed to improve patients' quality of sleep. The number of patient demands, number of supplemental bolus doses, and total opioid use were also not changed in patients receiving basal infusions of opioids. Additionally, most PCA programming errors that have resulted in adverse side effects occurred during the use of basal infusions.[28] However, in selected opioid-tolerant patients with high opioid requirements, a background infusion may be used to deliver the equivalent of the usual opioid dose taken by the patient.[5] Use of a background rate of infusion may necessitate higher vigilance and/or increased monitoring of the patient.

Addition of ketamine (an *N*-methyl-D-aspartate [NMDA] receptor antagonist) to IV PCA solutions may improve analgesia in some, but not all, circumstances. NMDA receptors are associated with the early development of opioid tolerance.[30,31] Optimization of postoperative IV PCA after spine and hip surgery indicated the ideal ratio of morphine and ketamine to be 1:1 with a lockout interval of 8 min.[32] However, two studies showed that either ketamine as an adjunct for IV PCA did not improve pain or that the potential usefulness of ketamine was offset by a high incidence of adverse effects and a lack of opioid-sparing effects.[33,34] It is important to consider the possibility that ketamine can arouse psychomimetic effects and impair cognition.

Clonidine is an α2-adrenergic agonist with analgesic properties. Addition of clonidine to morphine PCA significantly reduced nausea and vomiting in a female population undergoing lower abdominal surgery.[35] However, other studies fail to show significant benefits from inclusion of clonidine with IV PCA.[36]

NONINTRAVENOUS PCAs

The defining concept of PCA is patient-demand drug administration. Although IV PCA is the most common and studied route of delivery, the two common alternative routes are patient-controlled epidural analgesia and patient-controlled peripheral nerve catheter analgesia.

Patient-controlled epidural analgesia (PCEA): In many situations, epidural analgesia is superior to IV PCA (Table 29-2). A meta-analysis demonstrated that for all types of surgery and pain assessments, all forms of epidural analgesia including PCEA provided superior postoperative analgesia compared with IV PCA.[37] This conclusion is corroborated by a systematic review of the analgesic efficacy of epidural analgesia versus systemic opioids.[38] In addition to providing better pain control, epidural analgesia also has the potential benefits of decreased morbidity such as fewer cardiopulmonary complications, less thromboembolism, better mental status, earlier restoration of gastrointestinal function, enhanced functional exercise capacity and health-related quality of life, and earlier discharge from the hospital.[39-42] However, the potential benefits of PCEA must be weighed against potential risks associated with the placement of a catheter, which can cause serious complications such as epidural hematoma, infection, or neurologic injury.[21] In particular, thromboprophylaxis with potent anticoagulants may limit use of PCEA.[43]

The beneficial postoperative effects of epidural analgesia are more apparent for high-risk patients or those undergoing higher risk procedures. Epidural analgesia with a local anesthetic combined with an opioid provides better postoperative analgesia than epidural or systemic opioids alone, and may improve postoperative outcome.[44,45] Use of local anesthetic alone may result in excessive motor blockade. Despite numerous investigations, the ideal PCEA epidural analgesic solution or the ideal delivery variables remain controversial. In contrast to IV PCA, a continuous background infusion is routinely used for PCEA. A background infusion can maintain a continuous segmental sensory neural blockade, but may increase the incidence of complications such as hypotension and motor blockade. With regard to the anesthetic mixture, addition of clonidine (2 μg/ml) to ropivacaine-fentanyl PCEA after total knee arthroplasty reduced the need for opioid rescue without jeopardizing hemodynamics.[46] Similarly, addition of clonidine (10-20 μg/hr) to bupivacaine-fentanyl PCEA produced both dose-dependent improvement in analgesia at rest and dose-dependent decrease in blood pressure and pulse rate and an increase in vasopressor requirement.[47] PCEA with clonidine plus local anesthetic can provide adequate analgesia in some circumstances, without the usual opioid-related side effects such as nausea or pruritus. In an attempt to reduce side effects and facilitate transition to oral analgesia, the PCEA settings can be reduced gradually rather than abruptly terminating the PCEA. This can be done, for example, by eliminating the basal rate 6 hr prior to stopping the PCEA.

Peripheral nerve catheter patient-controlled analgesia (PNC PCA): Nerve block techniques are increasingly popular for management of postoperative pain, particularly with orthopedic surgery (Table 29-3). Many common nerve blocks, including brachial plexus, sciatic, and femoral nerve blocks, are amenable to having peripheral nerve catheters inserted for extended postoperative analgesia. Peripheral nerve blockade on both the upper and lower extremities can improve postoperative analgesia and patient satisfaction.[50] Infections and neurologic complications, although rare,

TABLE 29–2 Suggested Guidelines for PCEA Orders (Starting Doses) Surgical Site

	Drug and Concentration	Basal Rate (ml/hr)	Demand Dose (ml)	Lockout (min)
Obstetric (labor)	Bupivacaine 0.025% + fentanyl 10 μg/ml	3	3	10
Obstetric (labor)	Ropivacaine 0.08% + fentanyl 2 μg/ml	5	5	10
Lower abdomen, lower extremity and vascular: lumbar epidural	Bupivacaine 0.0625% + fentanyl 5 μg/ml	4	4	10
Lower abdomen with thoracic epidural	Bupivacaine 0.125% + fentanyl 5 μg/ml	4	3	10
Hip or knee surgery	Bupivacaine 0.06% + hydromorphone 10 μg/ml	4	4	10
Hip or knee surgery	Bupivacaine 0.06% + clonidine 1 μg/ml	4	4	10
Bupivacaine + clonidine PCEA for abdominal hysterectomy	Bupivacaine 0.125% + clonidine 0.75 μg/ml	10-ml loading dose	5	10 NB: 30-ml limit within 4 hr

Source: Heitmiller and Schwengel;[48] Hospital for Special Surgery;[49] and Topcu, Lulcci, and Tekin.[65]

TABLE 29–3 Sample Peripheral Nerve Catheter PCA Regimens

Catheter	Surgery	PNC Solution	Basal Rate (ml/hr)	Demand Dose (ml)	Lockout (min)
Interscalene, infraclavicular	Rotator cuff repair; hand surgery	Ropivacaine 0.2%	6–8	2–4	20
Subgluteus or popliteal sciatic	Foot and ankle surgery	Ropivacaine 0.2%	5–8	3–5	20–60

Source: Hospital for Special Surgery;[61] Ilfeld and Enneking;[66] and Ilfeld, Morey, and Wright.[67]

are possible. In contrast with neuraxial blocks, there is less concern about interaction of anticoagulants and peripheral nerve blocks.[21] Ropivacaine may be associated with reduction of complete motor and sensory block, compared to bupivacaine.[51] Common concentrations of local anesthetic for PNC PCA include ropivacaine, 0.2% to 0.3%, and bupivacaine, 0.12% to 0.25%. Inclusion of opioids in PNC PCA solutions is probably unnecessary, as peripheral opioids may increase side effects without improving analgesia.[71,72] Addition of clonidine to ropivacaine for PNC PCA does not improve analgesia.[52]

A continuous infusion of local anesthetics is generally used in PNC PCA, as this improves analgesia compared to bolus dosing only.[52] A low-dose continuous infusion (combined with a demand dose) reduces local anesthetic consumption without compromising analgesia, in comparison with continuous infusion alone.[53] For moderately painful shoulder surgery, decreasing an interscalene catheter infusion of ropivacaine 0.2% from a basal rate of 8 to 4 ml/hr provided similar analgesia, but the reduction caused a higher incidence of breakthrough pain and sleep disturbance.[67]

SPECIAL CONDITIONS

In addition to management of adult postoperative pain, PCA can also be used for the management of labor pain, pediatric postoperative pain, and cancer pain.

LABOR PAIN

The most common modality for pain control in labor is epidural analgesia. PCEA is a highly effective way of providing safe and superior labor analgesia. A multicenter, randomized controlled trial found that IV PCA and PCEA had the same rates of cesarean delivery or instrumental vaginal delivery.[70] However, patients receiving IV PCA were more likely to receive antiemetic therapy, had more sedation, and more neonates in this group required naloxone and active resuscitation (52% vs. 31%). Patients receiving PCEA had better pain relief and greater satisfaction with their analgesia. Choice of epidural infusion mixture as well as PCEA regimen is still under debate. A meta-analysis comparing continuous epidural infusion (CEI) with PCEA without background infusion concluded that patients in labor receiving PCEA are less likely to require anesthetic interventions, require lower doses of local anesthetic, and have less motor block than those who received CEI.[55] Addition of a basal rate to PCEA may further improve labor analgesia. Demand-only PCEA was associated with higher incidence of breakthrough pain, higher pain scores, shorter duration of effective analgesia, and lower maternal satisfaction, compared to PCEA with background infusion.[56]

Despite the superiority of PCEA for pain control in labor, some parturients do not want epidural analgesia or have clinical conditions that contraindicate its use. In this situation IV PCA should be considered. Administration of opioids to parturients can cause the newborn infant to be sedated or have impaired respiration. Some practitioners limit exposure of the fetus to opioids by discontinuing IV PCA once the mother's cervix is dilated. Compared with bolus parenteral opioids, IV PCA facilitates titration of analgesia as labor progresses and can better compensate for interpatient variability in analgesic requirements. For this reason, IV PCA (compared to intermittent IM dosing) may provide better pain relief and reduce maternal sedation, respiratory depression, and nausea.[57] Compared to IM dosing, IV PCA for labor analgesia reduces umbilical cord blood opioid levels (indicating less placental drug transfer); in most cases IV PCA does not cause significant fetal depression.[57,58] Use of shorter-acting opioids for labor IV PCA (such as fentanyl, alfentanil, and remifentanil) has been advocated in the hopes of reducing neonatal respiratory depression.[58,59]

PAIN CONTROL IN PEDIATRIC PATIENTS

Patient-controlled analgesia can reduce pain effectively and safely for adolescents and children. The critical determinant of successful PCA implementation in the pediatric population is the ability of the patient to understand the basic principles of PCA use. As a result, children younger than 4 years of age are not good candidates for PCA use. Children aged 4 to 6 years can use PCA pumps with the encouragement of nursing staff and parents. Nonetheless, the success rate in this age-group is low. Children older than 7 years of age often can use PCA independently. Parental assistance for PCA use by young children has been advocated by some investigators. Implementation of formal parent education programs along with close observation by nursing staff is necessary if parent-controlled analgesia is to be considered. Parent-controlled analgesia, however, bypasses the basic safety system of PCA and has been discouraged in the postoperative setting. Basal opioid infusions have also been successfully used by some physicians in the pediatric population for postoperative analgesia. However, some studies have shown an increased risk of hypoxemia in children receiving basal narcotic infusions with PCA.[60] In a clinical context where continuous opioid infusions are deemed necessary, methods of detecting opioid-induced respiratory depression, such as pulse oximetry, should be considered. In addition to the caution required for the use continuous infusion in the pediatric population, concurrent administration of drugs with respiratory depressant effects should also be viewed with extreme vigilance. Typical PCA dosing for children is shown in Tables 29-4 through 29-6.

PAIN CONTROL IN CANCER PATIENTS

Patient-controlled analgesia is one of the multimodal methods of effective cancer pain management in the inpatient setting for both adults and pediatric patients. The dosages of narcotics used in treating cancer pain often surpass those

TABLE 29–4 Pediatric PCA Dosing

Drug	Bolus (mg/kg)	Lockout (min)
Morphine	10–20	7–15
Hydromorphone	5–15	15
Fentanyl	0.1–0.2	7–15

TABLE 29–5 Pediatric PCEA Dosing

Drug	Basal Rate (ml/hr)	Demand Dose	Lockout (min)	One-Hour Limit (ml)
Bupivacaine 0.06% + hydromorphone 10 μg/ml	0.1–0.3 ml/kg/hr	0.1 mg/kg	Minimum of 10 min	Max = 0.4 ml/kg/hr

Source: Hospital for Special Surgery.[61]

TABLE 29–6 Pediatric Peripheral Nerve Catheter PCA Dosing

Drug	Basal Rate (ml/hr)	One-Hour Limit (ml)
Ropivacaine 0.2%	0.1–0.2 ml/kg/hr	0.2 ml/kg/hr

Source: Hospital for Special Surgery.[61]

used postoperatively. Consequently, the utilization of basal continuous opioid infusions for the management of cancer pain is very valuable and, in contrast to postoperative pain management, should be encouraged.[62] Parenteral narcotics provide a vital route for providing analgesia in patients with moderate to severe cancer pain. One study demonstrated changing the route of opioid administration, including the use of PCA-administered parenteral narcotics, is an important tactic for patients who have intractable cancer pain.[63] Moreover, the use of methadone in PCA pumps, a practice uncommonly advocated for postoperative pain, is also a useful consideration in treating intractable cancer pain.[64]

KEY POINTS

- Patient-controlled analgesia is a programmable delivery system by which patients self-administer predetermined doses of analgesic medication at the push of a button. PCA can optimize drug delivery and improve satisfaction by enabling patients to titrate analgesia.
- Safe use of PCA requires the patient to control analgesic delivery. Increasing plasma concentrations of opioid usually cause sedation prior to causing clinically significant respiratory depression. Sedation usually impairs the ability of the patient to activate the PCA.
- The ideal opioid for IV PCA has rapid onset of action, high efficacy, and intermediate duration of action. Morphine, fentanyl, and hydromorphone fit these criteria.
- Opioid-naïve patients should not usually receive postoperative basal IV opioid infusions. Addition of a basal infusion to IV PCA may not improve postoperative analgesia, but may increase the risk of respiratory depression. Continuous infusions are often used for cancer patients, due to higher analgesic requirements associated with cancer pain.
- Patient-controlled epidural analgesia is recommended for routine use during labor analgesia. IV PCA for labor, although acceptable in some circumstances, provides worse analgesia and may potentially depress neonatal ventilation and neurologic activity.
- Patient-controlled epidural analgesia may provide superior postoperative analgesia for a variety of surgical procedures when compared with IV PCA. In addition to providing better pain control, epidural analgesia may have the potential benefits of decreased morbidity. However, the potential benefits of PCEA must be balanced against the potential risks associated with the placement of the catheter.
- Peripheral nerve catheter patient-controlled analgesia may be an ideal postoperative analgesic modality in the setting of rehabilitation following orthopedic and plastic surgery procedures that may otherwise be impeded by significant pain without the use of peripheral nerve catheters.
- Most children older than 7 years can understand the concept of PCA, and can safely use PCA. However, children younger than 4 years of age, or patients with mental or physical limitations, may not be able to effectively use a PCA machine.

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CHAPTER 30

Intrathecal Opioid Injections for Postoperative Pain

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Over the past two decades the use of single-dose intrathecal (IT) opioids has become commonplace in anesthetic practice. Since the first described use of IT morphine in 1979, hundreds of case reports and clinical investigations have been published on the IT administration of opioids. Human and animal studies have elucidated the mechanism of action of IT opioids, side-effect profiles, dose-response pharmacology, interaction with adjuvant agents, and clinical uses for a wide range of surgical cases. Common uses of IT opioids for postoperative analgesia include obstetric and gynecologic surgery, orthopedic joint and spine procedures, thoracic and vascular procedures, cardiac bypass, pediatric surgery, urologic procedures, and abdominal procedures.

MECHANISMS OF ACTION OF INTRATHECAL OPIOIDS

Nociceptive information is transmitted by multiple afferent neurons with small-diameter unmyelinated and thinly myelinated fibers (C-fibers and Aδ-fibers, respectively) playing a major role in the transmission of pain. Central terminals of small unmyelinated fibers are located in Rexed's laminae I, II, and III.[1] Opioid receptors exist in Rexed's laminae I, II, and V in the dorsal horn of the spinal cord. This provides the anatomic basis for selective analgesia by opioids injected into the cerebrospinal fluid (CSF). Spinal cord analgesia is likely mediated by μ- and κ-receptors. Experimental studies have shown that substance P is released into the CSF by electrical stimulation.[1] This release is inhibited by the administration of morphine into the CSF and possibly mediated by gamma-aminobutyric acid (GABA) presynaptically and glycine postsynaptically.

The pharmacologic properties of the various opioids determine their onset, duration of action, and side effects (Table 30-1). Lipophilicity (versus hydrophilicity) is the key property affecting the speed of onset and duration of action. Highly lipid-soluble drugs such as fentanyl and sufentanil have a faster onset but shorter duration of action when used intrathecally.[2,3] Shortly after injection, CSF levels are barely detectible as the drug is quickly distributed to the spinal cord.[3] This may result in a more segmental spread of analgesia and a lower concentration reaching the brain, decreasing the risk of delayed respiratory depression (e.g., 12 to 24 hr after injection). Hydrophilic opioids, such as morphine, have a slower onset and longer duration of action, and remain detectable in the CSF long after injection. Delayed respiratory depression may be more likely with morphine than other lipophilic drugs, as morphine remains in the CSF long enough to circulate rostrally to the brainstem and respiratory centers.

Only meperidine has strong enough local anesthetic properties to be used as a sole agent for surgery. IT injection of meperidine produces spinal anesthesia that is qualitatively similar to that achieved with conventional local anesthetics.[4] It is likely the combined action of its local anesthetic properties and its opioid receptor binding that allows meperidine to be used as the sole agent in spinal anesthesia. The onset of action for meperidine is similar to that of fentanyl despite being significantly less lipid soluble; however, its duration is longer than fentanyl. Meperidine has a shorter duration of action than morphine, as meperidine dissipates from the CSF four times faster than morphine.[4]

ADVANTAGES OF INTRATHECAL OPIOIDS

There are several advantages inherent to the use of IT opioids compared to intravenous and epidural opioids or IT and epidural local anesthetics (Table 30-2). Equianalgesic doses of IT opioids are typically a small fraction of those used for intravenous or epidural use.[5] The resultant serum levels, especially with morphine, are barely detectable, thus limiting the systemic effects while maximizing the analgesic properties.[5,6] The duration of analgesia for a hydrophilic opioid such as morphine is greater compared to intravenous or epidural administration.[1,7] A single IT injection of morphine 0.04 to 0.5 mg will provide up to 15 to 24 hr of analgesia.[8–11] IT morphine may be of benefit in certain clinical situations. For instance, IT opioids may provide an advantage over epidural catheters in operations where anticoagulation will be started immediately postoperatively, necessitating the removal of the epidural catheter at the conclusion of surgery.

Unlike neuraxially administered local anesthetics, which may result in vasodilation and hypotension, opioids do not per se cause adverse hemodynamic changes when applied intrathecally and may not significantly attenuate the neuroendocrine stress response even when administered in extremely large doses (4.0 mg).[12] In addition, opioids do not cause motor blockade or sensory loss, potentially allowing earlier ambulation.[13] IT opioids do provide a sparing effect for local anesthetics, allowing lower doses to be used intrathecally or epidurally while still maintaining adequate analgesia.[14] Meperidine, an opioid with local anesthetic properties, has been used effectively as the sole agent for spinal anesthesia.[4]

SIDE EFFECTS OF INTRATHECAL OPIOIDS

Unfortunately, IT opioids are not without a significant number of adverse effects (Table 30-3). Most of these are dose dependent and may be more common for agents

TABLE 30–1 Characteristics of Intrathecal Opioids

Opioid	Oil–Water Partition Coefficient*	Typical Adult Intrathecal Dose	Onset of Analgesia (minutes)	Duration of Analgesia (minutes)
Morphine	1.4	0.05–0.6 mg	30–60	480–1440
Meperidine	39	10–100 mg	2–12	60–400
Fentanyl	816	10–50 μg	5–10	30–120
Sufentanil	1727	2.5–12.5 μg	3–6	60–180

**A higher number reflects increased lipophilicity.*

TABLE 30–2 Advantages of Intrathecal Opioids

Long duration of action
Small doses required for equianalgesic effect
Almost undetectable vascular absorption
Ease of cannulating the intrathecal space
Minimal hemodynamic changes
No motor blockade
No sensory loss

TABLE 30–3 Side Effects of Intrathecal Opioids

Common	Uncommon
Mild respiratory depression	Respiratory arrest
Pruritus	Generalized muscle rigidity
Sedation	Nystagmus
Nausea	Epileptic seizure
Vomiting	Myoclonus
Urinary retention	Hyperalgesia
	Neurotoxicity
	Water retention

administered intrathecally than by other routes. They are less common in patients who are chronically exposed to opioids. Most, but not all, side effects are mediated via interactions with opioid receptors.

The most feared complications are respiratory depression and arrest. Shortly following the first description of the use of IT morphine in humans, cases of delayed respiratory depression were reported. The large IT doses of morphine (up to 20 mg) that had been used in the early 1980s were associated with an alarmingly high rate of respiratory depression.[1] It has been demonstrated that the risk of respiratory depression is dose related[15]; with few instances of clinically significant depression reported at doses less than 0.4 mg of IT morphine.[16] Isolated cases of respiratory depression, however, have been noted at even smaller doses.[17]

The incidence of respiratory depression is difficult to quantify, although from the available literature it appears to be less than 1% for IT opioids.[18,19] Indeed, the incidence of respiratory depression is less than 1% for opioids regardless of the route of administration.[19] A meta-analysis of IT morphine in spinal anesthesia noted that IT morphine did not increase the overall risk of respiratory compromise; however, higher doses of IT morphine were associated with more episodes of respiratory depression when compared to lower doses.[20] Furthermore, when added to a general anesthetic, IT morphine appears to be associated with an increase risk of respiratory depression (odds ratio = 7.86; 95% confidence interval [CI]: 1.54–40.3).[21]

Respiratory depression typically occurs within minutes to hours for the lipophilic opioids (fentanyl, sufentanil) with early respiratory depression (minutes) not being reported with a hydrophilic opioid such as morphine. For morphine, delayed respiratory depression characteristically occurs 6 to 12 hr after administration but has been reported up to 19 hr after IT injection.[22] Considerable hypoventilation may occur following IT morphine even in the presence of "normal" pulse oximetry and respiratory rate. Sedation may be another indicator of impending respiratory depression, although only arterial blood gas analysis will reliably identify hypercarbia. Supplemental oxygenation may prevent hypoxemia but may not correct the underlying etiology or even worsen hypoventilation and hypercarbia due to the elimination of hypoxic respiratory drive, especially when obstruction of the airway (e.g., obstructive sleep apnea) is implicated.

The risk of respiratory depression increases with the addition of systemic opioids or sedatives, increasing age, lack of opioid tolerance (i.e., opioid-naive state), obesity, and sleep apnea.[1,8,23] With hydrophilic opioids, respiratory depression occurs after the migration of opioid within the CSF to and reaction with opioid receptors in the ventral medulla.[20] Naloxone has been used effectively to treat respiratory depression from IT opioids, although there is a case report of naloxone-resistant respiratory depression following IT administration of opioids.[17] Naloxone will most likely need to be readministered or used as a continuous infusion due to its relatively short half-life. Long-acting opioid antagonists have also been used for treatment and prevention of respiratory depression.

The risk of postoperative respiratory depression after the use of IT opioids has stirred debate about whether intensive care unit–like monitoring is required after patients leave the postanesthesia care unit. With lipid-soluble opioids, this is not as much of an issue, as delayed respiratory depression would be highly unlikely. The risk of delayed respiratory depression from IT morphine, however, has prompted some institutions to require

admission to a monitored unit for all patients receiving IT morphine. Observational data indicate that respiratory depression from opioids (regardless of route of administration) is less than 1%,[19] is not higher with IT or neuraxial administration, and rarely occurs with IT morphine doses of less than 0.4 mg. A higher dose may be acceptable for opioid-tolerant patients. In addition, the requirement for monitored beds may in itself be reason enough to discourage the administration of IT opioids to patients who would otherwise benefit from such therapeutics. Patients with comorbidities such as sleep apnea, sedation, pulmonary disease, and mental status changes should be monitored closely after receiving IT opioids. IT morphine should not be used for ambulatory surgery. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration have been published.[24]

The most common side effect of IT opioids is pruritus.[22] Compared to placebo, IT morphine is associated with an increased risk of pruritus with higher doses being associated with a greater risk than lower doses (relative risk [RR] = 1.8, 95% CI: 1.4–2.2 for <0.3 mg morphine; and RR = 5.0, 95% CI: 2.9–8.6 for >0.3 mg morphine).[20] Pruritus is usually noted in the facial areas innervated by the trigeminal nerve; however, itching may also be generalized. Although IT opioid-induced pruritus is likely due to cephalad migration of the drug and interaction with opioid receptors in the trigeminal nucleus located superficially in the medulla,[22] the exact etiology is not clear. The incidence has been reported anywhere from 20% to 100% in various studies and may be dose dependent.[13,22,25,26] It is difficult to determine differences in the incidence of pruritus among the different opioids due to methodologic issues; however, it appears that patients who receive morphine have a higher incidence of pruritus than those who receive fentanyl.[22,27] The obstetric patient population has one of the highest incidences of pruritus.[22,25,26,28,29] Despite the relatively high incidence of pruritus, very few patients actually request treatment, as the pruritus is often noted as a problematic side effect only after clinician prompting. Itching does not appear to be histamine mediated nor is it related to systemic absorption of the drug. Antihistamines are minimally effective as a treatment; however, their sedating properties may relieve symptoms in some patients. Opioid receptor antagonists, such as naloxone, and opioid agonists–antagonists are effective in the treatment for pruritus.[22,30,31] Low-dose intravenous naloxone may be effective in attenuating pruritus but does not generally decrease the analgesic efficacy of IT opioids.[23,32] Propofol in a 2-mg dose may relieve pruritus without affecting analgesia, but is less effective than μ receptor antagonists.[31] Ondansetron may be an effective agent for treating spinal or epidural morphine-induced pruritus.[33] Prophylactic ondansetron 0.1 mg/kg intravenous (IV) has also been shown to reduce the incidence of pruritus after IT morphine.[34]

Nausea and vomiting are also common and troublesome side effects after IT opioid injection. Although the incidence is lower than that seen with pruritus, these patients more often require treatment. Nausea occurs in approximately 20% to 40% of patients receiving IT opioids.[22] Although the underlying mechanism is not related to systemic absorption, the incidence is comparable to IV and epidural administration. Nausea usually occurs within 4 hr of injection and may be more likely when IT morphine is used.[22] Numerous studies have shown a slight correlation between dose and nausea and vomiting, while others have failed to show a connection. The presumed mechanism is the cephalad migration of drug and subsequent interaction with opioid receptors in the area postrema.[22] A recent meta-analysis suggests that nausea and vomiting induced by IT morphine is not dose dependent. Compared to placebo, low doses of IT morphine (<0.3 mg) were associated with an increased risk of nausea (RR = 1.4; 95% CI: 1.1–1.7) and vomiting (RR = 3.1; 95% CI: 1.5–6.4); however, higher doses of IT morphine (>0.3 mg) did not result in an increased risk of either nausea (RR = 1.2; 95% CI: 0.9–1.6) or vomiting (RR = 1.3; 95% CI: 0.9–1.9) compared to lower doses.[20] Naloxone is generally effective in the treatment of nausea and vomiting induced by IT opioids. Long-acting opioid antagonists may not be as effective in treating nausea, but there may be a benefit if given prophylactically.[27,30,35,36]

Urinary retention following IT opioids is much more common than after equivalent doses given intravenously. The incidence of urinary retention varies considerably but occurs most frequently in males.[20] Urinary retention induced by IT opioids is not dose related, may be more frequent when IT morphine is administered, and is likely related to opioid receptor–induced inhibition of sacral parasympathetic nervous system outflow, resulting in detrusor relaxation and an increase in bladder capacity.[22] Naloxone may be effective in treatment, although bladder catheterization is frequently required.[22,37]

Sedation is a dose-dependent side effect of IT opioids that occurs with all opioids.[8] The incidence may be higher with sufentanil than with other opioids.[22,35,38,39] Respiratory depression should always be suspected when sedation occurs following IT opioids.[8,22] The difference in the incidence of sedation from IT, IV, and epidural routes is not well documented, but appears to be common regardless of the route of delivery. Opioid receptor antagonists are effective in decreasing the level of sedation.[30] Chronic opioid use and subsequent tolerance may decrease the incidence of sedation.

Herpes simplex labialis virus reactivation has been reported following IT morphine, although a causal relationship is not well established at this time.[40,41] Epidural morphine has also been postulated to cause reactivation of herpes, although no mechanism has been clearly identified. Opioids reach the sensory ganglia where the herpes virus lies dormant and may reactivate the virus through an unknown interaction.[40]

There are numerous other rare side effects linked with IT opioids in the literature. Generalized muscle rigidity in a neonate was reported following IT fentanyl during cesarean delivery.[42] Muscle rigidity and myoclonic movements, not mediated by opioid receptors, are also reported in adults.[22] Nystagmus, double vision, and convulsive movements of the eyelids have been described.[17] Epileptic seizure has also been reported following an IT morphine bolus.[43] Large doses of IT morphine have been linked to hyperalgesia in laboratory animals.[22]

CLINICAL USES OF INTRATHECAL OPIOIDS FOR POSTOPERATIVE ANALGESIA

Numerous case reports, randomized clinical trials, and dose–response studies have been completed over the last two decades related to the use of IT opioids for postoperative pain management in a variety of procedures including obstetric, orthopedic, abdominal, pediatric, and cardiac surgeries. The great majority of trials have evaluated the use of IT morphine due to its long-lasting analgesic effects. The lipophilic opioids do play a role in postoperative analgesia; however, their relatively short duration may limit their utility for single-dose IT administration in the management of postoperative pain.

There are more studies on the use of IT opioids in postoperative obstetric patients (excluding labor analgesia) than in any other patient population. In general, there has been a trend toward using lower doses of hydrophilic opioids, which provide reasonable levels of postoperative analgesia with a lower incidence of side effects (Table 30-4). Milner et al. demonstrated that 0.1 mg of IT morphine produces analgesia comparable to a dose of 0.2 mg but with significantly less nausea and vomiting.[44] A dose–response study comparing the use of 0.125, 0.25, or 0.375 mg of diamorphine for cesarean section demonstrated improved postoperative analgesia with the two higher doses at the cost of increasing pruritus and vomiting.[25] When comparing 0.1 mg and 0.2 mg doses of IT morphine to 3 mg of epidural morphine, Sarvela and colleagues concluded that the dose of 0.1 mg of IT morphine provided optimal postoperative analgesia for cesarean section patients.[26] Sufentanil (10 μg) improves and prolongs the duration of surgical analgesia in patients undergoing cesarean section but at the cost of increased hypotension and pruritus.[45] More recent studies have discovered genetic variants in the μ-opioid receptor, which may partially explain the variable responses to IT opioids for labor analgesia.[46]

Lower extremity orthopedic patients are frequently ideal candidates for regional anesthesia and IT opioids due to the presence of significant postoperative pain, which can be difficult to control. The addition of morphine 0.3 mg IT to patients receiving bupivacaine spinal anesthesia significantly reduces pain and IV morphine patient-controlled analgesia (PCA) requirements compared to patients receiving bupivacaine spinal anesthesia with placebo following knee arthroplasty with no significant difference in hypoxemia or apnea between the groups.[47] A dose–response study in patients undergoing major lumbar spinal surgery demonstrated that 0.3 to 0.4 mg of IT morphine provided superior analgesia compared to a dose of 0.2 mg and, although the arterial carbon dioxide tension was higher in the group who received 0.4 mg of IT morphine, no clinical signs of respiratory depression were noted.[16] The use of high-dose IT morphine (10–20 μg/kg) has been reported to provide excellent analgesia without significant respiratory depression in patients undergoing spinal fusion with instrumentation.[48] Patients who received doses of 20 μg/kg of IT morphine remained pain-free longer, required less additional narcotic, and had fewer respiratory complications.[48] A more recent study also noted that up to 0.2 mg of IT morphine provided effective analgesia for up to 48 hr without any need for additional systemic opioids in many patients undergoing orthopedic surgery.[49] IT morphine is clearly beneficial in reducing additional opioid requirements in patients undergoing orthopedic surgery, but the optimal dose is not clear. For patients who are opioid-tolerant, higher doses are probably acceptable while doses of less than 0.3 mg may be ideal for opioid-naive individuals.

IT opioids have also been used in cardiac surgery. While IT morphine has been demonstrated to provide pain relief following coronary artery bypass grafting

TABLE 30–4 Dose–Response Studies of Intrathecal Morphine

Study (Author, Year)	Study Population (*n*)	Trial Design	Doses Examined (mg)	Optimal Dose (mg)
Jacobson et al., 1988	ORTHO (33)	DB, RCT	0, 0.3, 1, 2.5	0.3–1
Boezaart et al., 1999	ORTHO (60)	DB, RCT	0.2, 0.3, 0.4	0.3
Kirson et al., 1989	GU (10)	DB, RCT	0, 0.1, 0.2	0.1
Sarma and Bostrom, 1993	GYN (80)	DB, RCT	0, 0.1, 0.3, 0.5	0.3
Yamaguchi et al., 1990	GI (139)	RCT	0, 0.04, 0.06, 0.08, 0.10, 0.12, 0.15, 0.20	0.06–0.12
Jiang et al., 1991	OB (63)	RCT	0, 0.025, 0.05, 0.075, 0.1, 0.125	0.075–0.125
Milner et al., 1996	OB (50)	RCT	0.1, 0.2	0.1
Kelly et al., 1998*	OB (80)	RCT	0, 0.125, 0.25, 0.375	—
Palmer et al., 1999	OB (108)	DB, RCT	0, 0.025, 0.05, 0.075, 0.1, 0.2, 0.3, 0.4, or 0.5	0.1
Sarvela et al., 2002	OB (150)	DB, RCT	0.1, 0.2	0.1

DB, double blind; GI, abdominal; GU, urologic; GYN, gynecologic; OB, obstetric (cesarean section); ORTHO, orthopedics; RCT, randomized controlled trial.
Studies: Boezaart AP, Eksteen JA, Spyu GV, et al: Intrathecal morphine. Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. Spine *24:1131–1137, 1999; Jacobson L, Chabal C, Brody MC: A dose–response study of intrathecal morphine: Efficacy, duration, optimal dose, and side effects.* Anesth Analg *67:1082–1088, 1988; Jiang CJ, Liu CC, Wu TJ, et al: Mini-dose intrathecal morphine for post-cesarean section analgesia.* Ma Zui Xue Za Zhi *29:683–689, 1991; Kelly MC, Carabine UA, Mirakhur RK: Intrathecal diamorphine for analgesia after caesarean section. A dose finding study and assessment of side-effects.* Anaesthesia *53:231–237, 1998; Kirson LE, Goldman JM, Slover RB: Low-dose intrathecal morphine for postoperative pain control in patients undergoing transurethral resection of the prostate.* Anesthesiology *71:192–195, 1989; Milner AR, Bogod DG, Harwood RJ: Intrathecal administration of morphine for elective caesarean section. A comparison between 0.1 mg and 0.2 mg.* Anaesthesia *51:871–873, 1996. Palmer CM, Emerson S, Volgoropolous D, et al: Dose–response relationship of intrathecal morphine for postcesarean analgesia.* Anesthesiology *90:437–444, 1999; Sarma VJ, Bostrom UV: Intrathecal morphine for the relief of post-hysterectomy pain—A double-blind, dose–response study.* Acta Anaesthesiol Scand *37:223–227, 1993; Sarvela J, Halonen P, Soikkeli A, et al: A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery.* Anesth Analg *95:436–440, 2002; Yamaguchi H, Watanabe S, Motokawa K, et al: Intrathecal morphine dose–response data for pain relief after cholecystectomy.* Anesth Analg *70:168–171, 1990.*
**Diamorphine.*

(CABG), the fear of bleeding complications in a patient who is fully heparinized may have limited the use of this technique. Numerous studies have used IT opioids in patients undergoing heart surgery with CABG without the subsequent development of epidural hematoma. An IT dose of 5 μg/kg morphine produces superior analgesia compared to IV PCA morphine over 24 hr in patients having off-pump CABG, although extubation times were significantly longer in the IT morphine group.[50] Alhashemi et al. also found that larger doses (0.5 mg) of IT morphine prolonged extubation time but improved analgesia.[51] They concluded that 250 μg is the optimal dose of IT morphine to provide significant postoperative analgesia without delaying tracheal extubation.[51] More recent data suggest that IT morphine (7 μg/kg) for patients undergoing cardiac surgery may actually result in earlier extubation and possibly decrease the length of the intensive care unit stay.[52]

An ample amount of literature now exists describing the use of IT opioids in pediatric patients. It is important to note that the standard doses often used in adults may be excessive in children. In a dose–response study using 0, 2, or 5 μg/kg of IT morphine in children 9 to 19 years of age undergoing a spinal fusion the two IT opioid groups had superior postoperative analgesia, with the 2 and 5 μg/kg doses having a similar effectiveness and side effect profile.[53] A retrospective study of 52 pediatric patients receiving either IT morphine or IV PCA nalbuphine for upper abdominal or thoracic surgery concluded that IT morphine provided superior pain relief without an increase in serious complications.[54] Although more dose–response studies are needed in pediatric patients, IT morphine in doses less than 10 μg/kg has been demonstrated to be effective in children 6 months of age or older.

IT opioid combinations will provide superior analgesia versus systemic opioids in patients undergoing vascular and thoracic procedures. Compared to those who received IV PCA morphine, patients who received a mixture of either 20 μg of sufentanil with 0.2 mg of morphine or 50 μg of sufentanil with 0.5 mg of morphine have improved pain control and minimal side effects with the exception of an increased frequency of urinary retention.[7,10] Although epidural analgesia with local anesthetics and opioids is likely superior to IT opioids in decreasing pulmonary complications after thoracotomy,[55] IT opioids may be a good alternative to epidural analgesia in situations where an epidural catheter cannot be maintained.

IT opioids have been demonstrated to provide excellent analgesia in abdominal procedures. A dose–response trial evaluating doses of IT morphine ranging from 0 to 0.2 mg in patients undergoing cholecystectomy concluded that 0.06 to 0.12 mg was the optimal dose range for maximal analgesia and minimization of side effects such as respiratory depression, vomiting, or pruritus.[9] The use of low-dose IT morphine (0.075–0.1 mg) in providing adequate postoperative pain control was confirmed in a subsequent study.[56] At least one study has suggested that IT morphine (0.3 mg), when combined with IV PCA with opioids in elderly patients undergoing major colorectal surgery, improves immediate postoperative pain and decreases parenteral morphine consumption.[57]

ADJUVANTS TO INTRATHECAL OPIOIDS

Numerous studies have been published that have used other IT agents in combination with IT opioids in an effort to improve analgesia while minimizing side effects. Most of these adjuncts are analgesics that do not interact with opioid receptors. Other adjunct agents are used to alleviate or prevent side effects of IT opioids, but may have varying degrees of analgesic properties.

Clonidine, an alpha-2 receptor agonist, has been used to improve analgesia in combination with IT opioids as well as with IT local anesthetics. Clonidine increases the duration of sensory and motor blockade from bupivicaine spinal anesthesia through several mechanisms.[58] Alpha-2 adrenergic agonists administered intrathecally may increase the antinociceptive threshold by activating descending noradrenergic pathways in the spinal cord.[59] The clinical data on the analgesic interaction between clonidine and opioids are equivocal. Grace and colleagues did not demonstrate any additional pain relief when 75 μg of IT clonidine was coadministered with 0.5 mg of IT morphine.[59] Another study also failed to demonstrate a benefit from the addition of oral clonidine to IT morphine.[60] In contrast, using a lower dose of IT morphine, Goyagi and Nishikawa demonstrated a decreased requirement for supplemental analgesia in patients receiving 5 μg/kg of oral clonidine.[61] Gautier et al. found that 30 μg of clonidine combined with 2.5 to 5 μg of sufentanil produced significantly longer analgesia than sufentanil alone.[39] Most of the evidence indicates that lower doses of 15 to 30 μg may be equally efficacious as larger doses while decreasing side effects such as sedation, hypotension, and bradycardia. Although the mechanism of potentiation appears to be mediated in the spinal cord, oral and IV administration of clonidine may also be effective in conjunction with IT opioids.[61]

CONCLUSION

IT opioids have been shown to be a safe and effective method of postoperative pain control. The benefit of long-lasting, noncyclic pain relief obtained with IT hydrophilic opioids, along with the lack of hemodynamic effects and motor blockade, makes this an excellent option for some patients. Patients should be assessed for adverse reactions, including nausea, vomiting, pruritus, respiratory depression, urinary retention, and sedation, following administration of IT opioids. These can be easily treated with currently available pharmacologic agents. The wide variety of surgical procedures that are conducive to the use of IT opioids offers many opportunities for incorporation of this modality. It is certainly not the ideal technique in many cases, but when used appropriately it may confer significant benefits to patients.

KEY POINTS

- The pharmacologic properties of IT opioids reflect the extent of the hydro- versus lipophilicity of the specific opioid: lipophilic opioids (fentanyl and sufentanil) have a shorter onset and duration of action, whereas hydrophilic

opioids (morphine) have a delayed onset and prolonged duration of action (and certain side effects such as delayed respiratory depression).

- Like opioids administered by other routes, IT opioids may result in widely recognized opioid-related side effects such as nausea, vomiting, pruritus, sedation, and respiratory depression. The incidence of respiratory depression from clinically relevant doses of IT opioids is no greater than when given by other routes. Frequent monitoring of patients who have received IT opioids is recommended; however, the need for an intensive care unit–like setting for postoperative monitoring of these patients is controversial.
- Delayed respiratory depression is more likely with hydrophilic opioids use; however, it is much less likely with the currently clinically accepted doses, which are lower than those used one to two decades ago. The following factors may contribute to the development of respiratory depression after IT opioid administration: opioid-naive state, concurrent use of systemic opioids or sedatives, age, and sleep or obstructive sleep apnea.

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CHAPTER 31

Epidural Opioids for Postoperative Pain

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The use of epidural opioids, either as a single injection or continuous infusion, is an important analgesic option for the treatment of postoperative pain. The clinician can choose from a range of available epidural opioids, each with its own pharmacokinetic profile that allows titration to the specific clinical scenario. Despite some of the side effects associated with epidural opioid administration, there are many advantages to using epidural opioids for analgesia, including some data that suggest an improvement in some important clinically oriented patient outcomes.

PHARMACOLOGY OF EPIDURAL OPIOIDS

An opioid administered into the epidural space will diffuse into the surrounding tissues including epidural fat and veins. Opioids that diffuse into epidural fat are no longer available to bind to opioid receptors and thus cannot produce analgesia. Opioids administered into the epidural space generally produce analgesia via two mechanisms: spinal and supraspinal/systemic analgesia. To produce supraspinally mediated analgesia, epidural opioids may be absorbed into plasma and redistributed to the brainstem via the bloodstream.[1] To produce spinally mediated analgesia, epidural opioids must diffuse through the spinal meninges into the cerebrospinal fluid (CSF). The interactions between the physiochemical properties of the spinal meninges and epidural opioids are complex and the permeability of an epidurally administered opioid through the spinal meninges is dependent on many factors including the lipid solubility of the opioid.[1] Once inside the CSF, epidural opioids interact with spinal opioid receptors located in lamina II of the dorsal horn of the spinal cord and achieve antinociception via presynaptic reduction of afferent neurotransmitter release and postsynaptic hyperpolarization of dorsal horn neurons.

One of the key pharmacologic properties of an epidurally administered opioid that determines its analgesic and side effect profile is the extent of its lipophilicity. After single-dose epidural administration, lipophilic opioids, such as fentanyl and sufentanil, generally have a relatively faster onset but shorter duration of action when compared to that of more hydrophilic opioids such as morphine and hydromorphone. The extent of lipophilicity also affects the side effect profile of the individual opioid. The relatively rapid clearance from the CSF of lipophilic opioids may limit the development of certain side effects such as delayed respiratory depression.[2,3]

Unlike opioids that are injected intrathecally and expected to produce analgesia via a direct effect on the spinal cord and redistribution within the intrathecal space, epidural opioids do not consistently produce analgesia through this pathway. The degree to which lipophilic opioids produce analgesia via a spinal or supraspinal mechanism is still somewhat controversial.[1,4] Although some data suggest that epidural fentanyl for labor analgesia may produce a selective spinal analgesic effect,[1,5] it is generally thought that lipophilic opioids will produce analgesia primarily by systemic uptake and redistribution of the lipophilic opioid to brainstem opioid receptors.[1] This systemic redistribution of epidurally administered lipophilic opioid is especially obvious when a continuous infusion is used for a prolonged period of time.[6] On the other hand, it is clear that the primary analgesic site of action for hydrophilic opioids is selectively spinal.[7,8] Once the epidurally administered hydrophilic opioid has penetrated the dural membrane into the CSF, the opioid will remain within the CSF to produce spinal analgesia and spread cephalad or rostrally in the CSF (due in part to its low lipid solubility) to act at the brainstem.[8] The rostral spread of hydrophilic opioid to the brainstem may be associated with facial pruritus, nausea, and sedation.[9]

INJECTION OF SINGLE-DOSE EPIDURAL OPIOIDS

A single-dose injection of neuraxial opioids can provide effective postoperative analgesia as a sole analgesic agent or in combination with other agents (e.g., local anesthetics or alpha-2 agonists); however, the analgesic profile (duration of analgesia and side effects) is dependent primarily on the degree of lipophilicity (vs. hydrophilicity) with hydrophilic agents such as morphine and hydromorphone producing a longer duration of analgesia versus lipophilic agents such as fentanyl and sufentanil. In light of the pharmacokinetic differences between the hydrophilic and lipophilic opioids, the agent or agents chosen should be tailored to the surgical procedure so as to optimize analgesia and minimize side effects. For instance, a single injection of a hydrophilic opioid like morphine typically provides 12 to 18 hr of analgesia at the risk of delayed respiratory depression and would be useful for postoperative analgesia in surgical inpatients with appropriate monitoring or regular assessments. For outpatient surgery, a lipophilic opioid like fentanyl may be more appropriate, as its analgesic onset is more rapid and duration of action is shorter (minimizing the risk of delayed respiratory depression) than hydrophilic opioids.

Both lipophilic and hydrophilic opioids may provide effective postoperative analgesia when administered in a single dose. When compared to intravenous fentanyl boluses, epidural fentanyl given via an epidural bolus has been shown to provide adequate pain relief as well as inhibit physiologic, hormonal, and metabolic responses observed in the postoperative period as indicated by lower blood glucose levels, arterial blood pressure, and plasma cortisol levels for the first 20 hr after surgery.[10] A single epidural bolus of a lipophilic opioid like fentanyl may be administered to provide a rapid (onset within 5–10 min) but

TABLE 31–1 Common Doses of Epidural Opioids*

	Single Dose	Continuous Infusion
Fentanyl	50–100 μg	25–100 μg/hr
Sufentanil	10–50 μg	10–20 μg/hr
Alfentanil	0.5–1 mg	0.2 mg/hr
Morphine	1–5 mg	0.1–1 mg/hr
Diamorphine	4–6 mg	—
Hydromorphone	0.5–1 mg	0.1–0.2 mg/hr
Meperidine	20–60 mg	10–60 mg/hr
Methadone	4–8 mg	0.3–0.5 mg/hr

**Doses based on use of neuraxial opioid alone. Lower doses may be effective when administered to the elderly or when injected in the cervical or thoracic region.*

relatively transient (up to 4 hr) postoperative analgesia. Diluting the epidural dose of fentanyl (typically 50–100 μg) in at least 10 ml of preservative-free normal saline may hasten onset and prolong the duration of analgesia possibly as a result of an increase in the initial spread and diffusion of fentanyl.[2,11]

A single epidural dose of a hydrophilic opioid is especially efficacious for prolonged postoperative analgesia.[12] Epidural morphine when administered as a single bolus has been shown to provide effective postoperative analgesia for a variety of procedures including cesarean sections and major abdominal vascular surgery.[12,13] Combining a hydrophilic opioid (e.g., morphine) and a lipophilic opioid (e.g., sufentanil) in a single epidural injection combines the short onset time produced by the lipophilic opioid and the long duration of analgesia produced by the hydrophilic opioid.[14]

Epidural analgesia may also provide for preemptive analgesia by administering an analgesic prior to nociceptive stimuli.[15] Epidural opioids given preoperatively in conjunction with ketamine result in a reduction in postoperative pain interventions, including epidural dosing.[16] Epidural administration (either as a single shot or continuous infusion) of a hydrophilic opioid is especially effective in scenarios where the epidural catheter location is not congruent with the site of surgical incision (e.g., lumbar epidural catheter for thoracic surgery). The doses of epidural morphine may need to be decreased for elderly patients and thoracic catheter sites.[2,17,18] Commonly used dosages for epidural administration of opioids are provided in Table 31-1.

CONTINUOUS INFUSION OF EPIDURAL OPIOIDS

Continuous infusions of epidural opioids will provide effective postoperative pain control for a variety of surgical procedures. When used alone for postoperative pain control, analgesic infusions of epidural opioids will not generally cause motor block or hypotension due to sympathetic blockade as may be seen in patients receiving a local anesthetic-based epidural regimen.[19] Similar to that seen with single-dose administration, there are important clinical differences between continuous epidural infusions of lipophilic (fentanyl, sufentanil) and hydrophilic (morphine, hydromorphone) opioids.

Although the precise site of analgesic action (spinal vs. supraspinal/systemic) for continuous epidural infusions of lipophilic opioids has not yet been elucidated, many randomized controlled trials suggest that the epidural infusions of lipophilic opioids produce analgesia primarily via a supraspinal/systemic mechanism.[20–22] In these trials there were no differences in plasma concentrations, side effects, or pain scores between those receiving either intravenous or epidural infusions of fentanyl.[20,21] Despite the presence of a trial suggesting a benefit with continuous epidural infusions of fentanyl,[23] the overall advantage of administering continuous epidural infusions of lipophilic opioids alone is minimal, with the possible exception of its use in obstetric analgesia.[1,19]

On the other hand, continuous epidural infusions of hydrophilic opioids produce analgesia primarily via a spinal mechanism.[24] Similar to what is seen with single-dose epidural administration of a hydrophilic opioid, continuous infusions of hydrophilic opioids may be particularly effective in providing postoperative pain control in cases where either the epidural catheter insertion location is not congruent with the site of surgery or when side effects (e.g., hypotension, motor block) limit the ability to use a local anesthetic-based epidural analgesic regimen. Use of a continuous epidural infusion of morphine may provide superior analgesia when compared to systemic opioids[6,25] or intermittent boluses of epidural morphine.[24,26]

Although continuous infusions of epidural opioids may be used alone and are effective in controlling postoperative pain, continuous infusions of epidural opioids are more commonly administered in conjunction with a local anesthetic. This combination may confer analgesic advantages over infusions using either a local anesthetic alone or opioid alone, although the incidence of side effects may or may not be diminished.[9,27–29] The choice of opioid varies among clinicians: many will choose to use a lipophilic opioid (fentanyl 2 to 5 μg/ml or sufentanil 0.5 to 1 μg/ml) as part of a patient-controlled epidural analgesic regimen to allow for rapid titration of analgesia[2,19,24]; however, use of a hydrophilic opioid (morphine 0.05–0.1 mg/ml or hydromorphone 0.01–0.05 mg/ml) as part of a local anesthetic–opioid epidural analgesic regimen may also provide effective postoperative analgesia.[2,24]

SIDE EFFECTS OF EPIDURAL OPIOIDS

Similar to that seen when administered systemically, epidural opioids exhibit the side effects of respiratory depression, pruritus, nausea, and vomiting. Many of these side effects appear to be dose dependent; however, the side effect profile is slightly different between lipophilic and hydrophilic epidural opioids. Hypotension is rarely directly attributable to epidural opioids and the difference in heart rate and mean arterial blood pressure between systemic opioid and epidural opioid administration is minimal.[30] It is important to always consider other causes for the side effects (e.g., hypovolemia and bleeding in the case of hypotension) before automatically attributing the etiology to epidural opioids. In addition, standing orders and nursing protocols for the monitoring of neurologic status (e.g., sensory and motor function) and side effects with physician notification of critical parameters should be

standard for all patients receiving continuous infusions of epidural opioids.

RESPIRATORY DEPRESSION

Respiratory depression may occasionally occur after administration of epidural opioids. Respiratory depression associated with epidural (and intrathecal) administration of opioids is dose dependent and the incidence is typically reported to be from 0.1% to 0.9%.[31–36] The incidence of respiratory depression with epidural opioids (when used in appropriate doses) is no higher than that seen with systemic administration of opioids. Continuous infusions of epidural opioids have no higher incidence of respiratory depression than does systemic opioid administration.[31,36] There is some controversy as to whether patients receiving continuous epidural infusions of hydrophilic opioids need intensive care–like monitoring to detect respiratory depression. It is noteworthy that several large-scale studies have demonstrated the relative safety of continuous epidural infusions of hydrophilic opioids on regular surgical wards, finding the incidence of respiratory depression to be less than 0.9%.[32,35,37,38] Factors that may increase the risk of respiratory depression developing in patients who have received epidural opioids include: thoracic surgery, presence of comorbidities, age, an opioid-naive state, and concomitant use of systemic opioids and sedatives.[36]

There are differences in the respiratory depressant profile between epidural lipophilic and hydrophilic opioids. Lipophilic opioids (e.g., fentanyl) administered in the epidural space are associated with early (typically within 2–4 hr of administration) rather than late (more than 2–4 hr after administration) respiratory depression. Lipophilic opioids are rapidly absorbed systemically from the epidural venous plexus and delivered to the brain and respiratory centers, thus the onset and resolution of respiratory depression from lipophilic opioids occurs relatively quickly. On the other hand, the onset of respiratory depression after epidural administration of hydrophilic opioids (e.g., morphine) is generally slower than that seen with epidural administration of lipophilic opioids. Hydrophilic epidural opioids are primarily delivered to the brain via relatively slower rostral migration in the CSF rather than the more rapid systemic absorption and redistribution of lipophilic opioids. Cephalad spread of hydrophilic opioids typically occurs within 12 hr following injection.[36] Respiratory depression from epidural administration of hydrophilic opioids can therefore occur later, typically within 6 to 12 hr after injection. Assessing the patient's respiratory rate alone may not be a reliable predictor of a patient's ventilatory status or detect impending respiratory depression.[33] Administration of naloxone (0.1–0.4-mg increments) is generally effective in reversing respiratory depression; however, a continuous infusion of naloxone (0.5–5 μg/kg/hr) may be needed since the duration of action of naloxone is shorter than the respiratory depressant effect of epidural opioids.[2,36] Recently, practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration have been published.[39]

NAUSEA AND VOMITING

Nausea and vomiting occur in 20% to 50% of patients after a single dose of epidural opioid[9,40,41] and the overall incidence in those receiving continuous infusions of epidural opioids is reported to be 45% to 80%.[42–44] The development of opioid-induced nausea and vomiting after administration of epidural opioids appears to be dose dependent.[45–47] Nausea and vomiting from epidural opioids result from interactions with opioid receptors in the area postrema and chemotactic trigger zone of the medulla. For epidurally administered hydrophilic opioids, nausea and vomiting may be related to the cephalad migration of opioid within the CSF to the area postrema in the medulla.[9] Treatment of epidural opioid-induced nausea and vomiting may include the use of naloxone, droperidol, metoclopramide, dexamethasone, transdermal scopolamine, and even a small dose of propofol.[42,48–50]

PRURITUS

The etiology of epidural opioid-induced pruritus is unclear and may be related to activation of an "itch center" in the medulla, interaction with opioid receptors in the trigeminal nucleus or nerve roots, or changes in the sensory modulation of the trigeminal and upper cervical spinal cord due to cephalad migration of the opioid; however, opioid-induced pruritus does not appear to be associated with peripheral histamine release.[9] Pruritus from epidural opioids may occur in as many as 60% of patients compared to a 15% to 18% incidence with systemic opioid use.[51–53] Whether epidural opioid-induced pruritus is dose dependent is uncertain, with some systematic data indicating no evidence of a dose-dependent relationship,[51] while other studies suggest the presence of such a relationship.[54,55] Naloxone, naltrexone, nalbuphine, and droperidol appear to be effective in the treatment of epidural opioid-induced pruritus.[52] Use of epidural morphine is associated with postpartum reactivation of herpes.[56]

URINARY RETENTION

Administration of epidural opioids may result in urinary retention that is related to a decrease in detrusor muscle strength contraction secondary to spinal opioid receptor activation.[9] When compared to systemically administered opioids (occurrence of approximately 18%),[9,51] the incidence of urinary retention from epidurally administered opioids appears to be much higher (70%–80%).[54,57] The development of urinary retention does not appear to be dose dependent.[57,58] Low-dose naloxone may be effective in treating epidural opioid-induced urinary retention but at the risk of reversing analgesia.[59]

PATIENT OUTCOMES AND EPIDURAL MORPHINE

The use of a local anesthetic-based epidural anesthetic–analgesic technique may be associated with a decrease in perioperative morbidity and mortality.[60] The analgesic and physiologic benefits of a local anesthetic-based epidural solution may be attributed in part to the attenuation or

even complete suppression of pathophysiological changes that occur in the perioperative period. Unlike local anesthetics, use of an opioid-based epidural analgesic solution typically can only confer partial attenuation of perioperative pathophysiology despite the superior analgesia provided by epidural morphine versus systemic opioids. Thus, the beneficial effect of epidural morphine on patient outcomes may not be as apparent when compared to local anesthetic-based epidural techniques.

Administration of epidural morphine may modify the perioperative stress response, although to a lesser extent when compared to local anesthetics.[61] Unlike what occurs with local anesthetics, use of epidural morphine will still allow transmission of nociceptive information through the central nervous system. Because of the inability to completely suppress the neuroendocrine stress response, epidural opioids do not consistently prevent the perioperative increases in cortisol, epinephrine, or glucose but may attenuate increases in levels of norepinephrine.

Despite the fact that epidural morphine can only partially attenuate the perioperative pathophysic response, there are data suggesting an improvement in patient outcomes with the perioperative use of epidural morphine compared to systemic opioids (Table 31-2). Several relatively large-scale randomized trials suggest that epidural morphine for postoperative analgesia may decrease perioperative mortality.[62–64] Randomized data also suggest that postoperative epidural morphine analgesia when compared to systemic opioids may decrease both cardiovascular and pulmonary complications.[62–65] In addition, a meta-analysis examining the effects of various analgesic regimens on pulmonary outcomes revealed that the use of epidural morphine (vs. systemic opioids) will decrease the incidence of postoperative atelectasis.[66] However, the use of epidural morphine either alone or as part of a local anesthetic–morphine infusion does not facilitate return of postoperative gastrointestinal function when compared to systemic opioids.[60]

EXTENDED-RELEASE EPIDURAL MORPHINE

Recent development of an extended-release epidural morphine (EREM) may provide analgesia for 48 hr after a single dose. The current clinically available formulation utilizes microscopic lipid-based particles with numerous internal vesicles containing morphine. Each vesicle is separated from the adjacent chambers by synthetic analogs of naturally occurring lipid membranes.[67] Following injection of EREM into a patient, the lipid membranes reorganize and the drug is released.[67] Several randomized controlled trials have been conducted investigating EREM for postoperative analgesia. Analysis of individual patient data from clinical trials suggests that the use of EREM (vs. intravenous patient-controlled analgesia) may result in improved patient satisfaction but with a higher rate of pruritus.[68] Although it is not clear whether use of EREM will result in a higher incidence of respiratory events compared to

TABLE 31–2 Outcome Studies of Epidural Morphine vs. Systemic Opioids for Postoperative Analgesia

Study (Author, Year)	Study Population (n)	Trial Design	Morbidity (EA vs. SYST)
Park et al., 2001	ABD (1021)	RCT	22% vs. 37%*
Tsui et al., 1997	ABD–THOR	RCT	EA improved pulmonary (EA: 13% vs. 25%; $P = 0.002$) and CV (EA: 21% vs. 43%; $P < 0.001$) outcomes and LOS (EA: 22 ± 20 vs. 30 ± 37; $P = 0.005$)
Major et al., 1996	ABD (65)	OBS	Improvement in EA for CV ($P = 0.0002$)/pulmonary ($P = 0.019$) outcomes, LOS ICU ($P = 0.024$)
Liu et al.,1995	ABD (54)	RCT	No difference in GI recovery between epidural and systemic opioids
Beattie et al., 1993	Mixed (55)	RCT	Improvement in EA for CV ischemia (EA: 17.2% vs. 50%; $P = 0.01$) and tachyarrhythmias (EA: 20.7% vs. 50%; $P < 0.05$)
Her et al., 1990	ABD (49)	OBS	Improvement in EA for need for ventilatory support ($P = 0.0002$), respiratory failure ($P = 0.018$), and LOS ICU (EA: 2.7 days vs. 3.8 days; $P = 0.003$)
Hasenbos et al., 1987	THOR (129)	RCT	Improvement in EA for pulmonary complications (EA: 12.1% vs. 38%)
Rawal, 1984	ABD	RCT	Improvement in EA for pulmonary complications (EA: 13% vs. 40%), GI function (EA: 56.7 ± 3.1 hr vs. 75.1 ± 3.1 hr; $P < 0.05$), and LOS (EA: 7 ± 0.5 days vs. 9 ± 0.6 days; $P < 0.05$)

ABD, abdominal surgery; CV, cardiovascular; EA, epidural morphine analgesia; GI, gastrointestinal; ICU, intensive care unit; LOS, length of stay; OBS, observational trial; RCT, randomized controlled trial; SYST, systemic opioid analgesia; THOR, thoracic surgery.

Studies: Beattie WS, Buckley DN, Forrest JB: Epidural morphine reduces the risk of postoperative myocardial ischaemia in patients with cardiac risk factors. Can J Anaesth *40:532–541, 1993; Hasenbos M, van Egmond J, Gielen M, et al: Post-operative analgesia by high thoracic epidural versus intramuscular nicomorphine after thoracotomy: III. The effects of pre- and post-operative analgesia on morbidity.* Acta Anaesthesiol Scand *31:608–615, 1987; Her C, Kizelshteyn G, Walker V, et al: Combined epidural and general anesthesia for abdominal aortic surgery.* J Cardiothorac Anesth *4:552–557, 1990; Liu SS, Carpenter RL, Mackey DC, et al: Effects of perioperative analgesic technique on rate of recovery after colon surgery.* Anesthesiology *83:757–765, 1995; Major CP Jr, Greer MS, Russell WL, et al: Postoperative pulmonary complications and morbidity after abdominal aneurysmectomy: a comparison of postoperative epidural versus parenteral opioid analgesia.* Am Surg *62:45–51, 1996; Park WY, Thompson JS, Lee KK: Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study.* Ann Surg *234:560–569, 2001; Rawal N, Sjostrand V, Christoffersson E, et al: Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function.* Anesth Analg *63:583–92, 1984; Tsui SL, Law S, Fok M, et al: Postoperative analgesia reduces mortality and morbidity after esophagectomy.* Am J Surg *173:472–478, 1997.*

**Data represented are a subgroup (aortic aneurysm repair) of the study that which showed no overall difference. Morbidity data are combined.*

traditional epidural morphine or systemic opioids, a recent meta-analysis suggest that EREM (vs. intravenous patient-controlled analgesia) is associated with significantly higher odds of respiratory depression.[69] Local anesthetic (e.g., test dose) should not be administered immediately after injection of a dose of EREM; however, preliminary data indicate that any interaction may be minimized by waiting 15 min after a local anesthetic dose before injecting the EREM.[70]

CONCLUSION

Epidurally administered opioids are a valuable analgesic option in the treatment of postoperative pain. The lipid solubility of the specific epidural opioid is the primary determinant of its clinical analgesic (and side-effect) profile. Single-dose hydrophilic opioids can provide prolonged pain relief in inpatient surgical populations, whereas lipophilic opioids will provide postoperative pain relief of a shorter duration. Continuous infusions of hydrophilic opioid alone provide effective postoperative analgesia even when the catheter insertion site is not congruent to the incision site. Continuous infusions of lipophilic opioid alone will not provide a selective spinal site of action; but because of their titratability, lipophilic opioid infusions are most commonly seen as part of a local anesthetic–opioid solution in patient-controlled epidural analgesia. Hydrophilic opioids, particularly morphine, may improve patient outcomes especially in high-risk patients.

KEY POINTS

- As is seen with intrathecal opioids, the pharmacologic properties of epidurally administered opioids reflect the extent of the hydro- versus lipophilicity of the specific opioid: lipophilic opioids (fentanyl and sufentanil) have a shorter onset and duration of action whereas hydrophilic opioids (morphine, hydromorphone) have a delayed onset and prolonged duration of action (and certain side effects such as delayed respiratory depression).
- Epidural opioids exhibit the same side effects (respiratory depression, pruritus, nausea, and vomiting) as opioids given systemically. Many of these side effects appear to be dose dependent; however, the side effect profile is slightly different between lipophilic and hydrophilic epidural opioids. The incidence of respiratory depression is similar regardless of the route of administration (epidural vs. systemic). Certain groups of patients may be at higher risk for developing respiratory depression after epidural administration of opioids.
- The clinician should consider the analgesic and side-effect profile of epidural lipophilic and hydrophilic opioids and tailor these for individual clinical scenarios (e.g., avoiding a long-acting hydrophilic opioid such as morphine for ambulatory surgery).
- Unlike neuraxially administered local anesthetics; use of epidural morphine can only partially attenuate the perioperative pathophysiologic response. However, several studies have shown that perioperative use of epidural morphine (vs. systemic opioids) may result in an improvement in patient outcomes, such as reductions in cardiovascular–pulmonary complications and even decreased mortality.

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CHAPTER 32

Intra-Articular and Intraperitoneal Opioids for Postoperative Pain

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INTRA-ARTICULAR OPIOIDS

The use of arthroscopic techniques in orthopedic surgery has gained a preeminent role as diagnostic and therapeutic procedures for the knee, hip, ankle, shoulder, and hand. Arthroscopy is typically an outpatient procedure, and although touted as being less painful than open surgical procedures, is nevertheless associated with postoperative pain that is at times severe. Oral and systemic analgesics, including opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), have been used with varying degrees of success to combat postoperative pain, but with various attendant side effects also reported. The intra-articular (IA) injection of local anesthetics and adjuvants has been considered efficacious in modulating postoperative pain, but support for their routine use is limited. Recently, in Europe, there has been a trend toward using large volumes of diluted local anesthetics and adjuvants intra-articularly for managing acute pain associated with major knee joint replacement surgery. It remains to be seen whether this trend toward large-volume articular infusion of various cocktails makes its way to the United States, and although opioids are conspicuously not included in all of these large volume protocols, it is compelling to think that there may be some rationale for using this multimodal approach to managing acute pain.

IA local anesthetics have demonstrated modest and short-acting efficacy in a systematic review of the literature.[1] Mu-agonist opioids, most notably morphine, have support for use in moderate to severe pain when administered IA, but whether the resultant analgesia is due to a local or systemic effect is debatable.[2–5] NSAIDs have consistently demonstrated a benefit in modulating postoperative pain when injected IA, yet there is a concern that they may inhibit or retard bone healing. The use of the alpha-2 agonist clonidine IA has demonstrated a modest and limited reduction in postoperative pain, although the same controversy exists as to whether these benefits are mediated systemically or are local phenomena. Other agents, such as ketamine, corticosteroids, and neostigmine, are currently undergoing IA trials but current support for their use is sparse.

INTRA-ARTICULAR MORPHINE

Morphine is the prototypical μ-receptor opioid agonist to which all other opioids are compared. In humans, morphine produces analgesia, sedation, euphoria, and a reduction in the ability to concentrate on a task. Other sensations include nausea, subjective feeling of warmth, dry mouth, and pruritus, particularly perinasally. Systemically administered morphine increases pain thresholds and modifies the perception of noxious stimulation. In contrast to nonopioid analgesics, morphine is effective against pain arising from visceral structures in addition to that arising from skeletal muscles, joints, and integument. Peak effect occurs in about 45 to 90 min, and duration of action is about 4 hr.

A significant number of papers have been dedicated to the injection of IA morphine sulfate, most notably into the knee joint following diagnostic arthroscopy. This subject has produced significant controversy in the published literature: some investigators demonstrated a benefit to IA morphine following knee arthroscopy[6–9] while others did not.[10–14] Niemi et al in a randomized and double-blind study showed that the need for postoperative ketoprofen was less after 1 mg morphine compared to IA saline.[15] Khoury et al demonstrated that morphine alone or combined with bupivacaine IA provided postoperative analgesia of delayed onset but of remarkably long duration, and longer than that provided by IA bupivacaine alone.[16] Similar results were observed by Jaureguito et al.[17] The injection of local anesthetic (bupivacaine) and morphine after knee surgery provided superior analgesia than either agent alone.[18] In another study the combination of morphine and bupivacaine IA provided superior postoperative analgesia when compared to IA saline, IA morphine, or IA bupivacaine, as determined by pain scores (visual analog scale, VAS) and analgesic use.[19] However, Solheim et al showed no benefit of using IA morphine, 5 mg via an IA catheter, after knee arthroscopy in patients who had moderate or severe pain.[20] This recent data, culled from studying 60 patients who each had an IA catheter placed at the end of surgery for either morphine or saline administration, would contradict some of the earlier clinical impressions of a beneficial role for IA morphine when used before the surgical stimulus, that is, as preemptive analgesic regimens.

IA morphine may not provide comparable analgesia to that provided by continuous peripheral nerve blocks following surgical arthroscopy of the knee. When IA morphine (1 mg) was compared to IA bupivacaine or continuous lumbar plexus (three-in-one) blocks for postoperative analgesia after knee arthroscopy, the lumbar plexus blocks were found to be superior to the IA morphine or IA local anesthetic.[21]

Other local anesthetics besides bupivacaine have also been compared to IA morphine. When compared to IA morphine alone (1 or 5 mg) or morphine plus ropivacaine (5 mg and 75 mg), IA ropivacaine alone (150 mg) was noted to provide superior analgesia after knee arthroscopy but only in the early postoperative period.[22] No difference was noted in the pain scores or the tramadol consumption between the groups by 24 and 48 hr postoperatively.[22]

Other adjuvant agents such as clonidine and ketorolac were compared to morphine, either alone or in combination

with morphine. A combination of clonidine (1 μg/kg), 30 ml of bupivacaine (0.25%), and morphine (3 mg) provided superior postoperative analgesia compared to the IA bupivacaine or either adjunct used in combination with the local anesthetic.[23] Another study compared IA morphine/bupivacaine with IA morphine/bupivacaine combined with systemic (intramuscular) diclofenac (75 mg). The group who received the combination therapy demonstrated the lowest VAS scores and lowest postoperative fentanyl use after knee arthroscopy.[24]

A nonpharmacologic adjunct to IA morphine was suggested by Whitford et al. They found that analgesia was superior in a group of patients in whom the thigh tourniquet was maintained for 10 min after the IA morphine administration.[25] The optimum analgesic dose of IA morphine appears to be 1 to 2 mg.[26] Doses up to 5 mg have been used, but do not appear to confer any specific advantage to more modest ones. As to the optimal time of administering morphine IA for knee surgery, it was found that analgesia was superior when the IA morphine (3 mg) was given before incision compared to its administration postoperatively.[27]

The type of arthroscopic knee surgery may be a factor in determining the efficacy of IA morphine. A prospective, randomized, double-blind study compared "low-inflammatory surgery" (arthroscopy, menisectomy) and "high-inflammatory surgery" (anterior cruciate ligament [ACL] reconstruction, lateral release, patellar shaving, plicae removal).[28] IA bupivacaine (25 ml, 0.25%), morphine (5 mg), or saline was administered at the end of surgery and postoperative pain scores and ketorolac usage were followed. Bupivacaine IA proved more effective in mediating pain in the "low inflammatory" group while morphine IA was better in the "high inflammatory" group. The results are interesting in that the selection of the IA agent may depend on the nature of the surgical procedure.[28] Earlier studies showed the efficacy of IA morphine after ACL ("high inflammatory") surgery.[29,30] Unfortunately, other studies showed no benefit from IA morphine following ACL reconstruction when compared to femoral nerve block,[31] epidural block,[32] or multimodal analgesia using NSAIDs, external cooling, and IA bupivacaine.[33]

There is some controversy in interpreting the literature on the efficacy of IA morphine after arthroscopic knee surgery. In an attempt to clarify the apparent discrepancies, Jadad et al described a 5-point qualitative scale to assess the efficacy of this intervention.[3] In a subsequent review of the literature assessing the IA effects of morphine, Kalso and coworkers noted only four studies that scored more than 4 points on this 5-point scale.[2] These investigators did not perform a meta-analysis of the information since they believed there was a lack of an adequate number of high-quality studies. Their conclusion was that morphine probably had a mild effect on postoperative pain when injected IA in humans. In the review by Gupta et al, all human studies were included in their meta-analysis unless there was compelling reason to exclude them.[4] Their analysis led them to conclude that a definite but mild analgesic effect of morphine was evident for up to 24 hr postoperatively. Furthermore, they felt that this analgesic effect was probably not dose dependent, nor could a systemic effect of IA morphine be excluded. A recent review by Kalso et al looked at all studies in which the postoperative pain was 5 or more on a 10-point VAS.[5] In doing so, they excluded all studies wherein the postoperative pain intensity was "mild." They concluded that IA morphine has definite analgesic properties in cases where postoperative pain intensity is moderate to severe. On the other hand, Meiser and Laubenthal argued that their review of 34 randomized, controlled studies concerning IA morphine after knee surgery would not support meta-analysis of the data since study designs differ substantially.[34]

Any study that attempts to promulgate an antinociceptive action of IA morphine (or similar μ-agonist opioids) should hypothesize its mechanism of action. Stein et al used immunocytochemistry and autoradiography and found that synovial opioid peptides and opioid receptors are abundant in pronounced synovitis. Furthermore, they deduced that opioids expressed in inflamed tissues do not produce tolerance to peripheral morphine analgesia, and that there is no major downregulation of peripheral opioid receptors. They extrapolated this information to suggest that IA opioids might have a role in mediating chronic arthritis pain and other inflammatory conditions.[35] Keates et al used radioligand binding to determine whether opioid-binding sites could be induced during inflammatory states produced in the radiocarpal joints of canines.[36] They found that opioid-binding site densities in articular and periarticular tissues in inflammatory states were approximately 100 times larger than the respective published densities in brain tissues, leading them to speculate that the use of IA opioids has a scientifically valid basis.[36] Similar findings were noted in a study using a rat model of inflammation that demonstrated the potency of IA morphine did not diminish during the onset of induced arthritis.[37] Perfusion of inflamed rat knee joints with exogenous endorphin-1 produced a significant reduction in synovial vascular permeability and a fall in protein exudation. Destruction of knee joint unmyelinated afferent nerve fibers by capsaicin treatment significantly attenuated the anti-inflammatory effects of endorphin-1, suggesting that the peptide (and, hence, perhaps exogenously administered opioid analgesics) acts via a neurogenic mechanism.[38]

The effects of IA opioids may be mediated through the G-protein–coupled receptors affecting the cAMP pathway. Elvenes et al, using immunodetection polymerase chain reaction and Western blotting, demonstrated that human osteoarthritic cartilage and cultured chondrocytes possess the μ-opioid receptor. Stimulation of chondrocytes with beta-endorphin resulted in decreased phosphorylation of the transcription factor cAMP responsive element binding protein (CREB), an effect reversible by naloxone.[39] Studies such as these have led other investigators to hypothesize that IA morphine might be beneficial in the treatment paradigm of patients suffering from chronic arthritis states. Indeed, synovial leukocyte counts are reduced following IA morphine but not following IA saline, indicating that morphine may have anti-inflammatory effects in chronic osteoarthritis of the knee.[40] Likar et al found in a double-blind, cross-over study that IA morphine provided outstanding and long-lasting analgesia in patients suffering from chronic osteorthritis of the knee.[41]

Morphine has been used IA following other types of surgical procedures besides knee arthroscopy, including anterior cruciate ligament (ACL) reconstruction,[42,43] total knee arthroplasty (TKA),[44–48] rotator cuff repair,[49,50] shoulder arthroscopy,[51] and ankle arthroscopy.[52] Morphine IA (1 mg) has even been touted as an effective adjuvant to managing pain following temperomandibular joint (TMJ) surgery, although it proved to be less effective in this regard than did mepivacaine at 30 mg.[53]

IA morphine has been used as adjuvant therapy for ACL reconstruction surgery in adults[42] and for pediatric patients.[43] In adults, IA morphine (0.2 mg/ml) in combination with ropivacaine and ketorolac provided superior analgesia to IA morphine plus ropivacaine alone for pain at rest and with movement when used as IA patient-controlled regional analgesia (PCRA).[42] For pediatric ACL patients, IA morphine (5 mg) added to bupivacaine-clonidine provided inferior analgesia versus combined femoral-sciatic nerve blocks using bupivacaine-clonidine.[43]

Catheter-IA morphine (4 mg) in combination with ropivacaine (90 mg) and ketorolac (30 mg) provided superior analgesia and reductions in morphine use in a group of patients undergoing Bankart procedures who administered ropivacaine using PCRA versus patients treated with placebo regimens.[50] Following open rotator cuff repair under interscalene brachial plexus block, three groups of patients received IA boluses of 0.25% bupivacaine with 1 mg morphine, 50 μg fentanyl, or 10 μg sufentanil added. The IA morphine proved superior to the other two opioids with regard to pain scores and rescue opioid doses over the first 24 hr.[49] However, following shoulder arthroscopy for subacromial decompression in 32 patients, IA morphine 5 mg was only equivalent to a saline IA injection.[51] The difference in the results following shoulder surgery may represent a preferential effect of morphine in the "high-inflammatory" surgeries (open procedures) compared to "low-inflammatory" states (arthroscopy). When IA morphine was added as a component of multimodal analgesia following arthroscopic ankle surgery, there was a significant reduction in pain, joint swelling, time of immobilization, duration of sick leave, and return to physical activity. Attributing the success of this modality to the morphine (5 mg) is limited by the fact that the morphine was added to bupivacaine (15 mg) and methylprednisolone (40 mg). Which of these adjuncts was most efficacious or how the combination was more successful than either agent alone was not investigated.[52]

In a group of 37 patients undergoing TKA, IA morphine 1 mg and postoperative intravenous (IV) patient-controlled analgesia (PCA) was compared to epidural morphine and a PCA-only group. There was no difference among the three groups with regard to VAS scores, morphine requirements, or stress hormone levels, indicating that IA morphine for TKA offers no benefit over epidural analgesia or PCA analgesia.[44]

Recently, there has been a trend toward providing multimodal analgesia using cocktails of various agents administered intra-articularly for patients undergoing total knee arthroplasty procedures. Some of these reports have utilized large-volume, dilute local anesthetics alone, but there are also several studies wherein opioids have been added as adjuvants to an admixture given through an IA catheter.[44–47] Rasmussen et al demonstrated improved pain scores and enhanced rehabilitation after TKA using IA morphine plus ropivacaine in continuous infusions.[45] Lombardi et al demonstrated improved analgesia, reduced blood loss, and decreased requirements for rescue analgesics following TKA performed with intra-articular morphine plus bupivacaine to which epinephrine was added, versus no injection whatsoever.[44] In a study of 90 patients, performed in randomized, prospective, double-blind fashion, patients received either 40 ml of 0.75% ropivacaine plus epinephrine plus 5 mg morphine, or the same agents without morphine, or 50 ml of normal saline solution (NSS). All subjects received IV PCA morphine to treat breakthrough pain. There was no difference in VAS pain scores or the use of rescue medications, or attainment of range-of-motion (ROM) parameters.[46] However, Fu and colleagues compared IA morphine plus betamethasone plus bupivacaine versus IA NSS and noted a statistically significant reduction in morphine consumption with the IA cocktail, a reduction in VAS with rest and activity at 24 and 36 hr, a reduction of the incidence of nausea and vomiting, and an improved ROM at 15 days following surgery.[47] Clearly, there is much left to be learned concerning the optimal use of multimodal, catheter-injected, intra-articular use of opioids and adjuvant medications following major total joint replacement surgery.

In summary, there is clinical evidence that supports the use of IA morphine given preemptively, for pain occurring following certain types of knee manipulation, including arthroscopic surgery, while there is conflicting evidence in support of the use of IA morphine for major reconstructive procedures.

INTRA-ARTICULAR MEPERIDINE

Meperidine is a synthetic opioid agonist at μ- and κ-opioid receptors derived from phenylepiperidine. Several analogs are derived from meperidine including fentanyl, sufentanil, alfentanil, and remifentanil. Structurally, meperidine is similar to atropine, and it possesses a mild atropine-like antispasmodic effect. It is about one-tenth as potent as morphine and its duration of pharmacologic action is about 2 to 4 hr.

Meperidine has been injected IA in doses of 10 to 200 mg, alone or in combination with local anesthetics and tenoxicam. In a study comparing IA local anesthetic (lidocaine 2%) plus meperidine (10 mg) with local anesthetic plus meperidine (10 mg) and tenoxicam (20 mg) the authors found that the latter regimen provided superior pain relief from 4 hr postoperatively onwards.[54] A study limitation includes the lack of a control local anesthetic group. Westman et al. conducted a series of studies on IA meperidine for knee and ankle arthroscopy analgesia. They compared IA meperidine to prilocaine in ankle arthroscopy. The use of IA meperidine resulted in lower VAS pain scores at rest but not during movement.[55] When IA or intramuscular meperidine (10 mg) was compared to morphine (1 mg) or fentanyl (10 μg) for knee arthroscopy, no difference between the groups was noted although there was a tendency for improved analgesia in the IA

meperidine group.[56] The same group demonstrated that IA meperidine was superior to prilocaine for analgesia following knee arthroscopy, at least in the 100 mg and 200 mg meperidine groups.[57] However, there was significant systemic absorption and side effects at these doses, negating any definitive determination as to whether or not the effects were centrally mediated or locally mediated. In another study by the same investigators, IA meperidine (200 mg) was compared to meperidine plus epinephrine and a control group receiving IA local anesthetic only for knee arthroscopy.[58] Epinephrine did not extend additional benefit to the meperidine group, which had the best analgesia 1 to 4 hr postoperatively. It appears from the studies by Westman et al[55] that IA meperidine is effective following knee surgery in doses of about 100 to 200 mg. It is not certain whether the local anesthetic properties of meperidine influenced the results or whether a systemic effect resulted from the generous doses (200 mg) used in the studies.

INTRA-ARTICULAR FENTANYL AND SUFENTANIL

Fentanyl is a phenylpiperidine derivative synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is about 75 to 100 times more potent than morphine. A single dose of fentanyl administered intravenously has a more rapid onset than morphine and a shorter duration of clinical effect, although the elimination half-life is longer than that of morphine.

IA fentanyl has been studied in doses ranging from 10 to 100 μg. IA bupivacaine was noted to provide superior analgesia compared to IA fentanyl in the immediate postoperative period, for up to 2 hr, following knee arthroscopy. There was no difference in the analgesic efficacy between the two groups after 2 hr.[59] In direct comparison to IA morphine, IA fentanyl does not appear to confer particular advantages for postoperative analgesia after knee arthroscopy. While Varkel et al. showed that fentanyl 50 μg IA was superior to 3 mg morphine IA beginning 1 hr postoperatively and persisting up to 8 hr, the postoperative pain in both treatment groups was rated as mild, and the difference in VAS pain scores was not significant.[60] Soderlund et al used small IA doses of fentanyl (10 μg), morphine (1 mg), or meperidine (10 mg) for knee arthroscopy and found no difference in the postoperative analgesia between the different opioids.[56] This study included 7 groups of 10 patients each, including a placebo group control, and no parameter was significantly different between any of the groups studied. When compared to 1 mg morphine IA, fentanyl 100 μg IA failed to provide equivalent analgesia for up to 48 hr postoperatively when either agent was added to 10 ml of 0.25% bupivacaine following knee arthroscopy.[61]

It might be expected that sufentanil would provide results similar to those of fentanyl when used IA since sufentanil is a thienyl analog of fentanyl. However, sufentanil has a greater affinity for opioid receptors than fentanyl, and is about 12 times as potent.[62] Sufentanil is extensively protein bound (92.5% vs. fentanyl at 79% to 87%) and is highly lipid soluble. Its elimination half-life is intermediate between that of fentanyl and alfentanil.[63] Vranken et al[64] compared IA sufentanil, 5 or 10 μg, and IV saline vs. IA saline and IV sufentanil 5 μg for knee arthroscopy. The IA sufentanil significantly reduced pain levels and postoperative consumption of analgesics. The larger dose of sufentanil (10 μg) did not provide additional analgesia over the smaller dose.[64]

In a prospective, double-blind study of 45 patients undergoing knee arthroscopy who were randomized into one of three groups, IA sufentanil (5 μg) was injected postsurgery and was compared to morphine (3 mg) or NSS given IA. While both sufentanil and morphine were effective in reducing pain scores for up to 14 hr, sufentanil proved superior to morphine.[65] In another double-blind, randomized, and prospective study, 60 patients received IA NSS, or IA sufentanil (10 mcg) alone or with methylprednisolone (40 mg) administered at the termination of knee arthroscopy. Pain levels at rest and with movement were lowest in the sufentanil plus steroid group, while both groups were superior to NSS alone, as expected.[66] Mayr et al, in prospective, randomized fashion, demonstrated that preoperative IA fentanyl (100 μg) added to 8 ml bupivacaine (0.5%) compared favorably to femoral nerve block using prilocaine and bupivacaine, and was superior to the analgesia provided by postoperative IA block, for ACL reconstruction surgery in adults.

In conclusion, IA fentanyl analgesia in doses up to 100 μg or sufentanil up to 10 μg both appear to be modestly successful in modulating nociception after knee arthroscopy. However, the studies to date do not justify their routine inclusion in periarticular injectates, particularly when compared to IA morphine.

INTRA-ARTICULAR TRAMADOL

Tramadol is a synthetic narcotic with a weak μ-receptor agonist activity. It also enhances the function of the spinal descending inhibitory pathway by inhibition of reuptake of both 5-hydroxytryptamine (5-HT) and norepinephrine and stimulate the presynaptic release of 5-HT. Tramadol is available in injectable form in Europe. Zeidn et al randomized patients undergoing arthroscopic partial meniscectomy to receive either 20 ml of 0.25% bupivacaine (B) or 100 mg tramadol (T), or a combination of 0.25% bupivacaine and 100 mg tramadol (BT) to a total volume of 20 ml by the IA route after surgery. Their results showed significantly lower VAS pain scores, lower analgesic consumption, and shorter time to unassisted ambulation and discharge in the combination (BT) group.[68] Other investigators have also identified tramadol IA as being effective for providing postoperative analgesia following outpatient knee arthroscopic surgery. Alagol et al found that 100 mg IA tramadol was superior to 50 mg without incurring increased side effects.[69] Beyzadeoglu et al found that postoperative administration of 100 mg IA tramadol plus periarticular bupivacaine 10 ml (0.5%) provided superior analgesia to IA bupivacaine and incisional bupivacaine.[70] Tuncer et al noted an improvement in pain levels if tramadol IA 100 mg was administered preemptively versus postoperatively following arthroscopic knee surgery.[71] In summary, IA tramadol 100 mg appears to have analgesic effects after knee arthroscopies and medial meniscectomies.

INTRAPERITONEAL OPIOIDS

Unlike the studies on IA opioids where several clinical studies were performed, there is little clinical evidence supporting the use of opioid analgesics via the intraperitoneal (IP) route. Many studies on IP analgesia have been conducted in animals, and extrapolation to the human postsurgical arena is at best tentative. IP opioids have been studied following laparoscopic gynecologic surgery, laparoscopic cholecystectomy, and open intra-abdominal procedures. Results are inconclusive in the majority of cases.

ANIMAL STUDIES SUPPORTING INTRAPERITONEAL OPIOID ADMINISTRATION

Niv et al hypothesized that the simultaneous application of morphine intrathecally and intraperitoneally would produce a synergistic effect, similar to that noted when morphine is given simultaneously into the spinal cord and cerebral ventricles.[72] Using male Wistar rats, they determined that there was a supra-additive antinociceptive effect of the combined therapy.[72] Intrathecal and IP remifentanil, alfentanil, and morphine were examined in a rat model tested for hind-paw thermal withdrawal latency. All opioids demonstrated a dose-dependent analgesic response after intrathecal or IP administration. The order of IP potencies in the study was remifentanil > alfentanil > morphine, while the duration of analgesia was morphine > > alfentanil > remifentanil.[73] The side effect profiles were best with morphine > alfentanil > remifentanil.[73] The clinical significance of these findings may be simply that the highly lipid-soluble agents are potent analgesics when administered IP, but are also associated with greater risk. Reichert et al evaluated possible preemptive analgesic effect of IP opioids in a mouse visceral pain model. While a potent antinociceptive effect was demonstrated by IP morphine administered prior to IP acetic acid (a frequently used model of inflammation), IV morphine had no effect when given preemptively. This supports the concept of IP opioids acting during inflammatory states via a peripheral opioid receptor mechanism.[74] The IP administration of the N-methyl-D-aspartate (NMDA) antagonist ketamine in rats resulted in a synergistic effect to spinally administered fentanyl as assessed by the tail-flick test, but not by the electrical current threshold test.[75] In that study, IP ketamine served as a chemical cofactor to augment spinal analgesia induced by fentanyl. IP fentanyl, morphine, and oxycodone all reduced tail-flick latency in a group of male Wistar rats that was significantly more potent when the simultaneous IP administration of the neurosteroid alphadolone accompanied each agent. The steroid alone had no effect as an antinociceptive agent when given IP, implying that certain agents may augment IP antinociception produced by opioids.[76]

HUMAN STUDIES ON INTRAPERITONEAL OPIOIDS

IP opioids have been used following laparoscopic cholecystectomy,[77–81] laparoscopic gynecologic surgery,[82–85] and after open intra-abdominal procedures.[86]

Schulte-Steinberg et al[77] found that neither interpleural nor IP morphine administration reduced analgesic requirements following laparoscopic cholecystectomy surgery. In their study of 110 patients in six groups, only interpleural bupivacaine (0.25%, 30 ml) proved efficacious in that regard. O'Hanlon et al,[78] however, noted a reduction in pain scores and analgesic requirements in a group of 46 patients who received IP meperidine plus bupivacaine compared to a similar group who received the meperidine intramuscularly plus IP bupivacaine. The only adverse effect noted was an increased rate of nausea in the IP meperidine group.[78] In a double-blind, randomized study IP bupivacaine (0.25%, 30 ml) and morphine (2 mg) were shown to provide early (first 6 hr postoperatively) analgesia superior to IP saline or IP bupivacaine plus IV morphine.[79] After the first 6 hr, however, the analgesia was superior in the group who received IP bupivacaine and IV morphine.[79] Tramadol has recently been compared IP (100 mg) versus the same dose given IV for analgesia following laparascopic cholecystecomy surgery. In this study of 61 patients randomly assigned to the IP or IV tramadol group in a prospective, double-blind fashion, the IV tramadol provided superior pain relief compared with the IP tramadol.[80] In another study of IP tramadol, there was no improvement in pain scores or outcome whether or not tramadol 100 mg was added to bupivacaine 0.25% (50 ml) following laparoscopic cholecystecomy surgery.[81]

In summary, some studies support the use of IP morphine or meperidine after laparoscopic cholecystectomy, while another study suggests that IP analgesia is superior to IP opioid administration.

Morphine and meperidine IP have also been used following laparoscopic gynecologic surgery. In patients undergoing tubal ligation surgery, Colbert et al[82] noted that a combination of IP meperidine (50 mg) and bupivacaine (0.125%, 80 ml) resulted in lower pain scores than IP bupivacaine and intramuscular meperidine. On the other hand, Keita et al[83] did not observe improvement in pain scores or analgesic requirements when 3 mg morphine was added to 20 ml bupivacaine 0.5% IP in a group of patients who underwent laparoscopic gynecologic surgery.

Memis and colleagues compared tramadol (100 mg) or clonidine (1 μg/kg) added to bupivacaine IP and found that both adjuvants were superior to bupivacaine alone, but that there was no difference in the analgesia between them.[84] In a study of 250 women undergoing laparoscopic gynecologic surgery in a two-center, double-blind, placebo-controlled, randomized protocol using five parallel groups, IP meperidine and ropivacaine, alone or in combination, did not produce better pain relief or opioid-dose sparing when compared to systemic opioid administration.[85]

In a randomized study wherein IP morphine 50 mg was administered to 15 patients undergoing major abdominal surgery the analgesia was inferior to that provided by the same dose of morphine given intravenously.[86] The one benefit of the IP morphine was a reduction in morphine-6-glucuronide levels when compared to IV morphine, implying a difference in pharmakokinetics between the two routes of administration.[86]

In summary, a few clinical studies supported the use of IP meperidine after laparoscopic procedures. The role

of IP morphine after laparoscopic and major abdominal surgeries is not well defined because of the scarcity of clinical data.

KEY POINTS

- IA morphine, in some studies, has been shown to provide improved analgesia after knee arthroscopy when compared to local anesthetic alone or to saline placebo.
- IA morphine may be more beneficial for use in "high inflammatory" arthroscopic knee surgery (e.g., anterior cruciate ligament reconstruction, lateral release, patellar shaving, and plicae removal) than for use in "low-inflammatory" surgery (knee arthroscopy for meniscectomy).
- IA morphine has not shown promising results after shoulder arthroscopy or total knee arthroplasty, and its use following ankle arthroscopy remains to be defined.
- IA fentanyl, sufentanil, and meperidine have less support for use following arthroscopic surgery than does the use of IA morphine.
- There is some suggestion that IP meperidine plus bupivacaine is beneficial following laparoscopic cholecystectomy and gynecologic surgery, although this is an evolving area of scientific study associated with some controversy.
- The IP administration of morphine has not been demonstrated in human studies to exert a beneficial effect following laparoscopic surgery.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 33

Continuous Peripheral Nerve Blocks

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Providing a continuous peripheral nerve block (CPNB)—also called "perineural local anesthetic infusion"—involves the percutaneous insertion of a catheter directly adjacent to the peripheral nerve(s) supplying the surgical site (Fig. 33-1), as opposed to a "wound" catheter placed directly at a surgical site. Site-specific, potent analgesia may then be provided with few, if any, side effects. CPNB was first described in 1946 using a cork to stabilize a needle placed adjacent to the brachial plexus divisions to provide a "continuous" supraclavicular block.[1]

INDICATIONS FOR ACUTE PAIN MEDICINE

As with all procedures, CPNB is associated with inherent risks (see section below on complications). Therefore CPNB is usually provided to patients expected to have at least moderate postoperative pain of a duration greater than 24 hr that is not easily managed with oral opioids. However, opioid requirements and opioid-related side effects may be decreased with the use of CPNB following mildly painful procedures. Because not all patients desire, or are capable of accepting, the extra responsibility that comes with the catheter and pump system, appropriate patient selection is crucial for safe CPNB, particularly in the ambulatory environment. Although recommendations for the use of various catheter locations for specific surgical procedures exist,[2] there is little published data specifically illuminating this issue. In general, axillary, cervical paravertebral (CPVB), infraclavicular, or supraclavicular infusions are used for surgical procedures involving the hand, wrist, forearm, and elbow; interscalene, CPVB and intersternocleidomastoid catheters are used for surgical procedures involving the shoulder or proximal humerus; thoracic paravertebral catheters are used for breast or thorax procedures; psoas compartment catheters are used for hip surgery; fascia iliaca, femoral, and psoas compartment catheters are used for knee or thigh procedures; and popliteal or subgluteal catheters are used for surgical procedures of the leg, ankle, and foot. The authors recommend using an interscalene catheter for shoulder or proximal humerus procedures; infraclavicular catheter for more distal procedures of the upper extremity; a transabdominal plane catheter for inguinal or lower abdominal procedures; a femoral catheter for knee surgery; and a popliteal-sciatic catheter for foot/leg procedures.

EQUIPMENT AND TECHNIQUES

STIMULATING VERSUS NONSTIMULATING CATHETERS

Up to 40% of catheters have been reported misplaced upon insertion.[3] There are multiple techniques and equipment available for catheter insertion. One common technique involves locating the target nerve using nerve stimulation via an insulated needle, and then injecting a bolus of local anesthetic via a needle to provide a surgical block, followed by the introduction of a "nonstimulating" catheter.[4] However, upon using this technique, it is possible to provide a successful surgical block, but inaccurate catheter placement. With the use of ultrasound guidance, the catheter tip may be directly viewed if inserted 1 cm past the needle tip, and then the needle withdrawn over the catheter with the operator continuously visualizing the catheter tip location to ensure it is not dislodged. If ultrasound is not utilized, some investigators first insert the catheter and then administer a bolus of local anesthetic via the catheter in an effort to avoid catheter tip misplacement, with a reported failure rate of 1% to 8%. Alternatively, catheters which deliver current to their tips have been developed in an attempt to improve initial placement success rates.[5] These catheters provide feedback on the positional relationship of the catheter tip to the target nerve prior to local anesthetic dosing. While there is evidence that passing current via the catheter may improve the accuracy of catheter placement with minor benefits in the lower extremity,[6–9] the nonstimulating catheters of these three studies were advanced 4 to 10 cm past the needle tip which greatly increases the risk of the catheter tip-to-nerve distance and decreasing the effectiveness of the local anesthetic infusion.[10] Further study is required to identify the optimal equipment for perineural infusion.

ULTRASOUND-GUIDED CATHETER INSERTION

For ultrasound-guided procedures, the term "long axis" is used when the length of a nerve is within the ultrasound beam, compared with "short axis" when viewed in cross-section.[11] A needle inserted with its length within a two-dimensional ultrasound beam is described as "in plane," while a needle inserted across a two-dimensional ultrasound beam is "out of plane."[11]

Needle In-Plane, Nerve in Short-Axis Approach: This is the most-frequently published single-injection peripheral nerve block orientation because this view allows for easier identification and differentiation from surrounding structures.[11] When the long axis of the needle is inserted within the ultrasound plane, the needle tip location can be more easily identified relative to the target nerve. Local anesthetic spread may be observed if the initial local anesthetic bolus is placed through the needle, and adjustment of the needle tip made when necessary. However, when the perineural catheter is inserted past the needle tip, it has the tendency to bypass the nerve given the perpendicular orientation of the block needle and target nerve,[12] although there are certain anatomic locations that will often allow a catheter to be passed and remain perineural.[13,14] Some practitioners have advocated either passing the catheter a minimal distance past the needle tip, or advancing the

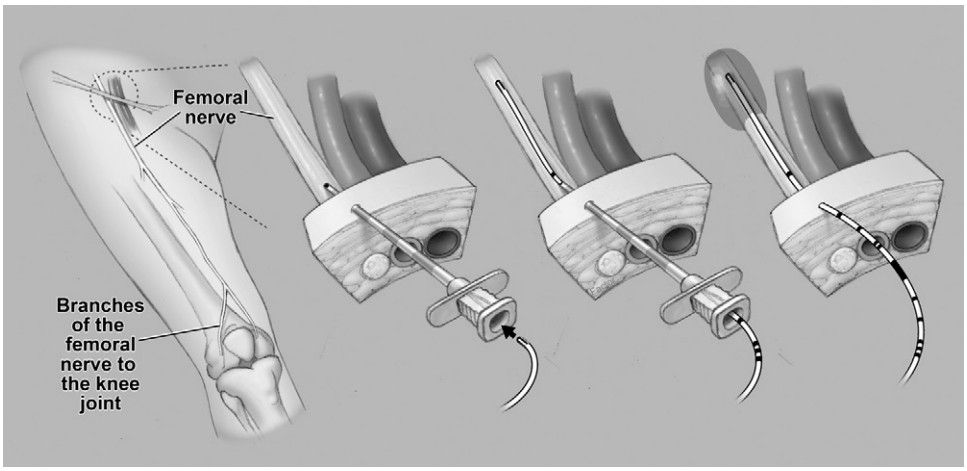

FIGURE 33-1 Insertion of a femoral perineural catheter used to provide a continuous peripheral nerve block.

catheter further initially and then, after needle removal, retracting the catheter such that its orifice(s) lie a minimal distance (<2 cm) past the original needle tip position[15] (although others have suggested this may result in a dislodged catheter tip as the needle is withdrawn over the catheter, especially by trainees). Some advocate using an extremely flexible perineural catheter in an attempt to keep the catheter tip in close proximity to the target nerve if the catheter is inserted more than a minimal distance.[16–18] Still others describe reorienting the needle from an in-plane to a more parallel trajectory and inserting a stimulating catheter to better monitor catheter tip location.[19]

There are multiple benefits of the needle in-plane, nerve in short-axis approach. First, practitioners may learn only one technique because it may be used for both single-injection and catheter insertion procedures. Furthermore, it may be used for nearly all anatomic catheter locations, even for deeper target nerves.[18] If a 17- or 18-gauge needle is used, the needle tip may be more-easily identified and remains within the ultrasound plane due to its rigidity compared with smaller gauge needles.[20] While some have speculated that the use of a large needle is more painful, seven prospective studies reported a median catheter-insertion pain score of 0 to 2 on a 0-to-10 numeric rating scale (10 = most pain imaginable) when the needle track was first anesthetized with lidocaine via a 25- to 27-gauge needle.[15,17,18,21–24] In addition, the potential benefits of using a larger needle gauge (fewer needle passes given the relative ease of keeping a rigid, larger-gauge needle in plane; less risk of undesired tissue contact due to misinterpretation of the needle shaft for the needle tip) must be weighed against the potential risks (increased patient discomfort; increased tissue trauma; increased injury if a vessel is punctured).

There are disadvantages of this approach as well. They include new needle entry sites relative to the nerve compared with more traditional nerve stimulation modalities that typically use a parallel needle-to-nerve insertion; challenges keeping the needle shaft in-plane[25]; difficult needle tip visualization for relatively deep nerves[26,27]; and, as noted above, the catheter tip may bypass the target nerve given the perpendicular orientation of the needle and nerve.[12] If an extremely flexible catheter is used in an attempt to minimize this issue, it is sometimes difficult to thread past the tip of the placement needle.

Needle Out-of-Plane, Nerve in Short-Axis Approach: There are potential benefits of this approach. They include a generally familiar parallel needle-to-nerve trajectory used with traditional nerve stimulation techniques (and also vascular access); and because the needle is parallel to the target nerve, the catheter theoretically may remain in closer proximity to the nerve, even when threaded more than a centimeter past the needle tip.[15,21] However, a disadvantage of this technique is the relative inability to visualize the advancing needle tip,[15,28] which some speculate increases the likelihood of unwanted contact with nerves, vessels, peritoneum, pleura, or even meninges.[29] Practitioners often use a combination of tissue movement and "hydro-location" in which fluid is injected and the resulting expansion suggests the needle tip location (either with or without color Doppler flow).[28,30] It has been suggested that for superficial catheters (e.g., interscalene and femoral), the consequent "longitudinal" orientation of needle with nerve makes precise visualization of needle tip less critical, as the needle tip tends to remain relatively close to the nerve if the needle tip is advanced beyond the ultrasound beam. However, for deeper nerves, this technique is not as straightforward as guiding the needle tip to a target nerve as in the in-plane technique described above, and may be more difficult (and, at times, nearly impossible) to master.[26,27]

Needle In-Plane and Nerve in Long-Axis Approach: Superficially, this technique appears to have the benefits of both previously described approaches, with few limitations. The nerve can be viewed along with the needle shaft/tip, and the catheter monitored as it exits the needle parallel to the target nerve. The difficulty lies is keeping three structures—the needle, nerve, and catheter—in the ultrasound plane.[31] In addition, to view the nerve in long axis, the nerve itself must be relatively straight; and there can be only one target nerve as opposed to multiple trunks or cords as found within the brachial plexus. Evidence of this technique's difficulties may be found in the scarcity of published reports.[31,32]

Limitations on the length of this chapter precludes a discussion of multiple additional ultrasound-related issues,

such as transducer selection, the concomitant use of nerve stimulation (an important tool in a subset of patients),[33] and various methods for catheter tip localization.[34] Although many proponents voice firm opinions based on their personal experience, little clinical data exist comparing aspects of any one placement technique with another.

INFUSION MANAGEMENT

Currently, there is insufficient information to determine if there is an optimal local anesthetic for CPNB. The majority of perineural infusion publications have involved bupivacaine (0.1–0.25%) or ropivacaine (0.1–0.4%), although levobupivacaine and shorter-acting agents have been reported. The main determinant of CPNB effects—local anesthetic concentration and volume or simply total drug dose—remains unknown; although there is evidence that for continuous posterior lumbar plexus blocks, local anesthetic concentration and volume do not influence nerve block characteristics, suggesting that local anesthetic dose (mass) is the primary determinant of perineural infusion effects.[35] There are no adjuncts added to local anesthetics that have been demonstrated to provide benefits during CPNB.[36–38] Additionally, epinephrine and opioids have been added to local anesthetic infusions, but there are currently insufficient published data to draw any conclusions regarding the safety of the former or the efficacy of the latter.

Many variables probably affect the optimal regimen, including the surgical procedure, catheter location, physical therapy regimen, and the specific local anesthetic infused. For procedures resulting in at least moderate postoperative pain, a basal infusion optimizes benefits such as analgesia and sleep quality.[39–42] Providing patients with the ability to self-administer local anesthetic doses increases perioperative benefits such as improving analgesia, minimizing supplemental opioids, and allowing a decreased basal infusion rate which minimizes the risk of limb weakness and maximizes the infusion duration for ambulatory patients with a finite local anesthetic infusion pump reservoir volume.[40–42] Unfortunately, insufficient information is available to base recommendations on the optimal basal rate, bolus volume, or lockout period accounting for the many variables that my effect these values (e.g., catheter type, location, surgical procedure). Until recommendations based on prospectively collected data are published, practitioners should be aware that investigators have reported successful analgesia using the following with long-acting local anesthetics: basal rate of 4 to 8 ml/hr, bolus volume of 2 to 5 ml, and lockout duration of 20 to 60 min.

The dosing issue has particular importance for lower extremity CPNB. Although inhibition of pain fibers is the primary goal for postoperative CPNB, currently available local anesthetics approved for clinical use decrease other afferent (e.g., non–pain-related sensory and proprioception) and efferent (e.g., motor) nerve fibers as well,[43] resulting in undesirable side effects such as muscular weakness.[44] There is growing evidence that lower extremity CPNB may increase the risk of patient falls,[7,45–48] although to what degree the perineural local anesthetic infusion was a contributing factor in these cases remains unknown because the studies were neither designed nor powered to detect such (presumably) rare complications. Nonetheless, patient falls during perineural infusion are now being highlighted in the surgical and anesthesiology literature.[45,49] Until additional data are available, practitioners may want to consider steps that may minimize the risk of falls, including minimizing the dose/mass of local anesthetic; providing limited-volume patient-controlled bolus doses that allow for a decreased basal dose without compromising analgesia in some cases[41,50]—although not all[40]; using a knee immobilizer and walker/crutches during ambulation[45]; and educating physical therapists, nurses, and surgeons of possible CPNB-induced muscle weakness and necessary fall precautions.

POTENTIAL RISKS/COMPLICATIONS

Two of the largest prospective investigations to date involving over 2100 patients combined suggest that the incidence of CPNB-related complications is very low—at least as low as, if not lower than, single-injection techniques.[51,52] Smaller prospective studies involving continuous infraclavicular and popliteal perineural infusions suggest a similar incidence of complications.

The reported range of what has been called "secondary block failure" is 0% to 40%.[3] The incidence of this complication is presumably dependent upon many factors, including the experience of the practitioner, equipment, and technique, as well as patient factors such as body habitus. Although definitive data is currently lacking, it is probable that the use of ultrasound will improve catheter insertion success rates.[53–55] Ultrasound also decreases other risks as well, such as vascular puncture (reported between 0% and 11% with nerve stimulation),[55] perineuraxis catheter placement, as well as intravascular and intraneural catheter insertion.[56] Prolonged Horner's syndrome due to neck hematoma is a rare complication, but has been reported. While a hematoma may require weeks for resolution (months for a Horner's syndrome), practitioners and patients should be reassured with the multiple case reports of complete neural recovery following hematoma resolution.

Nerve injury is a recognized complication following placement of both single-injection and CPNB, presumably related to needle trauma and/or subsequent local anesthetic/adjuvant neurotoxicity. The prospective clinical evidence from human subjects suggests that the incidence of neural injury from a perineural catheter and ropivacaine (0.2%) infusion is no higher than following single-injection regional blocks.[51,57–59] There is also evidence that in diabetes, the risk of local anesthetic–induced nerve injury is increased.[60]

The most common complication during perineural infusion is simply inadvertent catheter dislodgement (0–30%). Every effort to optimally secure the catheter must be made to maximize patient benefits (Fig. 33-2). Measures have included the use of sterile liquid adhesive (e.g., benzoin), sterile tape (e.g., Steri-Strips), securing of the catheter–hub connection with either tape or specifically designed devices (e.g., Statlock), subcutaneous tunneling of the catheter (Fig. 33-3), and the use of 2-octyl cyanoacrylate glue.[61] Using a combination of these maneuvers, investigators have reported a catheter retention rate

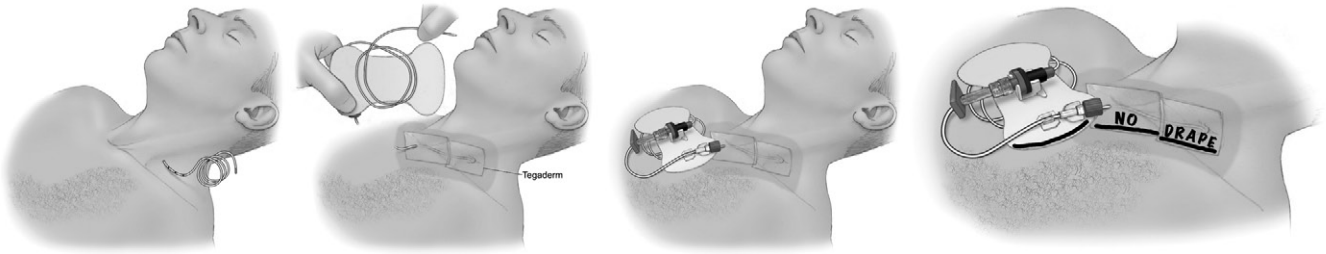

FIGURE 33-2 Securing an anterolateral interscalene perineural catheter used to provide a continuous peripheral nerve block.

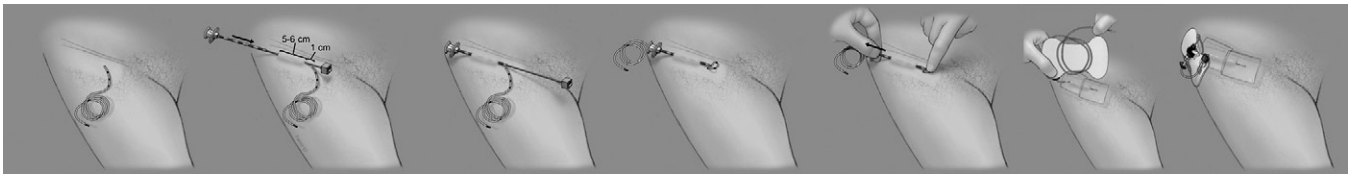

FIGURE 33-3 Tunneling a femoral stimulating catheter (Stimucath, Arrow International/Teleflex Medical, Reading, PA) used to provide a continuous peripheral nerve block.

of 95% to 100% for over 5 days of infusion. Other complications occurring during infusion include phrenic nerve block and ipsilateral diaphragm dysfunction during interscalene CPNB, local anesthetic toxicity (incredibly rare), and infection. While catheter-site bacterial colonization is relatively common, clinically relevant infection is not. In prospective investigations of interscalene,[51,57] posterior popliteal,[59] and multiple-site[52] catheters involving over 2700 patients combined, infection rates varied from 0% to 3% with one psoas compartment abscess forming following femoral CPNB. In these few cases, all infections completely resolved within 10 days.[52] There are additional potential CPNB complications, such as catheter knotting (do not pass the catheter >5 cm past the needle tip), retention (with the Arrow Stimucath),[41] and shearing (do not withdraw the catheter back into the needle unless the design is approved for this maneuver).

CONCLUSIONS

There is a large and growing body of evidence that CPNBs provide a multitude of clinical benefits. However, because of the relatively recent evolution of modern techniques, illuminating data are often unavailable. Future prospective investigation is required to determine the optimal catheter design(s), insertion technique(s), insertion approach(es), infusate(s), delivery regimen, infusion duration, and true incidence of complications. Only by prospectively comparing various approaches will their relative benefits and drawbacks be truly revealed and the science of perineural infusion advanced.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 34

Pediatric Postoperative Pain

Patrick K. Birmingham, MD, FAAP

Historically underrecognized and undertreated, pediatric pain management has improved dramatically over the last twenty years. Advances in pain assessment, pharmacologic studies of opioid and nonopioid analgesics in children, and development of physician-directed hospital-based acute pain services have been important factors in this development.

ANATOMIC AND PHYSIOLOGIC DIFFERENCES

The rational use of analgesics in pediatric patients, particularly neonates and infants, requires recognition of maturational changes that take place after birth in both body composition and core organ function.

Total body water represents about 80% of body weight in full-term newborns. This drops to 60% of body weight by 2 years of age, with a large proportional decrease in extracellular fluid volume. The larger extracellular and total body water stores in infancy lead to a greater volume of distribution for water-soluble drugs. Newborns have smaller skeletal muscle mass and fat stores, decreasing the amount of drug bound to inactive sites in muscle and fat. These stores increase during infancy.

Cardiac output is relatively higher in infants and children than adults, and is preferentially distributed to vessel-rich tissues such as the brain, allowing for rapid equilibration of drug concentrations. Immaturity of the blood–brain barrier in early infancy allows increased passage of more water-soluble medications such as morphine. This combination of increased blood flow to the brain and increased drug passage through the blood–brain barrier can lead to higher central nervous system drug concentrations and more side effects at a lower plasma concentration.

Renal and hepatic blood flow is also increased in infants relative to adults. As glomerular filtration, renal tubular function and hepatic enzyme systems mature, generally reaching adult values within the first year of life, increased blood flow to these organs leads to increased drug metabolism and excretion.

Both the quantity and binding ability of serum albumin and α-1 acid glycoprotein (AAG) are decreased in newborns relative to adults. This may result in higher levels of unbound drug, with greater drug effect and toxicity at lower overall serum levels. This has led to lower local anesthetic dosing recommendations in neonates and young infants, although neonates have shown the ability to acutely increase AAG levels while on continuous local anesthetic infusions. The difference in serum protein quantity and binding ability disappears by approximately 6 months of age.

Neurotransmitters and peripheral and central pathways necessary for pain transmission are intact and functional by late gestation, although opiate receptors may function differently in the newborn than in adults. Cardiorespiratory, hormonal, and metabolic responses to pain in adults have also been well documented to occur in neonates.

The spinal cord and dura mater in the newborn and infant extend to approximately the third lumbar (L3) and third sacral (S3) vertebral level, respectively, and reach the adult levels of approximately L1 and S1 to S2 by about 1 year of age. The lower-lying spinal cord in young infants is thus theoretically more vulnerable to injury during needle insertion at mid- to upper-lumbar levels. The intercristal line connecting the posterior superior iliac crests, used as a surface landmark during needle insertion, crosses the spinal column at the S1 level in neonates versus the L4 or L5 level in adults. There is less and more loosely connected fat in the epidural space in infants versus adults, explaining in part the relative ease with which epidural catheters inserted at the base of the sacrum can be threaded to lumbar or thoracic levels in infants and small children.

PAIN ASSESSMENT

Depending on developmental age and other factors, the pediatric patient may be unable or unwilling to verbalize or quantify pain like his adult counterpart. Nonetheless, a number of developmentally appropriate pain assessment scales have been designed for use in both infants and children. They are based on self-report, behavioral and/or physiologic measures (Table 34-1) and have been tested, validated and employed in research protocols (Table 34-2). Children over approximately 8 to 10 years of age may be able to use the standard adult numeric rating or visual analog scale to self-report their pain. Specialized self-reporting scales are available for children and can be used in patients as young as 3 years of age (Fig. 34-1). Behavioral or physiologic measures are available for younger ages and for developmentally disabled children (Table 34-3).

NONOPIOID ANALGESICS

ACETAMINOPHEN

Acetaminophen (paracetamol) is very commonly used in pediatric patients, alone or in combination with other analgesics. It is often administered rectally in the perioperative period in infants or children for whom oral intake is not an option. More recent studies indicate higher dosing, at least initially, is needed if given rectally (Table 34-4). Suppository insertion prior to surgical incision does not appear to significantly alter acetaminophen kinetics and may result in more timely analgesia in the early postoperative period. Higher-dose rectal acetaminophen has been shown to be equianalgesic to intravenous ketorolac following tonsillectomy and to have a significant opioid-sparing effect in children undergoing outpatient surgery. An intravenous prodrug form of acetaminophen is also available in

TABLE 34–1 Age and Measures of Pain Intensity

Age	Self-report Measures	Behavior Measures	Physiologic Measures
Birth to 3 yr	Not available	Of primary importance	Of secondary importance
3 yr–6 yr	Specialized, developmentally appropriate scales available	Primary if self-report not available	Of secondary importance
>6 yr	Of primary importance	Of secondary importance	

From McGrath PJ, Beyer J, Cleeland C, et al: Report of the Subcommittee on Assessment and Methodologic Issues in the Management of Pain in Childhood Cancer. Pediatrics *86:816, 1990.*

TABLE 34–2 Measurement Tools for Postoperative Pain Research in Pediatrics

Measurement Tool	Domain Assessed
Behavior Score	Postoperative pain
Beyer's Oucher Scoring System	Postoperative pain
CHEOPS	Postoperative pain
CHIPPS	Postoperative pain
COMFORT Scale	Postoperative pain
CRIES Scale	Postoperative pain
FLACC	Postoperative pain, cognitively impaired
NCCPC-PV	Postoperative pain, nonverbal, developmentally delayed
Objective Pain Discomfort Score	Postoperative pain
Objective Pain Score	Postoperative pain
Objective Pediatric Pain Scale	Postoperative pain
Observational Pain Scale	Postoperative pain
PPMS	Postoperative pain
Bieri Faces Pain Scale	Postoperative pain

CHEOPS, Children's Hospital of Eastern Ontario Pain Scale; CHIPPS, Children and Infants Postoperative Pain Scale; CRIES Scale, Crying Requires oxygen for saturation <95%, Increased vital signs, Expression, Sleepless; FLACC, Face, Legs, Activity, Cry, and Consolability; PPMS, Parents Postoperative Pain Measure Scale; NCCPC-PV, Non-Communicating Children's Pain Checklist-Postop Version.
From Benzon HT, Dean K, Benzon HA, with permission.

some parts of the world and was recently approved for use in the United States.

Acetaminophen dosing in premature and term neonates is less well defined. Despite age-related differences in elimination pathways, overall elimination in small studies is similar between neonates, children and adults. Dose-dependent hepatotoxicity is the most serious acute side effect of acetaminophen administration. Acute hepatotoxicity appears to be less common and less likely to be fatal in children than adults.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also widely administered to children. Studies of intravenous, intramuscular, and rectal NSAID administration in pediatric surgical patients demonstrate reduced postoperative pain scores and decreased supplemental analgesic requirements. Intravenous ketorolac is used widely in children, with a generally good safety record. The clinical significance of NSAID effects on bleeding remains controversial, leading to its avoidance by some in procedures such as tonsillectomy. Bleeding, renal damage, and gastritis are more likely to occur with prolonged administration and in the presence of coexisting disease. The clinical significance of NSAID inhibitory effects on osteogenesis following bone surgery, as documented in animal studies, remains unclear. Acetaminophen and NSAIDs are often given in combination, as they work by different mechanisms and their toxicity does not appear to be additive.

ASPIRIN (ACETYLSALICYLIC ACID)

Aspirin is not used for postoperative pain management in infants and children because of a highly significant association with Reye syndrome. Reye syndrome is an acute, fulminant, and potentially fatal hepatoencephalopathy that occurs in children with influenza-like illness or varicella who ingest aspirin-containing medications.

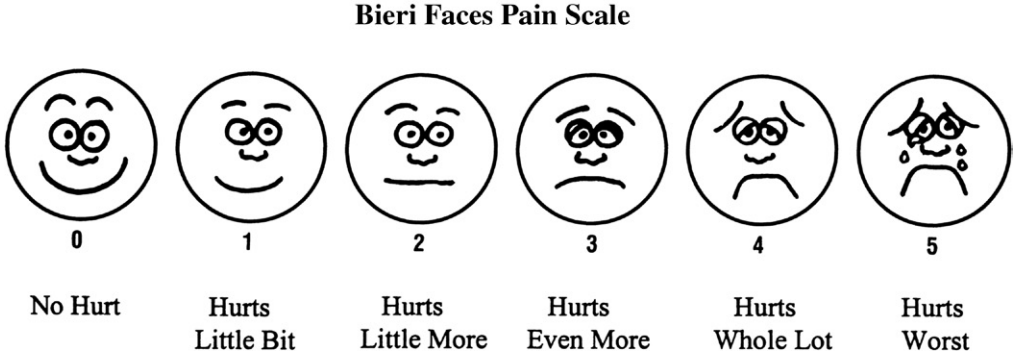

FIGURE 34-1 "These faces show how much something can hurt. This face (point to the left-most face) shows no pain. The faces show more and more pain (point to each from left to right) up to this one (point to right-most face). It shows very much pain. Point to the face that shows how much you hurt right now."

TABLE 34–3 FLACC Behavioral Pain Scale

Categories	Scoring 0	Scoring 1	Scoring 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, being talked to, distractable	Difficult to console or comfort

Note: Each of the five categories is scored from 0 to 2, for a total score range of 0 to 10. A revised scale (FLACC-R) adds additional descriptors in each of the five categories to aid pain assessment in developmentally disabled children.

Adapted from Merkel et al: The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nursing *23:293–297, 1997. Copyright 2002, The Regents of the University of Michigan. All Rights Reserved.*

TABLE 34–4 Nonopioid Analgesic Dosing

Medication	Dose (mg/kg)	Total Single Dose (mg)	Dosing Interval (hr)	Maximum Daily Dose (Patient <60 kg) (mg/kg)	Maximum Daily Dose (Patient ≥60 kg) (mg)
Acetaminophen* (oral)	10–15 mg/kg	650–1000	4	75–100	4000
Acetaminophen*† (rectal)	35-40 mg/kg loading dose; 20 mg/kg thereafter	Less defined	6	75–100	4000
Ibuprofen	6–10 mg/kg	400–600 mg	6	40	2400
Naproxen	5–6 mg/kg	250–375 mg	12	24	1000
Ketorolac	0.3–0.5 mg/kg IV	15 mg < 50 kg; 30 mg > 60 kg	6	2 (IV)	120
Tramadol	1–2 mg/kg	100 mg	6	8	400

Note: Dose ranges are approximate and may vary depending on individual patient assessment.

** Dosing in neonates and young infants is less defined, but approximately 50% of above recommendation.*

† No evidence of accumulation at 24 hr.

OPIOID ANALGESIA

Oral, parenteral, and epidural opioids are widely employed in infants and children to optimize postoperative comfort. Codeine is given orally in a dose of 0.5 to 1 mg/kg and often in combination with acetaminophen for mild to moderate pain. More potent oral opioids commonly administered to adults are also used in children (Table 34-5). Parenteral opioids are still given on an as needed basis to some patients, but alternative means of opioid delivery have been increasingly employed over the last 20 years.

PATIENT-CONTROLLED ANALGESIA

Patient-controlled analgesia (PCA) is used in children as young as 5 to 6 years of age, with morphine the most commonly used and studied opioid, and hydromorphone and fentanyl more commonly used alternatives (Table 34-6). Compared to PRN intramuscular opioids, PCA has been shown to be safe in children and provide more effective analgesia with greater patient satisfaction. A low-dose continuous or "background" infusion is sometimes added for patients following major surgery to optimize analgesia.

TABLE 34–5 Oral Opioid Analgesic Dosing Guidelines*

Medication	Potency Relative to Morphine	Typical Starting Dose (mg/kg)	Typical Dose (mg if >60 kg)	Dosing Interval (hr)
Morphine†	1	0.3	15–20	3–4
Codeine	0.1	0.5–1	30–60	4–6
Hydrocodone	1–1.5	0.1–0.2	5–10	4–6
Oxycodone	1–1.5	0.1–0.2	5–10	4–6
Hydromorphone	5–7	0.04–0.08	2–4	3–4
Methadone	1	0.1–0.2	10	6–12

** Dose ranges are approximate.*

† These doses refer to use of immediate release morphine.

TABLE 34–6 Patient-Controlled Analgesia Parameters*

Choice of Opioid	Morphine	Hydromorphone	Fentanyl
Loading dose (over 1–5 min)	0.05–0.20 mg/kg	1–4 μg/kg	0.5–2.0 μg/kg
Demand dose	0.01–0.02 mg/kg	2–3 μg/kg	0.2–0.4 μg/kg
Lockout time	5–15 min	5–15 min	5–15 min
1-hr limit (optional)	0.10–0.20 mg/kg	30–40 μg/kg	3–4 μg/kg
Continuous infusion (optional)	0.01–0.02 mg/kg/hr	2–3 μg/kg/hr	0.2–0.4 μg/kg/hr

** Dose ranges are approximate; selection of opioid and actual parameters depends on assessment of individual patient.*
Adapted from Birmingham PK: Recent advances in acute pain management. Curr Prob Pediatr *25:99–112, 1995.*

PARENT/NURSE-ASSISTED ANALGESIA

The concept of PCA has been expanded to allow parent- or nurse-assisted analgesia in select cases in which the patient is unwilling or unable, because of age, developmental delay, or physical disability, to operate the PCA button. This technique is used with caution as it does away with one of the safety features of PCA, in that the patient is theoretically less likely to self-overdose. Although more commonly used in infants and children with cancer treatment-related pain, such as oral mucositis with bone marrow transplantation, it has been safely used for postoperative analgesia as well. More recently the concept of parent- or nurse-assisted epidural analgesia has been introduced to optimize dosing flexibility and pain relief given via the epidural route.

CONTINUOUS INTRAVENOUS INFUSIONS

Continuous intravenous opioid infusions are used alone (or in combination with PCA) to provide pain relief following pediatric surgery. Compared to adults given morphine, neonates and premature infants have a longer elimination half-life, lower plasma clearance, and marked interindividual variability in plasma morphine concentration. For a given dose, they will achieve a higher plasma concentration for a longer duration. By approximately 6 to 12 months of age, the kinetics of morphine and fentanyl approach adult values, and children soon thereafter demonstrate increased plasma clearance and a shorter elimination half-life. Continuous morphine infusion rates and patient age ranges are summarized in Table 34-7.

REGIONAL ANALGESIA

"SINGLE-SHOT" CAUDALS

One of the most widely used pediatric regional techniques for postoperative analgesia is the "single-shot" caudal (SSC). Its popularity stems in part from the readily palpable landmarks and relative ease of caudal block insertion in infants and children versus adults. SSC is used in infants and children up to approximately 10 to 12 years of age having surgery from lumbosacral to midthoracic dermatome levels with anticipated moderate postoperative pain. Bupivacaine in concentrations of 0.125% to 0.25% is the most commonly used and studied local anesthetic for SSC. Injection volumes of 0.5 to 1.5 ml/kg will provide upper-lumbar to low-thoracic levels, respectively. An upper volume limit of 20 ml is generally used. The maximum recommended bupivacaine dose is 2.5 to 3.0 mg/kg, with an upper limit of 1.25 mg/kg recommended in early infancy. A test dose of 0.1 ml/kg (maximum 3 ml) of local anesthetic with 1:200,000 epinephrine (5 μg/kg) is used to ensure correct needle or catheter position. A 25% increase in T-wave amplitude, 10-beat/min increase in heart rate, or 10% increase in systolic blood pressure within 60 s of administration is considered a positive test dose. It is unclear whether block placement at the beginning versus the end of the procedure prolongs postoperative analgesia.

Although usually used alone, bupivacaine can be combined epidurally with fentanyl, morphine, the α-2-adrenergic agonist clonidine, or other additives to prolong the duration and/or density of analgesia. Delayed respiratory depression up to

TABLE 34–7 Continuous Intravenous Morphine Infusion for Postoperative Analgesia in Infants and Children

Age Range of Subjects (EGA)	Infusion (μg/kg/hr)	Comments	Number of Subjects
1–18 days (32–40 wk)	15	Some patients mechanically ventilated	20
1–49 days (35–41 wk)	6–40	Some patients mechanically ventilated; seizures at 32 and 40 μg/kg/hr; recommend rate of 15μg/kg/hr	12
3 mo–12 yr	14–21	Less total morphine than with time-contingent IM morphine	20
<1–14 yr	10–40	Spontaneously ventilating	121
14 mo–17 yr	10–30	Postoperative cardiac; able to wean from mechanical ventilation	44
1–15 yr	20	Superior to IM morphine	20
1–16 yr	10–40	Superior to IM morphine	46
3–22 yr	20–40	Cerebral palsy patients	55

EGA, estimated gestational age at birth; IM, intramuscular.
Source: Adapted from Birmingham PK, Hall SC: Drug infusions in pediatric anesthesia. In Fragen RF, editor: Drug infusions in anesthesiology, *ed 2, Philadelphia, 1996, Lippincott-Raven, pp. 193–224.*

TABLE 34–8 Suggested Pediatric Epidural Dosing Guidelines

Medication	Initial Bolus	Infusion Solution	Infusion Limits
Bupivacaine	≤2.5–3 mg/kg	0.0625–0.1%	≤0.4–0.5 mg/kg/hr
Ropivacaine	≤2.5–3 mg/kg	0.1–0.2%	≤0.4–0.5 mg/kg/hr
Fentanyl	1–2 μg/kg	2–5 μg/ml	0.5–2 μg/kg/hr
Morphine	10–30 μg/kg	5–10 μg/ml	1–5 μg/kg/hr
Hydromorphone	2–6 μg/kg	2–5 μg/ml	1–2.5 μg/kg/hr
Clonidine	1–2 μg/kg	0.5–1 μg/ml	0.1–0.5 μg/kg/hr

Note: These are approximate dose ranges. The actual dose selected depends on individual patient assessment. Infants <3–6 months of age generally receive a 30–50% reduction in initial dosing and hourly infusion rates of local anesthetic or opioid.

22 hr can occur with epidural morphine. Greater risk is seen in children less than 1 year of age and when parenteral opioids have also been given.

CONTINUOUS EPIDURAL INFUSIONS

Epidural local anesthetic infusions with or without opioids or α-2-agonists have been used in infants and children for postoperative analgesia. Bolus and infusion rate recommendations for bupivacaine, fentanyl, morphine, and clonidine are listed in Table 34-8. Lower infusion rates are generally recommended in neonates and infants less than 3 to 6 months old. This is because of lower protein binding and consequently higher free fractions of drug, and because of pharmacokinetic differences potentially resulting in higher plasma levels and prolonged drug half-life. Substitution of other opioids, such as those with mixed agonist-antagonist effects, may minimize clinical side effects. As a rule, optimal analgesia is obtained with the catheter tip positioned at or near the dermatomes to be blocked. It is possible in infants and smaller children to thread caudally inserted catheters to lumbar or thoracic levels. Catheter insertion may take place following induction of general anesthesia in infants and children who are unable or unwilling to cooperate with catheter placement while awake or sedated. Patient-controlled epidural analgesia has been successively used in children as young as 5 years of age.

Peripheral and truncal nerve blocks also play an increasing role in pediatric postoperative pain relief. These are typically performed under general anesthesia and increasingly with the use of ultrasound guidance. Ilioinguinal/iliohypogastric, rectus sheath, transverse abdominus plane, head and neck, and upper and lower extremity blocks are being done more frequently to provide analgesia in suitable candidates. Multicenter databases such as the Pediatric Regional Anesthesia Network (PRAN) have been created to accumulate additional information about the frequency of use and complication rate with both neuraxial and peripheral blocks in children.

KEY POINTS

- Anatomic and physiologic differences in neonates and young infants necessitate lower doses of epidural local anesthetics and intravenous opioids up to 4 to 6 months of life.
- Behavioral or physiologic measures of pain intensity are available for infants and children unable to self-report their pain.
- Aspirin is not routinely used for postoperative pain control in children because of an association with Reyes syndrome, a potentially fatal hepatoencephalopathy.
- Epidural analgesia by single injection or following epidural catheter insertion is commonly employed in infants and young children following induction of general anesthesia.
- Intravenous and epidural patient controlled analgesia can be used in children as young as 5 to 6 years of age.
- Nurse-or parent-assisted analgesia can be used in select circumstances for children unable or unwilling to operate an IV or epidural PCA button.

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CHAPTER 35

Chronic Pain after Surgery

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Approximately 40 million surgical procedures take place across North America each year, and by most conservative estimates 10% to 15% of those patients will go on to suffer chronic pain 1 year after surgery.[1] This is a silent epidemic of devastating proportions for those who suffer the pain and the associated emotional costs related to distress and for society as a whole who bear the financial cost of lost productivity and treatment of pain-related problems. Investigations in recent years have given better definitions of the extent of the problem, some of the factors that may predict the onset of chronic pain after surgery and methods of preventing chronic pain. In addition the future will bring us better definitions of the genetic basis of development of chronic pain allowing us to better counsel patients prior to different types of surgery regarding risk of chronic pain in relation to surgery and possibly allowing us to better aim the most intensive treatments at those patients in order to reduce morbidity. This chapter will discuss the extent of the problem of chronic postsurgical pain (CPSP), the factors associated with development, the typical presentation of CPSP, the genetics of CPSP, and possible methods of preventing CPSP.

WHAT IS CHRONIC PAIN AFTER SURGERY?

Without a good definition it is not possible to estimate the extent of a problem. Very few papers examining the epidemiology of chronic pain after surgery have used a consistent definition. This absence has led to large variability in estimation of chronic pain across different studies and has slowed progress in acquisition of knowledge in this area.

In their original paper on chronic pain after surgery, Crombie et al.[1] proposed a working definition as follows:

1. The pain should have developed after a surgical procedure.
2. The pain should be of at least 2 months duration.
3. Other causes of the pain should be excluded, such as recurrence of malignancy or infection.
4. The possibility that the pain is continuing from a preexisting problem should be explored and exclusion attempted.

This was the first worthy attempt to define CPSP and future studies would benefit from using such a consistent definition. However, an obvious problem with this definition is that some types of CPSP are related to a preexisting preoperative painful condition, such as phantom limb pain. Nevertheless, the use of a consistent definition of CPSP in the future will significantly help accurate description of the extent of the problem and allow better focus on the areas of greatest need.

EPIDEMIOLOGY OF CHRONIC PAIN AFTER SURGERY

The incidence of CPSP varies significantly by site of surgical procedure (Table 35-1); however, most reports support an incidence of at least 10% of patients having pain 1 year after surgery. Several high-quality reviews since the 1990s have highlighted the problem of chronic pain after surgery. Crombie et al.[1] highlighted the problem with their survey of greater than 5000 patients presenting to North British pain clinics, and found that surgery contributed to pain in 22.5% of those patients. In particular, pain in the abdomen, anal, perineal, and genital pain was associated with surgical procedures. Perkins and Kehlet[2] reviewed the evidence for CPSP and found an incidence of phantom limb pain of 30% to 81%, greater than 50% for chronic post-thoracotomy pain, postmastectomy pain syndrome in 11% to 57%, phantom breast pain in 13% to 24%, and post–breast surgery arm and shoulder pain in 12% to 51%. Chronic pain after cholecystectomy is common (3% to 56%) and the overall incidence of chronic pain after inguinal hernia surgery is 11.5%.

Despite improvements in methods of providing acute pain control since the 1990s, there have been no dramatic improvements in the incidence of CPSP. Studies examining pain after inguinal hernia repair,[3] breast surgery,[4] thoracic surgery,[5] and hip surgery[6] indicate that a very conservative estimate of approximately 10% of patients continue to suffer chronic pain following many types of surgery.

FACTORS ASSOCIATED WITH CHRONIC PAIN AFTER SURGERY

Factors that are associated with an increased likelihood of developing CPSP are summarized in Table 35-2. It is not known at the present time whether all of these factors are causally related (as opposed to associations) to development of chronic pain. These factors can be divided into preoperative, intraoperative, and postoperative factors. Preoperative factors include moderate to severe preoperative chronic pain, repeat surgery, and psychological factors. Intraoperative factors include surgery in a low-volume center, surgical approach (open vs. laparoscopic), and intraoperative nerve injury. Postoperative factors include acute pain (moderate to severe), radiation therapy, and neurotoxic chemotherapy.

Preoperative Factors

A consistent factor associated with development of acute and CPSP across many types of surgery is the presence of preoperative pain. This is of particular relevance to

TABLE 35–1 Incidence of Chronic Pain after Surgery by Surgical Site

Study	Surgical Procedure	Patients with Data	Follow-up	Incidence of Chronic Pain
Nikolajsen et al. 1997	Amputation	60	1 yr	Phantom pain 70%
Richardson et al. 2006	Amputation	52	6 mo	Phantom pain 78.8%
Jensen et al. 1985	Amputation	58	2 yrs	Phantom pain 59%
Tasmuth et al. 1997	Breast surgery	93	1 yr	13–33%
Nikolajsen et al. 1997	Cesarean section	220	1 yr	Scar pain 12.3%
Aasvang	Hernia repair	694	1 yr	56.6%
Grant et al. 2004	Hernia repair	750	5 yr	19% groin pain
Nikolajsen et al. 2006	Hip replacement	1048	12–18 mo prevalence	12.1% moderate–very severe pain
Borly et al. 1999	Open cholecystectomy	80	1 yr	26%
Meyerson et al. 2001	Sternotomy for cardiac surgery	318	1 yr	28%
Katz et al. 1996	Thoracotomy	23	18 mo	52%
Pertunnen et al. 1999	Thoracotomy	67	1 yr	61%
Gotoda et al. 2001	Thoracotomy	91	1 yr	41%

TABLE 35–2 Factors Associated with Development of Chronic Pain after Surgery

Preoperative Factors	Intraoperative Factors	Postoperative Factors
Moderate–severe pain of >1 mo duration	Surgical approach with risk of nerve injury	Moderate–severe acute pain
Repeat surgery	Nonlaparoscopic technique	Neurotoxic chemotherapy
Psychological factors	Surgery in low-volume center	Radiation therapy to site

anesthesiologists because we are often the main advocate for good quality postoperative pain management. The presence of preoperative pain is a risk factor for the development of early acute postoperative pain, pain in the days, weeks, and months following surgery.[7] A further amplifying factor is that the presence of severe acute postoperative pain also is a risk factor for development of chronic postsurgical pain. Kalkman et al.[8] examined preoperative factors predicting severe acute pain after surgery and found independent predictors of severe pain including preoperative pain, female gender, younger age, incision size, and type of surgery. Thomas et al.[9] examined patients having hip or knee replacement and spinal decompressive surgery and also found that predictors of severe postoperative pain included preoperative pain, female gender, and younger age. A very consistent factor in the development of CPSP is the presence of either severe preoperative pain, postoperative pain, or both. No other patient factor is as consistently related to the development of CPSP as pain itself.

Several factors may explain the consistent relationship of preoperative and severe acute postoperative pain predicting CPSP,[7] including the following:

1. Preoperative opioid tolerance leading to underestimation and underdosing of postoperative opioid analgesics.
2. Intraoperative nerve damage and the associated central nervous system changes such a central sensitization and "wind-up."
3. Sensitization of pain nociceptors in the surgical field.
4. Postoperative ectopic activity in injured primary afferents and collateral sprouting from intact nociceptive Aδ-afferents neighboring the area supplied by injured afferents.
5. Central sensitization induced by the surgery and maintained by further input from the surgical site during the healing process.
6. Structural changes in the central nervous system (plasticity) induced by nociceptive inputs with consequent reduction in normal inhibitory control systems leading to "centralization" of pain and development of pain memories.
7. Heretofore unidentified pain genes that may confer increased risk of developing both severe acute and chronic postsurgical pain.
8. Psychological and emotional factors such as emotional numbing and catastrophizing (see next page).
9. Social and environmental factors such as solicitous responding from significant others and social support (see next page).
10. Response bias over time—that is, some individuals have a tendency to report more pain than other individuals.
11. Publication bias in which findings of a significant relationship between pain before and after surgery are published, whereas negative findings are rejected and do not get published.

Psychosocial Factors

Several psychosocial predictors of chronic postsurgical pain have been identified including increased preoperative anxiety,[11] an introverted personality, less catastrophizing, social support and solicitous responding in the week after amputation, higher emotional numbing scores at 6 and 12 months,[12] fear of surgery, and "psychic vulnerability."[13]

Pain catastrophizing relates to unrealistic beliefs that the current situation will lead to the worst possible pain outcome. Consistently in the pain literature chronic pain patients who do not catastrophize fare better than patients who do. It is therefore somewhat paradoxical that the opposite has been found in the prediction of patients who are at risk of CPSP and may be an artifact of the method by which data were collected.[11]

Solicitous responding refers to the behaviors on the part of spouses or significant others who unwittingly reinforce patients' negative behaviors and thereby increase their frequency of occurrence. For example, an empathic spouse may reinforce negative behavior by insisting that her partner rest when in fact a more appropriate response would be to encourage activity. Such solicitous behaviors may in fact have the unintended consequence of increasing pain-related behaviors and contributing to pain-related disability. The reader is directed to the comprehensive review by Katz and Seltzer for further information.[7]

Intraoperative Factors

Three main surgical factors have a possible influence on the incidence of CPSP:

Experience of the surgeon. The experience of the surgeon can affect morbidity following surgery. Tasmuth et al.[14] studied patients after breast cancer surgery and found that patients who had surgery in low-volume units suffered more CPSP than patients in specialist units where higher numbers of patients had surgery. Other studies, however, have shown equivocal results. Courtney et al.[15] demonstrated no correlation between the grade of surgeon and severe pain after hernia repair.

Avoidance of intraoperative nerve injury. Many basic science studies have successfully demonstrated that intentional nerve injury in animals produces behaviors that resemble symptoms of neuropathic pain in humans. It would therefore make sense during surgical procedures on humans to reduce, as much as possible, any chance of causing intraoperative nerve injury. Many CPSP syndromes occur following surgery around significant nerve structures. Examples include pain after inguinal hernia repair (ilioinguinal and iliohypogastric nerves), axillary dissection (intercostobrachial nerve), and post-thoracotomy pain (intercostal nerves). When a nerve is injured, it emits a long-lasting, high-frequency burst of activity.[16–17] This activity is transmitted to the central nervous system where the massive excitatory stimulus activates postsynaptic NMDA receptors, leading to excitotoxic destruction of inhibitory interneurons,[18] disinhibition of pain pathways, and increased postoperative pain. The avoidance of intraoperative nerve injury would be a useful preventive measure and should be attempted wherever possible.

Use of minimally invasive surgical techniques where possible. Although the size of the surgical procedure does not correlate well with the incidence of CPSP, the type of procedure and how it is performed can influence CPSP. Wallace and colleagues studied incidence of chronic pain after different types of breast surgery and found that mastectomy had a much greater incidence of CPSP (53%) compared to breast reduction surgery (22%).[19] Cholecystectomy appears to show significant reductions in CPSP when a laparoscopic technique is used as compared to an open approach and these results have been confirmed by several studies.[20,21]

Genetic Factors

The study of the genetics of pain is in its infancy and there are no current research reports that provide data on genes that may predispose patients to CPSP. There are only a handful of reports that identify polymorphisms in human genes associated with chronic pain, including COMT (encoding catechol-O-methyl transferase), and 5-HTTLPR (the gene encoding the serotonin transporter), which has been found to associate significantly with severity of migraine,[22] burning mouth syndrome,[23] irritable bowel syndrome, and fibromyalgia. IL1RN (encoding the IL-1 receptor antagonist) and MC1R (encoding the melanocortin-1 receptor) in vulvodynia, IL23R in Crohn's disease, and GCH1 (encoding GTP cyclohydrolase, an enzyme catalyzing tetrahydrobiopterin, BH4, an essential co-factor for catecholamine, serotonin and nitric oxide production) have been implicated in persistent radicular pain following discectomy. Recent work has examined OPRM1 (encoding the μ-opioid receptor), including a systematic review[24] that attempted to determine the relationship of this gene to opioid sensitivity, side effects, or pain levels. Only 7% of the overall variance could be explained by genetic factors, and the authors concluded that only a minor degree of variance in the clinical setting could be related to pharmacogenetic factors. Despite the evidence of association between other genes and chronic pain conditions at this time any plan to incorporate genotyping information into the ability to predict who will develop chronic pain is premature.[25] Genetic factors relating to CPSP bear much promise; however, it is clear that significant amounts of work need to be done before they become useful in clinical practice.

PREVENTION OF CHRONIC PAIN AFTER SURGERY

Of the factors that are associated with generation of CPSP, several are within the direct control of anesthesiologists and surgeons in the perioperative period. Several studies have now demonstrated that severe acute pain after surgery is associated with an increased incidence of chronic pain. In a landmark study, Katz et al.[26] examined patients who had undergone lateral thoracotomy 18 months earlier and found that 52% of patients reported chronic pain. Of many factors, early severe postoperative pain was the only factor that significantly predicted development of long-term pain. In a study of trauma patients undergoing elective surgery, greater acute pain on postoperative day 4 was associated with

CPSP.[27] Iohom et al. recently examined the effect of a multimodal regimen on patients having breast cancer surgery and demonstrated a relationship between severe postoperative pain and subsequent CPSP.[28]

The relationship between severe acute pain and subsequent chronic pain is all the more worrying given that it appears a high proportion of patients continue to suffer moderate to extreme levels of pain after surgery.[29] Attempts to adequately prevent or treat severe acute pain may reduce the incidence of chronic pain. In addition, the ability to avoid intraoperative nerve injury and minimally invasive operative techniques both appear to reduce the chances of developing CPSP.

PREVENTIVE ANALGESIA

If severe acute pain after surgery can predispose to CPSP it follows that prevention of acute pain after surgery may help to reduce the incidence. In anesthesia and acute pain management, the practice of treating pain only after it occurs is slowly being replaced by a preventive approach. Although these methods have been developed primarily for reducing acute pain, the secondary aim of reducing transition to chronicity has also been a significant motivation. The theory that acute postoperative pain might be intensified by central sensitization induced by surgery was originally conceived by Crile[30] and later advocated by Wall[31] who suggested that "preemptive preoperative analgesia" would block central sensitization caused by surgical insult and thus reduce the severity of acute postoperative pain. Subsequent attempts to validate this concept of "preemptive analgesia" were limited by an overzealous definition attempting to prove that a preincisional intervention would be superior to the same intervention following incision.[32] This definition was flawed because surgical insult causing sensitization would be expected to occur throughout surgery and for several hours or days afterward. It was therefore really no great surprise that a subsequent meta-analysis[33] demonstrated no benefit of preemptive analgesia according to this definition. More recently, a more clinically relevant term—*preventive analgesia*—has been developed.[34] Preventive analgesia refers to the attempt block nociceptive input through the application of several analgesic agents acting at different sites (multimodal analgesia) starting prior to surgery and continuing for several hours or days following surgery. A successful preventive analgesic intervention would reduce or ablate pain for hours, days, or weeks following surgery and well beyond the duration of action of the initial analgesic intervention.[35] Several studies that have examined best analgesic methods including preventive analgesia have demonstrated benefits and these are described in the following sections according to the type of intervention.

LOCAL ANESTHETIC TECHNIQUES

Epidural analgesia provides significant acute pain benefits in the early perioperative period, especially for major abdominal and thoracic surgery, and several large studies have demonstrated these benefits.[36] However, the ability to prevent progression to chronicity has been less effective, with mixed results across several studies. Lavand'homme et al.[37] compared the epidural or intravenous route using local anesthetic, an opioid, or clonidine in one of four groups for patients undergoing major abdominal surgery. All patients received a bolus and infusion of low dose ketamine started preincision and maintained throughout the procedure. Patients in the intravenous alone group had much higher pain scores at rest and with movement compared to the other groups. The incidence of chronic pain in the intravenous alone group was significantly greater at 6 months (48%) and 12 months (28%) than other groups who had been given an epidural technique.

Gottschalk et al.[38] examined men undergoing radical prostatectomy randomizing either to epidural bupivacaine, fentanyl, or saline, followed by postoperative, patient-controlled epidural analgesia. Acute pain in the hospital was greatly reduced for the two groups who had been treated prior to incision, and incidence of pain 9.5 weeks (though not at 3.5 or 5.5 weeks) following surgery was significantly lower in the groups who had been treated in this way.

For patients having thoracotomy, Obata et al.[39] compared patients receiving preincisional epidural mepivacaine compared to the same intervention at the completion of surgery. Assessments at 3 and 6 months after surgery showed a significant reduction in post-thoracotomy pain in patients who received the preincisional epidural mepivacaine. Sentürk et al.[40] demonstrated significant benefit of an epidural compared to intravenous analgesic technique when used for patients having thoracotomy with patients in the epidural groups having significantly lower incidence and intensity of chronic post-thoracotomy pain. However, Ochroch et al.,[41] when randomizing patients to epidural bupivacaine and fentanyl either preincision or after rib approximation, could not demonstrate any differences in chronic pain 48 weeks after surgery.

The use of epidural analgesia for prevention of chronic phantom limb pain has been less effective. Despite early promise of the benefits of epidural analgesia in preventing postamputation pain a more rigorous study by Nikolajsen et al.[42] failed to demonstrate benefit. Up until recently, peripheral nerve blocks alone have had a disappointing effect on the incidence of CPSP despite their clear benefits in reducing acute postoperative pain. McCartney et al.[43] randomized 100 patients to either axillary block or general anesthesia for ambulatory upper limb surgery and despite significantly improved perioperative outcomes patients had identical incidence of pain 2 weeks following surgery. However, Iohom et al.[28] compared a multimodal analgesic regimen including both a paravertebral catheter and an intravenous COX2 inhibitor (parecoxib) followed by oral celecoxib with a standard treatment group (including postoperative diclofenac) for patients having breast cancer surgery. Patients in the paravertebral catheter group had significantly less acute pain and also a lower incidence of chronic pain at 2 to 3 months following surgery (0% vs. 85%).

NMDA RECEPTOR ANTAGONISTS

NMDA receptors play an important role in acute pain hypersensitivity states and the generation of CPSP. Several studies have demonstrated benefits of NMDA receptor antagonists in the prevention of pain following surgery.

McCartney et al. systematically reviewed this area,[35] and determined that both ketamine and dextromethorphan provide analgesic benefits beyond the clinical duration of action of either drug (5 half-lives). Longer-duration benefits are more controversial. Katz et al.[44] examined both short- and long-term effects of preoperative or postincisional intravenous fentanyl and low-dose intravenous ketamine, compared to a standard treatment receiving fentanyl but not ketamine, on postoperative pain on men undergoing radial prostatectomy under general anesthesia. Pain scores did not differ at any time during the first 3 postoperative days, although by the third day the hourly rate of opioid consumption was significantly less in the pretreated group. Unfortunately, no differences were seen in pain outcomes at 2 weeks and 6 months following surgery. Schley et al.[45] compared two groups of patients undergoing unilateral upper extremity amputation under continuous brachial plexus block. The treatment group also received a daily dose of the NMDA receptor antagonist memantine. In addition to improved acute pain control, the memantine group also had less chronic phantom pain at 4 weeks and 6 months (but not at 12 months) after surgery. Remérand et al.[46] studied patients having total hip arthroplasty under general anesthesia and randomized the treatment group to receive a preoperative bolus and then 24 hr continuous infusion of intravenous ketamine. At postoperative day 30, the ketamine group had less need for two crutches or a walking frame, and from day 30 to 180 decreased the number of patients with persistent pain at rest in the operated hip ($p=0.008$). However, Sen et al.[47] also compared ketamine, gabapentin, and placebo for patients having hysterectomy, and found that although opioid consumption was reduced in both ketamine and gabapentin groups only the gabapentin group had reduced incidence of incisional pain scores at the 1-, 3-, and 6-month follow-up visits.

GABAPENTIN AND PREGABALIN

Both gabapentin and pregabalin bind to the α2δ unit of the calcium channel and are useful components of multimodal analgesia, producing opioid sparing effects and reducing the severity of acute postoperative pain. A number of studies have also examined their effect on CPSP.[48] Fassoulaki et al.[49] randomized 50 patients having breast cancer surgery to either multimodal analgesia including gabapentin or placebo control. At 3 but not 6 months after surgery, patients in the multimodal group had significantly lower incidence of axilla pain (14 vs. 45%), morning pain (23% vs. 59%), and analgesic use (0% vs. 23%) compared with the placebo control patients.

Brogly et al.[50] examined the effect of gabapentin 1200 mg compared to placebo in a randomized study of 50 patients having thyroidectomy under general anesthesia. All patients also received a bilateral superficial cervical plexus block after induction. Although there were no obvious differences in acute pain (possibly masked by the cervical plexus block) patients in the gabapentin group did have a significantly lower incidence of neuropathic pain (4.3% vs. 29.2%) 6 months following surgery.

Buvanendran et al.[51] examined the effects of perioperative oral pregabalin started before total knee arthroplasty and continued for 14 days after surgery. Patients receiving oral pregabalin had less acute pain and also less neuropathic pain at 3 and 6 months following surgery. However, an earlier randomized study by Fassoulaki et al.[52] randomized patients having breast surgery to gabapentin, mexilitine, or placebo, and although they demonstrated better acute pain control, there was no difference in pain at 3 months following surgery.

NSAIDs

Nonsteroidal anti-inflammatory drugs have powerful analgesic effects and are effective components of a multimodal analgesic regimen for acute postoperative pain control. It is less certain at this time if they have any impact on the incidence of CPSP.

PREVENTIVE ANALGESIA SUMMARY

It is clear across numerous studies that providing effective acute pain control is best performed using multimodal analgesic techniques, including local anesthetics, opioids, and other agents such as NMDA receptor antagonists and/or gabapentin and associated drugs. Several studies indicate that there is an association between better acute pain control and reduction in CPSP. It would therefore seem wise to strive for best acute pain control for our patients in the knowledge that for some patients and procedures this will also translate into better long-term outcomes.

FUTURE STRATEGIES FOR PREVENTING CPSP

Good perioperative analgesia and minimization of surgical tissue injury will remain important goals for both anesthesiologist and surgeon in the perioperative period. The broader and more consistent use of multimodal analgesic techniques remain the simplest current method by which anesthesiologists could have a major impact on the development of CPSP. Screening strategies for psychological risk factors may be an important method in high-risk surgical procedures such as breast and thoracic surgery. Identification of the high-risk patient will allow more effective targeting of such patients with potent analgesic techniques in the perioperative period. The use of genetic screening for patients at risk of CPSP remains elusive and much more research will be required before this strategy becomes a reality.

Several interesting avenues of research focusing on novel analgesic targets are being developed, including GDNF[53] (glial-cell-line–derived neurotrophic factor), NK-1 (neurokinin 1) receptor antagonists,[54] voltage-gated Na channel blockade,[55] and purinergic receptor antagonists.[56]

CONCLUSION

Most people will experience surgery of one sort or another during their lifetime, and for a significant proportion this will lead to CPSP. The development of CPSP is common and dependent on numerous factors (Fig. 35-1). At the present time, anesthesiologists can make a difference by providing effective treatment of postoperative pain by including at least two modalities of multimodal analgesia, preferably starting before surgical incision. Other factors, including avoidance of intraoperative nerve injury and minimally

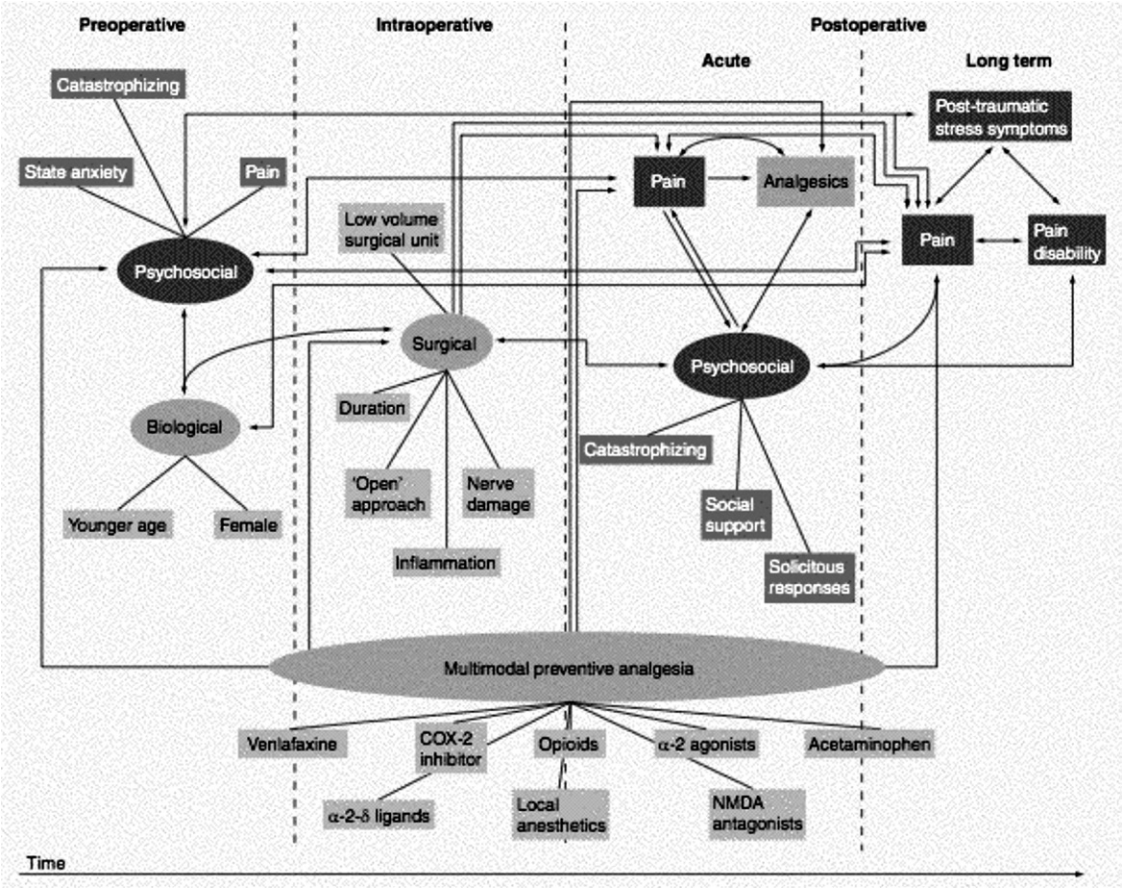

FIGURE 35-1 Schematic diagram of the processes involved in the development of chronic postsurgical pain showing the relationship between preoperative, intraoperative, and postoperative factors. *(From Katz J, Seltzer Z: Transition from acute to chronic postsurgical pain: risk factors and protective factors.* Expert Rev Neurother *9:723–744, 2009.)*

invasive techniques, may also help to reduce incidence of CPSP. Factors such as patient psychological and genetic factors are less easy to control; however, better understanding of these in the future may allow patients to properly consider the risks of developing CPSP and use aggressive and/or novel treatments to optimally prevent and manage CPSP.

KEY POINTS

- Chronic pain after surgery is common.
- Risk factors include patients with preexisting pain, psychosocial factors, age, gender, and possibly genetic susceptibility.
- CPSP can be prevented using good surgical technique (avoiding nerve damage and using minimally invasive techniques) and aggressive multimodal analgesia starting immediately prior to surgery.
- Future strategies should include more consistent use of multimodal analgesia across surgical populations and screening for high-risk patients using psychological and genetic factors.

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CHAPTER 36

Pain Management during Pregnancy and Lactation

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Complaints of pain occur in almost all pregnant and lactating women. Treatment of pain during pregnancy and lactation may affect the fetus or nursing child. Analgesics are commonly ingested during pregnancy.[1] Almost all drugs administered to the mother cross the placenta to the fetus, or are secreted in breast milk. The mechanisms of transport are similar to the transport of drugs across any membrane.[2] Diffusion is primarily passive and the drug concentration in the umbilical vein or breast milk depends on the concentration gradient, drug lipid solubility, degree of ionization and protein binding, and the diffusion capacity of the membrane (this may change as pregnancy progresses).[3] The effects on the fetus or nursing child will depend on the gestational or postconceptual age, as well as the amount and duration of drug exposure, and the specific drug.

Because most drugs cross the placenta and into breast milk, and because the effect of these drugs on the fetus and newborn are difficult to ascertain, efforts should be made to minimize maternal exposure to drugs and use nonpharmacologic therapies to treat pain. When drugs are necessary, the benefit should justify the risk (e.g., the untreated illness may pose a greater risk to the fetus than the medications used to treat the illness)[4] and the minimum effective dose should be used.

DRUGS DURING PREGNANCY

PHARMACOKINETIC CHANGES DURING PREGNANCY

The myriad of physiologic changes of pregnancy influence drug absorption, distribution, and elimination.[1] Changes in gastrointestinal function can alter oral drug absorption. Renal elimination is generally increased because of an increase in glomerular filtration rate. Hepatic metabolism may be increased, unchanged, or decreased, and the increase in total body water may alter drug distribution and peak concentrations. Protein binding is usually decreased; however, the free drug concentration may be unchanged because of increased drug clearance.

TRANSFER OF DRUGS ACROSS THE PLACENTA

The amount of drug that crosses the placenta depends on maternal cardiac output, fetal cardiac output, placental binding, and placental metabolism, as well as factors that influence passive diffusion across the placenta.[5] Maternal plasma levels of a drug depend on the site of administration (e.g., oral, intravascular, or epidural space), the total dose, the dosing interval, and other drugs that may be coadministered (e.g., epinephrine). The amount of drug to which the fetus is exposed also depends on fetal metabolism (fetal blood carrying drugs away from the placenta passes first through the fetal liver), fetal protein binding (about half of maternal protein binding), and the distribution of fetal cardiac output (fetal distress results in redistribution of blood flow to the vital organs).[3]

In general, good studies of human placental drug transfer and fetal exposure are limited. Interspecies differences in placental anatomy and function make animal model comparisons with humans risky. Ethical concerns have limited studies in pregnant women. Most studies of the placental transfer of anesthetic agents administered to the mother intrapartum report single measurements of drug concentration in the maternal and umbilical vein serum at the time of delivery (the fetal:maternal or F:M ratio). The measured fetal concentration does not reflect the effects of drug passage through the fetal liver, or the possibility of altered pharmacokinetics and pharmacodynamics in the fetus compared to the mother.

TERATOGENICITY

Possible adverse effects on the fetus of in utero drug exposure include structural malformations, intrauterine fetal death, altered fetal growth, neurobehavioral teratogenicity, acute neonatal intoxication or neonatal abstinence syndromes.[6] A major determinant of the effect of a drug on the fetus is the gestational age of the fetus. Traditionally, teratogenic effects of drugs have been defined as structural malformations. However, functional and behavioral effects are also likely to occur, and are much harder to identify. In addition, effects of fetal drug exposure may be delayed and only apparent later in life.[2] The mechanisms by which drugs cause teratogenicity are poorly understood, and may be direct or indirect (direct effect on the mother indirectly affects the fetus). There is interspecies variation in the ability of a drug to cause a specific congenital defect (e.g., thalidomide is not teratogenic in nonprimates).

The period of classic teratogenesis corresponds with the critical period of organogenesis and begins approximately 31 days after the first day of the last menstrual period until about 71 days after the last period.[7] Exposure to teratogens before 31 days results in an all-or-none effect (survival without a defect or loss of pregnancy). Fetal development, particularly the central nervous system, continues into the second and third trimesters, and indeed after birth. Therefore, fetal drug exposure at this time is not risk free.

Information on the teratogenic potential of many drugs comes from large-survey studies. These studies are often flawed because of reporting bias. They often do not control for other variables, including environmental exposures, exposure to multiple drugs (including alcohol, tobacco, nonprescription and illicit drugs), and the influence of the disease itself. Case reports of an association between

in-utero drug exposure and fetal anomalies are more likely to be published than if no anomaly occurred.[8]

FOOD AND DRUG ADMINISTRATION RISK CLASSIFICATION

The U.S. Food and Drug Administration (FDA) requires labeling of drugs using the Pregnancy Category System (Table 36-1). The FDA recognizes that this system is not always helpful to the prescribing physician and pregnant patient. For example, going from Category A to X does not necessarily mean increased risk of teratogenicity. Other Internet resources may provide more accurate and up-to-date information.[9]

SPECIFIC DRUGS

Aspirin use during pregnancy may be associated with an increased risk of gastroschisis. Pregnant women should not use aspirin (>150 mg/day) regularly.[9] Ibuprofen and naproxen during the first trimester do not appear to be teratogenic.[9,10] Prostaglandin inhibitors have been associated with narrowing of the ductus arteriosus in utero. This effect increases with gestational age, although it appears reversible when the medication is stopped.[2,9] Aspirin and other prostaglandin inhibitors may decrease amniotic fluid volume secondary to decreased fetal urine output, and they may prolong pregnancy and labor. An increased incidence of neonatal intracranial hemorrhage has been found in premature infants whose mothers ingested aspirin near birth. For these reasons, full-dose aspirin and nonsteroidal anti-inflammatory drug (NSAID) therapy should be avoided in the third trimester.[2,9] If a mild analgesic is indicated during pregnancy, acetaminophen is the drug of choice.

There is no evidence that maternal opioid agonist or agonist–antagonist exposure during pregnancy is teratogenic.[2,9] Chronic in-utero exposure to opioids may lead to neonatal abstinence syndrome. Acetaminophen combined with hydrocodone or oxycodone may be used to treat mild or moderate pain during pregnancy.

Bupivacaine and lidocaine were not associated with risk of teratogenicity in the Collaborative Perinatal Project.[2,3] The incidence of fetal anomalies was increased twofold in women who were exposed to mepivacaine; however, this group included a very small number of women, and so it is difficult to draw any conclusions from the data.

Several surveillance studies have found an association between maternal steroid use and orofacial clefts, while others have not.[2,7] A limited trial of epidural steroid therapy is probably associated with minimal fetal risk. The placenta inactivates prednisolone (the biologically active form of prednisone).[7]

Other adjuvant medications are often used in the treatment of chronic pain. There is no evidence that tricyclic antidepressant drugs are teratogenic.[11] There are conflicting data as to whether first trimester exposure to the selective serotonin reuptake inhibitors (SSRIs), in particular paroxetine, is associated with increased risk of major congenital heart anomalies.[12] Exposure to SSRIs in the third trimester before delivery may lead to a neonatal withdrawal syndrome,[13] and transient QT interval prolongation.[14] An increased risk of persistent pulmonary hypertension syndrome of the newborn has also been reported.[13] The long-term clinical consequences of these changes are not known. Data on the teratogenicity of buproprion in pregnant women is limited, but revealed no increase in the overall risk of malformations with some suggestion of increased risk of cardiac malformations.[15]

The anticonvulsants phenytoin, carbamazepine, and valproic acid all have been associated with fetal dysmorphic syndromes and should only be used when the risk outweighs the benefit.[9] Preliminary data suggest that lamotrigine may also carry an increased risk of fetal malformations.[2] There is evidence that both gabapentin and pregabalin cause malformations in rodent studies,[2] although data collected from the Gabapentin Pregnancy Registry (n = 51) did not identify an increased risk of adverse fetal outcome.[16]

Ergotamine is contraindicated in pregnancy, as it may be teratogenic, and it also causes uterine contractions.[9]

TABLE 36–1 U.S. Food and Drug Administration Pregnancy Category System

Category		Drugs
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.	None
B	Animal studies have revealed no harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. Or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.	Acetaminophen; butorphanol, nalbuphine; caffeine; fentanyl,* methadone,* meperidine,* morphine,* oxycodone,* oxymorphone;* ibuprofen, naproxen, indomethacin; prednisone, prednisolone
C	Animal studies have shown adverse fetal effects and there are no adequate and well-controlled studies in pregnant women. Or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.	Amitriptyline; aspirin, ketorolac; betamethasone, cortisone; codeine,* propoxyphene,* hydrocodone;* gabapentin; lidocaine; propranolol; sumatriptan; sertraline, fluoxetine; bupropion
D	Studies, adequate and well controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.	Imipramine; carbamazepine; diazepam; paroxetine; phenobarbital; phenytoin, valproic acid
X	Studies, adequate and well controlled or observational, in animals and pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.	Ergotamine

** Opioid agonists and agonist–antagonists are considered Risk Category D when used at high doses near term.*

There is no evidence that beta-blockers are teratogenic; however, they may be associated with intrauterine growth retardation.[7,9]

DRUGS DURING LACTATION

The amount of drug to which an infant is exposed during lactation depends on a number of maternal and infant factors. Maternal factors include maternal dose and dosing interval, the elimination half-life of the drug, the infant nursing pattern (volume and timing), and the amount of drug that actually crosses into breast milk.[2,7] The milk to plasma (M:P) ratio is an index of the amount of drug that is excreted into breast milk. Breast milk is slightly more acidic than plasma, and therefore passive diffusion favors drugs that are weak bases, lipid soluble, and have low protein binding.[1] The amount of drug to which the infant is actually exposed depends on infant pharmacokinetics, which may differ from maternal pharmacokinetics. The average infant dose is generally 1% to 2% of the maternal dose.[7] Even when the M:P ratio approaches 1, the infant plasma concentration rarely attains therapeutic levels.

Because the volume of colostrum is small, nursing neonates are exposed to minimal amounts of the drugs administered to the mother in the postpartum period.[7] Most milk is made during and immediately following nursing. Administration of drugs shortly after nursing, and avoiding long-acting drugs, may help minimize infant exposure. For mothers taking chronic medications, the in utero exposure is greater than the exposure during lactation. In general, the lowest effective dose should be used, and older drugs with a history of widespread use should be chosen.[17] It is best to use drugs that do not have an active metabolite.

AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics encourages breastfeeding. A policy statement summarizes the Committee on Drugs review of this topic and categorizes drugs into risk categories for nursing infants (Table 36-2). Most drugs are compatible with nursing. The following should be considered when prescribing drugs to lactating women[18]:

- Is drug therapy really necessary?
- The safest drug should be chosen, such as acetaminophen rather than aspirin for mild analgesia.
- If there is a possibility of risk to the infant, then one should consider monitoring infant serum levels of the drug.
- Having the mother take the medication just after she has breast fed the infant or before the infant is due to sleep can minimize drug exposure.

SPECIFIC DRUGS

Acetaminophen is considered the safest analgesic for nursing mothers. The infant of a mother taking acetaminophen 4 g/day was exposed to less than 5% the therapeutic infant dose.[17] There is controversy as to the use of aspirin in nursing mothers. Intermittent use should not pose a risk, but infants of mothers receiving chronic aspirin therapy should be observed for adverse side effects.[9,17] NSAIDs are considered compatible with nursing.[9,17,18]

Opioid agonist and agonist–antagonists cross freely into breast milk. The American Academy of Pediatricians considers opioids compatible with breastfeeding. These drugs undergo significant first-pass metabolism in the infant. However, infant plasma concentrations may be high enough to be associated with predictable side effects in the infant. Patient-controlled intravenous meperidine administered for postcesarean delivery analgesia had a negative impact on neonatal neurobehavioral scores compared to morphine.[19] The infants of nursing mothers ingesting opioids, particularly meperidine, should be monitored for adverse effects.

Less than 1% of the maternal dose of prednisone or prednisolone is recovered in breast milk.[2] Even at high maternal doses, this is unlikely to be enough to suppress infant adrenal function.[8]

The anticonvulsants carbamazepine, phenytoin, and valproic acid may be used safely during lactation. There are no data regarding the use of gabapentin or pregabalin during lactation.[2] The American Academy of Pediatrics classifies tricyclic antidepressants and SSRIs as drugs whose effects on the nursing infant are of potential concern. Low and undetectable serum concentrations of many antidepressants are detected in the serum of nursing infants but long-term studies are lacking.[20] Current guidelines suggest that the choice of a specific antidepressant be based on clinical factors, particularly previous efficacious treatments. Sertraline and paroxetine should be considered in lactating women who require these drugs for the first time.[20]

TABLE 36–2 Summary of Risk Categories for Drugs for Nursing Infants

Category	Drugs
Drugs for which the effect on nursing infants is unknown but may be of concern	Benzodiazepines, tricyclic antidepressants, buproprion, fluoxetine
Drugs that have been associated with significant effects on some nursing infants and should be given to nursing mothers with caution	Aspirin, ergotamine
Maternal medication usually compatible with breast-feeding	Acetaminophen, anticonvulsants, beta-blockers, local anesthetics, nonsteroidal anti-inflammatory drugs, opioid agonists, opioid agonists–antagonists, steriods, sumatriptan, sertraline, paroxetine

Source: Modified from the American Academy of Pediatrics 2001 Policy Statement: transfer of drugs and other chemicals into human milk. Pediatrics *108:776–789, 2001.*

Maternal administration of beta-blockers results in subtherapeutic levels in nursing infants.[1] Ergotamine has been associated with neonatal convulsions and gastrointestinal disturbances and should not be used in nursing mothers.[2,7] The use of sumatriptan during lactation has not been well studied.[9] The American Academy of Pediatrics considers sumatriptan compatible with breastfeeding[18]; infant exposure can be avoided by pumping and discarding milk for 8 hr after injection.[2] Serum concentrations of propranolol in the nursing infant are less than 1% of the therapeutic dose.[7]

IMAGING DURING PREGNANCY

The two factors that determine the possible effects of radiation exposure on the developing fetus are the gestational age and fetal dose of absorbed radiation. Risks of fetal radiation exposure include abortion, genetic mutation, and carcinogenesis.[21] At doses of less than 50 mGy, the risk of abnormalities is thought to be negligible; significant risk of malformation is increased only at doses greater than 150 mGy.[22] Although radiation exposure from imaging studies generally falls below 50 mGy, exposure should be avoided if possible until after the 15th week of gestation since radiation can be lethal to the fetus or cause severe defects with doses as low as 50 mGy.[21]

Although there is theoretical risk to using magnetic resonance imaging (MRI), no detrimental effects to the fetus have been documented. MRI is indicated during pregnancy when other nonionizing imaging methods, such as ultrasonography, are unsatisfactory, and the information obtained would otherwise require exposure to ionizing radiation.[21] Normal flouroscopy can deliver 10 to 50 mGy/min of exposure time, and thus should be avoided in pregnancy if possible.[22]

PAIN SYNDROMES DURING PREGNANCY AND LACTATION

PELVIC GIRDLE PAIN AND LOW BACK PAIN

Although definitions differ, the term *pelvic girdle pain* is used to describe pain in the symphysis pubis and/or pain in the regions of one or both sacroiliac (SI) joints and the gluteal region, whereas pregnancy-related low back pain refers to pain in the lumbar region.[23–25] The incidence of these syndromes during pregnancy is about 45% and around 25% in the postpartum period.[24] Risk factors include strenuous work, previous low back pain, or pain syndromes in a previous pregnancy.[23] The etiology of pelvic girdle pain is unclear, but may be related to mechanical, traumatic, hormonal, metabolic, or degenerative changes during pregnancy. Pain usually begins in the second trimester and resolves for most women within several weeks to months of delivery.[23] About 10% of women continue to have chronic pain for several years.

Pelvic girdle pain is usually located between the posterior iliac crests near the SI joints. It may occur in conjunction with symphysis pubis pain, and may radiate into the posterior thighs.[23,24] Few treatments have undergone rigorous scientific scrutiny. Patient eduction, pelvic belts, physiotherapy,and acupunture may be of benefit to some patients.[23,26] It is important to distinguish low back pain from posterior pelvic joint pain to optimize physical therapy and exercise recommendations.[23,24]

Acetaminophen is the drug of choice for minor pelvic and back pain. The short-term use of NSAIDs may be appropriate during the first and second trimesters. Severe back pain may require opioid therapy. Epidural steroid injection(s) may be indicated for acute radicular pain consistent with lumbar nerve root compression.

HEADACHE

Migraine headaches are unusual during pregnancy. The initial presentation of a migraine-like headache in pregnancy should prompt a search for another serious cause.[27]

KEY POINTS

- Pain is frequent during pregnancy and lactation. Many women suffer from pelvic girdle pain and back pain.
- Physiologic changes during pregnancy may alter drug pharmacokinetics and pharmacodynamics.
- Most drugs cross the placenta and cross into breast milk.
- Drug effects on the fetus may be direct or indirect (effect on the mother).
- Efforts should be made to minimize maternal exposure to drugs during pregnancy and lactation.
- Possible adverse effects of in utero drug exposure include structural malformations, intrauterine fetal death, altered fetal growth, neurobehavioral teratogenicity, acute neonatal intoxication, and neonatal abstinence syndromes.
- The effects of drugs on the fetus or nursing infant depend on the gestational or postconceptual age, the amount of drug and duration of exposure, and the specific drug.
- Drug pharmacokinetics and pharmacodynamics are altered in the fetus and neonates compared to the older child and adult.
- Information about fetal and neonatal effects of drugs administered to mothers is frequently incomplete.
- The decision to use drugs to treat pain during pregnancy and lactation should involve a risk:benefit analysis.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 37

Pain Control in the Critically Ill Patient

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Within the intensive care unit the concepts of hypnosis and analgesia are inexorably intertwined. Adequate treatment of pain and anxiety has been shown to decrease the stress response and psychological illness improving outcomes in critical care patients.[1] Critically ill patients experience both pain and anxiety from a multitude of factors. Along with obvious etiologies of pain such as preexisting diseases and trauma, patients in critical care settings often experience pain from prolonged immobility, routine nursing care (airway suctioning, dressing changes, and patient mobility) and monitoring and therapeutic devices (catheters, drains, and endotracheal tubes). Understandably, critical care patients also experience a significant degree of anxiety. Anxiety may stem from pain, being in an unfamiliar environment, and lack of control or even a fear of impending death. Significant anxiety may lead to agitation and delirium, complicating diagnosis and interfering with treatment leading to increased morbidity and mortality. Certainly, anxiolysis is difficult to achieve in a patient experiencing significant pain. Furthermore many of the medications used to treat pain have hypnotic effects. Thus, it is easy to understand how the concepts of hypnosis and analgesia have become interdependent goals of critical care therapy. However, this close relationship between these two distinct goals should not confuse the clinician as to the specific aim of each therapeutic agent. By understanding the tools for appropriate patient assessment and the pharmacologic agents available to accomplish these goals, one can better choose the appropriate agents for hypnosis and analgesia and thereby provide an appropriate sedation regimen to the critically ill.

GOAL ASSESSMENT

Pain assessment tools are difficult to implement in the critical care setting. An ideal assessment tool should provide simple, reliable data that guide therapy in a critical care setting. The most reliable and valid indicator of pain is a patient's self-report.[2] Unidirectional tools such as the numeric rating scale and visual analog scale rely on a patient's perception of their pain (Fig. 37-1). The numeric rating scale requires patients to rate their pain from 0 to 10, with 0 representing no pain and 10 representing the worst pain possible. The visual analog scale consists of a 10-cm horizontal line with descriptive phrases at either end, from no pain to severe pain to worst pain ever. Variations of the visual analogue scale include simplistic facial images rather than descriptive phrases. Despite the simplicity and reliability of these unidirectional pain assessment tools, they often are not useful in the critical care setting because patients are unable to communicate. Behavioral-physiologic scales use pain-related behaviors such as posturing and facial expressions along with physiologic indicators such as heart rate, blood pressure, and respiratory rate to assess pain intensity in patients who are unable to participate in unidirectional pain assessment scales. However, behavioral and physiologic markers are not specific for pain and may be misinterpreted in a critical care setting.[3] Agitation often clouds the behavioral-physiological pain picture, resulting in overestimation of a patient's pain, adding to the need to control anxiety. Although both unidirectional and behavioral-physiological scales provide reliable assessment in a majority of patients, pain assessment in patients requiring critical care therapy remains challenging to assess.

Titrating therapy to sedation levels allows for better outcomes as sole assessment of pain is complicated in critically ill patients. Both oversedation and undersedation can result in clinically significant adverse events. Undersedation may result in ventilator dysynchrony, increased oxygen requirements, self-removal of devices and possibly post-traumatic stress disorder from a stay in the critical care unit. Alternatively, oversedation may result in prolonged tracheal intubation and mechanical ventilation, increasing the chance of pneumonia and respiratory deconditioning. To this end, several sedation monitoring scales (Table 37-1) have been developed to aid in appropriate monitoring and titration of sedation levels.[4] With sedation assessment scales, sedation levels can be maintained by different care providers and therapeutic agents may be titrated to achieve desired levels of sedation. The Richmond Agitation Sedation Scale is user-friendly and therefore commonly used sedation scale with scores ranging from +4, a violent dangerous patient, to –5, an unarousable patient. A sedation score of 0 is most often therapeutically targeted as it correlates with an alert and calm patient.[5] The Ramsay Sedation Scale is the most simplistic and allows for a numeric score from 1 to 6 based on responsiveness of the patient.[6] However, it is more subjective and lacks clear descriptors between different levels. The Riker Sedation Agitation Scale scores a patient's level of sedation from 1 to 7 and is especially adapted to warn the clinician of extremes of sedation and agitation, which is not provided by the simplistic Ramsay Sedation Scale.[7] The Motor Activity Assessment Scale has been derived from Riker Sedation Agitation Scale and categorizes a patient's sedation level based on behavioral response to stimulation.[8] Adaptation to the Intensive Care Environment (ATICE) is a complex scoring system consisting of two domains, consciousness and tolerance.[9] The consciousness domain evaluates wakefulness and comprehension while the tolerance domain monitors agitation, ventilator dysynchrony, and facial expressions. As the name suggests, the ATICE scoring system aims to determine a patient's adaptation to the critical care setting. Other complex sedation scoring systems have also been constructed, but it is most important to become familiar with one system and standardize its use in an intensive care unit. Scoring should be consistent and reliable by different care providers to ensure patients are not

FIGURE 37-1 Unidirectional Pain Assessment Scales

oversedated or undersedated. Once sedation goals are met for a particular patient, they should be regularly re-evaluated to ensure therapy is being properly guided. Importantly, requirements for sedation are dynamic, generally declining as illness improves and thus must be reassessed frequently.[10]

Few objective measures are available to assess sedation. Vital signs such as heart rate, blood pressure, and respiratory rate are not specific or sensitive to sedation in the critically ill. Heart rate variability and lower esophageal sphincter tone are beginning to be used to objectively measure sedation. The bispectral index (BIS) aims to provide an objective measure of a patient's sedation by assigning a numerical value to a patient's electroencephalogram activity. The BIS has been shown to correlate with hypnotic drug effect in healthy elective surgery patients, but the BIS has not been as useful in the critical care setting.[11] BIS scores may vary between individuals with the same subjective level of sedation resulting in marked variability.[12] Furthermore the BIS may not correlate with sedation in patients with muscle activity or impairments of the brain. Currently, subjective scoring of sedation is the standard for assessing sedation in the critical care setting until more reliable objective tools are available.

THERAPEUTIC AGENTS

Patient comfort in the critical care setting is obtained with the use of both hypnotic and analgesic agents. Focusing first on providing analgesia and then on hypnosis may provide more effective sedation.[13] The lack of appropriate analgesia may lead to hyperesthesia and paradoxical agitation in the face of other sedative drug administration. Once adequate analgesia has been established, the remainder of the sedation regimen should be targeted at maintaining patient comfort, behavioral control, and an appropriate degree of amnesia with hypnotic agents. The value of a standardized approach to sedation with treatment using analgesic and sedation agents has been demonstrated to reduce oxygen consumption and autonomic hyperactivity[14] and improve outcomes.[15] Ideally, therapeutic agents should possess a rapid onset and offset of action with easy titration to therapeutic goals without the development of consequential side effects.

ANALGESIA

Appropriate attention to analgesia is an important step in all sedation protocols because most critically ill patients experience some degree of pain. Critical care staff should aim to minimize the production of pain by minimizing irritating stimulation, such as endotracheal tube traction on the carina and prolonged immobility. Despite aims to minimize pain production, supplemental analgesic therapy is often necessary for adequate pain control. Both opioid and nonopioid pharmacologic agents should be used to help control pain. With proper treatment of pain, better outcomes with quicker and more positive return to health can be expected.[16]

ANALGESIC AGENTS: NONOPIOIDS

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended first-line therapy for the treatment of pain.[2] Despite this recommendation, their use in the intensive care unit is a frequently forgotten adjunct to pain control. NSAIDs nonselectively inhibit cyclooxygenase, blocking the production of inflammatory mediators. Ketorolac, an NSAID, has been shown to have an efficacy comparable to moderate doses of commonly used opioids at doses of 30 mg IV every 6 hr.[17] However, clinical concerns of renal insufficiency and bleeding from platelet dysfunction and gastrointestinal tract mucosa limit the use of NSAIDs in the intensive care unit. Renal insufficiency results from the decreased of production of prostacyclins that increase renal blood flow. Normally, inhibition of prostacyclin production does not result in a decrease

TABLE 37–1 International Headache Society Diagnostic Criteria for Migraine

Migraine without Aura
At least five headache attacks
Headaches last 4–72 hr if untreated
Has at least two of the following, but not weakness:
Unilateral pain
Pulsating
Intensity is moderate to severe
Aggravated by routine physical activity
Has at least one of the following:
Phonophobia
Photophobia
Nausea
Emesis
Migraine with Aura
At least two headache attacks that also fulfill the characteristics of migraine without aura
Headaches usually follow the aura but may begin with it and last 4–72 hr if untreated
Has at least one of the following reversible symptoms (lasting 4 min to 60 min), but no weakness
Positive or negative visual symptoms such as scintillating scotomas, blind spot (scotoma), blurred vision, zig-zag lines, homonymous hemianopsia
Positive or negative sensory symptoms such as tingling or numbness
Basilar Migraine
At least two attacks of migraine with an aura whose symptoms are reversible and localize to the brainstem or are bihemispheric, but without weakness
Symptoms can include:
Dysarthria
Dizziness or vertigo
Bilateral visual symptoms, including temporary blindness
Diplopia
Nystagmus
Ataxia
Decreased level of consciousness
Bilateral paresthesiae
Tinnitus with or without decreased hearing
Aura without Headache
At least two attacks of symptoms typical of auras, but not weakness, such as visual, sensory or speech disturbances that resolve within 1 hr and are not followed by a headache
Hemiplegic Migraine
At least two attacks of migraine with a reversible aura of motor weakness that can last 1 hr to days
Also includes one of the following:
Positive or negative visual symptoms
Positive or negative sensory symptoms
Dysphasia or dysarthria
Frequently accompanied by symptoms typical of basilar migraine
If at least one first- or second-degree relative has a migrainous aura that includes motor weakness, it is *familial hemiplegic migraine* and is associated with a mutation in the neuronal calcium channel
If no first- or second-degree relative has a migrainous aura that includes motor weakness, it is *sporadic hemiplegic migraine*

Source: International Headache Society: The International Classification of Headache Disorders, 2nd edition. Cephalalgia *24(suppl 1):1–150, 2004.*

in renal function; however, in patients with hypoperfusion, hypovolemia, baseline renal impairment or older age, ketorolac may increase the incidence of NSAID-induced renal injury.[18] Additionally, use of ketorolac for greater than five days has been associated with an increase risk of renal dysfunction and both gastrointestinal and operative site bleeding.[19] Acetaminophen is commonly used to treat mild to moderate pain and as an antipyretic. The addition of acetaminophen, at doses of 1 g every 6 hr, to opioid therapy has been shown to produce greater pain relief than opioids alone.[20] Care should be taken to ensure that toxic doses of acetaminophen are avoided given that oral pain

medications are routinely given as a combination of opioid and acetaminophen. Particularly, patients with liver dysfunction or a history of alcohol abuse are at risk for hepatoxicity from acetaminophen. Although opioids remain the mainstay of analgesic therapy in the intensive care unit, nonopioids should be considered as possible supplemental agents.

ANALGESIC AGENTS: OPIOIDS

A careful understanding of the properties of individual opioids (Table 37-2) is essential to the appropriate use of these agents in the intensive care unit. Lipid solubility, protein binding and metabolism account for the pharmacokinetic differences between these agents. Opioids produce analgesia mainly by stimulating γ- and κ-receptors located both centrally and peripherally; however, interaction with other opioid receptors may lead to adverse effects. Unwanted effects of opioids include nausea, constipation, urinary retention, pruritus, and excessive sedation with possible respiratory depression. Severe constipation leading to ileus has been treated with some success using intravenous and parenteral opioid antagonists.[21] Respiratory depression occurs because the ventilatory response to hypercapnia is decreased, while the response to hypoxia is obliterated. These respiratory depressive qualities, however, are often helpful in treating ventilator-patient dysynchrony.[22] Hypotension is occasionally seen in hypovolemic patients as a decrease in sympathetic tone occurs after treatment of pain with opioid administration. The full opioid agonists, hydromorphone and fentanyl are the most frequently used analgesics in critically ill patients. The combination of opioids with benzodiazepines results in a synergistic effect that may permit dose reduction, thereby reducing the occurrence of undesirable side effects of both opioids and benzodiazepines.

Fentanyl is an opioid which has a rapid onset and short duration of action often necessitating continuous infusion therapy of 1 to 2 μg/kg/hr with 1 to 2 μg/kg initial loading doses to provide adequate pain control.[23] Prolonged effects, however, can be seen with protracted continuous administration necessitating frequent monitoring to avoid detrimental narcosis. Sufentanil and alfentanil are close chemical relatives of fentanyl with shorter onset and duration of action times. Sufentanil is a potent lipophilic narcotic with greater protein binding and smaller volume of distribution than fentanyl, resulting in a shorter duration of action. However, similiar to fentanyl, accumulation of sufentanil may occur with prolonged infusion, resulting in difficulty in predicting the duration of action. Alfentanil possesses a small volume of distribution secondary to protein binding and low lipid solubility, allowing for predictable duration of action. Despite the shorter duration of action of sufentanil and alfentanil when compared to fentanyl, the cost and unfamiliarity with use of both alfentanil and sufentanil limits the routine use of these agents in the critical care setting. Hydromorphone has a longer onset of action than fentanyl but also a longer duration of action, allowing for intermittent dosing at ranges of 10 to 20 μg/kg per 1-2 hr. Metabolism of hydromorphone may be influenced by the presence of underlying liver disease, renal disease, or alterations in protein binding. Thus, hydromorphone is reluctantly used in long-term infusions because accumulation of metabolites can lead to much difficulty in appropriate dosing. Morphine has a pharmacokinetic profile similar to hydromorphone but has a potent active metabolite that depends on renal excretion limiting its use in the critical care setting. Morphine may also rarely lead to significant hypotension mediated by vasodilatation from histamine release. Although popular in the past, meperidine is generally avoided for prolonged therapy due to accumulation of its neuroexcitatory metabolite, normeperidine, which can cause seizures. Meperidine also has vagolytic and histamine releasing side effects both of which may result in tachycardia. Remifentanil is an ultra-short-acting opioid as it is metabolized by nonspecific plasma esterases, providing the most predictability of duration of action of all the opioid agents. Remifentanil-based sedation regimens, at doses of 0.01 to 0.2 μg/kg/min, have shown to produce better sedation and decrease the length of ICU stays when compared to hypnotic-based regimens.[24] However, the cost of prolonged continuous infusions of remifentanil is prohibitive for its routine use in the critical care setting. Because critically ill patients often have altered peripheral blood flow, the use of intravenous dosing over intramuscular, subcutaneous, or transdermal delivery systems is often preferred. Demand-based patient-controlled analgesia (PCA) is often useful in allowing appropriate opioid dosing for pain control without oversedation and respiratory depression.[25] Because of their underlying critical illness, many patients in the intensive care unit do not possess the level of cognitive interaction required for appropriate PCA opioid dosing. Thus, the use of continuous opioid infusions has become quite popular but warrants concern about potential oversedation. More importantly, dosing of opiods must be carefully undertaken in critically ill patients. Understandably, a dehabilitated elderly patient may have drastically lower opioid requirements than a young, healthy trauma patient. It is best to diligently titrate medication to ensure adequate pain control without the development of harmful narcosis.

TABLE 37–2 Trigeminal Autonomic Cephalalgias

Type	Male:Female	Frequency	Duration
Cluster	5.5:1	1 or several/day	15–90 min
Hemicrania	1:3	Up to 30/day	5–45 min
SUNCT	8:1	5–30/hr	5–60 s

Source: International Headache Society: The International Classification of Headache Disorders, *2nd edition. Cephalalgia 24(suppl 1):1–150, 2004.*

HYPNOSIS

Hypnosis plays an important role in providing comfort to critically ill patients. After adequate treatment of pain, hypnotic agents help by providing anxiolysis, sedation, and amnesia, and decrease analgesic requirements. Benzodiazepines, propofol, and dexmedetomidine are the most commonly used hypnotic agents in the critical care setting.

HYPNOTIC AGENTS: BENZODIAZEPINES

Within the intensive care unit, benzodiazepines are the most commonly used hypnotic agents. Benzodiazepines interact with the γ-amino-butyric acid (GABA) receptor creating an increase in intracellular chloride concentration and subsequent hyperpolarization of the cellular membrane. This hyperpolarization of neuronal membranes explains the utility of the benzodiazepines as sedatives in addition to their frequent use as anticonvulsants. These agents block encoding of new information, resulting in anterograde amnesia and possibly decreasing the incidence of post-traumatic stress disorder from unpleasant intensive care therapy. Midazolam and lorazepam are the most common used benzodiazepines in the critical care setting and vary in their onset, duration of action, and metabolism (Table 37-3). Furthermore, individual patient characteristics, such as age and metabolism induction or inhibition, alter the pharmacokinetics and pharmacodynamics requiring individualized titration of these agents. Often, loading doses are needed to achieve a therapeutic level but then smaller as needed doses are often adequate to maintain a desired sedation level. If frequent doses are required to maintain desired sedation goal, continuous intravenous infusions should be cautiously considered because patient awakening times after continued prolonged use are quite unpredictable. The use of flumazenil, a benzodiazepine antagonist, may cause withdrawal symptoms resulting in increased oxygen consumption and is therefore avoided in the critical care setting.

Diazepam may possess the most enduring track record for use as a sedative. Its original formulation in propylene glycol made its use difficult secondary to the frequent venous irritation and thrombophlebitis, but this has been overcome by the use of a fat emulsion. Additionally, it is important to note that although diazepam has a relatively rapid onset of action and rapid awakening after small doses, lengthy therapy results in a prolonged sedative effect as the hepatic metabolism of diazepam results in the production of an active metabolite known as desmethyldiazepam forcing diazepam to be considered a long-acting agent. Interestingly the primary metabolic pathway of diazepam, the CYP2C19 hepatic enzyme subfamily, demonstrates significant genetic polymorphism resulting in marked metabolic variation. Many medications inhibit or stimulate the CYP2C19 enzymes complicating diazepam dosage requirements. As diazepam relies on hepatic metabolism, patients with hepatic dysfunction may experience a significant increase in the duration of action of this agent. The titration of diazepam to achieve appropriate levels of sedation in the critically ill patient is often challenging given the active metabolic byproduct and dynamic pathophysiologic nature of critically ill patients, altering hepatic metabolism.

Lorazepam is used frequently in the intensive care unit at doses of 1 to 2 mg every 1 to 2 hr. Lorezapam is the least lipophilic benzodiazepine and therefore, has a slower onset of action than other benzodiazepines. This drug has a favorable metabolic profile as it relies on hepatic glucuronidation, producing an inactive metabolite that makes elimination more predictable. Regardless, it is essential for the clinician to note that this intermediate acting benzodiazepine will require consistent vigilance in its use to prevent oversedation. Large doses of prolonged intravenous lorazepam should be avoided as they have been associated with acute tubular necrosis, lactic acidosis and hyperosmolar states. These are secondary to pathology from the carrying solvents, propylene glycol and polyethylene glycol.[25] Therefore, as-needed bolus doses of lorazepam are often preferred over continuous intravenous infusions.

Midazolam is frequently used in the preoperative and intraoperative areas at doses of 1 to 5 mg secondary to its water-soluble characteristics that allow the drug to become highly lipid soluble at physiologic pH allowing for a rapid onset. Midazolam relies on hepatic metabolism and significant accumulation of midazolam may occur in patients with hepatic dysfunction during prolonged therapy because of its high lipophilicity and large volume of distribution.[26] Additionally, it possesses an active metabolite, alpha-hydroxymidazolam, which relies on renal excretion prolonging its duration of action in patients with renal disease. Even though the rapid onset of this agent is ideal for acute therapy, the possible prolonged sedative effect of midazolam makes its use in the critical care setting objectionable.

TABLE 37–3 Comparison of Commonly Used Hypnotic Agents

Property	Lorazepam	Midazolam	Propofol	Dexmedetomidine
Rapid onset	−	+	++	+
Short duration	−	±	+	−
Cardiovascular/respiratory depression	−	±	+	−−
Inactive metabolites	+	−	+	+
Hepatic metabolism	+	+	−	+
Hepatic conversion to inactive products	++	−	−	+
Renal elimination of active metabolite	−	+	−	−
Inexpensive	+	±	−	−−

HYPNOTIC AGENTS: PROPOFOL

Like benzodiazepines, propofol is also a GABA receptor agonist. Propofol is commonly used to induce general anesthesia but can be used at lower doses as a hypnotic agent, producing a degree of amnesia less than benzodiazepines.[27] Hypnosis from propofol rapidly resolves even in patients with hepatic and renal impairment because redistribution of the medication away from the central compartment results in arousal. Propofol also acts as a vasodilator and a cardiac depressant, resulting in a dose-dependent decrease in blood pressure and possibly heart rate, respectively. Additionally, higher doses of propofol result in depression of respiratory drive. Despite the cardiovascular and pulmonary depression, the rapid onset and resolution of hypnosis make propofol a commonly used agent intensive care unit at doses between 10 and 50 μg/kg/min. Furthermore, propofol therapy may also have antioxidant or anti-inflammatory properties secondary to the preservatives EDTA or metabisulfite, respectively.[28]

Long-term continuous infusions of propofol, however, should be used cautiously. Propofol is prepared with a lipid emulsion carrier that may support bacterial growth. It is recommended that propofol be discarded 6 hr after initiation of use and that tubing carrying propofol by changed every 12 hr to avoid contamination. The phospholipid emulsion of propofol should be counted as a calorie source and may result in triglyceridemia and eventually pancreatitis. A rare but morbid complication of prolonged high-dose propofol therapy above 50 μg/kg/min, propofol infusion syndrome, results in mitochondrial injury, lactic acidosis, dysrhythmias, hyperkalemia, and rhabdomyolysis. Propofol provides superb short-term hypnosis as arousal is rapid. For longer-term sedation, however, other agents should be considered because propofol infusions are prone to complications with prolonged duration.

HYPNOTIC AGENTS: DEXMEDETOMIDINE

Dexmedetomidine is a α_2-agonist with an affinity for the α_2 receptor 7 times greater than clonidine. Activation of the post-synaptic α_{2A}-receptor results in hypnosis, mild amnesia and significant analgesia that reduces the need for supplemental opioids. A hypnotic effect is produced by dexmedetomidine that resembles induction of normal sleep at doses between 0.2 to 1.0 μg/kg/min. The hypnotic effect of dexmedetomidine is unique, in that patients, when left undisturbed, will sleep; but when aroused with gentle stimulation, patients will be cooperative and follow commands. This effect is mediated by activation of the α_{2A}-receptor in the locus ceruleus. Attention to environmental control becomes essential as disturbances easily awaken patients. Dexmedetomidine also provides for mild anterograde amnesia; however, benzodiazepines should be considered to ensure amnesia. The major advantages of dexmedetomidine are that it produces virtually no respiratory depression while providing sedation and reducing analgesic opioid requirements. It has been shown to facilitate extubation in patients who have previously failed extubation attempts due to severe agitation.[29] Dexmedetomidine may have a superior anti-inflammatory profile with improved immune function compared to other hypnotic agents which could be particularly beneficial in patients suffering from sepsis.[30]

Some adverse effects of α_2-agonists include enhancement of vagal effects by creating a pharmacologic sympathectomy resulting in hypotension and bradycardia. However, if therapy is initiated rapidly at a high dose, a transient hypertension and tachycardia may occur. This is then followed by hypotension and bradycardia mediated by the α_{2A}-receptor inhibiting sympathetic tone in the peripheral vascular system. However, the hemodynamic effects of α_2-agonists are relatively similar to those induced by other drugs used commonly in sedation regimens. The cost of dexmedetomidine is cited as prohibitive for routine use, but both favorable clinical and economic outcomes have been reported.[31]

DELIRIUM

Patients requiring intensive care therapy often become delirious. Delirium often is confused with dementia. Dementia is a progressive disease with a decline in memory and cognitive skills and rarely presents acutely. Conversely, delirium is an acute reversible change in mental status. It is characterized by fluctuating levels of arousal associated with sleep–wake cycle disruption brought on by the reversal of day–night cycles and is associated with worse outcomes and increased long-term mortality.[32] Patients suffering from delirium can be hypoactive, hyperactive, or even have mixed levels of activity.[33] Hyperactive delirium is easily recognized as patients are agitated and combative interfering with therapeutic measures; however, hypoactive delirium, which is characterized by calm appearance, decreased mobility and inattention, is actually associated with a worse prognosis. Ideally, delirium should be assessed using the DSM-IV criteria by a psychiatric expert. The DSM-IV assessment, however, is involved and often impossible in an acutely ill patient. The CAM-ICU (Fig. 37-2), Confusion Assessment Method for the ICU, rapidly and accurately assesses delirium in critically ill patients.[34] In a critically ill patient with an acute change or fluctuating mental status, the CAM-ICU aims to evaluate inattention, altered level of consciousness, and disorganized thinking. In order to be diagnosed with delirium, a patient must not be heavily sedated and demonstrate inattention along with either altered level of consciousness or disorganized thinking. If delirium is suspected, therapy should involve both medications and environmental modification. Sleep is essential for recovery from illness. Critically ill patients are often rendered unconscious by sedative agents, but hypnotic induced coma is not equivalent to natural sleep. Cognitive, cardiopulmonary, and immune functions suffer with sleep deprivation.[35] In particular disruption of the sleep cycle is associated with the development of delirium. Modifying the critical care environment to promote normal day–night sleep–wake cycle can promote sleep. In particular, controlling noise, lighting, and minimizing therapies during nighttime will allow for better sleep. Relaxation, massage, and music therapy have also been used to promote sleep in the critically ill. Additionally, zolpidem at 5 to 10 mg may provide benefit as a sleep aid in the critically ill.[36] In addition to sleep and normalizing the day–night cycle, reorientation, informing patients of their ongoing clinical situations, and allowing for patients to have some control of their care is thought to improve delirium. Control of pain and anxiety is essential

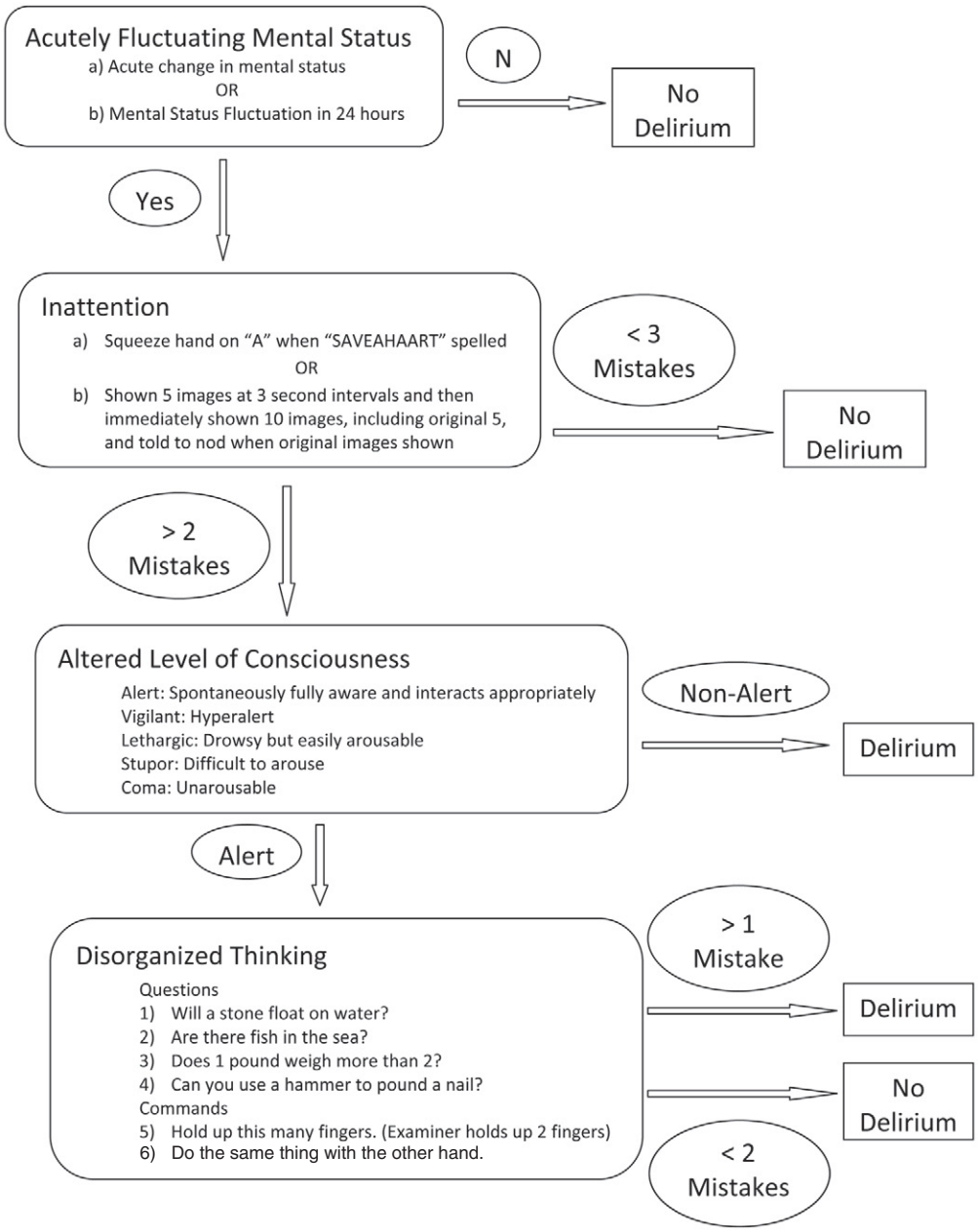

FIGURE 37–2 The Confusion Assessment Method for the ICU (CAM-ICU).

to avoid delirium. Undermedicating with hypnotics and analgesics may drive a patient to agitation, leading to delirium. On the other hand, overmedication with sedatives and analgesics may lead a patient to be more confused, leading to a paradoxical increase in agitation and delirium.[37] After appropriate sedation and analgesic therapy, haloperidol 0.5 to 5 mg every 5 min until agitation is controlled is often used as an adjunct in patients who have a component of hyperactive delirium. Haloperidol antagonizes dopamine-mediated neurotransmission, stabilizing cerebral function. Unstructured thought patterns are thought to be inhibited, producing a flat sedative affect.[38] Intravenous loading dose injection of haloperidol with repeat loading doses is routinely used to treat delirium acutely. Once delirium is controlled, haloperidol therapy should be regularly scheduled over a few days followed by tapering doses over several days. Monitoring for extrapyramidal symptoms, neuroleptic malignant syndrome, hypotension, and QT prolongation is recommended specifically as QT prolongation can lead to torsades de pointes. Fortunately, such idiosyncratic effects are rarely seen, and haloperidol remains helpful in treating delirium in many critically ill patients. Olanzapine, a newer agent for the treatment of delirium, has similar efficacy to haloperidol but with fewer extrapyramidal side effects at doses of 2.5 to 5 mg daily.[39] Hypoactive delirium, on the other hand, may actually be exacerbated by sedative medications. Interestingly, lorazepam has been found to be an independent risk factor for the development of delirium in ICU patients.[40] Delirium is common occurrence in critical care patients. Surveillance for this morbid complication of critical care along with appropriate pharmaceutical and environmental therapy is essential for improved critical patient care.

NEUROMUSCULAR BLOCKING AGENTS

A discussion of neuromuscular blocking agents may seem inappropriate when considering patient comfort in the intensive care unit. However, the frequent use of neuromuscular blocking agents and confusion about their mechanism of action warrants some discourse. With the aggressive use of sedation regimens and recognition of prolonged weakness from neuromuscular blocking agents, neuromuscular blockade use has declined significantly in the critical care unit. However, on rare occasion paralysis with neuromuscular blockade is desired for the critically ill patient. One of the most common reasons to utilize neuromuscular blocking agents in the intensive care is patient–ventilator dyssynchrony.[41] Such dyssynchrony can result in increased airway pressures which may predispose the patient to ventilator induced lung injury. Additionally, adequate oxygenation and ventilation can become extremely difficult in many patients with dysynchrony. In the past, the most frequent form of treatment for this problem was administration of neuromuscular blockade. However, it is essential to realize that these drugs do not provide analgesia. They merely provide paralysis. Thus, not only does it become difficult to assess pain, agitation, and mental status, these agents can actually worsen patient anxiety by preventing patient movement in the presence of inadequate sedation. As one can imagine, many patients would find such a situation emotionally distressing. Thus, frequently the best approach to treatment of these patients consists of increasing opioid delivery to the patient. Because opioids provide respiratory depression, patient–ventilator dysynchrony can be ameliorated by the use of an agent which will depress the patient's ventilatory drive without risking the side effects of prolonged paralysis from a neuromuscular blocking agent.

In addition to treating dysynchrony, neuromuscular blocking agents are also used to decrease oxygen consumption in patients with tenuous oxygen supply versus demand. Such individuals may benefit from neuromuscular paralysis by decreasing metabolic oxygen consumption needs to minimal. Individuals with evidence of anaerobic metabolism despite maximal maneuvers to increase tissue oxygen delivery may be able to return to a state of aerobic metabolism. Such treatment with a neuromuscular blocking agent must not be viewed as definitive, but rather, a temporary means of controlling an oxygen supply versus demand imbalance.

Highly agitated patients who present a significant risk to themselves of self-harm may also benefit from short-term use of neuromuscular blocking agents. Patients who are at high risk of life-threatening self-extubation and those who remain uncooperative with potentially life-saving diagnostic studies may be appropriate candidates for the use of short-term neuromuscular blockade when attempts at maximal analgesia and sedation have failed. Additionally, in appropriate candidates, neuromuscular blockade can be used to facilitate tracheal intubation or central venous catheterization when prior attempts at sedation have failed.

In addition to the risk of prolonged weakness due to neuromuscular blockade, the decision to use neuromuscular blocking agents in patients with a history of frequent tonic-clonic seizures or status epilepticus must occur only after careful consideration. It is important to realize that intact neuromuscular function provides the clinician with a constant monitor of potentially life-threatening seizure activity. However, in the patient who has received a neuromuscular blocking agent, this monitor is now unavailable. Thus, a risk exists that the patient may develop cerebral seizure activity without the awareness of healthcare providers. Such unrecognized, untreated, prolonged cerebral seizure activity can then lead to irreversible neurologic injury and even brain death.

The greatest concern to neuromuscular blockade use is prolonged paralysis, particularly in patients receiving steroid therapy. The most commonly used neuromuscular blocking agent in the critical care unit is cisatracurium at infusion rates of 1 to 5 μg/kg/min as it undergoes Hoffman degradation. Only temperature and pH alter the pharmacokinetics; therefore patients with renal and hepatic dysfunction can be treated with cisatracurium with minimal concern for prolongation of action. Ideally, before neuromuscular blockade use is initiated, plans should be made to discontinue use of the agent with conversion to another therapy. Often, this entails increasing the sedation regimen but may also entail improving oxygen delivery or treatment for seizure activity.

CONCLUSION

Maintaining sedation is an extremely important goal in the care of critically ill patients, but this aspect of their care frequently becomes lost in the myriad of physiologic derangements encountered in the critically ill patient. All sedation regimens have potentially adverse side effects that can endanger the patient's well-being and can prolong the clinical course.[40] Sedation regimens have been implicated in the development of depression and post-traumatic stress disorder after intensive care unit stays.[42] Furthermore, daily interruption of sedative treatment has been shown to reduce the length of a patient's ICU stay.[43] Even patients with coronary artery disease have been shown to have reduced lengths of critical care unit stays despite the surge of catecholamines and resultant cardiac stress associated with daily sedation interruptions.[44] The current clinical trend is to provide a lighter level of sedation using shorter-acting agents.[45] However, discontinuation of sedative and analgesic medications must be undertaken carefully. Patients with continued use of medication for greater than 1 week are at risk for neuroadaptation and physiologic dependence and may develop withdrawal symptoms with discontinuation of therapy.[46] In order to design a proper sedation regimen, multiple critical endpoints and factors must be considered. These include duration of desired sedation, drug side effects, potential complications of the sedation regimen and costs; such costs include not only the drugs alone, but also, the aforementioned side effects and complications as well. Thus, it is essential that all members of the critical care team be aware of the sedation and analgesia plan, adhere to it, and be aware of the potential shortcomings of the plan so that appropriate adjustments can be made as the patient's condition changes or adverse effects emerge. Only with a systematized and consistent approach to sedation can efficacious and cost-effective care to tenuous critically ill patients be provided.

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Access the reference list online at http://www.expertconsult.com

Chronic Pain Syndromes

CHAPTER 38

Migraine Headache and Cluster

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MIGRAINE HEADACHE

EPIDEMIOLOGY

Migraine headache represents a very common benign headache syndrome; it is sometimes referred to as a vascular headache. Approximately two-thirds of migraines occur in women. The prevalence in North America, ascertained through epidemiologic studies, is 12% to 17.6% in females and 4% to 6% in males. Prior to puberty, the prevalence of migraine in boys and girls is similar; during and after adolescence, the incidence increases more rapidly in girls. In females, prevalence increases up to the age of about 40, after which it decreases; the decrease becomes steeper as women approach menopause. Among those with severe migraine, about 25% have four or more migraines per month. More than 80% of patients with severe migraines experience headache-related disability, which ranges from decreased productivity to time off work during an attack. The cost in productivity may exceed $20 billion per year in the United States. Although the cause of migraines is unknown, the risk of suffering from migraines is about 50% higher among those who have a first-degree relative with migraines; however, genetic factors appear to account for fewer than 50% of all migraines.[1–4]

PATHOPHYSIOLOGY

The pain-generating structures of the head include the venous sinuses, meningeal and large cerebral arteries, basal meninges, muscles, skin, and cranial nerves V, IX, and X. A plexus of largely unmyelinated fibers arises from the trigeminal ganglion (cranial nerve V) and innervates the cerebral and pial arteries, the venous sinuses, and the dura mater; this plexus is referred to as the trigeminovascular system. A similar plexus arises from the dorsal roots of the upper three cervical nerves and innervates comparable structures in the posterior fossa. The neurons in the trigeminovascular system contain substance P, one of the major nociceptive neurotransmitters of primary sensory neurons; calcitonin gene-related peptide (CGRP), which causes vasodilatation and when infused intravenously into susceptible individuals triggers headache; and neurokinin A, which is similar in structure and function to substance P. When the trigeminal ganglion is stimulated and causes antidromic activation of the trigeminovascular system, these peptide neurotransmitters are released near the blood vessels they innervate; this results in vasodilatation with consequent extravasation of plasma, or so-called sterile neurogenic inflammation. Leakage of plasma proteins from the dilated blood vessels in turn stimulates the trigeminal nerve endings and causes nociceptive orthodromic signals to the trigeminal ganglion—the end result of this sterile neurogenic inflammation is the perception of pain in and around the head. Neurogenic inflammation is blocked by substances that act as agonists on a subset of serotonin (5-hydroxytryptamine, or 5-HT) receptors: the 5-HT_{1D} and 5-HT_{1B} receptors. The major drugs used to abort acute migraine attacks are agonists at the 5-$HT_{1D/1B}$ receptors. Drugs that act as agonists at these sites are thought to reduce neurogenic inflammation by inhibiting the trigeminal nerve endings and by their actions on blood vessels—their vasoconstricting action may or may not be necessary for analgesia. Agonists at the 5-$HT_{1D/1B}$ receptors include ergot alkaloids (ergotamine, dihydroergotamine) and triptans (sumatriptan and others). Similarly, stimulation of pain-generating structures in the head activates neurons in the trigeminal nucleus caudalis and in the dorsal horn at the upper cervical levels.[5–7]

Thus, stimulation of the trigeminal ganglion, through antidromic release of neurotransmitters, results in increased cerebral and extracerebral blood flow. Stimulation of the dorsal raphe nucleus, a serotonergic nucleus in the midbrain, also increases cerebral blood flow. In contrast, stimulation of the nucleus caeruleus, the major source of central noradrenergic input, causes a decrease in cerebral blood flow.

Interneurons in the spinal cord and brainstem that are part of the descending pain modulation system use enkephalins and γ-aminobutyric acid (GABA) as neurotransmitters. An ascending serotonergic pathway in the midbrain raphe region relays painful stimuli to the ventroposteromedial (VPM) thalamus via the quintothalamic tract. A descending endogenous pain modulating system originates in the periaqueductal gray region of the midbrain, one of whose major relay structures is the nucleus raphe magnus in the medulla. After this relay, the descending pain modulating system connects with the spinal tract of the trigeminal nerve and the dorsal horns of the first through third cervical nerves. Stimulation of the periaqueductal gray region causes headache. The major neurotransmitters of this pain-modulating system are norepinephrine, serotonin, and enkephalins.[5,6] In patients

who have migraine with aura it is thought that the cortex, particularly the occipital cortex, is hyperexcitable. The cause of this hyperexcitability is unknown but may relate to decreased intracellular magnesium levels, to a dysfunction of brain mitochondria, or to abnormal calcium channels. The aura phase of migraine begins as a wave of cortical neural excitation, accompanied by hyperemia, and is followed by an electrical wave of spreading neural depression and oligemia that advances at a rate of 2 to 6 mm/minute (a rate similar to that of the developing aura). During the oligemic phase, blood flow remains above the ischemic threshold. Neither the spreading neural excitation/hyperemia nor the ensuing spreading depression and oligemia respect vascular territories—they are thus thought to represent neural, not vascular, phenomena.[8] The trigeminovascular system might be activated through polysynaptic pathways from the activated cortex, or directly by the same mechanism that causes the aura.[5] Aura usually precedes, but sometimes accompanies, the headache phase of migraine. Spreading neural depression and oligemia in the cortex might also occur in migraine without aura.

A growing body of evidence points to the importance of dopamine in the pathophysiology of migraine and its associated symptoms.[9] Dopamine receptor hypersensitivity may be responsible for the nausea, vomiting, hypotension, and dizziness that frequently accompany, and sometimes characterize, attacks of migraine. These symptoms can be elicited by low doses of dopamine or by dopamine agonists—especially in migraneurs. Antiemetics, most of which are dopamine receptor antagonists (especially at the D2 receptor), are frequently useful, and sometimes effective in and of themselves in treating migraine attacks.

DIAGNOSIS

The diagnosis of migraine is made by a suggestive clinical history and a normal neurologic examination (Table 38-1). The classic description of migraine is that of a recurrent headache lasting 2 to 72 hr, of moderate to severe intensity, pulsating, aggravated by routine physical activity, and associated with nausea, emesis, photophobia, phonophobia, and/or osmophobia. The major subtypes of migraine are migraine with aura and migraine without aura. The most frequent migrainous aura consists of visual symptoms such as bright spots, dark spots, tunnel vision, or zigzag lines (fortification spectra). Other common auras include numbness or paresthesias in one arm or side of the body. The aura is followed (or sometimes accompanied) by an intense, crescendo head pain, frequently unilateral or retro-ocular; it may be described as pounding, throbbing, pressure-like, exploding, stabbing, or vise-like.[10] Migrainous auras, particularly visual ones, occasionally occur independently of pain; these are called migraine equivalents. Typically, the headache phase lasts from 30 min to 1 day. Occasionally the headache becomes intractable and lasts a week or longer: this is status migrainosus. There seems to be a slightly increased risk for stroke among migraineurs, particularly in women who have migraine with aura. The absolute number of strokes in this population remains low and epidemiologically, the increase in risk is most easily defined for women older than age 40 or 50.[11–13]

A migraine whose aura seems to originate in the brainstem or involve both hemispheres is called basilar migraine.[14] A typical aura in basilar migraine might present with bilateral visual loss or blindness. Following, or independent of the visual phenomena, patients may complain of vertigo, dysarthria, diplopia, tinnitus, ataxia, a decreased level of consciousness, or bilateral sensory (paresthesias) or subjective motor symptoms (there should be no objective weakness); sometimes nausea and emesis are prominent. Some patients present with other types of auras such as a dysphasia, and as such may resemble a transient ischemic attack (TIA), a stroke, or an evolving neurologic catastrophe.

Some patients develop severe headache, sometimes described as exploding, related to exertion: these are exertional migraines. Exertional migraines can develop while engaged in heavy work or sports, lifting weights, or during sexual climax[15] (the latter are more frequent in males). On the other hand, a severe ocular headache that presents with ophthalmoplegia (usually of the oculomotor nerve and includes a dilated pupil) is no longer considered an "ophthalmoplegic migraine." The ophthalmoplegia can last hours to months and is now believed to represent an inflammatory neuritis or the Tolosa–Hunt syndrome.[10] Painful ophthalmoplegia usually has a dramatic presentation and always warrants a careful evaluation.[16]

Given a typical history and reasonable clinical judgment, a migraine can be recognized and treated as such. Occasionally the clinical circumstance requires that the physician be more circumspect and make an effort to exclude other causes for headache that, if left undiagnosed and untreated, will result in an adverse patient outcome. Some other causes for headache include a cerebral aneurysm with or without subarachnoid hemorrhage, vascular malformations with or without hemorrhage, venous thrombosis, central nervous system infections, space-occupying lesions, increased intracranial pressure, vascular dissection, and arteritis.[10,16,17]

TREATMENT

Migraines can be treated abortively (after they start) or prophylactically (with daily medication aimed at reducing the frequency or intensity of the headaches).

The following drugs are useful for the treatment of acute migraine headaches (abortive treatment).

- Triptans[18] (Imitrex, Maxalt, Zomig, Frova, Relpax, Amerge, and others) are 5-$HT_{1D/1B}$ receptor agonists. These drugs are available in a variety of forms. For example: Imitrex is available in an autoinjector, as a tablet, and as a nasal spray; Maxalt and Zomig are available as tablets and as orally disintegrating tablets; Zomig is also available as a nasal spray. In general, injectable preparations have a quicker onset of action, followed by nasal sprays and orally disintegrating tablets and tablets that must be swallowed. These different formulations allow treatment to be tailored to the patient's needs. Patients whose headaches are accompanied by significant nausea and vomiting, or whose productivity depends on a timely return to work, might prefer an injectable preparation or a nasal spray. Orally disintegrating

TABLE 38–1 International Headache Society Diagnostic Criteria for Migraine

Migraine without Aura
At least five headache attacks
Headaches last 4–72 hr if untreated
Has at least two of the following, but not weakness:
Unilateral pain
Pulsating
Intensity is moderate to severe
Aggravated by routine physical activity
Has at least one of the following:
Phonophobia
Photophobia
Nausea
Emesis
Migraine with Aura
At least two headache attacks that also fulfill the characteristics of migraine without aura
Headaches usually follow the aura but may begin with it and last 4–72 hr if untreated
Has at least one of the following reversible symptoms (lasting 4 min to 60 min), but no weakness
Positive or negative visual symptoms such as scintillating scotomas, blind spot (scotoma), blurred vision, zigzag lines, homonymous hemianopsia
Positive or negative sensory symptoms such as tingling or numbness
Basilar Migraine
At least two attacks of migraine with an aura whose symptoms are reversible and localize to the brainstem or are bihemispheric, but without weakness
Symptoms can include:
Dysarthria
Dizziness or vertigo
Bilateral visual symptoms, including temporary blindness
Diplopia
Nystagmus
Ataxia
Decreased level of consciousness
Bilateral paresthesiae
Tinnitus with or without decreased hearing
Aura without Headache
At least two attacks of symptoms typical of auras, but not weakness, such as visual, sensory or speech disturbances that resolve within 1 hr and are not followed by a headache
Hemiplegic Migraine
At least two attacks of migraine with a reversible aura of motor weakness that can last 1 hr to days
Also includes one of the following:
Positive or negative visual symptoms
Positive or negative sensory symptoms
Dysphasia or dysarthria
Frequently accompanied by symptoms typical of basilar migraine
If at least one first- or second-degree relative has a migrainous aura that includes motor weakness, it is *familial hemiplegic migraine* and is associated with a mutation in the neuronal calcium channel
If no first- or second-degree relative has a migrainous aura that includes motor weakness, it is *sporadic hemiplegic migraine*

Source: International Headache Society: The International Classification of Headache Disorders, 2nd edition. Cephalalgia *24(suppl 1):1–150, 2004.*

tablets also are useful in patients with significant nausea and vomiting. Approximately 60% to 80% of patients achieve significant relief from a triptan; however, the headache will recur in up to one-third of patients. A second dose of the same preparation, taken 2 to 24 hr after the first, may again provide significant relief. A triptan should not be used again for at least 24 hr after the second dose. Triptans should not be administered within 24 hr of another substance with vasoconstricting properties (e.g., another triptan, ergotamine, dihydroergotamine, or isometheptene). Triptans should not be administered within 2 weeks of discontinuation of a

monoamine oxidase inhibitor or methysergide. Triptans should not be prescribed to patients with ischemic or other heart disease or uncontrolled hypertension; they should be avoided in patients with complicated auras such as dysphasias and confusional states and in basilar migraine. The major side effects of triptans include a sensation of chest pressure, flushing, tingling, dizziness, and dysphoria. These usually resolve in less than 1 hr. Vasoconstrictor drugs should be avoided during pregnancy and are relatively contraindicated in basilar migraine. Although each of the triptans has unique pharmacokinetic properties, clinically there is little practical difference between them. That said, the different formulations allow treatment to be individualized and if a patient does not respond well to, or suffers unacceptable side effects from one triptan, they may tolerate or respond better to another. For example, in patients whose pain returns within a few hours of taking a triptan, one with a longer half-life (Frova, Amerge) can be tried instead.

- Ergotamine tartrate is an older drug with 5-HT agonist activity that also is very effective for migraine.[16,19] One to 2 tablets are taken at the onset of the headache or aura, followed by 1 tablet every 30 min until the headache is gone or until a maximum of 5 tablets per headache or 10 tablets per week have been consumed. If consumed in excess, ergotamine-containing preparations can cause vasospastic complications and are emetogenic.
- Isometheptene (Midrin) is another older but effective drug with 5-HT agonist and sympathomimetic (vasoconstrictive) activity.[16,19] Midrin also contains dichloralphenazone, a mild sedative-hypnotic drug similar to chloral hydrate. One to 2 capsules are taken at the onset of the headache or aura, followed by 1 capsule every hour until the headache is gone or until a maximum of 5 capsules per headache or 10 capsules per week have been consumed. Isometheptene has fewer vasospastic complications than ergotamine. Vasoconstrictor drugs (triptans, ergots, and isometheptene) should be avoided during pregnancy and are relatively contraindicated in basilar migraine.
- Preparations containing butalbital (such as Fioricet, which also contains acetaminophen and caffeine, or Fiorinal, which contains aspirin and caffeine) are effective and can be used alone or together with one of the vasoconstricting abortive drugs (a triptan, ergotamine, or isometheptene). One to two tablets can be taken every 4 hr as needed. Barbiturate-containing preparations cause drowsiness and can be habit forming if used excessively.[16,19]
- Narcotic-containing preparations, such as those with codeine, hydromorphone, or hydrocodone (in combination with aspirin or acetaminophen), are used too frequently, particularly in the emergency room and should be used only as drugs of last resort. Narcotics bind opiate receptors and mask pain, but they do not bind serotonin receptors and therefore do not interrupt the putative pathophysiologic mechanism of migraine. The short- and long-term complications associated with the frequent use of narcotics argue that they should be used sparingly at best.[16,19]
- Antinauseants, such as prochlorperazine, chlorpromazine, or metoclopramide, by virtue of their effect on serotonin receptors, are effective against migraine pain. Their action as antagonists of the D2 dopamine receptor helps control the associated gastrointestinal symptoms and this makes them excellent adjuvant drugs.[16,19,20]
- Dihydroergotamine (DHE), is generally administered parenterally but also is available as a 4 mg/mL nasal spray. Administered by the intravenous or intramuscular route, the dose should not exceed 2 to 3 mg in 24 hr. Administered over 1 or several days, intravenous DHE remains the drug of choice for treatment of status migrainosus. Vasoconstrictor drugs should be avoided during pregnancy and are relatively contraindicated in basilar migraine.[16,19]
- Nonsteroidal anti-inflammatory drugs (NSAIDs) work for some patients with mild to moderate migraine pain. Ketorolac, which can be administered intramuscularly, and indomethacin, which also is available as a suppository, may be particularly useful. Some patients with mild headache or headaches that do not last long respond well to over-the-counter analgesic preparations.[16,19] Aspirin, particularly combined with acetaminophen and caffeine (Excedrin), remains an effective and inexpensive over-the-counter treatment.[21] Recently the FDA approved diclofenac combined with potassium bicarbonate (Cambia) for the treatment of migraine. Initial clinical data suggest Cambia is as effective as a triptan in onset of action and control of symptoms. It is a drug worth considering in patients in whom vasoconstricting drugs are contraindicated or who cannot tolerate the side effects of vasoconstricting drugs. At this time it is not yet commercially available.
- Corticosteroids are sometimes useful when used for a limited time and under strict medical supervision. They can be used alone or with other abortive medication for the relief of an intractable migraine (status migrainosus). Both short- and long-term use of steroids entails significant potential for morbidity.[16,19]

The *chronic use* (averaging at least 10 times per month over a prolonged period of time) of any of the triptans, NSAIDs, acetaminophen, butalbital, narcotics, ergotamine, DHE, and isometheptane can lead to development of a medication overuse, or rebound, headache syndrome.[17,22–25] Chronic use of these compounds more than twice per week should be discouraged. Prophylactic regimens generally are not effective in the setting of rebound. The treatment of medication overuse headache is discontinuation of all analgesics (including triptans, ergots, etc.). Painkiller withdrawal frequently results in a temporary but dramatic exacerbation of the pain that can last several days. The physiologic washout period, during which patients may continue to experience frequent headaches, lasts at least 2 weeks; patients should continue to refrain from analgesic medications for a total of 10 to 12 weeks although the physician should use judgment with respect to treatment of an occasional breakthrough migraine during that period. If patients require analgesics at least twice per week, they should be offered a prophylactic regimen.

The following drugs are useful for prophylactic treatment:

- Beta-blockers, such as propranolol, metoprolol, atenolol, timolol, and nadolol, are frequently effective first-line prophylactic drugs; propranolol and timolol are FDA approved for migraine prophylaxis.[2,26] In most healthy people 60 to 80 mg once per day of a long-acting propranolol preparation can be started and the dosage can be adjusted as necessary. Side effects include dizziness from bradycardia or hypotension, fatigue, depression, worsening of symptoms in patients with asthma or chronic obstructive pulmonary disease, gastrointestinal distress, blunting of hypoglycemic symptoms in patients with diabetes, and vivid dreams.
- Anticonvulsants such as valproic acid (Depakote and Depakote ER) and carbamazepine have been used as prophylaxis against migraine for a long time.[2,27] Depakote and Topamax are FDA approved for migraine prophylaxis. The usual starting dose for Depakote ER is 500 mg per day; the dose should be adjusted as necessary at 2- to 4-week intervals. Valproic acid can cause weight gain, hair loss, tremor, abdominal distress, and easy bruisability. Frequent side effects of Topamax are mental confusion and paresthesia; another is weight loss, which has made this drug increasingly popular. In addition, Topamax is an inhibitor of carbonic anhydrase and it has been reported to be useful in treating the syndrome of idiopathic increased intracranial pressure (previously called pseudotumor cerebri).
- Antidepressants, particularly amitriptyline at a starting dose of 10 to 25 mg at bedtime, are very active prophylactic drugs. [2,16,19] Most patients who respond to tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, or desipramine) usually do so at doses of 25 to 200 mg at bedtime; occasionally a patient may require more. Tricyclics help induce sleep, which may constitute one of the mechanisms by which they help migraneurs. The major side effects from tricyclics relate to their anticholinergic action and include a dry mouth, excessive daytime sleepiness, dizziness, urinary retention, glaucoma, cardiac arrhythmias, and photosensitization. The specific serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) might be tried in patients who do not respond or who develop intolerable side effects from tricyclic drugs. The major side effects of the SSRIs and SNRIs include jitteriness, tremors, gastrointestinal distress, decreased libido, and occasionally headaches. In addition, these drugs are relatively contraindicated in patients who use triptans, as they may suffer from excessive serotonin stimulation (serotonin syndrome). The association between migraine and depression (depressed patients have more migraines and migraines are a risk factor for depression) make antidepressants a good choice for prophylaxis.
- Calcium channel blockers, such as verapamil, are occasionally useful as prophylactic agents.[2,16,19] Calcium channel blockers are worth a try when first-line agents fail; they also appear to be more useful in patients with cluster headaches.
- Lithium carbonate may be useful in patients with frequent migraines who do not respond to more traditional prophylactic regimens.[16,19] The major indication for lithium is in the treatment of an ongoing cluster headache.
- Individualized injections of botulinum toxin A into the pericranial muscles (frontalis, temporalis, and glabellar muscles) has been reported to increase significantly the number of headache-free days in some patients with chronic migraine. The beneficial effect may last up to 90 days postinjection. Investigators continue to present positive results for this treatment approach despite continued controversy.

SELF-HELP STRATEGIES

The following are self-help strategies that can minimize the incidence of migraines.[2]

- If the patient consumes caffeinated beverages (coffee, tea, soda, cocoa), total caffeine should be limited to less than 400 mg per day (to avoid caffeinism) and the intake should include weekends, vacations, and holidays (to avoid a caffeine withdrawal headache).
- If they trigger headaches, foods high in tyramine (a substance metabolized to serotonin), which is thought to play a role as a migraine trigger, can be avoided. Some foods high in tyramine are chocolate, aged cheeses, yogurt, sour cream, soy sauce, chicken liver, banana, avocado, nuts, and yeast extracts (including beer).
- Foods high in nitrates can be avoided, as these might precipitate a migraine by virtue of their vasodilating properties. Some foods high in nitrates include processed meats (hot dogs, salami, bacon, ham, sausage, corned beef) and other canned, smoked, or aged meats.
- Some patients are sensitive to certain food additives. Two examples include monosodium glutamate, frequently used in restaurants and added to cooked, packaged, and canned foods as a flavor enhancer, and aspartame (NutraSweet). These substances contain glutamate, an excitatory neurotransmitter.
- Many migraneurs are sensitive to alcoholic beverages.[16,19] Alcohol tends to dilate blood vessels.
- Miscellaneous, but not unusual, causes of migraine include new medications,[15] stressful situations, post-stress situations, lack of adequate rest or changes in sleep habit, allergies, and noncompliance with a prophylactic regimen. Patients should not allow themselves to become dehydrated, either during a headache or between headaches. If bright light is an irritant during or between headaches, patients should wear optical-quality sunglasses that block at least 85% of incident sunlight (and 100% of ultraviolet light) when outdoors.

TRIGEMINAL AUTONOMIC CEPHALALGIAS

The trigeminal autonomic cephalalgias (TAC) represent a group of three headache disorders characterized by the occurrence of pain in the distribution of the first division of the trigeminal nerve accompanied by prominent parasympathetic autonomic features in the same distribution. These headaches are: cluster, hemicrania (paroxysmal hemicrania and hemicrania continua), and short-lasting unilateral

neuralgiform headache with conjunctival injection and tearing (SUNCT). The headaches are distinguished by their predominance in either males or females, their frequency, and their duration (Table 38-2). In addition, all present with some combination of ocular redness, tearing, swelling, miosis, or ptosis; additional symptoms can include forehead sweating and rhinorrhea.[10]

Cluster headache lasts longest and presents with circadian periodicity but, overall clusters tend to occur relatively infrequently, such as yearly. SUNCT have the shortest duration but a high frequency of attacks. The duration and frequency of paroxysmal hemicrania is intermediate. Hemicrania continua is characterized by continuous pain with exacerbations.[28,29]

CLUSTER HEADACHE

Cluster headaches, unlike migraine, affect predominantly males; the prevalence is 0.1% to 0.3% of the population. A family history of cluster is not as common as a family history of migraine. In the majority of cases, attacks begin between the ages of 20 and 40.

Pathophysiology

The pathophysiologic mechanism of cluster headaches is not known. Some investigators believe that cluster headache lies within a continuum of head pains that include cluster and severe migraine at one extreme and tension-type headache at the other. Thus, at least to some degree, the underlying mechanism of most chronic, recurring headache syndromes would be shared. Some of the clinical features of cluster, which seem to reflect local vasoactive phenomena, support the argument that neurogenic inflammation also plays a role in this headache type.[5,29]

Diagnosis

Cluster headache is diagnosed by a suggestive clinical history and a normal neurologic examination. Typically, severe pain, which lasts between 15 and 90 min, awakens the patient. The pain is unilateral and periorbital; it may include the temple, forehead, and cheek (the distribution of the first division of the trigeminal nerve). The syndrome is accompanied by lacrimation, conjunctival injection, nasal stuffiness, ptosis (with or without eyelid edema), and miosis ipsilateral to the pain. During a cluster phase, the headaches, which can be single or multiple in a 24-hr period, occur with circadian predictability and tend to have a similar duration. Unlike patients with migraine, who seek a dark, quiet environment, patients with cluster tend to pace, scream, or appear agitated; nausea and vomiting are uncommon. A bout of cluster may last several days or several months.[10] An attack can be provoked by alcohol.

TABLE 38–2 Trigeminal Autonomic Cephalalgias

Type	Male:Female	Frequency	Duration
Cluster	5.5:1	1 or several/day	15–90 min
Hemicrania	1:3	Up to 30/day	5–45 min
SUNCT	8:1	5–30/hr	5–60 sec

Source: International Headache Society: The International Classification of Headache Disorders, 2nd edition. Cephalalgia *24(suppl 1):1–150, 2004.*

Treatment

In general, the drugs that are used to treat migraine are useful in cluster except that the role for treatment aimed at aborting an acute headache is limited because the attack has usually run its course by the time the agent has exerted its effect.[28] Therefore, cluster is best treated early on with prophylactic drugs with the aim of interrupting the cluster. The major limitation of drugs aimed at interrupting the cluster (drugs used in migraine prophylaxis) is their slow onset of action, with most requiring 2 to 4 weeks to demonstrate activity at the initial dose, and similar intervals for subsequent dose adjustments.

Interrupting the Cluster

The following drugs are useful for interrupting the cluster.

- Calcium channel blockers, such as verapamil, are occasionally useful and frequently prescribed.[30] Verapamil usually requires administration at relatively high doses, 240 to 480 mg/day, to be effective.
- Anticonvulsants such as valproic acid (Depakote and Depakote ER) and carbamazepine can be useful to help abort a cluster. The usual starting dose for Depakote ER is 500 mg per day; the dose should be adjusted as necessary at 2- to 6-week intervals. Valproic acid can cause weight gain, hair loss, tremor, and abdominal distress.
- Lithium carbonate can be useful in patients with cluster; in fact, cluster remains the major indication for lithium in the treatment of headaches.
- Antidepressants, particularly amitriptyline at a starting dose of 10 to 25 mg at bedtime, are sometimes added to an anticluster regimen but there is no good evidence for their activity. Tricyclics help induce sleep, which may constitute one of the mechanisms by which they help patients with cluster. The major side effects from tricyclics relate to their anticholinergic effects and include a dry mouth, excessive daytime sleepiness, dizziness, urinary retention, glaucoma, cardiac arrhythmias, and photosensitization.
- Beta-blockers, such as propranolol, metoprolol, atenolol, timolol, and nadolol, are also used frequently for cluster. In most healthy people 60 to 80 mg once per day of a long-acting propranolol preparation can be started and the dosage can be adjusted as necessary. Side effects include dizziness from bradycardia or hypotension, fatigue, depression, worsening of symptoms in patients with asthma or chronic obstructive pulmonary disease, gastrointestinal distress, blunting of hypoglycemic symptoms in patients with diabetes, and vivid dreams.
- Corticosteroids are useful as adjuvants to other drugs in breaking a cluster. They should be started simultaneously with one of the other prophylactic drugs. Corticosteroids are to be used for a limited time and under strict medical supervision. Both short- and long-term use of steroids entails significant potential for morbidity.

Given the regularity and sometimes circadian predictability of the headache onset during a cluster, ergotamine, isometheptane, a triptan, or a NSAID can be administered up to several hours prior to an anticipated attack, for example at bedtime. When used for a limited time, this strategy can be useful to prevent a headache until the prophylactic drugs become effective.

- Among the NSAIDs, indomethacin appears to be more active than others. It also can be used in anticipation of a headache to block its onset. Indomethacin can be administered in doses up to 150 mg/day but tends to irritate the gastric mucosa. Other NSAIDs might work for some patients with milder headaches. In general, the onset of action of oral formulations tends to occur at about the time the current headache has run its course.

Treatment of an Acute Cluster Headache

As stated above, the onset of action of most analgesics tends to occur at about the time the current headache has run its course. However, inhaled oxygen remains the standard for treatment of an acute cluster headache.[31] Oxygen should be administered at 12 L/minute through a nonrebreather mask for 15 min as soon after the onset of the attack as feasible. The treatment can be repeated after a brief interval. Patients should be prescribed the oxygen for home use.

It is not clear if parenteral or nasal formulations of a triptan might be useful in this setting, especially for headaches of longer duration.

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania occurs more frequently in women. The syndrome consists of frequent, unremitting, unilateral headaches exhibiting a frequency of a few to more than 20 per day; the headaches last 5 to 45 min each. The pain, throbbing or boring, is localized on one side of the head, around the eye and temple (in the distribution of the first division of the trigeminal nerve). As in cluster, the pain is accompanied by autonomic (parasympathetic) phenomena: redness and tearing of the eye, eyelid swelling, nasal congestion, and/or rhinorrhea.[10,32] Ptosis is sometimes seen. Patients usually sit quietly. The hallmark of hemicrania is that it responds completely and dramatically to indomethacin, which can be administered in doses up to 150 mg/day and, as long as it is tolerated, can be used for long periods of time. Concurrent use of indomethacin with a proton pump inhibitor might decrease gastric irritation.

SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE WITH CONJUNCTIVAL INJECTION

SUNCT is a rare headache that occurs almost exclusively in males. Bursts of stabbing, throbbing, or burning pain around the eye or temple, lasts 5 seconds to 5 min and occurs in paroxysms of up to 30 per hr (with an average of 5 to 6/hr). Here too, the pain is accompanied by autonomic (parasympathetic) phenomena in the distribution of the first division of the trigeminal nerve: redness and tearing of the eye, eyelid swelling, nasal congestion, and/or rhinorrhea.[10] The headaches tend to not respond well to most treatments but might be amenable to prophylactic treatment with anticonvulsants including lamotrigine and oxcarbazepine.[33]

KEY POINTS

- The incidence of migraines in females increases into the early forties.
- Consuming more than about 400 mg of caffeine per day can predispose to chronic migraines.
- Basilar migraine can present with mental status changes.
- Vasoconstrictor drugs, such as triptans, are contraindicated in basilar migraine.
- Analgesic overuse (use of analgesics 10 or more days per month) can lead to chronic daily migraine.
- The trigeminal autonomic cephalalgias include cluster, hemicrania, and SUNCT.
- Cluster is best treated acutely with oxygen, and prophylactically with valproic acid or verapamil.
- Hemicranias—paroxysmal or continua—are singularly responsive to treatment with indomethacin.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 39

Tension-Type Headache, Chronic Tension-Type Headache, and Other Headache

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EPIDEMIOLOGY

Tension-type headache (TTH) is the most common headache type and also the most difficult to classify.[1] Many different, and equally vague, terms have been applied to this headache or to what probably are variants of the same syndrome. Headaches in general are thought to affect more than 90% of the population at one time or another, with about 15% of those fitting the description of migrainous or vascular headache. This leaves about 70% of the population with some variant of TTH.[2] Moreover, almost all patients with migraine, cluster headache, trigeminal nerve neuralgias, and other recurring cephalgic syndromes have interposed TTH.[3–5]

DIAGNOSIS

TENSION-TYPE HEADACHE AND CHRONIC TENSION-TYPE HEADACHE

The pain of a TTH tends to be duller, less intense, and less localized than that of a migraine or a cluster attack. The pain usually lasts several hours to a day, but it may continue for days or weeks. During a severe TTH patients can experience photophobia, phonophobia, nausea, and occasionally emesis. Pain referred to the neck is common; patients also frequently complain of "a knot in the neck," but the neurologic examination should be normal.[6]

The major variants of TTH are those with disorder of the pericranial muscles, those without disorder of the pericranial muscles, and chronic TTH (CTTH) (with or without disorder of the pericranial muscles). Those with disorder of the pericranial muscles are characterized by tenderness on palpation of those muscles, increased activity on electromyography (EMG), or both. TTH without disorder of the pericranial muscles lacks those characteristics. CTTH, previously called chronic daily headache, is diagnosed in a patient with a headache frequency of 15 days per month or 180 headaches per year averaged over a 6-month period.[6] Fibromyalgia and the myofascial pain syndrome also are associated with frequent or chronic daily headaches.

ANALGESIC MEDICATION OVERUSE HEADACHE (MOH)

A common variety of chronic daily headache occurs in patients with headaches of any sort, tension-type or episodic migraine in particular, in whom these temporarily exacerbate and become more frequent. Patients begin using analgesic preparations (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen, aspirin, butalbital, narcotics, ergot derivatives, triptans) on a regular basis (generally 10 times or more per month) and eventually develop analgesic overuse, or rebound, headaches.[7–10] It stands to reason that patients should be advised against using analgesics more than twice per week over a prolonged period of time. If they require analgesics at least twice per week, they should be offered a prophylactic regimen.

In adolescents (age 12 to 14 at the time of diagnosis), the cause and prognosis of CDH might be distinct from those in adults. Many of these children seem to have personal or family history of migraine. When followed for up to 8 years, 40% continue to experience CDH after 1 year, 25% after 2 years, and 12% after 8 years. Without specific medical intervention, the majority of adolescents with CDH seem to evolve into adults who suffer from episodic migraine, episodic TTH.

The mainstay of treatment for MOH is total withdrawal from analgesics for a period of time not shorter than 2 months. The patients most likely to be headache-free at the end of that time are migraneurs (67% reduction) and those with mixed TTH and migraines (37% reduction); patients diagnosed with TTH alone are less likely to report large reductions in headache frequency but do report large reductions in pain intensity. The initial several days to 2 weeks following analgesic withdrawal might be the most difficult and are frequently punctuated with a severe rebound headache; antiemetics and maintaining hydration, as well as patience, are effective. Using steroids during this period has no effect on outcome. One additional characteristic of patients with MOH is that drugs administered with prophylactic intent tend to not work unless analgesics are discontinued. Patients whose MOH is typified by the regular use of narcotics or barbiturates may require a controlled tapering off of the drugs as well as management of potential withdrawal symptoms.

A particularly severe, persistent, or unusual headache should always prompt consideration of alternative explanations, and, when appropriate, these should be investigated thoroughly.[1,3,6,11] For example, temporal arteritis should be considered in an elderly patient with a persistent headache of recent onset whether or not other typical elements are present in the history and physical examination. In these patients an erythrocyte sedimentation rate (ESR) or a sensitive C-reactive protein (s-CRP) should be ordered immediately, and consideration should be given to treatment with a corticosteroid and to a temporal artery biopsy. Likewise, one would not want to miss an infectious meningitis, the sentinel bleed of an aneurysm, an undiagnosed intracranial vascular malformation, a subdural hematoma, acute hydrocephalus, venous thrombosis, or an arterial dissection. Idiopathic intracranial hypertension (previously called pseudotumor cerebri) usually presents in overweight

young women with chronic headaches, a normal examination, a normal scan, and papilledema—although a subset of these patients do not have papilledema.[6,12] The diagnosis is made when a lumbar puncture reveals an otherwise normal fluid under high pressure (at least 20 to 25 cm H_2O). Therefore, when dictated by clinical judgment, imaging, lumbar puncture, or other tests deemed necessary are indicated.

PATHOPHYSIOLOGY OF TENSION-TYPE HEADACHE

The pathophysiologic bases for TTH and CTTH are unknown. Some investigators believe that TTH lies at one end of a physiologic spectrum that includes severe migraine and cluster at one end and TTH at the other. Under this assumption, at least to some degree, the underlying mechanism of most chronic, recurring headache syndromes would be shared.[13–15] The muscle contraction theory of TTH relates pain to prolonged contraction, or spasm, of cervical or pericranial muscles but no objective data support the theory. Most patients with a headache, migrainous or TTH, have pericranial muscle tenderness or sore spots; however, many individuals without headache also have them. There is no particular distinguishing characteristic among patients with headache, pericranial muscle tenderness, and increased EMG activity in those muscles. In fact, even the degree of pericranial muscle tenderness and the level of EMG activity in those muscles do not correlate. On the other hand, during a headache, patients with a more severe headache tend to have more tender pericranial muscles. Thus, the relationship between tenderness of the pericranial muscles, EMG recordings from those muscles, and headaches is not straightforward.

The relationship between cervicogenic disorders and headache is similarly unclear, although most painful disorders of the neck are associated with some sort of headache. Cervical pain can be referred to the head from intervertebral discs, interspinous ligaments, zygapophyseal joints, the periosteum, paracervical muscles, carotid and vertebral arteries, and from irritation of the C1, C2, and C3 nerve roots. The dorsal rami of the first three cervical nerve roots supply the sensory innervation to the neck and to the scalp caudal to the innervation of the trigeminal nerve, and to the meninges and arteries of the posterior fossa. Headache also can arise from pathology in the area of the foramen magnum. Some examples include a Chiari I malformation, the Dandy-Walker syndrome, atlantoaxial dislocation (e.g., from rheumatoid arthritis), Paget's disease of the bone, and basilar invagination.

TREATMENT

As with other headache types, both abortive and prophylactic treatment strategies are available for the treatment of TTH and CTTH.

Abortive Treatment Strategies

For the occasional TTH, an over-the-counter (OTC) analgesic preparation is all that is required. The number of OTC preparations continues to increase, and although they are generally safe, the lay population has little basis on which to decide how to choose among them or how to use them properly. Most people decide on a preparation either on a trial-and-error basis or are swayed by the marketing ("for tension headache," "for sinus pain," "multisymptom relief," "PM" preparations, etc.). Several OTC analgesic preparations involve combinations of drugs (e.g., aspirin plus acetaminophen) and may contain caffeine. Caffeine combined with analgesics such as aspirin, acetaminophen, and ibuprofen enhances their analgesic effectiveness. Stronger headaches may require an analgesic (aspirin, acetaminophen, or ibuprofen) in combination with either codeine or butalbital. Some of these preparations also include caffeine.Used infrequently, the additional analgesic effectiveness obtained by adding codeine or butalbital comes with little increase in adverse effects or risk of dependence.

If aspirin or acetaminophen, with or without codeine, butalbital, or caffeine, is ineffective in controlling the headache, the choice of an alternative analgesic should proceed in an orderly fashion by testing in turn members of different NSAID chemical categories at adequate doses. Indomethacin is reported to be more effective than alternative NSAIDs for pain of cephalic origin; it is particularly effective in treating hemicrania (see Chapter 37). Occasionally a patient responds well to stress management modalities or acupuncture (anyone considering acupuncture should ascertain the qualifications of the practitioner and insist on new, not sterilized, needles for every session), but it is impossible to predict accurately in whom these modalities are likely to be beneficial. The major chemical categories of NSAIDs include

- Carboxylic acids—includes aspirin, which is an acetylated acid, as well as salsalate and choline magnesium trisalicylate, which are nonacetylated
- Propionic acids—ibuprofen, naproxen, ketoprofen, and fenoprofen
- Aryl and heterocyclic acids—indomethacin, diclofenac, sulindac, and tolmetin
- Fenamic acids—mefenamic acid and meclofenamate
- Enolic acids—piroxicam and phenylbutazone
- Pyrrolo-pyrrole—ketorolac
- Cyclooxygenase 2 (COX-2) inhibitors—celecoxib

Prophylactic Treatment Strategies

Fortunately, CTTH and TTH that are frequent or otherwise annoying respond to many of the agents used in migraine prophylaxis. It is possible that this reflects on the presumed common mechanism that is felt to underlie both disorders.

Antidepressants, particularly amitriptyline or nortriptylene at a starting dose of 10 to 25 mg at bedtime, are active prophylactic drugs.[16] Most patients who respond to tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, or desipramine) usually do so at doses of 25 to 200 mg at bedtime; an occasional patient may require more. Tricyclics help induce sleep, which may constitute one of the mechanisms by which they help. The major side effects from tricyclics relate to their anticholinergic effects and include a dry mouth, excessive daytime sleepiness, dizziness, urinary retention, glaucoma, cardiac arrhythmias,

and photosensitization; they can also cause weight gain. The specific serotonin reuptake inhibitors (SSRIs) and specific serotonin-norepinephrine reuptake inhibitors (SNRIs) might be tried in patients who do not respond or who develop intolerable side effects from tricyclic drugs. The major side effects of the SSRIs and SNRIs include jitteriness, tremors, gastrointestinal distress, decreased libido, and occasionally headaches. In addition, these drugs are relatively contraindicated in patients who use triptans, as they may suffer from excessive serotonin stimulation (serotonin syndrome).

Beta-blockers, such as propranolol, metoprolol, atenolol, timolol, and nadolol, can be tried and sometimes prove effective.[17] In most healthy people, 60 to 80 mg once per day of a long-acting propranolol preparation can be started and the dosage can be adjusted as necessary. Side effects include dizziness from bradycardia or hypotension, fatigue, depression, worsening of symptoms in patients with asthma or chronic obstructive pulmonary disease, gastrointestinal distress, blunting of hypoglycemic symptoms in patients with diabetes, and vivid dreams.

Anticonvulsants such as valproic acid (Depakote and Depakote ER) are sometimes worth a try to prophylax against frequent TTH.[18] The usual starting dose for Depakote ER is 500 mg/day; the dose should be adjusted as necessary at 2- to 6-week intervals. The author usually adjusts the dose in 500-mg increments and recommends the extended release preparation (ER) to maintain once per day dosing. Valproic acid can cause weight gain, hair loss, tremor, and abdominal distress.

Although still controversial, a botulinum toxin A injection into the most tender pericranial muscle(s) or directly into a trigger point has been reported to increase significantly the number of headache-free days in patients with CTTH. The results are less encouraging when the injections are prescribed for TTH that does not strictly meet the criteria for CTTH. Results also are less encouraging when the injections are applied in a standardized, rather than individualized, fashion. For example, when all patients are injected into the same muscles rather than into the muscle or muscles that are specifically tender, the results are discouraging.

OTHER CHRONIC HEADACHE TYPES

"SINUS" HEADACHE

Patients frequently complain of "sinus headaches."[3–5,19] They present after a variety of diagnostic tests have failed to corroborate the diagnosis and after one or more courses of antibiotics, antihistamines, decongestants, nasal steroids, and analgesics have failed to provide significant relief. Those patients almost invariably also self-medicate with a variety of OTC preparations, the hallmark of which is that they display the words "sinus" and "relief" prominently on the label; they also combine an antihistamine, a decongestant, and an analgesic (with or without caffeine). Needless to say, these are not true sinus headaches and most of those patients have some degree of medication overuse headache at the time of presentation. Most patients complain of periorbital pain and might also experience a sensation of nasal stuffiness. Patients attribute the origin of the pain to the adjacent sinuses. However, these head pains are unaccompanied by purulent discharge, fever, or localized tenderness, and they are not seasonal. True sinus pain occurs when the ability of the sinus to drain is impaired by an acute blockage of the osteum (e.g., following an upper respiratory infection or for some anatomic reason), a bacterial infection takes hold, the mucosa becomes inflamed, and pressure builds in the sinus. One caveat is that true sinus or nasal inflammation can be a trigger for migraine. The rest of these "sinus headaches" are likely multifactorial but may represent a mild migraine in which the local sterile inflammation and parasympathetic activation mediated through the trigeminal nerve, gives the impression of sinus pressure, a TTH, or CTTH.[3–5,19] The care of these patients needs to be coordinated so that the various potential components of the headache are adequately addressed and treated.

SLEEP DISORDERS

Habitual snoring is increasingly being recognized as a cause of chronic daily headache.[20] Sleep-disordered breathing such as that caused by sleep apnea may precipitate headaches from the resultant hypoxemia and hypercapnia (which causes cerebral vasodilation). Snoring, with or without sleep apnea, can disrupt sleep architecture or interrupt sleep, either of which can result in headaches. If a history suggestive of snoring, repeated nocturnal arousals, or paroxysmal leg movements during sleep is obtained, a diagnostic polysomnogram will provide invaluable information. Treatment of the sleep disorder might not provide complete headache relief but it usually provides some. Hypnic headaches represent another syndrome of recurring head pain that awakens patients from REM sleep.[21] The headache most commonly has its onset after the age of 50, is about twice as frequent in women as in men, has its onset about 2 to 4 hr after falling asleep, and lasts about 30 to 60 min. This headache responds best to treatment with either indomethacin or lithium.

POST-TRAUMATIC HEADACHE

Post-traumatic headache occurs frequently following mild to moderate closed head injury or a whiplash injury (rapid flexion and extension trauma of the neck); loss of consciousness need not have occurred. In addition to headache, the syndrome may include pain in the neck or shoulders, dizziness, cognitive complaints, and disturbances of sleep, mood, and/or personality. The syndrome should begin within 2 weeks of the injury; it is considered acute if it lasts 8 weeks or less and chronic if it lasts longer, although this distinction is arbitrary. These sequelae may reflect underlying brain injury relating to the trauma and also injury to the head, face, jaw, and neck. This headache is treated in accord with the general principles mentioned above but with additional consideration being given to addition of physical therapy and to identification and treatment of a possible contributing occipital nerve neuralgia. An occipital neuralgia (also called "cervicogenic"

headache) can arise from injury around the area of the C2–C3 zygapophyseal joint, which is common in whiplash; the pain, paresthesiae, or dysesthesiae usually are referred to the occipital scalp. On examination, the nerve is tender to palpation or percussion along the course of the dorsal ramus of C2, particularly around the cranial insertion of the trapezius muscle, lateral to the occipital protuberance. Treatment of occipital neuralgia is a nerve block with or without adding a drug useful in the treatment of neuropathic pain such as gabapentin.

Trauma can also result in a chronic cerebrospinal fluid (CSF) leak with consequent CSF hypotension and a chronic low-pressure headache. This headache, usually associated with an opening CSF pressure of 90 mm of water or less, typically manifests when the patient assumes a sitting or standing position and improves when the patient lies down. Most post-traumatic leaks arise around the cervico-thoracic junction. Treatment is similar to that of a postlumbar puncture (post-LP) headache.

KEY POINTS

- Chronic tension-type headaches are frequently caused by analgesic overuse, that is, using analgesic medication 10 or more times per month.
- Prophylactic medication usually does not work in the setting of analgesic overuse headache.
- "Sinus headaches" are rarely that; they usually represent analgesic overuse or parasympathetic symptoms of a milder migraine.
- Sleep-disordered breathing can cause headaches, particularly in patients whose sleep architecture is disrupted or sleep is interrupted.
- Post-traumatic headaches can include occipital neuralgia and CSF hypotension from a chronic CSF leak.

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CHAPTER 40

Postmeningeal Puncture Headache and Spontaneous Intracranial Hypotension

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Postdural puncture headache (PDPH) was first described in 1898 by August Bier, after performing a spinal anesthetic. He described a severe headache that was worse with standing or sitting and reduced in the recumbent position. Bier hypothesized that the headache was caused by the loss of cerebrospinal fluid (CSF) during the spinal anesthetic placement.[1] Given that the CSF is encased by the arachnoid mater and not necessarily the dura, a more correct term for PDPH, as described by Harrington et al., is meningeal puncture headache (MPH); however, the most commonly used term remains PDPH.[2] An orthostatic bilateral headache following meningeal puncture is the pathognomonic symptom for PDPH. The absence of an orthostatic component should lead to a search for other causes, leaving PDPH as a diagnosis of exclusion. Although extremely rare, Liu reported two cases of PDPH that were worse in the recumbent position and improved when standing.[3] The headache is characteristically occipital and/or frontal and always bilateral. Symptoms associated with PDPH can include neck stiffness, nausea, vomiting, photophobia, diplopia, scalp paresthesia, upper and lower limb pain, auditory changes including tinnitus, hypoacousia, and can include mental status changes.[4,5] Noninfectious arachnoiditis has been described with associated urinary and fecal incontinence, blindness, subdural hematomas, intracerebral hemorrhage, and seizures.[6,7] Headache commonly presents within the first 24 to 48 hr following a dural puncture; however, there have been many reports of headache presenting as much as 7 days later. Reamy reports a PDPH presenting as 12 days after the dural puncture in a parturient.[8] Most headaches resolve within 7 days, but in rare cases they can persist for several months.[9]

PATHOPHYSIOLOGY

The pathophysiology of the PDPH is not completely understood. There are several proposed hypotheses. One is based on the Monro-Kellie rule and another on mechanical traction. Both hypotheses accept that CSF escapes through a known or probable dural puncture at a rate that exceeds CSF production. The Monro-Kellie rule is that in an intact skull the sum of the volumes of brain, CSF, and intracranial blood are constant and, therefore, with CSF volume loss, compensatory vasodilatation and venous hypervolemia occur, which may contribute to the headache.[3,9] Average CSF production is 500 ml/day with an average adult intrathecal volume of 150 ml.[9] CSF leakage from a dural puncture, leading to a loss of CSF pressure, contributes to a loss of buoyancy supporting the brain and is one theory that contributes to the headache.[10] The higher the level of lumbar puncture, the less the hydrostatic pressure at the dural puncture site, which may explain why PDPHs are not commonly associated with cervical punctures.[9] The uncompensated loss of CSF leads to a subarachnoid deficit of CSF and often a reduction in the subarachnoid pressure. The normal CSF opening pressure in the horizontal position is 70 to 180 mm H_2O.[3] Although CSF hypotension (CSF pressure <60 mm H_2O) is often noted, the significance of the reduction in subarachnoid pressure is unclear because it does not consistently correlate with the presentation of headache.[11,12] The headache been not been demonstrated to be related to the amount of CSF leaked.[13] It is probable that the headache is related to sudden alterations in CSF volume, as proposed by Raskin, who theorized that the sudden loss of CSF volume and the change in pressure differential between the inside and outside of the intracranial venous structures result in venous dilatation.[14,15] The direct traction hypothesis states that the reduction in CSF total volume, especially in the spinal region, allows the brain to shift caudally placing traction on the pain-sensitive intracranial structures and causing cerebral vasodilatation that produces the classic headache symptoms. Pain-sensitive intracranial structures include the dura, cranial nerves, and bridging veins. The ophthalmic branch of the trigeminal nerve, which refers pain to the frontal region, innervates the bridging veins and the dura. In addition to causing pain, traction on bridging veins can cause a tear in the dura, thus leading to a potential subdural hemorrhage.[16]

The posterior fossa structures are innervated by the glossopharyngeal and vagus nerves that refer pain to the occipital region. Traction of the vagus nerve can also stimulate the chemoreceptor regions of the medulla, causing nausea and vomiting. Finally, traction on the upper three cervical nerves presents as occipital, cervical, and shoulder pain and stiffness. Schabel et al. reported one case of arm pain following dural puncture that resolved with an epidural blood patch (EBP).[17]

In addition to generating pain, traction, or pressure on the abducens nerve (CN VI), intracranial hypotension can cause nerve palsy with paralysis of the lateral rectus muscle; this can manifest as diplopia. Another proposed mechanism for the visual changes is secondary to crowding of the optic chiasm, observed on the MRI of patients with intracranial hypotension.[18] Finally, oculomotor nerve (CN III) and trochlear nerve (CN IV) palsies have been attributed to intracranial hypotension due to brainstem compression and ischemia.[19]

In contrast, the Monro-Kellie hypothesis proposes that a reduction in intracranial CSF volume is compensated for by increased intracranial blood volume, because the sums of the brain, CSF, and blood volumes are said to be stable.

In accordance with the Monro-Kellie rule, this increase in blood volume causes cerebral vasodilatation, which activates the trigeminovascular system, similar to migraine attacks. The input reaches the thalamus through the quintothalamic tract and refers pain to the ophthalmic branch and the first three cervical roots. This hypothesis is supported by MRI observations of contrast enhancement of the thickened meninges in PDPH secondary to dural venous dilatation.[20] Decreased intracranial pressure is probably a secondary cause because not all patients with classic PDPH have intracranial hypotension.[11]

ROLE OF THE ARACHNOID MATTER IN THE PATHOGENESIS OF CSF LEAK

Reina et al. demonstrated that the dura mater is composed of 78 to 82 overlapping layers in multiple orientations, therefore making a hole exclusively parallel or across the fibers impossible.[21] Furthermore, as early as 1938 Weed postulated that the arachnoid might be the barrier between the dura and the CSF.[22] In 1967 Waggener and Beggs, based on electron microscopy observations, labeled the arachnoid membrane as a physiologic barrier impermeable to CSF.[23] However, Nabeshima et al. demonstrated by electron microscopy that tight junctions exist only in the outer layer of the arachnoid, similar to those found in capillary endothelium of the brain. The cells of the dura do not contain tight junctions.[22] In light of these anatomic observations, the concept of exclusive dural puncture to access the CSF and cause a CSF leak is not correct. In a study to differentiate the comparative permeability of the three meningeal layers, Bernards and Hill found the arachnoid mater to be the principal diffusion barrier to CSF.[24] Although anesthesiologists probably mean to include puncture of the arachnoid when they discuss PDPH, the importance of arachnoid puncture for CSF access should be emphasized.

DIAGNOSIS

The diagnosis of a PDPH is described according to the International Classification of Headache Disorders. It is primarily based on the history of a dural puncture or possible dural puncture that worsens within 15 min after sitting or standing and improves within 15 min after lying down, with at least one symptom among neck stiffness, tinnitus, hypacusia, photophobia, and nausea. The time period within which the headache appears is debatable and can occur within a day or take as long as 12 days to develop. These factors will largely establish the diagnosis of PDPH that can be accompanied by a multitude of signs and symptoms as illustrated above. Because the diagnosis of PDPH is largely based on a thorough history and physical examination, it is important to note that certain critical signs and symptoms may indicate concomitant intracranial pathology. The most important of these signs is a changing pattern of the headache. For example, the headache is no longer postural, becomes constant or localized unilaterally, or there is new-onset nausea and vomiting.[25] Another critical change is increasing neurologic alterations, which include sedation, seizures, and new-onset motor and/or sensory deficits. The presence of these signs and symptoms necessitates neurology consult and additional diagnostic studies. Based on case reports, the differential diagnosis of PDPH with changing symptomatology should include intracerebral hemorrhage, infection, eclampsia, and cerebral venous thrombosis.

INCIDENCE

The incidence of PDPH has a very wide range, from 1% to 63%.[26] The determinants of this difference in incidence include the needle size, the design of the needle tip, and the orientation of the needle bevel during meningeal puncture.[27] The smaller needle diameters correlate with a lower incidence of PDPH. One study showed that with a 22-gauge Quincke, the rate of PDPD was 11%, whereas with a 25-gauge pencil-point needle, the incidence of PDPH was 7%; however, this has the obvious flaw of the presence of different needle tips as well.[28] It is important to realize that most unintentional dural punctures during epidural anesthesia occur with a 17-gauge Tuohy needle, which is a cutting needle. In an in vitro study comparing epidural needle diameter and CSF leakage, Angle et al. found reduced CSF leakage with a 20-gauge versus a 17-gauge Tuohy needle puncture.[29] The effect of needle tip design may be more important for lowering incidence of PDPH.[30]

The incidence of PDPH with a 20- to 22-gauge cutting needle is estimated to be 36%; for a 22-gauge atraumatic needle, the incidence is estimated to be less than 2%.[30] There is a lower incidence of PDPH with a larger-diameter blunt-tip needle when compared with a smaller-diameter cutting needle. One study showed a 2.7% incidence of PDPH with a 27-gauge Quincke needle versus 1.2% incidence with a 25-gauge Whitacre needle.[31] The proposed mechanism behind this difference is that a blunt-tip needle divides but does not disturb the continuity of the dural fibers, versus a cutting tip needle, which cuts the dural fibers. Electron microscopy studies show that a blunt-tip needle produces an irregular hole in the dura versus the clean puncture observed with a cutting needle[30] (Figs. 40-1 and 40-2). From this observation, it is proposed that an increased inflammatory reaction occurs with the blunt-tip needle that promotes hole closure thus reducing the amount of CSF leakage.

The orientation of the bevel to the dura during dural puncture has been proposed as a factor affecting the amount of CSF leakage and the incidence of PDPH. In an in vitro study, Cruickshank and Hopkinson showed a 21% reduction in the leakage of CSF if the bevel was parallel to the long axis of the spinal cord.[32] Norris et al. in a study of 1558 parturients compared the risk of dural puncture and PDPH between orienting the epidural needle parallel or perpendicular to the long axis of the spinal cord during epidural catheter placement. Although both groups had a similar incidence of dural puncture, patients in the parallel orientation group reported significantly less PDPH and required fewer EBPs.[33] In a more recent analysis, Richman et al. also found that a parallel rather than perpendicular insertion of the needle would result in a statistically significant lower incidence of PDPH, 10.9% versus 25.8%, respectively.[27] We know from electron microscopy that the dura mater is a meshwork of collagen and the elastic fibers lack a specific orientation, but the cells of the arachnoid mater are oriented parallel to the long axis of the spinal

cord, which may explain the rate reduction of PDPH using the parallel insertion technique.

RISK FACTORS

Independent risk factors of PDPH include a higher incidence in women versus men, pregnancy, a higher incidence in the age-group 20 to 50 years, and a higher incidence in patients with lower body mass index.[34] It was previously thought that PDPHs were rare in children, but it has been demonstrated to occur with equal frequency in children of all ages.[28,35] Vercauteren et al. referred to a higher incidence of PDPH after diagnostic dural punctures performed by neurologists and neuroradiologists.[36] This is most likely due to the use of larger-gauge needles and less procedural experience. There is also a higher incidence in patients with a headache prior to the dural puncture and a history of prior PDPH. Singh et al. performed a 5-year audit of accidental dural punctures and postdural puncture headaches in obstetric anesthesia. Of 40,894 consecutive parturients, they found a rate of 0.73% accidental dural puncture and 0.49% PDPH,[37] although higher rates have been quoted between 1% and 2.6%.[31] Choi et al. showed that in parturients who had an unintentional dural puncture during labor epidural analgesia, more than 50% had a PDPH.[38]

PREVENTION

Prevention of PDPH centers on needle size, needle tip, and bevel orientation during dural/arachnoid puncture. The smallest needle with a noncutting tip oriented parallel to the long axis of the spinal cord will reduce the incidence of PDPH. In a comparative outcome study of known subarachnoid punctures with 18-gauge Tuohy needles, Ayad et al. found that placing an intrathecal catheter through the dural puncture reduced the incidence of PDPH and leaving the catheter in place for 24 hr after delivery reduced the incidence to only 3%.[39] Other proposed preventive procedures include prophylactic EBPs and epidural saline injections and infusions. In a small study, Charsley and Abram found that intrathecal injection of 10 ml normal saline reduced the incidence of PDPH.[40] Little evidence exists for prophylactic EBPs, although they are commonly done.[41]

TREATMENT

Treatment for a PDPH should only be initiated once the diagnosis has been clearly established based upon history, physical examination, and appropriate diagnostic tests. Treatment options should be balanced with the understanding that 85% of PDPHs last less than 5 days, and, although rare, PDPHs can be associated with significant morbidity.[42] The initial treatment for PDPH is conservative therapy, usually pharmacologic and noninvasive. Recumbent bed rest relieves the symptoms of PDPH but has no therapeutic benefit. Aggressive hydration is a common therapy despite the fact that there are no studies to support its effectiveness. Medications reported beneficial in the treatment of PDPH include the methylxanthines, caffeine and theophylline, sumatriptan, adrenocorticotropic hormone, and corticosteroids.[2] Caffeine, a potent central nervous system stimulant, causes cerebral vasoconstriction, and is the most widely used pharmacologic therapy. Caffeine is administered as an oral dose of 300 mg or intravenously as 500 mg in 500 to 1000 ml normal saline over 2 hr; the intravenous dose can be repeated over the next 2 to 4 hr.[43] Although caffeine is safe and effective, there have been reports of seizures, anxiety, and arrhythmias associated with its use, and the existing literature does not seem to support caffeine as a therapeutic agent to treat PDPH.[2] Caffeine is contraindicated in patients with a history of seizure disorder and in patients with pregnancy-induced hypertension. The effect of caffeine is transient and the dose must be repeated because it does not address the underlying pathology.[44] Theophylline, another cerebral vasoconstrictor effective in the treatment of PDPH, is not widely used or supported in the literature. Other pharmacologic agents such as serotonin agonists (sumatriptan) and corticotrophin are infrequently used and have been found to be ineffective in the treatment of severe PDPH. Meanwhile, Bussone et al. found in their nonrandomized study frovatriptan to be useful in the prevention of PDPH in patients undergoing diagnostic lumbar punctures.[4]

Once the pharmacologic and other noninvasive options have been exhausted without relief and the patient is unable to wait for the natural resolution of the headache, more invasive options can be explored. Epidural treatments for PDPH include the administration of saline, colloids, fibrin glue, and blood.[2] The gold-standard treatment for PDPH is an epidural blood patch (EBP).[45] There are numerous variations of the EBP; however, the standard and most common treatment remains the epidural autologous blood patch. This treatment offers complete resolution of symptoms in a large proportion of patients. In the remaining patients, it reduces headache severity and allows them to return to their everyday activities.[45] The contraindications to an EBP are similar to those for any spinal or epidural procedure.[4] The first is patient refusal in general or for a specific reason. In the case of concerns of Jehovah's Witnesses about blood transfusions, there are reports of alternative patching materials.[34] Second, the patient's coagulation status must be assessed and judged to be within normal limits to reduce the risk of an epidural hematoma.[46] Finally, it is not recommended to place an EBP in a septic patient, or through a localized infection or febrile patient due to the obvious concern of introducing bacteria into the epidural space. Concerns about an EBP in HIV-positive patients are unfounded because HIV crosses the blood-brain barrier early in the course of the disease.[47] The mechanism of EBP is controversial; however, it is generally thought to be two fold. There is an initial early effect, which occurs within minutes, secondary to compression of the dura toward the cord and reduction in the intradural volume. The EBP blood spreads both longitudinally and circumferentially, thus enveloping the entire dural sac. The reduction in the spinal intradural volume shifts the CSF cephalad, thus resuspending the brain and reducing traction. In agreement with the Monro-Kellie rule, this intracranial shift in CSF also reduces the intracranial blood volume and cerebral vasodilatation. Due to this early effect, patients often report rapid relief following an EBP. However, using postepidural blood patch MRI, the compressive mass effect of a blood patch has resolved

at 7 hr postpatch. A second, more lasting effect is due to sealing of the dural/arachnoid tear with a gelatinous plug. This sealing of the dural/arachnoid hole prevents further loss of CSF and allows for regeneration and restoration of the CSF volume. The plug acts as a bridge until permanent repair of the dural/arachnoid hole occurs. The occurrence of this second effect is more variable and accounts for the failure of the EBP despite initial relief.

Risk factors for EBP failure include placement sooner than 24 hr after dural puncture, using inadequate volumes of autologous blood, and performance of the procedure with residual lidocaine in the epidural space. Due to the proposed mechanical plugging nature of the patch, avoiding increases in intrathecal pressure is recommended until natural healing of the dural/arachnoid tear has occurred. A repeat blood patch often has more lasting benefit due to both the patch effect and performance of the blood patch later in the natural time course of healing the tear. There are no documented long-term effects of epidural blood patch. Ong and Blanche were unable to find any conclusive impact of an EBP on the efficacy of future epidural anesthetics.[48,49] The technique of an EBP, first described by Gormley in 1960, is straightforward and based on the placement of a single-shot epidural.[50] It usually requires two people, one to locate the epidural space and the other to obtain the blood. Sterility is of the greatest importance both during epidural space localization and during blood collection. The patient position during the procedure can be sitting or lateral decubitus depending on the difficulty in locating the epidural space and patient ability to tolerate the upright position. Selection of the level of placement should be guided by the observation that 15 ml of blood preferentially spreads cephalad six segments and caudad three segments, or one spinal segment per 1.6 ml of blood.[51] It is therefore common to select a site caudad to the suspected dural tear. Colonna-Romano and Linton report a lumbar EBP successfully used to treat a PDPH due to a C6–C7 cervical dural puncture.[52] This may be related to the increase in the subarachnoid pressure and the resultant cerebral vasoconstriction and deactivation of the brain adenosine receptors. Because of anatomic considerations, more caudad levels also have a reduced risk of direct cord compression. Although historically different volumes of blood have been used, the ideal target volume is 20 ml.[53] This is the most widely accepted and cited volume if the patient tolerates placement. If the patient complains of excessive back or leg pain or pressure during injection, less volume can be placed. Chen et al. found that a volume of 7.5 ml of autologous blood in the epidural space was comparable to 15 ml of blood in its analgesic effect on PDPH, but with less nerve root–irritating pain during injection.[54] After the EBP, the patient should remain supine with the legs slightly elevated. An intravenous fluid can be administered during this time. In a small study, Martin et al. found that 2 hr in the supine position post-EBP provided 100% relief versus 60% relief in patients who remained supine for only 30 min.[55] Although initial relief can be as high as 100%, the overall long-term relief of PDPH from an initial EBP is between 61% and 75%.[56] Alternative dural patching materials include epidural fibrin glue and epidural Dextran-40.[57] Although both of these materials were reported as successful, they are not widely used due to cost and safety concerns, especially when compared to autologous blood. Mindful of these concerns, Dextran-40 may be an alternative in patients who are Jehovah's Witnesses. Alternatives to the epidural blood patch include epidural saline bolus and/or infusions, and surgical exposure and repair of the dural tear. Epidural saline bolus or infusions have *not* been shown to be an effective alternative and often require more interventions with a lower success rate. Surgical exposure and repair of a dural tear is a more invasive procedure generally reserved for severe cases of PDPH that have not responded to an EBP.

Complications after an EBP are rare. The most common complication is mild low back and radicular pain following the procedure that resolves spontaneously in a few days and can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs).[58] Other possible complications include epidural hematoma, infection, and arachnoiditis due to unintentional subdural/subarachnoid injection of the blood. There are two reported cases of facial nerve paralysis following EBP, which resolved spontaneously.[59] Mokri reports one case of symptomatic intracranial hypertension following an EBP.[60]

SUMMARY

PDPH and its management is a well-known and widely accepted entity in the anesthesia community. A postural headache is the cardinal sign that can indicate a postdural puncture headache. In the setting of a dural puncture or possible dural puncture with pathognomonic symptoms, the diagnosis of PDPH should be straightforward. Although generally nonfatal, it can have significant comorbidity and should be treated seriously.

SPONTANEOUS INTRACRANIAL HYPOTENSION

Spontaneous intracranial hypotension (SIH) is a syndrome with symptoms similar to meningeal puncture headache but the patient has no previous history of meningeal puncture.[61,62] The syndrome was initially described by Schaltenbrand in 1938.[63] Often self-limiting, it can also result in a life threatening condition such a subdural hematoma.[64,65]

This syndrome is usually suspected in a patient with postural headache that occurs after a fall, trauma, whiplash, exercise, or violent coughing.[61,66] Symptoms include headache, nausea and vomiting, blurred vision, tinnitus, vertigo, and photophobia. The triad of postural headache, low CSF pressure on diagnostic lumbar puncture, and meningeal enhancement on the MRI in a patient without any history of dural puncture leads one to suspect the presence of SIH.

The commonly accepted etiology of SIH is leakage of the CSF through a weakness of the spinal meninges such as meningeal diverticulum, or small tears in the root sleeves or perineural cysts (Tarlov cysts). The diagnosis of SIH is confirmed by low cerebrospinal fluid (CSF) pressure on diagnostic lumbar puncture and meningeal enhancement on the magnetic resonance imaging of the cranium.[66,67] Diagnostic lumbar puncture usually shows a low CSF pressure (below 60 cm H_2O). Occasionally there

is no spontaneous flow and the CSF has to be aspirated. The CSF protein, and red cell and white cell counts are usually increased. The MRI of the cranium shows meningeal enhancement, subdural fluid collection, and caudal displacement of the cerebellar tonsils.[68] Meningeal enhancement is usually thickest in patients with low intracranial pressure[68] and subdural fluid collections are only seen in patients with meningeal enhancement. The spinal MRI of patients with SIH usually shows epidural or paraspinal fluid collections and collapse of the dural sac.[68,69] It is interesting to note that the meningeal enhancement slowly decreases when the patient improves with treatment and may take 3 to 5 months for the meningeal changes to resolve.[70]

Spinal MRI has been recommended to confirm the presence of epidural CSF collection; it is also a non-invasive.[69] Most clinicians proceed to radionuclide cisternography (RC) because it is presumed to be the standard confirmatory test in the diagnosis of the syndrome.[71] However, the site of the CSF leak is rarely demonstrated with cisternography. The presence of SIH is indirectly proven by the lack of ascent of the injected dye, rapid disappearance of the radioisotope from the CSF (within 4 hr)[68] and the early appearance of the radioisotope in the urinary bladder.[61,62,66,72] The radioisotope is presumed to leak through a meningeal rent into the epidural space, subsequently taken up by the epidural vessels and carried into the systemic circulation and excreted by the kidneys.[61] Early appearance of the radioisotope in the bladder within 2.5 hr is considered early filling,[73] and reports have shown appearance of the radioisotope as early as 45 to 90 min after injection.[10] RC may directly show the site of leak when radioactivity is located beyond the expected dural border in the epidural space[73] or there is assymetrical activity outlining the spinal nerve roots in a "Christmas tree" or "railroad pattern" of radioisotope activity.[70] However, the site of leak may not be demonstrated in cisternography. This is because after injection of the radioisotope, the patient is brought back to the radiology department to have images taken at several time intervals; the leak of the radioisotope may have occurred between images. Several reports have shown the inability of RC in demonstrating the site of leak,[70,72,74,75] its sensitivity being approximately 60%.[72,74] A Valsalva maneuver may improve RC's ability to demonstrate the site of leak by increasing the subarachnoid pressure and improving the chance of the CSF to actively leak and shown on the RC.[76] Other disadvantages of RC include poor spatial resolution,[72] its invasiveness, and possible radioisotope extravasation through the needle tract, resulting in inaccuracy in its interpretation.[76]

Some investigators recommend CT myelography, magnetic resonance myelography, and radioisotope myelocisternography to demonstrate the site of leak.[70] CT myelography may be performed instead of radionulide cisternography because it has a better localizing power and gives finer details.[69] Although there have been no studies comparing comparing CT myelography with radionuclide cisternography, it is probably ideal to perform CT myelography rather than RC.[69,72,77–79]

Epidural blood patch (EBP) is the treatment of choice for SIH, and it appears that EBP is less effective in SIH than in postdural puncture headache.[80,81] The lower success rate may be related to the injection of the blood away from the site of the CSF leak, the presence of multiple CSF leaks, and the rare occurrence of CSF leak at the anterior aspect of the dura or the nerve root sleeve.[81]

Initially, it was thought that most CSF leaks occur in the thoracolumbar level[71]; more recent publications showed the leak to be anywhere in the spine,[69,76] anywhere in the thoracic levels,[70] or mostly in the lumbosacral levels.[73] From these reports, it can be noted that the site of leak can occur anywhere in the spine. In the absence of cisternography or CT myelography demonstrating the exact location of CSF leak, most pain medicine practitioners inject the blood at the mid-thoracic area and cover the upper lumbar and the lower thoracic levels.[51] If one or two EBPs are not effective, then a CT myelography should preferably be performed before another EBP is performed to delineate the vertebral level and the side of the CSF leak and note the presence of multiple leaks.

The occurrence of multiple leaks in a patient with SIH is rare. Arai et al.[78] and Benzon et al.[79] reported patients with multiple CSF leaks. Arai et al. performed four epidural blood patches, twice at the upper thoracic and once at the lower thoracic and lumbar areas.[78] Benzon et al.[79] performed three epidural blood patches, all at the thoracic regions; the first two blood patches were injected through a midline approach, while the third one was injected through a left paramedian approach since several sites of leak were noted on that side. If one or two EBPs are not effective, then a CT myelography should preferably be performed before another EBP is performed to delineate the vertebral level and the side of the CSF leak.

Surgical intervention is warranted if multiple EBPs are ineffective and the patient's condition deteriorates.[74] Surgery for SIH is challenging and close follow-up is recommended since some patients develop recurrent CSF leak.[82]

SUMMARY

Spontaneous intracranial hypotension (SIH) is characterized by the same symptoms as PDPH although the patient had no previous history of meningeal puncture. The CSF pressure is low on diagnostic lumbar puncture and there is meningeal enhancement on the MRI. CT myelography or radionuclide cisternography confirms the diagnosis and helps determine the exact site of CSF leak. Several epidural blood patches may be required to treat the headache.

KEY POINTS

POSTDURAL PUNCTURE HEADACHE

- The crucial components of PDPH are a history of dural/arachnoid puncture and a postural bilateral headache on examination.
- The occurrence of headache after dural/arachnoid puncture is not directly related to the amount of CSF leaked or the subarachnoid pressure. The headache may be secondary to a sudden alteration in CSF volume and subsequent cerebral vasodilatation.

- Concomitant intracranial pathology may be present in patients with PDPH. The signs and symptoms include the presence of a significant nonpostural component of the headache, a changing pattern of the headache (postural headache becoming nonpostural in character), bilateral headache that becomes unilateral, and those with new-onset and severe nausea and vomiting.
- The prevention of headache depends mostly on size and design of the needle tip. Based on studies, the criteria guiding needle selection should be based on the smallest practical needle diameter with a noncutting tip design.
- The initial therapy of PDPH for the first 24 hr should be conservative relying mainly on medications. Approximately 85% of PDPHs resolve spontaneously in 5 days.
- The initial and rapid relief from an EBP is secondary to circumferential compression of the dura and reduction of the intradural volume. This shifting of the vertebral subarachnoid CSF cephalad causes a resuspension of the cerebral structures and a reduction of the traction of the pain-sensitive intracranial structures, and decreased cerebral vasodilatation. The lasting relief from the EBP is related to sealing of the dural/arachnoid hole.
- Caffeine and theophylline block brain adenosine receptors, causing cerebral vasoconstriction. The acute increase in the subarachnoid pressure after an EBP may deactivate adenosine receptors and relieve the headache.

SPONTANEOUS INTRACRANIAL HYPOTENSION

- Spontaneous intracranial hypotension (SIH) is characterized by symptoms similar to meningeal puncture headache in a patient with no history of meningeal puncture.
- The commonly accepted etiology of SIH is leakage of the CSF through a weakness of the spinal meninges such as meningeal diverticulum, or small tears in the root sleeves or cysts.
- The triad of spontaneous intracranial hypotension consists of postural headache, low CSF pressure on diagnostic lumbar puncture, and meningeal enhancement on the MRI.
- Radionuclide cisternography shows lack of ascent of the injected dye, rapid disappearance of the radioisotope from the CSF, and the early appearance of the radioisotope in the urinary bladder.
- CT myelography may be performed instead of radionuclide cisternography because it has a better chance of showing the location of the CSF leak and gives finer details.
- Epidural blood patch (EBP) is the treatment of choice for SIH and several EBPs may be required if there are multiple sites of leak as shown by CT myelography.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 41

Cervicogenic Headache

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Cervicogenic headache was initially defined as unilateral headache that is provoked by neck movement or pressure over tender points in the neck with associated reduced range of movement of the cervical spine. The headache occurs in nonclustering episodes and is usually nonthrobbing in nature, originating from the neck, and spreading over the head.[1–3] It is sometimes difficult to differentiate among cervicogenic headache, migraine, and tension-type headache based only on the clinical presentation.[4–6] However, diagnostic blockade of the nerve supply of these cervical structures or intra-articular injection of local anesthetic into the affected joint help establish the diagnosis; in fact, this is now considered a major criterion for the diagnosis of cervicogenic headache.[7] Also, it was long thought that cervicogenic headache should be only unilateral, but recent reports state that cervicogenic headache can be either unilateral or bilateral.[7]

These clinical findings prompted the development of the new diagnostic criteria for cervicogenic headache by the International Headache Society (IHS) in 2004, as follows:[8]

A. Pain, referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfills criteria C and D.
B. Clinical, laboratory, and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck is known to be, or generally accepted as, a valid cause of headache.
C. There is evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following:
   1. Demonstration of clinical signs that implicate a source of pain in the neck.
   2. Abolition of headache following diagnostic block of a cervical structure or its nerve supply using placebo or other adequate controls. Abolition of headache means complete relief of headache, indicated by a score of 0 on a visual analog scale.
D. Pain resolves within 3 months after successful treatment of the causative disorder or lesion.

Clinical signs acceptable for criterion C1 must have demonstrated reliability and validity. Clinical features such as neck pain, focal neck tenderness, history of neck trauma, mechanical exacerbation of pain, unilaterality, coexisting shoulder pain, and reduced range of motion in the neck are not unique to cervicogenic headache. These may be features of cervicogenic headache, but they do not define the relationship between the disorder and the source of the headache.

ETIOLOGY

Cervicogenic headache is referred pain from cervical structures innervated by the upper three cervical spinal nerves. Thus possible sources of cervicogenic headache are: atlanto-occipital joint, atlantoaxial (AA) joints, C2–C3 zygapophysial joint, C2–C3 intervertebral disc, and upper cervical spinal nerves and roots. Other serious causes of occipital headaches should be ruled out, such as posterior cranial fossa lesions and vertebral artery dissection or aneurysm.[9]

Tumors, fractures, infections, and rheumatoid arthritis of the upper cervical spine have not been validated formally as causes of headache, but are nevertheless accepted as valid causes in individual cases.

Cervical spondylosis and osteochondritis are not accepted as valid causes of cervicogenic headache. Also, when myofascial tender points are the cause, the headache should be coded under tension-type headache.

NEUROANATOMY AND NEUROPHYSIOLOGY

The spinal nucleus of the trigeminal nerve extends caudally to the outer lamina of the dorsal horn of the upper three to four cervical spinal segments. This is known as the trigeminocervical nucleus, which receives afferents from the trigeminal nerve as well as the upper three cervical spinal nerves. Convergence between these afferents accounts for the cervical-trigeminal pain referral. Therefore, pain originating from cervical structures supplied by the upper cervical spinal nerves could be perceived in areas innervated by the trigeminal nerve branches such as the orbit and the frontotemporoparietal region (Fig. 41-1).

The concept of the trigemiocervical convergence was well demonstrated by showing that noxious stimulation of the greater occipital nerve increases central excitability of supratentorial afferents,[10] and stimulation of the dura mater increases trigeminocervical neuron responsiveness to cervical input.[11]

COMMON SOURCES OF CERVICOGENIC HEADACHE

ATLANTOAXIAL JOINT

The lateral atlantoaxial joint (AAJ) may account for up to 16% of patients with occipital headache.[12] Distending the atlantoaxial joint with a contrast agent was shown to produce occipital pain, and injection of local anesthetic into the joint relieves the pain.[12,13] Clinical presentations suggestive of pain originating from the lateral atlantoaxial joint include occipital or suboccipital pain, focal tenderness over the suboccipital area, restricted painful rotation of C1 on C2, and pain provocation by passive rotation of C1. These clinical presentations are not specific and therefore cannot be used alone to establish the diagnosis.[9] The only means of establishing a likely diagnosis is a diagnostic block with intra-articular injection of local anesthetic.[12] The pathology of lateral atlantoaxial joint pain is usually

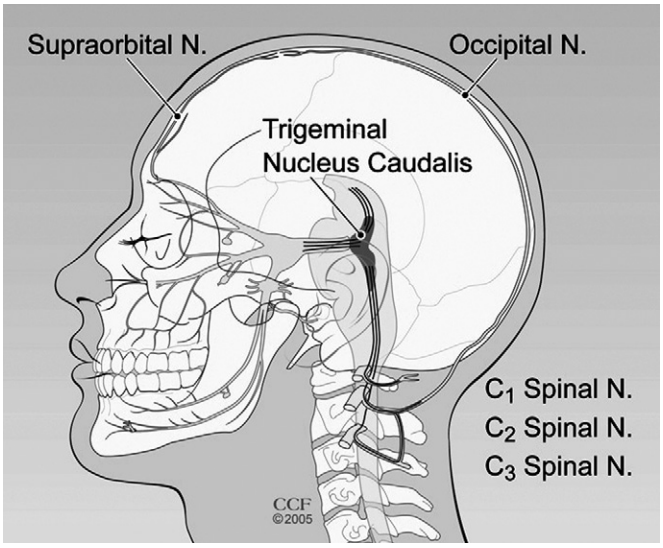

FIGURE 41-1 The trigemino-cervical complex. *(Reprinted with permission from Cleveland Clinic)*

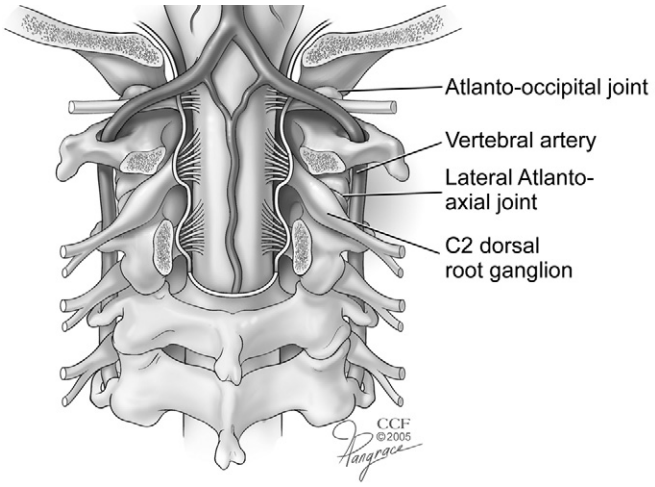

FIGURE 41-2 Illustration showing the relationship of the atlantoaxial and atlanto-occipital joints to the vertebral artery. *(Reprinted with permission from Cleveland Clinic)*

post-traumatic or osteoarthritis.[14,15] However, the presence of osteoarthritic changes on imaging studies does not mean that the joint is necessary painful. On the other hand, the absence of abnormal findings on imaging studies does not preclude the joint from being painful.

Intra-articular steroids are effective in the short-term pain relief originating from the lateral atlantoaxial joint.[16,17] One report showed favorable long-term outcome after both pulsed and thermal radiofrequency lesioning of the AAJ capsule.[18] In intractable cases not responsive to more conservative management, arthrodesis of the lateral atlantoaxial joint may be indicated.[19]

Atlantoaxial joint intra-articular injection has the potential for serious complications, so it is crucial to be familiar with the anatomy of the joint in relation to the surrounding vascular and neural structures (Fig. 41-2). The vertebral artery is lateral to the atlantoaxial joint as it courses through the C2 and C1 foramina. Then it curves medially to go through the foramen magnum crossing the medial posterior aspect of the atlanto-occipital joint (Fig. 41-2). The C2 dorsal root ganglion and nerve root with its surrounding dural sleeve crosses the posterior aspect of the middle of the joint. Therefore, during atlantoaxial joint injection, the needle should be directed toward the posterolateral aspect of the joint. This will avoid injury to the C2 nerve root medially or the vertebral artery laterally (Figs. 41-3 through 41-5).[12,17] Meticulous attention should be paid to avoid intravascular injection because the anatomy may be variable. Injection of a contrast agent should be performed under real-time fluoroscopy, preferably with digital subtraction, prior to the injection of the local anesthetic, as negative aspiration is of low sensitivity. Inadvertent puncture of the C2 dural sleeve with CSF leak or high spinal spread of the local anesthetic may occur with atlantoaxial joint injection if the needle is directed a few millimeters medially. Spinal cord injury and syringomyelia are potential serious complications if the needle is directed farther medially.[20]

Recently, ultrasound-assisted AAJ injection was reported in an effort to add more safety to the procedure because ultrasound can identify the relevant soft tissue structures

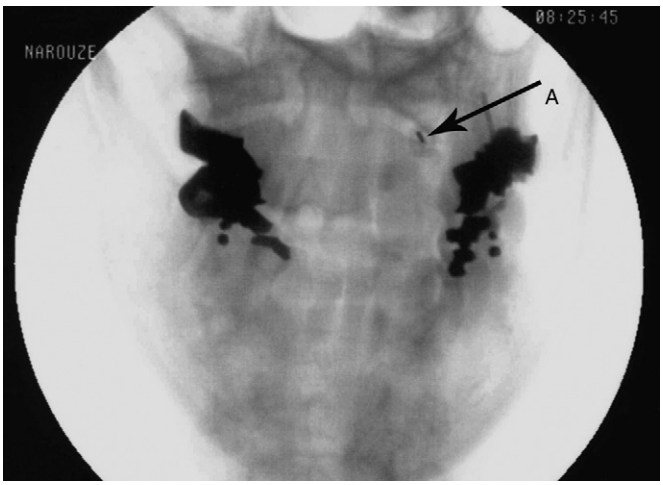

FIGURE 41-3 Anteroposterior view showing the needle in a tunnel view inside the lateral part of the lateral atlantoaxial joint. *(Reprinted with permission from Ohio Pain and Headache Institute)*

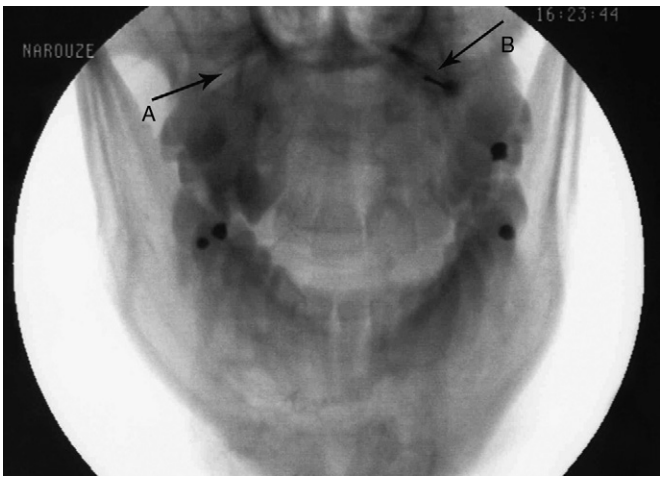

FIGURE 41-4 **A,** The lateral atlantoaxial joint. **B,** The tip of the needle and the contrast agent within the lateral atlantoaxial joint. *(Reprinted with permission from Ohio Pain and Headache Institute)*

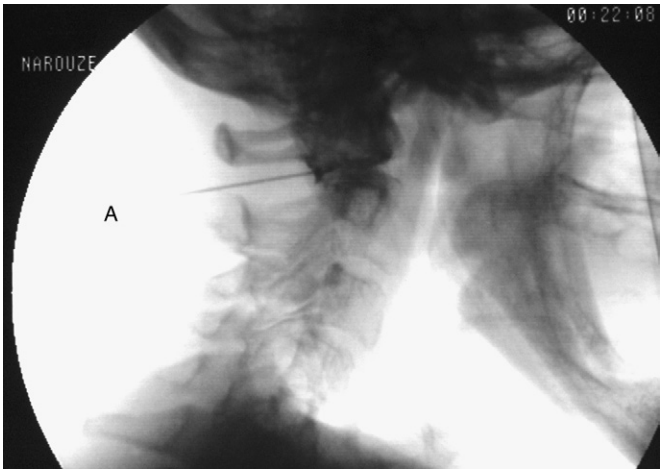

FIGURE 41-5 Lateral view showing the tip of the needle and the contrast agent within the lateral atlantoaxial joint. *(Reprinted with permission from Ohio Pain and Headache Institute)*

near the joint (e.g., vertebral artery and C2 dorsal root ganglion).[21]

C2–C3 ZYGAPOPHYSEAL JOINT AND THIRD OCCIPITAL HEADACHE

The C2–C3 zygapophyseal joint is innervated by the third occipital nerve, which is the superficial medial branch of the dorsal ramus of C3.[22] Pain stemming from this joint (named third occipital headache) is seen in 27% of patients presenting with cervicogenic headache after whiplash injury.[23] Tenderness over the C2–C3 joint is the only suggestive physical examination finding and a diagnostic third occipital nerve block is mandatory to confirm the diagnosis. Earlier reports showed that radiofrequency neurotomy of the third occipital nerve was not effective.[24] However, with improved radiofrequency technique, complete pain relief was obtained in 88% of patients with third occipital headache (Fig. 41-6).[25] On the other hand, Barnsley et al.[26] reported the lack of efficacy of intra-articular steroids for chronic pain stemming from the cervical zygapophyseal joints.

THIRD OCCIPITAL NERVE NEUROLYSIS

The third occipital nerve is the superficial medial branch of C3 dorsal ramus. It supplies the C2–C3 zygapophysial joint while crossing the joint laterally. Also it supplies part of the semispinalis capitis muscle, and its cutaneous branch supplies a small area of skin below the occiput.[21] Third-occipital radiofrequency ablation (RFA) was shown to be effective in the treatment of headache stemming from the C2–C3 joint. There is usually incomplete lesioning of the third occipital nerve because of its variable anatomy.[23] The use of the three needles technique to accommodate all variations in the anatomy of the third occipital nerve from just lateral to the joint line to above or below the joint and creating consecutive lesions no more than one electrode width from adjacent lesions markedly improve the results[25] (Fig. 41-6).

Numbness in the cutaneous distribution of the third occipital nerve is very common after RFA, whereas dysesthesia and hypersensitivity (typically at the border of the area

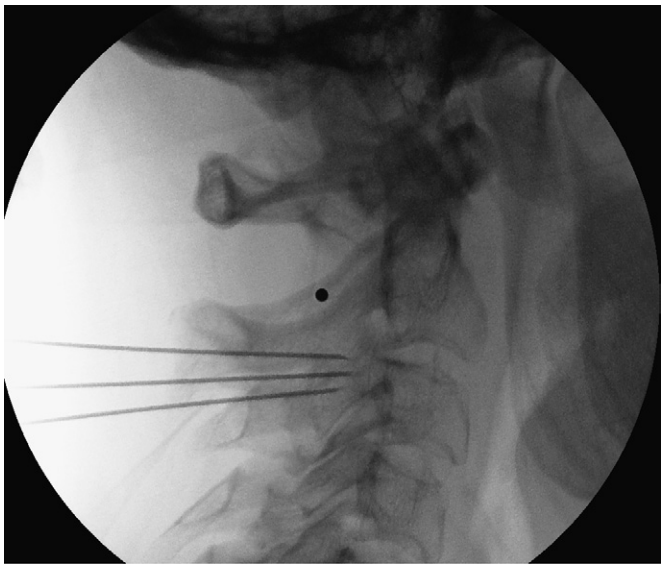

FIGURE 41-6 Lateral view showing three radiofrequency needles appropriately placed, at the equator of the C2–C3 joint, above and below the joint line. *(Reprinted with permission from Ohio Pain and Headache Institute)*

of numbness) occur in up to 50% of cases. These are temporary complications that usually persist for only a few days to weeks.[23,24] Temporary ataxia has been reported in most patients as third occipital neurotomy partially denervates the semispinalis capitis muscles with the resultant interference of the tonic neck reflexes.[23,24]

OCCIPITAL NEURALGIA

According to the second edition of the International Classification of Headache Disorders (ICHD), occipital neuralgia is coded separately under cranial neuralgias.[8] It is discussed because of its close relevance to cervicogenic headaches. The diagnostic criteria include the following:

A. Paroxysmal stabbing pain, with or without persistent ache between paroxysms, in the distribution(s) of the greater, lesser, and/or third occipital nerves.
B. Tenderness over the affected nerve.
C. Pain eased temporarily by local anesthetic block of the nerve.

Occipital neuralgia was long thought to be the result of entrapment of the greater occipital nerve as it emerges from the trapezius muscle. However, surgical nerve release gives only short-term relief in about 80% of cases, whereas nerve excision provides short-term relief in about 70% of patients.[27,28] Occipital neuralgia must be distinguished from occipital referral of pain from the atlantoaxial or upper zygapophyseal joints or from tender trigger points in neck muscles or their insertions.[8]

The greater occipital nerve is the terminal branch of the dorsal ramus of C2 with contribution from C3, whereas the lesser occipital nerve is a branch of the dorsal ramus of C3 with contributions from C2. Segmental nerve blocks at C2 and C3 may be necessary to make the diagnosis in some cases.[29] Cryoneurolysis, radiofrequency ablation, and more permanent neuroablative approaches such as dorsal

rhizotomy at C1–C3 and partial posterior rhizotomy at C1–C3 showed variable responses.[30–33]

OCCIPITAL NEUROSTIMULATION

Percutaneous occipital nerve stimulation, unlike other neuroablative techniques, offers the potential for a minimally invasive, low-risk, and reversible approach to managing occipital neuralgia and some types of intractable primary headache.[34,35] PET scan studies showed increased regional cerebral blood flow in areas involved in central neuromodulation in chronic migraine patients treated with occipital nerve electrical stimulation.[36] A percutaneous trial of peripheral nerve stimulation is performed using subcutaneous electrodes placed superficial to the cervical muscular fascia in the suboccipital area. If effective, a permanent implant may be carried out using the same electrode lead type or paddle-type surgical lead and attached to a pulse generator implanted in the infraclavicular area, flank, upper buttock, or abdomen (Figs. 41-7 and 41-8).

The most frequent complication of the subcutaneous techniques of neurostimulation is lead migration necessitating revision the electrodes placement. Various anchoring techniques have been described to improve lead stability; however, the problem persists.[37]

In one review, lead migration was found to be 33% and 60% 6 months and 1 year postimplant, respectively.[38] The use of self-anchoring leads (e.g., tined leads) looks promising. In a series of 12 patients, only one patient had a few millimeters of lead migration with little change in the stimulation pattern, and no loss of efficacy[39] (Fig. 41-9).

The other potential problem with ONS is a painful stimulation-induced muscle contraction that is related to the depth of the implanted lead (e.g., deep placement at the level of the suboccipital muscles). Subcutaneous implant of the ONS lead with ultrasound guidance looks very attractive, as the lead can be placed under direct vision in the correct plane superficial to the muscles.[21]

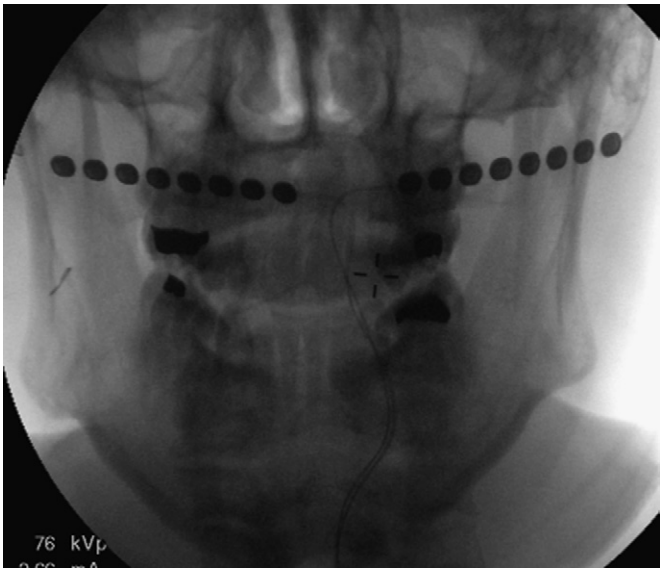

FIGURE 41-7 Anteroposterior view showing bilateral occipital surgical leads. *(Reprinted with permission from Ohio Pain and Headache Institute)*

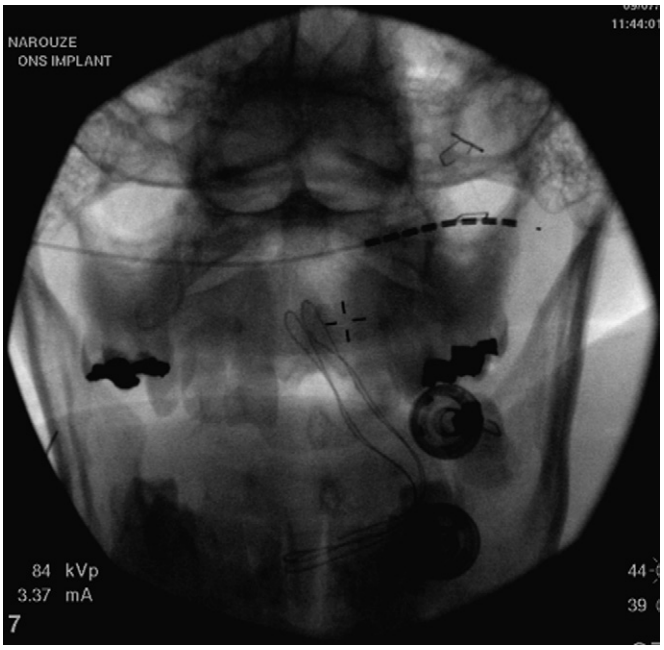

FIGURE 41-8 Anteroposterior view showing right occipital percutaneous lead. *(Reprinted with permission from Ohio Pain and Headache Institute)*

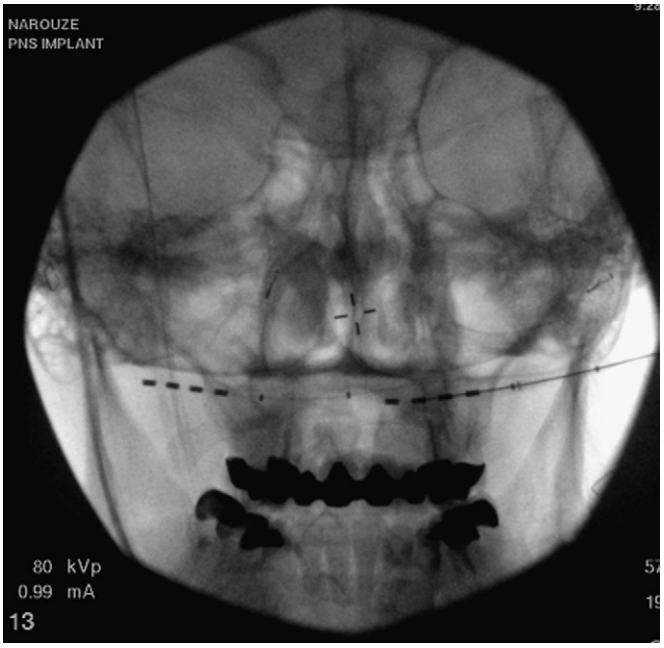

FIGURE 41-9 Anteroposterior view showing bilateral occipital self-anchoring leads. *(Reprinted with permission from Ohio Pain and Headache Institute)*

C2 NEURALGIA

C2 neuralgia is a distinctive type of occipital neuralgia caused by lesions affecting the C2 nerve root or dorsal ganglion, such as neuroma, meningioma, or anomalous

vessels.[40,41] The C2 root lies posterior to the lateral atlantoaxial joint; thus, disorders or inflammation of this joint may lead to irritation or entrapment of the nerve root.[42] C2 neuralgia manifests as intermittent lancinating occipital pain that is associated with lacrimation, ciliary injection, and rhinorrhea. Abolition of pain by selective C2 nerve root block is essential to make an accurate diagnosis. Thermocoagulation, decompression, or C2 ganglionectomy may be indicated in intractable cases that respond poorly to pharmacotherapy and other conservative management.[9]

CERVICAL MYOFASCIAL PAIN

Trigger points in the posterior neck muscles, especially the trapezius, sternocleidomastoid, and the splenius capitis, have been proposed as a cause of headache.[43,44] According to the second edition of the International Classification of Headache Disorders (ICHD), headaches causally associated with cervical myofascial tender spots are coded as episodic or chronic tension-type headache associated with pericranial tenderness.[8]

Moreover, these tender points usually overlie the zygapophyseal joints, so it is difficult to distinguish them from underlying painful joints.[9] Needling therapies in the management of myofascial pain showed no efficacy beyond that of placebo.[45] The use of botulinum toxin is controversial. It might be effective in the management of migraine and chronic daily headaches; however, its efficacy in myofascial pain and cervicogenic headaches is still debatable.[46–48]

CERVICAL DISCOGENIC PAIN

C2–C3 provocative discography, but not at the lower levels, can reproduce cervicogenic headache.[49] Radiofrequency lesioning was shown to be effective in obtaining some pain relief for a few months in one study.[50] However, cervical disc interventions are not commonly performed because of the potential for esophageal penetration leading to discitis or vascular injury.

SUMMARY

In summary, cervicogenic headache is one of the most debatable and challenging areas in headache medicine. Patients usually benefit the most from a multidisciplinary approach incorporating physical therapy, pharmacotherapy, psychotherapy (biofeedback and relaxation therapy), alternative medicine (acupuncture), and the judicious utilization of interventional pain management modalities.

KEY POINTS

- Cervicogenic headache is referred pain from cervical structures innervated by the upper three cervical nerves.
- The diagnostic criteria of cervicogenic headache, according to the International Headache Society, include the following: (1) pain referred from a source in the neck, (2) evidence of a disorder within the cervical spine or soft tissues of the neck as a cause of the headache, (3) abolition of the headache following a diagnostic block, and (4) resolution of the pain after successful treatment of the causative disorder.
- Pain from the C2–C3 zygapophyseal joint is called third occipital headache. The improved success rate of neurolysis of the third occipital may be secondary to improved technique. This includes the use of three needles to accommodate variations in the anatomy of the third occipital nerve.
- The criteria for occipital neuralgia include pain in the distribution of the occipital nerves, tenderness over the affected nerve, and relief from local anesthetic blockade of the occipital nerve.
- Occipital nerve stimulation may have central neuromodulatory effects in chronic migraine patients. The most frequent complication of subcutaneous placement is lead migration.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 42

Orofacial Pain

Jason E. Pope, MD ✪ **Samer Narouze,** MD, MSc, DABPM, FIPP

The incidence and prevalence of orofacial pain in the general population is very high. Care and emphasis should be placed on correct diagnosis and treatment rather than on symptomatic management. Each disorder will be described according to the classification and diagnostic criteria published in the *International Classification of Headache Disorders*, second edition (ICHD-2). The pathophysiology of the disorder, the clinical picture, and the management (both medical and interventional if applicable) will be reviewed.

The ICHD-2 criteria provide a systematic classification for headache and orofacial pain and are divided into three parts: the primary headaches, the secondary headaches, and cranial neuralgias central and primary facial pain.[1]

We will focus mainly on Sections 11 and 13 of the ICHD-2 (Table 42-1). However, before considering the diagnoses that are commonly attributed to orofacial pain, it is relevant to provide a brief comment on eliciting the key components of the history and physical examination in the evaluation of headache and orofacial pain. It is important to take a stepwise, systematic approach to the patients pain. This requires a fundamental knowledge of the ICHD-2 criteria. It should be noted that in one series of 97 consecutive patients presenting to a tertiary care neurologic facility, 29% were not classifiable using the ICHD-2 criteria.[2]

An appropriate physical examination includes a thorough neurologic assessment (including gait, pronator drift, Romberg's sign, and reflex testing, that is, Hoffman and Babinski signs), heart and carotid auscultation, fundoscopic examination, cervical range of motion (ROM including atlantoaxial and atlantooccipital joint), a musculoskeletal evaluation with careful detail to myofascial tenderness and trigger points, maneuvers that provoke radicular signs (Spurling's test), cervical facet examination, and Waddell's signs of nonorganic pain (tenderness to palpation, stimulation, distraction, regional disturbance in function, and overreaction). Tables 42-2 and 42-3 list findings and characteristics indicating the need for neuroimaging evaluation, respectively.[3]

ANATOMY AND PATHOPHYSIOLOGY

The trigeminal system provides the relay system for pain and touch sensation to the face, as well as motor function to the muscles of mastication. The trigeminal system is a bilateral structure that spans from the midbrain to the medulla and is composed of four nuclei: the mesencephalic nucleus, the main sensory nucleus, a spinal nucleus of V, and the motor nucleus. The caudal portion of the trigeminal system nucleus is referred to as the spinal nucleus of V and is composed of three regions, in cephalad to caudal order, the subnucleus oralis, the subnucleus interplaris, and the subnucleus caudalis. The subnucleus caudalis is very similar in structure and function to the dorsal horn and extends down to the second or third cervical level. The primary afferent synapses ipsilaterally in the nucleus caudalis and then the second-order neuron crosses to join the contralateral spinothalamic tract. The trigeminal pathway is termed the ventral trigeminothalamic tract and terminates in the ventral posteromedial (VPM) nucleus of the thalamus.

Activation of nuclei in close proximity to the trigeminocervical complex may explain the associated aura and symptoms attributed to different headache disorders by either activation of wide dynamic neurons, ephaptic transmission, or by sheer close proximity to the complex (solitary nucleus, nucleus ambiguous, or dorsal nucleus of vagus nerve).

Goadsby demonstrated the trigeminocervical convergence mechanism (Fig. 42-1). He electrically stimulated the superior sagittal sinus of adult monkeys and C-fos was expressed in the superficial laminae of the dorsal horn of C1 and C2, but none in C3.[4]

Anthony examined patients with occipital headache and he summarized that "projection of pain . . . overlap between trigeminal nucleus and upper cervical cord . . . form a column of cells forming the posterior horn . . . to C4."[5] Consequently, the trigeminocervical complex with the hypothesized reciprocal interactions described by Goadsby, appear to introduce potential neuromudulatory/ablative sites for a variety of headache disorders, contrary to the accepted headache generator foci.

HEADACHE ATTRIBUTED TO DISORDER OF CRANIAL BONE

The diagnostic criteria include pain in one or more regions in the head and face with clinical, laboratory, or imaging evidence of a lesion within the cranial bone known to be valid evidence of generating headache (Table 42-4). The source of the pain must be in close temporal association to and is maximal over the bone lesion, and with resolution of the pain after successful treatment of the bone lesion. Most disorders of the skull are not painful, with the exception of osteomyelitis, multiple myeloma, and Paget's disease.

HEADACHE ATTRIBUTED TO DISORDER OF NECK

These constellations of disorders involve pain referral from neck structures to the head/and or face. The diagnostic criteria hinges on what is excepted as "being generally accepted as valid cause of headache."

CERVICOGENIC HEADACHE

Cervicogenic headache is pain attributed to a disorder or lesion within the cervical spine or soft tissues that is generally accepted to cause headache or facial pain. (Please refer to Chapter 41).

TABLE 42–1 ICHD-2 Classification Headings

Part I: The Primary Headaches
1. Migraine
2. Tension-type headache
3. Cluster headache and other trigeminal autonomic cephalalgias
4. Other primary headaches
Part II: The Secondary Headaches
5. Headache attributed to head and/or neck trauma
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to nonvascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
12. Headache attributed to psychiatric disorder
Part III: Cranial Neuralgias Central and Primary Facial Pain and Other Headaches
13. Cranial neuralgias and central causes of facial pain
14. Other headache, cranial neuralgia, central or primary facial pain

TABLE 42–2 Headache with "Red Flag" Symptoms and Signs That Require Further Work-up

Sudden onset of headache (thunderclap headache)
Fever, rash, and/or stiff neck (meningismus) associated with the headache
Papilledema (optic nerve head swelling)
Dizziness, unsteadiness, dysarthria, weakness, or changes in sensation (numbness or tingling) especially if profound, static, and occurring for the first time
Migraine auras or other previously experienced neurologic migraine accompaniments lasting longer than 1 hr
Presence of confusion, drowsiness, or loss of consciousness
Headache is triggered by exertion, coughing, bending, or sexual activity
Headache is progressively worsening and/or resistant to treatment
Previously experienced headache characteristics or accompaniments have substantially changed
Persistent or severe vomiting accompanies the headache
Headaches beginning after age of 50 are associated with a higher risk of arteritis or intracranial tumors. Inquire about unexplained weight loss, sweats, fevers, myalgia, arthralgia, and jaw claudication, which are typical accompaniments of giant cell (temporal) arteritis
Headache occurring in a patient with human immunodeficiency virus or cancer
Frequent emergency department or acute care use
Daily or near-daily use of pain relievers or the need to take more than the recommended dosage of pain relievers to control headache symptoms

TABLE 42–3 Indications for Neuroimaging in Headaches

Urgent
Thunderclap headache with neurologic deficit
Headache with altered mental status or seizure
Prior intervention (if reduced intracranial compliance focal defects suspected, meningismus)
Routine
Thunderclap headache without focal neurologic deficit
Change in headache characteristics (severity, side shift, worsening)
Headache accompanied by neurologic deficit or abnormality (disequilibrium, pronator drift, weakness, papilledema)
Headache in immunocompromised patients, cancer patients

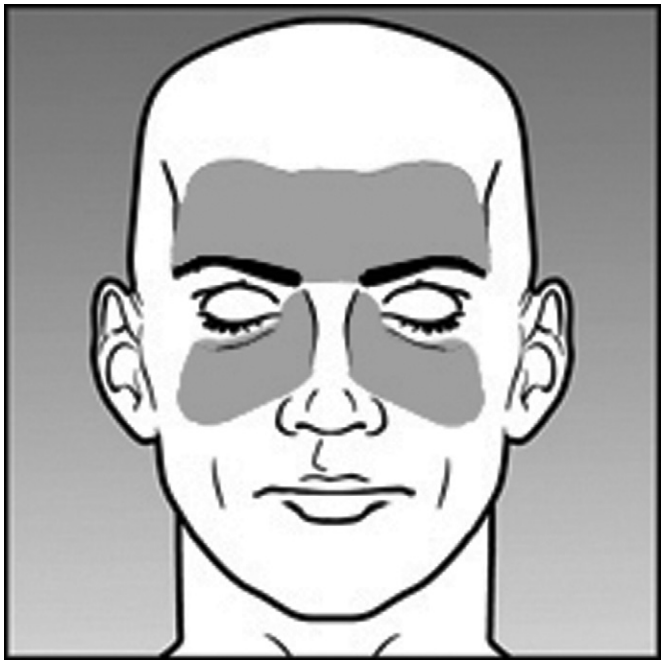

FIGURE 42-1 Paranasal sinus.

RETROPHARYNGEAL TENDONITIS

Retropharyngeal tendonitis (also called longus colli tendonitis) is described as either unilateral or bilateral nonpulsatile pain in the posterior neck radiating to the occiput or entire head accompanied by swollen prevertebral soft tissue measuring more than 7 mm in adults anterior to the upper cervical vertebral bodies. The pain is exacerbated by neck extension, and less commonly with neck rotation and swallowing. The transverse process of the upper three vertebral bodies is tender to palpation. The pain is alleviated within 2 weeks of treatment with anti-inflammatory medications. Imaging studies are needed to rule out carotid dissection and in some cases CT aspiration of amorphous calcific material from the swollen periverterbal tissues.[6]

Acute retropharyngeal tendinitis typically occurs in the third through sixth decade of life and presents as a triad of neck pain, odynophagia, and fever. Treatment is usually conservative and includes NSAIDS or a short course of corticosteroids and it is self-limited in most cases.[7,8]

CRANIOCERVICAL DYSTONIA

Craniocervical dystonia (CCD) is characterized by crampy or "tension-type pain" in the posterior neck radiating to the occiput or entire head accompanied by defective posture of the head or neck due to muscular hyperactivity. The pain is exacerbated by muscle contraction, movement, external pressure, or sustained posture. The pain resolves within 3 months of successful treatment of the underlying muscle hyperactivity. These dystonias include pharyngeal dystonia, spasmodic torticollis, mandibular dystonia, or lingual dystonia.[9]

The prevalence of craniocervical dystonia was estimated to be 1.1 to 6.1 per 100,000 people with an incidence of 1.1 per 100,000 per year.[10,11] Studies on the pathophysiology of CCD suggest functional defects in dopamine signaling.[12] Treatment involves physical therapy, muscle relaxants, and botulinum toxin injections.

HEADACHE ATTRIBUTED TO RHINOSINUSITIS

This is a secondary cause of frontal headache and pain in one or more region of the face, ears, or teeth that is accompanied by clinical, radiographic, endoscopic, or

TABLE 42–4 Secondary Headaches or Facial Pain Attributed to Disorder of Facial and Cranial Structures

ICHD-2	ICD-10	Diagnosis
11	[G44.84]	Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
11.1	[G44.840]	Headache attributed to disorder of cranial bone
11.2	[G44.841]	Headache attributed to disorder of neck
11.2.1	[G44.841]	Cervicogenic headache
11.2.2	[G44.842]	Headache attributed to retropharyngeal tendonitis
11.2.3	[G44.841]	Headache attributed to craniocervical dystonia
11.3	[G44.843]	Headache attributed to disorder of eyes
11.3.1	[G44.843]	Headache attributed to acute glaucoma
11.3.2	[G44.843]	Headache attributed to refractive errors
11.3.3	[G44.843]	Headache attributed to heterophoria or heterotropia (latent or manifest squint)
11.3.4	[G44.843]	Headache attributed to ocular inflammatory disorder
11.4	[G44.844]	Headache attributed to disorder of ears
11.5	[G44.845]	Headache attributed to rhinosinusitis
11.6	[G44.846]	Headache attributed to disorder of teeth, jaws, or related structures
11.7	[G44.846]	Headache or facial pain attributed to temporomandibular joint (TMJ) disorder
11.8	[G44.84]	Headache attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth

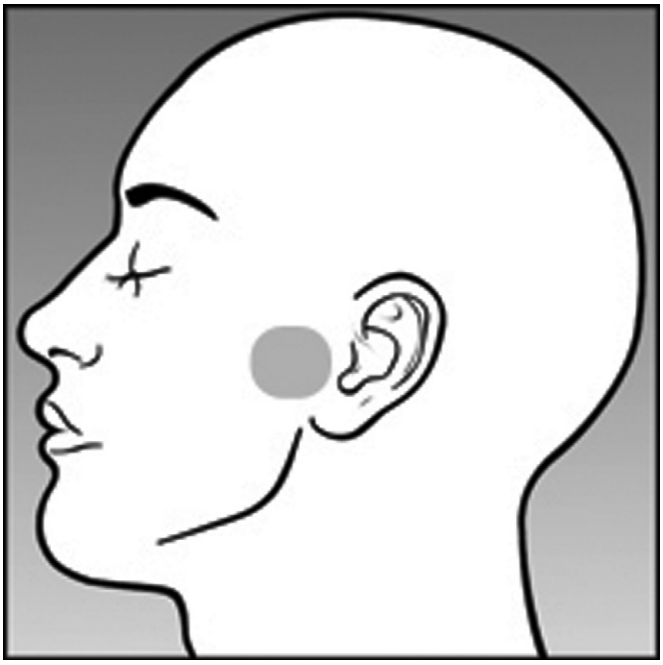

FIGURE 42-2 TM joint articular disorders.

laboratory evidence of acute rhinosinusitis (Fig. 42-2). Clinical causes include purulence within the nasal cavity, nasal obstruction, new onset hyposmia/anosmia, and/or fever. The headache/facial pain onset must be congruent with the acute rhinosinusitis and must resolve within 7 days after remission or successful treatment. Conditions that are not considered as causing this headache include deviated septum, nasal turbinate hypertrophy, and sinus membrane atrophy. Chronic sinusitis is not validated as a cause of headache or facial pain unless there is an underlying acute exacerbation.

HEADACHE ATTRIBUTED TO DISORDER OF TEETH, JAWS, OR RELATED STRUCTURES

Disorders of the teeth, jaws, or related structures typically cause toothache and facial pain, and less commonly headache. Pain from the teeth may be referred and cause diffuse headache, as in periodontitis or pericoronitis as a result of infection or traumatic irritation around the wisdom teeth. The pain is both temporally and structurally related to a disorder of the teeth and/or jaw and is relieved within 3 months of successful treatment of the underlying pathology.

Acute periodontal nociceptive pain is treated with rest (reduced mechanical stimulation), NSAIDs, topical local anesthetics, and analgesics. Chronic periodontal disease is an immune mediated inflammatory process that results in destruction of the teeth and the surrounding anchoring bone.[13]

Typically, intraoral lesions are self-limited and resolve within a few weeks. If symptoms persist, dental or ENT referral is warranted. Some common painful mucosal conditions are listed in the Table 42-5.[14]

TABLE 42–5 Common Intraoral Causes of Oral Pain

Category	Condition
Infections	Herpetic stomatitis
	Varicella zoster
	Candidiasis
	Acute necrotizing gingivostomatitis
Immune/autoimmune	Allergic reactions (toothpaste, mouthwashes, topical medications)
	Erosive lichen planus
	Benign mucous membrane pemphigoid
	Aphthous stomatitis and aphthous lesions
	Erythema multiforme
	Graft-versus-host disease
Traumatic and iatrogenic injuries	Factitial, accidental (burns: chemical, solar, thermal)
	Self-destructive behaviors (rituals, obsessive behaviors)
	Iatrogenic (chemotherapy, radiation)
Neoplasia	Squamous cell carcinoma
	Mucoepidermoid carcinoma
	Adenocystic carcinoma
	Intracranial tumors
Neurologic	Burning mouth syndrome and glossodynia
	Neuralgias
	Postviral neuralgias
	Post-traumatic neuropathies
	Dyskinesias and dystonias
Nutritional and Metabolic	Vitamin deficiencies (B12, folate)
	Mineral deficiencies (iron)
	Diabetic neuropathy
	Malabsorption syndromes
Miscellaneous	Xerostomia, secondary to intrinsic or extrinsic conditions
	Referred pain from esophageal or oropharyngeal malignancy
	Mucositis secondary to esophageal reflux
	Angioedema

Source: Adapted from Mehta NR, Scrivani SJ, Maciewicz R: Dental and facial pain. In Benzon HT, et al, editors: Raj's practical management of pain, *ed 4, Philadelphia, 2008, Mosby/Elsevier, pp 505–528.*

HEADACHE OR FACIAL PAIN ATTRIBUTED TO TEMPOROMANDIBULAR JOINT DISORDER

This is characterized by recurrent pain in one or more regions of the head/face from the temporomandibular joint (TMJ). It is precipitated by jaw movements, chewing, decreased or irregular range of motion, and TMJ tenderness that resolves within 3 months after successful treatment of TMJ disorder. These disorders include disc displacements, osteoarthritis, or joint hypermobility, rheumatoid arthritis, and can be associated with myofascial pain and headache.

The temporomandibular joint is a bicondylar joint that contributes to the important functions of mastication and speech. The joint is unique in that the articular surface is covered by fibrocartilage instead of hyaline cartilage. A fibrocartilaginous disc is located between the condyle and and the articular fossa and separates the joint cavity into the superior ad inferior compartment.[15]

Intracapsular disorders include rheumatoid arthritis, osteoarthritis, and articular disc displacement (Fig. 42-3), while extracapsular disorders include myofascial masticatory pain (Fig. 42-4). Bruxism is hypothesized to contribute to TMJ pain secondary to myofascial strain, tooth attrition, capsulitis, and adhesion formation.

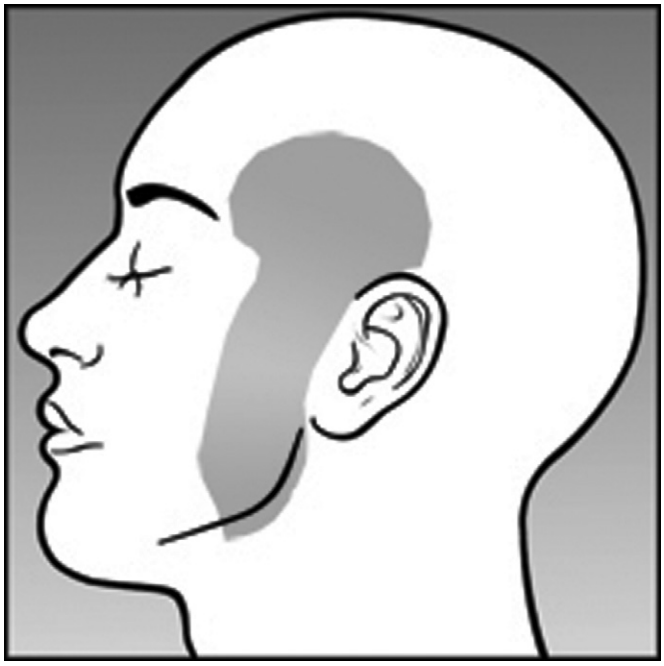

FIGURE 42-3 TM muscle disorders.

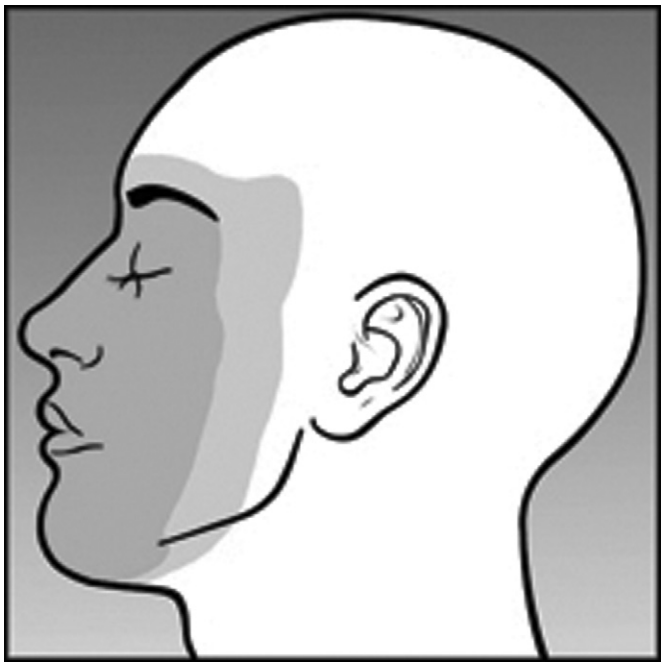

FIGURE 42-4 Trigeminal neuralgia.

Radiographic examination is usually not helpful. However, when severe symptoms persist after failure of conservative management (splints), periapical radiographs, CT, or MRI is warranted. MRI should not dictate therapy, as asymptomatic individuals have evidence of disc displacement.

Treatment includes treatment of any secondary causes such as infection, treatment of somatization component (stress, anxiety), elimination of nocturnal clenching, jaw exercises, and pharmacologic therapy (muscle relaxants, neuropathic pain medications), anti-inflammatory medications). Local anesthetic/steroid and/or botolinum toxin injections may be indicated in selected cases.[16–18] Surgery should be considered in patients who do not respond to conservative treatment if anatomic disruption is noted.[15] The procedures include total and partial meniscectomy, disk repair, lysis of adhesions, lavage, and in rare instances total joint arthroplasty.[15,19] Total TMJ replacement has a poor outcome.

CRANIAL NEURALGIAS AND CENTRAL CAUSES OF FACIAL PAIN AND OTHER HEADACHES

These headache and facial pain disorders are the most recognized causes of severe morbidity, none more so than trigeminal neuralgia. Table 42-6 allows for a coherent approach to the cranial neuralgias, and we will focus on the disorders that can elicit oral and facial pain.

TRIGEMINAL NEURALGIA (TIC DOULOUREUX)

Trigeminal neuralgia is a unilateral pain disorder characterized by brief painful episodes described as is typically classified as intense, sharp, and stabbing within the innervation of the one or more divisions of the trigeminal nerve. The disorder usually starts in the second or third divisions (Fig. 42-4), with the first division affected in less than 5% of the patients (Table 42-7). The right side is more frequently affected, in a 3:2 ratio.[20]

Involvement of the first division hints towards a postinfectious HSV. The duration of the paroxysmal attack can vary from seconds to 2 min and may be precipitated by trivial stimuli from the trigeminal nerve (such as small trigger areas in the nasolabial folds) or by stimuli remote to the trigeminal area, such as other sensory stimulation (i.e., lights, sounds, or tastes). It may occur spontaneously without any identified triggers. If there is a causative lesion identified, outside of vascular compression, then trigeminal neuralgia is secondary, or "symptomatic trigeminal neuralgia." Concomitantly, there is no clinically evident gross neurologic deficit. The pain is usually unilateral, although bilateral presentations have been reported with more central causes like multiple sclerosis. In between attacks, the patient is normally asymptomatic, although some people with longstanding trigeminal neuralgia report a dull background pain. There also appears to be a refractory period, where another attack cannot be elicited.

TABLE 42–6 Secondary Headaches Attributed to Cranial Neuralgias and Central Causes of Facial Pain

ICHD-2	ICD-10	Diagnosis
13	[G44.847, G44.848, or G44.85]	Cranial neuralgias and central causes of facial pain
13.1	[G44.847]	Trigeminal neuralgia
13.1.1	[G44.847]	Classical trigeminal neuralgia
13.1.2	[G44.847]	Symptomatic trigeminal neuralgia
13.2	[G44.847]	Glossopharyngeal neuralgia
13.2.1	[G44.847]	Classical glossopharyngeal neuralgia
13.2.2	[G44.847]	Symptomatic glossopharyngeal neuralgia
13.3	[G44.847]	Nervus intermedius neuralgia
13.4	[G44.847]	Superior laryngeal neuralgia
13.5	[G44.847]	Nasociliary neuralgia
13.6	[G44.847]	Supraorbital neuralgia
13.7	[G44.847]	Other terminal branch neuralgias
13.8	[G44.847]	Occipital neuralgia
13.9	[G44.851]	Neck-tongue syndrome
13.10	[G44.801]	External compression headache
13.11	[G44.802]	Cold-stimulus headache
13.11.1	[G44.8020]	Headache attributed to external application of a cold stimulus
13.11.2	[G44.8021]	Headache attributed to ingestion or inhalation of a cold stimulus
13.12	[G44.848]	Constant pain caused by compression, irritation, or distortion of cranial nerves or upper cervical roots by structural lesions
13.13	[G44.848]	Optic neuritis
13.14	[G44.848]	Ocular diabetic neuropathy
13.15	[G44.881 or G44.847]	Head or facial pain attributed to herpes zoster
13.15.1	[G44.881]	Head or facial pain attributed to acute herpes zoster
13.15.2	[G44.847]	Postherpetic neuralgia
13.16	[G44.850]	Tolosa-Hunt syndrome
13.17	[G43.80]	Ophthalmoplegic "migraine"
13.18	[G44.810 or G44.847]	Central causes of facial pain
13.18.1	[G44.847]	Anesthesia dolorosa
13.18.2	[G44.810]	Central poststroke pain
13.18.3	[G44.847]	Facial pain attributed to multiple sclerosis
13.18.4	[G44.847]	Persistent idiopathic facial pain
13.18.5	[G44.847]	Burning mouth syndrome
13.19	[G44.847]	Other cranial neuralgia or other centrally mediated facial pain

TABLE 42–7 Distribution of Pain in Idiopathic Trigeminal Neuralgia

Trigeminal Division	Prevalence
V1 only	4%
V2 only	17%
V3 only	15%
V1 and V2	14%
V2 and V3	32%
V1, V2, and V3	17%

Source: Adapted with changes from Rozen TD: Trigeminal neuralgia and glossopharyngeal neuralgia. Neurol Clin *22:185–206, 2004.*

The incidence of trigeminal neuralgia is 4 to 13/100,000 people,[20] with approximately 15,000 new cases annually in the United States.[21] Females are 1.5 times more likely to have trigeminal neuralgia then men.

The pathogenesis of trigeminal neuralgia appears to be most commonly caused by compression of the trigeminal root by tortuous or aberrant vessels, as identified by MRI. The trigeminal nerve is the fifth cranial nerve and resides in the Meckel's cavity posterolateral to the cavernous sinus adjacent to the sphenoid bone. Medial to the ganglion in Meckel's cavity is the internal carotid artery, which is located in the posterior portion of the cavernous sinus. The ophthalmic division (V1) courses in the lateral wall of the cavernous sinus and exits via the superior orbital fissure. The maxillary division (V2) exits the skull

base through the foramen rotundum inferolateral to the cavernous sinus. It then enters the pteyrogopalatine fossa. The manibular (V3) component courses along the base of the skull and exits the cranium via the foramen ovale.

Treatment centers on prevention and abortive therapy. There have been few systematic reviews describing treatment approaches.[22–24] Trigeminal neuralgia usually responds to pharmacotherapy and should be employed before interventions are attempted. Generally, after patients fail conservative treatment, young patients with MRI evidence of vascular compression should be considered for microvascular decompression. Elderly patients or those with no evidence of vascular compression may be a candidate for gamma knife or radiofrequency thermoablation. Conservative treatment strategies include antidepressants and antiepileptics. First-line therapy is carbamazepine or oxycarbamazepine, while second-line treatment is baclofen. Other neuropathic pain medications have been trialed in treatment, but there has been no clear evidence for efficacy.[22]

Interventional modes of treatment include decompressive, ablative, and neuromudulatory strategies using surgical and percutaneous routes[22,25–32] (Table 42-8).

GLOSSOPHARYNGEAL NEURALGIA

Glossopharyngeal neuralgia is an uncommon facial pain syndrome characterized by transient severe, sharp, stabbing pain experienced in the ear, base of tongue, tonsillar fossa, or beneath the angle of the jaw. It is unilateral in presentation, lasts for seconds to 2 min, and may be precipitated by swallowing, talking, coughing, chewing, or yawning. The incidence is between 0.2% and 1.3% of trigeminal neuralgia and typically begins after the sixth decade.[20] The pain is transmitted via the auricular and pharyngeal branches of the glossopharyngeal nerve, along with the auricular and pharyngeal branches of the vagus nerve. Approximately 2% of patients lose consciousness during the pain paroxysms. If a causative lesion is identified, then the neuralgia is secondary, and becomes "symptomatic glossopharyngeal neuralgia."[33]

The glossopharyngeal nerve exits the brain stem and descends through the base of the skull through the jugular foramen. It has contributions from the solitary nucleus, the nucleus ambiguous, and the inferior salivatory nucleus. Its branches include the tympanic, stylopharyngeal, tonsillar, carotid sinus, linguinal branches, and communicating branches to the vagus nerve.

Vascular impingement of the nerve roots has been implicated in the pathophysiology of glossopharyegnal neuralgia, commonly microvascular compression by the posterior cerebellar artery.[34] Treatment is primarily conservative medical management with anticonvulsants and analgesics. Refractory cases to conservative management are candidates for surgical or percutaneous treatments, including lesioning and nerve blocks.

NERVUS INTERMEDIUS NEURALGIA (GENICULATE NEURALGIA, RAMSAY-HUNT SYNDROME)

This is a rare disorder characterized by transient bouts of pain in the internal auditory canal, not attributed to any structural lesion, and is intermittent in onset and may last for seconds to minutes. Disorders of salivation, lacrimation, or taste can accompany the pain and are commonly associated with herpes zoster. Typical cases of Ramsay-Hunt Syndrome (RHS) demonstrate the triad of auricular vesicles, ipsilateral facial palsy, and vestibular/cochlear symptoms. Nervus intermedius neuralgia typically occurs after the fifth decade.[34]

The nervus intermedius is part of the facial nerve (cranial nerve VII) and is located between the motor component of the facial nerve and the vestibulocochlear nerve (cranial nerve VIII). It contains sensory branches (external auditory meatus, floor of mouth, and palate, and

TABLE 42–8 Interventional Approaches to Trigeminal Neuralgia

A. Surgical Approaches	
Microvascular decompression (MVD)	The vessels in contact with the trigeminal root entry zone are coagulated or separated from the nerve using an inert sponge.[25]
B. Percutaneous Approaches	
Gamma knife	Stereotactic radiation therapy: high dose of irradiation to a small section of the trigeminal nerve leading to nonselective damage.[26]
Percutaneous balloon microcompression	Pressure-induced ischemia. The technique may be more suitable for treatment of V1 trigeminal neuralgia of the first branch as the corneal reflex tends to remain intact.[27,28]
Percutaneous glycerol rhizolysis	Under fluoroscopy, predetermined volume of glycerol is injected for neurolysis.[29]
Percutaneous radiofrequency thermocoagulation	This is usually considered for the elderly patient who is high risk for surgical MVD. The outcome may be less favorable than MVD, but it is less invasive with lower morbidity and mortality rates.[22]
Pulsed radiofrequency ablation (RFA)	Although it would seem a safer alternative than the commonly used thermal RFA, its efficacy is questioned in a randomized controlled study.[30]
C. Neuromodulation	
Gasserian ganglion	Neuromodulation stimulation was reported either via a subtemporal craniotomy,[31] or a percutaneous approach.[32]

mucosa of nose, and provides taste to the anterior two thirds of tongue,) and parasympathetic fibers (superior salivatory nucleus) of the facial nerve. It joins the motor root of the facial nerve in the facial canal, at the geniculate ganglion.

Conservative treatment involves the use of neuropathic pain medications. The treatment of herpes zoster, if RHS is suspected, or surgical decompression.[35]

SUPERIOR LARYNGEAL NEURALGIA

This is characterized by severe pain paroxysms, lasting seconds to minutes, in the lateral aspect of the throat and submandibular region and underneath the ear, precipitated by swallowing, shouting, or turning of the head. A trigger point is identified along the lateral aspect of the ipsilateral hyoid bone or hyothyroid membrane that is relieved by superior laryngeal nerve block, ablation, and/or resection of the superior laryngeal nerve.

The superior laryngeal nerve is a terminal branch of the vagus nerve (cranial nerve X) and receives sympathetic input from the superior cervical ganglion. It divides into the internal and external superior laryngeal nerve (which innervates the cricothyroid muscle). The recurrent laryngeal nerve innervates all other laryngeal muscles, particularly the abductors, and when damaged can cause vocal cord paralysis (injury results in unilateral adduction of vocal cord) and bilaterally can cause airway obstruction.

NASOCILIARY NEURALGIA (CHARLIN'S NEURALGIA)

This is a transient, lancinating pain in the nostril that radiates to the medial/frontal region. It lasts seconds to hours. It is precipitated by touching the ipsilateral nostril and abolished by blockade of the nasociliary nerve.

The nasociliary nerve is a branch of the ophthalmic nerve (V1) and enters the orbit between the lateral rectus muscles and continues obliquely beneath the superior rectus and superior oblique muscle to the medial wall of the orbital cavity. The terminal branches include the posterior ethmoidal nerve, the long cilliary nerves, the infratrochlear nerve, the communicating branch of the ciliary ganglion, and the anterior ethmoidal nerve.

SUPRAORBITAL NEURALGIA

This pain disorder is characterized by transient or constant pain in the forehead and supraorbital area supplied by the supraorbital nerve (terminal branch of the ophthalmic nerve V1). The pain can be precipitated or reproduced by pressure over the nerve in the supraorbital notch and diagnosis is confirmed by pain relief with local anesthetic blockade.

OTHER TERMINAL BRANCH NEURALGIAS

These causes of facial pain are usually caused by neuritis of the terminal peripheral branches of the trigeminal nerve, exclusive to the nasociliary and supraorbital nerves. Pain is characterized by constant or transient pain in an area innervated by the trigeminal terminal branches. There is tenderness over the affected nerve, which is abolished by local anesthetic blockade. The terminal branches of the trigeminal nerve include the infraorbital, lingual, alveolar, and mental nerves (Fig. 42-5).

OCCIPITAL NEURALGIA

Occipital neuralgia is described as paroxysmal stabbing and sharp pain in the distribution of the greater or lesser occipital nerves or third occipital nerve, sometimes accompanied by paresthesia or dysesthesia or tenderness overlying the nerve that is involved. This is discussed in Chapter 41. The constant pain is caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions.

OPTIC NEURITIS

Optic neuritis is described as pain behind one or both eyes accompanied by central vision impairment due to a central or paracentral scotoma. It is not caused by compressive lesion but is thought to be due to optic nerve (CNII) inflammation. The onset of pain and visual impairment are separated by less than 1 month and the pain is self-limited with resolution within 4 weeks. If pain precedes the visual impairment by more than 4 weeks, then it is classified as "probable optic neuritis." Optic neuritis is often a presenting manifestation of multiple sclerosis.

OCULAR DIABETIC NEUROPATHY

This condition is described as pain around the eye and forehead with paresis of one or more ocular cranial nerves in a patient with diabetes mellitus. Usually the pain is centered on one eye with pain developing over approximately 2 hr. The cranial nerve paresis is most commonly the third cranial nerve (oculomotor) and less commonly, the fourth (trochlear) and sixth (abducens) cranial nerves. The neuropathy typically develops within 7 days of onset of pain and is not attributed to another disorder. It is important to rule out other causes of cranial nerve palsies, including infection, infarction, hemorrhage, or neoplasm. Consequently, appropriate neuroimaging and perhaps biopsy is warranted.

HEAD OR FACIAL PAIN ATTRIBUTED TO HERPES ZOSTER

Head or facial pain can be caused by herpes zoster. The pain usually precedes the herpetic eruption by less than 7 days, and the pain is congruent with herpetic nerve eruption. Typically, pain resolves within 3 months. The herpetic zoster affects the trigeminal nerve in approximately 10% of patients, with the V1 or ophthalmic division most commonly affected (80% of the time) (Fig. 42-6). In contrast, idiopathic trigeminal neuralgia usually affects the V2/3 distribution. Herpetic lesions of the face are not confined to the trigeminal system; it can also involve the geniculate ganglion (causing an eruption near the external auditory meatus). Consequently, ophthalmic herpes can be associated with third, fourth, and

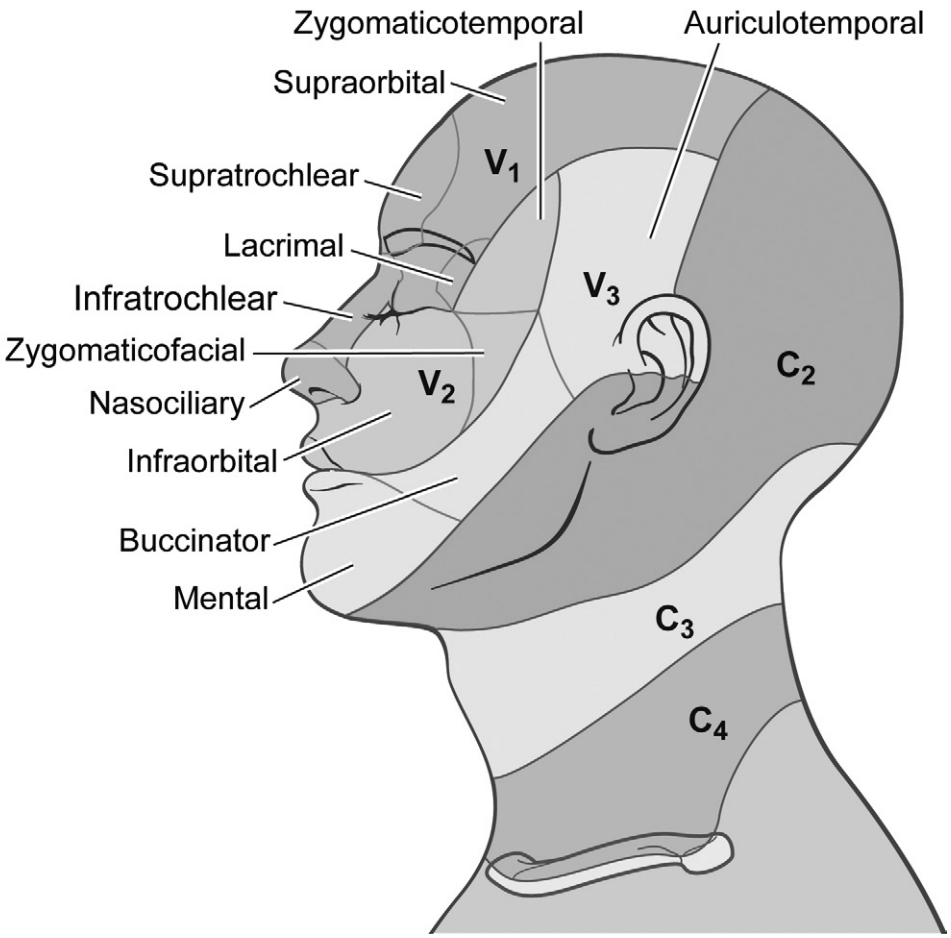

FIGURE 42-5 Dermatomes head and neck lateral.

six cranial nerve palsies. Zoster can be a harbinger for a more insidious disease process, as it occurs in 10% of patients with lymphoma and 25% of patients with Hodgkin's disease.

Postherpetic neuralgia (PHN) is facial pain in the distribution of the affected nerve that persists 3 months after the skin eruptions. Herpes zoster infection increases with age, with an incidence of 3.4/1000 people per year overall, with more than 10/1000 in patients over the age of 65.[36] Similarly, it afflicts 50% of patients who have contracted zoster over the age of 60 years and the incidence continues to increase with advanced age.[37]

The pathophysiology of acute herpes zoster correlates with the replication of varicella zoster virus and spread within the dorsal root or ganglion and along the peripheral sensory nerve. It may disseminate locally to adjacent structures, including the spinal cord. The characteristic dermatomal distribution is related to the anatomical or functional disruption of the nervous system. Necrosis of the dorsal root ganglion, the presence of the virus within the nerve elements, and atrophy of the dorsal horn characterize PHN. The exact underlying mechanism remains unclear despite the identified pathological changes, although deafferentation, adrenergic receptor activation, and reduction in presynaptic inhibition may contribute to central sensitization.[38–40]

Management of herpetic pain includes antiviral medications. The more bioavailable medications valaciclovir and famciclovir are more effective than acyclovir[41] in treating acute herpes zoster. The efficacy of steroid use is equivocal. Neuropathic pain medications include anticonvulsants (gabapentin, pregabalin) and antidepressants (amitriptyline, nortriptyline). Other medications commonly employed include topical agents (lidocaine patch), capsacin, opioids, and NMDA antagonists. Sympathetic blockade (e.g., stellate ganglion blockade) may be helpful specially if performed within the first year.[42] In extreme cases, some patients may resort to surgery, including cordotomy, rhizotomy, sympathetcomy, trigeminal tractomy, mesencepalotomy, retrogasserian rhizotomy, or superfical greater petrosal neurotomy.[43]

TOLOSA-HUNT SYNDROME

This syndrome is characterized by episodic orbital pain with paralysis of one or more of the third, fourth, and sixth cranial nerves that resolves spontaneously. Usually, it has a waxing and waning course. The unilateral orbital pain can persist for weeks if untreated. There may be a granuloma demonstrated radiographically or noted via a biopsy. It is a painful ophthalmoplegia; the pain and paresis occur within 2 weeks of onset and resolve within 72 hr of treatment with corticosteroids. It can also involve divisions of the trigeminal nerve, along with the facial, optic, and acoustic nerves. It is important to carefully exclude other causes of the painful ophthalmoplegia including inflammatory

(vasculitis, sarcoid), infectious (meningitis), and endocrinologic (diabetes mellitus) causes. It may also be due to cancer (pain is due to a mass effect) or to a primary headache (migraine).

CENTRAL CAUSES OF FACIAL PAIN

Central causes of facial pain include anesthesia dolorosa, central poststroke pain, facial pain secondary to multiple sclerosis, persistent idiopathic facial pain, and burning mouth syndrome. The pathophysiology is poorly elucidated; however, two processes have been implicated: neuritis with reduction in nerve threshold for a given painful stimulus or a reduction in inhibition from "loss of inhibition."

Characteristically, the pain complaint can vary significantly. The pain may be cramping, constricting, crushing, or shooting/lancinating in character. There may be a pins and needles sensation or dysethesia. Physical examination may show allodynia. Triggering stimuli include extreme temperatures and emotional distress.

ANESTHESIA DOLOROSA

Anesthesia dolorosa is a painful anesthesia or hypesthesia in the distribution of the trigeminal, or one of its divisions, or occipital nerve. It is caused by a lesion of the relevant nerve or its central connections and is characterized as persistent pain with diminished sensory loss in the distribution of the nerve. It is often related to surgical trauma via rhizotomy or thermocoagulation of the occipital nerve or the trigeminal ganglion. Anesthesia dolorosa was reported in up to 1.6% and 3% of cases after glycerol rhizotomy and radiofrequency rhizotomy, respectively, in the treatment of trigeminal neuralgia.[22,44,45]

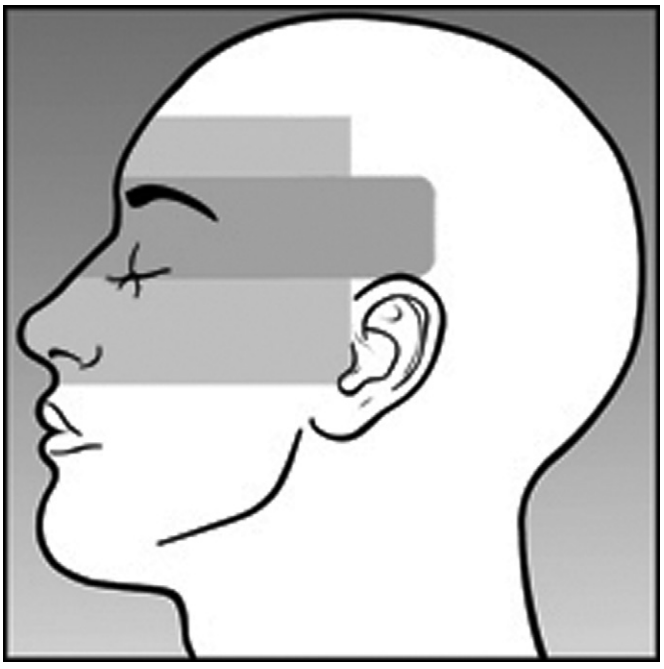

FIGURE 42-6 Acute and postherpetic neuralgia.

CENTRAL POSTSTROKE PAIN

Central poststroke pain is a unilateral pain and dysesthesia associated with loss of sensation to pinprick, touch, and temperature of the ipsilateral face. There is usually a history of symptoms suggestive of stroke, with a lesion demonstrated radiographically. The pain and dysesthesia develop within 6 months after the stroke, is usually persistent, and is usually attributed to a lesion of the trigeminothalamic pathway, thalamus, or thalamocortical projection. It may affect the trunk and limbs on the ipsilateral or contralateral side. Some estimate prevalence of 8% to 11% in patients who have had a stroke.[46]

FACIAL PAIN ATTRIBUTED TO MULTIPLE SCLEROSIS

This is characterized by unilateral or bilateral facial pain with or without an associated dysesthesia attributed to a demyelinating lesion in the pons or trigeminothalamic pathway in patients who have multiple sclerosis. In young people with trigeminal neuralgia and side-switch, one needs to be suspicious of multiple sclerosis. Trigeminal neuralgia occurs in 1% to 2% of patients with multiple sclerosis.[47]

PERSISTENT IDIOPATHIC FACIAL PAIN (ATYPICAL FACE PAIN)

This is facial pain that is present daily and persists for the majority of the day, but does not have features attributed to any of the other cranial neuralgias. It is confined to a poorly defined area of the face and is "deep" in location, not associated with sensory loss or other physical signs. It is not attributed to any other disorder. The pain is commonly in the nasolabial fold or side of the chin and may spread to the upper or lower jaw with a more generalized distribution. It may be triggered by surgery or injury to the face, cheek, and gums. Like ophthalmoplegias, atypical face pain can be a harbinger of a disease. Ipsilateral lung carcinoma can be preceded by referred ear, facial, or temple pain secondary to invasion of the vagus nerve.

Education, counseling, and support are essential components of the management strategy. Few reports suggest a role for sphenopalatine ganglion block and radiofrequency ablation in intractable cases.[48]

BURNING MOUTH SYNDROME

This pain is characterized by an intraoral burning sensation wherein no medical or dental etiology is demonstrated. The mouth pain is daily and persistent for most of the day. Associated symptoms include subjective dryness of the mouth, paresthesia, and altered taste. This condition predominately affects woman, and 30% to 50% of patients improve spontaneously.

CONCLUSION

Oral and facial pain can be an overwhelming complex diagnostic exercise. However, with a careful history, and detailed examination, an appropriate treatment plan can be employed. The etiology and complex interrelationships

affect the clinical presentation, and the need for a multidisciplinary approach, with the appropriate subspecialty referrals, is crucial for successful treatment.

KEY POINTS

- Diagnosis guides management; an algorithmic approach is necessary to treat patients with headache and facial pain. Accurate diagnosis requires knowledge of the ICHD-2 criteria, and stepwise elimination of primary and secondary headaches.
- Red flags in the history and physical examination require further investigation.
- Treatment centers on preventive and abortive strategies. The appropriate timing for interventional treatment needs to be measured against the severity of the impact the pain has on the patient.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 43

Overview of Low Back Pain Disorders

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Pain originating from the spine usually manifests as pain in the low back and neck, and infrequently as pain in the upper lumbar and mid back areas. Spinal pain (SP) can be grouped into three broad categories: acute pain when the pain duration is between 2 to 4 weeks; subacute pain when the pain persists for up to 12 weeks; and chronic pain, when the pain continues for more than 12 weeks. Chronic SP could be further categorized as persistent or recurrent pain.

EPIDEMIOLOGY

Although acute SP is frequently self-limiting, chronic SP is often persistent and recurring in character. Almost 30% of the patients with acute onset low back pain (LBP) will progress to develop chronic LBP that is typically recalcitrant to available treatments.[1,2] This fact is evidenced by the decreased likelihood of return to work with increasing SP duration. The workers who were off work for 6 months with LBP had lifetime return to work rate of only 50%; this rate further dropped to 25% for workers who were off work for 1 year, and to less than 5% for those who were off work for 2 years.[3] Despite the availability of a wide array of treatment choices to SP patients offered by both conventional and other approaches, morbidity from SP has continued to rise sharply, satisfaction among SP patients has remained low, and SP has remained the most prevalent cause of pain and disability in advanced industrialized nations.[1,2] In addition to its chronic unrelenting nature, chronic SP patients are also prone to psychosocial, behavioral, and substance abuse– and disability-related issues. Chronic SP therefore poses substantial challenges to individuals, their families, and the community as a whole.

The epidemiologic studies of chronic SP are approximative by nature, because the conditions causing SP in general are nonhomogenous and are often inadequately defined. The lifetime incidence of LBP is therefore reported variably, ranging from 14% to as high as 90%.[1,2,4] Acute LBP has been ranked as the fifth most common reason for all physician visits; in a given year almost 50% of adults will have LBP.[5] The financial and socioeconomic impact of SP to society is also colossal. For instance, the direct costs of health care for LBP disorders in the United States have been estimated at over $20 billion annually, whereas the indirect cost estimates are even higher, at over $50 billion annually.[6,7] In the United States, LBP has been cited as the most prevalent reason for lost work time, workers' compensation claims, and early social security disability.[8]

RISK FACTORS

The risk factors associated with SP have been classified into three broad categories: biomechanical, psychosocial, and personal. The biomechanical risk factors are determined by spinal loading, and typically include parameters such as physical stress and the asymmetry of physical tasks.[9,10] The psychosocial risk factors pertain to psychogenic stress and are often related to job satisfaction, responsibility, and variety.[11,12] Personal risk factors have been acknowledged as physical, familial, anthropometric, gender, and personality traits.[13,14] The following risk factors have been associated with the development of spinal pain:

- Jobs that are stressful and that require heavy lifting and use of heavy equipment[15]
- Cigarette smoking[16,17]
- Psychiatric, emotional, and personality issues[11,12]
- Obesity[17]
- Spinal deformities and endplate injury[18]
- Genetic predisposition[19]
- Peripheral vascular disease[20]

ANATOMY

The human vertebral column consists of 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 3 to 5 coccygeal vertebrae. Except for the sacral and coccygeal vertebrae, which are normally fused, two adjacent vertebral bodies and an intervening intervertebral disc comprise a vertebral motion segment. The linear array of adjacent spinal motion segments forms the continuum of the spinal column that houses dorsally the neural elements of spinal cord and nerve roots of the cauda equina. The latter are encompassed dorsally and laterally by the neural arch, which is comprised of spinous processes, spinal laminae and the ligamenta flava posteriorly, and pedicles and intervertebral foraminae laterally. In addition to the linkage of the vertebral bodies by intervertebral discs, the adjacent vertebral bodies are articulated dorsally by a pair of synovial joints, the zygapophysial or facet joints. Various components of the spinal column also enable attachment of the omnipotent trunk muscles and spinal ligaments. The most significant of the spinal ligaments include the anterior and posterior longitudinal ligaments and ligamentum flavum. The incredible forces applied to the spinal column are transmitted to the lower extremities by two large synovial-fibrous joints, the sacroiliac joints.

The vertebral bodies are largely composed of cancellous bone housed in a thin layer of cortical bone. The intervertebral discs (IVDs) are made of annulus fibrosus (AF), nucleus pulposus (NP), and vertebral endplates. The distinction between the AF and NP is most apparent at the lumbar levels and diminishes with advancing age. Both the NP and AF are populated by sparsely present cells immersed in abundant intercellular matrix. Cells populating the NP are found in clusters and are chondrocyte-like, whereas the cells found in AF have fibrocytic features.[21] The matrix composition of the two disc compartments is also significantly different. NP matrix is jelly-like, and is made

of high concentration of water and proteoglycans, whereas matrix constituting AF is high in collagen arranged in the form of interlacing lamellae. These collagenous lamellae are firmly attached to the adjacent vertebral bodies and are most dense anteriorly.[21] Although the cancellous vertebral bodies and the spinal canal contents are highly vascular, the IVDs are mostly avascular and the largest avascular structure in the body. The normal NP and inner third of the AF completely lack any vasculature; moreover, the avascular cartilaginous endplates act as a barrier separating the vertebral body vasculature from the IVD contents.[21]

Innervation of the IVDs and the neural canal contents (Fig. 43-1) is mainly by nerve plexuses along the anterior and posterior longitudinal ligaments.[22] The nerve plexus along the posterior longitudinal ligament receives its input mainly from the sinuvertebral nerve and the gray rami communicans, while the plexus along the anterior longitudinal ligament is contributed to mainly by the gray rami communicans.[22] The sinuvertebral nerve originates from the segmental spinal nerve as it exits the intervertebral foramen; it re-enters the vertebral canal and contributes mostly to the posterior longitudinal plexus. In addition to the segmental spinal nerve, the sinuvertebral nerve also receives contribution from the gray rami communicans.[22] The posterior longitudinal ligament plexus innervates the ventral half of the vertebral column, including the anterior dura and posterior intervertebral discs. The gray ramus communicans nerve emerges from the spinal segmental nerve; soon after, it enters the intervertebral foramina and runs anteriorly along the inferior third of the vertebral body. It connects to the sympathetic trunk before branching into lateral and anterior branches to innervate the lateral and anterior disc annulus of the disc levels above and below. The posterior primary ramus, soon after its division from the anterior primary ramus, branches into medial and lateral branches. The medial branch of the posterior primary ramus supplies most dorsal spinal column components, including facet joints, posterior neural arch components, and spinous processes. The AF of the IVD therefore has complex innervation from several sources and multiple spinal segments, including contributions from the sinuvertebral nerves, segmental spinal nerve, gray ramus communicans nerve, and the sympathetic trunk; thus, a normal IVD has rich autonomic connections. The latter may contribute to the hyperalgesia often exhibited by the chronically painful disc. Although almost all components of a spinal motion segment have been implicated in generating pain, the pain receptors—mostly mechanoreceptors—are found mainly in the spinal ligaments, paraspinal muscles, vertebral body periosteum, and the outer third of the AF and facet joints.[21,23]

PATHOPHYSIOLOGY

The forces applied to the spinal column are borne directly and efficiently by the vertebral bodies and the IVDs.[24] The flexibility and remarkable range of motion exhibited by an active spine depend almost entirely on the cumulative plasticity exhibited by the individual IVDs. The individual IVD, however, is only moderately plastic and the NP, like the vertebral body, is practically incompressible due to its high water content. The compressive forces applied to the IVD are borne by the NP and are distributed equally to the AF as a tensile force.[25]

NP incompressibility is maintained almost exclusively by the hydrostatic pressure generated by its proteoglycan

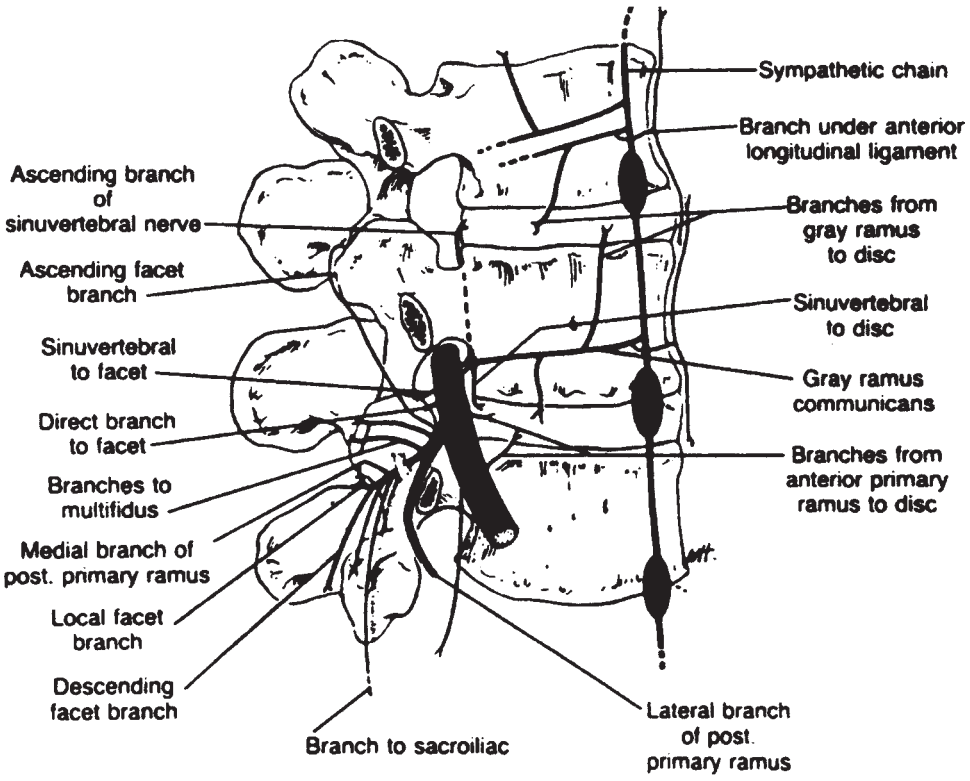

FIGURE 43-1 Segmental innervation of the lumbar spine. *(From Paris SV: Anatomy as related to function and pain. Symposium on Evaluation and Care of Lumbar Spine Problems.* Orthop Clin North Am *14:475–489, 1983.)*

content,[21] which is a function of intricate metabolic processes.[26] Being mostly avascular, IVD obtains metabolic requirements almost exclusively by diffusion from capillary plexuses in adjacent vertebral bodies and the outer AF. Discal catabolic activities are in addition facilitated by discal matrix metalloproteinases (MMPs).[27] A delicate balance therefore exists in the NP between the anabolic activities of the disc cells and the enzymatic catabolic activities. The IVD also lacks scavenger cells and the macromolecular end products of disc metabolism accumulate in the disc over time.[28] This arrangement is at best tenuous and the IVD cells function in a precarious anaerobic environment that can be adversely effected by a host of hereditary and environmental factors.[29] Dysfunction and decline in the viable NP cells,[26] enhanced MMP activity,[30] and increased disc cytokines and proinflammatory mediator concentration[31] can start a vicious cycle that can reduce NP proteoglycan and water content and consequent loss of disc hydrostatic pressure. The ensuing laxity of the NP exposes the AF to direct compressive forces.[25] In addition, the AF cells can undergo degenerative changes similar to those in the NP and result in loss of AF collagen. The cumulative effect of increased AF stress and collagen loss may lead to eventual AF failure with the consequent development of annular tears and fissures.[32]

Structural changes within the IVD alter its biomechanical properties and cause it to shrink and become less plastic. These changes in the IVD dynamics increases stress on adjacent vertebral motion segment and may propagate degenerative changes in several contiguous spinal structures. Some of these changes include sclerosis and hypertrophic new bone formation in adjacent vertebral bodies—Modic changes,[33] accelerated degenerative changes in the adjacent IVDs, hypertrophy and arthritis of the facet joints, sacroiliac joint dysfunction, and paraspinal myofascial syndrome.[34] Hypertrophic changes in the discs, facet joints and ligamenta flava may leads to narrowing of the spinal canal and the intervertebral foraminae. These stenotic changes may cause symptoms from compression of the spinal cord and the spinal nerve roots.[35] However despite the aforementioned, the spinal degenerative changes are commonly seen in asymptomatic individuals and their presence correlate poorly to patients' symptoms.[36,37]

TABLE 43–1 Etiology of Spinal Pain

Mechanical Spinal Pain
Herniated discs
Spondylosis or degenerative disc disease
Discogenic pain, internal disc disruption, or annular tears
Spondylolisthesis or displacement of one vertebral body over the other
Spondylolysis or defect in pars interarticularis without the vertebral slippage
Spinal instability or anomalous movement between the contiguous vertebral bodies
Foraminal stenosis or skeletal hypertrophy causing symptoms of nerve root compression
Spinal canal stenosis or neurogenic claudication or myelopathic symptoms and signs
Facet arthropathy
Musculoligamentous strains or sprains
Myofascial pain syndrome
Congenital spinal conditions such as kyphosis or scoliosis
Nonmechanical Spinal Pain
Primary and metastatic neoplasms of the spine or its neural contents
Infections, such as osteomyelitis of the vertebral bodies, septic discitis, paraspinal or epidural abscess
Noninfectious inflammatory spinal disorders such as ankylosing spondylitis, Reiter's syndrome, psoriatic spondylitis, and inflammatory bowel disease
Traumatic or pathologic fractures such as vertebral body compression fractures and dislocations
Metabolic disorders of the spine such as Paget's disease
Miscellaneous conditions such as Scheuermann's disease or osteochondrosis, and hemangiomas
Referred or Visceral Spinal Pain
Pelvic visceral disorders such as prostatitis, endometriosis, or pelvic inflammatory disease
Renal disease such as nephrolithiasis, pyelonephritis, or perinephric abscess
Vascular disease such as abdominal aortic aneurysm
Gastrointestinal disease such as pancreatitis, cholecystitis, or perforated bowel

ETIOLOGY

The differential diagnosis of SP has conventionally included specific and nonspecific causes (Table 43-1). Specific SP evidently originates from a definite pathophysiologic cause in contrast to nonspecific SP, which lacks a clear etiology. Although approximately 90% of all SP patients have conventionally been branded as having nonspecific SP,[38] this number is probably inexplicably high for diverse reasons. SP could originates not only from a variety of spinal column components such as IVDs, facet joints, paraspinal muscles, ligaments, and the various neural elements, but it can also initiate from adjacent spinal structures such as abdominal or pelvic viscera, sacroiliac and hip joints, and the adjoining neural plexuses. The pathologic conditions afflicting the spine could be widely diverse, ranging from an array of ubiquitously present benign degenerative conditions to rare, but often serious, neoplastic, vascular, infectious, traumatic, metabolic, or compressive lesions. The topographic localization of the spinal pain is often vague, as innervation of various spinal components is characteristically multisegmental, predominantly autonomic, and typically with extensive interneuronal convergence within the spinal cord.[39] The clinical presentation of the various SP syndromes is similar, and they are often present concomitantly, such as frequent simultaneous presence of degenerative disc disease, spinal stenosis, facet arthritis, and sacroiliac joint dysfunction. The range of spinal imaging techniques commonly employed for the diagnosis of SP may show similar abnormalities in symptomatic as well in asymptomatic individuals.[36,37]

In addition to the aforementioned types, SP has also been broadly divided into mechanical, nonmechanical, and visceral pain categories. Mechanical SP is ubiquitous and may be defined as pain emanating from the benign

degenerative conditions afflicting the various spinal structures, such as IVDs, facet joints, and the neural elements, or the immediately adjacent paraspinal structures, such as muscles, ligaments, periosteum and blood vessels. A range of terms has traditionally been used to describe mechanical SP such as lumbago, spondylosis, segmental or somatic dysfunction, ligamentous strain, subluxation, and facet joint, sacroiliac, or myofascial syndromes. The various conditions causing mechanical SP follow:

- Herniated discs
- Spondylosis or degenerative disc disease
- Discogenic pain, internal disc disruption or annular tears
- Spondylolisthesis or displacement of one vertebral body over the other
- Spondylolysis or defect in pars interarticularis without the vertebral slippage
- Spinal instability or anomalous movement between the contiguous vertebral bodies
- Foraminal stenosis or skeletal hypertrophy causing symptoms of nerve root compression
- Spinal canal stenosis or neurogenic claudication or myelopathic symptoms and signs
- Facet arthropathy
- Musculoligamentous strains or sprains
- Myofascial pain syndrome
- Congenital spinal conditions such as kyphosis or scoliosis

Nonmechanical SP is rare and typically has a more sinister etiology. It may result from widely diverse pathologic conditions, such as the following:

- Primary and metastatic neoplasms of the spine or its neural contents
- Infections, such as osteomyelitis of the vertebral bodies, septic discitis, paraspinal, or epidural abscess
- Noninfectious inflammatory spinal disorders such as ankylosing spondylitis, Reiter's syndrome, psoriatic spondylitis, inflammatory bowel disease
- Traumatic or pathologic fractures such as vertebral body compression fractures and dislocations
- Metabolic disorders of the spine such as Paget's disease
- Miscellaneous conditions such as Scheuermann's disease or osteochondrosis and hemangiomas

Visceral or referred SP is pain of extra spinal etiology that is referred to the low back, neck or dorsal spine. Referred SP is also less prevalent than mechanical SP, and can often be distinguished from the SP of other etiologies by the lack of spinal stiffness and the pain-free range of spinal movements. The etiology of visceral SP includes:

- Pelvic visceral disorders such as prostatitis, endometriosis, or pelvic inflammatory disease
- Renal disease such as nephrolithiasis, pyelonephritis, or perinephric abscess
- Vascular disease such as abdominal aortic aneurysm
- Gastrointestinal disease such as pancreatitis, cholecystitis, or perforated bowel

CLINICAL EVALUATION

Despite the diagnostic complexities and the daunting list of causal conditions, the majority of SP is caused by benign self-limiting conditions with symptoms characteristically resolving within 1 to 3 months.[40] A comprehensive history and physical examination are important determinants in the diagnosis of various SP syndromes.

HISTORY

A detailed history of SP patient should note the following (Table 43-2):

- Location and any radiation of pain, especially in the dermatomal distribution
- Characteristics of pain, such as burning, lancinating or aching quality
- Severity of pain; especially noted should be patient's ability to function and sleep at night
- Circumstances of onset of pain such as a history of trauma
- Factors aggravating and relieving the pain
- Patient's age
- Presence of any constitutional symptoms such as fever, malaise, or weight loss
- Special pain features such as night pains, bone pain, morning stiffness, and history of claudication
- Neurologic symptoms such as numbness, tingling, and weakness, along with any bowel or bladder dysfunction, and especially urinary retention and urinary or fecal incontinence
- History of any previous treatments and their efficacy
- Patient's detailed past medical and surgical history
- Assessment of social and psychological factors that may affect patient's pain
- Functional impact of the pain on the patient's work and activities of daily living

TABLE 43–2 Symptom Evaluation of Spinal Pain Patients

Location and any radiation of pain, especially in the dermatomal distribution
Characteristics of pain, such as burning, lancinating, or aching quality
Severity of pain, especially patient's ability to function and to sleep at night
Circumstances of onset of pain such as history of trauma
Factors aggravating and relieving the pain
Patient's age
Presence of any constitutional symptoms such as fever, malaise, or weight loss
Special pain features such as night pains, bone pain, morning stiffness, and history of claudication
Neurologic symptoms such as numbness, tingling, and weakness, along with any bowel or bladder dysfunction; especially urinary retention and urinary or fecal incontinence
History of any previous treatments and their efficacy
Patient's detailed past medical and surgical history
Assessment of social and psychological factors that may affect patient's pain
Functional impact of pain on patient's work and activities of daily living

PHYSICAL EXAMINATION

A comprehensive general physical and a detailed neurologic examination should be performed in all the patients with SP. Specific spinal examination should include:

- Assessment of gait.
- Range of spinal motion.
- Determination of local spinal and paraspinal tenderness.
- Specific tests for the clinical diagnosis of various SP syndromes, including those for nerve root irritation, facet syndrome, and sacroiliac joint dysfunction, are discussed in this book in the various chapters designated to these syndromes.

"RED FLAGS" IN PATIENT'S CLINICAL EVALUATION

Due to the high prevalence of SP, its frequent spontaneous resolution, the rarity of serious spinal disorders, and the frequent presence of abnormal findings in asymptomatic individuals, indiscriminate diagnostic testing for SP disorders would lead to inappropriate diagnosis and poor treatment results.[41] Therefore, in the United States the Agency for Health Care Policy and Research (AHCPR) developed guidelines to recognize clinical features that would signify the presence of conditions such as fractures, tumors, and infections that can pose significant threat to life or neurologic function—"the red flags" (Table 43-3).[41] Recognition of these notable clinical signs is essential as their existence would require further diagnostic testing to either rule out a serious condition or to confirm the presence of a benign diagnosis. However, it is probable that a serious spinal condition may go undetected despite a careful appraisal for these characteristic "red flags." In general, patients with benign mechanical SP should have pain mainly with spinal movements such as sitting, bending, lifting, or twisting, and the pain should improve over the course of few days to weeks. Diagnosis that cannot be confirmed, such as muscle sprain or ligamentous strain, should seldom be used in the presence of the "red flags" as this would further delay the appropriate workup; the latter is frequently the reason for serious spinal conditions being identified late in their course. The characteristic "red flags" follow.

TABLE 43–3 "Red Flags" in Patient's Clinical Evaluation

Age	<20 or >50 years of age
Duration of symptoms	Symptoms over 3 months indicate a less serious etiology
History of trauma	History of significant traumatic injury, or mild trauma in an elderly patient or in a patient with a serious medical condition
Presence of constitutional symptoms	Fever, chills, malaise, night sweats, unexplained weight loss, and so on
Presence of systemic illness	History of cancer, recent bacterial infections, intravenous drug abuse, immunosuppression, organ transplantation, and corticosteroid use
Unrelenting pain	Pain not relieved with rest, supine position, and analgesics
Presence of cauda equina syndrome	Caused by massive midline disc herniation or rarely by spinal metastases, hematoma, epidural abscess, traumatic compression, acute transverse myelitis, and abdominal aortic dissection. Symptoms include bilateral, but often unequal, lower extremity radicular pains and weakness, gait disturbances, abdominal discomfort and overflow incontinence. Physical examination exhibits neurologic dysfunction, saddle anesthesia, diminished anal sphincter tone, and urinary bladder retention. Diagnosis must be made by imaging the entire spine. Treatment is urgent decompressive surgery

Age: Patients less than 20 or over 50 years of age are suspect, as younger patients have a higher incidence of congenital and developmental anomalies, while older patients have a greater likelihood of neoplasms, pathologic fractures, serious infections, and life-threatening extraspinal pathologic conditions.

Duration of symptoms: Symptoms lasting over 3 months indicate a less serious etiology.

History of trauma: History of significant traumatic injury or mild trauma in an elderly patient or in a patient with a serious medical condition may indicate traumatic spinal injury.

Presence of constitutional symptoms: Examples such as a history of fever, chills, malaise, night sweats, and unexplained weight loss indicate a more sinister etiology of SP.

Presence of systemic illness: Patients with a history of cancer, recent bacterial infections, intravenous drug abuse, immunosuppression, organ transplantation, and corticosteroid use are at higher risk for pathologic fractures, epidural and vertebral body abscesses, and metastasis.

Unrelenting pain: Pain of a benign etiology is typically relieved with rest and the supine position, especially at night, while pain from a serious pathologic conditions is typically unrelenting, worse at night, and unresponsive to rest and analgesics.

Presence of cauda equina syndrome (CES): This syndrome is caused by acute compression of the spinal cord or the nerve roots of the cauda equina. CES is characteristically caused by a massive midline IVD herniation or a smaller disc herniation in a previous stenotic spine.[42,43] Rarely, CES may be caused by spinal metastases, hematoma, epidural abscess, traumatic compression, acute transverse myelitis, or abdominal aortic dissection.[44] Typical symptoms include bilateral, but often unequal, lower extremity radicular pains and weakness, gait disturbances, abdominal discomfort from urinary retention, and overflow incontinence. In addition to the positive findings on neurologic examination, the patient's physical examination typically exhibits saddle anesthesia—diminished sensation in the buttocks and perineum—diminished anal sphincter tone, and the evidence of urinary bladder retention. Due to the possibility of spinal cord compression at higher levels, CES must be diagnosed by imaging of the entire spine.[45] CES is one of the rare neurosurgical emergencies that requires urgent decompressive surgery in order to reduce permanent neurologic disability.[44]

DIAGNOSTIC TESTING

As the most commonly used tests for diagnosis of SP syndromes, especially the imaging studies, would reveal abnormal findings in asymptomatic individuals,[36,37,46,47] it is necessary that the imaging findings are corroborated with patient signs and symptoms. The diagnosis is not based solely on the test results. Additionally, as SP conditions are commonly self-limiting and benign, in the absence of "red flags" in the clinical history, diagnostic testing is not recommended for SP of less than 4 to 6 weeks.[41,48] Ordering tests selectively should then prevent inappropriate diagnosis and treatment and thus poor outcomes.[41] In addition to the diagnosis of specific SP syndromes, diagnostic tests are also used to determine the site of surgical or minimally invasive pain intervention. Following are the diagnostic modalities frequently used in the diagnosis of SP.

PLAIN RADIOGRAPHY

Plain radiography allows evaluation of the bony spinal anatomy. It can reliably diagnose pathologic spinal lesions such as fractures, deformities, transitional vertebra, and spondylolisthesis. Subtle spinal abnormalities seen on plain radiography, such as lumbar lordosis, disc space narrowing, arthritic changes, ossification of the vertebral end plates, and abnormal range of spinal movements or spinal instability, are frequently encountered in asymptomatic individuals.[49,50] Spinal radiography therefore exhibits a high rate of abnormal findings in asymptomatic individuals.[47,51] Major drawbacks of plain spinal radiography include its inability to visualize the soft tissue structures and their abnormalities, such as herniated disc, neural element compression, and soft tissue neoplasms. Spinal x-rays may therefore appear normal even in the presence of significant spinal soft tissue pathology. Spinal roentgenograms have traditionally been the earliest imaging test performed in the evaluation of patients with SP, chiefly because they are relatively inexpensive, widely available, and easy to perform. Therefore, although the routine use of spinal radiography has been discouraged,[47,52] in the presence of "red flags" in the clinical history, spinal roentgenograms are often the initial screening tests.

Traditional plain radiography sequences includes anteroposterior (AP), lateral, and oblique views. In the AP view indicators of normal spinal morphology include vertical alignment of the spinous processes, smooth undulating borders created by lateral masses, and uniformity among the disc spaces. Misalignment of the spinous processes suggests a rotational injury such as unilateral facet dislocation. The AP view of the lumbar spine should include the entire pelvis to allow the assessment of acetabulum and femoral heads and the lower portion of the thoracic spine due to the high occurrence of injury between T12 and L2 spinal levels. The lateral views provides a superior image of the vertebral bodies, facet joints, lordotic spinal curvature, disc space height, and spondylolisthesis. Decreased disc space height is a relatively non specific change and may indicate disc degeneration, disc space infection, and postsurgical changes. Oblique views, taken with the x-ray tube angled at (45 degrees), provide enhanced views of the neural foraminae and pars interarticularis. These views best demonstrate foraminal abnormalities and spondylosis. Flexion-extension views are typically used to demonstrate spinal instability as a cause of chronic pain. However, these views can also be used in trauma patients to assess ligamentous injury. When used to diagnosis ligamentous injury, the flexion-extension views should be used exclusively in patients with otherwise normal radiographs and who in addition are neurologically intact, are cooperative, and are able to recognize early onset of pain or neurologic symptoms with spinal movement.

BONE SCINTIGRAPHY

Bone scintigraphy creates images by scanning for the presence of radiographic compounds such as technetium-99m phosphate or gallium-67 citrate. Thus, whereas plain radiography and computerized and magnetic resonance scanning reveals simple morphologic changes, bone scintigraphy detects biochemical osseous processes and is valuable when clinical findings are suspicious of spinal osteomyelitis, neoplasms, or occult fracture. Primary spinal tumors, such as osteoid osteoma, osteoblastoma, aneurysmal bone cyst, and osteochondroma, are typically benign and show as active lesions on bone scintigraphy. Osseous spinal metastases typically appear as multiple foci of increased tracer uptake that are asymmetrically scattered. Occasionally, aggressive bony tumors, such as myeloma, may not invoke an osteoblastic response and may therefore yield a negative bone scan. Also, in occasional extreme cases of spinal metastases diffusely increased tracer uptake may result in a false-negative bone scan. Topographic location of the spinal osseous tumors is also pertinent. Lesions affecting the pedicles are typically malignant, while facet joint lesions are apt to be benign. The vertebral body and spinous process lesions are just as likely to be benign or malignant. Bone scintigraphy with the addition of single-photon emission computed tomography (SPECT) provides a three-dimensional spinal image and enhanced topographic tumor location. SPECT has been used to distinguish benign from malignant osseous neoplasms.[53,54]

COMPUTED TOMOGRAPHY

Computed tomography (CT) uses radiologic data to generate contiguous, overlapping axial images of the scanned area. The imaging data can also be reformatted to construct views in any desired plane. Spinal CT is most useful in evaluating osseous details of the spine in an axial plane particularly the facet joints and the lateral recesses. It is most valuable in diagnosing fractures, tumors involving the spine, and in showing the relative position of one osseous structure to another, such as partial or complete dislocations and spondylolisthesis. The resolution of the soft tissue structures on spinal CT is inferior to magnetic resonance imaging (MRI). Spinal CT cannot reliably distinguish between herniated IVD and epidural scar tissue and amongst various spinal canal lesions such as neoplasms of the spinal cord or the nerve roots. The routine use of spinal CT for the diagnosis of the soft tissue intraspinal canal lesions is therefore discouraged.[55] When combined with myelography (CT myelogram), the results are

comparable to spinal MRI and CT myelogram can be used as a substitute when MRI is contraindicated.[55] One significant limitation of spinal CT is motion artifact, the ensuing indistinct images and the chance of imprecise diagnosis of less distinguishing lesions, such as nondisplaced fractures. Radiation exposure is another significant hazard that limits the extent to which spinal CT can be employed. Spiral CT reduces exposure time, radiation hazard and motion artifact. Three-dimensional CT is a newer modality that provides higher resolution three dimensional images of the spine. This modality is currently being used only for complicated spinal problems such as failed back surgery syndrome.

MAGNETIC RESONANCE IMAGING

The powerful magnetic fields generated in the MRI scanner align the water molecules or protons, constituting the bulk of the body mass, in the direction of the magnetic fields applied. Brief bursts of radiofrequency (RF) waves are then applied and the resulting electromagnetic fields alter the proton alignment. Cessation of the RF field results is the protons decaying to their original state and releasing energy as photons, which are detected by the MRI scanner. The protons in the various tissues return to the equilibrium state at dissimilar rates and an image of various soft tissues is therefore created. By changing timing of the various scanner sequences, like the echo time (T_E) and the repetition time (T_R), the contrast between the various body tissues can be altered. T_2 weighted images use a spin echo (SE) sequence, with long T_E and long T_R intervals, and the water-containing tissues appear, whereas while fat-rich or water-deprived tissues appear dark. T_1 weighted images in contrast use a gradient echo (GRE) sequence, with short T_E and short T_R sequencing, and the tissue contrast on T_1 weighted images is the opposite of the T_2 weighted images. The cerebrospinal fluid appears dark on T_1 weighted images, and it appears white on T_2 weighted images. On T_1 weighted images a normal IVD appears dark and homogenous, whereas it appears brighter on T_2 weighted images—the NP with its greater water content appears brighter than the AF.

Although high quality osseous images can be achieved with spinal CT, MRI is currently considered the gold standard in spinal imaging. MRI provides sharper distinction between the various soft tissues, and the overall soft tissue resolution is superior. MRI offers excellent images of the spinal canal and its neural contents, the neural foraminae and the exiting nerve roots, and the disc spaces and its contents. MRI also allows evaluation of complete spine in various planes. A contrast enhanced MRI can be performed when greater distinction between various soft tissues is required, such as differentiation between scar tissue and recurrent IVD herniation in patients with a history of previous spine surgery. However, in contrast to spinal CT, which uses radiopaque contrast agents such as iodine or barium comprised of higher atomic weight elements than the surrounding tissues, MRI uses contrast agents such as gadolinium and manganese that enhance tissue resolution by their paramagnetic properties. MRI is considered relatively safe with no known biological effects. Limitations of MRI, however, include lengthy examination time, claustrophobia, and its effects on metallic objects. MRI is contraindicated in the presence of ferromagnetic implants, such as cardiac pacemakers, intracranial aneurysm clips, mechanical heart valves, and intraocular foreign bodies. Metallic stabilization devices used in spinal surgery cast artifacts and may render spinal imaging almost unattainable. Like other spinal imaging modalities, spinal MRI may frequently detect findings in asymptomatic individuals.[36,37]

ELECTRODIAGNOSTIC STUDIES

Electrodiagnostic studies encompass the following:

Electromyography (EMG): Study of spontaneous or evoked skeletal muscle electrical activity.
Nerve conduction studies (NCV): Study of conductive abilities of the motor and sensory nerves.
Evoked potentials: Study of brain electrical activity evoked from various nervous system locations, such as somatosensory-evoked potentials (SSEPs) and motor-evoked potentials (MEPs).

The electrodiagnostic studies are useful in localizing the pathologic lesion, determining the extent of the neural injury, predicting the course of recovery, and in determining whether the radiologic abnormalities observed are the likely source of patient's symptoms.[56] These tests are especially useful when the clinical evaluation is inconclusive in distinguishing between radicular and peripheral neuropathic symptoms. EMG or NCVs however provide scant information on the symptom etiology, and the abnormal findings may take several weeks before they are first recognized. The use of SSEPs and MEPs is generally limited to identifying intraoperative nerve injury during spinal surgery. Compared to spinal imaging, the electrodiagnostic studies appear less sensitive; however, they have greater diagnostic specificity.[57]

PSYCHOSOCIAL TESTING

Screening for nonphysical factors is crucial in the management of SP patients. Psychological, occupational, and socioeconomic factors can complicate both the assessment and the treatment of SP patients. For example, patients with work dissatisfaction are at a greater risk for LBP with have poor outcomes.[58] Moreover, patients with affective disorder, such as depression, and those with a history of substance abuse are also more prone to chronic pain disorders. Pending litigation and disability issues also adversely affect SP treatment.

OTHER DIAGNOSTIC TESTS

A variety of other diagnostic and laboratory tests, such as complete blood count (CBC), urine analysis (UA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RH-factor), anti-nuclear antibodies (ANA) and HLA-B27 antigen, are useful when nondegenerative conditions, such as tumors, infections, and rheumatologic disorders, are considered a cause of SP.

MANAGEMENT OF SPINAL DISORDERS

NONINVASIVE TREATMENTS

Following are various noninvasive treatments employed in the treatment of SP (Table 43-4).

Rest

Strict bed rest has traditionally been the mainstay of acute SP treatment. The current evidence, however, suggests that for SP treatment prolonged bed rest is harmful,[59] and bed rest of more than a week is imprudent.[60] Furthermore, the continuation of daily activities and early return to work has been reported to shorten the chronic disability and duration of work absence.[61,62]

Pharmacologic Therapy

- *Nonsteroidal anti-inflammatory drugs (NSAIDs):* These drugs are often considered moderately effective for the short-term relief of acute LBP.[63] Nevertheless, the support for the use of NSAIDs in the treatment of chronic LBP is lacking. Additionally, information as to which specific NSAID is more effective for SP is also lacking.[64]
- *Narcotics:* The short-term use of narcotics may be contemplated for the relief of acute SP. Conversely, a need for prolonged narcotic therapy should prompt reevaluation of patient's motivations and the source of SP. Due to the chronicity of SP, these patients are at an increased risk of developing tolerance and addiction with prolonged narcotic use. These medications should therefore be limited to acute SP and exacerbations of chronic SP.[65]
- *Muscle relaxants:* The use of muscle relaxants has been shown to reduce pain, muscle tension, and immobility in patients with SP.[66]
- *Corticosteroids:* These are often prescribed orally, and often parenterally, in the treatment of acute IVD herniation; nevertheless, there is little evidence in the literature to support this practice.[67,68]
- *Calcitonin:* This drug has been shown to be beneficial for pain ensuing from spinal stenosis caused by Paget disease.[69]

Physical Therapy

Physical therapy and rehabilitation interventions used in the management of SP include the following[70]:

- Body mechanics, ergonomics, posture awareness, and activities of daily living (ADL) training
- Strengthening and stretching exercises
- Organized functional training programs
- Therapeutic massage
- Joint mobilizations and manipulations
- Mechanical traction
- Biofeedback
- Electrical muscle stimulation
- Transcutaneous electrical nerve stimulation (TENS)
- Application of superficial and deep thermal modalities
- Cryotherapy
- Work hardening

TABLE 43–4 Treatments for Spinal Pain

Noninvasive Treatments for Spinal Pain	
Rest	
Pharmacologic therapy	Nonsteroidal anti-inflammatory drugs Narcotics Muscle relaxants Corticosteroids Calcitonin
Physical therapy	Body mechanics, ergonomics, posture awareness, and activities of daily living (ADL) training Strengthening and stretching exercises Organized functional training programs Therapeutic massage Joint mobilizations and manipulations Mechanical traction Biofeedback Electrical muscle stimulation Transcutaneous electrical nerve stimulation (TENS) Application of superficial and deep thermal modalities Cryotherapy Work hardening
Acupuncture	
Spinal manipulation	
Minimally Invasive Treatments for Spinal Pain	
Injection therapy	Epidural steroid injections Facet joint injections Sacroiliac joint injection Trigger pain injections
Neuroablative procedures	Chemical neurolysis Cryoablation Radiofrequency ablation
Intradiscal procedure	Discography Percutaneous disc decompression Intradiscal electrothermal therapy Intradiscal bioculoplasty
Spinal Surgery	
Decompression surgery	Discectomy Microdiscectomy Endoscopic discectomy Decompression for fixed osseous stenosis
Fusion	Anterior fusion Posterior fusion Circumferential fusion Transforaminal lumbar interbody fusion
Disc arthroplasty	SB Charite III ProDisc Maverick Flexcore
Spinal reconstruction	Various techniques

The treatment goals of various physical therapy modalities include:

- Pain relief
- Reduction in muscle spasm
- Improved range of spinal motion (ROM)

- Improved strength
- Postural correction
- Improvement in functional status

Although the precise role of the various physical therapy modalities in the treatment of SP is not fully obvious, the evidence is suggestive of the beneficial effects of general exercise programs. Strengthening exercise programs that target the paraspinal musculature, and general exercise programs that promote weight loss are considered most beneficial in alleviating LBP, promoting return to work, resuming normal daily activities and reducing the need for surgical intervention.[71] There is inadequate evidence that specific back exercises and passive physical therapy techniques such as thermotherapy, therapeutic massage, biofeedback, mechanical traction, therapeutic ultrasound, and TENS produce valuable clinical improvement in patients with SP.[72]

Acupuncture

An analysis of 11 randomized controlled trials (RCTs) on the use of acupuncture in patients with nonspecific LBP led to the following conclusions: (1) overall methodologic quality of the RCTs was low; (2) none of the trials clearly evaluated acupuncture; (3) although moderate evidence existed of the efficacy of acupuncture, it was comparable to trigger-point injection and TENS; (4) evidence on the efficacy of acupuncture was lacking when compared to no treatment; and (5) there was limited evidence that acupuncture was as effective as placebo or sham treatment.[73] The authors of this review recommended against the routine use of acupuncture for the treatment of LBP.[73] Similar conclusions were presented in a comparable review.[74]

Spinal Manipulation

A number of RCTs and several meta-analyses of the use of spinal manipulations for the treatment of both acute and chronic LBP are available.[75–77] Overall, the results of these studies demonstrate that although there may be some advantage of manipulative therapy in the treatment of acute LBP, no statistical or clinical advantage of spinal manipulations over the conventional therapy for the treatment of chronic LBP exists.

Biofeedback Treatments

Biofeedback entails external feedback, which translates physiologic muscle activity (often using EMG) into visual or auditory signals that help the patient reduce muscle tension and pain. There is limited evidence that biofeedback techniques are ineffective for the treatment of chronic LBP, and studies of the use of these techniques in the treatment of acute LBP are lacking.[78]

MINIMALLY INVASIVE TREATMENTS

The minimally invasive treatments for SP (Table 43-4) such as a range of spinal injections (Fig. 43-2), neuroablation techniques, and percutaneous disc procedures are discussed in detail in the sections of this book pertained to the specific pain syndromes.

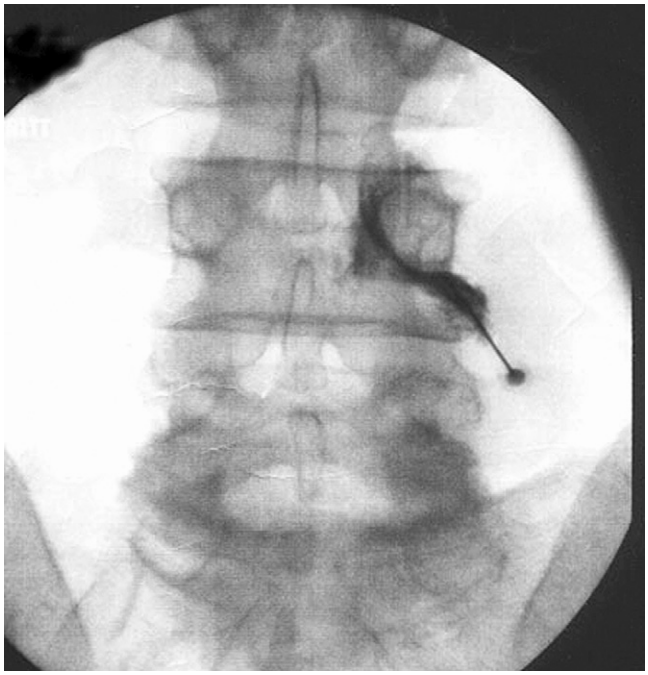

FIGURE 43-2 Fluoroscopic image of right-sided L4–L5 transforaminal steroid injection. Dye injection prior to steroid demonstrating proper position and backflow along L4 nerve root sheath.

SURGICAL TREATMENT

Although a detailed discussion of the various surgical treatments available for SP patients is beyond the scope of this book, an overview is pursued in this section. The majority of surgical treatments intending to relieve SP (Table 43-4) typically incorporate an element of neurologic decompression and/or fusion; more recently, though, disc replacement surgery has been regularly employed.

Spinal Decompression

Disc decompression surgery is typically reserved for patients with a herniated IVD, with distinctive symptoms of persistent radicular pain, positive straight leg raise test, and the imaging studies confirming the presence of herniated IVD. The target for surgical decompression is determined by careful correlation of patient's symptoms and the lesions on the imaging studies. Classical discectomy has been in vogue since Mixter and Barr's classic report in 1934.[79] Classical discectomy has since remained the most commonly performed spinal-surgery procedure to which all other disc surgeries are commonly compared. Popularized in the late 1970s, the microdiscectomy procedure is less invasive and aims to permit faster recovery and early return to work.[80,81] Although the various discectomy techniques differ, the procedure in essence involves laminectomy or laminotomy, release of ligamentum flavum, removal of the herniated disc fragments, and a vertical annulotomy for the removal of nonherniated disc material. More recently, minimal invasive endoscopic discectomy has been performed, which involves limited exposure through an 18-mm tubular retractor (Figure 43-3).

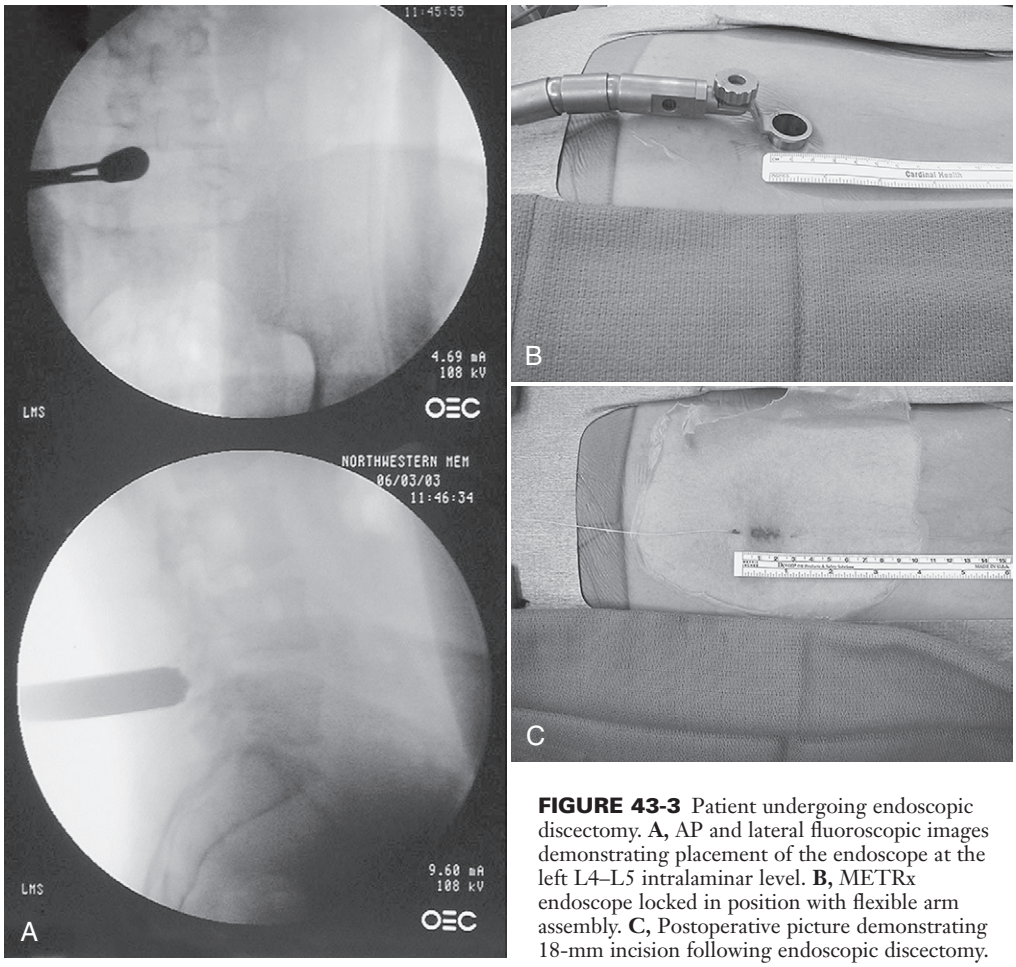

FIGURE 43-3 Patient undergoing endoscopic discectomy. **A,** AP and lateral fluoroscopic images demonstrating placement of the endoscope at the left L4–L5 intralaminar level. **B,** METRx endoscope locked in position with flexible arm assembly. **C,** Postoperative picture demonstrating 18-mm incision following endoscopic discectomy.

In older patients the nerve root compressive symptoms are often the result of local degenerative changes involving the disc, facet joints, and the local ligaments. Such changes may include disc bulges and herniations, facet and ligamentous hypertrophy, osteochondral spurs, and spondylolisthesis. Surgical decompression for these patients characteristically involves osseous decompression of the neural foraminae, central canal, and the lateral recess. In many such cases, especially in the presence of spondylolisthesis and when greater than 50% of the facet joints are resected, a fusion procedure may needed in addition to avoid the ensuing spinal instability.

Spinal Fusion

Although spinal fusion surgery has been performed for the past 100 years, it has been particularly popular in recent years. Common indications, for spinal fusion surgery include ensuing instability after decompressive spinal surgery and diverse causes of mechanical SP such as spondylolysis, spondylolisthesis, degenerative arthritis, spinal instability, discogenic pain and scoliosis. During the spinal fusion surgery the dysfunctional spinal motion segments—including the incriminating disc and the painful degenerative joints—may be resected and the spine is characteristically rigidly stabilized by using various mechanical fusion devices such as pedicular screws, interpedicular fixation plates, and intervertebral spacers such as cylindrical cages (Figure 43-4). Mechanical spinal instrumentation, however, is subject to fatigue failure and eventual fracture unless osseous spinal fusion is attained by osteogenesis, classically by the use of bone graft in the vascularized tissue bed. The key elements required for spinal osteogenesis include precursor cells capable of transformation into bone-forming osteoblasts, osteoconductive materials that would serve as scaffolds for the formation of new bone, and osteoinductive growth factors that will promote differentiation of progenitor cells into osteoblasts.[82] Autologous bone graft remains the gold standard osteogenetic material because it contains all three essential elements. Limitations of autologous bone graft, however, include the amount of available graft material and the morbidity associated with harvesting autologous bone graft. These limitations have led to the use of other osteogenetic materials including bone graft extenders—demineralized bone matrix, calcium carbonate, hydroxyapatite-tricalcium phosphate, bone graft substitutes, and, more recently, osteoinductive substitutes, such as recombinant human bone morphogenic protein (BMP).[83] Spinal fusion can be performed by either posterior, posterolateral, anterior, or combined circumferential (360°) approach. More recently, a transforaminal lumbar interbody fusion (TLIF) technique is used, which provides the

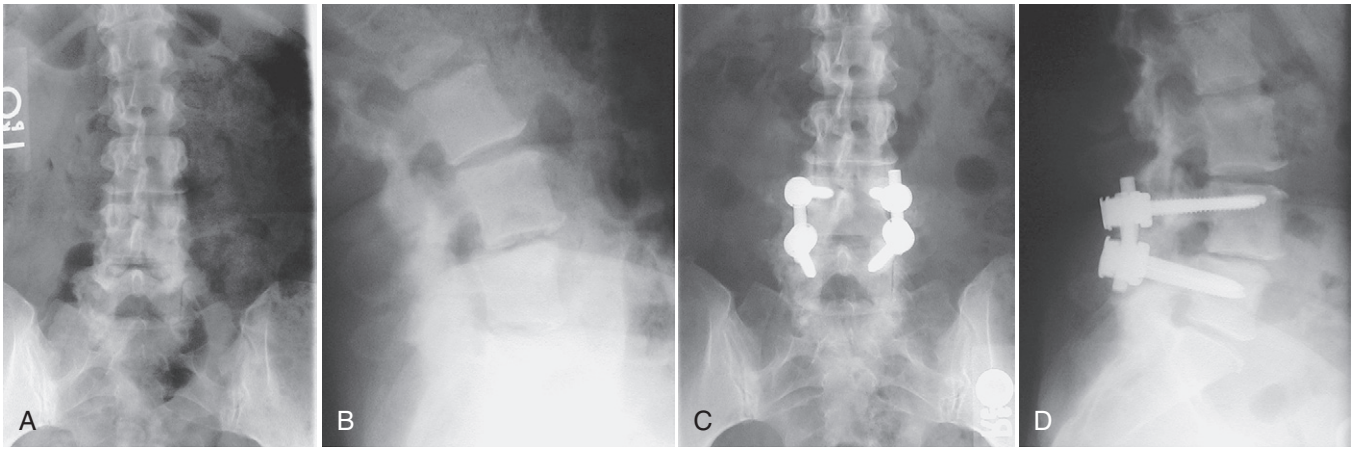

FIGURE 43-4 **A,** AP and, **B,** lateral lumbar spine radiographs demonstrating Grade 1 spondylolisthesis in a 47-year-old woman with disabling back and leg pain refractory to nonoperative treatment. **C, D,** Postoperative radiographs demonstrating stable fusion 1 year following posterior decompression and fusion with supplemental instrumentation. Note the robust fusion mass bridging transverse processes laterally. The patient is pain free and has returned to full level of activity including triathlons and skiing.

advantages of a circumferential fusion through a lower-risk posterior approach.[84] The actual fusion rates after fusion surgery vary from 80% for posterolateral fusions to 97% for circumferential fusions.[85] The results of the spinal fusion surgery vary vastly depending on the condition for which the surgery is performed. When performed for spinal deformities and spondylolisthesis, the results reported are generally favorable.[86,87] However, treatment of degenerative disc disease and discogenic pain with spinal fusion has remained controversial and the reported success is modest.[88] Patients with discogenic pain tend to have greater clinical benefits when the incriminating disc is removed.

Disc Arthroplasty

Despite its popularity, spinal fusion surgery remains a salvage procedure, as it reduces spinal mobility and increases stress and consequently degeneration at adjacent spinal levels. The concept of disc arthroplasty was envisaged to avert these shortcomings of spinal fusion surgery. During disc arthroplasty the offending disc is surgically removed and replaced by an artificial disc. When compared to spinal fusion, the major benefit of disc replacement surgery include preservation of spinal range of motion and decreased adjacent spinal segment degeneration. The primary indication for disc arthroplasty is recalcitrant disabling LBP secondary to discogenic disc disease, which is confirmed by MRI and discography. The exclusion criteria include evidence of nerve root compression, facet, and sacroiliac joint arthropathy. In contrast to the prolonged rehabilitation that typically follows spinal fusion surgery early and progressive spinal motion and functional recovery is characteristically encouraged after disc arthroplasty.

Although disc replacement surgery has been advocated since the 1950s, it was not until the early 1980s that a viable design with encouraging results was introduced. Several types of artificial discs are currently marketed; these include SB Charite III, ProDisc, Maverick, and Flexcore. The Link SB Charite III is currently the most commonly used prosthesis. It consists of two cobalt-chrome endplates, with a sliding polyethylene core. The endplates are anchored to the vertebral bodies by teeth and later by the bony in-growth. The biomechanical studies of artificial disc replacement demonstrate increased range of motion in flexion, extension, and torsion, whereas relative immobility was seen in lateral bending. Although the initial clinical results of artificial disc replacement are encouraging, this technique remains largely untried.[89]

Spinal Reconstruction

Spinal reconstruction is contemplated when the disease progression either destroys the structural integrity of the spine or produces deformity that alters its normal biomechanics. Conditions requiring spinal reconstruction surgery may include traumatic spine injuries, spinal infections and tumors, and spinal deformities such as scoliosis and kyphosis. More recently adverse consequences of failed prior spinal surgery are a major cause of spinal reconstruction surgery. The principles of spinal reconstruction surgery include resection of diseased tissues, soft tissue, and bony release to allow spinal realignment and rigid fixation to maintain spinal stability until the biologic fusion is achieved. Proper spinal realignment must restore the physiologic lumbar lordosis and thoracic kyphosis. An appropriate graft or implant length must be selected to maintain this sagittal balance. Spinal reconstruction typically involves anterior release in the form of vertebral body (corpectomy) and disc (discectomy) resection and posterior release that incorporates chevron osteotomies.[90] In severe cases of spinal scoliosis the rib cage itself may become ankylosed and may require release in the form of rib head resections, rib osteotomy, and pedicle subtraction osteotomy.[91,92] Once the spinal segment is appropriately realigned it must be rigidly fixed to maintain the alignment, until the successful osseous fusion is achieved (Fig. 43-5). The various currently used instrumentation systems include pedicle screws connected by rods, hooks, and sublaminar cables.

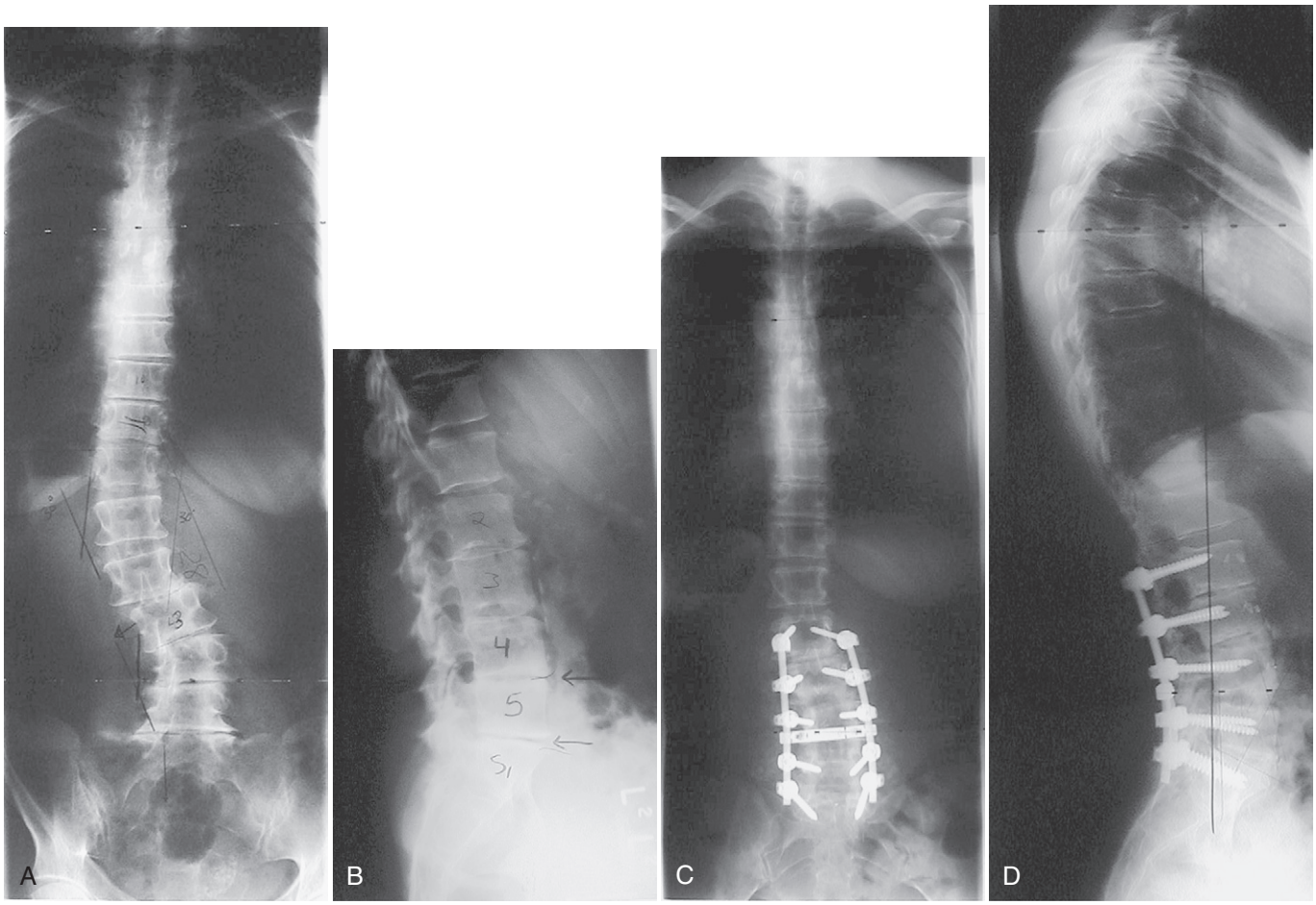

FIGURE 43-5 A 64-year-old woman with degenerative scoliosis and disabling low back and radicular leg pain. **A,** AP radiograph demonstrates severe lateral listhesis at L2–L3 and L3–L4 resulting in symptomatic compressive neuropathy. **B,** Lateral radiograph demonstrating severe disc degeneration and consequent loss of lumbar lordosis. She was treated with anterior–posterior fusion, instrumentation, and decompression. **C,** AP radiograph demonstrates correction of lateral listhesis and tilt. **D,** Lateral film shows excellent restoration of lumbar lordosis with structural interbody allograft.

CONCLUSION

Patients with SP frequently have pain emanating from multiple co-existing pain generators; the diagnosis of a specific pain syndrome consequently is often uncertain. In addition, with their propensity to show positive results in asymptomatic individuals and relatively unimposing findings in many patients with SP, the available diagnostic tests are frequently unable to precisely diagnose the basis of patient's pain and therefore the target for various treatments. This situation is further aggravated by the fact that the available treatments for SP are not universally effective. It is therefore not surprising that due to the frequent lack of adequate explanation for their symptoms and poor treatment results, chronic SP patients are often resentful towards the care they have received and may develop in addition a variety of behavioral, substance abuse, disability, and other psychosocial issues. To avoid these predicaments, it is vital that patients with chronic SP clearly understand the nature of their spinal disorder, develop reasonable expectations from their treatments and care providers, and have realistic outlook for their quality of life.

Because acute SP frequently has a favorable natural history, in the absence of progressive neurologic deficits or "red flags," expectant and symptomatic treatment may be sufficient. This may include a short period of rest and analgesics and early return to function and normal activities. On the contrary, due to its persistent and recurrent nature and with often accompanying psychosocial issues, chronic SP may best be treated by adopting a multidisciplinary approach with addition of psychosocial, rehabilitative, and functional restoration. An exercise program may be introduced in all patients to minimize the risk of recurrent SP. Furthermore, SP patients should be educated in their role for preventing spinal injury and in reducing their ongoing pain. Some of these general preventative instructions may include measures as simple as assuming appropriate posture for sitting, driving, and lifting; attempts to lose weight; smoking cessation; and adopting a healthy lifestyle.

Because the invasive spinal procedures are often associated with significant risks and can be exorbitantly expensive, the potential risks of these procedures must be carefully weighed against any potential benefits. Due to the self-limiting nature of many painful spinal conditions, the invasive spinal procedures are best suited for the small group of patients who have failed to improve with more conservative treatments. Despite an ever-growing array of invasive

treatment options available, each patient must be uniquely and thoroughly evaluated before a specific treatment option is recommended. Flagrant and improper use of the various invasive spinal procedures exposes SP patients to unnecessary risks at an extreme cost to the individual patient and the society as a whole.[93]

KEY POINTS

- Spinal pain is prevalent in general population, and it is considered the most common reason for lost work time, workers' compensation claims, and early social security disability.
- Acute spinal pain is typically self-limiting, whereas chronic spinal pain could often be persistent, recurring, and frequently associated with psychosocial, behavioral, and substance abuse– and disability-related issues.
- Intervertebral disc cells function in a precarious anaerobic environment that can be adversely affected by a host of hereditary and environmental factors.
- The structural changes within the disc could change the disc dynamics that may lead to degenerative changes within the spinal motion segment and the contiguous spinal structures.
- The origin of spinal pain is versatile and it can originate from a range of spinal column components and from structures adjacent to the spine.
- The innervation of the various spinal components is complex and the topographic localization of the spinal pain is often vague.
- The ubiquitous nonspecific or mechanical spinal pain caused by benign degenerative conditions must be differentiated from a wide range of other uncommon but often perilous pathologic conditions.
- The diagnosis of the various spinal pain syndromes is often made arduous by the lack of specific diagnostic tests.
- Due to its high prevalence and frequent spontaneous resolution, spinal pain should be further appraised only when red flags are present in the clinical evaluation of a spinal pain patient.
- In the absence of progressive neurologic deficits or the red flags, acute spinal pain should be treated symptomatically, whereas chronic spinal pain is best treated by implementing a multidisciplinary approach.
- Invasive spinal procedures are best suited for a small group of patients with unrelenting chronic spinal pain who have failed to improve with conservative treatments.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 44

Interlaminar Epidural Steroid Injections for Lumbosacral Radicular Pain

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Injections of epidural steroids have been used for more than 40 years, and their history has been reviewed in detail elsewhere.[1–6] Use of caudal steroid injections to treat sciatica in the United States was first reported by Goebert and colleagues. They reported improvement in 66% of 113 patients with sciatica given caudal epidural hydrocortisone in a prospective study.[7] Numerous other publications subsequently appeared describing the results of epidural steroid injections (ESIs). The practice of lumbar ESI, performed near the level of nerve root involvement with smaller volumes of diluent, was advocated by Winnie et al. in 1972.[8] Hickey observed progressive increase in the number of responders to a series of three ESIs given every 2 weeks, with much greater improvements after the second and third ESI, supporting a common pattern of clinical practice.[9] The use of cervical ESI was initially summarized in three separate reports in 1986.[10–12] More precisely targeted ESI techniques have included insertion of fluoroscopically guided caudal catheters and transforaminal approaches to the lateral and anterior epidural space. Transforaminal ESI techniques are discussed in another chapter. Controversies about indications for ESI, efficacy, safety, ideal route of administration, and benefit of fluoroscopic guidance continue.[13]

THE INFLAMMATORY MODEL FOR BACK PAIN AND RADICULAR PAIN

Most back pain seen in the primary care setting is largely due to muscular and ligamentous strain and spasm. In a secondary referral setting, more complex, severe, and chronic pain is seen. This sort of back pain may arise from the facet joint and the paraspinal muscles in the dorsal compartment, which is innervated by the medial and lateral branches of the dorsal rami. Back pain may also arise from the anterior and posterior longitudinal ligaments and the annulus of the disc in the ventral compartment, which is innervated by the sympathetic chain and the sinuvertebral nerves. Mechanical back pain is primarily somatic pain. An annular tear may lead to continued leakage of nucleus pulposus material and associated chronic inflammation and altered central processing. Radicular pain results from chemical irritation and inflammation of the nerve root, which may be swollen and edematous. When McCarron et al.[14] injected autologous nucleus pulposus material into the epidural space of dogs, they demonstrated intense inflammatory changes of the spinal cord and nerve roots as well as fibrosis of the dura and epidural fat. The inflammatory model of radicular pain is further supported by several basic science studies. Injection of nucleus pulposus material in an animal model resulted in attraction of leukocytes, thrombus formation, and increased vascular permeability.[15] Disc herniation (HNP) results in release of large amounts of phospholipase A2 (PLA2),[16] which favors production of prostaglandins[17] and leukotrienes from cell membrane phospholipids, and resultant inflammation, sensitization of nerve endings, and pain generation. Elevated levels of leukotriene B4 and thromboxane B2, products of PLA2 activity, were measured in biopsies of patients operated on for lumbar disc herniation.[18] The levels of inflammatory mediators observed varied with the type of disc herniation, being highest with noncontained HNP. External pressure on nerve roots by bone can result in venous obstruction, neural edema,[19] and eventual fibrosis of the nerve and surrounding tissues. Nerve root edema has been observed surgically and demonstrated with computed tomographic scanning in patients with herniated discs.[20,21] Surgical disc samples from patients with disc herniation contain extremely high levels of PLA2.[16] This enzyme liberates arachidonic acid from cell membranes. Degenerative disc disease and tears of the annulus fibrosus may result in leakage of this enzyme from the nucleus pulposus, producing chemical irritation of the nerve roots. The primary indication for ESI is radicular pain due to nerve root inflammation, irritation, and edema.

DRUGS USED FOR EPIDURAL INJECTION

The most well-studied steroids used in ESIs are methylprednisolone acetate and triamcinolone diacetate. The concentration of both is typically 40 to 80 mg/ml; the most common therapeutic dose range is 40 to 80 mg. No study has compared the effectiveness of these two agents, and both have been reported to be effective, safe, and long acting. Steroid drugs are often diluted with normal saline or local anesthetic with equivalent results. The volume of injectate varies greatly with the site of injection. The injection of 3 to 5 ml has been used in the lumbosacral epidural space. These volumes bathe both the injured nerve root that is adjacent to the disc pathology and additional nearby roots that are also inflamed,[20] while others have suggested limiting volume to focus on same-level disease. In the less capacitant cervical space, 2 to 4 ml should be adequate to bathe the cervical roots at several levels. When the caudal route is selected, a larger volume (approximately 10–15 ml) is used to ensure adequate spread of injectate to the midlumbar level.

MECHANISM OF ACTION

Olmarker and colleagues[22] observed abnormal nerve conduction and nerve fiber degeneration after epidural application of autologous nucleus pulposus in pigs, which

was significantly reduced by intravenous administration of methylprednisolone. Lee et al.[23] studied the effect of loosely ligating lumbar nerve roots on the subsequent development of thermal hyperalgesia and elevated PLA_2 levels in rats. Epidural injection of betamethasone, compared to saline, accelerated the reduction in PLA_2 activity and the recovery from thermal hyperalgesia in this model.

Steroids induce synthesis of a PLA_2 inhibitor, preventing release of substrate for prostaglandin synthesis. Steroids inhibit the inflammatory process at an earlier step than systemic, nonsteroidal anti-inflammatory drugs (NSAIDs). This may benefit the many patients with a chemical rather than a compressive radicular pain syndrome and negative radiologic studies. Steroids may also decrease back pain due to inflammation and sensitization of nerve fibers in the posterior longitudinal ligament and annulus fibrosus.[6]

In addition to their anti-inflammatory effect, steroids also block nociceptive input. Corticosteroids suppress ongoing discharge in chronic neuromas and prevent the development of ectopic neural discharges from experimental neuromas.[24] This suppression of neural discharge has been attributed to a direct membrane stabilizing action of the steroid. Local application of methylprednisolone acetate was found to reversibly block transmission in C fibers but not in αfibers.[25]

INDICATIONS

Many authors have attempted to identify which patients are most likely to benefit from ESI. White and colleagues[26] observed how 304 patients responded to ESI and correlated these findings with the cause of their back pain. Response to ESI was predicted by nerve root irritation, recent onset of symptoms, and the absence of psychopathology. ESI was therapeutic for patients with herniated disc and either nerve root irritation or compression. These latter two factors were also associated with efficacy in patients with spondylolisthesis or scoliosis. Relief was transient in patients with chronic lumbar degenerative disc disease or spinal stenosis. Many other studies have reported efficacy for patients with radicular pain syndromes or herniated nucleus pulposus. In a review, Benzon[20] summarized the questionable benefit of ESI in patients with chronic low back pain, degenerative bony pathology, or previous back surgery.

Hacobian and associates[27] retrospectively evaluated 50 patients with lumbar spinal stenosis, back pain, or pseudoclaudication who were treated with one to three ESIs. Initial results included complete relief in 8%, partial relief in 52%, and failure in 40%. The duration of pain relief was longer than 6 months in 26%, 1 to 6 months in 33%, and less than 1 month in 40%. Overall, 60% of these patients improved, but only 15% had a prolonged response. Ciocon et al.[28] reported significant pain relief in 30 elderly patients with lumbar spinal stenosis and leg discomfort, treated with three caudal ESIs at weekly intervals and followed every 2 months for 10 months. There were significant decreases in the Roland Morris's 5-point pain-rating scale at each time interval, but this was the only outcome measure used. Patients with severe spondylo listhesis or herniated disc were excluded. In a randomized controlled trial (RCT), Fukusaki et al.[29] studied the effect of lumbar ESI on patients with degenerative spinal stenosis and neurogenic claudication, severe enough to limit ambulation to less than 20 minutes. The clinical response was similar to that seen by Hacobian et al.,[27] and ESI had no beneficial effect on ambulation when compared to epidural local anesthetic alone.

Three studies have investigated predictors of response to lumbar ESI. Abram and Hopwood[30] prospectively investigated factors contributing to treatment success in 212 patients. Three factors were strongly associated with favorable response to injection: (1) advanced educational background, (2) a primary diagnosis of radiculopathy, and (3) pain duration of less than 6 months. Three factors that correlated with treatment failure were (1) constant pain, (2) frequent sleep disruption, and (3) being unemployed due to pain. Subsequently, Hopwood and Abram[31] analyzed factors associated with failure of ESI in 209 patients. There was a threefold increase in treatment failure with prolonged pain of more than 24 months' duration and with nonradicular diagnosis. A twofold increase in poor outcome was related to lack of employment because of pain, smoking, and symptom duration of 6 to 24 months.

Sandrock and Warfield[32] suggest that the five most important factors influencing the outcome of ESI are accuracy of the diagnosis of nerve root inflammation, shorter duration of symptoms, no history of previous surgery, younger age of the patient, and location of the needle at the level of pathology. Bosscher[6] recently summarized four selection criteria for ESI: an intention to produce short-term pain relief during physical therapy/rehabilitation; evidence of nerve root involvement; unfavorable response to 4 weeks of conservative therapy; and no contraindications to injection. Patients with radicular pain should fit into one of these categories: sensory signs and symptoms of radiculopathy, disc herniation, tumor infiltration of nerve root, postural back pain with radicular symptoms, or acute back pain and radicular symptoms superimposed on more chronic back pain.[6]

EFFICACY

The extensive literature on the efficacy of ESIs leaves much to be desired. Most studies were purely anecdotal, retrospective, and not randomized, controlled, or blinded. Patient populations were poorly defined and not homogeneous: patients who were studied had both acute and chronic pain, some had back surgery, and their back pain was secondary to various causes. Finally, treatment protocols were variable, outcome criteria were not well established, measurement tools were inadequate, and timing of follow-up observations was not standard.

Investigators who reviewed the literature came to different conclusions. Although Kepes and Duncalf[1] concluded that the rationale of ESI was not proved, Benzon[2] noted it to be effective in acute lumbosacral radiculopathy. Review articles on the subject also were not in complete agreement. Spaccarelli[33] concluded that ESI was efficacious in lower-extremity radicular pain syndromes at

intermediate-term follow-up (2 weeks to 3 months), but that no difference could be expected at long-term follow-up. Koes and associates[34] found no suggestion of efficacy for ESI in patients with chronic low back pain without sciatica. However, they stated that 6 of 12 studies showed ESI to be more effective than the control treatment for patients with sciatica, while the other 6 showed it to be no better and no worse than the reference treatment. They concluded that the efficacy of ESI has not been established. This does not contradict the earlier conclusions of Benzon[2] that ESI may be effective in patients with acute lumbosacral radiculopathy.

A consistent verdict on treatment efficacy has not been supported by the available controlled studies. An additional analysis of this literature was published by Watts and Silagy.[35] Efficacy was defined as pain relief (at least 75% improvement) in the short term (60 days) and in the long term (1 year). ESI increased the odds ratio of pain relief to 2.61 in the short term and to 1.87 for the long-term relief of pain. Efficacy was independent of the route of administration (i.e., caudal or lumbar). This analysis provided quantitative evidence that the epidural corticosteroids are effective in the management of lumbosacral radicular pain when injected by either the lumbar or the caudal route.

There have been three prospective, randomized, double-blind, placebo-controlled studies of patients with documented herniated disc and pain present for less than 1 year who received lumbar ESI (Table 44-1). Dilke and associates[36] showed significantly better pain relief and better rates of return to work with ESI than with interspinous ligament saline injections at 3 months' follow-up. Snoek and colleagues[37] reported greater subjective and objective improvements after ESI compared with placebo injection, but this difference did not reach statistical significance. Their study used undiluted steroid in a 2-ml volume and evaluated patients after 24 to 48 hr (compared with 6 days in the study by Dilke and colleagues[36]). The minimum time interval for initial evaluation of response approaches 1 week. This can be derived from the observations of Green et al.[38] on the response to ESI: 37% experienced relief within 2 days, while 59% responded only after 4 to 6 days. Carette and coworkers[39] administered ESI up to three times and found that the differences in improvement between groups were not significant, except for improvements in the finger-to-floor distance ($p = 0.03$) and in sensory deficits at 3 weeks, and in leg pain at 6 weeks. These improvements were observed in the methylprednisolone group at 3 weeks and 6 weeks, but there were no significant differences after 3 months. ESI did not offer significant functional benefit, nor did it reduce the need for surgery in about 25% these patients within 12 months. Hopwood and Manning[40] criticized this study for selection of a patient population most likely to be sent for surgery, and for noncomparable placebo control, inadequate power, and nonstandard treatment. In a prospective randomized clinical trial, Buchner et al.[41] administered three ESIs to patients with HNP who were under 50 years of age. They reported significant improvement in straight-leg raising and non-significant improvement for pain relief and mobility after 2 weeks, but no significant benefits in the treatment group at 6 weeks and 6 months.

Bush and Hillier[42] employed caudal epidural steroid or normal saline injections in a randomized, double-blind, placebo-controlled study of clinically well-defined patients with radicular pain, paresthesias, and positive straight-leg raise. They found significantly better pain relief at both 4 weeks (visual analog scale 16.0 vs. 45.0) and 52 weeks (14.2 vs. 29.6) for ESI compared with placebo.

Manchikanti et al.[43–46] prospectively studied the efficacy of caudal epidural steroid injections of local anesthetic and local anesthetic and steroid in the following group of patients: (1) discogenic pain without herniation or radiculitis, (2) disc herniation and radiculitis, (3) postsurgery syndrome, and (4) spinal stenosis. While limited by low sample sizes and no true placebo arm, Manchikanti showed that caudal epidural injections of local anesthetic and steroid may have efficacy in improving pain and function in all four groups. Results were best in the disc herniation and radiculitis group in which 79% to 91% of subjects showed significant functional improvement. Results were positive but not as impressive in the postsurgery syndrome and spinal stenosis groups, which had response rates of 55% to 70%.[43–46]

Prospective long-term follow-up studies after ESI are lacking. Persistent benefit after ESI was reported by Dilke and coworkers[36] after 3 months (36% complete and 55% partial relief); by Green and associates[38] (41% sustained relief for at least 1 year); and by Bush and Hillier[42] at 52 weeks (earlier benefit was maintained or improved), all in patients with discogenic, radicular pain. Abram and Hopwood[30] also monitored patients who received ESI and observed persistent improvement at 6 and 12 months in those who initially responded. They reported that the patients had significantly better pain reduction and better rates of return to work than patients who failed ESI. In a more heterogeneous group of patients, White and

TABLE 44–1 Results of Well-Controlled Studies on Lumbar Epidural Steroid Injections for Patients with Acute Herniated Disc

Study	Study Design	Duration		Response
Dilke et al.[36]	P, R, DB	≤1 year	MP, 80 mg in 10 ml NS vs. 1 ml NS, lumbar	60% vs. 31% initial pain relief; less pain, less analgesic use, and less failed return to work at 3 months
Snoek et al.[37]	P, R, DB	1–3 weeks	MP, 80 mg in 2 ml NS vs. 2 ml NS, lumbar	25–70% improvement in multiple outcome measures; not significantly different from 7–43% in placebo group
Carette et al.[39]	P, R, DB	<1 year	MP, 80 mg in 8 ml NS vs. 1 ml NS, lumbar	Less sensory deficit and leg pain; functional disability and incidence of surgery the same

P, prospective; R, randomized; DB, double blind; MP, methylprednisolone; NS, normal saline.

coworkers[26] reported persistent improvement after 6 months in 34% of patients with acute pain and in 12% of patients with chronic pain.

One major review showed inconclusive or lacking benefit with ESIs. After reviewing 18 trials with 1179 patients, Staal et al. in 2009 stated that the evidence did not support the use of ESIs in subacute and chronic low back pain, but that there may be specific responder subgroups.[47] Argoff and Sims-O'Neill stated in a commentary that "the benefit afforded by these injections is quite limited."[48] The greatest limiting factor to generating Class A evidence for ESIs has been the widespread acceptance of ESIs as a therapeutic intervention. Because ESIs are so accepted, many researchers have had difficulty enrolling subjects into a study where a placebo injection is a possibility.

CERVICAL INJECTION

Reports on the use of cervical ESI to treat cervical radiculopathy and various other diagnoses began to appear in 1986.[10–12] There have been no blinded, controlled, randomized studies to assess the efficacy of this procedure (Table 44-2).[49–51] Stav and colleagues[49] reported on 50 patients with chronic, refractory neck and arm pain who were treated with physical therapy and continued NSAIDs. All patients had degenerative disc disease, osteoarthritis of the cervical spine, or both, with or without radiculopathy. In addition, all had had pain for longer than 6 months Cervical ESI proved to be superior to posterior neck intramuscular injections for short- and long-term pain relief, improved range of motion, decreased analgesic consumption, and recovery of the capacity to work. At 1-year follow-up, good to excellent results were found in 68% of the patients in the ESI group versus 12% in the intramuscular injection group.

Ferrante and colleagues[52] attempted to find predictors of clinical outcome in a retrospective review of 100 patients who received cervical ESI. Radicular pain predicted a better outcome; radiologic diagnosis of a normal scan or of disc herniation predicted a poor outcome. The authors recommended selection of patients for cervical ESI by the presence of radicular pain and either physical or radiologic findings corresponding to the painful nerve root.

Strub et al. looked prospectively at the short-term benefits of cervical ESI in 161 patients and found that 83% of injections resulted in pain relief. Patients with radicular symptoms into the fingers and those with multilevel degenerative changes had a higher likelihood of success, while those requiring opiate analgesics had lower odds of attaining pain relief.[53]

USE OF FLUOROSCOPIC GUIDANCE

Many reports[54–56] suggest that needle misplacement without fluoroscopic guidance is a common reason for treatment failure with ESI. Mehta and Salmon[54] reported that placement of Tuohy needles, using a loss-of-resistance (LOR) technique to identify the lumbar epidural space, was too superficial in 17% of cases. Renfrew et al.[56] documented incorrect needle placement for caudal ESI by novice trainees 48% of the time, but also at a 15% rate by experienced practitioners. Epidural injection after correct needle placement and negative aspiration proved to be intravenous in 9.2% of cases. Manchikanti and colleagues[57] proposed that use of fluoroscopy would decrease technical failures with ESI up to 50% to 60%. Stitz and Sommer[58] reported 74% success on the first attempt at caudal needle placement in 54 patients; their initial success rate increased to 91% in the presence of easy landmarks and absence of palpable subcutaneous air. They concluded that fluoroscopic guidance remains the gold standard for caudal epidural injection in adults. In a study of ESI without fluoroscopic guidance in 200 patients randomly assigned to injection site, 93% of lumbar and 64% of caudal injections were correctly placed.[59] The odds ratio for successful placement was reduced to 0.34 in the presence of obesity (BMI $>$ 30 vs. BMI $<$ 30).

Epidural needle size may influence success rate for lumbar ESI using a LOR technique. Liu and associates[60] achieved a success rate of 92% with 20-gauge Tuohy needles, significantly less than with standard 17- or 18-gauge needles. Reliability of the LOR technique was lower with increased patient age (>70 years) and male sex. Fredman and colleagues[61] reported successful blind entry into the epidural space after multiple attempts in 88% of previously operated patients, location at the intended level in just 50%, and spread of contrast to the site of pathology

TABLE 44–2 Results of Prospective Reports on Interlaminar Cervical Epidural Steroid Injections*

Study	Study Design	No. of Patient	Population	Response
Stav et al.[49]	P, R, D	50	Chronic neck and arm pain for longer than 6 months	68% good to very good after cervical ESI vs. 12% after IM neck injection at 1-yr degenerative disc and cervical spine disease follow-up
Castagnera et al.[50]	P, R, C	24	Chronic cervical radicular pain for longer than 12 months, no nerve compression	71% had at least 75% decrease in VAS at 3 months
Bush and Hillier[51]	P, D	68	Cervical radiculopathy, with neurologic signs for 1–12 months	76% pain-free and 24% improved (average 2, range 1–4 on a 10-point scale)

** No well-controlled studies of cervical, epidural steroid injections are available.*
C, controlled; D, descriptive; P, prospective; R, randomized; VAS, visual analog scale; ESI, epidural steroid injection; IM, intramuscular.
Source: Adapted from, Molloy RE, Benzon HT: The current status of epidural steroids. Curr Rev Pain *1:61–69, 1996.*

only 26% of the time. A retrospective review of 38 cervical ESIs detected a 53% rate of false LOR on the first attempt, unilateral spread in 51%, and ventral epidural spread in only 28%. The authors concluded that fluoroscopy with epidurography can improve accuracy of blindly performed cervical ESIs by ensuring correct needle placement and delivery of medication to the area of pathology.[62] In practice, intravascular spread can be seen and has been implicated in complications even when aspiration is negative.[63] After a review of complications in cervical ESIs, Abbasi et al. concluded that fluoroscopic guidance is "crucial to minimize complication rates."[64] The preponderance of evidence would suggest that use of fluoroscopy with contrast epidurography should increase accuracy of needle placement in the epidural space and targeted delivery of injected medication to the site of pathology, which may often be unilateral spread into the anterior epidural space. When Parr et al. looked at outcomes of blind lumbar interlaminar epidural injections, the results, while positive, were not stellar.[65] The most reasonable exception would be for initial lumbar ESI in younger, nonobese, nonoperated patients. The transforaminal approach has also been proposed to increase success of ESIs. The efficacy and safety of this technique are considered in another chapter.

COMPLICATIONS

Complications of ESI can be separated into those related to epidural technique and those related to injected drugs. Technical side effects include back pain at the injection site and temporarily increased radicular pain and paresthesias without persistent morbidity. Acute anxiety, lightheadedness, diaphoresis, flushing, nausea, hypotension, and vasovagal syncope may occur, especially during procedures performed with the patient in the sitting position. In patients who may not tolerate a perturbation in vital signs, injections may be better tolerated in an operative setting and after medical optimization of pre-existing health conditions. Headache may occur after accidental dural puncture, the most common complication of epidural injection. In experienced hands, this complication should occur in less than 1% of attempted epidural injections. MacDonald[66] cited an incidence of 0.33% for 5685 lumbar epidural injections. Waldman[67] reported dural puncture in 0.25% of 790 cervical epidural injections. Nonpostural headache due to subarachnoid air injection has been reported; Katz and colleagues[68] reported immediate onset of headache attributed to injection of air into subdural space. Pneumocephalus has also been observed after cervical ESI.[69]

Retinal hemorrhage had been associated with rapid, large-volume caudal steroid injection performed under general anesthesia.[70] Transient blindness by the same mechanism has been reported in 10 cases after lumbar ESI.[71] Significant epidural hemorrhage appears to be rare in the absence of coagulopathy, although recent case reports after cervical ESI are of serious concern. Williams and associates[72] reported a case of acute paraplegia caused by epidural hematoma formation after a seventh cervical ESI in a patient who had used indomethacin regularly for 6 years. Ghaly[73] reported bilateral upper extremity radicular pain with Tuohy needle insertion for cervical ESI, followed within 30 min by Brown-Sequard syndrome due to epidural hematoma. Stoll and Sanchez[74] observed delayed onset of acute cervical myelopathy due to a large epidural hematoma, presenting 8 days after cervical ESI, in a healthy young man without risk factors for bleeding. Early diagnosis of epidural hematoma and immediate surgical decompression and evacuation are essential to reduce the risk of permanent neurologic deficit. Reitman and Watters[75] reported the first case of anterior spinal subdural hematoma after cervical ESI. The patient developed neck pain and progressive quadriparesis within 8 hr. The postoperative course was complicated by partial recovery, meningitis, and eventual death. Two cases of intrinsic spinal cord damage and permanent neurologic symptoms developed within 24 hr after cervical ESI; intravenous sedation during the procedure appears to have interfered with patient report of acute neurologic symptoms.[76] One case of paraplegia after interlaminar ESI was reported in a patient with posterior spinal fusion from L2 to S1 in whom the epidural was done at the L1–L2 level. The authors speculate that the paraplegia occurred secondary to either a discal herniation or cord ischemia due to dominant radiculomedullary artery injury similar to the injuries described clasically with transforaminal techniques.[77] This sort of ischemic injury has been attributed to occlusion of vessels by particulate steroids. The risk of occlusion may be decreased by using a nonparticulate steroid or using a particulate steroid with smaller average particle size such as betamethasone.[78] Abbasi et al. reviewed the literature on complications of interlaminar cervical epidural injections and found the rates to vary from 0% to 16.8%. Minor complications that came to full resolution within 24 hr, such as flushing, vasovagal episodes, exacerbation of symptoms, and insomnia, occurred in up to 17% of patients. Major complications with long-term sequalae were exceedingly rare. Further, the authors concluded that complications could be reduced with increased level of expertise, fluoroscopic guidance, placement of needle at C6–C7 or lower (where the epidural space is more capacitant), and with preinjection review of patient imaging.[64]

Infectious complications of ESI include bacterial meningitis and epidural abscess. Meningitis is unlikely to develop unless unintentional dural puncture occurs. Dougherty and Fraser[79] reported two cases of bacterial meningitis after attempted ESI. One patient had accidental lumbar puncture before steroid injection; dural puncture was neither diagnosed nor ruled out with a local anesthetic test dose in the other case.

Epidural abscess was reported by Shealy[80] in 1966 after a series of four epidural injections of steroids in a patient who had coexistent local spinal metastatic disease. Cancer cells were identified in the purulent material, but no bacteria were cultured. Five other cases of epidural abscess were reported between 1984 and 1997; one after cervical, three after lumbar, and one after caudal ESI.[81–85] Cultures grew *Staphylococcus aureus* in all five patients. Three patients had diabetes mellitus, two had multiple (i.e., three) injections, one had a surgical infection with *S. aureus* 2 weeks before ESI, and one had breast cancer with spinal metastasis

located in the sacrum. All patients presented 3 days to 3 weeks after injection with fever, spinal pain, radicular pain, or progressive neurologic deficit; this scenario should elicit a high index of suspicion for epidural abscess. Rapid diagnosis and therapy, including surgical drainage, appears necessary if one hopes to achieve patient recovery with intact neurologic function. Magnetic resonance imaging (MRI) appears to be the procedure of choice for the diagnosis of epidural abscess.[82] The combination of diabetes and steroid immunosuppression may predispose to epidural abscess formation. Two other patients developed a thoracic epidural abscess after repeated epidural injections of bupivacaine and steroid to treat neuropathic pain secondary to herpes zoster infection.[86,87] Additional reports of epidural abscess after cervical[88] and lumbar[89] ESI have appeared recently; and lumbar discitis after caudal ESI[90] has also been observed. As part of a consensus statement, Hebl described the following major important components of aseptic technique: removal of watches and jewelery, antiseptic hand washing, protective barriers, hats and masks, sterile gloves, proper choice and use of skin sterilizing solution, proper draping and maintenance of sterile field, and proper dressing technique.[91]

Complications related to the drugs used for ESI include pharmacologic effects of steroids and possible neurotoxicity. Temporary development of Cushing's syndrome,[92] weight gain, fluid retention, hyperglycemia, hypertension, and congestive heart failure have all been reported after ESI. Kaposi's sarcoma was observed after intra-articular steroid injection, and it later recurred after ESI.[93] A single case of allergic reaction to ESI was reported by Simon and coworkers.[94] Very delayed onset of a cutaneous, respiratory, and gastrointestinal reaction was noted, and was reproduced with subsequent exposure to triamcinolone. Adrenal suppression is a well-known result of ESI. Plasma cortisol levels are decreased for up to 3 weeks after epidural injection of 80 mg of methylprednisolone acetate. Kay and colleagues[95] described the effects of three weekly epidural triamcinolone injections on the pituitary–adrenal axis in humans. Depressed levels of adrenocorticotropic hormone (ACTH) and cortisol, and abnormal cortisol response to synthetic ACTH, were noted for up to 1 month after ESI. Relative adrenal insufficiency should be considered when major surgical stress occurs within 1 month after ESI. Spinal epidural lipomatosis has been observed recently after multiple ESIs, and it may produce symptoms due to neural compression. The development and subsequent resolution of lipomas, after discontinuation of steroid injections, have been documented with serial MRI scans.[96,97]

Neurotoxicity has been attributed to spinal injections of depot steroids or to their preservatives. Adhesive arachnoiditis has been reported after repeated intrathecal steroid injections in patients with multiple sclerosis. There are no case reports of arachnoiditis after ESI alone. Abram and O'Connor[98] reviewed the risk of complications from ESI. They were unable to find a single report of arachnoiditis in 64 series describing these injections in about 7000 patients. They did, however, collect many reports of spontaneous arachnoiditis without prior spinal injections. Aseptic meningitis has been reported three times after intrathecal steroid injection and once after ESI.[99] These patients had headache, fever, and other systemic symptoms; and their cerebrospinal fluid was characterized by low glucose with elevated protein and leukocytes.

Nelson has questioned both the efficiency and the safety of intraspinal methylprednisolone acetate. He recommended against its intrathecal use because of potential polyethylene glycol toxicity. He also attempted to implicate epidural injection as dangerous because of hypothetical migration into the subarachnoid space as well as accidental subdural or intrathecal injection. He believes that this may occur often with attempted epidural injection, especially after previous injections or back surgery.

Relevant animal data on neurotoxicity after ESI are limited. MacKinnon and coworkers[101] investigated the effects of various steroids injected into or near rat sciatic nerves. Nerve injury occurred only after direct intrafascicular injection. Benzon and associates[102] examined the effect of polyethylene glycol exposure on the electrophysiology of sheathed and unsheathed rabbit nerves. They demonstrated no effect from the clinically relevant 3% or even a 10% concentration, but reversible decrements in conduction at 20% and 30% and no conduction at 40%. Abram and colleagues[103] studied the effects of serial intrathecal steroid injections on the rat spinal cord, finding no demonstrable analgesia with formalin pain testing and no histologic changes 21 days after injection. They concluded that accidental intrathecal injection during attempted ESI has a low potential to cause harm.

Abram and O'Connor[98] made several recommendations to avoid further complications of ESI. They suggested a meticulous aseptic technique, especially in diabetic patients, to prevent infectious sequelae. They indicated that high-dose or repeated injections (more than one to three) have no support in the literature. They also recommended use of a local anesthetic test dose to prevent accidental, undetected intrathecal steroid injection and possible neurotoxic effects. The purported benefit to the patient must be weighed against the more likely risk of hemodynamic consequences when contemplating local anesthetic versus saline epidural injection.

INTERLAMINAR VERSUS TRANSFORAMINAL APPROACH

Placing a needle transforaminally should theoretically result in a better delineation of the nerve root and possibly better anterior epidural spread. There are several head-to-head efficacy studies, which are discussed in Chapter 45. One major well-designed study compared the contrast flow patterns between transforaminal and parasagittal interlaminar epidural injections. In this study, Candido et al.[104] were able to obtain better anterior epidural spread using a parasagittal interlaminar approach. Further, the authors were able to complete their interlaminar procedures with far lower total fluoroscopy times. With the concerns over neurologic injury associated with transforaminal injection, interlaminar injections still remain very common, especially at the cervical level. Further, interlaminar injections are simpler to perform for those with less expertise in fluoroscopy and less interventional pain experience. A great limitation with the interlaminar approach is the obliteration of

the posterior epidural space from previous surgery, which would make needle entry into the posterior epidural space more difficult.

CURRENT ROLE

The efficacy of ESI has not been conclusively demonstrated, and it is unlikely that a definitive study will be completed.[40] Nevertheless, many studies have confirmed very good short- to intermediate-term success rates in selected patients. Reviews by Rowlingson,[105] Abram,[106] and Hammonds[107] state the case for continued use of this therapy as part of the overall management of patients with acute radicular pain, herniated disc, or new radiculopathy superimposed on chronic back pain or cervical spondylosis. The analysis by Watts and Silagy[35] and the review by Spaccarelli[35] support the efficacy of ESI in lumbosacral radicular pain syndromes. This conclusion is challenged but not disproved by Koes and associates.[34] The presence of nerve root irritation is required to justify use of ESI. However, this therapy may be less efficacious in patients with neurologic deficits and a large disc herniation than in those with acute radicular pain alone.[39] Thorough patient evaluation, consideration of benefits and risks, and informed patient consent are essential to active selection of patients for this treatment (Table 44-3). Reliable patient follow-up and comprehensive management of physical, occupational, and emotional rehabilitation are necessary to avoid a too narrowly focused, block-oriented approach to these patients. ESI should be avoided if there is concern about localized or systemic infection or clotting function. One should also consider the added risk of infection with diabetes and the reduced chance of success if there has been previous back surgery, prolonged symptoms, substance abuse, disability, or litigation issues.[108]

The authors' technique for ESI has been described.[20] Methylprednisolone acetate 80 mg, or triamcinolone diacetate, is employed as the steroid drug. The diluent usually is normal saline, with the total being 3 to 5 ml at the lumbar level, 2 to 4 ml at the cervical level, and 10 to 15 ml when the caudal approach is selected. Lumbar ESI is performed as close to the level of radicular pathology as possible, often using a paramedian approach to target the lateral aspect of the interlaminar epidural space on the involved side. Cervical ESI is most often performed at the C7–T1 level; entry at higher levels is not advisable because of the noncontinuity of the ligament flavum at these levels. A guided epidural catheter is inserted and advanced to the desired level under fluoroscopic control. A similar technique may be employed for targeted caudal or lumbar ESI.[109] The injection is not repeated if there is complete relief. If partial relief occurs, a second injection is offered, but a third injection is only rarely used. Repeat injections are not offered when benefit is transient, but may be considered after prolonged responses of 6 to 12 months or longer.

Fundamentally, epidural steroid injections, while not proven in efficacy, are definitely a very safe intervention. With proven safety, a fairly large body of evidence for efficacy, and general establishment as a therapy, ESIs should play a role as part of a multidisciplinary plan to manage back, neck, and radicular pain syndromes. With exclusion of patients who may not tolerate steroid medications (or dosing alterations) and with exclusion of patients with significant infection control problems and bleeding diathesis, ESIs can be done very safely. The use of fluoroscopic guidance has become very common and the injection of dye showing epidural spread provides definitive proof that the injection was made in the epidural space.

REFERENCES

Access the reference list online at http://www.expertconsult.com

TABLE 44–3 Evaluation Criteria: Selection of Patients for Epidural Steroid Injection

	Positive Factors	Negative Predictive Factors	Increased Risk
History	Radicular pain Radicular numbness Short symptom duration Absence of significant psychological factors	Axial pain primarily Work-related injury Unemployed due to pain High number of past treatments High number of drugs taken Compensation due to pain Litigation pending Previous back surgery Smoking history Very high pain ratings	Immunosuppression Diabetes Peptic ulcer disease Tuberculosis AIDS Bacterial infection
Examination	Dermatomal sensory loss Motor loss correlated to symptoms Positive straight-leg raise	Myofascial pain prominent	
Laboratory	Abnormal EMG findings related to symptoms Lumbar herniated disc Cervical spondylosis	Normal cervical spine imaging results Cervical herniated disc	

Sources: Data from Rowlingson and Kirschenbaum[12]; White et al.[26]; Abram and Hopwood[30]; Hopwood and Abram[31]; Ferrante et al.[52]; Abram and Anderson[110]; and Jamison et al.[111]

CHAPTER 45

Selective Nerve Root Blocks and Transforaminal Epidural Steroid Injections

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The rationale for epidural steroid injections has been discussed in the preceding chapters in this book. Radicular pain can be caused by various entities. The pain from "sciatica" can be caused by mechanical compression by herniated discs, chemical irritation from ruptured disc, foraminal stenosis secondary to spondylosis, or vascular compromise. Although mechanical compression was believed to be the most common reason for sciatica, a large number of patients with mechanical compression on magnetic resonance imaging remain asymptomatic (36%).[1,2] Mechanical compression of "normal" nerves during surgery causes numbness and paresthesias rather than pain. Other studies have found that the most likely cause of radicular pain is from chemical inflammation around the nerve root.[3,4]

Human discs contain high levels of phospholipase A2 (PLA 2) along with other inflammatory mediators such as metalloproteases and nitric oxide.[5] PLA 2 is the enzyme responsible for the liberation of arachidonic acid from cell membranes at the site of inflammation, and levels are increased in herniated discs relative to normal discs. PLA 2 also acts as a catalyst in generating prostaglandins, leukotrienes, platelet activating factor, and lysophospholipids, all of which cause inflammation in experimental models.[6–8] The injection of autologous nucleus pulposus into the epidural space of dogs caused inflammatory changes in the dural sac, spinal cord, and nerve roots in contrast to no changes seen with the injection of saline.[9] A similar study done in pigs resulted in pronounced reductions in nerve conduction velocities of nerve roots in the cauda equina.[10]

Corticosteroids have been studied extensively in their ability to suppress inflammation.[11] Experimental models have demonstrated a reduction of inflammation when methylprednisolone was applied directly to neural structures. The mechanism of action is most likely related to the steroids ability to inhibit phospholipase A2 activity. In the same pig study described above, the administration of IV methylprednisolone prevented the reduction in nerve conduction velocities.[12] Steroids may also have a local anesthetic and antinociceptive effect.[13]

Epidural steroid injections, though controversial in some medical societies, have become the mainstay of conservative management of radicular pain.[14] The transforaminal or selective nerve root approach to the epidural space was first described as early as 1952 for diagnosis of radiculopathy and reintroduced for the management of back pain by Derby in 1992.[15] The evolution of the transforaminal approach was based on the idea that injecting a concentrated steroid around inflamed neural structures will provide better and longer lasting relief of radicular pain than introducing the same steroids in the dorsal epidural space. This goes along with the theory that radicular pain occurs because of pathology in the ventral epidural space from disc protrusion, extrusion, leakage of nucleus pulposus, or mechanical compression. Axial back and neck pain are more complicated in that it can be caused by both ventral and dorsal elements. Irritation of the posterior longitudinal ligament or internal disc disruption can cause the same type of pain that muscle strains/sprains, facet arthropathy, or ligamentum flavum pain.[16–20]

The transforaminal approach is more complex than the interlaminar approach, and there is increased risk of morbidity; thus, sound medical judgment and technical expertise are an absolute necessity. The more cephalad the injection, the higher the risk for catastrophic complications such as spinal cord injury or stroke.

ANATOMY

The technique of selective nerve root block (SNRB) and transforaminal epidural steroid injection are essentially the same, except that the final needle position relative to the foramen, and the purposes of the injection, are slightly different. The term *selective nerve root* has been questioned because volumes as low as 1 to 2 ml typically cover more than one nerve root. Furthermore, the fascial plane of the final needle location is the same and even a technically perfect, extraforaminal needle placement, may show contrast spread proximally into the epidural space (Fig. 45-1).

The approach to the injection does, however, differ for the cervical versus thoracic versus lumbar spine because of the anatomic orientation of the foramen and the surrounding structures differ slightly. The cervical level is the most "risky" in that the vascularity in the foramen is extensive, and susceptible arteries are in the immediate vicinity of the foramen at the C3–C6 levels. The largest case series of 504 patients published by Furman et al., reported that 19.4% had intravascular injections during contrast injections.[21] The rate of intravascular detection increases to 32% if digital subtraction angiography is utilized.[22]

The foramen at the cervical level face slightly anterior and oblique; thus, the supine or lateral position is optimal. The cervical foramina are bounded posteriorly by the superior articular process (SAP) of the lower vertebra and anteriorly by the lower end of the upper vertebral body, the uncinate process of the lower vertebra, and the intervertebral disc. Its roof and floor are formed by the pedicles of consecutive vertebrae. The superior portion of the foramen contains epiradicular veins and the lower most portion contains the spinal nerve. Arterial branches arise either from the vertebral arteries or the deep or ascending cervical arteries to supply the nerve roots (radicular arteries) and spinal cord (medullary arteries). The branches off of the cervical arteries are at most

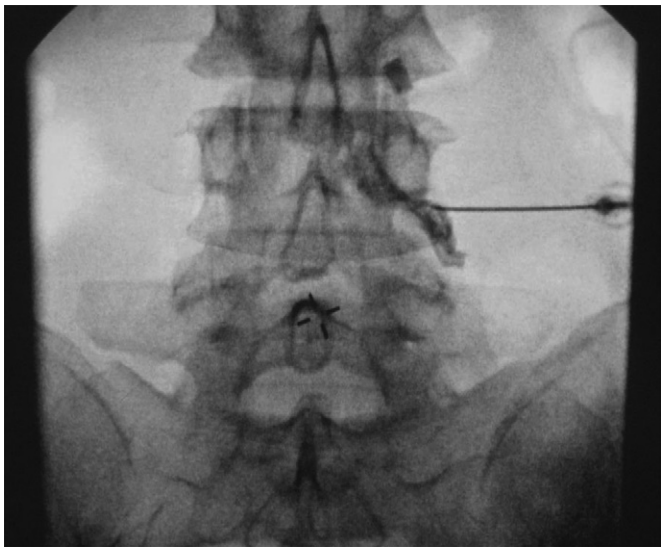

FIGURE 45-1 Lumbar selective nerve root block. Note that even with extra foraminal needle placement, there is contrast that spreads medially into the epidural space.

risk of penetration during a cervical transforaminal epidural steroid injection (TFESI) or SNRB.[20,23–25]

At the thoracic level, the foramen faces more posterior and lateral relative to the cervical level. The boundaries are similar, but at this level, the ribs, pleura, and mediastinum are the surrounding structures that are at risk of penetration along with the radicularis magna at the lower thoracic levels.[23] As thoracic disc herniations and nerve root irritations are not as common as the cervical or lumbar regions, the injections are done much less frequently.

The foramina at the lumbar levels face laterally. The anterior border includes the upper vertebra and intervertebral disc, the posterosuperior and the posteroinferior borders are comprised of the inferior articular process (IAP) and SAP, respectively, with the pedicles forming the roof and the floor. The artery of Adamkiewicz, or arteria radicularis magna, is the main arterial supply to the lower two-thirds of the spinal cord. It enters the spinal canal anywhere from T7 to L4, usually on the left side between T9 and L1 vertebrae.[26] Trauma to this artery can lead to anterior spinal artery syndrome and paraplegia.[23,24]

PATIENT SELECTION AND EQUIPMENT

The indications for SNRBs and transforaminal epidural steroid injections are the same and include:

- Radiculitis/radiculopathy
- Lumbar disc displacement without myelopathy
- Axial pain
- Diagnostic for vague symptoms or multilevel pathology
- Postlaminectomy with recurrent pain
- Spinal/foraminal stenosis

Contraindications include the following:

- Patient refusal
- Bleeding disorders
- Elevated coagulation studies

Equipment and materials include the following:

- C-arm fluoroscope (CT also used) and fluoroscopic table
- Monitors
- 22- or 25-gauge Quincke needle, variable length up to 7 in, depending on patient size
- Corticosteroid—methylprednisolone, triamcinolone, betamethasone, dexamethasone
- Contrast dye—Omnipaque M-185 or Isovue M-200

TECHNIQUES

The techniques for SNRB and transforaminal epidural steroid injection are essentially the same except for the final needle location. Volumes as low as 1 to 2 ml typically cover more than one nerve root and false positives can occur because several nerve roots can be anesthetized.[19] The final needle position is slightly lateral to the intervertebral foramen for the SNRB, and the tip is guided more toward the center rather than subpedicular and anterior.[24] For the cervical level, the needle is kept more lateral to the foramen to avoid spread of contrast to adjacent levels along with lower volumes of local anesthetic.[24]

LUMBAR TECHNIQUE

The procedure can be done prone or lateral, most practitioners prefer prone.[23,24] Fluoroscopy is utilized to determine the correct level of injection and approach. The area is prepped with either chlorohexanol or Betadine and draped in usual sterile fashion. The C-arm is then positioned obliquely to visualize the foramen optimally, usually 15 to 30 degrees, Scotty dog view, with the transverse process over the vertebral body. A less oblique view can be utilized to keep the needle lateral to the foramen and better target a single nerve, but as mentioned above, even small volumes can spread to adjacent levels. The goal is for the needle to be coaxial with the C-arm, just under the pedicle and lateral to the pars interarticularis, above the superior articular process inferiorly. This approach avoids the nerve root, and thus avoids periprocedural paresthesias. An anteroposterior view is obtained with the fluoroscope to determine the mediolateral location of the needle. If the needle tip encounters bony resistance, this is most likely the pars interarticularis and the needle should be walked just inferior, anterior, and medial past this level. Once the needle tip is just under the pedicle medially, the fluoroscope is rotated to the lateral view and the needle is advanced slowly into the foramen until the tip is in the anterior one-third of the foramen, just under the pedicle.[23,24]

The patient may experience a paresthesia, at which point it is best to slightly withdraw; the paresthesia must disappear prior to injection of contrast. After negative aspiration for blood, 1 to 2 ml of radiographic contrast is injected under live fluoroscopy to confirm anterior epidural spread in the case of the transforaminal injection, or nerve root spread for the SNRB (Figs. 45-1 to 45-3). For the L1 and L2 levels, digital subtraction angiography should be utilized in the AP and lateral view to better

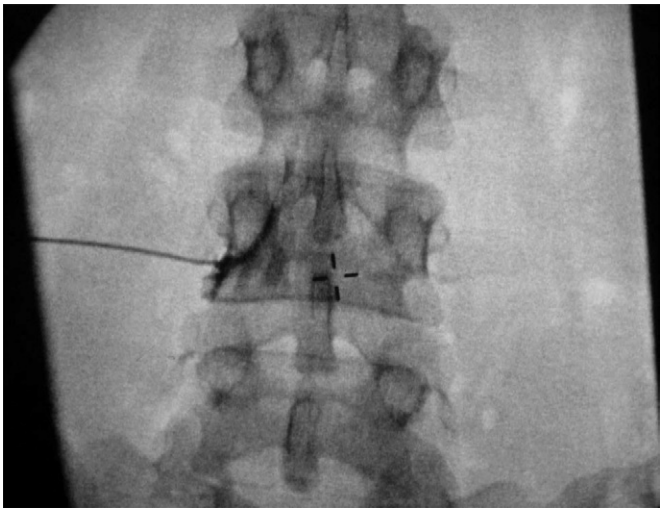

FIGURE 45-2 Lumbar transforaminal epidural steroid injection.

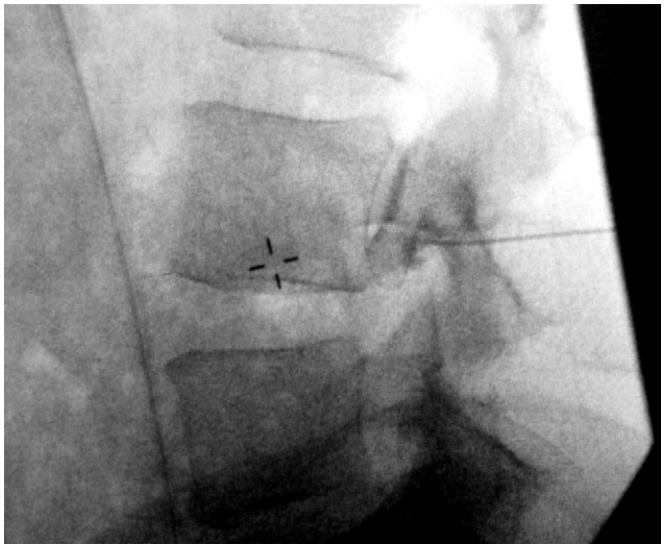

FIGURE 45-3 Lateral view of lumbar transforaminal epidural steroid injection demonstrating both anterior and posterior epidural contrast pattern.

detect potential vascular spread and the needle tip should be kept slightly posterior in the foramen to avoid the artery of Adamkiewicz. The L5 level presents unique challenges in that the iliac crest is in the line of the needle and may obstruct its path to the foramen. Normally, this can be avoided by angling the C-arm more cephalad to line up the inferior end plates of the L5 vertebral body. The path of the needle is a triangular area formed by the superior articulating process of S1, the inferior border of the transverse process of L5, and the iliac crest. The obliquity of the C-arm can be manipulated until the triangle is visualized, the area may be seen with less obliquity.[23] The needle is advanced from a lateral to a medial direction, medial to the iliac crest, until the tip of the needle projects inferior to the pedicle.

The patient lies prone for blockade of the S1 nerve root. The C-arm is in straight anterior–posterior (AP) projection or with 5 to 10 degrees of ipsilateral lateral angulation.[23] The image intensifier, which is above the patient, may have to be angled caudocranially (toward the patient's head) to have a better view of the sacral foramen. The needle is advanced through the posterior sacral foramen until the first sacral root is encountered. Lateral views are taken to ensure that the needle tip is in the caudal epidural space and not inserted too deep into the pelvis.

Once the appropriate contrast pattern is seen in the anterior epidural space, an AP image is then obtained to confirm spread of contrast perineurally and/or epidurally as well as confirmation that no vascular or intrathecal spread has occurred. Additional contrast maybe injected in this view for confirmation. Theoretically, the final target for the SNRB is for the needle to be extraforaminal whereas with the transforaminal epidural, it is ideal to be in the anterior and superior portion of the foramen (Figs. 45-1 to 45-3).[23,24] Once appropriate spread of contrast is seen in the ventral epidural space without vascular or intrathecal uptake, a mixture of 1 ml of saline (or 1% lidocaine or 0.25% bupivicaine) and either 40 to 80 mg of triamcinolone, 6 mg of betamethasone, or 4 to 8 mg of dexamethasone are injected incrementally (Fig. 45-3).

THORACIC TECHNIQUE

The T9 to T12 levels are done similarly to the L1 and L2 levels. The C-arm is not rotated quite as oblique to avoid potential pneumothorax, and the needle is not advanced quite as anterior to avoid the artery of Adamkeiwicz.[23,26] For the T1 to T8 levels, the C-arm should not be rotated more than 15 degrees to avoid pneumothorax, and to maintain better visualization of the foramen. At these levels, only the prone position is utilized, but theoretically, the lateral position can be used.

The rest of the procedure is done similar to the lumbar levels in that a needle is advanced coaxially with the C-arm of the fluoroscope to the posterior and medial portion of the foramen. It is important to realize that it is very difficult to enter the foramen if the needle tip is too cephalad and too medial because the foramen will be missed completely. Once the needle tip is seen just medial and inferior to the pedicle, real-time fluoroscopy with the injection of 1 to 2 ml of contrast under AP and lateral imaging is utilized to confirm appropriate spread (Fig. 45-4). The substances injected are the same as for the lumbar technique, but, methylprednisolone is not recommended because of its larger particle size.[27]

CERVICAL TECHNIQUE

The cervical level is usually approached in the supine position with the head neutral and a shoulder roll in place. A cushion is useful to keep the patient comfortable and to keep the head in place. The head maybe turned for the lower levels if it makes the needle entry easier. The practitioner must recognize that the image is now a PA rather than an AP image unless the C-arm is inverted.[24] The fluoroscope is rotated oblique ipsilaterally to visualize all of the borders of the foramen. The initial target is the most posterior and inferior part of the foramen in order to avoid the vertebral artery anteriorly or placing the needle to medially into the spinal canal.[24] The goal is to make contact with the superior articular process posteriorly to gauge the medial

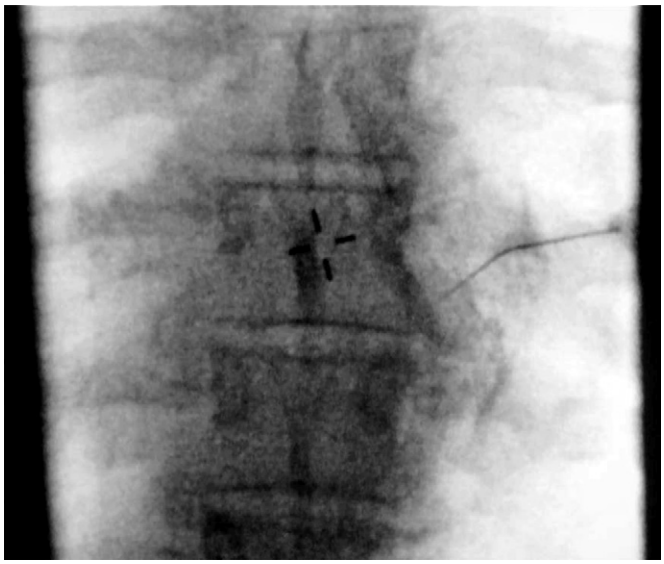

FIGURE 45-4 Thoracic selective nerve root block.

safety margin (Fig. 45-5A). In order to do this, a coaxial view of the needle is crucial. Once the needle contacts the posterior portion of the foramen, the needle can be walked slightly anteriorly into the foramen (Fig. 45-5B). The fluoroscope is then rotated back to PA to determine the medial location of the needle tip. If the patient experiences a paresthesia, contrast can be injected under either live fluoroscopy or digital subtraction angiography. Digital subtraction angiography (DSA) should be used for all cervical transforaminal or selective nerve root injections because the consequence of not detecting intravascular spread of contrast can lead to catastrophic complications (Figs. 45-6 and 45-7). The needle should not be advanced more than one-third of the facet column on the AP view.[24] If perineural or epidural spread is not noted, the needle can be advanced slightly farther in the PA plane. Once appropriate epidural or perineural spread is noted without vascular uptake, a mixture of 1 ml of saline (or 1% lidocaine) and either 40 mg of triamcinolone, 6 mg of betamethasone, or 4 mg of dexamethasone are injected slowly.

For C1 to C4 levels, the lateral position may be ideal, but for C4 to C8, the supine position is better to keep the shoulders out of the way of the image. If vascular penetration occurs, it would be highly advisable to abort the injection or restart from the skin.[24] In theory, the pencil-point needle may be less likely to cause vascular trauma, but no comparative study has been published to date.

COMMENTS ON SELECTIVE NERVE ROOT BLOCKS

The presence of pain during an SNRB is not a very reliable sign that the needle touched the nerve root sheath. The needle may have irritated sensitive structures such as the joint capsule, periosteum, and annulus fibrosus and may cause referred pain to the leg. The patient may be quite nervous and states that the pain elicited is concordant with the radicular pain even when it is not.[28] The interventional pain physician should advance the needle slowly, under lateral fluoroscopy, once the tip of the needle is in the intervertebral foramen to minimize trauma to the nerve root. The response of the patient after the diagnostic local anesthetic injection is probably more important in ascertaining the nerve root involved in the patient's pain.

Several studies demonstrated the applicability of SNRBs.[28–30] In a retrospective study of 62 patients, Dooley et al.[29] found four possible responses to the injection, as follows:

1. Patient has concordant pain and the pain is completely relieved for the duration of the local anesthetic.
2. Patient has concordant pain but the pain is not relieved by the local anesthetic.
3. Typical pain is not reproduced on needle insertion but the pain is relieved by the local anesthetic.
4. Pain is not concordant and is not completely relieved by the local anesthetic.

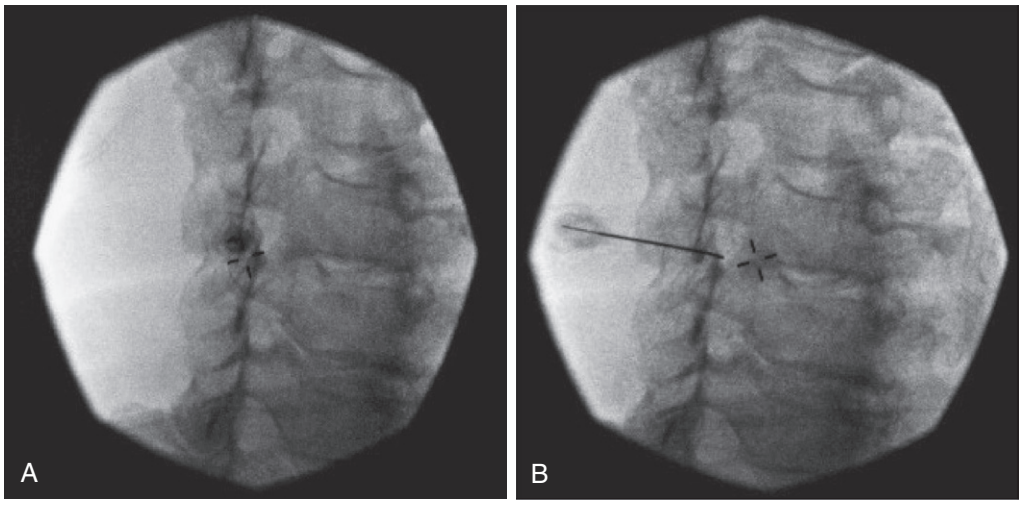

FIGURE 45-5 **A,** Initial needle placement posterior over the superior articular process. **B,** Needle walked anteriorly off of the superior articular process.

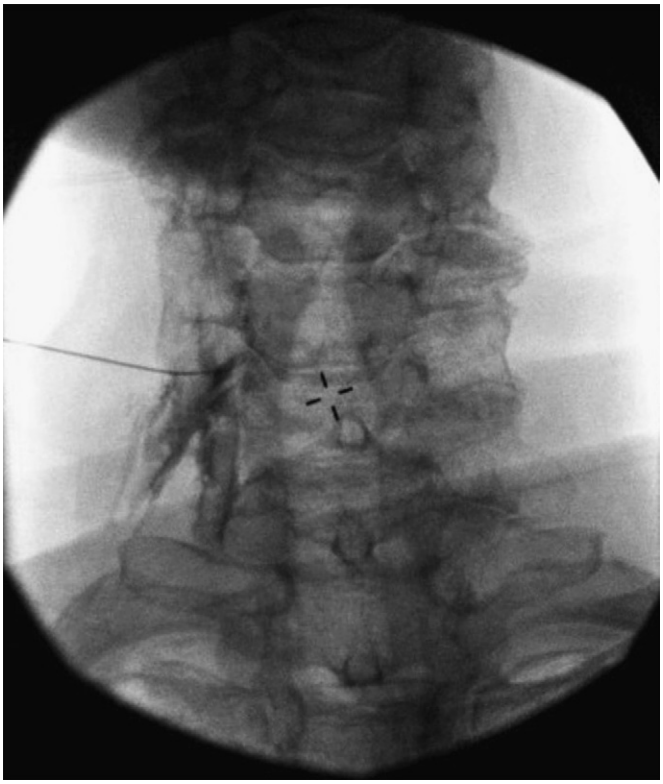

FIGURE 45-6 AP view of correct placement for cervical transforaminal epidural steroid injection.

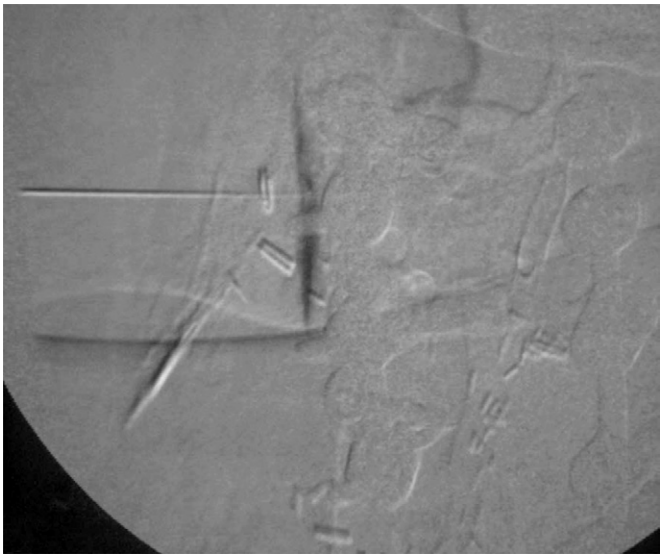

FIGURE 45-7 Digital subtraction image of cervical transforaminal epidural steroid injection.

Most of their patients that had response one had a good response to surgery. The causes included herniated disc, lateral recess stenosis, central canal stenosis, or pedicular kinking. The patients who had concordant pain but not relieved by the local anesthetic (response 2) either had peripheral neuropathy or multilevel involvement. The patients who did not have concordant pain had other abnormalities such as metastatic carcinoma, multilevel pathology, nerve root cutoff secondary to spinal stenosis, or anomalous nerve roots on surgical exploration.

In another study,[30] the nerve root block correctly identified the symptomatic level in 18 of 19 patients. These patients underwent surgery and did well. The authors compared the results of SNRB with radiculography and CT and concluded that SNRB is a more useful test than the two other modalities. Myelography and CT are difficult to interpret after spine surgery[29,30] and may not always identify the offending single nerve root.

COMPLICATIONS

Spinal injections may cause infectious, cardiovascular, neurologic, and bleeding complications.[31–39] Exposure to x-ray radiation and adverse, allergic, and anaphylactic reactions to the medications and the dye are added risks. Risks specific to TFESI and SNRBs include trauma to the spinal nerve, intrathecal injection if the needle penetrates the dural root sleeve, or segmental epidural when the medication is injected into the epidural space via the neural foramen. Trauma to the artery of Adamkiewicz may cause paraplegia and trauma to the segmental artery, which travels with the nerve root, may result in segmental cord infarct. Cervical TFESIs and SNRBs are inherently riskier. Spinal cord trauma, arterial injury, blindness, and brain or spinal cord infarct are added risks. The use of methylprednisolone in lumbar selective nerve root injections is controversial, its use in cervical SNRBs is not recommended. This is because methylprednisolone has the largest particle size of all of the steroids and easily precipitates.[27] If injected through the any of the susceptible arteries including the vertebral, ascending cervical and deep cervical arteries,[25] it may cause a segmental spinal cord infarct or settle in an end-artery in the brain causing a small infarct. Triamcinolone has intermediate particle and maybe used. Betamethasone has the smallest size and should preferably be used if available. The efficacy of non-particulate steroids such as dexamethasone has not been established.

OUTCOMES

Two early review articles came up with two different conclusions. Kepes and Duncalf,[40] after a review of spinal and systemic steroids, concluded that these interventions were not effective in relieving backache. Benzon,[41] on the other hand, reviewed epidural steroids only and concluded that the injections were effective in relieving lumbosacral radiculopathy. After a review of the studies, Benzon noted that the indication for epidural steroid injections is nerve root irritation.[41] A meta-analysis of 11 randomized controlled trials involving 907 patients showed the short-term efficacy of epidural steroids in sciatica and that the efficacy was independent of the route of injection.[42] Still, the use of epidural steroids was controversial. Bogduk[43] noted that epidural steroids lack legitimate rationale and lack empirical proof of their efficacy. A study by Carette et al.[44] showed that epidural steroids afforded short-term (3 months) improvement in leg pain and sensory deficits in patients with sciatica due to herniated disc but offered no significant functional benefit and did not reduce the need for surgery. The short-term efficacy of the injections can

be clinically useful, however. It provides pain relief during spontaneous resolution of a herniated disc (aggressive conservative management results in partial or complete resolution in 76% of disc herniations[45]), and minimizes opioid dependence and hospitalizations.[42]

Boswell et al.,[46] Depalma et al.,[47] Young et al.,[16] Abdi et al.,[48] and most recently Roberts et al.,[49] have published systematic reviews of lumbar transforaminal epidural steroid injections with all concluding that there is evidence to support transforaminal epidural steroid injections (TFESI). Boswell, Young, Abdi, and Roberts all concluded that there was strong evidence for the use of TFESI for the short- and long-term treatment and management of radicular pain. De Palma found that limited to moderate evidence existed for lumbar TFESIs, but no conclusive evidence. Buenaventura[50] also found strong evidence to support TFESI use for short- and long-term relief in managing chronic low back and lower extremity pain. The efficacy of transforaminal epidural steroid injections has been studied relative to control as well as relative to interlaminar approaches. These studies are summarized in Tables 45-1 and 45-2.

Weiner et al.[51] found that transforaminal epidural steroid injections were effective in patients (n = 30) with herniated disc who were previously unresponsive to bed rest and nonsteroidal anti-inflammatory agents. Immediate relief of symptoms was obtained in 27 patients. Twenty-eight patients were followed for an average of 3.4 years and 22 of them had considerable and sustained relief. The patients' average Low Back Outcome Score improved from 25 (out of 75) compared to 54 before the injection.

Lutz et al.[52] found that 75% of patients (n = 69) with lumbar HNP and radiculopathy (average duration of 22 weeks) responded to transforaminal injections. To achieve these results, an average of 1.8 injections was administered per patient. It was noted that the patients who had preinjection symptom duration of less than 36 weeks had 79% successful outcome. In another outcome study, Botwin et al.[53] found that seventy-five percent of patients (n = 34) with degenerative lumbar stenosis who were unresponsive to physical therapy, anti-inflammatory medications, or analgesics, had greater than 50% reduction in their pain scores, 64% had improved walking

TABLE 45–1 Prospective Controlled Studies on Transforaminal Epidural Steroid Injections

Author	Study Type	Intervention (Number of Injections)	Control	Outcome Measure	Follow-up	Result/Success Rate
Weiner[51]	P, O	TFESI	No injection	Low Back Outcome Score	3.4 years	78%
Lutz[52]	P, O	TFESI	No injection	Pain score, standing and walking tolerance	80 weeks	75%
Botwin[53]	P, O	TFESI	No injection	Pain score, standing and walking tolerance	12 mo	75%
Vad[54]	P, R*, C, SB	TFESI (1–3)	TPI	F-F, RM, NRS, PSS	12 mo	84% vs. 48%
Riew[55]	P, R, C, DB	TFESI (1–4)	TF-B	Surgery refusal	13-28 mo	71% vs. 33%
Karppinen[56]	P, R, C, DB	TFESI (1)	TF-S (1)	VAS, ODI, NHP, PE, Cost	12 mo	Better 2 and 4 week, no difference at 3, 6, and 12 mo
Ng[58]	P, R, C, DB	TFESI (1)	TF-B (1)	ODI, VAS, PSS, walking	12 weeks	No difference

C, controlled; DB, double-blind; F-F, finger-to-floor distance; NHP, Nottingham Health Profile; NRS, numeric rating scale; O, outcome; ODI, Oswestry Disability Questionnaire; P, prospective; PE, physical exam; PSS, patient satisfaction score; R, randomized; RM, Roland Morris Disability Questionnaire; S, saline; B, bupivacaine; SB, single-blind; TFESI, transforaminal epidural steroid injection; TPI, trigger point injection; VAS, visual analog scale.
** Randomized by patients' choice.*

TABLE 45–2 Studies Comparing Transforaminal versus Interlaminar Epidural Steroid Injections

Author	Study Type	Intervention	Control	Outcome Measure	Follow-up	Diagnosis
Kolsi[60]	P, R, O, DB	TFESI (1)	ILESI	VAS, F-F, Schober, EIFEL, analgesic use	28 days	HNP, radicular pain
Thomas[61]	P, R, O, DB	TFESI (1)	ILESI (blind)	VAS, F-F, Schober, RM, SLR, D, N, surgery	6 mo	HNP, radicular pain
Ackerman[62]	P, R, O, DB	TFESI (1–3)	ILESI	NRS, ODI, Beck, CDP	24 weeks	L5-S1 HNP, S1 R
Candido[63]	P, R, O, SB	Parasagittal ILESI (1–3)	TFESI	CFP, VAS	6 mo	HNP, DDD, SS, UR
Lee[64]	P, R, O, DB	Bi-TFESI	ILESI	NRS, PSI, RM	4 mo	HNP vs. SS

Beck, Beck Depression Inventory; C, controlled; CFP, contrast flow pattern; D, Dallas pain score; DB, double-blind; DDD, degenerative disc disease; EIFEL, French version of Roland-Morris Disability Questionnaire; F-F, finger-to-floor distance; HNP, herniated nucleus pulposus; ILESI, interlaminar epidural steroid injection; N, neurologic exam; NHP, Nottingham Health Profile; NRS, numeric rating scale; O, outcome; ODI, Oswestery Disability Questionnaire; P, prospective; PSI, patient satisfaction index; PSS, patient satisfaction score; R, randomized; RM, Roland-Morris Disability Questionnaire; SB, single-blind; SLR, straight-leg raise; SS, spinal stenosis; TFESI, transforaminal epidural steroid injection; UR,unilateral radiculopathy; VAS, visual analog scale.

tolerance, and 57% had improved standing tolerance at 12 months after transforaminal injection. The injection consisted of 12 mg betamethasone and 2 ml of 1% lidocaine with an average of 1.9 injections per patient.

Vad et al.[54] found that 84% of patients that underwent a TFESI demonstrated benefit over trigger point injections with saline. A total of 48 patients underwent either a TFESI with 1.5 ml each of betamethasone acetate (9 mg) and 2% xylocaine or 3-ml trigger point saline injections in the lumbar paraspinal areas.[54] Although the study was prospective and controlled, the randomization was by patient's choice. The patients were followed at 3 weeks, 6 weeks, 3 months, 6 months, and 12 months. The success rates were statistically different: 84% (21 of 25) for the TFESI and 48% (11 of 23) for the trigger point injections. The patients' Roland-Morris low back score increased from a mean of 9 to 22 in the transforaminal group compared to an increase from an average score of 10 to 18 in the trigger point group. The finger-to-floor distance (F-F) decreased from 70 to 20 cm in the TFESI group compared to 65 to 24 cm in the trigger point group. The improvement in the trigger point saline injection group may have been partly due to the lumbar stabilization program prescribed to all the patients studied. The lumbar stabilization program consisted of exercises emphasizing hip and hamstring flexibility and abdominal and lumbar paraspinal strengthening.[54]

Riew et al.[55] found that TFESIs when compared to transforaminal injections of bupivicaine alone, were effective in decreasing the need for surgery. A randomized, double-blind study compared the efficacy of TFESI in preventing lumbar spine surgery.[55] The 55 patients studied had radiographic confirmation of nerve root compression secondary to a disc herniation or spinal stenosis and were referred for back surgery. The patients either had SNRBs with bupivacaine–betamethasone or bupivacaine alone. The doses were either 1 ml 0.25% bupivacaine or 1 ml bupivacaine with 1 ml betamethasone (6 mg). Twenty-nine of the original 55 patients, who initially requested surgery before their treatments, decided not to have the operation after the injections. Of the 28 patients who had the betamethasone–bupivacaine injection, 20 decided not to proceed with the operation. This was in contrast to 9 of 27 patients in the bupivacaine group.[55]

Karppinen et al.[56] found good positive short-term results with a single TFESI when compared to a single injection of saline, but found that the saline group had less back pain at 3 months. The study was a randomized, double-blind trial of 160 patients with sciatica secondary to a disc abnormality: a bulge, contained disc herniation, or an extruded disc. The patients who had the steroid injection had better short-term results (immediate results and at 2 and 4 weeks) as evidenced by less leg pain and improved lumbar flexion, straight leg raise, and patient satisfaction. By the 3, 6, and 12 months follow-up, however, no differences were noted in their evaluation outcomes.[56] A subgroup analysis of this trial demonstrated the efficacy of the steroid injection in preventing surgery in contained disc herniations but not in disc extrusions.[57]

Ng et al.[58] studied 86 patients, 43 in each group, with chronic unilateral radicular pain and found no significant difference in efficacy between the TFESI group versus the bupivicaine alone group as both groups demonstrated improvement. The authors concluded that a shorter duration of pain was a predictor of better outcome. There are two criticisms of this study. The first is that the duration of symptoms was an average of 5 months longer for the steroid group. The second is that bupivacaine is not a true placebo. Devulder et al.[59] examined 60 patients with postlaminectomy pain and chronic nerve fibrosis and found no significant difference in the visual analog scale (VAS) score between TFESI and injection with other substances.

The other group of studies compares the efficacy of interlaminar epidural steroid injection (ILESI) versus TFESI. Kolsi et al.[60] studied 30 patients with severe radicular pain or femoral neuralgia and found that there was no significant difference in pain relief when administered a fluoroscopically guided ILESI versus TFESI. Data were only collected at 1, 7, 14, 21, and 28 days with both the recording physician and the patient blinded to the study. Outcome measures included VAS for leg and back pain, percent improvement, analgesic use, F-F measure, Schober measure, and EIFEL score (French version of Roland-Morris Disability Questionnaire) with all measures improving for both groups. All of the patients were then seen at 8-month follow-up with three patients in each group requiring surgery. The remaining 24 patients were free from radicular pain.

Thomas et al.[61] studied 31 patients hospitalized with acute radicular pain of less than 3 months and a herniated nucleus pulposus on imaging. He found that a single TFESI provided better pain relief than a blind, ILESI. Both the patient and the recording physicians were blinded. Outcome measures included VAS, Schober, F-F, straight leg raise, Dallas pain scale questionnaire and Roland-Morris Disability Questionnaire (RM) scores on days 6 and 30, as well as 6 months postinjection. At day 6, the TFESI group demonstrated superior improvements in VAS, Schober, F-F, straight leg raise test, and only the TFESI group demonstrated improvement in Dallas and RM scores. At 30 days, both groups demonstrated improvement in all parameters with TFESI superior to ILESI on VAS. At 6 months, both groups were significantly improved with VAS and Dallas scores while the TFESI group demonstrated better RM scores. The surgical rate was slightly higher in the TFESI ($n = 5$) versus the ILESI ($n = 4$).

Ackerman et al.[62] studied 90 patients with L5-S1 disc herniations on imaging, severe S1 radicular pain (VAS 7) and S1 radiculopathy on EMG. The control group received either an ILESI ($n = 30$) or caudal ESI ($n = 30$) while the intervention group underwent a TFESI. All patients were randomized to receive one to three fluoroscopically guided injections (repeated every 2 weeks if only partial pain relief). Outcome measures—a 0-to-10 pain score, Oswestry Disability Questionnaire, Beck Depression Inventory, and contrast dispersion—were recorded at 2, 12, and 24 weeks. All three groups demonstrated improvement in all parameters 2 weeks after the prior ESI with the only statistically significant difference being in the pain score with TFESI being better at 2 weeks. At 12 and 24 weeks, pain scores were improved in all groups without a significant difference. The TFESI group received on average 1.5 injections, while the ILESI group

and caudal ESI group received 2.2 and 2.5 injections, respectively. The authors concluded that, in general, there was a higher incidence of complete relief with ventral epidural spread and there was a higher incidence of ventral epidural spread with the TFESI method.

Candido et al.[63] studied 57 patients with low back and unilateral radiculopathy secondary to herniated nucleus pulposus, degenerative disc disease (DDD), or spinal stenosis. The study's primary outcome measure was ventral contrast pattern which was greater in the parasagittal Interlaminar (IL) ESI relative to the posterior TFESI. Both groups of patients improved with no difference in VAS scores.

Lee et al.[64] compared the effectiveness of ILESI with bilateral TFESI in patients with disc herniation ($n = 93$) or spinal stenosis ($n = 99$) related axial back pain (over 3 months duration). Patients were randomized to receive either intervention with a numeric rating scale, patient satisfaction index, and RM 5-point pain score measured at pretreatment, 2 weeks, 2 months, and 4 months. Relatively large volumes were injected in each approach (4.5 ml per TFESI per side, and 9 ml for ILESI). There was no difference in outcome with the herniated disc group as both groups improved, but the spinal stenosis group demonstrated a higher success rate as measured by the RM 5-point scale and patient satisfaction index with the bilateral TFESI group at 2 weeks, 2 months, and 4 months. The authors concluded that bilateral TFESI was more effective than ILESI for axial back pain related to spinal stenosis.

There are no comparative outcome studies for fluoroscopically guided cervical ILESI and TFESI.

KEY POINTS

- Epidural steroid injections are indicated in patients with lumbosacral radiculopathy. The beneficial effect of the steroids is secondary to its anti-inflammatory effect and specific antinociceptive effect. The anti-inflammatory effect is probably related to inhibition of phospholipase A_2. Local application of methylprednisolone inhibits the transmission of impulses through the C-fibers but not in the Aβ fibers.
- Epidural steroids are more effective in patients with acute lumbosacral radiculopathy. Patients with chronic radiculopathy respond to the injections better if they have a symptom-free interval or their new radiculopathy involves a nerve root different from the one involved in their previous radiculopathy.
- Pain during an SNRB is not a reliable sign that the nerve root was touched. Other structures such as the facet joint, periosteum, and annulus fibrosus may have been touched and cause referred pain to the leg.
- Fluoroscopy should be used for all transforaminal injections and based on one study, for ILESI as well.
- In the transforaminal approach the tip of the needle should be placed in the area of the "safe triangle." The safe triangle is bounded superiorly by the pedicle and by the outer margin of the exiting nerve root and the border of the vertebral body on either side.
- Digital subtraction angiography is recommended for injections above L2 and absolutely should be performed for cervical level injections.
- The use of methylprednisolone for lumbar TFESI is controversial; it is contraindicated for use at the cervical and thoracic levels. This is because it has the largest particle size and it precipitates easily.
- Compared to the ILESI approach, better results with less number of injections are expected with the transforaminal approach because of more frequent and reliable ventral epidural spread.
- Prospective, randomized studies demonstrate that the transforaminal approach has better results than trigger point injections for the treatment of radicular back pain. Transforaminal injections with bupivacaine–methylprednisolone are better than bupivacaine or saline injections.
- Duration of pain is predictive of outcome with injections with better results obtained with less than 12 months duration of pain.
- Future studies need to include the optimum number of injections, optimum amount and type of corticosteroid, cost effectiveness of injections, and randomized, double-blind, multicenter study of more homogeneous populations against placebo (not saline or local anesthetic injected transforaminally). Finally, a comparison is needed of ILESI versus TFESI in the cervical region relative to outcome and ventral epidural spread.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 46

Facet Syndrome: Facet Joint Injections, Medial Branch Blocks, and Radiofrequency Denervation

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Spine pain is one of the leading causes of medical disability in the world. Most people will experience some type of neck and/or back pain throughout their life, with lifetime prevalence estimates as high as 84% for back pain[1] and 67% for neck pain.[2] Among all musculoskeletal disorders, low back pain (LBP) is the number-one reason patients seek medical attention and is the leading cause of disability. Between 2002 and 2004, the overall estimated financial costs for spine conditions, including lost wages, were estimated at over $200 billion.[3] This ranks only behind joint pain as the most expensive musculoskeletal medical condition.

The causes of neck and LBP are complicated and often difficult to diagnose. The etiology is usually multifactorial, including muscles, ligaments, discs, nerve roots, and zygapophysial (facet) joints. The zygapophysial joint (facet joint) is a potential source of neck, shoulder, mid back, low back, and leg pain. It is also a potential source for headaches. Interventions for facet joint pain are second only to epidural steroid injections as the most commonly performed pain procedure in the United States. In 2006, interventions for facet pain represented approximately 37% of all pain interventions from Medicare, a 624% increase from 1997.[4]

ANATOMY AND FUNCTION

The facet joints are paired structures that sit posterolaterally to the vertebral body, and along with the intervertebral disc, comprise the three-joint complex. This complex works together to stabilize the joint and allow for different movements depending on the level. Facet joints are true synovial joints formed from the superior articular process of one vertebra and the inferior articular process of the vertebra above. The volume capacity of the joints is 1 to 1.5 ml and 0.5 to 1.0 ml in the lumbar and cervical regions, respectively.[5] The position of the joint relative to the sagittal and coronal planes helps determine the role the joint plays in the restriction of motion. The lumbar facets vary in angle but are aligned lateral to the sagittal plane, with the inferior articular process facing anterolaterally and the superior articular process facing posteromedially.[6] The upper lumbar facet joints are oriented more parallel to the sagittal plane (26–34 degrees), while the lower lumbar facets tend to be more closely aligned with the coronal plane.[7] The thoracic facets are the most vertically oriented joints, allowing for lateral flexion without axial rotation. In the cervical region, the shape and orientation of the joint differ between the upper and lower joints.[8] The C2–C3 joint, the most frequent cervical facet pain generator, is aligned approximately 70 degrees from the sagittal plane and 45 degrees from the axial plane, which inhibits rotation and anchors the C2 vertebra as a rotational pivot for the atlantoaxial joint (C1–C2). The area of greatest mobility in the cervical spine is at C5–C6, the second most affected cervical facet joint, which is where the cervical facets transition to their posterolateral position. The medial branch is the terminal division of the posterior ramus that provides sensory innervation to the facet joint (Fig. 46-1). This smaller posterior division of the nerve root is divided into lateral, intermediate, and medial branches. The lateral branch in the lumbar region provides innervation to the paraspinous muscles, skin, and sacroiliac joint, while the small intermediate branch innervates the longissimus muscle. The medial branch is the largest of the divisions. It innervates the facet joint, multifidus muscle, interspinal muscle and ligament, and the periosteum of the neural arch. Each facet joint is innervated by two medial branches, the medial branch at the same level and the level above (i.e., the L4–L5 facet joint is innervated by the L3 and L4 medial branches) (Fig. 46-2). The position of the medial branch in the lumbar spine does not vary significantly. It divides from the posterior primary ramus and wraps around the transverse process of the level below at the junction of the transverse process and superior articular process (i.e., the L3 medial branch lies on the transverse process of L4). The nerve traverses the dorsal leaf of the intertransverse ligament of the transverse process and courses underneath the mamilloaccessory ligament, splitting into multiple branches as it crosses the vertebral lamina (see Fig. 46-2). The mamilloaccessory ligament can become calcified and be a source of nerve entrapment, especially at L5. The main variation in the lumbar spine is at L5, where it is the primary dorsal ramus itself that is amenable to blockade.[9] The thoracic spine is similar to the lumbar spine in terms of innervation, with each joint supplied by two medial branches. However, in the thoracic spine the medial branches assume different courses depending on the level.[10] The nerve swing laterally to circumvent the multifidus muscle, thereby removing multifidus contraction as a means of needle confirmation prior to denervation. The superolateral corner of the transverse process is the most consistent point for blockade (Fig. 46-3A and B).

The innervation of the cervical facets is more varied and complicated. There are eight cervical nerve roots, which exit above the corresponding vertebral body. Similar to the lumbar and thoracic regions, the C3–C4 through the C7–T1 joints receive innervation from the medial branches at the same level and the level above. The nerves curve around the waist of the articular pillars, except at C7 and C8, where the anatomy is more variable.[11] Medial branches at higher levels are held tightly to the periosteum with tight fascia and the tendons of the semispinalis, which makes positioning more predictable

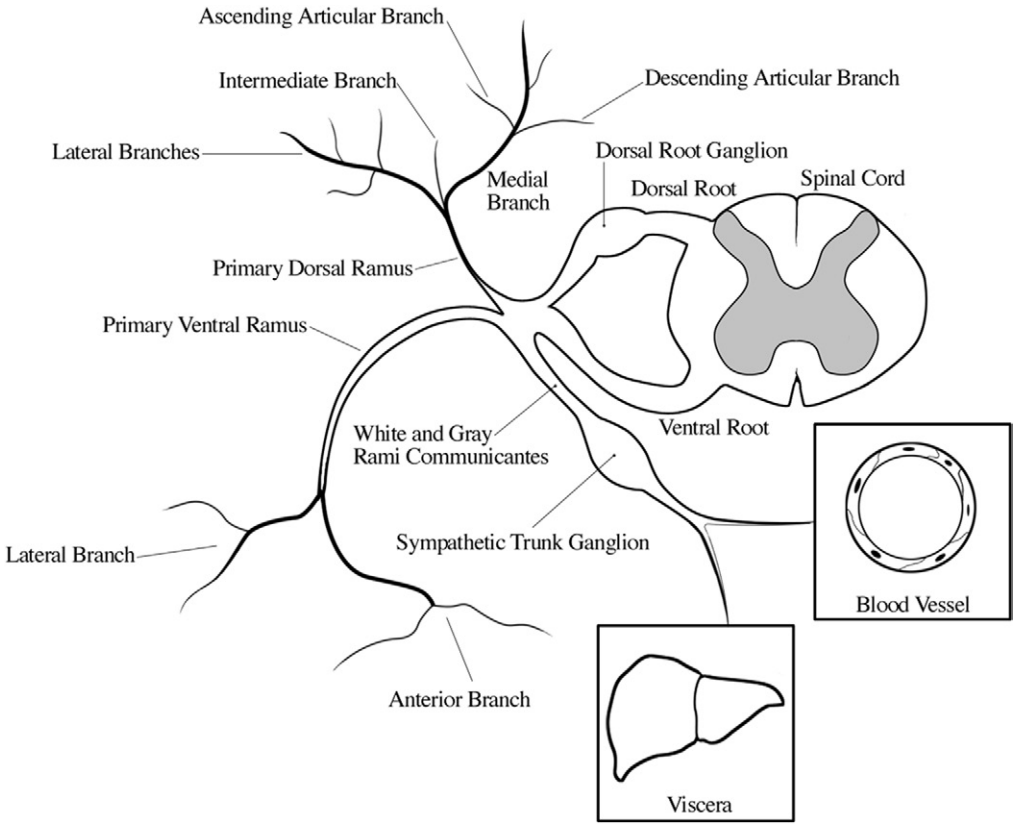

FIGURE 46-1 Spinal cord and segmental spinal innervation. The medial branch can be seen branching from the dorsal primary ramus, along with the intermediate and lateral branches. *(From Cohen SP, Raja SN: Pathogenesis, diagnosis and treatment of lumbar zygapophysial [facet] joint pain.* Anesthesiology *2007;106:591-614)*

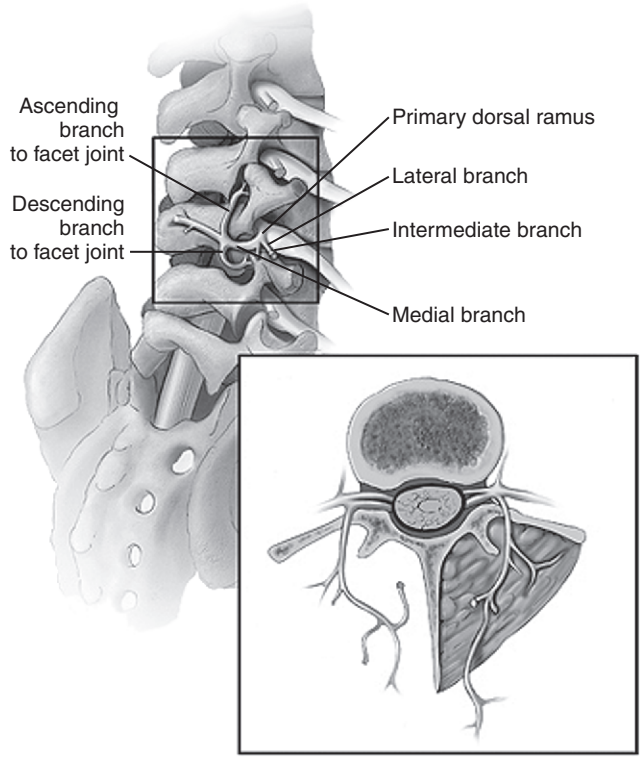

FIGURE 46-2 Lumbar facet innervation. A right lateral oblique figure demonstrating the medial branches innervating the facet joints, along with paraspinous muscle innervation. *(From Cohen SP, Raja SN: Pathogenesis, diagnosis and treatment of lumbar zygapophysial [facet] joint pain.* Anesthesiology *2007;106:591-614)*

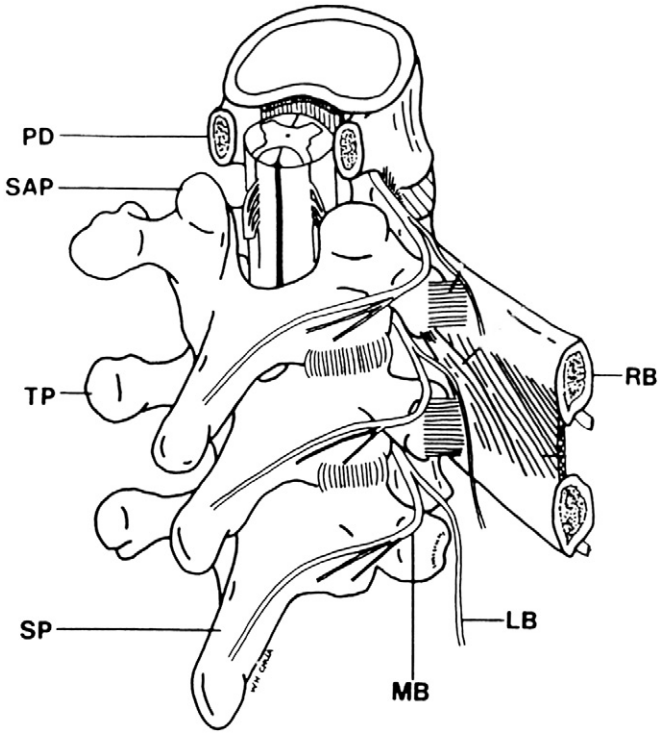

FIGURE 46-3 Thoracic facet innervation. The commonly accepted target point of medial branch is seen along the superolateral portion of the transverse process. *(From Chua WH, Bogduk N: The surgical anatomy of thoracic facet denervation.* Acta Neurochirugia *1995;136:140-144)*

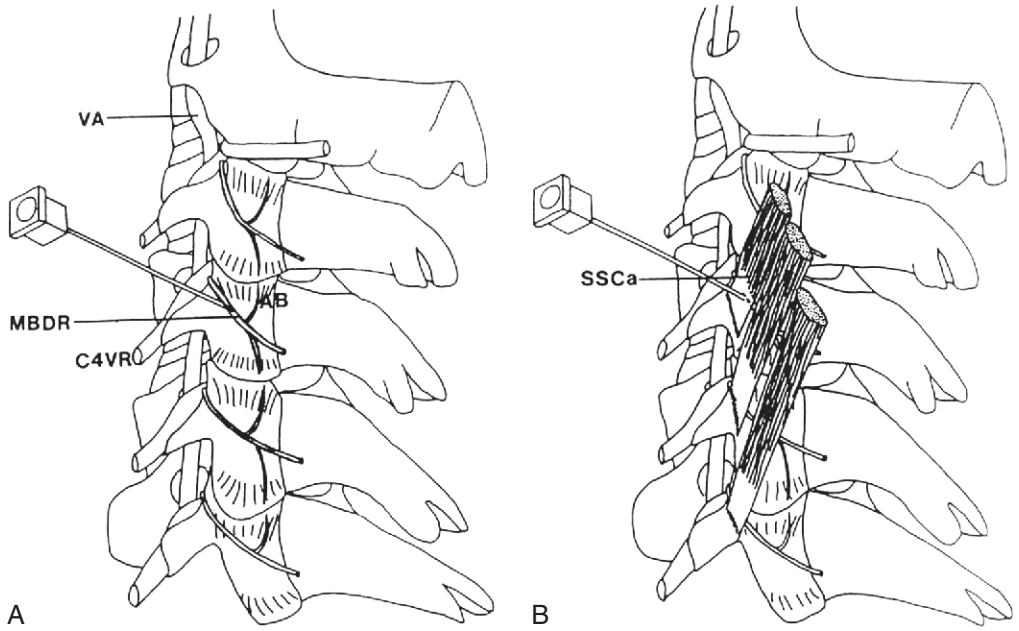

FIGURE 46-4 **A,** In these posterolateral sketches of the cervical region, the medial branch can be seen crossing the articular pillars. **B,** The semispinalis capitis lies over the medial branch, which may hold the local anesthetic in place after a diagnostic block. *(From Barnsley L, Bogduk N: Medial branch block are specific for the diagnosis of cervical zygapophysial joint pain.* Reg Anesth *1993;18:343-350)*

(Fig. 46-4 A and B). The majority of the innervation of the C2–C3 joint comes from the dorsal ramus of C3. The C3 dorsal ramus divides into two separate medial branches, the larger of which is known as the third occipital nerve. The C2 dorsal ramus divides into up to five branches, the largest of which is the greater occipital nerve.[12] Pathology involving branches of the C2 and C3 dorsal rami are a common source of occipital headaches. The facet joints contain a rich supply of encapsulated, unencapsulated, and free nerve endings.[13] Previous work has established the presence of Substance P and calcitonin gene-related peptide reactive nerve fibers in cadaveric facets.[14] Inflammatory mediators, including prostaglandins, interleukin-6, and tumor necrosis factor-α, have been demonstrated in the facet cartilage of patients undergoing surgical therapy for degenerative lumbar disease.[14] Recent studies have demonstrated that leakage of these cytokines through the ventral joint capsule may be partially responsible for radicular symptoms in spinal stenosis.[15] In addition, subchondral bone and intra-articular inclusions of facet joints have nerve endings, signifying that structures besides the joint capsule may be potential pain generators.[16]

PATHOPHYSIOLOGY

With the exception of whiplash injuries and major spine trauma,[17–19] facet arthropathy and facet-mediated pain are seldom due to acute injury. Instead, years of repetitive strain, intervertebral disc degeneration, and minor trauma are more commonly implicated. Similar to other degenerative joint diseases, there is a poor correlation between pain and the degree of inflammation or degeneration. Facet arthropathy is known to occur more commonly in the elderly, which is consistent with the concept of a degenerative disorder.[20,21]

CADAVERIC AND ANIMAL STUDIES

Cadaveric studies have demonstrated that the greatest degree of motion and strain in the lumbar spine occurs in the lowest two facet joints (L4–L5 and L5–S1).[22] At these joints, strain is maximized by forward flexion. In the most caudad joints (L3–S1), the greatest degree of strain is observed with contralateral bending, whereas the opposite is seen at L1–L2 and L2–L3. Fusion of an intervertebral level has been shown to accelerate degeneration at adjacent levels.[23,24]

Whereas facet joint pain is not normally considered an active inflammatory state, chronic strain and repetitive stimulation can lead to fluid collection and joint distention.[25] If the intervertebral foramen is already narrowed from other pathology (intervertebral disc herniation, osteophyte formation, etc.), a hypertrophied facet joint may further compress the nerve root, thereby manifesting in a radicular pain. In some cases, spasm of the paraspinous musculature can occur.[26]

HUMAN STUDIES

The presence of facet arthropathy is more common in the elderly. The intervertebral disc and facets work in concert such that degeneration of the intervertebral disc creates additional strain on the facet joints and vice versa.[27] The two most caudal facet joints (L4–5 and L5–S1) are associated with the greatest degree of degenerative disc disease, and are most commonly affected. Less common causes of facetogenic pain include inflammatory arthritis and pseudocysts.

Facetogenic pain can also result from trauma, especially rapid deceleration injuries. In one study, capsular and articular damage was observed in 77% of facet joints in

people who died from motor vehicle accidents.[28] The most common presentation of trauma-induced facet pain is whiplash injury, which may account for over 50% of cases of chronic neck pain following motor vehicle accidents.[29] However, trauma still only accounts for a small portion of cervical facetogenic pain (13%–23%).[30]

PREVALENCE

The prevalence of facet pain is a source of controversy. The lumbar facet joints are the most commonly affected due to the high frequency of LBP in the general population. However, the cervical facet joints account for a higher percentage of chronic neck pain than the lumbar facet joints in patients with chronic LBP. One limiting factor in determining the true incidence of facet pain is that the diagnosis cannot be made by historical, physical exam, or radiologic findings. The most reliable method to determine facetogenic pain is with image-guided medial branch or intra-articular facet joint blocks.[31]

The prevalence of lumbar facet pain varies widely in the literature, with the best estimates ranging between 10% and 15%.[32,33] Although comparative medial branch blocks (MBBs) have been endorsed as a diagnostic standard, the other branches of the dorsal primary ramus will also invariably be blocked, which may overestimate the prevalence.[34–36] Another source of error is that most epidemiological studies evaluating the prevalence of lumbar facet joint pain excluded patients with radicular symptoms, despite the fact that facet arthropathy can cause neuroforaminal stenosis.[37]

Estimating the prevalence of cervical facet pain is equally challenging, with some of the most elegant clinical studies conducted exclusively in patients with whiplash injuries.[17,18,32] However, the best studies utilizing double blocks have generally reported prevalence rates ranging between 49% and 60% in patients with chronic, nonradicular neck pain. Among patients with chronic mid and upper back pain (BP), the estimated prevalence varies between 40% and 50%.

DIAGNOSIS

HISTORY AND PHYSICAL EXAMINATION

Many studies have investigated the ability of history and/or physical examination to predict response to diagnostic facet blocks. Although clinical symptoms and pain referral patterns can help guide physicians, the specificity is very poor. The terms "lumbar facet syndrome" and "facet loading" were coined from a small, poorly designed retrospective study of 22 patients done in 1988.[38] Subsequent larger and methodologically sound studies failed to validate these findings,[30,39,40] Yet, many pain physicians continue to rely on misguided signs and symptoms as being diagnostically significant. Recently, tenderness to palpation in the cervical and lumbar paraspinous region was found to be a positive predictor of outcome in two large, retrospective studies, but these findings need to be confirmed prospectively.[30,41]

Pain referral patterns can provide clues for diagnosis. Studies have been conducted by provoking pain in healthy volunteers (i.e., distending the joint capsule and stimulating medial branches) and investigating pain patterns in patients whose symptoms are relieved by diagnostic blocks. Similar to other sources of spinal pain, the referral patterns associated with facet pain tend to be variable.[32,39]

Although there is a great deal of overlap between different spinal levels, and different structures (i.e., facet joints and discs) at the same level, when the results of provocation and analgesic studies are combined, some patterns emerge (Figs. 46-5 and 46-6). In the lumbar region, the upper facet joints tend to refer pain into the flank, hip and upper lateral thigh.[39] For lower levels, pain is generally experienced in the posterolateral thigh and occasionally the calf. In the cervical spine, upper facet arthropathy usually manifests as pain felt in the posterior upper neck and occipital region.[32] Pathology involving middle cervical facet joints tends to radiate into the lower neck and supraclavicular region, while lower cervical facetogenic pain typically causes pain in the base of the neck and scapular region.

RADIOLOGY

Although it is common for patients with chronic spinal pain to have multiple imaging studies performed, radiologic examination has limited utility in the diagnosis of facet-mediated pain. Whereas the lumbar facet joints account for a small percentage of chronic LBP cases, the prevalence of facet pathology on computed tomography

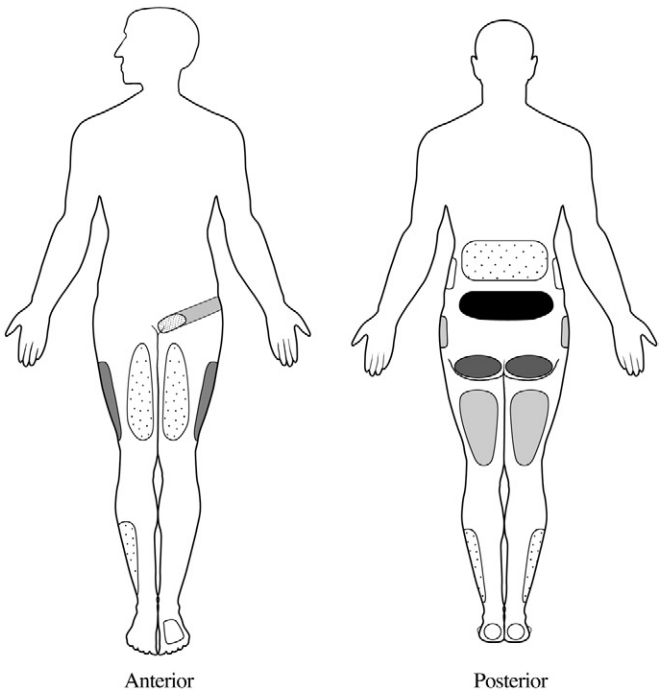

FIGURE 46-5 The referral patterns for lumbar facets are shown from the most common areas in the low back (darkest regions) to the less common areas in the flank and feet (lightest regions). Although there are some facet joints associated with particular patterns, there is a great deal of overlap between the levels. Therefore a particular level cannot be identified by referral patterns. *(From Cohen SP, Raja SN: Pathogenesis, diagnosis and treatment of lumbar zygapophysial [facet] joint pain.* Anesthesiology *2007;106:591-614)*

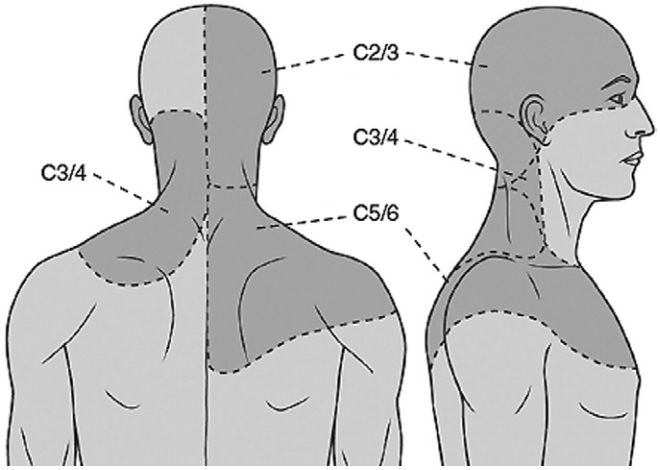

FIGURE 46-6 Cervical facet pain referral patterns. The upper cervical facet joints are associated with upper neck and head pain, whereas the lower levels tend to be associated with pain in the lower neck and scapula. *(From Bogduk N, Marsland A: The cervical zygapophysial joints as a source of neck pain.* Spine *1988;13:615)*

(CT) scans is between 40% and 85%, with the rate significantly increasing with age.[42,43] Similar rates of abnormal findings have been found in asymptomatic volunteers who undergo cervical and thoracic MRI.[44,45] Studies using MRI, CT, and other imaging studies to predict response to facet blocks have been decidedly mixed, with most showing a poor correlation.[30,41]

DIAGNOSTIC BLOCKS

The inability to predict facet pain through history, physical or radiologic examination has led to the widespread use of medial branch and intra-articular facet blocks for diagnosis. Although diagnostic MBBs have been used in multiple studies,[46–48] some technical and anatomic considerations limit their diagnostic utility. Studies have demonstrated that volumes as small as 0.5 ml cover 6 cm^2 of tissue. Hence, the intermediate and lateral branches are likely to be anesthetized with typical injection volumes, thereby blocking afferent transmission from portions of the paraspinous musculature and sacroiliac joint. A recent randomized study demonstrated a clinically relevant improvement in specificity without undermining sensitivity when 0.25 ml of local anesthetic was used for cervical MBBs compared with 0.5 ml.[49] The use of intra-articular facet injections can reduce issues related to the inadvertent spread of local anesthetic, but can be technically challenging. Furthermore, excessive volumes of local anesthetic solution can rupture the joint capsule, leading to spread into the intervertebral foramen epidural space, and paraspinous musculature.[25,48,50] Although it is often written that MBBs provide comparable relief and diagnostic utility to intra-articular injections, the lack of any randomized crossover studies preclude definitive conclusions from being drawn.

FALSE-POSITIVE DIAGNOSTIC BLOCKS

Both medial branch and intra-articular blocks are associated with high rates of false-positive results. False-positive rates have ranged from 25% to 40% in the lumbar spine,[39] and from 25% to 30% in the cervical spine.[51,52] Although some experts have advocated comparative local anesthetic blocks as an alternative to "placebo-controls," this paradigm is not without limitations. A randomized, double-blind study of cervical MBBs in 50 whiplash patients with neck pain using normal saline, lidocaine and bupivacaine in random order found comparative blocks (serial lidocaine and bupivacaine injections) to be highly sensitive (88%) but only marginally specific (54%).[52]

Potential causes of false-positive blocks include placebo response, sedation, excessive superficial local anesthesia, and the spread of local anesthetic to other pain-generating structures.[53] It is our belief that the use of sedation for diagnostic blocks should be limited, as even benzodiazepines can lead to muscle relaxation and interfere with a patient's ability to assess pain relief. However, this assumption has been challenged by some, who argue that using a more stringent pain relief threshold (>80%) mitigates against a higher false-positive rate.[54]

Several steps can be taken to negate or minimize the role of other factors in false-positive blocks. Dreyfuss et al.[9] found that for lumbar MBB, targeting a lower point midway between the upper border of the transverse process and mamilloaccessory ligament significantly reduced epidural and foraminal spread compared to the conventional target point at the superomedial border of the transverse process. Cohen et al.[49] showed that reducing the volume of injectate from 0.5 to 0.25 ml for cervical MBB resulted in a greater than 50% decrease in spread to adjacent pain-generating structures. In a randomized, double-blind study by Ackerman et al.,[55] the authors found that injecting superficial lidocaine down to the facet joint or medial branch resulted in a greater than fivefold increase in positive blocks than when patients received superficial saline. One way to reduce the need for superficial injection is to use a single-needle technique, which was demonstrated in a randomized crossover study to decrease the amount of superficial lidocaine by 40%, whereas providing comparable pain relief and contrast spread to the traditional multiple-needle technique.[56] Recommendations to limit false-positive blocks are listed in Table 46-1.

FALSE-NEGATIVE BLOCKS

False-negative blocks have garnered less attention than false-positives, but can be a source of misdiagnosis and failure to select appropriate candidates for treatment. A study conducted in volunteers estimated the incidence of false-negative blocks to be 11%.[57] However, a probable

TABLE 46–1 Techniques to Reduce False-Positive Rates for Lumbar Medial Branch Blocks

1. Avoid the use of sedation and analgesics.
2. Use injectate volumes of ≤0.5 ml.
3. Limit volume of skin local anesthesia.
4. Aim for lower target point on transverse process.
5. Use a single-needle approach.
6. Consider use of comparative local anesthetic blocks.

cause in this study was deemed to be "aberrant innervation," which negates its impact on candidate selection for denervation (i.e., they would likely not benefit anyway). One of the principal causes of false-negative blocks is thought to be vascular uptake, which has been reported to range between 6% and 30% per level.[57,58] One study found that when vascular uptake occurs, even if the needle is repositioned, analgesia will be obtained only half the time.[57] The most reliable means to detect vascular uptake is with real-time fluoroscopy.[58] Other potential causes of false-negative blocks are failure to discern between baseline and procedure-related pain, and missing a target nerve(s).

SELECTION CRITERIA: 50% VERSUS 80% RELIEF, SINGLE VERSUS DOUBLE MEDIAL BRANCH BLOCKS

A great deal of debate has centered on selecting patients for denervation, with the two primary arguments revolving around the percent pain relief and the number of blocks. The thresholds for pain relief studied are somewhat arbitrary, as previous research has determined a 2-point or 30% decrease in pain to be clinically meaningful.[59] There have been no prospective studies evaluating the influence of pain relief after MBB on radiofrequency (RF) outcome, but multiple retrospective analyses have found no difference in results between using 50% and 80% relief as the cutoff for a positive block.[30,40,60,61]

The issue of how many blocks should be performed is also the subject of considerable controversy. The argument in favor of double blocks is bolstered primarily by the high false-positive rate of uncontrolled blocks, whereas those who advocate single blocks point to time and cost constraints, the comparable complication rate between diagnostic blocks and RF denervation, and the fact that confirmatory diagnostic procedures are not used to select patients for surgery and other interventions. Multiple retrospective studies evaluating outcomes for lumbar facet, cervical facet, and SI joint RF denervation have failed to find a difference in success rates between patients selected with one and two diagnostic blocks.[61] In a large, multicenter, randomized study comparing the cost effectiveness of 0, 1, and 2 blocks before lumbar-facet RF denervation, although the RF success rate was highest in the double-block group (64%), the overall success rate was 50% higher in the 0-block group (33% vs. 16% vs. 22%, respectively). In the cost-benefit analysis, the cost per effective treatment was $6054 in the 0-block group, $16,236 in the single-block group, and $14,238 in the double-block group.

TREATMENT

PHARMACOTHERAPY AND NONINTERVENTIONAL TREATMENT MODALITIES

The focus for treatment of spinal pain has become heavily weighted toward interventions. Despite the lack of quality studies comparing pharmacologic and alternative therapies to interventions, starting with conservative management is a reasonable approach. There is strong evidence for nonsteroidal anti-inflammatory drugs and acetaminophen for spinal pain, though the effect size is small. Antidepressants and muscle relaxants have also been shown in controlled trials to be effective for spinal pain; however, the evidence for muscle relaxants is much stronger for acute pain.

Similar to other pain conditions, physical activity and weight loss are likely to benefit BP patients. Exercise and yoga programs have been shown to decrease relapses in BP, and seem to be more beneficial in patients with chronic pain. Spinal manipulation is superior to sham treatment for acute and chronic spinal pain, but the long-term benefits remain to be proven. Acupuncture also appears effective for spinal pain, but has not been shown to be superior to other treatments. Comorbid depression, anxiety, and other psychological disorders are common in patients with chronic spinal pain, and have been shown to predict poor response to treatment. Therefore, a multidisciplinary approach that includes psychotherapy, if indicated, is essential to optimize outcomes.[62]

INTRA-ARTICULAR CORTICOSTEROID INJECTIONS

Despite the conceptual appeal for intra-articular steroid injections, study results have been mixed at best. In addition to other methodological flaws, many clinical trials failed to preselect patients with diagnostic blocks prior to allocating them to treatment. In the best-designed studies, no sustained benefit has been demonstrated.[63,64] However, several uncontrolled studies have found that patients with an active inflammatory process, as demonstrated by positive SPECT scans, may demonstrate intermediate-term relief.[39]

RADIOFREQUENCY DENERVATION OF THE MEDIAL BRANCH

The most commonly performed treatment for facet-mediated pain is RF denervation. There have been eight placebo-controlled studies for lumbar facet pain and two for neck pain (Table 46-2). Some of these studies failed to appropriately select candidates through diagnostic blocks,[65] while others failed to utilize optimal technique (i.e., placing the electrode parallel to the nerve), making the results difficult to interpret.[65,66] Overall, however, the results argue favorably for the use of denervation in well-selected patients.

The medial branch is denervated by placing the active tip of a RF needle at the location of the nerve. For the lumbar region, the active tip is optimally positioned at the junction of the transverse process and lateral neck of the superior articular process in an orientation parallel to the nerve. In the cervical region, the active tip should be placed along the center of the articular pillar at most levels. Sensory stimulation is usually performed prior to denervation, with most experts recommending a threshold of no more than 0.5 volts. Motor stimulation is considered a safety measure to ensure adequate distance from motor fibers, though the elicitation of multifidus muscle contraction has also been used to guide

TABLE 46–2 Outcomes of Randomized Controlled Trials of Lumbar and Cervical Medial Branch Denervation

Author, Year	Patients Studied	Duration of Follow-up (months)	Methodologic Scoring	Results	Notes
King and Lagger, 1976[75] Lumbar spine	60 patients with LBP/leg pain and paraspinous tenderness. Three groups: (1) RF of primary posterior ramus, (2) RF of muscle at area of maximal tenderness (myotomy), (3) stimulation by no RF	6	MQ = 2 CR = 5	Group 1, 27% with relief. Group 2, 53% with relief. Group 3, 0% with relief.	No diagnostic blocks prior to randomization. Included patients with sciatica. Used three 120-s lesions without electrical stimulation to determine appropriate placement.
Gallagher et al., 1994[76] Lumbar spine	41 patients with "clear cut" (30 patients) or "equivocal" (11 patients) relief after intra-articular facet injection with local anesthetic and steroid; Randomized to RF or sham.	6	MQ = 2 CR = 6	In patients with "clear cut" response to intra-articular block, RF improved pain scores compared with sham. No difference between groups in patients with "equivocal" response to intra-articular block.	Did not define "clear cut" or "equivocal." Poor description of anatomic landmarks. Not blinded. RF needle placed perpendicular to medial branch.
van Kleef et al, 1999[68] Lumbar spine	31 patients with ≥ 50% relief after MBB; Randomized to RF or sham.	12	MQ = 5 CR = 8	3 month follow-up 9/15 in RF group vs 4/16 in sham group reported ≥ 50% relief. 12 month follow-up 7/15 in lesion group and 2/16 in sham group reported ≥ 50% relief.	Diagnostic blocks with 0.75 ml of local anesthetic. Placed RF probe perpendicular to the medial branch for denervation.
Sanders and Zuurmond, 1999[77] Lumbar spine	34 patients with chronic LBP with ≥ 50% relief after single lidocaine intra-articular block; Half received medial branch denervation, other half had intra-articular facet denervation.	3	MQ = 1 CR = 6	Both groups improved; however, intra-articular RF group improved more.	Diagnostic blocks with 1 ml. RF of medial branch done at inferolateral aspect of facet capsule and upper border of transverse process. Three intra-articular lesions done.
Leclaire et al., 2001[78] Lumbar spine	70 patients with chronic LBP with > 24 hours of significant relief after intra-articular lidocaine plus steroid; Compared RF with sham procedure.	3	MQ = 4 CR = 8	RF group with modest improvement in Roland Morris (p = 0.05) and VAS (p = ns) scores at 3 mos. No change Oswestry score or other outcomes.	Did not define "significant relief" for diagnostic block. Greater than 24-hour relief not consistent with lidocaine pharmacology. Landmarks not noted for RF and needle not placed parallel to medial branch.
Tekin et al., 2007[70] Lumbar spine	60 patients with chronic LBP with ≥ 50% relief from single MBB at either L1-3 or L3-5 received either sham, pulsed RF, or RF denervation	12	MQ = 4 CR = 8	Continuous RF > pulsed RF and sham for pain; nonsignificant difference between pulsed RF and sham. For ODI, continuous RF and pulsed RF > sham.	Used 0.3 ml for diagnostic blocks. Proper technique for blocks and RF. Study not powered to detect differences among treatment groups.
Nath et al., 2008[79] Lumbar spine	40 patients with chronic LBP who obtained > 80% relief from 3 LA blocks.	6	MQ = 4 CR = 6	RF group > control group in all outcome measures, although the benefits were modest.	40 patients randomized out of 376 screened. Created six empirical lesions without stimulation.
Van Wijk et al., 2005[66] Lumbar spine	81 patients with chronic LBP with ≥ 50% relief from 2 level intra-articular facet block with LA. RF compared with sham.	12	MQ = 5 CR = 7	No differences at 3 mos between groups for combined score of pain, physical activity, and analgesic intake. Global perceived effect greater in RF compared with sham at 3 mos.	Blinding ended at 3 mos with patients with persistent relief followed for 12 mos.

TABLE 46–2 Outcomes of Randomized Controlled Trials of Lumbar and Cervical Medial Branch Denervation—cont'd

Author, Year	Patients Studied	Duration of Follow-up (months)	Methodologic Scoring	Results	Notes
Lord et al., 1996[19] Cervical spinex	24 patients with neck pain ≥ 3 mos after MVA that failed conservative therapy. Diagnosed through placebo-controlled (saline vs LA) MBB. Compared 80°C RF vs 37°C control between C3-C7 medial branches.	3 (12 mos in patients with persistent relief)	MQ = 5 CR = 8	Time to return of 50% of pre-denervation pain was 263 days in RF group vs 8 days in placebo group ($p < 0.04$). At 27 wks, 7/12 patients in RF group and 1/12 in placebo group remained pain free.	Excluded patients with exclusively C2-3 pain. Five patients in RF group had numbness in skin associated with denervated area.
Stovner et al., 2004[65] Cervical spine	12 patients with unilateral cervicogenic HA with comparative blocks of medial branches and greater occipital nerve. Compared cervical medial branch RF vs sham.	24	MQ = 4 CR = 7	At 3 mos, 4/6 in RF group vs 2/6 in sham group with meaningful improvement (30% improvement). No differences at 6 mo.	RF group with better response to diagnostic blocks. Only recruited 12 patients in almost 2.9 yrs. Excluded patients with active litigation.

Notes: Methodologic quality (MQ) score based on 5-point scale previously described.[80] A score ≥3 indicates high MQ. Clinical relevance (CR) score based on patient selection parameters and RF technique description (0–9 scale) as described by Guertz et al.[81]
HA, headache; LA, local anesthetic; LBP, low back pain; MBB, medial branch block; MVA, motor vehicle accident; NS, nonsignificant; pts, patients; RF, radiofrequency; VAS, visual analog scale.
Source: Adapted from Brummett CM, Cohen SP: Facet blocks, facet joint injections, medial branch blocks, rhizotomy. In Benzon HT, Rathmell JP, Wu CL, Turk DC, Argoff CE, editors: Raj's Practical Management of Pain, *ed 4, New York, 2006, Mosby, pp. 1003–1037.*

needle placement.[67,68] Prior to denervation, local anesthetic with or without steroid can be injected to reduce procedure-related pain, enhance lesion size, and prevent neuritis. The duration of analgesia following RF denervation varies widely between studies, with most demonstrating between 6 months and 1-year relief.[19,67,69] Although data are limited, repeat denervation appears to provide comparable relief to the initial procedure.[70]

SURGERY

Surgery is occasionally done for facet pain despite the absence of convincing data to support it.[39] Some surgeons purposefully or inadvertently transect the medial branch during pedicle screw placement, which can provide some pain relief. However, when all data are synthesized, surgery is not recommended as a treatment for facetogenic pain.

COMPLICATIONS FROM MINIMALLY INVASIVE INTERVENTIONS

The most feared risk of RF denervation is thermal damage to the ventral nerve root due to incorrect needle placement, which is rare when motor stimulation is utilized. Postdenervation neuritis is the most common complication, but significant postprocedure pain occurs in less than 10% of cases. This can be reduced even further with prophylactic corticosteroid administration. Some patients describe transient numbness or dysesthesias, which are usually minor and self-limting.[71] Rarely, breaks in insulation or equipment malfunction can lead to burns.[37,72] Infectious complications are very infrequent, and appear to be even less common with RF than diagnostic blocks.[73]

CONCLUSION

Pain arising from the facet joints is a common source of pain and disability. With the exception of whiplash, facet pain is usually due to chronic degeneration. There are no historical or physical examination findings pathognomonic for diagnosis, but clinical assessment is important for ruling out other sources of pain and selecting candidates for interventions. Intra-articular or MBBs remain the "gold standard" for diagnosis, but are characterized by a high false-positive rate and lack of specificity. Most, but not all, studies have shown RF denervation to be safe and effective. In carefully selected patients, it can provide significant relief for 6 months to 1 year.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 47

Pain Originating from the Buttock: Sacroiliac Joint Syndrome and Piriformis Syndrome

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ANATOMY, FUNCTION, AND INNERVATION

The sacroiliac joint complex is the largest spinal joint the body, averaging 17.5 cm^2 in size. It is most frequently classified as an auricular-shaped diarthrodial joint because at various junctures it contains a fibrous joint capsule containing thick synovial fluid, cartilaginous surfaces, and an intricate set of ligamentous connections (Fig. 47-1). However, it is somewhat unique among synovial joints in that it is not readily mobile, there is discontinuity in the posterior capsule, and the thinner, iliac articulation is composed of fibrocartilage instead of hyaline cartilage.[1,2]

The SI joint is supported by a network of myofascial structures that help promote movement, support, and stability. These structures include the gluteus maximus and medius, biceps femoris, piriformis, the latissimus dorsi via the thoracolumbar fascia, and the erector spinae. The joint is primarily designed for stability and weight-bearing, though small degrees of rotation (<3 degrees) and translation (<2 mm) occur.[3,4] Previous attempts to establish a causative relationship between pain and motion abnormalities have been unsuccessful.[5]

The nerve supply of the SI joint complex is a subject of great contention and relevance for interventional pain practitioners. To summarize the literature, the posterior joint and the surrounding ligaments appear to receive innervation from the S1-S3 dorsal rami, with most studies noting a contribution from L5 (Fig. 47-2).[1] A recent cadaveric study found that in 59% of joints, the long posterior sacroiliac ligament also receives afferent input from S4.[6] Although many experts cite other sources of innervation such as from the L4 dorsal ramus and the superior gluteal and obturator nerves, these references appear to derive mostly from older studies conducted in the late 19th and early 20th centuries.[7,8]

Questions surrounding the innervation of the ventral SI joint, though less clinically relevant, are no less controversial. Whereas some studies have reported nerve filaments stemming from the ventral rami of L4–S2,[7] other experts cite contributions from levels as cephalad as L2.[9] Even more contentious is that others have failed to find any ventral neural contribution to the SI joint.[10]

The premise that both intra- and extra-articular structures can be sources of pain is incontrovertible. An electrophysiologic study conducted in cats identified mechanoreceptors in both the joint capsule and adjacent muscles, with most (26/29) residing within the capsule.[11] Among these receptor units, 28 were classified as nociceptive and one proprioceptive. Broken down by region, 16 were found in the proximal third, 11 in the middle third, and two in the distal third. Immunohistochemical studies in human cadavers have also found evidence of calcitonin-gene–related peptide and substance P immunoreactive nociceptors in both capsular and interosseous ligaments.[12] Clinical studies have documented pain provocation in patients and asymptomatic volunteers with both capsular distension and ligamentous provocation.[13–17]

EPIDEMIOLOGY

There are several problems with ascertaining the prevalence of SI joint pain. These include but are not limited to the lack of any "gold standard" for diagnosis, perspective (i.e., interventional pain specialists generally attribute a greater proportion of low back pain [LBP] to SI joint pathology than surgeons), the population studied and method of diagnosis.

In five prevalence studies using the reference standard of concordant pain relief with lidocaine and bupivacaine as the criterion for diagnosis,[18–22] the incidence of false-positive uncontrolled SI joint blocks has ranged between 0%[21] and 43%,[22] with the median being 17%. Among these same studies, the reported prevalence rates for SI joint pain in patients with chronic LBP varied between 10% and 45%, with a median of 26%. One flaw with these studies is that all of them based their criterion response on solely intra-articular injections, which likely excluded individuals with predominantly extra-articular pathology (Table 47-1).

Studies using different diagnostic criterion have yielded similar results. Schwarzer et al.[17] conducted a prevalence study in 43 consecutive patients with chronic LBP predominantly below L5 using fluoroscopically-guided intra-articular SI joint injections. The authors diagnosed SI joint pain based on three criteria: greater than 75% pain relief following intra-articular local anesthetic infiltration, ventral capsular tear on post-arthrography CT scanning, and concordant pain provocation during capsular distension. Using analgesic response as the sole criterion for diagnosis, the prevalence of SI joint pain was found to be 30% (95% confidence interval [CI] = 16–44%). When combining pain relief with a ventral capsular tear was used as the diagnostic criteria, the prevalence rate dropped to 21%. Only seven patients satisfied all three diagnostic criteria, for a lower-limit prevalence rate of 16%. In the largest prevalence study conducted in 1293 patients with nonspecific LBP, Bernard and Kirkaldy-Willis[23] estimated that 22.5% suffered from SI joint pain based on history and physical exam. Overall, SI joint pathology appears the primary generator in between 15% and 30% of patients with chronic axial LBP below L5.

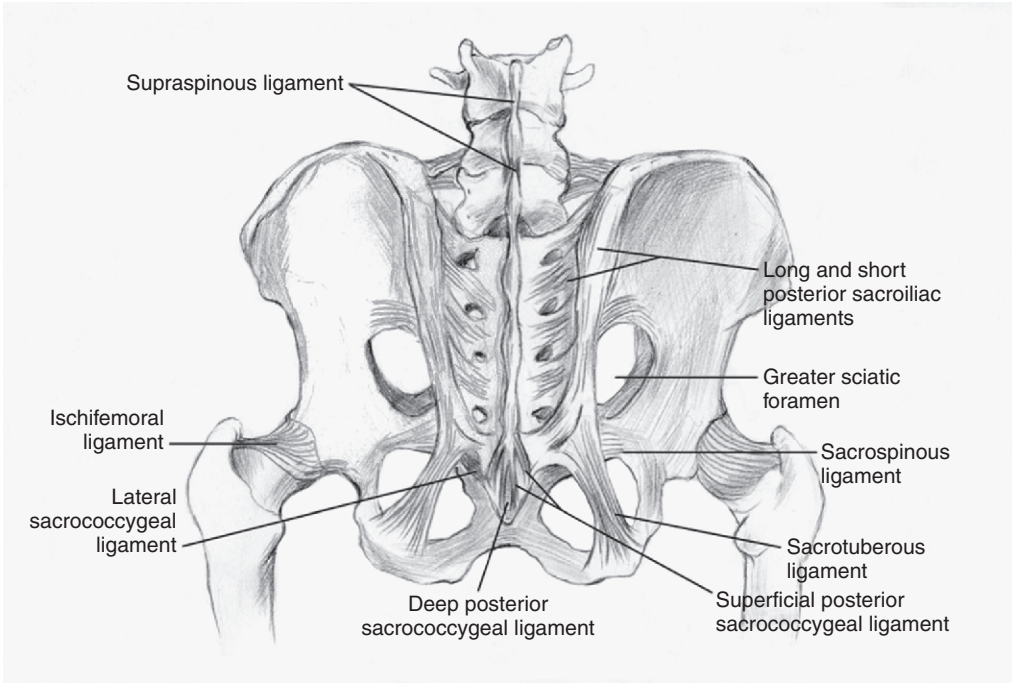

FIGURE 47-1 Posterior view of the articulations and associated ligaments of the sacroiliac joint and surrounding structures. *Sources: Drawing by Jee Hyun Kim. From Cohen SP: Sacroiliac joint pain: a comprehensive review of anatomy, diagnosis and treatment.* Anesth Analg *101:1440–1453, 2005.*

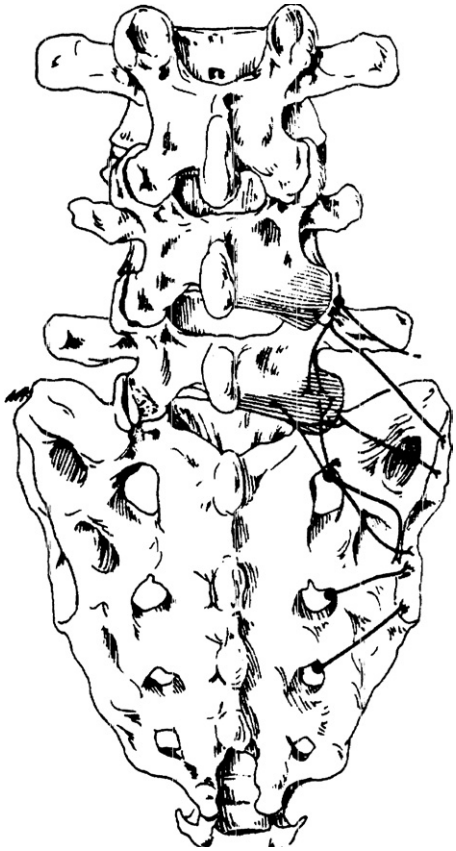

FIGURE 47-2 Innervation of the posterior sacroiliac joint region. A descending branch of the L4 primary ramus innervates the L5–S1 facet joint and the sacroiliac joint. The L5 and S1 primary rami also innervate the L5–S1 facet joint and the sacroiliac joint. Finally, the S2 and S3 sacral nerves innervate the sacroiliac joint. *Source: Paris SV: Anatomy as related to function and pain. Symposium on Evaluation and Care of Lumbar Spine Problems.* Orthop Clin North Am *14:475, 1983.*

ETIOLOGY

The mechanism of injury to the SI joint complex has previously been described as a combination of axial loading and abrupt rotation.[1] On an anatomic level, pathologic changes affecting myriad structures comprising the SI joint can lead to nociception. These include capsular or synovial disruption, ligamentous injury, myofascial pain, hypo- or hyper-mobility, extraneous compression or shearing forces, cysts, abnormal joint mechanics, micro- or macro-fractures, chondromalacia, and inflammation. In patients with persistent nociceptive input, central sensitization can play a contributing role (Table 47-2).

Mechanistically, there are numerous reported etiologies for SI joint pain. To simplify matters, these causes can be divided into intra- and extra-articular sources. Arthritis and infection are two examples of intra-articular causes of SI joint pain. Extra-articular sources include enthesopathy, fractures, ligamentous injury and myofascial pain. Supporting different etiologies is the observation that clinical studies have demonstrated significant pain relief following both intra- and peri-articular SI joint injections.[24–27]

Distinguishing between intra- and extra-articular pain generators is clinically relevant when planning treatment. A recent study by Dreyfuss et al. found that multi-site lateral branch blocks were more effective at blocking pain from ligamentous probing than for the discomfort elicited during capsular distension.[15] In contrast to intra-articular pathology, extra-articular pain is more likely to be unilateral, occur in younger individuals, present with more prominent tenderness, and be associated with a specific inciting event or biomechanical etiologies.

Numerous factors can predispose to the insidious development of SI joint pain. Risk factors that operate by increasing the stress borne by the SI joints include obesity, leg length discrepancy, gait abnormalities, persistent strain or low-grade trauma (e.g., jogging), scoliosis,

TABLE 47–1 Characteristics of Diagnostic Prevalence Studies Using Double-Blocks as Reference Standard

Authors	Subjects	Interventions	Diagnostic Criteria	Results
Maigne et al.[20]	54 patients with chronic unilateral LBP with or without radiation to posterior thigh	Intra-articular blocks using 2 ml of lidocaine and bupivacaine on separate occasions. Authors avoided anesthetizing periarticular ligaments	>75% pain relief, with the bupivacaine block lasting >2 hr	Prevalence rate 8.5%; false-positive rate 17%
Manchikanti et al.[19]	20 patients with chronic LBP without neurologic deficits	Intra-articular blocks with unspecified volume of lidocaine and bupivacaine on separate occasions	Not noted	Prevalence rate 10%; false-positive rate 20%
Irwin et al.[22]	158 patients with chronic LBP with or without lower extremity pain	Intra-articular blocks with 2 ml of lidocaine and 2 ml bupivacaine and steroid on separate occasions	>70% pain relief, with the bupivacaine block lasting >4 hr	Prevalence rate 27%; false-positive rate 43%
Laslett et al. [21]	48 patients with buttock pain, with or without lumbar or lower extremity symptoms, without signs of nerve root compression	Intra-articular blocks with <1.5 ml of lidocaine + steroid and bupivacaine on separate occasions	>80% pain relief with lidocaine and bupivacaine	Prevalence rate 26%; false-positive rate 0%
van der Wurff et al.[30]	60 patients with chronic LBP below L5 with or without lower extremity symptoms, without neurologic symptoms	Intra-articular blocks with 2 ml lidocaine and bupivacaine on separate occasions	>50% pain relief with lidocaine and bupivacaine, with the bupivacaine block lasting >4 hr	Prevalence rate 45%; false-positive rate 12%

LBP, lower back pain.

TABLE 47–2 Causes of Intra-Articular and Extra-Articular Sacroiliac Joint Pain

Intra-Articular	Extra-Articular
Arthritis (e.g., osteoarthritis, rheumatoid)	Trauma/fractures
Spondyloarthropathy	Ligamentous injury
Trauma	Myofascial pain
Infection	Enthesopathy
Cystic disease	Pregnancy
	Cystic disease

pregnancy, and surgery, especially fusion to the sacrum. Spine surgery may cause post-procedural SI joint pain by increasing load bearing, weakening the surrounding ligaments, iatrogenic violation of the SI joint complex, and postsurgical hypermobility.[1] Pregnancy predisposes women to SI joint pain via the combination of increased weight gain, exaggerated lordotic posture, the mechanical trauma of parturition, and hormone-induced ligamental laxity. Rarely, sacroiliac subluxation has also been causally related to back pain in pregnancy.

Between 40% and 50% of patients with injection-confirmed SI joint pain cite a specific inciting event. In investigations by Chou et al., Schwarzer et al., and Cohen et al., the leading precipitating events in descending order for trauma-induced SI joint pain were motor vehicle collisions, falls, cumulative strain, and pregnancy.[17,28,29]

DIAGNOSIS AND PRESENTATION

HISTORY AND PHYSICAL EXAM

Sacroiliac joint pain can be difficult to distinguish from other sources of LBP. Numerous studies have established that no single historical or physical examination sign can reliably diagnose a painful SI joint.[16,17,20] Several reviews have sought to evaluate the validity of a battery of physical examination tests in establishing the sacroiliac joint(s) as the primary pain generator. These reviews have generally shown that mobility and alignment tests are inadequate in identifying SI joint-mediated pain.[1,30] For provocative maneuvers the results have been mixed. Whereas some reviews have determined that a combination of provocative maneuvers can accurately discriminate between SI joint and other sources of spinal pain,[31,32] others have reached equivocal[30,33,34] or negative[35] conclusions.

Nevertheless, studies have suggested that a thorough history and examination can provide important clues to etiology, and inform further diagnostic workup. Some of the more common findings used to select candidates for SI joint blocks are pain predominantly localized below L5, pain exacerbated by rising from a sitting position, and tenderness overlying the joint. In contrast to other causes of mechanical LBP such as myofascial, facetogenic, and discogenic pain, SI joint pain is more likely to be unilateral and follow a specific inciting event.[17,28,29]

PAIN REFERRAL PATTERNS

Several investigators have sought to determine pain referral patterns from SI joints. The pain may radiate from the buttock to the ipsilateral thigh, groin, lumbar region or posterior thigh and leg, but there is no pathognomonic radiation pattern for pain from the SI joint (Fig. 47-3). In a provocative study conducted in 10 asymptomatic volunteers, Fortin et al.[13] found that all subjects experienced pain in the ipsilateral buttock, which sometimes radiated into the posterolateral upper thigh. In a retrospective review by Slipman et al.[36] conducted in 50 patients with injection-confirmed SI joint pain, the authors found the most common referral patterns to be focal pain in the

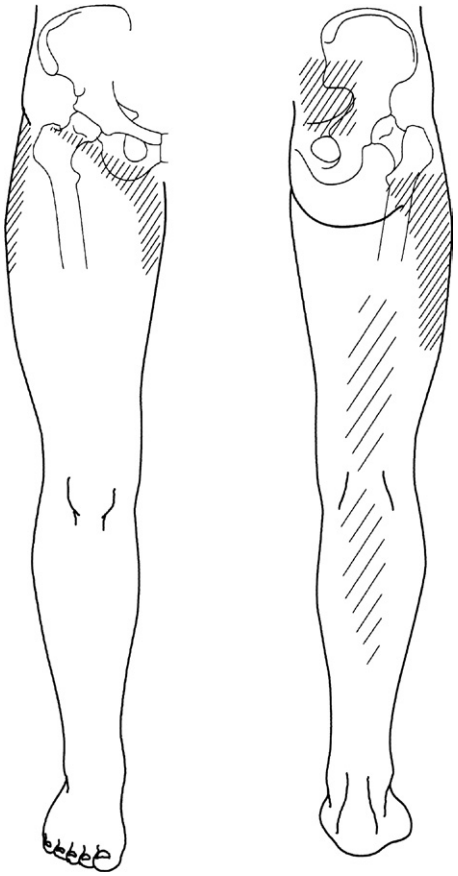

FIGURE 47-3 Location of pain in a patient with sacroiliac joint syndrome.

buttock (94%) and lower lumbar region (72%), and extension into the ipsilateral lower extremity (50%), groin area (14%), upper lumbar region (6%), and abdomen (2%). Twenty-eight percent of patients experienced pain radiating below their knee, with 12% reporting foot pain. Finally, Cohen et al.[29] examined pain referral patterns in an analysis of SI joint radiofrequency (RF) denervation outcome predictors conducted in 77 patients with positive screening blocks. Forty-three percent experienced symptoms localized to the buttock and lower lumbar region, with 35% noting pain referred to their thigh(s). Consistent with Slipman,[36] the authors also noted a high percentage of unusual pain patterns, with 23% reporting lower leg pain, and 20% complaining of extension into their groin.

RADIOLOGICAL IMAGING

Results of studies correlating radiologic findings with the results of diagnostic blocks have been similarly disappointing. Studies by Slipman et al.[37] and Maigne et al.[38] found sensitivities of 13% and 46%, respectively, for the use of radionuclide bone scanning in the identification of a painful SI joint. Despite the high specificities in these studies (90% for Maigne and 100% for Slipman), the low sensitivities indicate that bone scanning will fail to detect a majority of cases. Poor correlation between symptoms and diagnostic injections have also been found for computed tomography and x-ray stereophotogrammetry.[5] In a retrospective analysis by Elgafy et al.,[39] CT imaging was found to be 57.5% sensitive and 69% specific in diagnosing SI joint pain.

In contrast, MRI and CT scanning are the gold standards for detecting SI joint involvement in patients with seronegative spondylarthropathy. Whereas MRI may be more sensitive for detecting inflammation and the accompanying structural changes, CT remains the reference standard for disease states in which bone destruction or ossification can occur.

INJECTIONS

It is well accepted that an analgesic response to an SI joint injection is the most accurate means to diagnose a painful SI joint complex (Fig. 47-4). In studies that have sought to determine the predictive value of historical and physical examination signs, etiologies, and referral patterns, response to low volume (< 2 ml) SI joint blocks have generally been used as the reference standard. In almost all cases, these injections have been intra-articular. Although some of the injectate may extravasate into adjacent ligaments and muscles, diagnostic capsular injections may underestimate the true prevalence of pain from the SI joint complex by failing to anesthetize the surrounding soft tissues.

The false-positive rate of uncontrolled SI joint blocks is around 20%. This has led some experts to recommend using "double-blocks" with two local anesthetic drugs having different half-lives, or placebo-controlled blocks, as the best way to identify a painful SI joint. The main problem with the double-block paradigm is that the correlation between the duration of benefit and the pharmacokinetics of the active local anesthetic is very weak.[40] A study conducted using double comparative blocks in

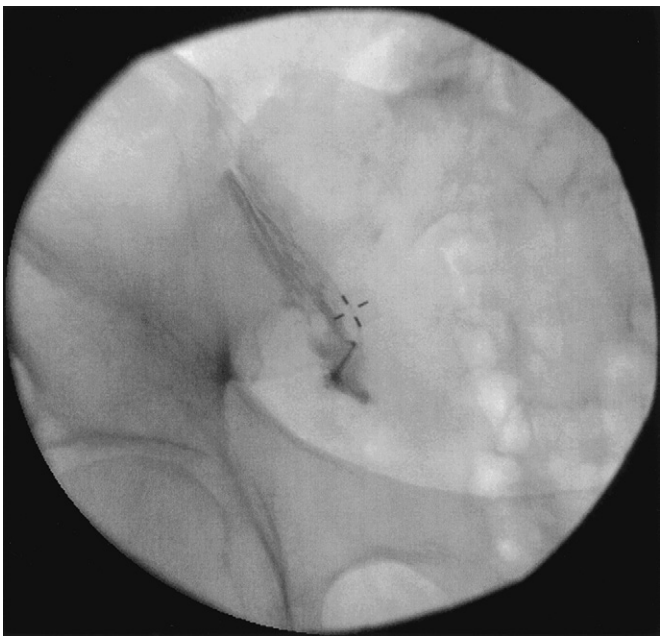

FIGURE 47-4 Fluoroscopic image of the sacroiliac joint after injection of radiopaque dye.

patients with suspected cervical facet arthropathy found that this diagnostic paradigm may be associated with a significant false-negative rate, which means that many patients with the condition would be misdiagnosed.[41] The double-block diagnostic paradigm is also not cost-effective when selecting candidates for RF denervation.[42] Although one might expect higher success rates for RF denervation when candidates are chosen based on their response to controlled blocks, direct comparisons have thus far not borne this out in clinical studies conducted for SI joint pains.[29]

TREATMENT

CONSERVATIVE

The conservative treatment of SI joint pain should ideally address the underlying etiology. True and functional leg length discrepancies can be treated with shoe lifts and physical therapy, respectively. True leg length discrepancies result in increased stress and abnormal force vectors on the ipsilateral lower extremity. Because these are common in asymptomatic individuals, and many people already compensate for their lower extremity length difference by altering their gait or posture, most experts recommend starting out cautiously with inserts that correct only half the incongruity, and implementing them gradually. In one study conducted in 798 patients with chronic low back or hip pain and 359 controls, Friberg[43] found that 75% of patients had leg length asymmetries of at least 5 mm vs. 43.5% of the asymptomatic cohort. Functional leg length discrepancies usually occur as a result of muscle weakness or inflexibility at the pelvis or ankle. Specific causes include pelvic obliquity, adduction, or flexion contractures of the hip, and genu valgum and varum. The treatment of apparent leg length discrepancies entails aggressive physical therapy that targets the underlying etiology. If malalignment is suspected, osteopathic or chiropractic manipulation has been reported to be of value,[44] although prospective controlled studies are lacking. For patients with spondyloarthropathies, immunomodulating agents such as cytokine inhibitors and methotrexate may reduce disease progression, alleviate pain, and improve function.

Practice guidelines have found exercise to be beneficial for nonspecific chronic low back pain, but it may be particularly beneficial in patients with SI joint pain.[45] Biomechanical models have shown contraction of the transversus abdominus muscle to be associated with reduced laxity of the SI joint, and suggest that isolated contraction of transversely oriented musculature (e.g., pelvic floor muscles and piriformis) can stabilize the joint.[46] In a study by Mooney et al.,[47] the authors found five women with injection-confirmed SI joint pain who had electromyographic-documented hyperactivity of the ipsilateral gluteus muscles and contralateral latissimus muscle compared with an asymptomatic control group. After a 2½-month exercise program, all patients achieved a significant reduction in pain and a return of electromyographic patterns to normal. In the majority of patients who do not have a correctable etiology, pharmacotherapy should be considered as one arm of a multidisciplinary treatment regimen. Because no studies have specifically targeted patients with SI joint pain, the results of clinical trials conducted in nonspecific LBP patients must be extrapolated. In patients with acute non-neuropathic back pain, both NSAIDs and muscle relaxants may be effective, though the treatment effect is small. In patients with chronic LBP, there is weak evidence supporting the use of tricyclic antidepressants.[48]

INJECTIONS

Multiple reviews, guidelines, and meta-analyses have evaluated SI joint injections, reporting disparate results. Whereas some reviews conclude there is reasonable evidence for intra-articular steroids for the intermediate term (>6 months), others conclude that there is negative evidence.[1,49] These discrepancies appear to be rooted in perspective (i.e., reviews conducted by interventional pain physicians tend to be more positive than those conducted by epidemiologists), and the disparities in the articles analyzed. Among the four randomized trials, three of which were placebo controlled, all demonstrated significant benefit.[24,26,27,50] Three were conducted in patients with spondylarthropathies[24,26,27] and one was done in children.[50] Two studies, both by the same group of investigators, evaluated periarticular injections.[26,27] However, only one of the placebo-controlled studies followed patients longer than 2 months, and this study enrolled only 10 patients.[24] Because of the low numbers, the authors were not able to demonstrate statistically significant differences in medication usage or functionality between the treatment and control groups. However, 7 of the 12 joints injected with corticosteroid continued to have good pain relief at 6-month follow-up. Whereas both studies evaluating periarticular injections demonstrated decreased spontaneous pain, provoked pain and tenderness, neither assessed functional capacity.[26,27]

There are a host of uncontrolled studies evaluating the long-term effects of SI joint injections. In four observational studies conducted in over 100 patients with spondylarthropathy, when data are combined, over 85% of the subjects obtained significant pain relief lasting for an average of 10 months.[51–54] Comparable results have been obtained in patients without spondylarthropathy,[55,56] and with repeat injections.[57] Although good results have been anecdotally reported with "blind" injections,[58] a study by Rosenberg et al. found that only 22% of nonradiologically guided SI injections extended into the joint space[59] (Tables 47-3 and 47-4).

NEUROABLATION

Neuroablative techniques, especially radiofrequency denervation, have become the treatment of choice for patients in whom conservative treatments fail to provide long-term symptom palliation.

The first report by Ferrante et al.[60] described performing sequential RF lesions in the posteroinferior aspect of the joint by leapfrogging an electrode at less than 1-cm intervals. In this retrospective review, only 36% of patients reported more than 50% pain relief lasting at least 6 months. Considering that only a small

TABLE 47–3 Randomized, Controlled Studies Evaluating Sacroiliac Joint Injections

Author, Year	Study Design	Subjects	Interventions	Results	Comments
Fischer, 2003[50]	Randomized, controlled	89 children with juvenile spondyloarthropathy; 56 were responders to NSAIDs (control group) and 33 were nonresponders (treatment group)	Treatment group received steroid without LA injections plus NSAIDs; control group was continued on NSAIDs alone	87.5% who received injections reported decreased pain complaints over the 20-mo follow-up (VAS pain score decreased from 6.9 to 1.8). The control group showed similar improvements in pain scores, with no difference between groups	Dx made clinically and by MRI evidence of sacroiliitis. One-third of patients who received injections demonstrated continued joint destruction
Luukkainen, 2002[27]	Randomized, controlled study	24 patients without spondyloarthropathy	All patients underwent unilateral, periarticular injections; 13 patients received steroid and LA, with 11 patients receiving saline and LA	At 1-mo follow-up, VAS pain scores decreased significantly more in the steroid group than saline group	Injections were periarticular, not intra-articular; Dx made by PE; no pt had radiologic evidence of sacroiliitis
Maugars, 1996[24]	Placebo-controlled, double-blind	10 patients with spondyloarthropathy, 13 joints	13 total joints injected; 6 were injected with steroid and LA and 7 with saline; 6 of 7 placebo patients were reinjected with steroid at 1 mo	5 steroid joints had good or very good pain relief at 1 mo vs. 1 in placebo group; overall, 12/14 SI joints had good or very good results at 1 mo, 8/13 at 3 mo and 7/12 at 6 mo	Dx made by PE and radiologic studies; one pt developed radicular pain that lasted 3 wk
Luukkainen, 1999[26]	Randomized, controlled study	20 patients with seronegative spondyloarthropathy	All patients underwent unilateral, periarticular injections; 10 received corticosteroid without LA; 10 received normal saline with LA	At 2-mo follow-up, VAS pain scores decreased significantly in the steroid but not saline group	Injections were periarticular, not intra-articular; Dx made by PE and radiologic studies

Dx, diagnosis; LA, local anesthesia; pt, patient; PE, physical examination; SI, sacroiliac; VAS, visual analog scale.

TABLE 47–4 Alternative Treatments for Sacroiliac Joint Pain

Visco supplementation
Acupuncture
Alternative exercise programs (e.g., yoga/Tai Chi)
Cognitive-behavioral therapy/relaxation techniques
Neuromodulation
Proliferative therapy (prolotherapy)

portion of the joint was denervated, these findings are not surprising. Others have attempted intra-articular phenol neurolysis with better results, but the inherent risks curtail its utility.[61]

Subsequent attempts at RF ablation targeting the lateral branches of the primary dorsal rami have met with more auspicious results, with most studies reporting sustained relief lasting at least 6 months in over 60% of subjects.[62–65] However, these studies have utilized widely dissimilar selection criteria and targeted different nerves, ranging from the all inclusive L4–S4 levels to S1–S3 (Fig. 47-5). One study targeted only the L5 dorsal ramus but created additional lesions in the posterior interosseous ligaments,[66] whereas another group selected nerves based on concordant sensory stimulation.[64] The uniformly high success rates in uncontrolled studies using disparate methodology has raised many questions regarding selection criteria, technique, and the validity of the results.[67]

Anatomic studies have demonstrated that the lateral branches which provide nociceptive and proprioceptive input from the SI joints vary in number and location, from patient to patient, side to side and level to level.[64] This makes capturing all afferent input using conventional RF techniques, wherein the typical lesion diameter ranges between 3 mm and 4 mm in a single plane, technically challenging. Several techniques have been adapted to enhance lesion size and overcome this obstacle, including bipolar lesioning, internally cooled electrodes, and replacing RF electrodes with cryoprobes.[68,69] Although good anecdotal results have reported with bipolar electrodes,[68] which may act to create continuous strip lesions between the two electrodes, this technique is limited by wide variations in tissue impedance around the sacral foramen, which can result in asymmetric heating patterns. For cryoanalgesia, the main downside is the shorter duration of benefit.[69]

Both controlled and uncontrolled studies support the use of cooled RF.[65,70] In a randomized, placebo-controlled study conducted in 28 patients, Cohen et al.[70]

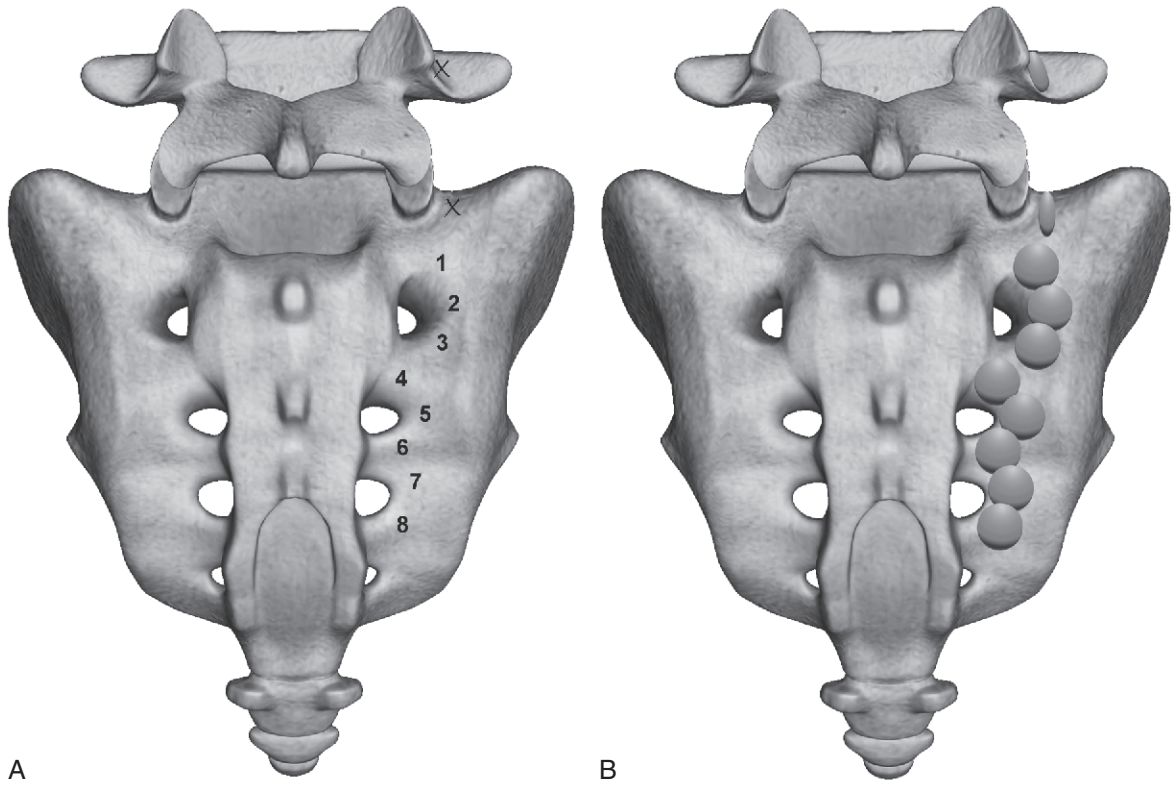

FIGURE 47-5 Schematic diagram illustrating: *A*, Target points for right-sided conventional (L4 and L5) and cooled (S1–S3) radiofrequency denervation at the junction of the L5 superior articular and transverse processes (L4 primary dorsal ramus), the sacral ala (L5 primary dorsal ramus), and S1–S3 foramina (lateral branches). *B*, Anticipated lesions at each of the target points. *Source: Cohen SP, Hurley RW, Buckenmaier CC 3rd, et al: Randomized, placebo-controlled study evaluating lateral branch radiofrequency denervation for sacroiliac joint pain.* Anesthesiology *109:279–288, 2008.*

found that 64% and 57% of patients experienced more than 50% pain relief at 3- and 6-month follow-up, respectively, with comparable improvements in function and medication reduction. In subjects who experienced a successful outcome, the median duration of benefit was about 8 months.

Radiofrequency denervation may not benefit everyone with SI joint pain. Targeting the posterior nerve supply does not address pain emanating from the ventral aspect of the joint, and a study by Dreyfuss et al.[15] found that lateral branch blocks were more effective at preventing pain secondary to extra-articular (i.e., ligamentous) stimulation than from capsular distension. In an attempt to better delineate those patients most likely to respond to SI joint RF denervation, Cohen et al.[29] conducted an analysis of demographic and clinical factors affecting outcomes in 77 patients. Overall, 52% of the 77 patients continued to experience greater than 50% pain relief at 6 months post-procedure. Not surprisingly, age greater than 65 years (perhaps because elderly patients are more likely to have intra-articular pathology), higher preprocedure pain scores, opioid usage, and pain extending below the knee were associated with treatment failure. A weak association was found between a positive outcome and the use of cooled RF probes. Because internally cooled electrodes remove the constraint of tissue charring on lesion expansion, it can increase lesion diameter by 200% to 300%, and volume by a factor of 8.

SURGICAL STABILIZATION

Sacroiliac joint arthrodesis has been previously employed to treat fractures, instability/dislocations, and pain secondary to degenerative changes. Among these indications, SI joint arthropathy is the most controversial, with study results being confounded by poor selection criteria and diverse outcome measures. In a recent review, Cohen and Hurley[71] found limited evidence to support SI joint arthrodesis for arthritis. When stability or stabilization is the primary indication, diagnostic blocks have not been shown to improve outcomes, though the methodologic flaws preclude any definitive conclusions from being drawn.

CONCLUSIONS

Sacroiliac joint pain is a common cause of chronic axial LBP, accounting for between 15% and 30% of cases. Although some reviews have found batteries of provocative maneuvers to be reasonable means of identifying a painful SI joint(s), the gold standard for diagnosis remains diagnostic blocks. However, uncontrolled blocks are associated with a significant false-positive rate.

Sacroiliac joint pain can be classified into intra- and extra-articular causes. For both, treatment represents a significant challenge. When a specific, remediable cause can be identified (e.g., leg length discrepancy or muscle weakness), treatment should be based on correcting

the underlying pathology. Corticosteroid injections may provide short or intermediate-term relief in well-selected patients with both intra-and extra-articular joint pain, but the evidence for long-term benefit is mainly anecdotal. Finally, there is moderate evidence supporting RF denervation to treat pain arising from SI joint(s).

PIRIFORMIS SYNDROME

Piriformis syndrome is an uncommon and often misdiagnosed cause of buttock and leg pain, with reported incidence rates typically ranging between 5% and 8%, but sometimes cited as high as 36%, among patients with low back pain.[72–75] In this section the following topics are discussed: (1) the anatomy of the piriformis muscle and anatomic abnormalities that cause piriformis syndrome;[76,77] (2) etiologies of the syndrome; (3) signs and symptoms associated with the syndrome; and (4) treatments of the syndrome.

ANATOMY OF THE PIRIFORMIS MUSCLE AND THE SCIATIC NERVE

The piriformis muscle originates from the anterior surface of the S2–S4 sacral vertebrae, the capsule of the sacroiliac joint, and the gluteal surface of the ilium near the posterior surface of the iliac spine.[76] It runs laterally through the greater sciatic foramen, becomes tendinous, and inserts into the piriformis fossa at the medial aspect of the greater trochanter of the femur. The piriformis muscle is innervated by branches of the ventral rami of the L5, S1, and S2 spinal nerves. The sciatic nerve, posterior femoral cutaneous nerve, gluteal nerves, and the gluteal vessels pass below the piriformis muscle.

Six possible anatomic relationships occur between the sciatic nerve and the piriformis muscle[72,78,79]: These include an undivided sciatic nerve passing below or above the piriformis muscle, an undivided nerve passing through the piriformis, a divided nerve passing through and below the muscle or through and above the muscle, and a divided nerve passing above and below the muscle.

Several investigators[78–80] noted that the most common arrangement was the undivided nerve passing below the piriformis muscle (84-98%) followed by the divisions of the sciatic nerve between and below the muscle (12%). When the muscle was split, the tibial component of the sciatic nerve passed below the piriformis muscle while the common peroneal nerve passed through the muscle.[80] Anomalies of the piriformis muscle and the sciatic nerve can cause sciatica. The compression usually occurs between the tendinous portion of the muscle and the bony pelvis. In patients in which the piriformis muscle is anterior to the sciatic nerve, the compression of the nerve occurs between the superior border of the piriformis and the superior margin of the greater sciatic foramen.

A case report described a patient whose sciatica was relieved after the lower head of the bipartite piriformis muscle was surgically cut.[76] Another patient had a fascial constricting band around the sciatic nerve and a piriformis muscle lying anterior to the nerve.[77] Resection of the fibrous band and the piriformis muscle restored the normal relationship of the muscle and nerve and relieved the patient's hip and buttock pain and sciatica. Several authors have recommended surgical release of the muscle and its fascia for sciatic nerve entrapment caused by piriformis syndrome.[81,82]

PATHOPHYSIOLOGY, SIGNS AND SYMPTOMS, AND TREATMENT

Etiologies and predisposing factors of the syndrome include trauma to the pelvis or buttock,[72] hypertrophy or spasm of the piriformis and/ or adjacent gemelli muscles,[76] female gender, pregnancy, anatomic abnormalities of the piriformis muscle or the sciatic nerve,[76,77] leg-length discrepancies (a minimum of half an inch difference in leg lengths), obesity, cerebral palsy secondary to hypertonicity, lumbar hyperlordosis, and infection.[83]

Microtrauma to the piriformis muscle may occur from oversue injuries as seen in athletes or in people doing heavy manual labor. A history of trauma is usually elicited in approximately 50% of the cases: the trauma is usually not dramatic and may occur several months before the initial symptoms. Trauma to the buttock leads to inflammation and spasm of the muscle. Inflammatory substances such as prostaglandins, histamine, bradykinin, and serotonin are released from the inflamed muscle and may irritate the sciatic nerve resulting in a pain–spasm–inflammation–irritation–pain vicious cycle.[80,84] The stretched, spastic, and inflamed piriformis muscle may compress the sciatic nerve between the muscle and the pelvis.

Other investigators consider piriformis syndrome to be a form of myofascial pain syndrome. Isolated involvement of the piriformis muscle is uncommon and usually occurs as a part of soft tissue injuries resulting from rotation and/ or flexion movements of the hip and torso.[73] In addition to the piriformis muscle itself, pathology involving the superior and inferior gemelli muscles, and the obturator internis, can lead to buttock pain with or without lower extremity radiation. Not infrequently, the tendinous portion of the piriformis muscle, which is often the major site of pathology (e.g., enthesopathy) combines with the tendons of the obturator and gemelli muscles before their insertion on the greater trochanter. Piriformis syndrome may occur after total hip replacement surgery or laminectomy.[81] The scar tissue after laminectomy impinges on the nerve roots and "shortens" the sciatic nerve, rendering it prone to repeated tension and trauma by the piriformis muscle.[81]

The differential diagnoses of piriformis syndrome include the myriad causes of low back pain and sciatica; patients with piriformis syndrome, however, usually do not have neurologic deficits unless there is compression or irritation of the sciatic nerve. Facet syndrome, sacroiliac joint dysfunction, trochanteric and ischial bursitis, myofascial pain syndrome, pelvic tumor, endometriosis, and conditions irritating the sciatic nerve should be considered in the differential diagnoses of piriformis syndrome. These conditions can be ruled out by a complete medical history and physical examination; diagnosis of piriformis syndrome is usually arrived at only after exclusion of these possibilities.[80]

Some of the cardinal features of the syndrome include the following[72,80]:

- History of trauma to the sacroiliac and gluteal regions
- Pain in the buttock that radiates to the ipsilateral hip or down the ipsilateral leg
- Pain with maneuvers that stretch the piriformis muscle (Lasegue and Freiberg tests)

Patients with piriformis syndrome usually complain of buttock pain with or without radiation to the ipsilateral leg.[72] The buttock pain usually extends from the sacrum to the greater trochanter since the muscle inserts into the medial aspect of the greater trochanter.[72,73,80] Some patients may have paralumbar pain. Gluteal pain radiating to the ipsilateral leg is usually present if the piriformis muscle irritates the sciatic nerve.[80] The pain is generally aggravated by prolonged sitting, as in driving or biking, or when getting up from a sitting position.[72,73] Pain occurs with bowel movements due to the proximity of the piriformis muscle to the lateral pelvic wall, and is worse after sitting on hard surfaces. Female patients may complain of dyspareunia.[72]

Physical examination of the patient may reveal a pelvic tilt or tenderness in the buttock from the medial edge of the greater sciatic foramen to the greater trochanter.[72] A spindle-shaped mass may be felt in the buttock and there may be piriformis tenderness on rectal and pelvic examinations.[72,73] The pain is aggravated by hip flexion, adduction, and internal rotation. Neurologic signs are usually absent, although there maybe numbness in the lower leg or foot from compression of the sciatic nerve by the piriformis muscle. The straight leg raising test may be normal or limited, with numbness occurring when the sciatic nerve is irritated. The following physical examination signs may be helpful in confirming the presence of piriformis syndrome:

- Pace sign: pain and weakness on resisted abduction of the hip while the patient is seated, (i.e. the hip is flexed).[80]
- Lasegue sign: pain on voluntary flexion, adduction, and internal rotation of the hip.[80,84]
- Freiberg sign: pain on forced internal rotation of the extended thigh.[80] This is due to stretching of the piriformis muscle and pressure on the sciatic nerve at the sacrospinous ligament.

The incongruity of the Lasegue and Freiberg signs is secondary to the function of the piriformis muscle: it is an adductor of the flexed thigh[73,80] and an external rotator of the extended hip.

The diagnosis of piriformis syndrome is made predominantly on clinical grounds, although electromyography (EMG), computed tomography (CT), and magnetic resonance imaging (MRI) may show abnormalities. EMG may detect myopathic and neuropathic changes including a delay in the H-reflex with the affected leg in a flexed, adducted, and internally rotated (FAIR) position as compared with the same H-reflex in the normal anatomic position.[85] A three–standard-deviation prolongation of the H-reflex has recently been recommended as the physiologic criterion for piriformis syndrome. CT and MRI of the soft tissues of the pelvis often show an enlarged piriformis muscle,[84] whereas bone scan may demonstrate increased radioactive uptake.[86]

The treatment of piriformis syndrome includes physical therapy combined with the use of anti-inflammatory drugs, analgesics, and muscle relaxants to reduce inflammation, spasm, and pain.[72,73] Physical therapy involves stretching of the piriformis muscle with flexion, adduction, and internal rotation of the hip[72,73] followed by pressure applied to the piriformis muscle. Abnormal biomechanics caused by posture, pelvic obliquities, and leg length inequalities should be corrected. Ultrasound treatments can help reduce the pain. Early treatment with nonsteroidal antiinflammatory drugs, physical therapy, and injections is effective in 75% to 80% of the patients.[87] Patients who do not respond to conservative therapy are candidates for local anesthetic and steroid injections. Most injections are into the piriformis muscle with or without perisciatic nerve injections. Caudal steroid and local anesthetic injections have been anecdotally reported to be effective, presumably because the injected solution diffuses along the nerve root sleeves to the proximal part of the sciatic nerve and blocks the nerves that innervate the piriformis muscle.[88]

TECHNIQUES OF PIRIFORMIS MUSCLE AND PERISCIATIC NERVE INJECTIONS

Initial publications on piriformis muscle injections were done blindly.[72,73] The perisciatic injection of Hanania and Kitain[89] is similar to the classic posterior (Labat) approach to sciatic nerve block. The sciatic nerve is located with a nerve stimulator, the needle is withdrawn a few centimeters, and 40 mg methylprednisolone in 5- to 10-ml dilute local anesthetic is injected. Newer techniques involve identification of the piriformis muscle with a muscle EMG or with the use of CT guidance. In the technique of Fishman et al.,[90] fluoroscopy, and EMG are used to identify the piriformis muscle. Correct needle placement is confirmed with muscle EMG and injection of contrast media. The steroid is then injected into the piriformis muscle.

In the CT-guided approach,[91] the muscle is identified and insertion of the needle is guided radiologically. Local anesthetic (2 ml 0.5% bupivacaine) with steroid is injected into the muscle, which may replaced by the injection of 100 units of botulinum toxin type A (BTX-A) if spasm or hypertrophy is noted. One advantage of this approach is that it may better facilitate injections targeting the tendinous insertions of the external rotators of the hip (e.g., piriformis, gemelli, obturator internus muscles).

Another technique uses the lower border of the sacroiliac joint as the landmark.[80] The patient is placed prone and the lower border of the sacroiliac joint, greater sciatic foramen, and the head of the femur are identified by fluoroscopy. A 15-cm insulated needle connected to a nerve stimulator is inserted 1 to 2 cm lateral and 1 to 2 cm caudal to the lower border of the sacroiliac joint (Fig. 47-6). The needle is advanced perpendicularly until a motor-evoked response of the sciatic nerve is obtained at a depth between 7 and 10 cm. The evoked motor response of the foot can be inversion, eversion, dorsiflexion, or plantar flexion. The needle is pulled back 0.3 to 0.5 cm, to avoid intraneural injection, and corticosteroid (40 mg) mixed with saline is injected to avoid sciatic nerve block. Injection of steroid perisciatically is recommended even in the absence of signs of sciatic nerve entrapment, because nerve inflammation is common in this condition. The needle is then pulled back

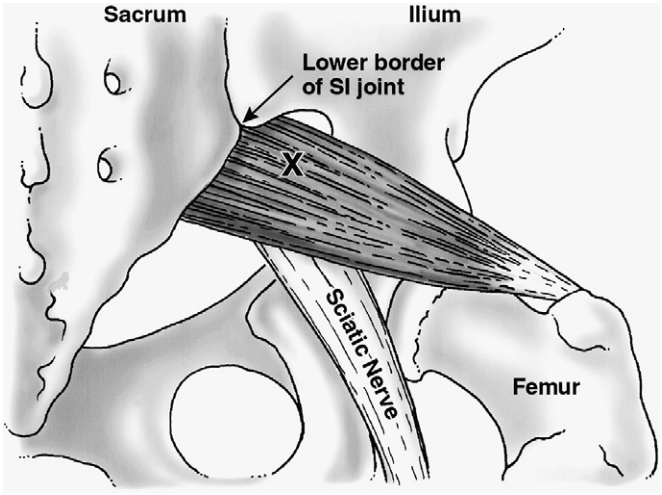

FIGURE 47-6 Posterior view of the sacrum, ilium, and greater trochanter of the femur, illustrating the course of the piriformis muscle, sciatic nerve, and the site of injection (marked "X"). *Source: Benzon HT, Katz JA, Benzon HA, Iqbal MS: Piriformis syndrome: anatomic considerations, a new injection technique, and a review of the literature.* Anesthesiology *98:1442–1448, 2003, with permission.*

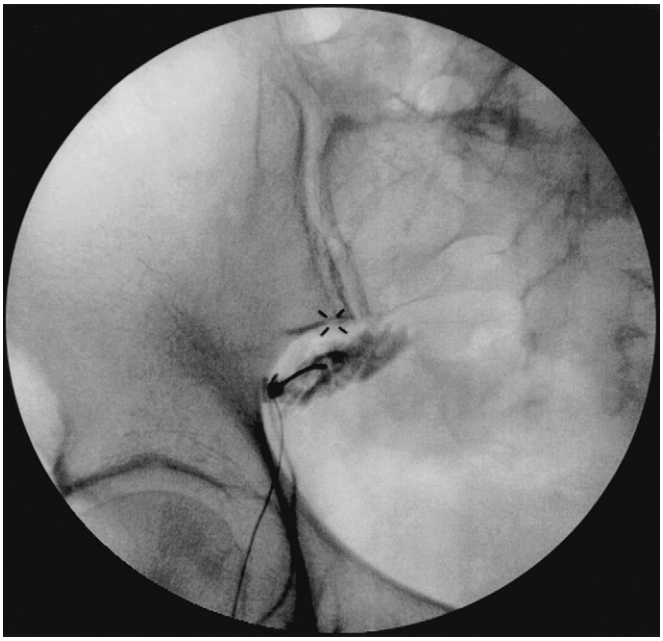

FIGURE 47-7 Fluoroscopic image of the insulated needle in the piriformis muscle with the muscle being outlined by the injected radiopaque dye.

an additional 1.0 cm so that the tip of the needle lies in the belly of the piriformis muscle. A small volume of radiopaque contrast is injected (some use air to outline the muscle especially in the presence of contrast allergy) to confirm needle position before more steroid (40 mg), this time mixed with local anesthetic, is injected to reduce muscle swelling and/or spasm (Fig. 47-7). Methylprednisolone (40 mg) (or 40 mg triamcinolone) in 6 to 8 ml local anesthetic, is injected into the muscle to reduce the swelling and/or spasm.[80] In our clinical experience, some patients experience sustained relief for up to 3 months with the local anesthetic–steroid injections.[80]

Botulinum toxin may be injected into the muscle if the patient has a transient response to steroid and local anesthetic. Botulinum toxin blocks the release of acetylcholine at the neuromuscular junction, resulting in prolonged relaxation. Recovery depends on neuromuscular sprouting and reinnervation of the muscle, which generally takes several weeks to months. A prospective study of 29 patients who had low-dose botolinum toxin injection type A (150 units) showed pain relief and improved quality of life lasting more than 12 weeks after the injection.[92] An earlier randomized study compared BTX-A with methylprednisolone in patients with "myofascial piriformis pain."[91] The patients in both groups showed marked reduction in their pain scores 30 days after the injection with no significant difference between the two groups. However, the patients who received botulinum injections had significantly lower pain scores 60 days after the injection.[91]

The typical doses of botulinum toxin employed are 100 mouse units for BTX-A (Botox)[91] and 5000 to 10,000 units for botulinum toxin type B (Myobloc).[93] Reported complications include plexopathy, polyradiculoneuritis, and local psoriasiform dermatitis.

Surgery may be entertained in recalcitrant cases or when there is a documented anatomic abnormality of the piriformis muscle. The muscle may be excised, divided, or thinned.[72,73,76,82] Surgical management can lead to improvement, with resumption of patients' daily activities and return to work, in approximately 75% of patients.[94] The obturator internus, gemelli, and quadratus femoris muscles share common functions with the piriformis muscle and can compensate for the loss of piriformis muscle function.[72,80]

KEY POINTS

- Sacroiliac joint pain can be caused by intra- and extra-articular causes.
- Several tests confirm the diagnosis of SI joint syndrome. An analgesic response to an SI joint injection is the most accurate means to diagnose a painful SI joint complex.
- Corticosteroid injections may provide short or intermediate-term relief in well-selected patients but evidence for long-term benefit is mainly anecdotal.
- There is moderate evidence supporting RF denervation to treat pain arising from the SI joint.
- The pain of piriformis syndrome is located in the buttock and radiates to the ipsilateral hip. It may radiate to the leg in an L5–S1 distribution if the sciatic nerve is compromised.
- The physical examination signs to confirm piriformis syndrome include the Pace, Lasegue, and Freiberg signs.
- The diagnosis of piriformis syndrome is usually made by the presence of the above symptoms and positive provocative tests in a patient with a history of trauma.
- Perisciatic and piriformis muscle injections of steroid and local anesthetic may result in relief that lasts several months. If the relief is transient, injections of botulinum toxin may provide longer relief.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 48

Myofascial Pain Syndrome

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Myofascial pain (MP) is a soft tissue pain syndrome with local and referred pain arising from trigger points (TPs). The term muscular rheumatism of Sir William Osler's time gradually gave way to the term *nonarticular rheumatism*, and more recently, to the newer term *soft tissue pain syndromes*, which can be abbreviated as STP.[1] Local STPs include bursitis (subacromial, olecranon, trochanteric, prepatellar, and pes anserine), tenosynovitis (biceps, supraspinatus, infrapatellar, and achilles), and enthesopathies (lateral epicondylitis and medial epicondylitis). Regional STPs include myofascial pain syndrome (myofascial pain syndrome involving muscles of the trunk and extremities), myofascial pain dysfunction syndrome (myofascial pain syndrome involving facial muscles), and complex regional pain syndrome (types I and II). Generalized STPs involve fibromyalgia syndrome (FMS), chronic fatigue syndrome (FMS-like when widespread body pain present), and hypermobility syndrome. Regional STPs such as MP are limited in anatomic distribution over a specific region or quadrant of the body.

Trigger points generating MP are localized painful areas of skeletal muscle containing taut bands that can be exquisitely sensitive to digital pressure. TPs may be active or latent. Active TPs are present in patients with painful regional conditions. Latent TPs are asymptomatic but may be revealed by deep palpation on physical examination. Latent TPs have been found in the shoulder girdle muscles of 45% to 55% of healthy young adults.[2]

Myofascial pain often coexists with other acute and chronic painful musculoskeletal conditions including (1) head and neck pain (temporomandibular disorders, cervical degenerative disc disease, cervical facet arthropathy, neck pain after whiplash injury, cervicobrachial syndrome, cervicogenic and chronic tension-type headache), (2) thoracolumbar back pain (degenerative disc disease, kyphosis, scoliosis, lumbar facet arthropathy), (3) pelvic pain, and (4) upper and lower extremity pain. It is more common in women than in men and may be present independent of other pain generators.[3] MP is distinct from fibromyalgia. MP is most effectively treated with a multimodal therapeutic regimen including injection, physical therapy, postural or ergonomic correction, and treatment of underlying musculoskeletal pain generators.

PREVALENCE

Reliably establishing the prevalence of myofascial pain syndrome (MPS) proves to be challenging as there are no widely accepted diagnostic criteria. One study designed to evaluate the prevalence of MPS in an academic internal medicine practice was performed by Skootsky and colleagues.[4] Of 201 patients initially screened, 54 patients had initial complaints of musculoskeletal pain and were studied further. Those that had pain conditions potentially related to MPS had a careful TP examination performed. MPS was diagnosed when digital pressure on the TPs for a standardized time period intensified regional pain, and the pain referral pattern corresponded with established referral maps. Ultimately, 16 patients were diagnosed with MPS, representing 30% of patients with musculoskeletal pain, and 8% of the 201 originally screened patients.

MPS can be commonly found in select patient populations. MPS is more commonly seen in patients with chronic tension-type headache,[5] temporomandibular disorders and pain in the face–jaw region,[6,7] and in post-whiplash syndrome[8] than in the general patient population. One cross-sectional study surveyed 111 older adults with chronic low back pain versus twenty who were pain free.[9] They were assessed by clinical history and physical examination. Biomechanical and soft tissue pathologies were significantly more common in older adults with chronic low back pain (90%) than in pain-free patients with MP (10%).

PATHOPHYSIOLOGY

While much remains to be discovered about the etiology of MPS, several theories regarding its pathophysiology have been advanced in recent years. Underlying biomechanical and postural factors may interact with neurologic factors (e.g., radiculopathy), psychological elements including depression and anxiety, and hormonal and nutritional imbalances. These factors (in sum or in part) may create an autonomic dysregulation and, ultimately, central spinal cord sensitization which can amplify the experience of MPS. Vasoactive mediators, algogenic neurotransmitters and inflammatory mediators including bradykinin, norepinephrine, serotonin, calcitonin gene–related peptide, substance P, tumor necrosis factor alpha, and interleukin 1-B have been identified in the hyperirritable loci of TPs.[10–12] These substances sensitize nociceptors and are responsible for the sensory experience of MP, including referred pain and the local twitch response (LTR).

The motor phenomena of MP have been hypothesized to be caused by excessive acetylcholine (ACh) leakage, which creates dysfunctional endplates that are responsible for taut muscle band formation. Excessive ACh release causes sustained muscle contraction by increased depolarization of the postjunctional endplate. Evidence of maximal sarcomere shortening in TPs has been found in canine and human subjects.[13] A positive feedback cycle may be created by the interplay of increased ACh release, sarcomere shortening, and the release of sensitizing substances. In a study investigating the hypothalamus-pituitary-adrenocortical and sympathetic-adrenal-medullary system responses to experimentally induced stress in patients with myofascial pain, plasma concentrations of cortisol, epinephrine, and norepinephrine were found to be significantly higher in myofascial pain patients than in healthy controls.[14]

The taut muscle band present in MPS has a higher resting tension and contains hypercontracted muscle fibers.

Chronicity may increase local energy consumption and cause areas of tissue hypoperfusion and ischemia. Vasoactive mediators are released in the setting of muscle ischemia, causing increased ACh release, exacerbation of local ischemia, and sensitization of peripheral nociceptors, thereby causing pain. Abnormal spontaneous electrical activity is present at the site of TPs, with excessive ACh release creating endplate noise seen on electrophysiological studies at the neuromuscular junction.[15] Spontaneous electrical activity is observed as having two components: a constant, low amplitude background activity of approximately 50 μV, and intermittent higher amplitude spikes of 100 to 700 μV. Spontaneous electrical activity occurs more often in TPs than in normal tissue and displays aberrant patterns in TPs. Therefore, this spontaneous electrical activity is distinct from normal miniature endplate potentials. The abnormal electrical activity observed in TPs is thought to be directly related to excessive ACh release.

The clinical manifestation of abnormal electrical activity in the TP is a local twitch response (LTR), thought to be mediated by a segmental spinal reflex.[16] Snapping palpation or needling the TP causes a brisk muscle contraction in the taut band. The location of the LTR is called the "sensory locus," which has been correlated histologically with sensory receptors.[17] The "active locus" is the site where spontaneous electrical activity is recorded, the waveforms of which correspond to published reports of motor endplate noise. According to this model, the sensory locus and the active locus act as the nociceptor and the motor endplate and are distributed throughout muscle. Where these align and are highly concentrated, we observe myofascial TPs (Box 48-1).

Vasoactive mediators such as those released in the taut bands of MP have been known to sensitize peripheral nociceptive nerve fibers such as those found in skeletal muscle. In a sensitized state, nociceptors spontaneously discharge with a lower threshold to painful stimulation and also exhibit discharge to non-painful stimuli.[18] Over time, this heightened abnormal peripheral sensory input creates a state of central neuronal sensitization.[19]

Box 48-1 Commonly Accepted Diagnostic Characteristics of Myofascial Trigger Points

DIAGNOSTIC HISTORY

- Regional pain
- Onset with sudden muscle overload
- Onset with sustained muscular contraction in shortened position
- Onset with repetitive activity (symptoms increase with increasing stressfulness)

DIAGNOSTIC PHYSICAL EXAMINATION

- Taut band
- Focal spot muscle tenderness
- Pressure-elicited referred pain pattern
- If active, pressure elicits pain recognized as familiar

OTHER CLINICAL CHARACTERISTICS

- Local twitch response—confirmatory, difficult to elicit
- Prompt release of taut-band tension by specific myofascial trigger-point therapy
- Central/attachment myofascial trigger points

Simons DG: Review of enigmatic MTrPs as a common cause of enigmatic musculoskeletal pain and dysfunction. *J Electromyogr Kinesiol* 2004;14:95–107.

DIAGNOSIS

In a survey of 403 responding clinician members of the American Pain Society, 88.5% considered myofascial pain syndrome (MPS) to be a valid clinical disorder, and 81% believed it was distinct from FMS.[20] A careful history and physical exam remain the cornerstone of effective diagnosis. The most common presentation of MPS includes the following diagnostic criteria: regional body pain and stiffness, limited range of motion of the affected muscle, twitch response produced from a taut band, referred pain from a TP to a zone of reference, and resolution of the symptoms with local anesthesia applied to the TP.[21] MP may occur after injury, and chronic strain with repetitive microtrauma or without clear precipitating event. Aberrant body mechanics or postural instability may initiate or perpetuate the problem. The quality of pain tends to be a deep "aching" of variable intensity, and the pain is confined to a specific anatomic region. Characteristic referred pain patterns are associated with specific muscles, although these referral patterns are often unreliable.[22]

It is essential to have hands-on formal training in the physical examination of MP and TPs to achieve a reliable result.[1] Musculoskeletal examination should be performed with the objective of identifying orthopedic or neurologic dysfunction that may play a role in generating MP. Although there are no universally accepted diagnostic criteria for MP, physical findings may be helpful in establishing a diagnosis. A distinct pattern of TP findings may reveal itself in MP after a given insult.[8] Active TPs may be identified by palpation with gentle digital pressure oriented across and perpendicular to the muscle fibers. TPs are present as a taut muscle bands within skeletal muscle, and palpation of these points may elicit involuntary muscle contraction, the twitch response or "jump" sign. These painful TPs limit full range of passive motion in the afflicted muscle group. While these findings have been suggested as diagnostic criteria,[23–25] investigators have found it problematic to demonstrate consistent agreement in the presence or absence of TPs among examiners in blinded studies with control groups.[26–28] Inconsistencies may be attributed in part to a lack of standardized examination technique as well as variability in the interpretation of examination findings. Variability in muscle anatomy, physical conditioning and deconditioning pose obstacles as well. The most reproducible diagnostic findings on physical examination include observation of a TP in an affected muscle, referral of pain to a zone of reference, and reproduction of the patient's usual pain on physical exam.

Differential diagnosis of MP should include (1) musculoskeletal and neuropathic disorders such as arthritis, degenerative disk disease, radiculopathy, bursitis, and tendonitis; (2) autoimmune or infectious etiologies; (3) metabolic and endocrine dysfunction including hypothyroidism; (4) psychiatric disorders including depression and anxiety; and (5) fibromyalgia. It has been postulated that MPS may be an evolving component of fibromyalgia syndrome (FMS). While on the surface there are similarities, several

TABLE 48–1 Clinical Distinctions between Myofascial Pain Syndrome and Fibromyalgia Syndrome

Clinical Feature	Myofascial Pain	Fibromyalgia
Pain pattern	Local or regional	Generalized
Least distribution	A single muscle	11 tender points
Muscle spasm	+++	++
Trigger points	Local, regional	Not a feature
Tender points	Not a feature	Common, widespread
Taut band	++	–
Twitch response	++	–
Referred pain	+++	–
Fatigue	+	++++
Sleep disturbance	+++	++++
Paresthesias	Regional	Distal
Headaches	Referred head pain	Occipital origin
Irritable bowel	Not a feature	+++
Swelling sensation	+	++

Note: The number of plus sign reflects the significance of correlation and implication in clinical feature.
Source: McMahon SB, Koltzenburg M, editors: Wall and Melzack's textbook of pain, *ed 5, Philadelphia, 2006, Elsevier, pp 669–681.*

well-documented findings argue against the connection between MPS and FMS (Table 48-1). Patients with FMS do not exhibit widespread tender subcutaneous nodules in skeletal muscles. Additionally, FMS tender points do not refer pain to a zone of reference as do the TPs in MPS. The common TPs in MPs can coexist with the widespread tender points of FMS.

TREATMENT

PHYSICAL MODALITIES

A comprehensive multimodal therapeutic approach is optimal in the treatment of MPS, with the goal of patient education, reduction of pain, and restoration of function. This requires an informed and understanding clinician to coordinate care in a systematic fashion. As the pathogenesis of MP frequently involves postural defect, repetitive microtrauma, and muscle fiber shortening, it is logical that guided physical modalities play a significant role in treatment. On the other hand, ergonomic and behavioral modifications are commonly employed in treatment plans, although there is little clinical evidence of significant outcomes.

Guided stretching has been well documented as successful in reducing MP. This fits mechanistically with the model of shortened sarcomeres in MPS. Travell and Simons described passive stretching of the muscle groups after application of sprayed vapocoolant.[17] The sudden cooling of the vapocoolant in a defined area reduces discomfort from stretching, allowing more vigorous stretch. Noting significant improvement with this method, Travell and Simons termed this the "single most effective treatment" for TP pain. Structured physical therapy with a well-trained professional can incorporate these techniques along with strengthening, postural realignment, relaxation techniques, and massage.

A randomized controlled trial (RCT) by Gam et al. studied the effects of ultrasound, massage, and exercises on patients with MP in the neck and shoulders.[29] While there was no relative difference in pain reduction within the ultrasound group, there was a reduction in the number of TPs, although this reduction was characterized as weak. In an RCT of ultrasound applied to myofascial TPs, Srbely et al. demonstrated significant antinociceptive effects on both infraspinatus and gluteus medius pain pressure threshold at 1, 3, and 5 min, but not at 10 and 15 min.[30]

There is some evidence of benefit from complementary, manual, and exercise therapies, but the methodologic quality of these studies tends to be flawed.[31] Acupuncture, transcutaneous electrical nerve stimulation (TENS), and laser therapy may be of benefit as part of a comprehensive strategy in refractory cases. It is noted (somewhat controversially) that classical acupuncture points may show clinical correspondence to the location of TPs.[32] Melzack et al. reported 100% anatomic and 71% clinical pain correspondence of myofascial TPs with classical acupuncture points.[33] More studies are needed (particularly RCTs) in order to draw definitive conclusions about the roles of acupuncture, TENS, and laser therapy in the treatment of MPS. At present, the sum of the evidence is contradictory or inadequate.[34]

PHARMACOTHERAPY

Systemic medications are often useful additions to a comprehensive treatment plan. Although few RCTs exist to support their efficacy, nonsteroidal anti-inflammatory drugs (NSAIDs) and antidepressants have been employed to relieve pain associated with TPs. NSAIDs provide symptomatic relief but at the price of long-term side effects. These effects include cardiovascular morbidity and mortality, gastritis, and renal dysfunction. There is a paucity of RCTs detailing evidence of the effectiveness of NSAIDs in MPS. Rather, data from studies of other pain syndromes (arthritis and fibromyalgia) are used to guide treatment of MPS. Ibuprofen has been shown to be effective in acute myofascial strain, significantly reducing pain in a study of 77 emergency department patients. These effects were not significantly improved with the addition of the muscle relaxant cyclobenzaprine.[35] The tricyclic antidepressant amitriptyline has been studied in patients with chronic tension-type headache in a double-blind, placebo-controlled crossover study and significantly reduced myofascial tenderness and headache intensity more than placebo.[36]

Muscle relaxants are widely used in MP to reduce muscle spasm, to relieve pain, and to improve sleep disturbance related to MPS pain. The alpha-2 adrenergic agonist tizanidine has been cited as helpful in patients with chronic neck or low back pain in a review of the literature. However, RCTs are needed to assess the risk–benefit ratio of muscle relaxant therapy.[37]

Systemic opioids (including mixed opioid analgesics such as tramadol) have been widely used, especially when the patient has failed more conservative medications. Tramadol has demonstrated reduction in pain and core symptoms in clinical trials with fibromyalgia patients but not in patients with regional pain syndromes like MP.[38] As there

is little evidence of the efficacy of opioids in MPS, side effects, and consequences of longer-term use are concerning. The occurrence of tolerance, with a loss of efficacy occurring over time, frequently leads to dose escalation. With long-term use and dose escalation comes the risk of opioid-induced hyperalgesia (a N-methyl-D-aspartate [NMDA]–mediated phenomenon) that is characterized by escalating pain (often insidiously) in response to increasing opioid analgesic dose.[39] In addition to side effects of gastrointestinal slowing, nausea, sedation, respiratory depression, pruritus, and dysphoria, opioids can cause hormonal changes and lead to osteopenia by influencing the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis. Inappropriate use of opioids, including addiction and diversion, has emerged as a major societal problem in recent years, and demands responsible physician prescribing and monitoring practices within the guidelines of an informed-consent opioid contract or agreement.

Lidocaine patches may be an effective noninvasive therapy for MP in an appropriately selected patient population. In an RCT of patients with MPS, a total of 60 subjects received lidocaine patch, placebo patch, or local anesthetic TP injection.[40] Subjective pain-related symptoms significantly decreased for the lidocaine patch and injection groups. Similarly, pain thresholds increased significantly. Pain-related symptoms and thresholds did not change for the placebo group. Patients in the lidocaine patch group noted less discomfort from therapy than the injection group.

TRIGGER POINT INJECTION

Trigger point injection (TPI) is a widely used invasive therapy wherein a needle is guided directly into a TP that has been previously identified on physical examination. TPI is best utilized in a series of injections and as part of a comprehensive treatment plan that includes guided, structured, physical therapy. This strategy can be particularly beneficial when TPI is initially employed to reduce pain in patients otherwise intolerant of physical therapy or stretching, allowing the physical modalities to be more effective.[41] Saline, corticosteroids, a variety of local anesthetics including lidocaine and bupivacaine, botulinum toxin serotype A (BoNT-A), and dry needling have all been used and studied. Stimulation of the local twitch response in direct needling of the TP is valuable in achieving immediate effect.[42] There is good evidence to suggest that there is no advantage of one injection therapy over another, or of any drug injectate over dry needling.[43] In a systemic review of 23 RCTs, Cummings and White concluded that any effect derived from TPI is likely derived from the needle itself, rather than any specific substance injected, as there was no difference in therapeutic benefit of "wet" needling versus "dry" needling.[43] Their review also suggested that pain reduction with saline TPI is equal to pain reduction with local anesthetic TPI, both being significant. Although adding corticosteroid preparation to local anesthetic is a common practice, it has not been reliably shown to reduce pain more than TPI with local anesthetic alone. Despite the widespread practice of TPI for MP, there is no consensus regarding the number of injection points, frequency of administration, and volume or type of injectate. Controlled studies are needed to evaluate the comparative efficacy of TPIs and their potential benefits in long-term pain reduction, if any.

BOTULINUM TOXIN

Botulinum toxin serotype A produces sustained and prolonged relaxation of muscles by inhibiting release of ACh at the motor endplate and is itself an analgesic inhibiting central sensitization.[44] Commercially prepared, botulinum toxin serotype A is expensive, and should be employed with care by a well-trained physician. Although this therapy is promising, results of RCTs have been mixed. Ferrante et al. found no statistically significant improvement compared to placebo with BoNT-A injection into TPs for cervicothoracic MP.[45] They concluded that although it is intuitive for the clinician to consider therapeutic injection of BoNT-A as a treatment for MP (given its a priori similarity to TPI), peculiarities inherent to the use a toxin in lieu of dry needling or local anesthetic must be accounted for (i.e., toxin spread through fascial planes), including the effects of dosing of toxin, volume of injectate, muscles chosen to inject, postural relations and abnormalities, and injection technique. Harden et al.[46] were able to identify a short-term (12-week) reduction in MP of chronic tension-type headache with BoNT-A injection as compared to placebo. Graboski et al.[47] found no significant difference in BoNT-A versus 0.5% bupivacaine injected into TPs of patients with MPS, though both were effective in reducing pain below baseline level. Venancio et al.[48] studied 45 MP patients who were assigned randomly to one of three groups: dry needling, 0.25% lidocaine TPI, and BoNT–A TPI, and assessed over a 12-week period. While all three groups showed favorable response to treatment, the BoNT-A group demonstrated less use of rescue medication, and less postinjection local sensitivity.[48]

New theories regarding the use of botulinum toxin for the treatment of MP de-emphasize injection into the TP per se but focus upon selection of patients with significant features of overlap among cervical MPS, headache syndromes, and spasmodic torticollis. It is hypothesized that patients with cervicobrachial MPS reminiscent of spasmodic torticollis (with and without headache) may benefit from institution of botulinum toxin therapy. It is hypothesized that botulinum toxin's role is to help restore aberrant biomechanics and postural abnormalities in conjunction with restorative and rehabilitative physical therapy.[49]

CONCLUSION

MP is widely prevalent in many patients with regional musculoskeletal pain. The challenging nature of myofascial pain syndrome with its complex interaction of underlying biomechanical, neurologic, and psychological factors requires an astute, well-trained clinician for early diagnosis and effective treatment. Current data suggest that patients with MP tend to do worse than patients with discreet musculoskeletal pathology such as disk herniation.[50] MP can often be refractory to treatment. If the patient is unable to participate in an active functional rehabilitation program due to the limitations of pain, then a comprehensive

approach should be considered. A multidisciplinary approach may include psychological counseling for coping strategies, relaxation techniques and biofeedback, cognitive behavioral therapy, and complementary and alternative medicine in addition to standard medical evaluation and management. When a comprehensive program is employed early in the disease course, functional improvement in measures of decreased sick time, improved coping skills, and increased life satisfaction can be demonstrated in patients with whiplash trauma and other MPSs.[51] Should pain persist, it is important to assess the potential contribution of coexisting musculoskeletal or neurologic pathology to MP. The meticulous clinician should seek to identify and eliminate any underlying source of pain generation. However, despite an abundance of clinical experience and successful outcomes, we need better-designed, short- and long-term outcome studies on myofascial pain to assess the efficacy and efficiency of traditional and emerging therapies.

KEY POINTS

- Myofascial pain syndrome is a type of regional soft tissue pain syndrome involving muscles of the trunk and extremities.
- Although myofascial pain may generalize, it remains distinct from fibromyalgia.
- Hyperirritable loci of trigger points have been found to contain vasoactive mediators, algogenic neurotransmitters, and inflammatory mediators.
- Excessive acetylcholine leakage has been hypothesized to contribute to dysfunctional motor end plates, creating the sustained muscle contraction responsible for taut bands.
- The clinical manifestation of abnormal electrical activity in the trigger point is a local twitch response, thought to be mediated by a segmental spinal reflex. Snapping palpation or needling the trigger point causes a brisk muscle contraction in the taut band.
- Diagnostic findings in the physical examination include observation of trigger points in an affected muscle, referral of pain to a zone of reference, and reproduction of the patient's usual pain.
- Early diagnosis and treatment with a comprehensive multimodal approach is optimal.
- Passive stretching after application of sprayed vapocoolant is a well-documented treatment.
- While there is evidence of the efficacy of trigger point injection for myofascial pain, there is no evidence of the advantage of one injection technique over another, or the injection of any substance versus dry needling.
- Injection of botulinum toxin is an emerging therapy that may be considered in refractory cases of myofascial pain, although evidence of its efficacy is limited at present.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 49

Fibromyalgia

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Fibromyalgia (FM) is a medical condition that appears to involve disordered afferent processing and which may be associated with multiple symptoms including: chronic widespread pain, fatigue, sleep disturbances, cognitive alterations, mood disturbances, dysesthesias, stiffness, poor balance, oral and ocular symptoms (e.g., keratoconjunctivitis sicca), headaches, sexual dysfunction, impaired physical function, and psychological distress (Fig. 49-1). The core symptoms seen in FM and many other "central" pain syndromes are multifocal pain, fatigue, insomnia, cognitive or memory problems, and, in many cases, psychological distress. Some individuals in the population only have one of these symptoms, but most have many, and the precise location of the pain, and predominant symptom at any given point in time, may change over time. Common disorders that may coexist with fibromyalgia include regional musculoskeletal pain syndromes (e.g., low back pain, temporomandibular joint disorder [TMD]), chronic fatigue syndrome, irritable bowel syndrome (IBS), irritable bladder syndrome or interstitial cystitis, headaches, vulvodynia, and pelvic pain (often attributed to endometriosis). *Thus, in clinical practice, it is useful to consider a fibromyalgia-like or central sensitivity syndrome when individuals have multifocal pain combined with other somatic symptoms.*

It is estimated that 2% to 4% of the general population suffers from fibromyalgia,[1] making it the second most common rheumatic disorder behind osteoarthritis. These symptoms occur approximately 1.5 to 2 times more commonly in women than men.[1] However, approximately 10 times as many women meet American College of Rheumatology (ACR) criteria for fibromyalgia because the ACR criteria require more than 11 tender points as well as chronic widespread pain, and women are considerably more tender than men.

IMPACT OF FIBROMYALGIA SYNDROME ON FUNCTIONING AND QUALITY OF LIFE

Fibromyalgia affects all aspects of daily physical functioning. Women with FM have lower quality of life measures than women with other chronic conditions such as rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD) and diabetes mellitus.[2] Patients with FM report difficulty with multiple activities.[3] Sixty-two percent have difficulty climbing stairs, 55% have difficulty walking two blocks, and 35% have difficulty with activities of daily life.[3] Fibromyalgia can also negatively affect personal relationships, career, and mental health.

PATHOPHYSIOLOGY OF FIBROMYALGIA

Evidence of augmented pain and sensory processing are the most reproducible pathogenic features of these illnesses; however, the precise specific mechanisms that are responsible for producing fibromyalgia remain uncertain.

Once a diagnosis of fibromyalgia is established, the most consistently detected objective abnormalities involve pain and sensory processing systems. Since FM is defined in part by tenderness, considerable work has been performed exploring the potential reasons for this phenomenon. The results of two decades of psychophysical pressure pain testing in fibromyalgia have been very instructive. One of the earliest findings is that tenderness in FM is not confined to tender points, but extends throughout the entire body.[4] Theoretically, such diffuse tenderness could be due to psychological (e.g., hypervigilance) or neurobiological factors (i.e., factors that can lead to temporary or permanent amplification of sensory input).

In addition to heightened sensitivity to pressure, other types of stimuli are also perceived as being more painful by these patients. FM patients display a decreased threshold to heat, cold, and electrical stimuli.[5] Similar decreases in pain threshold have been noted in individuals with chronic widespread pain without 11 or more tender points.[6] Some investigators have found that people with FM display a low noxious threshold to other sensory stimuli such as auditory tones,[7] which suggests possible biological amplification of all sensory input. This theory is supported by functional imaging showing hyperactivity in the anterior insula, frontal cortex, cingulate cortex, and other regions of the brain.[8]

There are two different specific pathogenic mechanisms in FM that have been identified using experimental pain testing: (1) decreased descending analgesic activity, and (2) increased wind-up or temporal summation.

ATTENUATED DIFFUSE NOXIOUS INHIBITORY CONTROLS IN FIBROMYALGIA

In healthy humans and laboratory animals, application of an intense painful stimulus for 2 to 5 min produces generalized whole-body analgesia. This analgesic effect, termed *diffuse noxious inhibitory controls* (DNIC), is attenuated or absent in groups of FM and IBS patients compared to healthy controls.[4] A point of emphasis is that this finding of attenuated DNIC is not found in all FM or IBS patients, but is more common in patients than controls (Fig. 49-2).

The DNIC response is thought to be partly mediated by descending opioidergic and serotonergic-noradrenergic pathways. In FM, accumulating data suggests that opioidergic activity is normal or even increased, in that levels of cerebrospinal fluid (CSF) enkephalins are roughly twice as high in FM and idiopathic low back pain patients as in healthy controls.[9] The biochemical and imaging findings suggesting increased activity of endogenous opioidergic systems are consistent with the anecdotal experience that opioids are generally ineffective in FM and related conditions. In contrast, studies have shown the opposite for serotonergic and noradrenergic activity in FM.

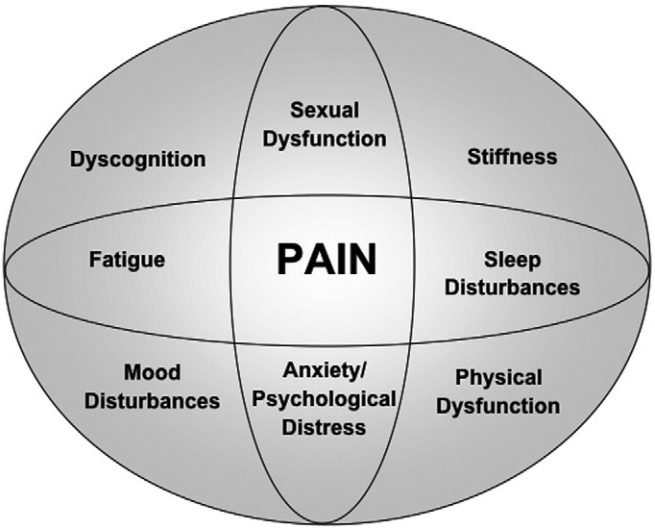

FIGURE 49-1 Fibromyalgia domains.

The principal metabolite of norepinephrine, 3-methoxy-4-hydroxyphenethylene (MPHG), is lower in the CSF of FM patients.[10] Further evidence for this mechanism comes from treatment studies, where nearly any type of compound that simultaneously raises both serotonin and norepinephrine (tricyclics, duloxetine, milnacipran, tramadol) has been shown to be efficacious in treating FM and related conditions.

INCREASED WIND-UP IN FIBROMYALGIA

Experimental pain studies suggest that some individuals with FM may have evidence of wind-up, indicative of central sensitization.[11] In animal models, this finding is associated with excitatory amino acid and substance P hyperactivity.[12] Independent studies have shown that patients with FM have approximately threefold higher concentrations of substance P in CSF compared with normal controls.[13] Other chronic pain syndromes, such as osteoarthritis and chronic low back pain, are also associated with elevated substance P levels. Once elevated, substance P levels do not appear to change dramatically, and do not rise in response to acute painful stimuli. Thus, high substance P levels appear to be a biological marker for the presence of chronic pain.

Another neurotransmitter in pain processing that likely plays some role in FM is the excitatory neurotransmitter glutamate. CSF levels of glutamate are twice as high in FM patients than controls.[14] A recent study using proton spectroscopy demonstrated that glutamate levels in the insula in FM change in response to changes in both clinical and experimental pain when patients are treated with acupuncture.

Brain imaging studies also support the existence of central pain augmentation in FM, IBS, and other related conditions.[15,16] Gracely et al. performed the first functional magnetic resonance imaging (fMRI) study of fibromyalgia patients in 2002.[15] When stimuli of equivalent

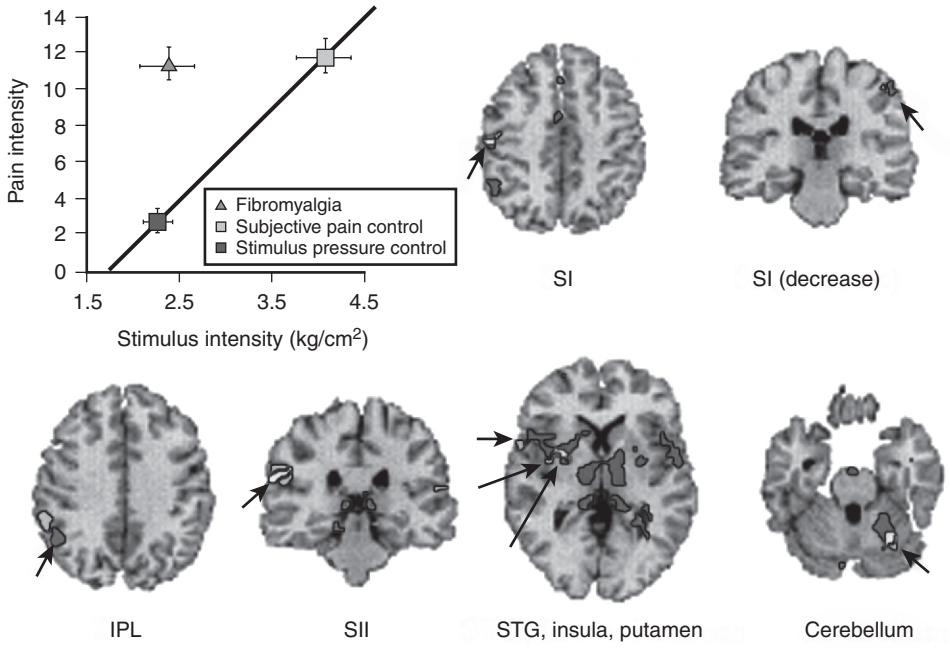

FIGURE 49-2 Stimuli and responses during pain fMRI scans. The similar pain intensities, produced by significantly less pressure in FM patients, resulted in overlapping or adjacent activations in the contralateral primary somatosensory cortex (SI), inferior parietal lobule (IPL), secondary somatosensory cortex (SII), superior temporal gyrus (STG), insula, and putamen, and ipsilateral cerebellum. In the fibromyalgia condition, a relatively low stimulus pressure (2.4 kg/cm^2) produced a high pain level (mean = 11.30, standard deviation [SD] = 0.90). In the stimulus pressure control condition, administration of a similar stimulus pressure (2.33 kg/cm^2) to control subjects produced a very low level of rated pain (mean = 3.05, SD = 0.85). In the subjective pain control condition, administration of significantly greater stimulus pressures to the control subjects (4.16 kg/cm^2) produced levels of pain (mean = 11.95, SD = 0.94) similar to those produced in patients by lower stimulus pressures. *(Source: Gracely RH, Petzke F, Wolf JM, et al: Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.* Arthritis Rheum *46:1333–1343, 2002).*

pressure magnitude were administered to FM patients and controls, the authors found increased regional cerebral blood flow in FM patients compared to subjects without pain. Regions of increased activity included the primary and secondary somatosensory cortex, the insula, and the anterior cingulate cortex, commonly observed regions of increased blood flow in normal subjects during painful stimuli.[15]

It appears as though pain and sensory processing is controlled by the same type of "yin-yang" balance that many other bodily systems are, with some hormonal or neurotransmitter systems leading to increases, and others to decreases. For example, just as high levels of pro-inflammatory cytokines, or low levels of anti-inflammatory cytokines, can move an individual toward hyperimmune function, there are neurotransmitters that are similarly known to either increase or decrease pain transmission in the CNS. Overall, the analogy of an increased "volume control" or gain" setting on pain and sensory processing is supported by studies from a variety of sources. Similar to essential hypertension, where a variety of root causes can lead to elevated systemic blood pressure; these disorders represent "essential hypertension of pain and sensory processing pathways." Elevated levels of neurotransmitters that tend to be pronociceptive (Fig. 49-3, left side) or reduced levels of neurotransmitters that inhibit pain transmission (i.e., on the right side of figure) have a tendency to increase the volume control, and drugs that block neurotransmitters on the left or augment activity of those on the right are often found to be effective treatments.

The arrows in Fig. 49-3 indicate the direction of abnormalities in neurotransmitter levels identified to date in fibromyalgia. Research has indicated a strong genetic and familial component to the development of fibromyalgia. First-degree relatives of individuals with fibromyalgia display an eightfold greater risk of developing fibromyalgia than those in the general population.[17] These studies also show that family members of individuals with fibromyalgia are much more tender than the family members of controls, regardless of whether they have pain or not. Family members of FM patients are also more likely to have IBS,

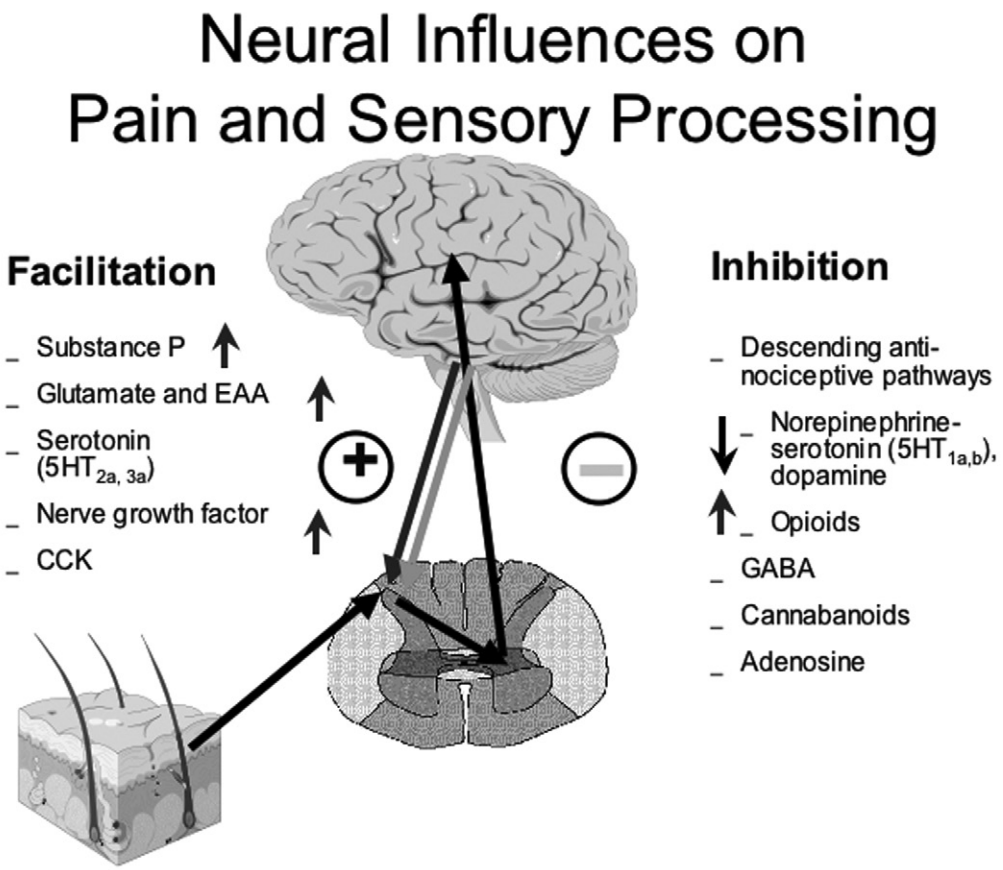

FIGURE 49-3 Neural influences on pain and sensory processing. Recent studies have made it clear that an individual's "set point" or "volume control setting" for pain is set by a variety of factors, including the levels of neurotransmitters on the left that either facilitate pain transmission (turn up the gain or volume control) or those on the right that reduce pain transmission. Thus, high levels of neurotransmitters on the left, or low levels of those on the right, would be capable of causing the diffuse hyperalgesia (increased volume control) seen in a variety of chronic pain states. The *arrows* indicate the levels of these neurotransmitters in the cerebrospinal fluid (CSF) of individuals with fibromyalgia. You can see that there are high levels (2 to 3 times than in healthy controls) of a number of neurotransmitters on the left, and low levels of one set of neurotransmitters (serotonin, norepinephrine, dopamine) on the right. The only neurotransmitter system that has been studied in FM and not shown to be abnormal in a direction that would cause hyperalgesia or an increased volume control is the opioidergic system, which seems to be appropriately increased in FM. This may help explain why opioidergic drugs do not seem to work very well for these central pain states, such as in FM.

TMD, headaches, and a host of other regional pain syndromes.[18] This familial and personal coaggregation of functional pain syndromes was originally termed *affective spectrum disorder*,[19] and more recently *central sensitivity syndromes* and chronic multi-symptom illnesses.[20] Twin studies suggest that approximately half of the risk of developing these conditions is due to genetic and half due to environmental factors.[21]

DIAGNOSIS AND ASSESSMENT OF FIBROMYALGIA

The ACR research criteria for FM[22] require that an individual have both a history of chronic widespread pain and over 11 of a possible 18 tender points on examination; however, these criteria have been criticized for their failure to recognize the presence of associated FM symptoms that must be addressed to optimally manage the disorder.[23] ACR criteria are not used by one-third of rheumatologists, and 25.5% of patients being treated for FM by rheumatologists do not satisfy these criteria.[24] Current FM criteria aggregate and confound diagnostic status and symptom severity, features that should be separated to enable better evaluation and management.[24] Since the 1990 ACR Fibromyalgia criteria were first published over 20 years ago,[22] the focus on tender points has begun to wane. The Manchester criteria,[25] used for epidemiologic studies, employs a whole body pain diagram to indicate areas of pain, thereby obviating the need for tender points.

Based on a survey mailed to 12,799 patients with rheumatoid arthritis, osteoarthritis, or FM, Wolfe et al.[26] found that pain in a subset of 19 primarily nonarticular sites differentiated fibromyalgia syndrome from the other two diseases.[26,27] These studies led to proposed diagnostic criteria that assess widespread pain along with symptoms of fatigue, sleep disturbance and cognitive dysfunction.[28] These criteria do not require tender points, expand the definition of FM to include symptoms other than pain, and provide a measure of symptom-related severity.

PHARMACOLOGIC TREATMENT OF FIBROMYALGIA

Evidence for optimal treatment of fibromyalgia supports a multifaceted program comprising pharmacologic therapy and nonpharmacologic therapy (education, exercise, and cognitive behavioral therapy).[29]

PHARMACOLOGIC APPROACHES TO TREATMENT OF FM

Until 2007, there were no specific agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of fibromyalgia; thus pharmacologic therapy before this was entirely "off-label." Pregabalin, an α-2-δ ligand and antiepileptic drug, was the first FDA-approved agent for FM in 2007. In 2008, duloxetine, a selective serotonin-norepinephrine reuptake inhibitor (SNRI), was the second FDA-approved agent for fibromyalgia, and in 2009, milnacipran (also an SNRI) became the third drug approved for FM.

Antidepressants. The majority of clinical trials for FM have evaluated antidepressants, with most involving the older, tricyclic compounds. In a systematic review by Uçeyler et al. on the effectiveness of antidepressants in FM, the authors found amitriptyline, evaluated in 13 randomized controlled trials (RCTs), was efficient in reducing pain with a moderate magnitude of benefit (pain reduction by a mean of 26%, improvement in quality of life by 30%).[30]

Tricyclic Antidepressants (TCAs). The effectiveness of TCAs, especially amitriptyline and cyclobenzaprine, in treating the symptoms of pain, poor sleep, and fatigue associated with fibromyalgia is supported by RCTs.[31] Cyclobenzaprine, a centrally acting muscle relaxant structurally similar to amitriptyline, has been used to treat the musculoskeletal pain and sleep disturbances associated with FM.[32]

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs). Most of the serotonin-norepinephrine reuptake inhibitors (SNRIs) clinically available have more of an effect on serotonin reuptake than norepinephrine reuptake. SNRIs that have more of an effect on norepinephrine reuptake than serotonin reuptake are sometimes referred to as norepinephrine-serotonin reuptake inhibitors (NSRIs) (e.g., milnacipran). SNRIs tend to be better tolerated than older TCAs. Venlafaxine, the first SNRI available in the United States, tends to have clinically significant effects on norepinephrine reuptake only at higher doses and thus may be beneficial in FM when used at these higher doses.[33]

Duloxetine and milnacipran are two SNRIs that have shown efficacy in FM and are approved for treatment in the United States.[34,35] Choy et al. analyzed pooled data from four double-blind, placebo-controlled studies and a 1-year, open-label safety study evaluating duloxetine in FM.[36] Most adverse effects were mild to moderate in severity, with about 20% of patients requiring discontinuation of the drug.[37] Arnold and colleagues conducted a pooled analysis of four placebo-controlled trials that provided evidence that 12 weeks of treatment with duloxetine 60 to 120 mg/day effectively improves FM symptoms and may offer benefits beyond pain relief.[37] Milnacipran also demonstrated benefit in FM, including improvements in fatigue, physical functioning, and discomfort.[38–40]

Häuser et al. performed a meta-analysis with 18 RCTs (median duration, 8 weeks; range, 4 to 28 weeks) involving 1427 participants.[41] Overall, there was strong evidence for an association between antidepressant use and reduction in pain, fatigue, depressed mood, sleep disturbances, and quality of life. Effect sizes for pain reduction were large for TCAs, medium for MAOIs, and small for SSRIs and SNRIs.

α-*2*-δ *Ligands.* Pregabalin is a γ-aminobutyric acid (GABA) analog antiepileptic drug that binds to the α-2-δ subunit of calcium channels. The FREEDOM (Fibromyalgia Relapse Evaluation and Efficacy for Durability of Meaningful Relief) double-blind trial[42] evaluated the durability of pregabalin in 1051 FM patients who initially responded to the drug. By the end of the double-blind phase, 61% of those in the placebo group had lost therapeutic response compared with 32% in the pregabalin group.[42] Häuser et al. performed a meta-analysis evaluating

pregabalin that included this and four other studies.[43] There was strong evidence for a reduction of pain, improved sleep, and improved health-related quality of life (HRQOL), but not for depressed mood.[43] Concerns have been raised regarding the external validity of the studies, as patients with severe comorbid depression or on disability were generally excluded from participation.[44]

Gabapentin is an older and structurally similar α-2-δ ligand and antiepileptic drug which is not FDA approved for FM but has shown potential benefit. In a 12-week, double-blind, placebo-controlled study, Arnold et al. found gabapentin (1200–2400 mg/day) to be safe and efficacious in FM.[45]

Other Centrally Acting Agents. γ-Hydroxybutyrate, a GABA precursor with strong sedative qualities, has been shown to be beneficial in FM.[46] Russell et al. randomized 118 patients to receive 4.5 g or 6 g of sodium oxybate or matching placebo once per night for 8 weeks.[47] Significant benefit with regard to pain relief and subjective sleep quality was observed with both dosages of sodium oxybate.[47] Improvements on a pain intensity visual analog scale were significantly correlated with sleep outcomes.

Pramipexole is a dopamine agonist used for Parkinson's disease and restless leg syndrome that has been shown in one controlled study to improve pain and sleep in FM patients treated with concomitant analgesics.[48]

There have been no adequate RCTs of pure opioids in FM; however, anecdotal experience has not found this class of analgesics to be effective. Many in the pain field think that individuals with FM and other central pain states may even be at high risk of developing opioid-induced hyperalgesia when these drugs are used, but this has not been formally studied.

Tramadol is a compound that exerts weak analgesic effects by binding to the μ-opioid receptor, but the majority of its analgesic effects likely stem from serotonin/norepineprhine reuptake inhibition. Tramadol appears to possess some beneficial effects in the management of FM both alone and as a fixed-dose combination with acetaminophen.[49,50]

NONPHARMACOLOGIC TREATMENT OF FIBROMYALGIA

EXERCISE APPROACHES

At least 70 studies evaluating exercise in FM have been published since the early 1970s. A total of 4385 subjects completed 56 RCTs from 1998 to 2008.[51] These studies generally show that exercise is beneficial in FM for both physical symptoms and functional capacity.

The use of low-intensity, low-impact programs and the ability to individualize the protocol are crucial for optimal adherence to regimens.[51] Evidence for mixed-type or aerobic exercise is strongest, with mounting evidence for beneficial effects from strength training.[52–55]

The results of flexibility training, including yoga studies, are positive, but there is not yet a preponderance of evidence supporting flexibility training as a single modality.[55,56] More research needs to be done to evaluate the effectiveness of movement-based therapies in FM, such as Qi Gong and T'ai Chi, because emerging evidence in these modalities is positive.[57,58]

EDUCATIONAL APPROACHES

Rooks and colleagues[59] completed an RCT with 207 patients with FM assigned to one of four groups: (1) an aerobic and flexibility exercise group; (2) a strength training, aerobic, and flexibility exercise group; (3) the Fibromyalgia Self-Help Course; or (4) a combination of the three groups. The combination group showed the greatest improvement. It appears that education is most effective when accompanied by multimodal interventions.

BEHAVIORAL MEDICINE APPROACHES

Catastrophizing, or the belief that the worst possible outcome is going to occur, has been associated with pain severity, decreased functioning, and affective distress in FM.[60] In cognitive therapy, catastrophic thoughts, such as "My pain is terrible and there is nothing I can do about it," are reframed to "As bad as my pain might get, there are things I can do to make it a little better."[61] Behavior therapy is rooted in the theory that inner states (thoughts and feelings) are less important than operant behavior change techniques to increase adaptive behavior through positive and negative reinforcement, and to extinguish maladaptive behavior using punishment.[61]

All cognitive behavioral therapy (CBT) interventions are not equal, with many including only modest elements of cognitive therapy relying instead on behavioral interventions.[61] Furthermore, CBT may be somewhat operator-dependent and has specific programs for specific conditions/symptoms (e.g., insomnia [CBT-I], pain [CBT-P], stress [CBT-S]).

Relaxation Techniques. Relaxation techniques are commonly part of CBT for FM.[62] Relaxation techniques likely to be helpful for FM symptoms include progressive muscle relaxation (PMR), autogenic training, guided imagery, and meditation.

Thieme and Gracely performed a literature search that identified 14 RCTs assessing CBT and operant-behavioral therapy (OBT), five relaxation RCTs, five biofeedback RCTs, five hypnotherapy RCTs, and two writing intervention RCTs.[63] The highest effect sizes (r = 0.53–2.14) for pain reduction were found after CBT and OBT group treatments.[63]

MULTICOMPONENT TREATMENT OF FIBROMYALGIA

Häuser et al. performed a meta-analysis of nine RCTs with 1119 subjects (median treatment time 24 hr).[64] There was strong evidence that multicomponent treatment reduces pain, fatigue, and depressive symptoms, and improves quality of life and physical fitness post-treatment.[64] However, there was no evidence of its efficacy on pain, fatigue, sleep disturbances, depressive symptoms, quality of life, or self-efficacy pain in the long term. There was strong evidence that positive effects on physical fitness can be maintained in the long term (median follow-up of 7 months).[64] Both the American Pain Society and the Association of the Scientific Medical Societies in Germany assigned the highest level of recommendation to aerobic exercise, CBT,

amitriptyline, and multicomponent treatment. In contrast, the European League Against Rheumatism (EULAR) assigned the highest level of recommendation to pharmacologic treatments, including amitriptyline, tramadol, α 2-δ ligands (e.g., pregabalin), and SNRIs (e.g., duloxetine).

CONCLUSION

In the past few decades, our understanding of FM has evolved tremendously, and research has taught us about the mechanisms that may underlie chronic pain or other somatic syndromes in individuals without FM per se. A better understanding of the underlying mechanisms and most effective treatment(s) for this spectrum of illness is critical to rheumatologists, because as the work of Wolfe and others has taught us, many patients with chronic pain conditions may have a little, or a lot, of "fibromyalgia-ness." When this occurs, we need to treat both the peripheral and central elements of pain and other somatic symptoms.

KEY POINTS

- Fibromyalgia can be considered a discrete condition as well as a construct to help explain how/why individuals have multifocal pain and other somatic symptoms in spite of the lack of nociceptive input (i.e., peripheral damage/inflammation) that adequately accounts for the pain.
- The primary abnormality identified to date in FM and related pain syndromes is an increased gain or volume control in CNS pain processing (i.e., secondary hyperalgesia/allodynia).
- It is likely that this increased gain on pain and sensory processing is due in part to increased levels of excitatory neurotransmitters (e.g., glutamate, substance P) and/or low levels of inhibitory neurotransmitters (serotonin, norepinephrine, GABA, cannabinoids).
- Analgesics that work well for "peripheral/nociceptive" pain syndromes (e.g., NSAIDs, opioids) are largely ineffective in FM.
- The most effective classes of drugs in FM are centrally acting analgesics (e.g., tricyclics, SNRIs, and α-2-δ ligands).
- Nonpharmacologic therapies such as education, exercise, and cognitive behavioral therapy are very effective in FM and are typically underutilized in routine clinical practice.

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CHAPTER 50

Complex Regional Pain Syndrome

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Complex regional pain syndrome (CRPS) Types I and II (formerly known as reflex sympathetic dystrophy [RSD] and causalgia, respectively) was first reported by Weir Mitchell over a century ago following his observations that Civil War soldiers with peripheral nerve damage from gunshot wounds developed a constant burning pain, which he called *causalgia*. Almost half a century after Mitchell's observation, Sudeck in 1900 observed muscle atrophy and bony demineralization as a complication of infection in the limbs. The radiographic changes started as a "patchy osteoporosis of the small bones of the hands or feet and the distal metaphysis of the forearm or tibial bones," hence, the name *Sudeck's dystrophy*, due to the presence of patchy osteoporosis. Almost five decades later in 1947, the term *reflex sympathetic dystrophy* was coined by Evans to reflect the assumption that the sympathetic nervous system was involved in the abnormal activity observed in the periphery.

In 1994, the Special Consensus Group of the International Association for the Study of Pain (IASP) met to review the criteria for the clinical diagnosis of patients presenting with CRPS/RSD. The need for such a consensus among physicians charged with the care of these patients arose from recognition of the presence of an inhomogeneous set of signs and symptoms that were hitherto used to diagnose the disease with the resultant difficulty in confirming that all practitioners were treating the same condition. In addition there was a lack of evidence for a reflex mechanism and the variable presence of dystrophy. The term *complex regional pain syndrome* was therefore considered broad enough to allow the inclusion of patients who may show varying levels of sympathetic nervous system involvement in maintaining pain through the course of the disease process, hence the term *sympathetically mediated pain* (SMP) or *sympathetically independent pain* (SIP).[1]

EPIDEMIOLOGY

There is a paucity of epidemiologic data or outcome studies on CRPS, reflecting the absence of a universal agreement on the set of signs and symptoms that should be present in order to make the diagnosis in this group of patients. The true incidence of CRPS is unknown; however, results of two epidemiologic studies indicate that the incidence per person-years at risk of the disease ranges from 5.46 to 26.6/100,000 person-years at risk.[2] It occurs more commonly in females than males, with a ratio of 2:3 to 3:1, and with increasing age.[3] Veldman et al. in a prospective study of 829 patients, 76% of whom were female, found that the age ranged from 9 to 85 years (median age 42 years) with only 12 patients younger than 14 years.[4] Allen and associates reviewed epidemiologic data from a tertiary pain center on 134 patients. They found that the CRPS symptoms had existed for a mean duration of 30 months prior to presentation.[5] In addition, their data revealed that most patients had seen on average 4.8 physicians before referral to the tertiary center, with 17% having pending lawsuits and 54% a workman's (workmen's) compensation claim related to CRPS.[5] Over half the patients reported significant association of CRPS duration and myofascial dysfunction. This was the first study to examine the types of occupation held by CRPS patients at the time of injury. The data revealed that people in the service industries, such as restaurant workers, and police officers suffered almost twice as much as people in other professions; this may be related to the physical activity related to the job.[5] Other associated features that have been identified include the presence of social stressors at the time of development of the condition.[3] In spite of this finding, no specific psychological factors or personality trait has been found to predispose an individual to developing CRPS.[6]

Others have attempted to further examine epidemiologic variables in patient populations to enhance the characterization of the disease. In a recent web-based epidemiologic survey of complex regional pain syndrome, Raja and colleagues surveyed 1359 subjects to examine multiple variables (risk factors), including sociodemographic factors. The authors concluded that CRPS commonly occurs among younger females and often results from work-related injuries or surgery. The study also revealed that CRPS is associated with sleep disturbance, functional impairment, and suicidal ideation.[7] More recently, de Mos et al. examined outcomes of the disease with regards to the extent of long-lasting impairments. In a retrospective analysis for an average 5.8 years, 102 patients with CRPS were compared with matched reference patients with similar injuries without CRPS. Sixteen percent of the CRPS patients reported the CRPS to be still progressive, 31% were incapable of working, and the patients with poorest outcomes were those with upper extremity involvement. The authors concluded that although severe outcomes were rare, the majority of CRPS patients experience persistent impairment at 2 years or more after onset of the condition.[8]

PATHOPHYSIOLOGY

CRPS Type I and Type II differ only by the presence (Type II) or absence (Type I) of evidence of nerve injury. Pain is the hallmark of the condition, and commonly manifests as spontaneous pain, with hyperalgesia and allodynia. Associated signs include vasomotor and, sudomotor active disturbances and passive movement disorders in addition to trophic changes. CRPS Type II develops after defined nerve injury, whereas CRPS Type I develops following minor or major injuries with little or no obvious damage to the nerves in the involved extremity.

There have been numerous attempts to simplify the pathophysiologic mechanisms involved in the development of CPRS. However, it has become increasingly evident that there may be multiple mechanisms involved.

ALTERED CUTANEOUS INNERVATION FOLLOWING INJURY

Current evidence is in favor of the assumption that some degree of nerve injury is required however trivial to initiate the cascade of events associated with CRPS.[9,10] Oaklander et al. demonstrated that persistent minimal distal nerve injury (MDNI), specifically distal degeneration of small-diameter axons, which subserve pain and autonomic function, were responsible for the symptoms reported in CRPS I. The authors found that significantly lower densities of epidermal neuritis (on average 29% lower) were observed in CRPS-affected extremities as compared to the contralateral unaffected limb, these changes affected mainly nociceptive fibers. Similar changes in neurite density was not seen in non-CRPS conditions such as osteoarthritis.[10] In a study to determine if objective evidence for the presence of nerve damage in CRPS I exists, Albrecht et al. examined the skin samples from amputated upper and lower extremities form two CRPS patients to detect evidence of nerve injury using immunofluorescence techniques. They found a reduction in C and A-delta fiber density in the CRPS-affected limbs compared to the non-affected sites on the same limb as well as compared to healthy controls. In addition, abnormalities in the innervations around hair follicles and sweat glands were also observed. The causal relationship of the changes relative to the onset of CRPS is unclear.[11]

PERIPHERAL SENSITIZATION

Peripheral sensitization resulting from the persistent nociceptive afferent activity as a result of the initial tissue trauma is thought to occur.[12] Following local injury, the primary afferent fibers in the traumatized area release neuropeptides such as bradykinin and substance P, which result in increased firing of nociceptors to noxious stimuli and reduced firing threshold to mechanical and thermal stimuli; this may account for the hyperalgesia and allodynia pathognomonic of CRPS.[13] Furthermore, the local hyperalgesia is limited to the affected limb and not seen in the contralateral unaffected limb.[14] Examination of the extent of sensory impairment in 24 patients with CRPS I revealed that up to half of the patients with chronic CRPS I develop hyperesthesia to pinprick and temperature on the affected side or in the upper quadrant of the ipsilateral side.[15] The patients also demonstrated a higher incidence of hyperalgesia and mechanical allodynia in addition to motor impairment. These changes suggested a more widespread alteration of sensory perception in the pathophysiology of CRPS in this group of patients.

CENTRAL SENSITIZATION

The mechanism by which central sensitization occurs is akin to that described in peripheral sensitization. Persistent nociceptive input associated with nerve injury from tissue trauma results in increased activity of nociceptive neurons in the spinal cord.[16] The central sensitization is mediated by the induced release of neuropeptides such as bradykinin and substance P and the excitatory neurotransmitter glutamate acting at the spinal *N*-methyl-D-aspartic acid receptors.[17] This activity results in enhanced response to non-noxious stimuli (allodynia) and noxious stimuli (hyperalgesia).[16] CRPS patients demonstrate significantly increased wind-up to repeated stimuli applied to the affected limb compared with the unaffected contralateral limb or other limbs.[18,19] All these findings suggest the possibility of central sensitization as a mechanism of persistence of the symptoms associated with CRPS.

SYMPATHETICALLY MEDIATED PAIN

There has been an indication of an interaction between the sympathetic noradrenergic neurons in the periphery and the primary afferent neurons as part of the underlying mechanism of sympathetically maintained pain (SMP) in patients with CRPS I. Intradermal injection of epinephrine in CRPS patients results in the return of allodynia and spontaneous pain that had previously been relieved by sympathetic blockade, suggesting a peripheral adrenoceptor mediated mechanism in some patients.[20,21] Spontaneous pain may also be relieved by an infusion of the α-adrenergic blocker phentolamine. There also has been some suggestion that sympathetic nervous system innervations of deep somatic tissues may be as important as cutaneous innervations as a determinant of the sympathoafferent coupling that occurs particularly in the acute phase of CRPS.[22] Coupling may also occur not only to nociceptive afferents but to mechanoceptors and thermosensitive neurons.[23,24]

INFLAMMATORY MEDIATORS

There is some suggestion that elaboration of inflammatory mechanisms may be responsible for the acute phase of CRPS. This may occur either through the classic cascade of release of pro-inflammatory cytokines (interleukin-1β, IL-2, IL-6, and tumor necrosis factor-α) from mast cells and lymphocytes following tissue trauma, or secondary to neurogenic inflammation causing the release of cytokines and neuropeptides (including substance P and calcitonin gene–related peptide [CGRP]).[12,25,26] The neuropeptides can increase tissue permeability and cause vasodilatation, giving rise to the "warm CRPS" with edema. Substance P and TNF-α can engender osteoclastic activity, which may contribute to the osteoporosis seen in CRPS. In addition, CGRP can cause an increase in hair growth and sudomotor activity observed in CRPS patients.[9,27]

CORTICAL REORGANIZATION

In recent years, imaging studies, such as functional MR imaging (fMRI) and single-photon emission CT (SPECT), and mapping techniques based on electroencephalography (EEG) and magnetoencephalography (MEG) have indicated an important role of the central nervous system (CNS) in the pathogenesis of CRPS (see Schwenkreis et al.[28] for review). Cortical reorganization in central somatosensory and motor networks that may result in altered

central processing of tactile and nociceptive stimuli and cerebral organization of movement have been reported.[29] For example, Maihofner et al.[30] observed increased strength of magnetic fields and reduced distance between thumb and little finger representation in contralateral S1 cortex after tactile stimulation of the affected hand. Moreover, they observed a shift of the cortical S1 representation of the affected hand toward the lip representation and reported a correlation between the amount of cortical reorganization and the intensity of CRPS pain and the extent of mechanical hyperalgesia. In a follow-up study in the same group of patients a year or more after therapy, Maihofner et al.[31] found a reversal of cortical reorganization with clinical improvement, suggesting a relationship between S1 reorganization and chronic pain. The changes in cortical representations may explain not only the pain, but also a number of the other clinical features occurring in the course of the disease. Neurorehabilitative strategies that are targeted at restoring this impaired sensorimotor function, using strategies such as mirror therapies, are being investigated.

CLINICAL FEATURES

Since the achievement of the significant milestone in the classification of regional disorders with sudomotor or vasomotor abnormalities with the consensus-based criteria for CRPS by IASP in 1994 (Table 50-1), major strides have been taken to further refine the diagnostic criteria based on internal and external validation studies. This culminated in the Budapest Consensus in 2007 in which the diagnostic criteria was refined to include stricter criteria for clinical diagnosis and research studies.[32,33] The impetus for this improvement arose from the realization that since the definition of the diagnostic criteria by the IASP in 1994, fewer than 40% of the publications between 1996 and 2000 on CRPS met the criteria, and internal and external validation research suggested that CRPS may have been overdiagnosed.[34,35] The inclusion of "motor and trophic signs and symptoms" in addition to separating vasomotor signs and symptoms from sudomotor category improved specificity without losing sensitivity[33] (Tables 50-2 and 50-3).

The difference between CRPS I and II is the presence of a definable nerve injury (in CRPS II only). The signs and symptoms of both conditions are clinically indistinguishable and include sensory changes, edema, and vasomotor and sudomotor abnormalities. Pain is the key feature for both CRPS I and II. With CRPS I, the pain and associated clinical signs and symptoms are typically out of proportion

TABLE 50–1 International Association for the Study of Pain Diagnostic Criteria for CRPS I and CRPS II

CRPS I (Reflex Sympathetic Dystrophy)*	CRPS II (Causalgia)†
1. The presence of an initiating noxious event or a cause of immobilization.	1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.	2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.	3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.	

**Criteria 2 through 4 must be satisfied.*
†All three criteria must be satisfied.
Source: Stanton-Hicks M: Complex regional pain syndrome. Anesthesiol Clin North Am *21:733–744, 2003.*

TABLE 50–2 Proposed Clinical Diagnostic Criteria for CRPS

General definition of the syndrome:
CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the *clinical* diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
   Sensory: Reports of hyperesthesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign **at time of evaluation** in *two or more* of the following categories:
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry (<1 °C) and/or skin color changes and/or asymmetry
   Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

Note: For research purposes, *diagnostic decision rule should be at least one symptom* in all four *symptom categories and at least one sign (observed at evaluation) in two or more sign categories.*

TABLE 50–3 Summary of Decision Rules

Criteria/Decision Rule for Proposed Criteria	Sensitivity	Specificity
2+ sign categories and 2+ symptom categories	0.94	0.36
2+ sign categories and 3+ symptom categories	0.85	0.69
2+ sign categories and 4+ symptom categories	0.70	0.94
3+ sign categories and 2+ symptom categories	0.76	0.81
3+ sign categories and 3+ symptom categories	0.70	0.83
3+ sign categories and 4+ symptom categories	0.86	0.75

Source: Harden N, Bruehl S, Stanton-Hicks M, et al: Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med *8:326–331, 2007.*

to the inciting event. The pain is typically described as a burning deep-seated ache with a shooting quality and associated allodynia or hyperalgesia.[36] Up to 81% of patients meeting the criteria for CRPS have pain. Symptoms indicative of vasomotor abnormalities occurs in 86.9%, and sudomotor changes including hyper/hypohidrosis occur in 52.9% of patients with CRPS. Kinesophobia and motor weakness have been reported in 74.6%, and edema in 79.7%.[37]

DIAGNOSIS

The diagnostic criteria for CRPS Types I and II continue to be based on the patient's symptoms and signs. The current revised diagnostic criteria were developed to enhance the specificity and sensitivity of the previous diagnostic criteria. Studies on the external and internal validation of the IASP criteria suggest that patients should demonstrate at least one symptom in each of the following categories: sensory (hyperesthesia—increased sensitivity to sensory stimulation), vasomotor changes (temperature abnormalities, including skin and color changes), sudomotor (fluid retention—sweating abnormalities, edema), or motor (decreased range of motion, weakness, tremor, dyskinesia, or neglect). In addition, signs in at least two of the four categories indicated above should be noted on physical examination of the patient. A complete history and physical examination, including a through neurologic and vascular examination, will help differentiate from more common conditions that may mimic CRPS. These include neurologic conditions such as painful diabetic neuropathy, entrapment syndromes, discogenic disease, and thoracic outlet syndrome. In addition, vascular conditions should be considered as possible causes in the differential diagnosis, including deep venous thrombosis, cellulitis, vascular insufficiency, lymphedema, and erythromelalgia.[3]

Currently there is no diagnostic test considered to be a gold standard or objective test that is specific for CRPS. The following tests have been found to help make the diagnosis even though a negative result may not necessarily rule out the possibility of CRPS.

QUANTITATIVE SENSORY TESTING

This involves the use of standardized psychophysical tests of thermal, thermal pain, and vibratory thresholds to assess the function of large fiber, myelinated small fiber, and unmyelinated small afferent fibers. Static and dynamic allodynia, allodynia associated with pinprick, hyperalgesia related to mechanical and heat stimuli, and temporal summation (increased pain to repeated stimuli) may be abnormal in patients with CRPS.[38] Since no specific sensory pattern has been recognized with CRPS, assessment of the signs and changes over time may provide a tool to track response to treatment.

AUTONOMIC FUNCTION TESTS

This includes infrared thermometry and thermography, quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test (TST), and laser Doppler flowmetry.[38] The limitation of these tests is that most require special equipment and a setup that make clinical applications less viable. In addition, the specificity of abnormalities in these tests in the diagnosis of CRPS or their role as predictors of treatment success is unclear.

TEMPERATURE MEASUREMENT

The use of infrared thermometry and infrared thermography to assess small skin temperature differences between the sides of the body is reported to achieve sensitivity in the order of 76% and specificity of 100%.[39] The utility of this test clinically is dependent on maintaining controlled thermoregulation during measurements. This is difficult to achieve in most clinical situations. Therefore the measurements should be made under conditions where thermoregulation can be controlled to detect differences on both side for enhanced accuracy of the test. The direction of the temperature difference is dependent on the duration of the disease. Earlier in the disease process the affected limb may demonstrate elevated temperatures, while later on in the more chronic phase of the disease the affected side may show lower temperature compared to the unaffected side.[39]

VASCULAR ABNORMALITIES

In patient with the disease of less than 4 months' duration, vascular reflex responses may be assessed using Doppler flowmetry. The affected extremity may demonstrate higher perfusion.[40] In patients with duration of disease less than 15 months, skin perfusion was found to be either higher or lower, while in patients with a mean duration of 28 months the affected limb demonstrated a lower perfusion and ultimately lower temperatures.[40]

TROPHIC CHANGES

The value of a three-phase bone scintigraphy is in the ability to detect pathologic delayed uptake in the distal bones, such as metacarpophalangeal or metacarpal bones. This is thought to be highly sensitive, although the specificity for CRPS has been questioned.[38] X-ray

bone densitometry has also been reported to have a high sensitivity and specificity for CRPS. The ease with which these test may be carried out in clinical practice increases its potential usefulness.[38] Most of these changes have been reported to occur within the first year of the disease.[41]

TREATMENT

Improvements in diagnostic criteria and increased understanding of the pathophysiology of CRPS will help develop clinical trials of mechanism-based treatment modalities.[42] Currently, only a few evidence-based treatment modalities are available; thus, treatment typically involves therapies based on evidence accrued from other neuropathic pain conditions. The treatment philosophy still centers on a multimodal pharmacologic therapy (Table 50-4) and multidisciplinary team approach, with effective pain control, functional restoration, and enhancement of psychological well-being as the key elements (Fig. 50-1).

PHARMACOLOGIC THERAPY

Nonsteroidal anti-inflammatory drugs (NSAIDs): Although NSAIDs have not been widely studied in the treatment of CRPS, clinical experience demonstrates that NSAIDs can provide mild to moderate pain relief.[38] NSAIDs have been demonstrated to be of value in a retrospective study that examined the utility of intravenous regional anesthesia (IVRA) containing ketorolac; this study revealed that up to 69% of patients experienced partial to complete resolution of their pain.[43]

Antidepressants: Antidepressants have been used widely for the treatment of neuropathic pain. Norepinephrine and serotonin blockers and selective norepinephrine blockers like amitriptyline and desipramine, respectively, may exert their influence by modulating the noradrenergic and serotonergic descending pathways. The usual dose range for these drugs is about 10 to 75 mg by mouth at night time.[44–46] More selective serotonin reuptake inhibitors have not been demonstrated to be as effective as the above. The selective serotonin and norepinephrine reuptake inhibitor duloxetine has been shown to be effective in painful diabetic neuropathy.[46,47] These drugs have the added value of providing some mood elevation and sedation with improved sleep hygiene when taken at night. Caution is exercised with the use of tricyclic antidepressants in patients older than 65 years due to the potential for cardiac side effects.

Anticonvulsants: Gabapentin and pregabalin have been shown to be effective in diabetic neuropathy and postherpetic neuralgia (PHN). Studies in patients with CRPS have also demonstrated analgesic effect of gabapentin.[48,49] The Food and Drug Administration (FDA) has approved carbamazepine for trigeminal neuralgia and may be considered as a second-tier option for CRPS. The analog of carbamazepine, oxcarbazepine, which does not exhibit the side effects of liver and bone marrow toxicity, may be used as an alternative drug.

Opioids: There is a paucity of long-term studies on oral opioids in the treatment of CRPS or other neuropathic pain conditions. In a randomized placebo-controlled trial, Raja et al. demonstrated that patients with PHN preferred opioids (54%) over tricyclic antidepressants (30%), though the opioids offered only marginally greater pain relief.[44] Opioids should therefore be used as part of a multimodal pharmacologic treatment regimen, particularly if other single agents do not provide optimum analgesia.[45,47,50]

Novel Therapies: Free radical scavengers have been explored as possible treatment options. In a placebo-controlled

TABLE 50–4 Overview of Pharmacologic Agents Used in CRPS

Agent	Dose Range	Frequency	Common Side Effects
Antidepressants			
Amitriptyline	10–75 mg/day	Once a day (at night)	Sedation, anticholinergic effects
Nortriptyline	10–75 mg	Once a day (at night)	Sedation, anticholinergic effects
Desipramine	10–75 mg/day	Once a day (at night)	Least sedative/anticholinergic effects
Venlafaxine	37.5–340 mg/day	BID–TID	
Anticonvulsants			
Gabapentin	900–3600 mg/day	TID	Somnolence, memory impairment, tremors
Pregabalin	150–600 mg/day	BID–TID	Dizziness, somnolence, peripheral edema
Carbamazepine	100–1000 mg/day	BID–QID	Ataxia, sedation, nausea, liver damage, skin rash, bone marrow
Opioids			
Morphine (extended release)	15–60 mg	BID–TID	Nausea, vomiting, constipation, sedation, pruritus
Oxycodone (extended release)	10–60 mg	BID–TID	As for morphine
Methadone	5–20 mg	BID–TID	As for morphine

Source: Williams KA, Hurley RW, Lin EE, et al: Neuropathic pain syndromes (CRPS, PHN, PDN). In Benzon H, et al, editors: Raj's practical management of pain, *ed 4, New York, 2008, Mosby, pp 427–431.*

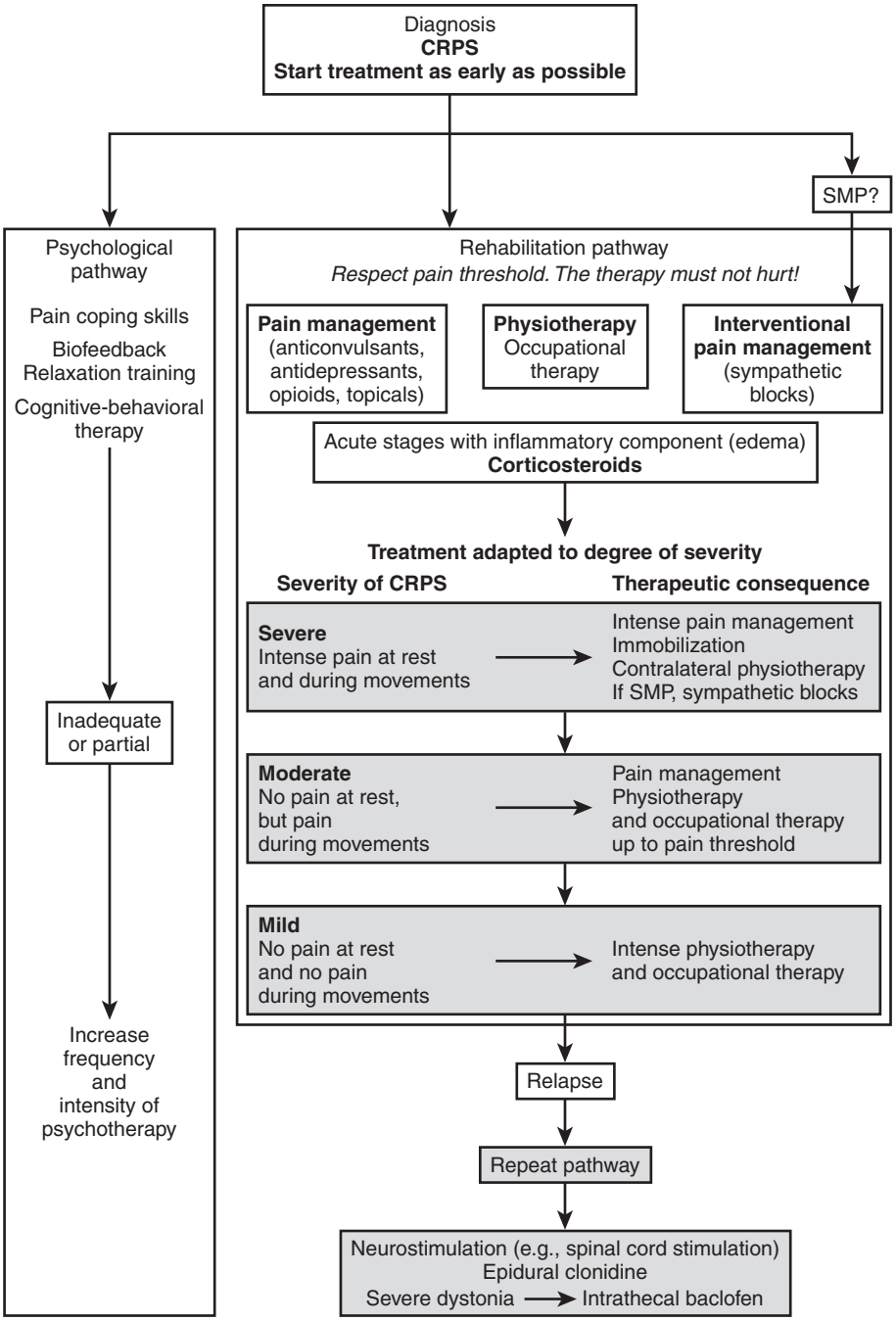

FIGURE 50-1 Treatment algorithm. *From Stanton-Hicks M: Complex regional pain syndrome.* Anesthesiol Clin North Am *21:733–744, 2003.*

trial, both topically applied dimethyl sulfoxide (DSMO) (DMSO-Benzon) 50%, and oral *N*-acetylcysteine (NAC) were found to be effective in CRPS Type I.[51] The naturally occurring antioxidant vitamin C has been observed to be associated with a lower incidence of CRPS when administered prophylactically to patients with closed radius fractures requiring internal fixation as compared with patients who did not receive vitamin C prophylactically.[38] Though the mechanism of action of calcium regulating drugs such as calcitonin is unknown in CRPS, intranasal calcitonin has been suggested to provide pain relief in patients with CRPS. Calcium-regulating drugs have also been used in the treatment of CRPS. Bisphosphonates have been shown to decrease pain and swelling in addition to enhancing range of motion in all placebo-controlled RCTs involving patients with CRPS. Calcitonin has also received considerable interest because its analgesic properties are derived from the release of β-endorphins. However, in most trials involving calcitonin in CRPS, there was no benefit associated with its administration.[52] The NMDA receptor antagonist has been tried in CRPS patients via several routes, including topically, in combination with bupivacaine and morphine epidurally, and more recently intravenously.[38] Further investigation is required to establish the place of all novel treatment modalities in the current armamentarium for CRPS.

INTERVENTIONAL THERAPIES

Intravenous Regional Anesthesia: There is no strong evidence to support the use of IVRA for sympatholysis in CRPS. Several agents, including guanethidine, reserpine, droperidol, ketanserin, atropine, and lidocaine-methylprednisolone, have been used.[52] The results of two small studies suggest that the combination of local anesthetics with bretylium or botulinum toxin can increase the analgesic duration of IVRA and lumbar sympathetic blocks, respectively.[52] When prilocaine and guanethidine were compared to placebo, no difference was shown after four blocks, whereas stellate ganglion blocks with bupivacaine and regional blocks with guanethidine demonstrated a significant improvement compared to baseline; both treatments showed comparable benefits.[38]

Sympathetic Nerve Blocks: Sympathetic blocks have been utilized both as a diagnostic tool to determine if neuropathic pain is sympathetically maintained (SMP) or sympathetically independent (SIP). Price et al. evaluated the diagnostic and therapeutic value of local anesthetics compared to saline in sympathetic blocks. They demonstrated that effects on pain and mechanical allodynia (lasting hours) was similar in both groups; however, the local anesthetic group showed a persistence of benefit beyond the duration of action of the local anesthetic (3–5 days).[53] They concluded that the immediate beneficial effect may be due to a nonspecific mechanism. Sympatholysis is associated with prolonged pain relief in patients who respond to the sympathetic block, and helps to differentiate between SMP and SIP. Ultimately, the clinical benefit of sympathetic ganglion blocks arises from the analgesia provided that allows for the implementation of intense physical therapy with modalities such as desensitization that help engender functional restoration in the affected limb.

Intrathecal Baclofen: CRPS can lead to dystonia often refractory to standard treatment, and baclofen a GABA (type B) receptor agonist that inhibits sensory input into the spinal cord has been shown to be effective in some patients with dystonia. Baclofen has therefore been tried as a treatment option in CRPS associated with dystonia. Intrathecal baclofen was successfully used in seven patients with CRPS refractory to benzodiazepines, levodopa, antiepileptic drugs, botulinum toxin, mannitol, surgical/chemical sympathectomy, and oral baclofen. Intrathecal therapy in CRPS requires further investigation.[52]

Spinal Cord Stimulation: There is increasing evidence to support the value of spinal cord stimulation (SCS) in the treatment of patients with CRPS who have experienced suboptimal benefit from conventional therapy.[54–58] As with the challenges of defining the pathophysiology of CRPS, the mechanism by which SCS provides pain control continues to be elusive. Several other questions that remain unanswered include the specifics of stimulation parameters, stimulation patterns, the criteria for a "successful" SCS trial, and the effects of SCS on the natural course of the disease. There has been one case report in an adult and a case series in adolescent girls aged 11 to 14 years, in which the use of SCS in a patient with CRPS resulted in complete resolution of the symptoms, with symptoms remaining abated at 1 to 8 years after the intervention.[59,60] In a 5-year follow up on patients with CRPS Type I, Kemler et al. reported results of a randomized controlled trial in which patients received either SCS plus physical therapy (PT) or PT alone. The authors found that during the first 2 years following implantation, the SCS-plus-PT patients reported greater reduction in pain. However, at the 3-year follow-ups and subsequent time points, the SCS-plus-PT group had similar results to the PT group regarding reduction in pain relief and all other variables measured. However, in a subgroup analysis the SCS-plus-PT group demonstrated a significantly greater global perceived effect to the treatment than the PT group alone.[61] In a systematic review of the clinical and cost-effectiveness literature, Taylor et al. found that SCS appears to be an efficacious and cost-effective treatment for CRPS Type I (level of evidence A) and Type II (level of evidence D).[62]

Functional Restoration: Functional restoration remains is the hallmark of successful treatment of CRPS. This is best achieved in a multidisciplinary setting with the occupational therapist initiating the early desensitization process and the physical therapist addressing muscle strength, flexibility, gait training, and overcoming the kinesophobia typically associated with advanced CRPS. A recreational therapist may be involved in the later stages of restoration to help the patient return to socialization and engagement in recreational activities that may have been neglected in the course of the disease.[38,58,63]

Motor Imagery Program: A motor imagery program (MIP) incorporates recognition of the limb laterality, imagined movements, and mirrored movements using a mirror box device. In a randomized controlled study involving patients with CRPS of the upper extremity after a wrist fracture, the patients received conventional treatment or MIP. At 6 and 12 weeks after completion of the six treatments, the patients in the MIP group had significantly less pain and decreased swelling. The beneficial effect of the treatment was replicated when the controls crossed over into the MIP group. This treatment modality is promising but requires further investigation.[52]

Psychotherapy: Depression and anxiety commonly occur in patients with chronic pain. This is amplified in CRPS as a result of the uncertainty associated with the cause, course, and treatment of the disorder. The risk of developing post-traumatic stress disorder is present in this patient population amid fears that the disease may progress or recur without warning. Instituting cognitive-behavioral therapy is the most effective psychological intervention found to produce long-lasting reduction in psychological symptoms in both children and adults with CRPS.[38,58,63]

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Access the reference list online at http://www.expertconsult.com

CHAPTER 51

Herpes Zoster and Postherpetic Neuralgia

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The objective of this chapter is to provide an overview of the epidemiology, natural history, pathophysiology, treatment, and prevention of herpes zoster and postherpetic neuralgia. Herpes zoster ("shingles") is a viral infection that is accompanied by acute pain in the majority of patients. The pain associated with herpes zoster does not resolve in a substantial number of patients, and postherpetic neuralgia (PHN) is diagnosed when herpes zoster pain persists. The results of research on PHN—a chronic peripheral neuropathic pain condition—have added greatly to knowledge of the pathophysiology and treatment of neuropathic pain.

HERPES ZOSTER

EPIDEMIOLOGY OF HERPES ZOSTER

Following a primary chicken pox infection, the varicella-zoster virus (VZV) establishes latency in sensory ganglia throughout the nervous system. Herpes zoster (shingles) is the reactivation of the virus and its spread from a single dorsal root or cranial nerve ganglion to the corresponding dermatome and neural tissue of the same segment.[1,2] Herpes zoster has the highest incidence of all neurologic diseases, occurring annually in approximately 1 million people in the United States, during the lifetimes of as much as 20% to 30% of the population, and in as many as 50% of those living until age 85.[1,3–6] The likelihood of recurrent zoster, however, is reported to be 5% or less,[1,5,7] and the true incidence may even be lower because a portion of these cases may have been zosteriform, recurrent herpes simplex infections.

A fundamental epidemiologic feature of zoster is a marked increase in incidence with aging. For example, the incidence of herpes zoster per 1000 person-years in a recent U.S. retrospective database study was 2.1 for persons aged 40 to 49 years, 4.2 for 50 to 59, 6.0 for 60 to 69, 8.6 for 70 to 79, and 10.7 for 80 and older.[7] In the placebo group in the zoster vaccine trial known as the Shingles Prevention Study (which was prospective, used active surveillance in a community-based population, and used PCR for definitive diagnosis of herpes zoster cases), the incidence of herpes zoster was 11.8 cases per 1000 persons per year in adults aged 60 and older.[8]

The incidence of herpes zoster is also significantly increased in patients with suppressed cell-mediated immunity—including HIV, AIDS, certain cancers, organ transplants (especially bone marrow transplant), immune-mediated diseases, and immunosuppressive treatments—compared to immunocompetent individuals.

Zoster epidemiology is ultimately determined by the transmission and spread of VZV in populations. The most important condition in the spread of VZV is the primary chicken pox infection, but latent and reactivated VZV infections also play important roles in maintaining VZV infection in populations.[9] Latently infected elderly adults and immunosuppressed patients are important reservoirs of virus because VZV is more likely to reactivate in these groups. When zoster occurs, VZV can be transmitted during the vesicular phase of the rash and cause primary infection when there is contact with a seronegative individual. A zoster exposure with a seropositive, latently infected individual may result in a subclinical reinfection and boost of humoral and cellular VZV immunity, but it is unlikely to cause varicella or herpes zoster.[9]

NATURAL HISTORY OF HERPES ZOSTER

The presentation of pain in herpes zoster is variable. In the majority of patients, a prodrome of dermatomal pain precedes the appearance of the characteristic unilateral rash.[10–12] This prodrome begins several days before rash onset in almost all cases, but a series of patients with prodromal pain preceding the appearance of the rash by 7 to more than 100 days has been reported.[13] Thoracic dermatomes are the most commonly affected sites in herpes zoster and account for 50% to 70% of all cases; cranial (especially the ophthalmic division of the trigeminal nerve), cervical, and lumbar dermatomes each account for 10% to 20% of cases, and sacral dermatomes are affected in 2% to 8% of cases.[14] The rash becomes vesicular after several days, then forms a crust, and loss of all scabs usually occurs within 2 to 4 weeks.

Pain in the affected dermatome accompanies the rash in most patients. Those who did not have a painful prodrome typically begin to experience pain at rash onset or shortly afterwards (Fig. 51-1). This acute herpes zoster pain gradually resolves before or shortly after rash healing in most cases. Severe acute pain in herpes zoster interferes with patients' abilities to carry out normal activities of daily living and, not surprisingly, is associated with greater use of analgesic medications.[15,16]

Dermatomal pain without a rash, referred to as *zoster sine herpete*, has also been described, and the finding of VZV DNA in the cerebrospinal fluid of patients with prolonged radicular pain and no rash provides evidence of this syndrome.[17]

In addition to acute pain, the morbidity of herpes zoster includes neurologic disorders and ophthalmologic, cutaneous, and visceral complications. The types of neurologic complications include motor neuropathy, cranial polyneuritis, transverse myelitis, meningoencephalitis, and cerebral angiitis and stroke after ophthalmic zoster.[7,16] Ophthalmologic complications have been described in 2% to 6% of zoster cases, including keratitis, uveitis, iridocyclitis, panophthalmitis, and glaucoma.[18] Elderly and especially immunosuppressed patients are at greater risk for most of the complications of herpes zoster.

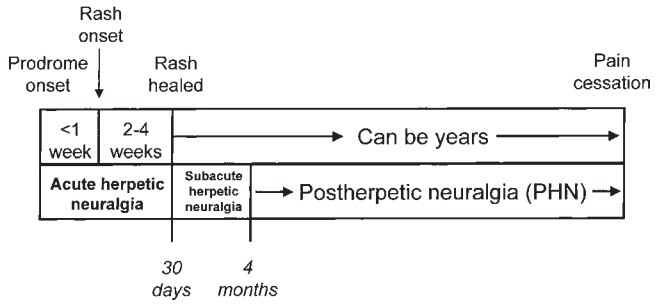

FIGURE 51-1 Timeline of pain experienced by herpes zoster patients.

TREATMENT OF HERPES ZOSTER

The main goals of the treatment of herpes zoster are to relieve acute pain and prevent postherpetic neuralgia. Treatment of herpes zoster patients with the antiviral agents acyclovir, famciclovir, valacyclovir, and brivudin (the latter only available in some European countries) inhibits viral replication and has been shown to reduce the duration of viral shedding, hasten rash healing, and decrease the severity and duration of acute pain.[2,19] The results of randomized controlled trials and meta-analyses are conflicting as to whether antiviral agents prevent PHN, partly because of heterogeneity in definitions of PHN and study design, although the duration of pain is decreased in some of these trials.[2,19–21] Therefore, based on reduction in acute pain and the potential for reduction in pain duration, antiviral therapy is recommended as first-line treatment in herpes zoster patients who are aged 50 years and older, have moderate or severe rash, have moderate or severe pain, have ophthalmic involvement, or are immunocompromised.[2,22] Famciclovir, valacyclovir and brivudin offer more convenient dosing and higher and more reliable blood levels of antiviral activity compared to acyclovir.

Some patients will not have their acute pain adequately controlled with antiviral therapy and simple analgesics. Approximately 20% of patients over age 50 continue to have pain 6 months after their rash despite antiviral treatment beginning within 72 hr of rash onset.[20] How then can acute pain and the risk of chronic pain be further reduced, beyond that currently achieved by antiviral therapy? Corticosteroids, opioids, gabapentin, tricyclic antidepressants, and neural blockade have been investigated or considered as strategies to achieve these goals.[22]

Randomized controlled clinical trials (RCTs) demonstrated that the addition of a corticosteroid reduced acute pain but did not contribute significantly beyond the benefits achieved by antiviral therapy alone in reducing prolonged pain.[23,24] The evidence from these trials indicated that corticosteroids do not prevent PHN.

A randomized controlled trial of oxycodone, gabapentin, or placebo in older adults with herpes zoster showed that oxycodone but not gabapentin provided significantly greater pain relief than placebo.[25] This trial was not powered to analyze PHN, and there are no other controlled trials of the effect of opioids or gabapentin on PHN when used during the acute phase of herpes zoster, except for a crossover study that showed greater pain relief with a single dose of 900 mg of gabapentin versus placebo.[26]

A placebo-controlled trial of amitriptyline 25 mg once daily for 3 months beginning within 48 hr of rash onset, and a reanalysis examining the subgroup of patients also treated with an antiviral, suggested that amitriptyline reduced the prevalence of PHN at 6 months.[27,28] However, amitriptyline is associated with a high rate of adverse events in older adults and this study is in need of replication. No trials have examined the effect of tricyclic antidepressants on acute pain in herpes zoster.

Regarding neural blockade, the results of a randomized controlled trial in patients with herpes zoster treated with oral antiviral therapy showed that a single epidural injection of steroids and local anesthetics relieved acute pain within the first month after rash onset significantly better than usual care but did not reduce the risk of developing PHN.[29] RCTs of multiple epidural injections, continuous epidural infusions, or repetitive paravertebral injections of anesthetics and steroids during herpes zoster reduced PHN or time to complete cessation of pain.[30–33] Although treatment of herpes zoster patients with multiple epidural injections or continuous epidural infusions is unlikely to be feasible in most settings, these data suggest that aggressive analgesia can be effective in patients with herpes zoster and ongoing moderate to severe pain.

Even if the risk of developing PHN is not reduced by combining antiviral therapy with analgesic or corticosteroid treatment in patients with herpes zoster, effective relief of acute pain is a critical treatment goal. For patients with moderate to severe pain, treatment with a strong opioid analgesic (e.g., oxycodone) is recommended in combination with antiviral therapy. If moderate to severe pain in patients with herpes zoster has not responded rapidly to treatment with an opioid analgesic and antiviral therapy, then the addition of a corticosteroid can be considered. For patients with pain that is inadequately controlled by antiviral agents in combination with oral analgesic medications and/or corticosteroids, referral to a pain specialist or pain center is recommended to evaluate eligibility for neural blockade.[22]

PREVENTION OF HERPES ZOSTER

A live attenuated zoster vaccine induces significant increases in the cellular immune response to VZV in older adults. Given that cellular immunity to VZV declines with age, the Shingles Prevention Study addressed the questions as to whether vaccination against VZV would decrease the incidence and/or severity of herpes zoster and PHN among older adults.[8]

The study was a randomized, double-blind, placebo controlled trial in 38,546 community-dwelling persons aged 60 and older. Subjects were followed for a median of 3 years. A total of 957 confirmed cases of herpes zoster (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of PHN (27 among vaccine recipients and 80 among placebo recipients) were included in the efficacy analysis. The zoster vaccine reduced the burden of illness (a pain severity by duration measure) due to herpes zoster by 61.1% ($p < 0.001$), reduced the incidence of PHN by 66.5% ($p < 0.001$), and reduced the incidence of herpes zoster by 51.3% ($p < 0.001$). Reactions at the injection site were more frequent among vaccine recipients but

were generally mild. Based on these findings, the U.S. Food and Drug Administration (FDA) licensed the zoster vaccine for the prevention of herpes zoster in immunocompetent adults aged 60 and older in 2006. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) unanimously recommended the vaccine for the prevention of herpes zoster in immunocompetent adults aged 60 and older and added the vaccine to the U.S. routine adult immunization schedule.[34] The effect that the zoster vaccine will have on the pain of herpes zoster and PHN will depend on the extent of vaccine uptake in the population and the durability of vaccine response, both of which are currently under investigation.

POSTHERPETIC NEURALGIA

EPIDEMIOLOGY AND NATURAL HISTORY

A variety of definitions of PHN have been used by clinicians and investigators, ranging from any pain persisting after rash healing to pain that has persisted at least 6 months after rash onset.[35] The results of recent studies, however, suggest that the pain associated with herpes zoster has three phases—an acute herpetic neuralgia that accompanies the rash and lasts for approximately 30 days after rash onset, a subacute herpetic neuralgia that lasts from 30 to 120 days after rash onset, and PHN, defined as pain that persists for at least 120 days after rash onset (see Fig. 51-1).[36–38] Although this provides a validated definition for research on PHN, it is probably unnecessary to distinguish between subacute herpetic neuralgia and PHN when treating patients with pain persisting after rash healing.

Because the proportion of herpes zoster patients with pain declines with time, estimates of the percentage of patients who develop PHN depend on its definition. In different clinic and community studies, 9% to 34% of adult zoster patients were reported to develop PHN defined variously as pain persisting after rash healing or for at least several months after rash onset.[2,7,35] There have been no systematic attempts to investigate the prevalence of PHN, and estimates of the number of cases have ranged from 500,000 to 1 million in the United States.[39]

PHN is a chronic pain syndrome that can last for years and cause substantial suffering and reduction in quality of life. As is true of other chronic pain syndromes, patients develop depression and other types of psychological distress as well as physical, occupational, and social disability as a consequence of their unremitting pain.[40–42]

There is evidence that pain in PHN can be discontinuous, with pain-free intervals of varying durations occurring.[43] Indeed, PHN can develop even in herpes zoster patients who have not had acute pain.[44]

The quality of pain in PHN compared to herpes zoster has been examined in several studies.[45–47] Sharp, stabbing pain was found to be more common in patients with zoster than in patients with PHN, whereas burning pain was more common in PHN patients and much less likely to be reported by patients with zoster. The investigators noted that the word *tender* was chosen by both groups of patients to describe allodynia (i.e., pain in response to a stimulus that does not normally provoke pain). These adjectives reflect the three different types of pain that have been distinguished in research on PHN—a steady throbbing or burning pain, an intermittent sharp or shooting pain, and allodynia.

There are a considerable number of recent studies in which risk factors for PHN have been investigated. Older age is the most well-established risk factor for PHN.[3,7] For example, as early as 50 years ago it was reported that persisting pain was infrequent in herpes zoster patients under 40 years of age, but that the proportion of patients with pain lasting 1 year or more approached 50% in those over age 70.[48] Many independent studies have reported that patients with more severe acute pain are at greater risk for PHN.[38,49] As noted above, the majority of herpes zoster patients have a painful prodrome before their rash appears, and several studies have found that these patients have a greater risk of PHN than patients who did not have a prodrome.[38,49] Greater severity and duration of the herpes zoster rash are additional risk factors for the development of PHN that have been identified in multiple studies.[38,49]

PATHOPHYSIOLOGY

Except for age and psychosocial factors, the risk factors for PHN that have been identified can all be considered concomitants of a more severe infection. More severe zoster infections are accompanied by greater neural damage, and it has been proposed that this neural damage contributes prominently to the development of PHN.[50] But the nature of this damage and the specific mechanisms by which it causes the persisting pain of PHN remain unclear. What limited knowledge there is of the pathophysiology of PHN derives from studies of neuropathology, sensory dysfunction, and pharmacologic response. At the present time, there is considerable agreement that different peripheral and central mechanisms contribute to PHN, and that the qualitatively different types of pain that characterize PHN probably have different underlying mechanisms. This suggests that there may be pathophysiologically distinct subgroups of patients with PHN or that more than one mechanism may be involved in individual patients or both.[51,52]

Watson and his colleagues[53] have conducted an elegant series of postmortem studies of patients of who were suffering from PHN at the time of death and of patients with a history of herpes zoster whose pain did not persist beyond rash healing. In these studies, dorsal horn atrophy and pathologic changes in the sensory ganglion were found on the affected side (and not on the unaffected side) in patients with PHN, but not in patients with a history of herpes zoster whose pain did not persist. In a more recent set of studies using punch skin biopsy, reductions in epidermal nerve fiber density were found in the affected dermatome but not on the contralateral unaffected side in patients with PHN.[54,55] Notably, in both the postmortem studies and the punch-skin biopsy studies, the the pathologic features were characteristic of only the affected side in patients with PHN and were not found in patients with a history of zoster whose pain did not persist.

Rowbotham, Fields, and Petersen[51,52,56,57] have conducted an important series of studies of sensory dysfunction and pharmacologic response that address the pathophysiology

of PHN. PHN patients with prominent allodynia were found to have relatively normal sensory function as assessed by thermal thresholds and were also more likely to report pain relief following local anesthetic infiltration with lidocaine than patients with primarily constant pain. These authors conclude that at least two different mechanisms may contribute to PHN, and propose that the mechanism of allodynia in PHN is abnormal activity in preserved primary afferent nociceptors that have been damaged by the varicella-zoster virus but that remain in continuity with their central targets. Activity in these "irritable" nociceptors may initiate and then maintain a state of central sensitization in which input from large fiber afferents that respond to nonpainful mechanical stimuli causes allodynia.

As opposed to patients with prominent allodynia, PHN patients with predominantly continuous pain were found to have sensory loss in the areas where they have the most pain. This suggests that continuous pain in PHN is caused by a different mechanism than allodynia, possibly involving central structural and functional changes accompanying deafferentation. These may include a structural reorganization of the spinal cord that involves abnormal synaptic connections, as well as functional abnormalities resulting from deafferentation involving hyperexcitability of dorsal horn neurons.

TREATMENT

Since publication of the first randomized controlled trials in the early 1980s, tricyclic antidepressants (TCAs) have been considered a first-line treatment for patients with PHN.[58] The efficacy of gabapentin, high-concentration capsaicin patch, lidocaine patch 5%, opioid analgesics, pregabalin, and tramadol, has now also been demonstrated by the results of RCTs in patients with PHN. These medications provide an evidence-based approach for the treatment of PHN.[59–65]

The initial choice of these medications should be guided by the adverse event profiles, potential for drug interactions, and patient comorbidities and treatment preferences, especially because there are no replicated data demonstrating superior effectiveness of one drug over another. In general, gabapentin, high-concentration capsaicin, lidocaine patch 5%, and pregabalin can be considered first-line treatments for PHN, whereas opioid analgesics, tramadol and TCAs are more typically second-line treatments because they generally require greater caution in the often elderly patient with PHN.[66]

Gabapentin. Patients with PHN have been treated with anticonvulsant medications for many years. Gabapentin, a second-generation antiepileptic drug, was associated with a statistically significant reduction in daily pain ratings as well as improvements in sleep, mood, and quality of life at daily dosages of 1800 to 3600 mg in two large clinical trials.[67,68] Side effects of gabapentin include somnolence, dizziness, and (less often) mild peripheral edema, which requires monitoring and possibly dosage adjustment but usually not treatment discontinuation. Gabapentin may cause or exacerbate gait and balance problems and cognitive impairment in the elderly. Dosage adjustment is necessary in patients with renal insufficiency, but its generally excellent tolerability, safety, and lack of drug interactions distinguish gabapentin from the other oral medications used in the treatment of PHN.

To reduce side effects and increase patient compliance with treatment, gabapentin should be initiated at low dosages—100 to 300 mg in a single dose at bedtime or 100 mg 3 times daily—and then titrated by 100 mg 3 times daily as tolerated. Because of variability in gabapentin absorption, the final dosage should be determined either by complete pain relief, which is rare, or by unacceptable side effects that do not resolve over a few weeks.

High-concentration capsaicin patch. The results of two RCTs in patients with PHN showed that a single application of a high-concentration patch versus a low-concentration control patch was efficacious in reducing pain from the second week after the capsaicin application throughout a subsequent 8-week period; this effect was also observed over 12 weeks in secondary analyses.[68,69] Application of the high-concentration capsaicin patch in patients with PHN was safe and well tolerated, and adverse events were limited to transient increases in pain associated with patch application and application-site reactions (e.g., erythema).

Because a single treatment application may be associated with sustained reductions in pain that last for 2 to 3 months, the high-concentration capsaicin patch has the potential to provide a novel addition to existing treatments for PHN, which are typically administered 1 or more times each day. However, the long-term benefits of the high-concentration capsaicin patch are unknown, and the safety and efficacy of repeated applications must be evaluated.

Lidocaine patch 5%. There are two published, double-blind, vehicle-controlled, randomized trials of lidocaine patch 5% in PHN.[70,71] In these studies, PHN patients with allodynia obtained statistically significantly greater pain relief with lidocaine patch 5% compared with vehicle-control patches containing no lidocaine. Lidocaine patch 5% is a topical preparation that has excellent safety and tolerability, and the only side effects involve mild skin reactions (e.g., erythema, rash). Systemic absorption is minimal but must be considered in patients receiving oral Class I antiarrythmic drugs such as mexiletine.

Treatment with the lidocaine patch 5% consists of the application of a maximum of three patches daily for a maximum of 12 hr applied directly to the area of maximal PHN pain and allodynia, which typically overlaps the affected dermatome. The lidocaine patch 5% is not approved for patients with herpes zoster, and it should not be used in patients with open lesions because the available formulation is not sterile. Importantly, whether the patient obtains satisfactory relief from lidocaine patch 5% will usually be apparent within 2 to 3 weeks and time-consuming dose escalation is not required.

Opioid analgesics. The efficacy of opioid analgesics in patients with PHN was first demonstrated in a double-blind study comparing intravenous morphine with placebo.[72] By providing evidence that PHN pain could be temporarily relieved by infusions of opioid analgesics, the results of this study suggested that longer-term oral treatment might also be efficacious. In two double-blind, placebo-controlled, randomized trials of oral opioid analgesics in PHN, controlled-release oxycodone titrated to a maximum dosage of 60 mg daily provided statistically

significant benefits on pain, disability, and allodynia[73] and controlled-release morphine titrated to a maximum dosage of 240 mg daily provided statistically significant benefits on pain and sleep but not on physical functioning and mood.[74]

The most common side effects of opioid analgesics are constipation, sedation, and nausea, as well as cognitive impairment and problems with mobility can occur in elderly patients. Opioid analgesics must be used very cautiously in patients with a history of substance abuse or suicide attempts, and accidental death or suicide can occur with overdose. Patients treated with opioid analgesics may develop analgesic tolerance (i.e., a reduction in analgesic benefit over time), although a stable dosage can often be achieved. All patients will develop physical dependence (i.e., withdrawal symptoms develop with abrupt discontinuation or rapid dose reduction), and must be advised that they should not abruptly discontinue their medication. The risk that substance abuse will develop in patients who do not have a history of substance abuse is not known but thought to be low in the generally elderly patient with PHN.

There are numerous short- and long-acting opioid analgesics available, and treatment can begin with a short-acting medication at morphine oral equianalgesic dosages of 5 to 15 mg every 4 hr as needed. After 1 to 2 weeks of treatment, the total daily dosage can be converted to an equianalgesic dosage of one of the available long-acting opioid analgesics (i.e., controlled-release morphine, controlled-release oxycodone, transdermal fentanyl, levorphanol, and methadone) while the patient continues taking the short-acting medication on an as needed basis. With careful titration and monitoring, there is no maximum dosage of opioid analgesics, but evaluation by a pain specialist may be considered when morphine equianalgesic dosages exceeding 120 mg daily are contemplated.

Pregabalin. Pregabalin is similar in structure to gabapentin and has demonstrated efficacy in RTCs of PHN.[75–77] In a multicenter trial of 173 PHN patients, pregabalin-treated patients had greater decreases in pain than patients treated with placebo (endpoint mean scores 3.60 vs. 5.29, $p = 0.0001$).[75] The proportions of patients with greater than 50% decreases in mean pain scores were greater in the pregabalin than in the placebo group (50% vs. 20%, $p = 0.001$). Dizziness, somnolence, peripheral edema, amblyopia, dry mouth and gait disturbances were the most common adverse effects of the medication.

Pregabalin should be initiated at 150 mg/day in two or three divided doses. Frail older patients may require lower starting doses. The dose may be increased to 300 mg/day in two or three divided doses within 1 week depending on clinical response and any adverse effects. The maximum dose of 600 mg/day in two or three divided doses can be considered if the patient does not have adequate pain relief at the risk of significantly higher frequency of adverse effects.

Tramadol. Tramadol is a norepinephrine and serotonin reuptake inhibitor with a major metabolite that is a *mu* opioid agonist. There is one published, double-blind, placebo-controlled, randomized clinical trial of tramadol in PHN,[78] and its results are consistent with studies of other chronic neuropathic pain syndromes.[59] Tramadol was titrated to a maximum dosage of 400 mg daily, and significantly relieved pain and reduced use of rescue medication compared to placebo. The side effects of tramadol include dizziness, nausea, constipation, somnolence, and orthostatic hypotension. These occur more frequently when the dosage is escalated rapidly and with concurrent administration of other drugs with similar side effect profiles. There is an increased risk of seizures in patients treated with tramadol who have a history of seizures or who are also receiving antidepressants, opioids, or other drugs that can reduce the seizure threshold. Serotonin syndrome may occur if tramadol is used concurrently with other serotonergic medications, especially selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors. Tramadol may cause or exacerbate cognitive impairment in the elderly, and dosage adjustment is necessary in patients with renal or hepatic disease. Abuse of tramadol is thought to be rare but has been observed.

To decrease the likelihood of side effects, tramadol should be initiated at low dosages—50 mg once or twice daily—and then titrated every 3 to 7 days by 50 to 100 mg/day in divided doses as tolerated. The maximum dosage of tramadol is 100 mg 4 times daily; in patients aged over 75, the maximum dosage of tramadol is 300 mg daily in divided doses.

Tricyclic antidepressants. An apt summary of studies of the efficacy of TCAs is provided by the title of an article summarizing the relevant literature, "Thirteen consecutive well-designed randomized trials show that antidepressants reduce pain in diabetic neuropathy and postherpetic neuralgia."[58] A recent meta-analysis concluded that TCAs significantly reduce pain in patients with PHN.[79] Amitriptyline is clinically the most widely used TCA in PHN because it is the TCA that has been most extensively studied in PHN and other neuropathic pain syndromes. However, amitriptyline is poorly tolerated and contraindicated in elderly patients.[80,81] In one of the few randomized, double-blind trials that have compared two different treatments in PHN patients, nortriptyline demonstrated equivalent efficacy to amitriptyline but was better tolerated.[82] Based on the results of this study, nortriptyline should now be considered the preferred TCA for the treatment of PHN; desipramine may be used in patients who experience excessive sedation with nortriptyline.

Despite the efficacy of TCAs in the treatment of PHN, their cardiac toxicity[83] and side effect profile require considerable caution when treating older patients with PHN. Dry mouth is the most common side effect, and constipation, sweating, dizziness, disturbed vision, and drowsiness also occur frequently. All TCAs must be used very cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, and autonomic neuropathy, and a screening EKG to check for cardiac conduction abnormalities is recommended before beginning TCA treatment, especially in patients over 40 years of age. TCAs must be used cautiously when there is a risk of suicide or accidental death from overdose, and TCAs may cause balance problems and cognitive impairment in the elderly. TCAs can block the effects of certain antihypertensive drugs and interact with drugs metabolized by P450 2D6 (e.g., cimetidine, Type 1C antiarrythmics). Because all SSRIs inhibit P450 D26, caution is necessary in the concomitant administration of TCAs and SSRIs to prevent toxic TCA plasma concentrations.

To decrease side effects, all TCAs should be initiated at low dosages—10 to 25 mg in a single dose at bedtime—and should then be slowly titrated as tolerated. It is often claimed that the analgesic effect of TCAs occurs at lower dosages than their antidepressant effect, but there is no controlled evidence of this. Consequently, TCAs should be titrated to dosages of at least 75 to 150 mg daily. For titration above 100 to 150 mg daily, blood levels and the EKG should be monitored. Irrespective of the TCA chosen, it is imperative that patients understand the rationale for treatment, specifically, that TCAs have an analgesic effect that has been demonstrated to be independent of their antidepressant effect. It is important to point out that there are no published randomized clinical trials of either selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine) or selective serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) in PHN and so it is unknown whether these classes of antidepressant medications are efficacious in PHN.

Sequential and combination pharmacologic treatment. There have been few clinical trials in which medications have been directly compared with one another in patients with PHN.[74,82,84,85] Such comparisons would not only make it possible to directly determine whether treatments vary in their efficacy, safety, and tolerability, but when conducted in the same patients, would also make it possible to evaluate the extent to which treatment response to one medication predicts response to another. For example, treatment responses to opioid analgesics and TCAs were uncorrelated in a recent three-period, placebo-controlled crossover trial, which suggests that when patients have not responded to one of these types of medication, they may still respond to the other.[74]

The prescription of combination pharmacotherapy for PHN is common in clinical practice. The efficacy of this practice has been the subject of recent studies of additive or synergistic benefits of combination treatment. In a 5-week double-blind crossover trial, patients with diabetic polyneuropathy or postherpetic neuralgia were randomized to daily active placebo (lorazepam), sustained-release morphine, gabapentin, and a combination of gabapentin and morphine.[84] Baseline mean daily pain (0–10) was 5.72. At maximum tolerated dose, pain was rated at 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin–morphine combination ($p < 0.05$ for the combination vs. placebo, gabapentin, and morphine). Results for PHN alone were not reported. Constipation, sedation, and dry mouth were the most common adverse effects. In a 6-week double-blind crossover trial, patients with diabetic polyneuropathy or postherpetic neuralgia were randomized to receive one of three sequences of daily oral gabapentin, nortriptyline, and their combination. Baseline mean pain intensity was 5.4 (0–10 scale). For patients with postherpetic neuralgia, pain with combination treatment (mean 2.5, confidence interval [CI] = 1.4–3.6) was lower than with nortriptyline (mean 2.9, CI = 1.7–4.0) or gabapentin alone (mean 3.4, CI = 2.2–4.5), but the overall effect of drug treatment was not significant ($p = 0.054$), possibly because of small sample size.[85] The most common adverse event was dry mouth secondary to nortriptyline. These results suggest that combination therapy may provide additional pain relief in some individuals with PHN who have responded to one or another agent. Disadvantages of combination therapy include an increased risk of adverse effects as the number of medications is increased.

Beyond first- and second-line treatment. A considerable percentage of PHN patients will not respond to medications when used alone and in combination. For these patients, there is a large number of alternative treatments that deserve consideration and referral to a pain management center should be contemplated, sooner rather than later. Invasive treatments may be considered when patients have failed to obtain adequate relief from other treatment approaches. These include sympathetic nerve blocks, which may provide temporary relief in patients with PHN but typically do not provide longer-lasting benefits.[86] Based on a review of 77 patients, it was reported that stellate ganglion blocks provided "good" pain relief in 50% of PHN patients who had pain for less than 1 year but in only 25% of patients who had pain for more than 1 year.[87] Similar data have also been presented by Winnie and Hartwell,[88] comparing sympathetic nerve blocks done within 2 months of the onset of zoster with blocks done more than 2 months after onset. Unfortunately, both of these studies were uncontrolled, making it impossible to distinguish greater efficacy of earlier treatment from the natural history of pain resolution in herpes zoster and PHN.

A study examining intrathecal administration of methylprednisolone[89] in patients with PHN received considerable attention because of the dramatic benefits that were described. However, intrathecal administration of methylprednisolone is not approved by the FDA and the well-known risks of intrathecal steroids include neurologic complications and adhesive arachnoiditis.

An uncontrolled study of spinal cord stimulation in 28 patients with PHN demonstrated long-term benefits in 82%, including pain relief of pain and improvements in daily functioning.[90] The authors reported that spontaneous improvement was ruled out by recurrence of pain following inactivation of the spinal cord stimulator. Confirmation of the benefits of spinal cord stimulation in patients with PHN will require use of adequate control groups.

It is important to conclude by emphasizing that the medications and invasive treatments that are currently available are rarely associated with the complete relief of PHN and evidence of their beneficial effects on quality of life is limited. Medical and invasive management of the patient with PHN should therefore be considered components of a more comprehensive treatment approach, which may include various nonpharmacologic treatments such as psychological counseling.[91]

KEY POINTS

- Herpes zoster (shingles) is caused by reactivation of the varicella-zoster virus (VZV), which establishes latency in sensory ganglia after primary infection (chicken pox).
- The characteristic unilateral dermatomal vesicular rash of herpes zoster heals within 2 to 4 weeks and is accompanied by pain in the majority of patients.
- Older age is associated with an increased risk of herpes zoster because of an age-associated decline in VZV-specific cell-mediated immunity.

- Antiviral therapy with acyclovir, famciclovir, valacyclovir, or brivudin in patients with herpes zoster inhibits viral replication and has been shown to reduce the duration of viral shedding, hasten rash healing, and decrease the duration of pain.
- The supplementation of antiviral therapy with opioids or corticosteroids may provide additional pain relief in herpes zoster patients with moderate to severe acute pain.
- Peripheral, sympathetic, and epidural nerve blocks with local anesthetics and/or corticosteroids appear to relieve acute pain in patients with herpes zoster, but their role in preventing PHN is uncertain because there are few randomized placebo-controlled trials.
- Postherpetic neuralgia refers to pain that continues after healing of the herpes zoster rash. This peripheral neuropathic pain condition causes substantial distress and disability and can last for years.
- Well-established risk factors for PHN in patients with herpes zoster include older age, more intense acute pain, more severe rash, and a prodrome of dermatomal pain before the rash appears.
- It is likely that different peripheral and central mechanisms contribute to PHN, and that the qualitatively different types of pain that characterize PHN have different underlying mechanisms.
- The efficacy of gabapentin, high-concentration capsaicin patch, lidocaine patch 5%, pregabalin, tramadol, tricyclic antidepressants, and opioid analgesics has been demonstrated by the results of RCTs in patients with PHN, and these medications provide an evidence-based approach to treatment. Combination therapy with opioids-gabapentin or nortriptyline-gabapentin may be more effective than either drug alone.

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CHAPTER 52

Postamputation Pain

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Amputation of a limb can lead to painful and nonpainful sequelae such as phantom sensations, telescoping, residual limb (aka "stump") pain, and phantom pain. Although the phenomena of abnormal sensations and pain in amputated limbs have been reported earlier by several physicians, Weir Mitchell is generally credited with coining the term "phantom limb" to describe the symptoms he observed in American Civil War soldiers. These phenomena occur in the majority of patients after limb amputation, although the nature, frequency, intensity, and duration of symptoms may vary considerably.[1,2] Although phantom pain has been reported most frequently following amputation (80%), amputees also have a high prevalence of residual limb pain (68%), and following lower extremity amputations, back pain (62%). At least 1 in 190 Americans is currently living with the loss of a limb. The number of amputees is expected to rise from 1.6 million in the year 2005 to 3.6 million in 2050. Forty-two percent of limb loss is considered "major" (i.e., not limited to fingers or toes). Vascular disease is responsible for approximately 77% of major limb amputations, while trauma (21%) and cancer (2%) are less frequent causes.[3,4] Among upper extremity amputees, trauma is the leading cause.

PHANTOM SENSATION

Phantom sensations are by definition nonpainful physical perceptions that occur after a traumatic or surgical amputation that is perceived as emanating from the missing body part. Phantom sensations are common after surgery, with an incidence of 90% during the first 6 months. A third of patients experience phantom sensations within 24 hr after their surgery.[5] Excision of a body part, however, is not essential for phantom sensations. Phantom sensation of the arm has been reported after avulsion of the brachial plexus without amputation of the limb.[6] Excision of other body parts such as tongue, bladder, rectum, breast, and genitalia may also present with phantom sensations.[6,7]

Nonpainful phantom sensation may have various manifestations including kinetic sensations, and kinesthetic and exteroceptive perceptions.[8] Kinetic sensations are exemplified by perception of movements in the amputated body region, such as flexion/extension of the toes. Kinesthetic perceptions are characterized by distorted representations in size or position of the missing body part (e.g., feeling that the hand or foot is twisted). Exteroceptive perceptions can include paresthesias, tingling, touch, pressure, itching, heat, cold, and wetness. Complete paraplegic and quadriplegic patients can also have phantom sensations.[6,7] Phantom sensations are commonly experienced in the distal portion of the limbs—hands and feet—possibly due to the rich innervation of these regions and the disproportionately large cortical representation of these regions in the homunculus.

TELESCOPING

Phantom limbs are also associated with a phenomenon called "telescoping": the perception of progressive shortening of the phantom body part resulting in the sensation that the distal part of the limb is becoming more proximal.[5] At the start of the phenomenon, the phantom sensation can feel so real that the patient may actually reach for objects or attempt to ambulate with a phantom leg.[6] However, with time phantom sensations of the distal extremities may change and become less distinct so that the patient may feel a hand close to the stump, but not feel the proximal arm or forearm. This phenomenon is common, occurring in one-fourth to two-thirds of limb amputees.

PHANTOM PAIN

Phantom pain is the perception of a painful, unpleasant sensation in the distribution of the missing or deafferentated body part. Phantom limb pain has been reported to occur in about two-thirds of postamputation patients in the first 6 months after surgery, and about 60% of patients still had significant phantom pain 2 years after surgery.[9] The cumulative incidence of phantom pain several years after surgery has been reported to be as high as 85%.[7,9] The pain can vary in character, duration, frequency, and intensity. It can present as sharp, dull, burning, squeezing, cramping, shooting, or as a shock-like electrical sensation.[7] Patients may occasionally complain of intermittent tremors or painful muscle spasms in the stump associated with paroxysms of phantom pain.

In a prospective study by Jensen and colleagues of 58 patients undergoing limb amputation, the authors found that phantom pain often changed in presentation within the first 6 months after amputation. The characteristic of the phantom pain changed from a mainly exteroceptive-like pain (knife-like or sticking), localized in the entire limb or at least involving proximal parts of the lost limb, to a mainly proprioceptive type of pain (squeezing or burning) localized in the distal parts of the amputated limb.[9] Forty-seven percent of patients had phantom pain within 24 hr after the amputation and 83% within the first 4 days. The study also demonstrated that the frequency, duration, and severity of the phantom pain decreased during the first 6 months, after which the characteristics of phantom pain did not change significantly. Sometimes, phantom pain can resolve spontaneously without treatment. Similar to other neuropathic conditions, phantom pain persisting longer than 6 months is extremely difficult to treat.[7]

The incidence of phantom pain seems to be independent of the patient's age, sex, previous health status, and cause of amputation.[7] One factor that increases the incidence of phantom pain after amputation is the presence of pain in the limb before the amputation.[5,9,10] In a prospective study

of 56 patients who had amputation of a lower limb, Nikolajsen and colleagues noted that the presence of preamputation pain significantly increased the incidence of both stump pain and phantom pain after 1 week, and the incidence of phantom pain after 3 months. Approximately 42% of the patients reported that their phantom pain resembled the pain they had experienced at the time of amputation.[10] Associations of phantom pain with phantom sensations and between phantom pain and stump pain have also been demonstrated for upper limb amputees.[11]

RESIDUAL LIMB PAIN

Stump pain or residual limb pain, is pain localized to the residual body part following amputation. Longitudinal studies report that the incidence of stump pain more than 2 years after amputation is about 20%. However, surveys of veterans suggest a higher incidence of pain (56%) in the residual limb and a more recent survey reported a 74% incidence.[12] The former observation may be related to the fact that younger age in general is a risk factor for chronic postsurgical pain.[13,14] Stump pain is often secondary to local pathologic processes such as infection; lesions of the skin, soft tissue, or bone; heterotopic ossification (>50% in traumatic amputations[15]); and local ischemia. These processes can generally be classified into the following categories: postsurgical nociceptive, neurogenic, prosthogenic, arthrogenic, ischemic, referred (usually from the spine or joints), sympathetically maintained, or abnormal stump tissue (e.g., adhesive scar tissue).[7] Stump pain can be superficial (localized to the scar region of the incision), felt deep in the distal stump, or encompass the whole residual limb. Stump pain can frequently be differentiated from phantom pain based on the fact that it is classically provoked or exacerbated by traction or pressure, which often occurs during the use of a prosthesis. The management of stump pain entails a detailed history and physical exam that includes ensuring a proper fitting prosthesis. Arthrogenic and referred stump pains are usually secondary to abnormal gait and asymmetrically distributed weight bearing, resulting in excessive stress on adjacent joints and/or lumbosacral spine structures. This can lead to bursitis, accelerated arthritis, sacroiliac joint disease, discogenic and facetogenic pain, and lumbosacral radiculopathy.

PHANTOM PHENOMENA AFTER MASTECTOMY

Phantom sensations are felt by 15% to 64% of patients who had mastectomy, with the average incidence around 30%. Most of these phantom sensations are felt intermittently, occurring once every 2 or 4 weeks. The incidence of phantom pain after mastectomy appears to be lower than after limb amputation: it ranges from 0% to 44% with an average of 20%.[16] The lower incidence may be related to the smaller cortical representation of breasts and the fact that breasts do not mediate kinesthetic sensory impulses.[17,18] The onset of phantom sensation and/or pain almost always occurs within 3 months of surgery, with most cases occurring within 1 month. The phantom pain is localized in the entire breast or around the nipple. The relationship between preamputation pain and phantom pain appears to be less after mastectomy than after limb amputation. In fact, preamputation pain has a stronger relationship with phantom sensations than with phantom pain. There is, however, a striking similarity in the location and character of the pain before and after mastectomy,[16] a phenomenon seen after other amputations.[19] The relationship between phantom pain and preamputation pain is more significant within the first month after mastectomy. In view of the high incidence of pain after breast surgery in general, the only way to distinguish between true "phantom" pain and other sources of postmastectomy pain (e.g., intercostal brachial neuralgia, neuroma) may be via a detailed history and physical exam.

THEORETICAL MECHANISMS

Identifying the mechanism(s) responsible for phantom sensations has generated intense and growing interest over the past two decades. Several lines of evidence suggest that phantom phenomena are the result of interactions between altered peripheral, spinal, and supraspinal mechanisms. The demonstration of spontaneous neuronal activity in the proximal end of cut nerves,[20] the presence of stump pathology in some patients with phantom pain, and the relief of phantom pain after the injection of local anesthetic into the painful stump have all been considered evidence supporting peripheral mechanisms of phantom pain.[5,20] Peripheral nerve damage during an amputation initiates axonal regeneration, resulting in a neuroma. A positive Tinel's sign (tapping on the injured nerve or neuroma leading to pain in the phantom limb or stump) represents a classic feature on physical examination. Afferent fibers in a neuroma develop ectopic activity, mechanical sensitivity, and chemosensitivity to catecholamines. Upregulation of voltage-sensitive sodium channels, downregulation of potassium channels, and expression of novel receptors in the neuroma alter the excitability of the affected neurons and increase afferent input. Injured neurons can generate new, nonfunctional connections (ephaptic cross-talk), resulting in increased afferent input to the spinal cord.[21] These changes may lead to spontaneous pain, and explain the amplification in pain caused by emotional distress and/or exposure to cold that leads to increased sympathetic discharge and circulating catecholamines. Total spinal anesthesia, cordotomy, cordectomy, and spinal cord stimulation have at best yielded only modest relief of phantom pain; in some cases spinal anesthesia can precipitate the development or rekindling of phantom pain that previously subsided.[22,23] Hence, central changes in the spinal cord, brainstem, and thalamus are thought to contribute to phantom pain.

Peripheral nerve injury leads to deafferentation—removal of afferent input to the dorsal column of the spinal cord—causing structural, neurochemical, and physiologic changes in central nervous system neurons. These changes result in functional alterations—plasticity—in central neurons that lead to spontaneous pain signals which are transmitted centrally. Peripheral sensory input at the level of the spinal cord also has inhibitory effects on

the central transmission of pain. Changes in the dorsal horn and the loss of afferent input lead to decreased impulses from brainstem reticular areas, which normally exert inhibitory effects on sensory transmission.[22] Therefore the absence of inhibitory effects of sensory input from the missing peripheral body part causes increased autonomous activity of dorsal horn neurons, in effect becoming "sensory epileptic discharges".[7,9] Evidence for spinal cord mechanisms is supported by the fact that anticonvulsants and lesions placed in the substantia gelatinosa are effective in treating phantom pain.[17]

The brain exhibits neuroplastic changes both in motor and sensory cortices. Cortical representation can be altered so that painful and nonpainful sensations in the phantom are a perceptual correlate of reorganizational processes in the somatosensory cortex.[21] Ramachandran and coworkers[24] reported that in upper limb amputees, sensations in the phantom limb could be elicited by brushing the face. Imaging studies have shown a shift of mouth representation in the somatosensory cortex to the zone previously represented by the arm and hand region (cortical reorganization) in upper limb amputees.[25] A strong correlation was also demonstrated between the magnitude of the shift and intensity of phantom limb pain. A summary of the factors thought to be relevant in the development of phantom pain is depicted in Figure 52-1.

TREATMENT

Amputation of a limb affects not only the physical functioning of the individual but may also have significant psychological, social, and societal consequences. Hence, early and aggressive management of amputees is critical. Surveys suggest that lasting relief from prescribed medications occurs in less than 10% of patients. However, few controlled clinical trials are available to guide the practitioner in the optimal management of postamputation pains, with most therapies being empirically based on their effectiveness in other neuropathic pain states.

CONTROLLED TRIALS OF PREOPERATIVE AND EARLY POSTOPERATIVE INTERVENTIONS

A systematic review by Halbert et al. identified eight studies that examined the treatment of acute phantom pain with preoperative, intraoperative, or early (<2 weeks) postoperative interventions such as epidural anesthesia, regional nerve blocks, intravenous calcitonin, and transcutaneous electrical nerve stimulation (TENS).[26] A controlled study evaluating intravenous calcitonin early in the postoperative period found a reduction in lower extremity phantom limb pain that persisted for most patients throughout their 1-year follow-up.[27] A clinical trial evaluating transcutaneous electrical nerve stimulation yielded mixed results for short-term relief, but no long-term benefit.[28] The administration of oral gabapentin from postoperative day 1 over a 30-day period failed to show any benefit on postamputation pain in the following 6 months.[29] The role of preoperative epidural anesthesia is unclear, with conflicting results from several studies. Preoperative epidural anesthesia with bupivacaine and morphine, administered 72 hr preoperatively, was reported to decrease the incidence of phantom pain for up to 1 year following lower extremity amputation.[30] Similar results were reported by Jahangiri et al.,[31] who found that epidural infusions of bupivacaine, diamorphine, and clonidine begun 24 to 48 hr before a lower limb amputation and continued for 72 hr postoperatively reduced the incidence of phantom pain for up to 1 year. However, a larger randomized, double-blind, placebo-controlled study comparing epidural bupivacaine-morphine anesthesia started 18 hr preoperatively to oral or intramuscular morphine failed to corroborate the previous findings.[32] A more recent randomized, controlled study comparing epidural ketamine-bupivacaine to epidural bupivacaine-saline also failed to demonstrate a treatment effect.[33] Taken together, these findings suggest that timing may be critical for any preemptive effect of regional anesthesia to be realized. For perineural anesthesia, there is even less evidence

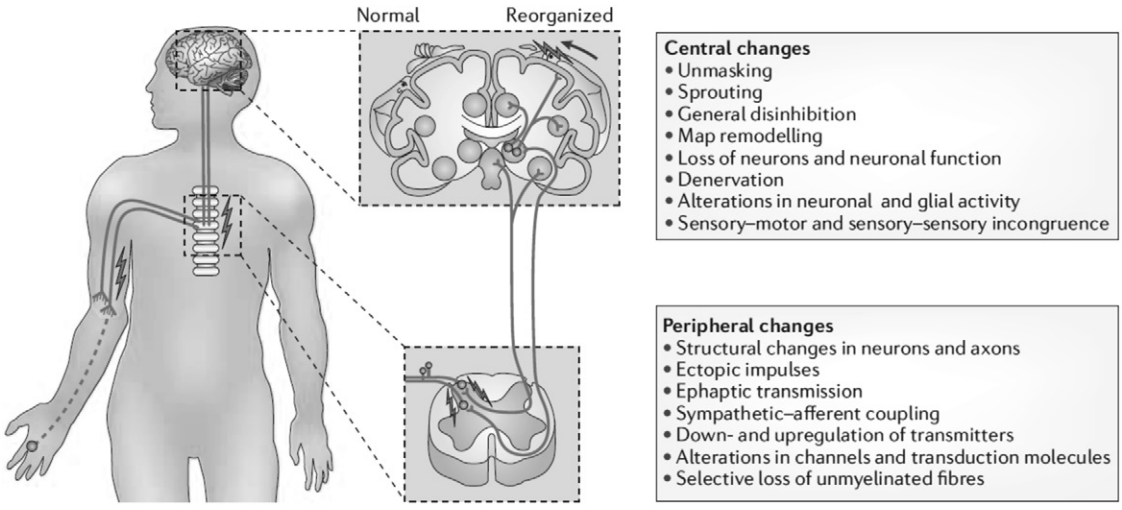

FIGURE 52–1 Potential mechanisms of postamputation pain. *Source: Flor H, Nikolajsen L, Staehelin Jensen T: Phantom limb pain: a case of maladaptive CNS plasticity?* Nat Rev Neurosci 7:*873–881, 2006.*

supporting its preemptive effects. A small (n = 21) randomized, controlled study by Pinzur et al.[34] found that sciatic nerve blockade begun postoperatively failed to prevent phantom pain, though it did decrease postoperative opioid consumption.

CONTROLLED TRIALS OF LATE POSTOPERATIVE INTERVENTIONS

Four studies examined the treatment of chronic phantom pain (36 days to 46 years) with interventions such as Farabloc (a metal threaded sock), ketamine infusion, and vibratory stimulation. These studies showed a modest reduction in the intensity of phantom pain, but the duration of follow-up was short term.

RESIDUAL LIMB PAIN

The first step in the management of stump pain is to identify a specific etiology for the pain that can be the target for developing treatment strategy. The stump should be carefully examined for a localized tender spot where a Tinel's sign can be elicited suggestive of a neuroma. The stump should also be examined for ulcers, potential sites of inflammation or bony abnormalities, evidence of ischemia, or recurrence in the case of malignancy. Consultation with an experienced prosthetist for rectifying an ill-fitting prosthesis is often helpful, as patients may experience exaggeration of their pain, or even precipitation of phantom pain and/or sensations from use of the prosthetic limb. This may result from pressure from the prosthesis at a site of a neuroma. In addition, changes in gait and altered body mechanics may result in musculoskeletal pain. Rehabilitation therapy to correct gait and postural compensations that result in arthritic or referred pain may be useful.

Reports suggest that TENS may be beneficial in 25% to 50% of patients with stump pain. Medication management will depend on whether the pain is suspected to be of somatic or neuropathic origin. In the former case, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) antagonists, and/or opioids may be indicated. Neuropathic pain resulting from neuromas should be treated with adjuvant analgesics such as tricyclic antidepressants (e.g., nortriptyline) and anticonvulsants (e.g., gabapentin).

Surgical therapies are indicated only when a specific rectifiable pathology is identified. Protruding bone, bony exostosis, wound infection, and poorly healed wounds are clear indications for surgery. A neuroma under constant pressure or near a joint resulting in repeated traction may be treated by excision of the neuroma and repositioning the nerve ending in bone or muscle. Similarly, surgical treatment of heterotopic ossification, which occurs in over 50% of traumatic major limb amputations, may be considered. Selective nerve blocks of peripheral nerves may be useful as a prognostic indicator of the success of excision of the neuroma.[35] One small case series found the perineuromal injection of the tumor necrosis factor inhibitor etanercept was effective in patients with stump pain less than 1 year in duration.[36] Dorsal root entry zone (DREZ) lesioning has not been effective in patients with isolated stump pain. Dorsal column stimulation was reported to be effective in 52% of patients early on, but the success rate declined to 39% after 5 years.[37]

PHANTOM PAIN

In the case of surgical amputations, educating and counseling the patient on the consequences of amputation, the rehabilitation process, and the prosthetic options should be initiated in the preamputation phase. Numerous treatment approaches have been attempted for phantom pain. These include a wide variety of medications, physical therapy, psychological interventions such as cognitive-behavioral therapies, complementary and alternative therapies, neurostimulation, and ablative procedures at various sites in the peripheral and central nervous systems. No one therapy has been uniformly effective, and there is a lack of controlled trials examining the effectiveness of these different therapies.

Numerous medical treatments have been proposed, but controlled trials have only been done with opioids, calcitonin, and ketamine, all of which have been shown to reduce phantom pain in the short term. First-line medication classes for the treatment of neuropathic pain include gabapentinoid anticonvulsants and antidepressants.[7,22] Controlled studies conducted for neuropathic pain have demonstrated that combination therapy with gabapentin and nortriptyline may result in supra-additive analgesia and less side effects than either agent alone.[38] Other drug classes, such as beta-blockers, neuroleptic agents, mexiletine, and capsaicin, are often employed as add-on or individual therapy when first line treatment is ineffective. For cramping pain, stump movement disorders, or flexor spasticity, baclofen or clonazepam may be effective.[22] Opioid therapy has been shown to provide short-term relief of stump and phantom pains.[39,40] Morphine was found to be superior to mexiletine and placebo in double-blind, randomized, placebo-controlled trial. However, the analgesic efficacy of morphine was low, and significant side effects were noted.[41]

Various physical modalities such as ultrasound, vibration, TENS, and acupuncture offer temporary relief with no proven meaningful long-term benefits.[42] These therapies rely on the gate control theory of pain transmission, which proposes that stimulation of large nerve fibers "closes the gate" and inhibits the transmission of pain centrally.

Surgical interventions have not been shown to be of significant benefit in phantom pain.[7] Spinal cord stimulation has been recommended to replace the loss of afferent input to the dorsal column and enhance the descending inhibition of pain transmission. However, the results with dorsal column stimulation have been inconsistent and compared to other neuropathic pain states, largely disappointing.[43,44] The same results have been found with DREZ lesions. Whereas the procedure has shown promise as a treatment for avulsion injuries, its long-term effects on phantom pain have been fair at best.[45]

Psychological interventions for phantom pain include hypnosis, biofeedback, cognitive and behavioral therapies, and support groups.[46,47] These interventions may facilitate adaptation to a change in body image, adaptation to chronic pain, and relief of grief and anger.[48] Mirror

therapy has been successfully used to alleviate phantom pain by exploiting the brain's predilection for prioritizing visual stimuli over proprioceptive and somatosensory input.[49] It involves strategically placing a mirror adjacent to the intact limb to give the illusion that the missing body part is present and can be purposefully moved. Because sensory experiences can be evoked by visual stimuli, mirror therapy increases spinal motor and cortical excitability (Fig. 52-2).[50,51] The simplicity and noninvasiveness of this treatment modality has led to application not only following limb loss but also in prevention of postamputation pain.[52]

Educational efforts, usually done in conjunction with psychological preparation, can also be beneficial when utilized in the pre-amputation and postamputation periods. These include early introduction and education regarding the use of a prosthesis, information on the care and treatment of the stump, and explanation of the rehabilitation process, which might include vocational retraining.

In summary, the management of postamputation pain remains a challenging endeavor that is only likely to increase in importance as the life expectancy of vascular and cancer amputees, and the survival rate of traumatic amputees, continue to rise. Persistent pain following major limb amputation occurs in a significant percentage of patients, with the most recent statistics suggesting cumulative prevalence rates exceeding 50% for both residual limb and phantom pain. There are myriad reasons for the modest results in treating postamputation pain, which include the high incidence of concomitant psychopathology that accompanies limb loss, the inherent difficulties involved in identifying specific pathophysiologic mechanisms that can be pharmacologically targeted, a relative paucity of clinical trials, and the low success rates in general for pain conditions that involve central mechanisms. At present, the optimal treatment of postamputation pain entails a multimodal approach that includes possible preemptive analgesia, psychotherapy, education and rehabilitation, polypharmacy, and if indicated, procedural interventions.

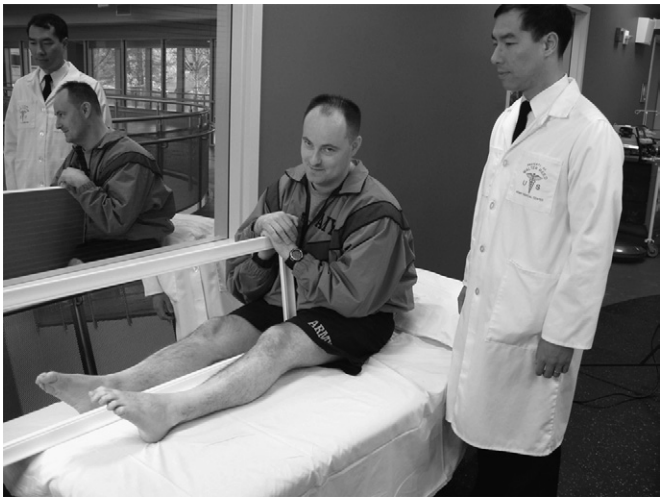

FIGURE 52-2 Mirror therapy. *Photograph courtesy Steven P. Cohen, MD. (Permission for publication obtained from patient and physician.)*

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CHAPTER 53

Central Pain States

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Central pain is a term used to describe the pain associated with a wide range of disorders of the central nervous system (CNS). Whereas the disorders themselves are heterogeneous in nature, there is a great deal of overlap in the central mechanisms precipitating pain and the treatment algorithms. The International Association for the Study of Pain (IASP) defines central pain as "pain initiated or caused by a primary lesion or dysfunction of the CNS."[1] Classically studied disorders of central pain include poststroke, spinal cord injury (SCI), traumatic brain injury, and multiple sclerosis (MS).[2] Central pain is often refractory to treatments, and complete pain relief is rare. Other chronic pain conditions, such as fibromyalgia, are associated with similar central neurotransmitter alterations and tend to respond to similar therapies.[3] In this chapter, we discuss the clinical presentations, pathophysiology, and therapeutic options for central pain of brain and spinal cord origin.

EPIDEMIOLOGY OF CENTRAL PAIN

The leading cause of central pain originating in the brain is stroke. With the exception of multiple sclerosis patients, classically described central pain disorders (stroke, SCI, etc.) are more commonly seen in men. The elderly are more affected in the cases of poststroke pain, while SCI and MS pain tend to affect younger patients.[4] Poststroke pain affects 2% to 8% of stroke victims, or approximately 30,000 patients in the United States alone.[5] In 1906, two French neurologists first described this poststroke "thalamic pain syndrome," also known as the "Dejerine-Roussy syndrome" in their honor.[6] The first postmortem studies of Dejerine-Roussy syndrome revealed that many of its victims had extrathalamic lesions, and modern imaging methods have confirmed and extended these findings. These pain-generating lesions extend from the first synapse of the dorsal horn, or trigeminal nuclei, to the cerebral cortex. The predominant etiology is vascular in origin, accounting for 90% of brain central pain (supratentorial 78% and infratentorial 12%) (Fig. 53-1). Extrathalamic sites are involved in 50% to 75% of cases.[5,7] Chronic poststroke pain more commonly occurs in the presence of right-sided thalamic lesions.[8]

Central pain of spinal origin is predominantly the result of trauma (see Fig. 53-1). Pain can also result from spinal cord tumors and demyelinating lesions, however. The incidence is reported to vary from 34% to 94% in patients with spinal cord injury (SCI)[9,10] and about 29% in MS patients.[11]

Central pain is also prevalent in patients with chronic degenerative diseases of the central nervous system (CNS). For example, almost 10% of patients with Parkinson's disease may have sensory complications, including pain[12]; and epilepsy can manifest as painful seizures. Also, in contrast to most pathologic processes affecting the CNS, clinicians cannot predict the development of central pain based on the location of a lesion. Many central pain patients maintain their ability to sense touch, vibration, and joint movements. This supports the belief that the central pain involves the spinothalamic tract and its thalamocortical projections. The highest prevalence of central pain is reported in cases of lesions in the spinal cord, medulla, and ventroposterior part of the thalamus.

TAXONOMY

A task force for the International Association for the Study of Pain (IASP) developed criteria for the pain associated with SCI (Table 53-1).[13,14] SCI pain is broadly divided into nociceptive and neuropathic with subclassification into second and third tiers based on the anatomic structures involved, site of pain, and etiology. Nociceptive pain may be musculoskeletal or visceral in nature. The former may be secondary to overuse of certain parts of the body to compensate for regions of paresis or result from secondary changes in bone or joints. Neuropathic pain is usually seen in areas of sensory abnormalities. Neuropathic pain has been subdivided on the basis of region, into at-level (radicular or central), above-level, and below-level pain to indicate the presumed site of the lesion responsible for pain generation.[15]

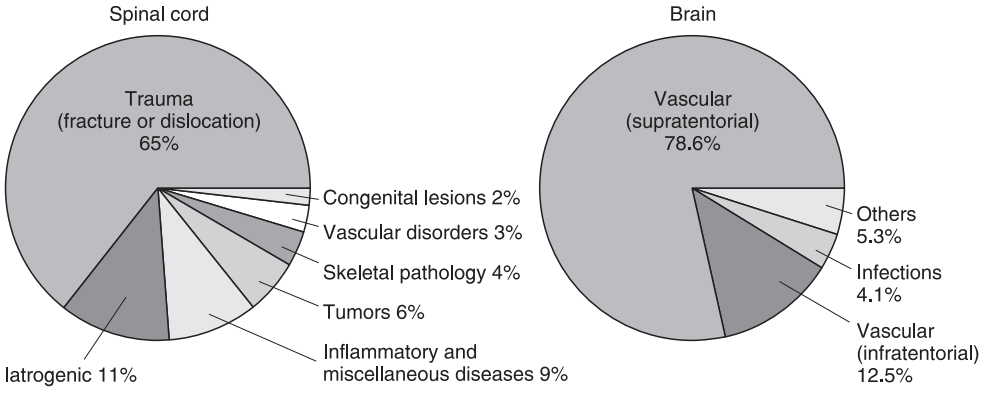

FIGURE 53-1 Etiology of central pain states.

TABLE 53–1 Taxonomy of Spinal Cord Injury Pain

Broad Type (Tier One)	Broad System (Tier Two)	Specific Structures and Pathology (Tier Three)
Nociceptive	Musculoskeletal	Bone, joint, muscle trauma or inflammation Mechanical instability Muscle spasm Secondary overuse syndromes
	Visceral	Renal calculus, bowel dysfunction, sphincter dysfunction, etc. Dysreflexic headache
Neuropathic	Above level	Compressive mononeuropathies Complex regional pain syndromes
	At level	Nerve root compression (including cauda equina) Syringomyelia Spinal cord trauma/ischemia Dual level cord and root trauma
	Below level	Spinal cord trauma/ischemia

From Siddall PJ, Yezierski RP, Loeser JD: Pain following spinal cord injury: clinical features, prevalence and taxonomy, *Seattle, 2000, IASP Press, Seattle.*

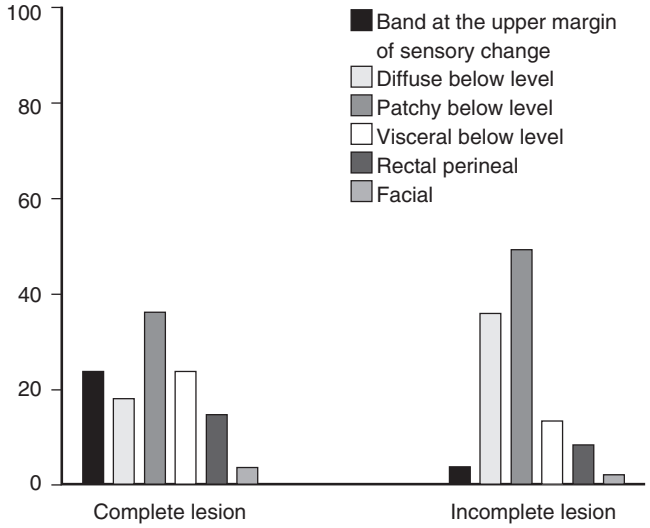

FIGURE 53-2 Pain following spinal cord injury. Acute and chronic pain is common following spinal cord injury. The type of pain reported does appear to change with time; however, musculoskeletal pain remains the most common complaint. The neuropathic pain reported can be seen above (*A*) or below (*B*) the level of the injury. *(Source: Siddall PJ, McClelland JM, Rutkowski SB, et al: A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury.* Pain *103:249–257, 2003.)*

Following SCI, it is reported that 91% of patients have pain 2 weeks after injury. This decreased to 64% at 6 months. Neuropathic at-level pain was present in 38% at 2 weeks and remained the same at 6 months. Neuropathic below-level pain occurred in 14% of subjects at 2 weeks and increased to 19% at 6 months. The prevalence and type of pain described following SCI over a 5-year period are shown in Figure 53-2.[16] The pain can be spontaneous or stimulus evoked. Longitudinal studies indicate that at-level pain has an early onset while the below-level pain develops months to years after the spinal injury.[16,17]

Central pain disorders are one of several types of "neuropathic pain," and the definition and diagnosis of neuropathic pain have been discussed at length by researchers throughout the world. The definition outlined by the IASP was "pain initiated or caused by a primary lesion or dysfunction in the nervous system." Some experts now believe that central neuropathic pain should be distinguished from peripheral neuropathic pain.[18] A new grading system for neuropathic pain is shown in Table 53-2.[18] Although a number of questionnaires and standardized self-report measures have been developed to detect neuropathic pain, the described grading system requires a physical examination. Whether this grading system will improve clinical care or advance research is not known. Disorders such as complex regional pain syndrome and fibromyalgia fall in to a grey zone with this system, as tests to diagnose the disorder are not widely accepted or specific and plausibility of these diseases is still debated by some despite existing evidence.

TABLE 53–2 Grading System for Neuropathic Pain

Criteria to be evaluated for each patient

1. Pain with a distinct neuroanatomically plausible distribution*
2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system†
3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test‡
4. Demonstration of the relevant lesion or disease by at least one confirmatory test§

Grading of certainty for the presence of neuropathic pain: definite neuropathic pain: all (1 to 4); probable neuropathic pain: 1 and 2, plus either 3 or 4; possible neuropathic pain: 1 and 2, without confirmatory evidence from 3 or 4.
*A region corresponding to a peripheral innervation territory or to the topographic representation of a body part in the CNS.
†The suspected lesion or disease is reported to be associated with pain, including a temporal relationship typical for the condition.
‡As part of the neurologic examination, these tests confirm the presence of negative or positive neurologic signs concordant with the distribution of pain. Clinical sensory examination may be supplemented by laboratory and objective tests to uncover subclinical abnormalities.
§As part of the neurologic examination, these tests confirm the diagnosis of the suspected lesion or disease. These confirmatory tests depend on which lesion or disease is causing neuropathic pain.

PATHOPHYSIOLOGIC MECHANISMS

Central pain states likely result from pathophysiologic changes caused by irritation of, or damage to, central pain pathways. The possible pathophysiologic mechanisms that cause and maintain central pain are complex and not well understood (for reviews, see Finnerup[2] and Hulsebosch[19]). Injury to the CNS may result in anatomic, neurochemical, inflammatory, and excitotoxic changes that result in a sensitized and hyperexcitable CNS.

Several neurotransmitters, such as glutamate, gamma-aminobutyric acid (GABA), norepinephrine, serotonin, histamine, and acetylcholine, are involved in the processing of noxious input along the pain pathway. The shift in firing from a rhythmic burst to a single spike is determined by noradrenergic, serotonergic, and cholinergic input to the reticular and relay cells of the thalamus. Similarly, excitatory

amino acids, such as glutamate, are released in the region of SCI and may lead to neuronal hyperexcitability. At the spinal cord level, substance P and cholecystokinin (CCK) might play an additional role by influencing the voltage-gated sodium and calcium channels. Potassium channels play a critical role in setting the resting membrane potential and controlling the excitability of neurons. A potassium channel, the M channel that regulates the excitability of central and peripheral neurons, is also considered to play a role in neuropathic pain states.[20]

Central pain in SCI may result from a combination of deafferentation-induced plastic changes in supraspinal areas along with abnormal input from a pain generator in the spinal cord (Fig. 53-3).[21] The changes in the CNS may include neuronal hyperexcitability. In SCI, NMDA receptor activation might trigger the intracellular cascade leading to the upregulation of neuronal activity/excitability that results in spontaneous and evoked neuronal hyperactivity/hyperexcitability and causes abnormal pain perception. Changes in voltage-sensitive sodium channels can also contribute to changes in nerve membrane excitability. Other important mechanisms might be a loss of endogenous inhibition, including reduced GABA-ergic, opioid, and monoaminergic inhibition. Wide dynamic range (WDR) neuronal hypersensitivity in excitotoxic or ischemic SCI models reveals changes similar to central sensitization following peripheral nerve injury. Analogous to epilepsy, SCI causes one neuronal population to generate hyperactivity and another to respond to this chaotic activity. It appears that a critical threshold in the size of this population must be reached before a patient will experience spontaneous pain.[10,22]

Advances in functional imaging have increased our understanding of the changes in the brain that are associated with many pain conditions.[23] Central glutamate levels are known to increase in response to pain in healthy humans,[24] and patients with fibromyalgia are known to have elevated central glutamate levels that directly correlate with response to painful stimuli.[25] Patients with fibromyalgia are also known to have decreased dopamine and opioid receptor availability in the forebrain. Decreased opioid binding has also been demonstrated in the pain-processing regions of patients with post-stroke pain.[26] The authors go on to suggest that the imbalance of excitatory to inhibitory mechanisms explain, in part, the reason for central pain. Interestingly, gray matter decreased in patients with chronic pain.[27,28] Whether the change in gray matter is premorbid or due to degeneration from an insult or inflammation from excitatory neurotransmitters (i.e., glutamate) is not known; however, a rat model of peripheral nerve injury was found to be associated with decreased size of the frontal cortex and comorbid anxiety. Patients with complete SCI are known to have a postinjury reorganization of the somatosensory cortex that correlates with pain intensity,[29] a finding previously demonstrated in amputees.[30] While neuroimaging has provided valuable insight to the field of pain, many new questions have now been posed and a great deal of work still needs to be done.

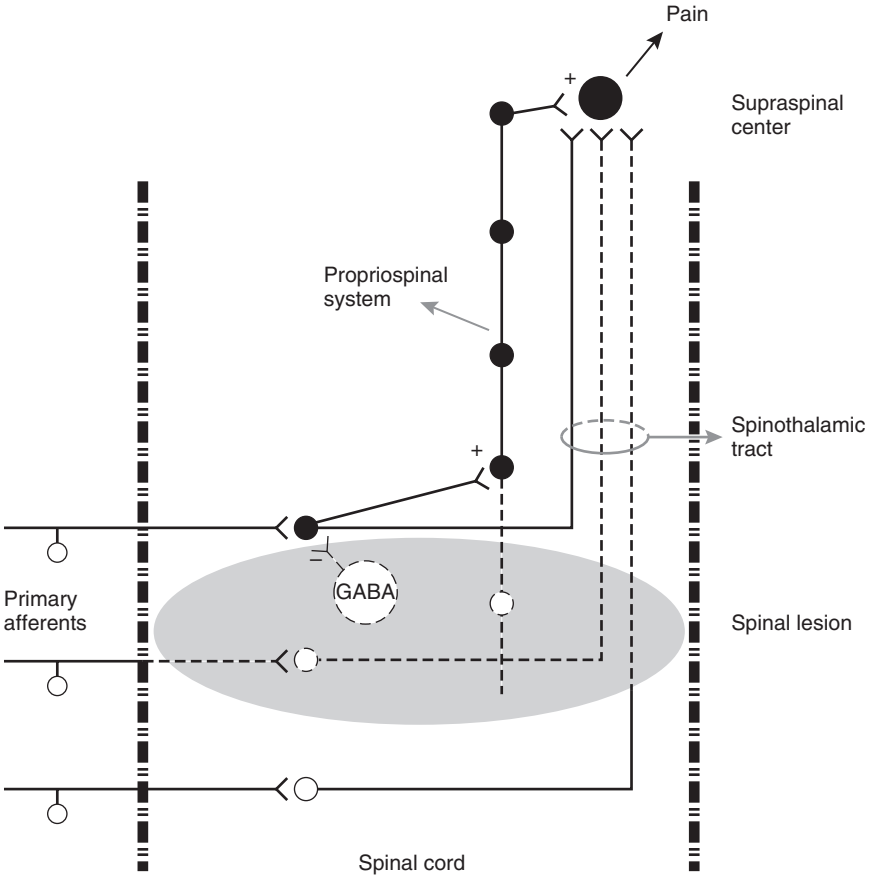

FIGURE 53-3 Proposed mechanism of central pain in spinal cord injury. Input from primary afferents can be distorted by two mechanisms. The spinothalamic tract projection neurons from below the spinal injury may be lesioned and give rise to deafferentation hyperexcitability in higher-order neurons including the thalamus. Second-order neurons in the dorsal horn at the rostral end of the spinal lesion may become hyperexcitable as a consequence of excitotoxic changes and disinhibition from damaged GABA-ergic neurons at the level of injury. Abnormal input from these second-order neurons in the rostral end of the spinal cord lesion may propagate via the propriospinal system to the deafferentated thalamic neurons resulting in pain referred to areas below injury level. *(Source: Finnerup NB, Jensen TS: Spinal cord injury pain—mechanisms and treatment.* Eur J Neurol *11:73–82, 2004.)*

Alterations of the sensory pathways and impaired descending inhibitory mechanism are associated with many pain conditions, including central pain. Craig and coworkers showed that, under normal conditions, the cool-sensitive pathway in the spinothalamic tract (STT) might suppress the forebrain's response to nociceptive STT activity.[31] Damage to this pathway may thus explain some of the phenomena seen in a central pain state. They hypothesize that, for central pain to occur, a lateral lamina I spinothalamocortical pathway lesion must be sufficiently large to produce contralateral sensory symptoms. This assumes that central pain is a release phenomenon resulting from the disruption of the normal integrative controls of sensory processing. The disruption of thermal sensibility results in a loss of the cold-induced inhibition of pain, with a resultant disinhibition of cold-evoked burning pain. Craig and coworkers suggested that the ventromedial posterior (VMPo) nucleus of the thalamus plays a critical role. Investigations in primates, however, strongly support the existence of a spinothalamocortical pathway from lamina I and the deep layers of the dorsal horn to the contralateral ventral posterior lateral (VPL) nucleus, which extends to area 1 of the S1 somatosensory cortex. A similar pathway might activate neurons of the SII cortex because direct projections connect the VPL and VPI (inferior) to SII and SI to SII.[32]

Lesions in the spinothalamocortical pathways can cause ectopic discharges in various neurons of the spinal cord and brain. Such ectopic neuronal discharges create an illusion of noxious input because of the imbalance between the lateral (inhibitory) and medial (excitatory) STT. This might explain why pain occurs more often in patients with partial lesions than in those with complete cord and thalamic injuries. It appears that severe CNS lesions, with total destruction of ascending sensory systems, do not lead to a central pain syndrome and that mild, moderate, or severe disruption of the anterolateral ascending system, with partial or complete preservation of the dorsal column/medial lemniscus functions, is most frequently associated with central pain syndrome. Furthermore, even during remission, dysesthesias and pain could be triggered by additional afferent input to the large fiber/dorsal column/medial lemniscus system and, once established, might not be abolished by additional deafferentation.

Sensory stimuli act on neural systems that have been modified by previous inputs, the "memory" of which significantly influences pain behavior. The fact that a memory is not activated by the development of a lesion might explain the long delay in the onset of central pain in some patients. The long-term potentiation that is important for this memory might be mediated by NMDA receptors and their influence on calcium conductance.[33,34] Thus, central pain frequently develops weeks or months after development of the lesion and is associated with sensory changes involving the spinothalamic pathways, especially changes in temperature perception.

The role of microglia in central pain is an area of great interest. Microglia are the macrophages of the brain and spinal cord that release inflammatory mediators in the event of injury or infection. The activation of microglia and subsequent inflammation is thought to precipitate a cycle of further inflammation and activation of astrocytes.[2,19]

CLINICAL PRESENTATIONS

The neuropathic component of central pain is often reported starting days to weeks after the CNS lesion and presents as a steady dysesthesia or neuralgia and may also have an evoked component. Although many tools and tests have been proposed to diagnose central pain, the wide range of types and presentations of central pain disorders makes no single measure completely sensitive or specific. The quality of the pain may be burning, aching, shooting, pricking, and tingling. The discomfort is generally constant but may wax and wane and often has a deep and/or a superficial component. In a minority of patients the pain is intermittent and daily. Nonpainful tactile, thermal, vibratory, auditory, visual, olfactory, and visceral stimuli can provoke or exacerbate spontaneous pain. Anxiety and/or fear can also exacerbate symptoms. Some patients with central pain exhibit the most striking symptoms seen in clinical practice. Patients with classic Dejerine-Roussy syndrome have a rapidly regressing hemiparesis and a sensory deficit to touch, temperature, and pain. Allodynia, hyperalgesia, and spontaneous severe paroxysmal pain on the hemiparetic side also often occur. These patients can exhibit hemiataxia, hemiastereognosia, and choreoathetoid movements. Patients with central pain may have any or all of these features, depending on the location of the underlying lesion. Organic signs on sensory examination of patients with thalamic lesions include the so-called thalamic midline split for sensory loss and pain. The fact that central pain of any cause is accompanied by delayed hyperalgesia supports the hypothesis of a polysynaptic response. Pain intensity for brainstem and suprathalamic lesions are moderate in intensity averaging 61 and 50 mm, respectively (on a 100-mm visual analog scale), while pain in thalamic lesions can be severe (average = 79 mm).[35] Many standardized measures have been developed to assess the different aspects of neuropathic pain as a means to develop specific treatment algorithms and further research efforts.

Patients with a history of spontaneous or evoked dysesthesia, hyperesthesia, or paresthesia should undergo specific but simple bedside testing. Sensory testing in the region where the pain is localized usually shows a paradoxic hypoalgesia (decreased sensitivity to painful stimulus). The region where the patient feels the pain often has decreased sensitivity to thermal stimuli, especially to cold. In fact, the intensity of the pain seems to be related to the magnitude of loss of thermal sensation. Testing for disturbed temperature sensation can be accomplished with a cold metal instrument, ice, or ethyl chloride spray. Touch can be tested with cotton wool, while pinprick sensation should be assessed using the contralateral side as a control. Chronic poststroke pain patients have an intact vibration sensation. Patients may exhibit *mitempfindung* (with sympathy), a phenomenon in which stimulation in one area of the body results in a simultaneous sense of the provoked sensation in another part of the body. These patients may also experience alloesthesia, in which a sensory stimulus on one side of the body is perceived on the other side. A subset of patients who experience burning pain lose the sensation

of cold, warmth, and sharpness. In another subgroup of patients who experience shooting/pricking/aching pain, tactile allodynia is predominant. Although some disturbance of sensory function is almost always present on physical examination, clinical findings are few or subtle in many patients. Quantitative sensory testing might reveal side-to-side asymmetries in cooling, warmth, and heat-pain sensation thresholds.

Testing for autonomic dysfunction may be important in patients with SCI. Lesions above the sixth thoracic level (splanchnic outflow) are often associated with autonomic dysreflexia. The dysreflexia is characterized by sudden dramatic increases in blood pressure, high or low heart rate, and headache after sensory input such as a full bladder. This point becomes especially important in SCI patients having surgery below the level of their lesion, including minor operations of the urinary (i.e., cystoscopy) or gastrointestinal (i.e., colonoscopy) systems where the viscera will be stimulated. Despite the fact that patients may lack sensation in the area to which they are having surgery, intense stimulation can precipitate major hemodynamic instability. Complications may include seizures and cerebral hemorrhage.

EXPERIMENTAL MODELS OF CENTRAL PAIN SECONDARY TO SPINAL CORD INJURY

Interesting insights about the mechanisms of central pain following SCI and the potential effects of drugs on pain behavior have been gained from experimental models in the rat. The Stockholm group led by Wiesenfeld-Hallin developed a model of photochemically induced spinal cord ischemia,[36,37] while Yezierski et al.[10,38] developed a model of excitotoxic SCI. Rats with lesions involving both white and gray matter develop instantaneous morphine-resistant tactile allodynia, which responds to the systemic GABA-B agonist baclofen, and can be prevented by pretreatment with the NMDA antagonist MK 801. Intrathecal morphine and clonidine reduced the allodynia. Injections of a CCK-B antagonist decreased allodynia.

THERAPEUTIC OPTIONS

The treatment of central pain is complicated and requires a complete evaluation of the patient's pain and goals for therapy. An important aspect of treating patients with central pain is to define and continuously review the goals of treatment. Patients must be told and periodically reminded that complete cessation of pain is unlikely. Hence, the goal of therapy is to improve function and reduce pain without creating intolerable side effects. In addition, including treatment strategies for each of the multiple components of the central pain syndrome is of paramount importance. Thus, the multiple psychological symptoms that come with most types of chronic pain and loss of physical function must be treated. The options available for managing central pain include pharmacotherapy, behavioral therapy, physical therapy, neuromodulation, other interventional therapies, and ablative neurosurgery. Table 53-3 shows a treatment algorithm modified from that which was proposed by Que et al.[39] for the treatment of SCI.

PHARMACOTHERAPY

The pharmacologic approach is based on a strategy of stepwise combination therapy. The mainstay of this therapy is antidepressants that possibly act by modulating the thalamic burst firing activity via its actions on locus coeruleus noradrenergic neurons and the serotoninergic cells in the dorsal raphe.[40] Amitriptyline is often effective in central poststroke control and SCI pain,[41] while some studies have not shown benefit.[42] Amitriptyline's benefit derives, in part, from its ability to prevent reuptake of noradrenaline and serotonin. Tricyclic antidepressants (TCAs) should be titrated to 50 to 100 mg/day. Insufficient plasma levels at this dose might indicate the need for higher doses. A small pilot study found that amitriptyline given at the time of a thalamic stroke failed to prevent time to or potential for chronic poststroke pain.[43] Similarly, findings in a controlled trial failed to support the use of amitriptyline in the treatment of chronic central pain of spinal cord origin.[42] While amitriptyline is the most studied TCA in central pain, the analgesic efficacy of nortriptyline has been demonstrated to be similar to amitriptyline with less side effects.[44,45] However, a combination of a TCA (e.g., amitriptyline), clonazepam, a benzodiazepine, and a nonsteroidal anti-inflammatory drug (NSAID) is reportedly a good regimen to control the common, steady, burning, dysesthetic component of this syndrome.[46]

Antiepileptic drugs (AEDs) are useful for the treatment of neuropathic pain. Currently, the most commonly prescribed AEDs are gabapentin and pregabalin. Both gabapentin and pregabalin appear to be effective in treating central pain, and there are no studies that allow for direct comparison between the two.[47] A recent study by Gilron et al.[48] demonstrated that the combination of a TCA and gabapentin was superior for the treatment of neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia when compared to either alone. A controlled study showed no benefit of using carbamazepine to treat central pain, but the study nonresponders did not have a neuralgic component to their pain.[35] The newer AEDs seem to act at multiple receptor types. In a controlled study pain scores decreased from 7 to 5 (10-point numeric rating scale) in patients with poststroke pain who were given 200 mg/day of lamotrigine.[49] In patients with incomplete SCI lamotrigine titrated to 400 mg/day significantly reduced pain at or below the injury level. Patients with brush-evoked allodynia and wind-up–like pain in the area of maximal pain were more likely to have a beneficial effect with lamotrigine than patients without these evoked pains. This trial, however, showed no significant effect of lamotrigine on spontaneous and evoked pain in patients with complete SCI.[50] Chiou-Tan and colleagues found mexiletine of no use in the treatment of central pain states of spinal cord origin.[51]

Opioids may benefit some patients; however, it is not first-line therapy. Patients who respond to a trial of opioid infusion may be prescribed long-acting opioids, such as the slow-release formulations or the transdermal preparation. In a controlled study the reduction in the intensity of neuropathic pain was significantly greater during treatment with a high dose (0.75 mg) than it was with lower doses of the μ-agonist levorphanol.[52] Patients with

TABLE 53–3 Central Pain Treatment Algorithm

Step 1. Identify problems.			
Determine existing problems and potential adverse sequelae.			
Identify biologic and psychological contributors to pain and their influence on the individual's pain experience.			
Determine the impact of pain on the patient's function.			
Determine how well the patient has adjusted to the disorder causing their central pain (SCI, stroke, MS).			
Determine the risk of and/or presence of additional consequences of pain and the disorder underlying the central pain (i.e., pressure sores, contractures, adverse drug effects).			
Step 2. Determine reasonable objectives/goals for patient and treating physician.			
Pain relief/reduction.			
Treatment of spasm—decrease frequency and/or severity.			
Increase exercise tolerance and improve function.			
Achieve independent living.			
Return to work.			
Step 3. Create multidisciplinary approach.			
Pharmacologic	**Interventional**	**Physical and Occupational Therapy**	**Psychosocial**
First line AEDs (gabapentin and pregabalin) *Second line* TCAs SNRIs Combinations with AED *Third line* Opioids SSRI *Fourth line* Ketamine infusion Lidocaine infusion	Specific to condition Limited evidence Mainly for refractory cases Neuromodulation SCS DBS MCS Intrathecal therapy Baclofen Morphine Clonidine Ziconotide Acupuncture Ablative therapies (DREZ, cordotomy)	Structured therapy and home exercises Postural re-education Spasticity treatment Bowel/bladder management Braces and devices to assist in home and work function Home/work remodeling Speech therapy	Psychiatric therapy Pharmacologic Counseling CBT Pain coping skills Relaxation Family support and education

Note: The treatment of central pain requires a careful assessment of the pain and problems associated with the patient's underlying disorder. Understanding goals and setting expectations are essential to creating an appropriate multidisciplinary treatment plan.
AEDs, antiepileptic drugs; CBT, cognitive behavioral therapy; DBS, deep brain stimulation; DREZ, dorsal reentry zone lesioning; MCS, motor cortex stimulation; MS, multiple sclerosis; SCI, spinal cord injury; SCS, spinal cord stimulation; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.
Source: Adapted from Que JC, Siddall PJ, Cousins MJ: Pain management in a patient with intractable spinal cord injury pain: a case report and literature review. Anesth Analg *105:1462–1473, 2007.*

central pain after stroke, however, were the least likely to report benefit. Another controlled trial revealed that intravenous morphine induces analgesic effects on some components of central neuropathic pain syndromes, but only a minority of patients may benefit from long-term opioid treatment.[53] Morphine significantly reduced the intensity of brush-induced allodynia, but had no effect on other evoked pains (i.e., static mechanical and thermal allodynia/hyperalgesia).

The efficacy of systemic lidocaine (5 mg/kg IV over 30 min) was evaluated in a double-blind, placebo-controlled, crossover trial on spontaneous and evoked pains (allodynia and hyperalgesia) in 16 patients with chronic poststroke ($n = 6$) or SCI ($n = 10$) pain.[54] Systemic lidocaine induced a significant and selective reduction of several components of pain caused by CNS injuries. The observed preferential antihyperalgesic and antiallodynic effects of lidocaine suggest a selective central action on the mechanisms underlying these evoked pains.

There are other less traditional drugs that have been studied in central pain and other neuropathic pain states that may have limited clinical utility but can be used to drive future research. Ketamine has been available since the 1960s but has found limited use outside of the perioperative setting due to its side effects and potential for abuse.[55] Some studies and reports note that ketamine may have a role in central pain, likely due to its unique NMDA antagonist properties, which is believed to be important in the manifestation of central neuropathic pain.[56–58] The optimal route of delivery, dosage, duration, and practicality are still not clearly defined. Another area of interest in refractory central pain is the use of cannabinoids.[59] While cannabis remains a controlled substance, some states have initiated programs for medical marijuana. In a randomized, double-blind, controlled study, an oral spray version of an oromucosal spray, cannabis-based medication was found to improve pain and sleep disturbance when compared to placebo.[60] Research is currently focused on selective cannabanoid receptor agonists that may offer less of the adverse psychoactive properties.

BEHAVIORAL THERAPY

Activities that promote general mental activity, including distraction techniques and physical therapy, seem to play a role in reducing the pain in central pain states. Peripheral sensory input and activation of fronto-orbital brain areas

inhibit specific and nonspecific pain pathways. Based on an examination of a series of case reports, Haythornthwaite and colleagues suggest that biofeedback, hypnosis, and cognitive-behavioral interventions all have a beneficial impact on neuropathic pain.[61]

PHYSICAL AND OCCUPATIONAL THERAPY

Physiotherapy may be beneficial, but treatments such as acupuncture, ultrasound, and massage are not effective for long-term treatment of central pain states. Transcutaneous electrical nerve stimulation (TENS) provides long-term benefits to patients with central poststroke pain and those with incomplete SCI.[35,62] Patients with functional changes or limitations due to the disorder associated with their central pain can greatly benefit from occupational therapy to allow patients to function better in their home or work environments.[39] Some patients will require braces or assist devices. These measures can allow for more independence and benefit the patient psychologically.

NEUROMODULATION

Neuromodulation is a more invasive and expensive modality for the treatment of central pain, which can be effective in well-selected patients. Spinal cord stimulation (SCS, also known as dorsal column stimulation) is often a better option than deep brain or motor cortex stimulation in patients with SCI, as SCS trials are safe, easy, and reversible. Dorsal columns should be functional above the level of injury to produce paresthesia. Patients with anesthesia dolorosa (pain in an anesthetic area) and patients with incomplete lesions are poor candidates. Patients who experience more than 50% pain relief during trial stimulation are potential candidates for an implant. In patients with treatment failure, deep brain stimulation (DBS) of the tactile relay nucleus of the thalamus or the lemniscal radiations offers hope. Data from Bendok and Levy suggest that paresthesia-producing DBS alleviates steady neuropathic pain.[63] Periventricular/periaqueductal gray (PVG/PAG) DBS is appropriate for nociceptive pain.

For brain-origin central pain, data from Tasker and colleagues show that brain stimulation relieves the steady dysesthetic component in 53% of patients and the evoked component in 25% of patients, but offers no help for the neuralgic component.[64] The neuralgic component is the component sometimes responsive to ablative neurosurgery. SCS is of no benefit for brain-origin central pain, although patients might report relief during a trial. Paresthesia-producing DBS and motor cortex stimulation are appropriate for the steady component of the pain. For those with allodynia or hyperpathia, PVG/PAG DBS seems to be beneficial.

Stimulating the motor cortex offers a new target for the neuromodulation of central pain. Yamamoto and colleagues concluded that patients whose pain was diminished by thiamylal and ketamine, but not by morphine, respond best to motor cortex stimulation.[65] Canavero and colleagues concluded that motor cortex stimulation controls spontaneous and evoked pain, but not the nonpainful paresthesias.[66] Patients who might respond well to motor cortex stimulation also respond to transcranial magnetic stimulation and to a GABA agonist (e.g., propofol).

OTHER INTERVENTIONAL THERAPIES

INTRATHECAL PUMPS

Intrathecal pumps have been used to treat a wide variety of pain conditions and spasticity.[67] The use of intrathecal medications poses issues of time and cost, along with additional potential for serious complications.[67,68] The most commonly administered medications are opioids (morphine, hydromorphone, and fentanyl), clonidine, and bupivacaine. The addition of clonidine to morphine was shown to be superior to either drug delivered alone in SCI.[69] Ziconotide, a nonopioid intrathecal medication, is a synthetic form of the cone snail toxin that is approved by the U.S. Food and Drug Administration for the treatment of chronic pain. Ziconotide is one of the few intrathecal medications that has demonstrated efficacy in a randomized, control trial[70]; however, its side-effect profile is significant[71] and some practictioners question its role in pain management.

Baclofen, a GABA agonist, has antinociceptive effects, and its intrathecal administration reduces allodynic responses in animal models of neurogenic central pain.[72] Well-designed clinical studies have demonstrated efficacy with intrathecal baclofen in the treatment of complex regional pain syndrome, which shares many of the attributes of the central pains discussed in this chapter.[73] Intrathecal baclofen can be helpful in treating pain and spasticity multiple types of central pain, including post-stroke, SCI and MS pain.[73–75] Trials range from a single shot of intrathecal baclofen to a multiple day intrathecal catheter trial. Once implanted, the daily dosing can be slowly increased to effect. As with all intrathecal pumps, there is potential for pump complications independent of the medication infused, thereby necessitating intensive monitoring and regular follow-up.[73]

ABLATIVE NEUROSURGERY

Ablative neurosurgery plays a role in the treatment of the neuralgic component of central pain. Percutaneous radiofrequency dorsal rhizotomy is an option for monoradicular pain syndromes. Ablative surgery includes cordotomy, cordectomy, and dorsal root entry zone (DREZ) lesioning. The goal of cordotomy and cordectomy is interruption of STTs. Cordectomy, the simplest destructive procedure, can benefit patients with complete lesions. It is not acceptable to most patients because it obviates their hope for eventual restoration of spinal cord function. Percutaneous/open cordotomy achieves the same results as cordectomy and is offered to patients with incomplete lesions, but carries the risk of aggravating bladder dysfunction and inducing ipsilateral limb paresis. DREZ is equally effective for the neuralgic and the evoked elements of spinal-origin central pain. Nashold and colleagues found this procedure most useful for the relief of end-zone pain (pain starting at the level of

injury and extending distally).[76] Pain extending diffusely, often sacrally distributed, and remotely distributed pain, described as phantom or diffuse burning pain, do not respond well to DREZ. Although the procedure preserves the hope for future spinal cord function and avoids risk of limb paresis, it can interfere with residual bladder function and requires a laminectomy and considerable skill.

In the past surgeons attempted to relieve central pain of cerebral origin with cordotomy, trigeminal DREZ, medial thalamotomy, and mesencephalic tractotomy. Destructive procedures on the cerebral cortex are of historic note only.

FUTURE DIRECTIONS

Ongoing and future research will help to understand the pathophysiology of pain as a disease, including central pain. In the immediate future, neuromodulation seems to hold great promise. New nonopioid analgesics targeting the associated neurotransmitter changes in chronic pain will likely have benefit. Medications specifically altering central glutamate levels and microglia activation may be particularly effective in patients with neuropathic pain. Advances in the study of the genetic factors associated with pain will hopefully allow for the early detection of patients at risk for chronic central pain after an injury (i.e., SCI). Whether early detection and aggressive therapy will improve outcomes is not known. The field of pharmacogenomics is rapidly advancing and may offer "personalized analgesia" for patients based on their genetic make up and pain condition.

KEY POINTS

- Central pain states are common sequelae of SCI and stroke.
- Pathophysiology of central pain is not understood.
- Alterations in several neurotransmitters occur, including glutamate, GABA, norepinephrine.
- Involvement of the spinothalamocortical pathway is strongly supported by animal models, but the precise pathway in humans is unknown.
- The three components of central pain (steady dysesthetic, intermittent neuralgic, and evoked) must all be treated. In central pain of brain origin steady and evoked components predominate, while in central pain of spinal cord origin steady and neuralgic components predominate.
- A multidisciplinary approach is recommended, and, because poorly controlled central pain carries a high suicide risk, psychosocial support is crucial.
- Pharmacotherapy should begin with a TCA.
- Membrane stabilizers should be considered for combination with TCAs as a second step.
- Opioids in small doses may be of benefit in some patients but are not first-line agents.
- More involved therapies can be considered in refractory cases, including neuromodulation, intrathecal therapy, and neuroablative procedures.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 54

Pelvic Pain

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Chronic nonmalignant pelvic pain syndromes are well described but poorly understood and often have a difficult course of treatment. This results in a frustrating experience not only for the patient but also the health-care provider. Thus, patients with these syndromes often suffer for many years having gone through a cycle of seeing many subspecialists and are frequently depressed. The question among physicians in the pain community is whether these symptoms are psychosomatic or if they even exist. However, extensive literature supports the existence and organicity of these syndromes. Chronic pelvic pain (CPP) is defined as nonmenstrual-related pain below the umbilicus that has continued for more than 6 months. It creates a functional disability, or requires prolonged medical or interventional therapy. Even after a thorough evaluation, the etiology may remain uncertain, and the pathology of disease and symptoms of pain may remain inconsistent. This chapter reviews the epidemiology, clinical presentation, differential diagnosis, and current treatment modalities of chronic nonmalignant pelvic pain syndromes. Despite the challenge in managing this pain, many patients can be offered effective treatment.

EPIDEMIOLOGY

CPP is an epidemic in its own right. Approximately 5% of the general population of women will experience CPP, with an increase in risk up to 20% in those with a previous diagnosis of pelvic inflammatory disease.[1,2] In the United States, a phone survey conducted by Mathias et al[2] to determine the prevalence of CPP in women aged 18 to 50 revealed that one in seven women were affected by some form of CPP. Recent studies showed that women of a reproductive age presenting to primary care practices with pelvic pain issues represent 39% of patients evaluated in that practice setting.[3,4] Women in their reproductive years in all settings were shown to represent 14.7% of patients,[1] with the greatest incidence of pelvic pain found to be in women ages 26 to 30.[5] Of all referrals to gynecologists, 10% are consultations for pelvic pain.[5,6] Among these gynecologic referrals, approximately 20% of them undergo hysterectomies and 40% laparoscopic surgeries.[7,8]

Although most pelvic pain occurs in women, men also may be diagnosed with CPP issues. Common causes of CPP in men are similar to those in women and often include chronic (nonbacterial) prostatitis, chronic orchalgia, and prostatodynia.[9] Although men may have chronic pain issues from many disorders such as urinary dysfunction and irritable bowel syndrome, those listed above represent male-specific causes of pelvic pain. Specifically, chronic prostatitis/CPP syndrome (CP/CPPS) alone is of significant interest in urology and accounts for up to 2 million office visits per year,[10] a large health-care burden in the United States. On an international level, a similar prevalence of CPP has been described in other countries among men and women.[11] In the United Kingdom, incidence of CPP is similar to that of migraine, back pain, and asthma.[11] In the United States during the early 1990s (1994 is the specific date), estimated direct medical costs for outpatient visits, in women aged 18 to 50 years, alone represent $881.5 million per year.[2] It has been noted that 15% of working women between the ages of 18 and 50 report time lost from paid work related to pelvic pain.[2] Overall, increased awareness of the cost of CPP and its impact on the patient's quality of life should heighten increased medical research and treatment of this syndrome.

Patients with cancer represent a unique category of pelvic pain patients who suffer from pain related to tumor, radiation, chemotherapy, or after surgery. Of note, in 1986, the World Health Organization established a step-ladder approach specifically for cancer pain patients that revolutionized analgesic care for 70% to 90% of these patients. This stepwise approach begins with nonopioid agents, proceeding to stronger agents as indicated by patients' clinical condition, with adjuvant agents incorporated including antidepressants, anticonvulsants, topical agents, nonsteroid anti-inflammatory drugs (NSAIDs), anxiolytics, and corticosteroids. Further approaches involved injection therapy, sympathetic blocks, neuroaugmentation, and neurolytic blocks. These recommendations continue to guide our treatment of patients with pain even today. This category of patients will be mentioned only briefly as the typical treatment pathway and goals of treatment are different for cancer patients, often influenced by life expectancy, tolerance, and tumor growth.[12]

CAUSES OF PELVIC PAIN

Unfortunately, CPP is poorly understood and thus poorly managed. Thirty percent to 50% of patients with CPP are classified as having "chronic pelvic pain without obvious pathology."[13] Of those patients afflicted with CPP seeking a surgical opinion, pursuing surgical interventions also does not often yield results. Among women who elect to have hysterectomies for pelvic pain relief, 25% of these patients continue to have unresolved pelvic pain.[13] Of patients who undergo exploratory laparoscopy, clinical diagnosis findings include the following: endometriosis accounts for one-third of patients, adhesions another third, and no pathology for the remaining third.[14] Based on studies to date, approximately 67% of women treated laparoscopically for pain with documented endometriosis, will note an improvement in pelvic pain that will last for at least 1 year.[15] To counter this, laparoscopy can also reveal significant pathology in patients with no pelvic pain at all.[15] Moreover, a randomized control study by Peters et al[16] revealed a short-lived benefit to procedures such as lysis of adhesions, which was effective for patients with severe

adhesions. On the other hand it had no significant benefit for patients with minimal to moderate adhesions.[16] Thus, a diagnosis, as well as subsequent appropriate treatment, is not a straightforward algorithm.

When assessing the pelvic pain patient, it is important to approach these patients in a multidisciplinary fashion. Both diagnosis and management of these patients require good integration and knowledge of all pelvic organ systems and other systems including musculoskeletal, neurologic, and psychiatric. A significant number of these patients may have various associated problems including bladder or bowel dysfunction, sexual dysfunction, and other systemic or constitutional symptoms. Other associated problems, such as depression, anxiety, and drug addiction, may also coexist. See Tables 54-1 and 54-2 for gender- and organ-specific causes of pelvic pain.

THEORIES OF CHRONIC PELVIC PAIN

The etiology of CPP is often difficult to pinpoint. Lacking a specific pathophysiologic explanation at this time, several theories for CPP have been postulated.

VASCULAR HYPOTHESIS

A vascular hypothesis, first initiated by Taylor in 1949 and more recently by Beard in 1984, may offer a clue into the mechanism of CPP. It has been noted that pain may be related to dilated pelvic veins in which blood flow is markedly reduced.[17–19] Pelvic venous incompetence is likely seen in 10% of women, and up to 60% of patients with this abnormality can develop pelvic congestion syndrome (PCS). These patients can find relief when the dilation is treated, such as with foam sclerotherapy followed by coil embolization to within a centimeter of vein origin.[20,21] Positive results have also been documented with medroxyprogesterone acetate 30 to 50 mg daily.[22,23] In addition, further studies by Foong[24] in 2000 showed a comparison of healthy pain-free women and women with CPP that displayed a clear difference in peripheral vascular response of women with and without pelvic pain due to congestion. This pelvic vein congestion showed a change in peripheral vascular reactivity which returned to normal after suppression of ovarian activity. Additional observational studies showed a reduction in pain for those patients in whom congestion was diminished by hormonal therapy.[25] It is possible that some alteration of normal ovarian function is responsible for the observed changes in peripheral blood flow in response to a rise in venous pressure in women with pelvic congestion.

ALTERATION OF STIMULI PROCESSING OR ORGAN FUNCTIONING

It has also been hypothesized that there is a rewiring in the stimuli processing or a reorganization of organ function. A separate study by Rapkin in 1995 suggested an alteration in processing of stimuli by the spinal cord and further brain processing of stimuli could occur in women with CPP,[25] a feature also shared by other chronic painful conditions.[26] In fact, undetected irritable bowel syndrome presents in up to half of the group of women referred for gynecologic investigation. Furthermore, studies assessing pain from distention of pelvic colon by inflation in irritable colon syndrome it was noted that pain was reported at significantly lower volumes of colonic balloon distention than did control subjects. There is a potential that visceral afferents may under a change in function similar to those of somatic nociceptors.[26,27] This begs the question: Does CPP represent the CRPS (complex regional pain syndrome) of the pelvis? Further research must be continued before definite conclusions can be made.

ETIOLOGY

Chronic pelvic pain is an unclear diagnosis, as pain can originate from any organ system, and thus a thorough review of systems is essential for proper assessment of a patient's pain. These assessments can be organized in a system-based review as well as a gender-specific review, as seen in Tables 54-1 and 54-2.[26–29]

MULTIDISCIPLINARY APPROACH

Based on a wide array of differential diagnosis as noted above, it is easy to recognize the range of problems related to pelvic pain and the wide range of health-care professionals that can be involved in the care of such a patient. A multidisciplinary team represents both the referral basis as well as the combined perspective for sources of pain and sources of treatment approaches: gynecologists, psychologists, physiotherapists, uro-gynecologists, gastrointerologists, neurologists, psychiatrists, social workers, internal medicine physicians, general surgeons, and pain medicine physicians are all involved in caring for these patients.[29] In

TABLE 54–1 Gender-Specific Causes for Pelvic Pain

Women	Men
Infection, endometriosis, dysmenorrhea (primary: menstruation, middleshmurtz; secondary: fibroids, adenolysis, IUD), dyspareunia, mononeuropathies, myofascial pain, vulvitis, cystitis, ovarian remnant syndrome, sympathetically mediated pain, pelvic congestion, pelvic fibrosis, pelvis neurodystonia, pelvagia	Prostatitis, chronic orchalgia, and prostatodynia, interstitial cystitis, ureteral obstruction
Irritable bowel syndrome and other gastrointestinal disorders	Irritable bowel syndrome and other gastrointestinal disorders
Sexual/physical abuse	Sexual/physical abuse
Cancer pain	Cancer pain
Psychiatric disorders	Psychiatric disorders
Surgical procedures (adhesions)	Surgical procedures (adhesions)

TABLE 54–2 Organ-Specific Causes for Pelvic Pain

Reproductive	Visceral: uterus, ovaries, bladder, urethra, Somatic: skin, vulva, clitoris, vaginal canal
	Adhesions, endometriosis, salpingo-oophoritis, neoplasm
Vascular	Dilated pelvic vein/pelvic congestion theory
Musculocutaneous	Ligamentous structures, muscular (iliopsoas, piriformis, quadrates lumborum, sacro-iliac joint, obturator internus, pubococcygeus)
	Skeletal (referred pain)
	Myofascial syndrome
	Pelvic floor muscle tension/spasm
Spinal	Degenerative joint disease, disc herniation, spondylosis, neoplasm of spinal cord/sacral nerve, coccydynia, degenerative disease
Neurologic	Neuralgia/cutaneous nerve entrapment (surgical scar in the lower part of the abdomen), iliohypogastric, ilioinguinal, genitofemoral, lateral femoral cutaneous nerve, shingles (herpes zoster infection), spine-related nerve compressions
Gastrointestinal	Irritable bowel syndrome, abdominal epilepsy, abdominal migraine, recurrent small bowel obstruction, hernia
Urologic	Bladder dysfunction, chronic (nonbacterial) prostatitis, chronic orchalgia, and prostatodynia
Psychological (psychosocial/ sexual)	Anxiety, depression, somatization, physical or sexual abuse, drug addiction, dependence, family problems, sexual dysfunction

this chapter, we will be discussing approaches by the pain medicine physician who will usually serve as a consultant offering medical and interventional therapies. The role of the pain management consultant involves evaluation of multiorgan systems, understanding common medical management, providing evidence-based interventional guidelines, and understanding recommendations for advanced therapies.

HISTORY AND PHYSICAL EXAM

There are many potential sources of CPP in various organ systems. A thorough history and physical exam are essential to attempt assessment, diagnosis, and treatment of pelvic pain issues.

The *history* must consist of a systematic review of systems assessments including gastrointestinal, musculoskeletal, vascular, genito-urinary, neurologic, and psychological (Table 54-3).

The *physical examination* must include abdominal, pelvic, musculoskeletal, neurologic, and psychiatric assessments. This review will focus on a more in-depth description of the musculoskeletal and neurologic evaluations, with the understanding that the abdominal and pelvic examination are components of any basic physical exam.

The focused *abdominal examination* is a core component of any physical exam, and especially important in the assessment of pelvic pain. Auscultation for sounds, bruits, organomegaly, and palpations in four quadrants are all components of an abdominal exam.

TABLE 54–3 History Assessment

Pattern of onset	Efficacy and toxicity of previous medications
Inciting event	Association with menstrual cycle
Quality (burning, aching, dull, sharp, cramping)	Incontinence
Duration and progression of complaints	Pregnancy
Constant or intermittent nature	Sexual activity
Exacerbating factors (position, eating, urination, defecation, valsalva)	Sudden weight loss or weight gain
Alleviating factors	Breast or endocrinologic difficulties
	Family history of ovarian, uterine, or breast cancer

A *pelvic examination* is an obvious component in the assessment of pelvic pain. An experienced physician should participate in a thorough examination of gynecologic, urologic, and overall pelvic health.

All organ systems are important, but as per Baker in 1993, "musculoskeletal dysfunctions contribute to the signs and symptoms of CPP (CPP) and in many cases may be the primary factor."[28] In addition, "coordination between the pelvic musculature and the pelvic visceral organs is essential for the proper functioning and integrity of the latter. The pelvic muscular element, which could well be the source of pain, must be evaluated."[29] See Table 54-4 for further details on the *musculoskeletal exam*.

The *neurologic examination* is a natural component of a thorough evaluation and differential for pelvic pain assessment. Table 54-4 outlines elements of a good physical exam and its neurologic correlations in the lower thoracic, lumbar, and sacral regions.

An often overlooked but essential component of a patient's exam is the *psychiatric assessment*. A thorough psychosocial or psychosexual history is needed when organic diseases are excluded or coexisting psychiatric disorders are suggested. Sufficient history must be obtained to evaluate depression, anxiety disorder, somatization, physical or sexual abuse, drug abuse or dependence, and family, marital, or sexual problems. A high incidence of physical or sexual abuse is found in 30% to 50% of patients with CPP of unknown etiology.[30] In fact, sexual abuse in patients before 15 years of age is associated with subsequent development of CPP.[31]

DIAGNOSTIC STUDIES

Tests can vary from blood work to radiologic evaluation, dependent upon physical exam findings. These exams include blood work, cultures, pregnancy testing, ultrasonography, x-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI), and diagnostic blocks.

PAIN MANAGEMENT PHILOSOPHY

CPP is a common problem and presents a major challenge to health-care providers because of its unclear etiology, complex natural history, and poor response to therapy. In order to treat patients effectively, the identification of the type of pain is absolutely necessary (Table 54-5). Thus, it is important for a physician to identify between

TABLE 54–4 Neuro-Musculoskeletal Examination

Muscle	Innervation	Referral Pattern	Symptoms
Iliopsoas	L1–L4	Lower abdomen, groin, anterior thigh, low back, and lateral trunk	Pain with hip extension and weight-bearing, especially at heel strike
Piriformis	L5–S3	Buttock, pelvic floor, and low back	Pain on standing, walking, and sitting
Quadratus Lumborum	T12–L3	Lower abdomen, anterior lateral trunk, anterior thigh, buttock, and sacroiliac joint	Pain in lateral low back with standing and walking
Sacroiliac Joint	L4–S3	Posterior thigh buttock, pelvic floor, low back	Pain on standing and walking and a possible "catch" on one side with bending
Obturator Internus	L3–S2	Pelvic floor, buttock, posterior thigh, and coccyx	"Pressure" in pelvic floor
Pubococcygeus	S1–S4	Pelvic floor, vagina, rectum, buttock	Pain on sitting, dyspareunia

TABLE 54–5 Types of Pain

Pain Category	Description
Nociceptive/somatic	Afferent A δ and C-fibers
Visceral	Solid or hollow organs
Sympathetic	After a nerve or limb injury, diffuse burning, allodynia, hyperpathia, sudomotor dysfunction, impaired blood flow
Neuropathic	Sharp lancinating pain

TABLE 54–6 Treatment Modalities

Medication	NSAIDs, antidepressants, anticonvulsants, opioids
Interventional	Trigger point injection, nerve blocks, sympathetic blocks, epidural steroid injections
Surgical	Spinal cord stimulator, intrathecal opioid pump

nociceptive, somatic, and visceral pain. Nociceptive pain arises from stimulation of specific pain receptors. It can be thermal (responds to heat or cold), mechanical (responds to stretching or crushing) or chemical. Somatic pain can originate in the musculoskeletal system. It can be defined as a sharp and well localized pain; moreover, it can often be reproduced. Visceral pain is usually dull and vague in location and can be difficult to locate.[32] Neuropathic pain has distinct characteristics of "burning," "tingling," and or "shooting." It can originate from the peripheral nervous system or from the central nervous system. Neuropathic pain can be sympathetically mediated as well. An example of sympathetically mediated pain is complex regional pain syndrome.[32] In addition, pain mechanisms can overlap and patients may present with a complicated overlapping type of pain. One must understand visceral hyperalgesia as well as referred pain from viscera. This "viscero-somatic convergence" is based on a principle that visceral innervations converge terminally in the spinal cord at the same level as overlying somatic structures. Thus, it is difficult to distinguish between somatic and visceral origins, resulting in "referred pain."[33,34] In reviews, only 15% of patients with abdominal pain had an accurate organ-specific diagnosis; this could be attributed to the viscero-somatic convergence.[35,36]

TREATMENTS

After identifying the type of pain, treatment modalities can be targeted to the patient's diagnosis. Medical and interventional treatment modalities (Table 54-6) are presented in detail. Furthermore, algorithms used at Weill Cornell Medical Center for the treatment of pelvic and perineal/rectal pain are presented here.

MEDICAL/PHARMACOLOGY TREATMENT

As the causes of pelvic pain can be quite varied, so can treatment modalities. Different genres of medications approach the treatment of pelvic pain using different mechanisms and there is an additional benefit that combination therapy may contribute to the success of pain management control for another subset of CPP patients. Medical treatment involves the art and science of medicine to provide efficacy and patient satisfaction while balancing side effects.

Nonsteroidal Anti-Inflammatory Drugs. These drugs reduce overall prostaglandin production throughout the body, and can be effective in the treatment of pelvic pain. As prostaglandins can protect the stomach and support platelets and blood clotting, NSAIDs may cause ulcers in the stomach and promote bleeding. Drug interactions of concern include blood thinners, such as warfarin, which can increase potential serious bleeding risks. NSAIDs reduce blood flow to kidneys and can affect kidney function. NSAIDs also may increase blood pressure and may antagonize antihypertensive medications. Often these agents can be prescribed at doses ranging up to 800 mg every 6 hours, but their use is limited by patient comorbidities such as chronic ulcers or bleeding disorders.[36]

Opioids. Opioids are a common therapeutic method for pain treatment in many disorders within the scope of pain medicine. Due to many side effects including nausea, vomiting, and respiratory depression, as well as complications of treatment including tolerance as well as potential for addiction and abuse, discussion in this chapter will not include this general analgesic treatment.

Oral Contraceptives. Oral contraceptives (OCPs) address a different mechanism for pelvic pain. Some women may have cyclic pelvic pain related to ovulation, Mittelschmirtz, endometriosis, or even premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome (PMS). By using hormonal regulation to block ovulation, this type of pain may be decreased.[37] The combination of OCP and

NSAIDs can create increased efficacy. Various OCP agents are available, but it is advised that referral to a gynecologist is appropriate for complete management and selection of an appropriate agent.[38–40]

Antidepressants. The analgesic effect of antidepressants has a postulated mechanism of action related to inhibition of monoamine reuptake, increase in the serotonin (5HT) and norepinephrine (NE) availability in descending inhibitory spinal pathways, with an increase in descending inhibitory tone, and decrease in ascending nociceptive transmission.[39] The pathophysiology behind these mechanisms still leaves room for further exploration. It is unclear whether an increase in serotonin or norepinephrine is the dominant force behind analgesia. In recent studies for patients with a diagnosis of depression, it is noted that tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and mixed reuptake inhibitors are equally effective.[39–41] Other studies show that norepinephrine is more important in pain inhibion; thus, mixed reuptake inhibitors are more effective than SSRIs.[42–44]

Tricyclic antidepressants have been shown to be efficacious in meta-analyses of neuropathic pain, fibromyalgia, irritable bowel syndrome, and in many sympathetically mediated pain syndromes. These agents may also augment effects of opioid analgesics and thus may be effective in preemptive analgesia. In studies and meta-analyses comparing this class of drugs to SSRIs in many different pain conditions, TCAs typically show superior efficacy.[45,46] The mechanism for analgesic effect is its own entity: analgesic effect occurs in the absence of depression and at doses lower than those used for depression with an earlier onset (i.e., within 1 week) than that required for an antidepressant effect.[45,46]

Anticonvulsants. For pain of a neuropathic nature, anticonvulsants can have a significant role. Studies comparing an anticonvulsant therapy agent (gabapentin) to an antidepressant therapy (amitriptyline) to a combination therapy are numerous. Results reveal that gabapentin alone or in combination with amitriptyline is better than amitriptyline alone in the treatment of female CPP. Moreover, side effects were also lower in groups treated with anticonvulsants alone.[47–50]

Other anticonvulsant agents (e.g., clonazepam, topiramate, lamotrigine, zonisamide, tiagabine) have also been used in CPP. As per the studies above, most evidence supports the beneficial relationship of anticonvulsants for neuropathic pain–related symptoms. Moreover, the increased success of anticonvulsant therapy and combination therapy over antidepressant agents alone significantly supports its use for CPP.[47–49]

INTERVENTIONAL PROCEDURES

Procedures may be performed for diagnostic reasons, therapeutic reasons, or both. Thus, it is important to have a clear sense of the anatomic innervations of the pelvic organs in order to perform the appropriate blocks (Table 54-7).

Temporary but consistent responses to nerve blocks may lead to more lasting procedures such as pulsed radiofrequency neuromodulation or neurolytic nerve blocks. Usually, neurolysis is indicated in cancer pain. A simplified version of interventional therapy to treat pelvic pain is listed in the following Weill Cornell Medical Center interventional algorithm for pelvic pain. With any intervention, it is important to pay attention to safety and sterility. Moreover, the presence of skilled support staff and appropriate monitoring and resusucitation equipment is also necessary. In addition, the use of block needles, nerve location devices, and imaging (i.e., x-ray image intensifier, ultrasound or CT) appropriate for the procedure is essential.[49]

- Trigger-point injection/botulinum toxin
- Peripheral nerve block (ilioinguinal/genitofemoral/pudendal)
- Epidural steroid injection (thoracic/lumbar/caudal)
- Sympathetic nerve block (hypogastric/ganglion of impar)
- Spinal cord stimulator
- Intrathecal pump

Trigger-Point Injections. These injections are used mostly for localized specific areas of tenderness related to myofascial pain or neuroma. These can be effective techniques for myofascial pain using various agents; local anesthetics, saline, and even simple needling have been found to be effective techniques for pain relief.[49,50] At the same time, myofascial trigger points have also been considered a source of pain and voiding symptoms as well as a trigger for neurogenic bladder inflammation for patients with interstitial cystitis and urethral syndromes.[51]

Botulinum Toxin. This agent is used mostly in cosmetic medicine, but botulinum toxin A is also useful as an effective adjuvant in chronic pain medicine. A randomized controlled trial (RCT) indicated that botulinum toxin type A (Botox) effectively treats CPP and the associated spasm of pelvic floor muscles in women. In this study of women aged 18 to 55 years, intravaginal injection of Botox into the pelvic floor muscles was shown to result in a statistically significant improvement of dyschezia and dyspareunia.[52] In a study comparing botulinum toxin A versus bupivacaine trigger point injections for myofascial

TABLE 54–7 Innervation of Pelvic Structures and Correlated Nerve Blocks

Pelvic Organs	Spinal Innervation	Sympathetic and Peripheral Nerves
Fallopian tubes, superior portion of uterine segment, ureters and bladder, appendix, broad ligament, proximal large bowel	T9–12, L1	Celiac plexus, hypogastric plexus
Abdominal wall	T12–L1, L1–L2	Ilioinguinal, genitofemoral
Inferior portion of uterine segment, ureters and bladder, superior vagina, distal colon, rectum, uterosacral ligaments	S2–S4	Inferior hypogastric plexus, inguinal, genitofemoral
Lower vagina, vulva, perineum	S2–S4	Ganglion impar, pudendal, genitofemoral, inguinal

pain treatment, both with adjuvant home-based rehabilitation programs, Graboski et al.[53] found similar efficacy in reducing pain when compared to baseline, but no significant difference between the two groups in duration or magnitude of pain relief, function, satisfaction, or cost of care (cost of injectate excluded). It is noted in studies that bupivacaine still remains a more cost-effective injectate.[52–55]

Epidural Steroid Blocks and Facet Joint Injections. Epidural steroid injections and facet joint injections are targeted therapy procedures used as dermatomal-directed therapy. It is essential that assessment of the exact source and dermatomal distribution of the pain source are elicited.[55,56]

Neural Blockade and Neurolysis. General principles for neural blocks include the diagnostic value of local anesthetic injection, and many physicians have observed improved pain in response to a series of local anesthetic injections (with or without steroids) in patients with chronic neuropathic nonmalignant pain. The mechanism of this seeming reversal of adverse neuroplastic changes is unknown. Once the nociceptive pathways have been identified, neurolysis may be of long-term benefit. Complications from neurolysis include possible neuroma formation, deafferentation pain, permanent motor or sensory deficits, orthostatic hypotension, diarrhea, sexual dysfunction, and bowel or bladder incontinence. Risk of neuroma formation varies with choice of technique. Neuroma formation is more likely with surgical or radiofrequency ablation than with alcohol, phenol, or cryolysis, because cutting or burning destroys the neural sheath.[57–59] Neuritis is another risk, but it occurs rarely with neurolysis of sympathetic nerves or visceral afferents.

Peripheral Nerve Blocks. These blocks are valuable for neuropathic pain or neuroma of somatic nerves of the pelvis, muscles, and bone. Neurolysis should be cautiously considered for severe nonmalignant pain that is refractory to conservative measures.

Superior Hypogastric Nerve Block (Presacral Nerve). Surgical presacral neurectomy has a long history of success for pain relief in pelvic visceral structures. A percutaneous technique to block the superior hypogastric plexus has been described for treatment of pelvic cancer pain. The plexus is located anterior to the L5 vertebral body and sacrum at the bifurcation of the common iliac vessels. The visceral afferents that travel through this plexus have their cell bodies located in the dorsal root ganglia from T10 to L2. Blockade of the superior hypogastric plexus has been reported to decrease pelvic pain by 70% in patients with cervical, prostate, or testicular cancer.[58,59] No complications were reported. This can be performed by a bilateral posterior approach with fluoroscopy.

Ganglion Impar (Ganglion of Walther) Block. The ganglion impar is the termination of the paired paravertebral sympathetic chains. This terminal end is a single ganglion located anterior to the sacrococcygeal junction. Blockade of this structure has been introduced within the last decade to manage intractable perineal cancer pain involving the sympathetic nervous system. Ganglion impar block and neurolysis has been reported to achieve 70% to 100% pain relief for perineal pain caused by cancer of the cervix, colon, bladder, rectum, or endometrium. The procedure is performed by inserting a needle directly through the sacrococcygeal ligament. The position is confirmed with injection of contrast medium under fluoroscopy. Local anesthetic or neurolytic solution is then injected, usually with a volume of 4 to 6 ml. Although effective, neurolytic procedures must be targeted to a specific population, most often they are used for the palliative treatment of chronic cancer patients. De Leon Casasola et al. found 69% efficacy in treating malignant CPP with neurolytic superior hypogastric block.[58,59] In addition, it must be mentioned that complications are possible and can lead to further painful dysfunction, including possible neuroma formation, neuritis, deafferentation pain, permanent motor and sensory losses, hypotension, diarrhea, sexual dysfunctional, and bowel and bladder incontinence.[58,59] Due to the irreversible nature of these blocks along with their side effects, careful consideration is necessary for its use in severe refractory nonmalignant pain.

Intrathecal and Epidural Block and Neurolysis. Intractable pelvic cancer pain with somatic involvement may be alleviated by destruction of the appropriate somatic sensory fibers. Intrathecal neurolysis is preferred for unilateral pain and carries a reduced risk of motor fiber destruction. In patients who have undergone a urinary diversion and colostomy, epidural or saddle block neurolysis is an effective means of achieving effective pain relief, but the risk of incontinence or lower extremity paresis is high.[58,59]

Neuromodulation: Spinal Cord Stimulation. Spinal cord stimulation (SCS) is an advanced treatment option for patients who have failed conservative management. The trial is on an outpatient basis with no surgery involved and thus is easily reversible. Those for whom the trial stimulation is effective can then consider having it implanted. Studies[60–65] have shown positive responses for many patients with long-term CPP. Kapural et al[62] presented positive data regarding five patients with chronic visceral pelvic pain who had been poorly responsive to pharmacotherapeutics, therapeutic injections, and other conservative therapies. These patients had received hypogastric diagnostic blocks with 1 to 4 weeks of complete relief followed by a stimulator trial preceding implantation of a SCS device. Over 33.6 months, average visual analog scale (VAS) scores dropped from 8 to 3, pain disability index changed from an average of 58 to 19.7, opioid use decreased from an average of 26 mg to 5 mg of morphine sulfate equivalent per day. Although anatomic assessment of pain can be attempted with SCS, the best location for a SCS lead placement—thoracic versus sacral—is still debated. Kapural et al. have reported reduction of severe refractory pelvic pain of visceral origin in six female patients using dual lead (compact or quad lead) placement at the T11–L1 level with an average rate of greater than 50% relief for all patients studied over a 30-month period.[62] Haque et al. have reported several patients with nociceptive pelvic and rectal pain responding to dual eight-electrode, lead placement in the area of the sacral nerve roots (S2, S3: retrograde).[63] Thoracic versus sacral lead placement has been assessed in several other studies. Most results note better pain relief in the thoracic lead trials. Potential explanations include a technically challenging placement of the retrograde leads and easy migration of the sacral lead after placement.[61–64]

Intrathecal Pump. An intrathecal morphine pump may be used, but careful selection of patients is very important. Most importantly, these patients should have cleared an independent psychological evaluation prior to consideration of this therapy.

Neurolysis/Neurosurgical Ablative Techniques. Neuroablation of selected nerves can be performed by using different techniques, including thermocoagulation (radiofrequency ablation), cryoablation, or injection of chemical agents (alcohol, hypertonic saline, phenol). Various surgical procedures may be considered to treat CPP. Surgical procedures include presacral neurectomy (superior hypogastric plexus excision), paracervical denervation (laparoscopic uterine nerve ablation [LUNA]), and uterovaginal ganglion excision (inferior hypogastric plexus excision).[65–68]

Presacral Neurectomy. This is the surgical removal of the presacral plexus, a group of nerves that conducts pain signals from the uterus to the brain. The procedure can be done laparoscopically. In a 1-year observational study, phenol presacral neurectomy provided a 73% reduction in analgesic use and improved sexual function. Furthermore, a prospective randomized double-blind trial in 2003 for women utilizing a presacral neurectomy versus laparoscopy, the former was found to have significantly lower values for pain intensity compared to control groups, thus indicating the possibility of a benefit to patients with CPP. Potential risks can include injury of the vena cava and thus an available vascular surgeon should be available for consultation.

Laparoscopic Uterine Nerve Ablation (LUNA). LUNA can allow for interruption of the nerves to the uterus and pelvis.[65–68] Sutton et al. completed a randomized, prospective study in which 62% of patients undergoing LUNA therapy had relief of symptoms compared to 23% of nonsurgical controls.[68] This efficacy has recently been questioned. A more recent RCT by Daniels et al. found that after a median follow-up of 69 months, there were no significant differences reported via VAS for the worst pain, noncyclical pain, dysmenorrheal, dyspareunia, or quality of life.[67]

ALTERNATIVE/COMPLEMENTARY PAIN MEDICINE

As with all therapies for pain syndromes, our solutions for CPP can be enhanced by a multimodal approach. In addition to medicinal and interventional treatment, complementary medicine can be an effective alternative. Complementary and alternative therapies are growing in popularity and are used by more than a third of the U.S. population.[69–71] Physical therapy, psychological counseling, behavioral relaxation, massage, therapeutic heat, ice, electrical stimulation, acupuncture, magnesium, vitamin B1, counseling, and orthotic devices can be useful and require further exploration by the care team involved. Topical heat at 38.9° C for 12 hr per day has been shown to be equally as effective as ibuprofen in patients with CPP related to primary dysmenorrhea.[72,73] Daily thiamine (100 mg) for 90 days in 556 patients resulted in an 87% cure rate up to 2 months post-treatment. Pelvic floor manual therapy for decreasing hypertonus in patients with symptoms of urgency/frequency and interstitial cystitis was also found to be effective.[73–75] Many opportunities still exist for further exploration of clinical evidence in this area.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

Specific mention of the Transcutaneous Electrical Nerve Stimulation (TENS) unit will be explored in greater detail as it is an increasingly popular tool in practice today. The TENS unit is a pulse generator with an amplifier and electrodes are used to deliver continuous or varying duration of electrical nerve stimulation to relieve pain. The stimulation causes myelinated afferents to activate segmental inhibitory circuits with a cumulative effect. Induction time can be cumulative but typical recommendations include 30 min to 2 hr BID, depending on the severity of the pain. Usually, the patient controls a modulated frequency between 0 and 100 Hz for pain control.[76] Studies have shown that the TENS units provide moderate pain relief in patients.[77,78] Counseling, device training, and appropriate patient selection are mandatory.

Acupuncture. This adjuvant therapy is used by more than 2 million people annually in the United States alone.[79] Acupuncture involves the use of metallic needles to penetrate the skin at specific points in the body; analgesia involves neurohumoral mechanisms via release of endogenous opiates and monoamines with evidence of sustained depression in spinal cord dorsal horn neurons.[80] A prospective study of 32,000 consultations with doctors and physiotherapists in 2001 revealed minimal adverse effects. The use of acupuncture for 1 year showed a 91% improvement in symptoms of CPP and 41% decrease in analgesic use.[81] A multicenter trial assessing the effects of acupuncture, stabilizing exercises, and standard medical treatment of women with associated pelvic pain revealed that the combination of acupuncture and standard treatment was found to be superior.[82–85] Studies assessing classic acupuncture points for relief of pain revealed that the acupuncture points selected for treatment of pain are actually trigger points. At the same time, it has been demonstrated that both patient expectation and practitioner behavior can result in greater placebo analgesia. In fact, some have postulated that acupuncture may have a "placebo-enhancing effect."[86] Thus, more remains to be explored in the realm of efficacy of acupuncture analgesic assessment.

CONCLUSION

A multidisciplinary approach to CPP that combines gynecologic, psychological, dietary, and physical therapy was found to more effective than medical and surgical management.[87] Pelvic pain is often difficult to diagnose and treat, resulting in frustrated patients lacking social support. A thorough assessment of multiorgan systems is critical along with appropriate use of diagnostic studies and nerve blocks. Using evidence-based medical treatment as described above further supports use of tricyclic antidepressants, anticonvulsants, and opioids in patients with CPP. Moreover, in patients who have failed medical and diagnostic treatment, the data for implantable therapies are promising. In the future, better knowledge of pathophysiologic mechanisms of CPP will offer novel treatment strategies.

KEY POINTS

- Chronic pelvic pain (CPP) usually persists for more than 6 months. Even after a thorough evaluation, the etiology of the pain may remain obscure, and inconsistency remains in the pathology of various disorders and pain.
- The prevalence of female pelvic pain is estimated to be one in seven women of reproductive age. Internationally, the prevalence of CPP is equivalent to that of asthma, back pain, or migraine.
- Both diagnosis and management of these patients require good integration and knowledge of all pelvic organ systems and other systems including musculoskeletal, neurologic, and psychiatric systems.
- Significant numbers of these patients may have various associated problems, including bladder or bowel dysfunction, sexual dysfunction, and other systemic or constitutional symptoms. Other associated problems, such as depression, anxiety, and drug addiction may also coexist.
- Various pathophysiologic hypotheses have been postulated regarding CPP. Vascular congestion syndrome and alteration of stimuli processing are two of the leading biological considerations for CPP.
- CPP can originate from any organ system and thus a thorough review of systems is essential to a proper assessment of a patient's pain. These assessments can be organized in a system-based review as well as a gender-specific review. It is also important to know the dermatomal patterns of gynecologic referred pain associated with pelvic organ innervation varying between T9 and S4.
- History must be conducted in a systematic review of systems organized assessment including gastrointestinal, musculoskeletal, vascular, genito-urinary, neurologic, and psychological.
- Tests can vary from blood work to radiologic evaluation, dependent on physical exam findings. These exams include blood work, cultures, pregnancy testing, ultrasonography, x-ray, CT, MRI, and diagnostic block.
- Evidence supports the beneficial relationship of multimodal therapy with NSAIDs, antidepressants, and anticonvulsants for CPP. Moreover, the increased success of anticonvulsant therapy and combination therapy over antidepressant agents alone significantly supports its use for CPP.
- Procedures may be performed for diagnostic reasons, therapeutic reasons, or both. Thus, it is important to have a clear sense of the anatomic innervations of the pelvic organs in order to perform the appropriate blocks. Temporary but consistent responses to nerve blocks may lead to more lasting procedures such as pulsed radiofrequency, neuromodulation, or neurolytic nerve blocks.
- In addition to medicinal and interventional treatment, complementary medicine can be an effective addition to the multimodal approach to CPP. Physical therapy, psychological, behavioral relaxation, massage, therapeutic heat, ice, electrical stimulation, acupuncture, magnesium, vitamin B1, counseling, and orthotic devices can be useful.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 55

Painful Peripheral Neuropathies

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Neuropathy is a general term used to describe disease of nerve function and structures. Neuropathies arise from many different etiologies (diabetic peripheral neuropathy, postherpetic neuropathy, chemotherapy-induced peripheral neuropathy, HIV neuropathy, and neuropathy of chronic renal failure) and can be painful or painless. They can affect the central nervous system (CNS), the peripheral nervous system, or both simultaneously. They result from physical injury, inherited genetic disorders, infection, autoimmune disorders, and most often systemic disease. Neuropathies can affect solely one single nerve, termed a *mononeuropathy*, or several separate nerves, which is termed a *polyneuropathy*. Cranial nerves can also be involved, though less frequently.

Pain is considered a normal, adaptive, or physiologic response when it results from nociceptors (pain receptors) having been activated by tissue disease or damage, called *nociceptive pain*. In contrast, neuropathic pain arises from spontaneous activity within the nervous system, or an aberrant response to "normal" sensory stimulation (e.g., fine touch evoking pain). Neuropathic pain is very common in the outpatient setting and second only to musculoskeletal pain.[1]

This chapter presents a brief overview of the evaluation of patients with painful peripheral neuropathy, describes an approach to the differential diagnosis of these disorders, and outlines the therapeutic modalities that may be useful in treating patients with neuropathic pain. The main disease process discussed is diabetic peripheral neuropathy.

TERMINOLOGY AND CLASSIFICATION

Neuropathy is a disturbance of function or pathologic change in a nerve. Mononeuropathy reflects changes in a single nerve. Mononeuropathy multiplex reflects changes in multiple single, discreet nerves. Polyneuropathy reflects changes in sensation in a diffuse, often bilateral, pattern that is not restricted to discreet nerves. Neuritis is a subtype of neuropathy reserved for an inflammatory process affecting the nerves. Neuropathy is not intended to apply to cases of neurapraxia including a blow, stretch, or epileptic discharge. The term *neurogenic* is intended to refer to "temporary" perturbations.

Neuropathic pain originally defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system[2] has been revised to now include "pain arising as direct consequence of a lesion or disease affecting the somatosensory system."[3] Because a clear and specific diagnostic tool to diagnose neuropathic pain and differentiate it from the other major categories of persistent pain does not exist, a grading system was also incorporated within the definition: neuropathic pain can be graded to be "possible," "probable," and "definite" based on clinical suspicion. Neuropathic pain can result from multiple causes and it can be categorized according to the site of initial injury (central nervous system, peripheral nervous system, or mixed) and the condition causing disease (Table 55-1).[4] Injury to the nervous system that results in persistent pain can occur anywhere from the peripheral nerve terminal to the cerebral cortex. Despite the differing locations and the myriad underlying causes for injury, patients with neuropathic pain often share similar sensations (Table 55-2).[5]

EPIDEMIOLOGY

Neuropathic pain affects approximately 2% to 3% of the general population.[6] This condition results in substantial physical and social disability. The estimated direct costs associated with the treatment of neuropathic pain in the United States were approximately $40 billion.[7] It affects the patient's mood, activities of daily living, quality of life, and work performance. As a result, these conditions result in substantial direct costs to the health-care system but also indirect costs resulting from use of the health-care system for the associated problems that are a result of the pain. These patients generate health-care costs that are three times higher than matched controls.[8]

MECHANISMS OF NEUROPATHIC PAIN

Several mechanisms are thought to be responsible for the development of neuropathic pain. These include changes in ion channel number and density resulting in central and peripheral sensitization. Other changes include cortical reorganization and disinhibition of neuronal circuitry, and cellular and molecular changes as a result of the immune response following the initial nerve damage. The sympathetic nervous system is also thought to play a role in maintaining neuropathic pain.[9]

PERIPHERAL

Following trauma to a nerve, sodium channels accumulate in a higher than normal concentration around the area of injury and along the entire axon, resulting in hypersensitivity of the nerve and ectopic foci. This is often the basis for the use of sodium channel blockers and membrane stabilizers in neuropathic pain.[10] It has also been suggested that nerve injury can result in the release of neuropeptides that might further cause peripheral sensitization through neurogenic inflammation.[2] Nerve injury also can result in sprouting of sympathetic fibers into the dorsal root ganglia of the affected nerve. In partially injured nerves the uninjured fibers may increase expression of α-adrenoreceptors. In both of these circumstances, sympathetically mediated pain may occur. This pain can often be blocked, at least

TABLE 55–1 Common Conditions Causing Neuropathic Pain Syndromes

Etiology	Terminology	Peripheral vs. Central Nervous System Etiology
Physical Injury/Trauma		
	Complex regional pain syndrome (CRPS), Type I (reflex sympathetic dystrophy or RSD)	Mixed?
	Complex regional pain syndrome (CRPS), Type II (causalgia)	Mixed?
	Radiculopathy	Peripheral > central
	Stroke (cerebrovascular accident)	Central
	Spinal cord injury	Central
Inherited/Genetic		
	Charcot-Marie-Tooth	Mixed
	Fabry's disease	
Infections/Autoimmune		
	Human immunodeficiency virus	Peripheral
	Herpes simplex virus	Peripheral > central
	Acute inflammatory demyelinating polyneuropathy	Mixed
Systemic Disease		
	Diabetes mellitus	Peripheral
	Kidney disorders/renal failure	Peripheral > central
	Vitamin deficiencies (beriberi, alcoholic pellagra, vitamin B12 deficiency)	Mixed
	Vascular disorders	Peripheral > central
	Chemical toxins (isoniazid, chemotherapy agents) (platinum, vinca alkaloids, taxanes), arsenic, thallium	Mixed
	Hypothyroidism	Peripheral
	Amyloidosis	Mixed
	Multiple myeloma	Mixed

TABLE 55–2 Abnormal Sensations of Neuropathic Pain

Paresthesias: Abnormal nonpainful sensations that may be spontaneous or evoked (tingling)

Dysesthesias: Abnormal pain that may be spontaneous or evoked (unpleasant tingling)

Hyperpathia: An exaggerated painful response evoked by a noxious or non-noxious stimulus

Allodynia: A painful response to a normally non-noxious stimulus (e.g., light touch is perceived as burning pain)

Hyperalgesia: An exaggerated painful response to a normally noxious stimulus

Spontaneous pain: Painful sensation with no apparent external stimulation

temporarily, by the application of sympathetic blocks or by the administration of systemic α-adrenoreceptor antagonists (phentolamine).[2] More recently, attention has focused on not only changes in the neuronal pathway following nerve damage, but also the complex interplay of neuronal support cells including Schwann cells, satellite cells in the dorsal root ganglia, spinal microglia, astrocytes, and components of the peripheral immune system. Processes in this interaction could contribute to the development and presence of neuropathic pain.[11] Another proposed but poorly documented mechanism is that of ephaptic transmission: peripheral nerve injury resulting in "cross-circuiting" of peripheral fibers. In theory, sympathetic efferents would be able to activate nociceptive afferent fibers, explaining spontaneous pain and worsening of pain with activation of the sympathetic nervous system in some patients with neuropathic pain. However, there is little evidence to support this longstanding theory.[12]

CENTRAL

The CNS undergoes changes with peripheral nerve injury. In fact, this mechanism may be a primary one in conditions where peripheral neuropathy results in reduced input to the CNS (postherpetic neuralgia, diabetic neuropathy). In diabetic neuropathy, there is little evidence that peripheral sensitization (as might be seen with increased sodium channels or with ephaptic transmission) occurs; rather the evidence points toward reduced neural input to the CNS.[13]

Several potential mechanisms exist for a central contribution to the pain from peripheral neuropathy. Loss of large fiber (A-β) sensory input could result in a reduction in non-nociceptive sensory input, thereby reducing the effectiveness of the "gate" as proposed by Wall and Melzack.[14] In experimental models of nerve injury, opioid and gamma-aminobutyric acid (GABA) receptors (both involved in inhibition of nociceptive transmission in the

CNS) are down regulated and the amount of GABA in the dorsal horn is reduced. Another mechanism suggests death of dorsal horn interneurons in lamina II (many of which are involved in inhibition of nociceptive transmission in the dorsal horn) by overexposure to excitatory amino acids (EAA). Cholecystokinin, involved in opioid receptor inhibition, has also been found to be upregulated in the spinal cord following experimental nerve injury.[2] The net effect of the above changes in the spinal cord results in "disinhibition" of nociceptive transmission, thereby creating an imbalance of painful over nonpainful impulses. These changes might also explain the relative opioid resistance seen in neuropathic pain.

A central mechanism that may explain the allodynia seen in some peripheral neuropathies involves A-β fiber sprouting and A-β fiber "phenotypic switching." A-β fibers normally synapse in all lamina of the spinal cord except lamina II, where C-fiber input predominates. However, following peripheral C-fiber nerve injury, A-β fiber "sprouting" into lamina II occurs, therefore allowing mechanical non-nociceptive input via the peripheral A-β fibers to trigger second-order pain pathways. A-β fibers in the dorsal horn also do not normally express substance P (as seen in C-fibers), but following peripheral nerve injury they can (phenotypic switching). When this happens, they thereby allow non-nociceptive input to trigger CNS nociceptive transmission.[2]

These mechanisms are likely far from complete in terms of explaining the changes in the CNS following peripheral nerve injury. It is very likely that significant changes also occur throughout the spinal cord even in levels not directly involved with the peripheral injury, including the contralateral side, midbrain, and cerebral cortex.[15] The wide variability in how individuals respond to peripheral nerve injury is likely the result of genomic differences. Differences in the ability of A-β fibers or sympathetic fibers to sprout, the amount of neuropeptide available for release peripherally, the susceptibility of inhibitory interneurons to EAA in the dorsal horn are all likely to be highly variable between patients. This may explain why patients with the same condition (e.g., diabetic neuropathy) may or may not have pain.[2] Animal models of neuropathic nociception demonstrate notable differences between strains in their reaction to peripheral nerve injury and in their responsiveness to analgesics.[16]

EVALUATION OF THE PATIENT WITH NEUROPATHIC PAIN

When a patient presents with signs and symptoms suggestive of neuropathic pain—most frequently allodynia, hypo- and/or hyper-algesia, and paresthesias—the first useful distinction to be made is the pattern of involvement. Focal lesions of peripheral nerves (mononeuropathies) result frequently from processes that produce localized damage and include nerve entrapment; mechanical injuries; thermal, electrical, or radiation injuries; vascular lesions; and neoplastic or infectious processes. In contrast, polyneuropathies often result in a bilateral and symmetric disturbance in function as a result of agents that act diffusely on the peripheral nervous system: toxic substances, deficiency states, metabolic disorders, and immune reactions. The diagnosis of painful polyneuropathy is most often made by history and standard neurologic examination. In some cases ancillary studies may be needed to document the disease process.[13]

HISTORY

Pain is often the presenting symptom for polyneuropathy but it rarely presents in the absence of other sensory abnormalities. Many of the terms used to describe these abnormalities are listed in Table 55-2; paresthesias ("tingling" or "pins and needles" sensations) are particularly common. However, since the characteristics of neuropathic pain are almost always multiple (e.g., varying combinations of burning, stabbing, aching, etc.), they cannot be used as a useful guide to determining the etiology of the neuropathy.[13] The location of the pain and other symptoms are frequently the most important pieces of historical information.

NEUROLOGIC EXAMINATION

In the patient suspected of having polyneuropathy, the clinician should focus on sensory evaluation. Strength and deep tendon reflexes are preserved in many patients with polyneuropathy. In addition to testing vibration, proprioception, and light touch, the sensory examination should include several special stimuli including light-touch rubbing, ice, single pinprick, and multiple pinpricks. Lightly stroking the affected area with a finger will assess for allodynia (pain provoked by non-noxious stimuli). Ice application will test for both temperature sensation and abnormal sensations such as pain and lingering after-sensations. Single pinprick testing may elicit a sensory deficit or hyperpathia (an exaggerated response to a normally painful stimulus). Repeated pinprick testing may elicit summation (pain growing more intense with subsequent stimuli) or lingering after sensations, both common findings in polyneuropathy.

ELECTRODIAGNOSTIC TESTING

Patients suspected of having polyneuropathy can be considered for electromyography (EMG) and nerve conduction velocity (NCV) studies, which may offer insights into whether the process is a demyelinating (reductions in nerve conduction velocities) or axonal (reductions in the amplitude of evoked responses) neuropathy. However, such differentiation rarely offers any change in therapy when managing neuropathic pain. These tests are best used to demonstrate large fiber involvement, but because many painful peripheral neuropathies involve small fibers these tests may be completely normal in patients with painful polyneuropathy.[17] Quantitative sensory testing (QST) may be the most useful in the assessment and longitudinal monitoring of painful peripheral neuropathies. While large fibers are assessed through the use of sensory thresholds to vibration, small fibers can be assessed by threshold for detection of heat, painful heat, cold, and painful cold stimuli. Thermography has been found to have little role in the assessment, management, or tracking of painful peripheral neuropathies despite much published

literature on the method. The role of skin biopsies remains controversial[18]; however, it has been used to successfully diagnose loss of small peripheral nerve fibers such as nociceptive afferents.[19]

DIFFERENTIAL DIAGNOSIS

After assembling the historical information, neurologic examination, and results of electrodiagnostic studies, the underlying etiology will most often be readily apparent. Neuropathic pain is often a result of polyneuropathy.[18]

METABOLIC CAUSES OF PERIPHERAL POLYNEUROPATHY—DIABETES

The reported frequency of neuropathy in patients with diabetes mellitus ranges from 4% to 8% at the time of initial presentation and rises to 15% to 50% after 20 to 25 years of follow-up.[20] Other studies report an incidence of neuropathy (not necessarily painful) of up to 66%, but clearly the likelihood of neuropathy increases with the duration of the disease.[21] The incidence of painful neuropathy was reported in one study to average about 11.6% in insulin-dependent diabetes mellitus (IDDM) and 32.1% in non–insulin-dependent diabetes mellitus (NIDDM).[22] The cause of diabetic neuropathy has not been determined with certainty.[23] Current hypotheses focus on the possibilities of metabolic and ischemic nerve injury.[24] Pathologic examination of nerves taken from diabetic patients has shown evidence of microvascular disease supporting the ischemic nerve theory. Metabolic abnormalities include (1) accumulation of sorbitol in diabetic nerve as excess glucose is converted to sorbitol by the enzyme aldose-reductase, (2) autooxidation of glucose resulting in reactive oxygen molecules, and (3) inappropriate activation of protein kinase C.[25] Other theories suggest that impaired nerve regeneration may contribute to the polyneuropathy in diabetes as demonstrated in animal models of nerve injury.[26]

Therapeutic strategies aimed at reducing sorbitol accumulation (aldose-reductase inhibitors) have demonstrated only minor improvements in neuropathy. There is strong evidence, however, that good glycemic control can prevent the appearance and worsening of polyneuropathy in patients with both IDDM and NIDDM. A major trial found that the incidence of neuropathy was reduced by 60% over a 5-year period with aggressive glycemic control.[27]

Diabetic neuropathy can be divided by the pattern of distribution of involved nerves (Table 55-3). The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It is predominantly a sensory disturbance. Patients often present with gradual onset of paresthesias and pain in the legs and feet. Symptoms begin in the toes and gradually ascend over months to years to involve more proximal levels. The fingertips and hands become involved later, usually when symptoms in the lower extremities have ascended to the knee level. Allodynia (e.g., pain in the feet brought on by even the light pressure of contact with bed sheets) and burning pain are common and are often worse at night. Examination shows graded distal sensory loss predominantly affecting vibration and position sensation. Reflexes may be diminished or absent. Electrophysiologic testing shows a decrease in the amplitude of evoked responses to a greater degree than reduction in nerve conduction velocities as the neuropathy progresses.[2] This reflects primarily axonal damage rather than demyelination. Severe sensory loss may allow repeated trauma to go unnoticed, resulting in development of foot ulcers and diabetic neuroarthropathy (Charcot's joints). This last condition is critical to identify in the diabetic patient with a unilateral, painful swollen foot.

TABLE 55–3 Classification of Neuropathies Associated with Diabetes Mellitus

Mononeuropathy	Cranial mononeuropathy
	Compression mononeuropathy
Mononeuropathy multiplex	Proximal motor neuropathy
	Truncal neuropathy
Polyneuropathy	Distal symmetric polyneuropathy
	Painful diabetic neuropathy
	Autonomic polyneuropathy

The syndrome of acute painful diabetic neuropathy may also occur in diabetics.[28] This uncommon disorder is characterized by the rapid onset of severe pain in the distal lower extremities characterized by constant burning in the feet, dysesthesia, allodynia, and lancinating leg pains. Examination shows little or no sensory loss with preserved reflexes. Electrophysiologic testing shows decreased amplitude or absent sensory potentials, but may also be normal. This type of neuropathy often remits within a year after blood sugars are controlled.

Autonomic neuropathy manifestation by abnormalities in tests of autonomic function occurs in 20% to 40% of diabetics.[28] Symptomatic autonomic neuropathy most often occurs as a component of distal symmetric polyneuropathy. Autonomic nervous system abnormalities include postural hypotension, impaired heart rate control (resting tachycardia and fixed heart rate), esophageal dysmotility, gastroparesis, and erectile dysfunction.

Lower extremity proximal motor neuropathy is an uncommon painful disorder associated with diabetes. It is characterized by acute or subacute onset of moderate to marked weakness and wasting of the pelvifemoral muscles accompanied by back, hip, and thigh pain with preserved sensation in the regions of pain. The condition may be painless or accompanied by pain described as a constant, severe, deep ache. Complete recovery occurs in 60% of patients over 12 to 24 months.

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) is sometimes referred to as diabetic amyotrophy, proximal diabetic neuropathy, diabetic polyradiculopathy, Bruns-Garland syndrome, or diabetic lumbar plexopathy. It usually affects individuals with diabetes mellitus Type II over the age of 50 years, and presents as an asymmetric weakness associated with pain in the legs that appears subacutely and progresses over weeks to months. Although motor function recovery is slow and often incomplete, the pain usually resolves.[29] Both microvascular inflammation and autoimmune mechanisms have been proposed, with no one clear treatment plan being particularly effective.[30]

Diabetic truncal neuropathy involves acute or gradual onset of unilateral pain in the chest or abdomen and may mimic myocardial infarction, intra-abdominal pathology, or spinal disorders.[31] Examination shows marked allodynia and hyperpathia in the distribution of pain. Truncal neuropathy occurs most often in longstanding diabetics and people over age 50. EMG typically demonstrates denervation in the abdominal or intercostal musculature.

Cranial mononeuropathies involving the oculomotor, abducens, trochlear, and facial nerves may occur in diabetic patients.[32] The most common of these is oculomotor neuropathy that is manifest as ophthalmoplegia and ptosis. The eye is deviated laterally and has impaired movement vertically and medially. Pain occurs in 50% of patients and may precede ophthalmoplegia by several days.

Entrapment neuropathies are believed to occur more frequently in patients with diabetes mellitus.[28] Carpal tunnel syndrome is believed to occur more than twice as frequently as in the nondiabetic population. This association must be kept in mind when evaluating the diabetic patient with an isolated peripheral mononeuropathy.

OTHER METABOLIC CAUSES OF PAINFUL PERIPHERAL NEUROPATHY

Metabolic causes other than diabetes mellitus (and excluding postherpetic neuralgia) are uncommon. Amyloidosis is a disease caused by extracellular deposition of amyloid, a fibrous protein. Amyloidosis can be primary, familial, or associated with other conditions such as multiple myeloma, chronic infectious or inflammatory states, aging, and long-term hemodialysis. The biochemical composition of the amyloid protein varies with the associated disease state. Deep aching and occasional shooting pains, distal sensory loss, and autonomic and motor involvement characterize painful peripheral neuropathy in amyloidosis.[28] As the neuropathy progresses, all modalities are affected, reflexes are lost, and there is motor involvement. Treatment of neuropathy associated with amyloidosis is aimed at the underlying condition when such is identifiable.

Multiple myeloma is due to malignant plasma cell growth. Painful neuropathy can appear in myeloma with or without amyloid deposition. The neuropathy is extremely variable in severity and rate of progression, ranging from a mild, predominantly sensory neuropathy to a complete tetraplegia.[33] Pain in myeloma often declines with successful treatment using chemotherapy, radiation therapy (especially for isolated plasmocytomas), or plasmapheresis.

Patients with untreated hypothyroidism may also develop painful sensorimotor neuropathy.[33] This uncommon disorder may present with longstanding pain in either the hands or the feet accompanied by weakness in the distal limb musculature. The neuropathy often resolves with successful replacement of thyroid hormone.[33]

NUTRITIONAL CAUSES OF PERIPHERAL POLYNEUROPATHY

Thiamine deficiency is seen in alcoholics, chronic dialysis patients, and people on restrictive diets. Thiamine deficiency appears to lead to beriberi, which consists of heart failure, vasodilatation, and peripheral neuropathy. Hand, foot, and calf pains with allodynia, decreased sensation, and motor involvement characterize the neuropathy. Administration of thiamine may reduce the symptoms of neuropathy, including pain.

The incidence of neuropathy in chronic alcoholism is about 9%.[33] Alcoholic neuropathy is characterized by motor and sensory deficits, often accompanied by pain.[33] The pain consists of aching in the legs or feet with intermittent lancinating pains. The upper limbs are rarely involved. Burning of the soles and allodynia may also occur. Alcoholic neuropathy occurs only after chronic and severe alcohol abuse and is invariably accompanied by severe nutritional deficiency. Pathologically, alcoholic neuropathy cannot be distinguished from beriberi, and both likely result from thiamine deficiency. Treatment consists of abstinence and thiamine supplementation.[33]

Pellagra is caused by niacin deficiency and is rarely seen in developed countries. Signs and symptoms include dermatitis, gastrointestinal complaints, neurasthenia, and spinal cord dysfunction. Pellagra is associated with a mixed, painful polyneuropathy similar to that seen with beriberi. A predominant feature of the sensorimotor neuropathy is spontaneous pain in the feet and lower legs, with tenderness of the calf muscles and cutaneous hyperesthesia of the feet. Treatment of pellagra with niacin often results in resolution of all symptoms except the peripheral neuropathy.[33]

TOXIC CAUSES OF PERIPHERAL POLYNEUROPATHY

Isoniazid is a frequently used antituberculous drug. Chronic administration in individuals with slow metabolism of the drug (slow acetylators) is associated with the development of painful neuropathy.[9] Initial symptoms of distal numbness and tingling paresthesias are later accompanied by pain, which may be felt as a deep ache or burning. The calf muscles are painful and tender, and walking often aggravates symptoms. Symptoms may be particularly troublesome at night. Prophylactic coadministration of pyridoxine (vitamin B6) prevents development of neuropathy; however, it is not therapeutic once the neuropathy develops.

The most common neurologic complication of cancer treatment is chemotherapy-induced peripheral neuropathy (CIPN), a common adverse effect of treatment with platinum-derived, taxane, and vinca alkaloid chemotherapeutic compounds.[34] These chemotherapeutic agents exert their cytotoxic effect by binding to DNA and producing interstrand and intrastrand cross-linkage, thus impairing DNA synthesis and transcription. These agents are first-line chemotherapeutic agents in the treatment of solid tumors. Although penetration into the CNS is relatively poor, high levels of this drug are found in dorsal root ganglia and peripheral nerves.[35] The development of CIPN is the most common reason a platinum-based chemotherapy regimen is changed to another agent, administered at a lower dose, or given in fewer or less frequent cycles of therapy.[36] This change in therapy represents a deviation from the optimal life-extending therapy. Symptoms of CIPN, therefore, may directly increase morbidity and indirectly mortality. The earliest

manifestations of neuropathy are decreased vibration sense in the toes and loss of ankle jerk reflexes. At larger doses, paresthesias may appear and progress to severe dysesthesias. The neuropathy is reversible, but recovery may take more than a year after discontinuation of the agent.

GENETIC CAUSES OF PERIPHERAL POLYNEUROPATHY

Other genetic neuropathies to consider are a clinically and genetically heterogeneous group. The most common types in this group are the Charcot-Marie-Tooth (CMT) disorders, which are subdivided into demyelinating and axonal forms, depending on EMG conduction studies. Most common symptoms in CMT include lower extremity motor symptoms (foot deformity, difficulty ambulating), hyporeflexia, and sensory loss. Other rare genetic neuropathies include the hereditary sensory and autonomic neuropathy (HSAN) that, depending on the subtype, appear in the second to third decades of life and manifest with decreased sensation in the feet and distal legs leaving patients prone to ulcer formation often leading to cellulitis and osteomyelitis. Other congenital neuropathies include distal hereditary motor neuropathies (dHMNS) that typically present with length dependent weakness and no sensory loss. Except for supportive treatment including orthotics, orthopedic interventions (e.g., for scoliosis, foot deformity), and pain management, there is no specific treatment to date.[37]

INFECTIOUS AND INFLAMMATORY CAUSES OF PERIPHERAL POLYNEUROPATHY

In developing countries, infectious neuropathies are very common. *Mycobacterium leprae*, although quite uncommon in North America and Europe, is among the leading cause. It usually affects the skin and nerves, but there also exists a pure neural leprosy in about 4% to 10%[40] of all leprosy cases. Symptoms are found primarily in the form of mononeuritis or mononeuritis multiplex.

Hepatitis C has also been linked to neuropathies, although here the clinical picture is varied, spanning from polyneuropathy to mononeuropathy (involving multiple or single nerves) to cranial neuropathy. Prevalence rates have been found as high as 10.6%. *Borrelia burgdorferi* has also rarely been associated with a chronic diffuse distal polyneuropathy, and is more common in North America than Europe.[38]

With the development and widespread use of highly active antiretroviral therapy (HAART) and the resulting decrease in opportunistic infections of the CNS, polyneuropathy has become the most prevalent neurologic complication associated with human immunodeficiency virus (HIV) infection.[39] Although symptomatic neuropathy occurs in 10% to 35% of those seropositive for HIV, pathologic abnormalities exist in almost all of those with end-stage AIDS.[40] There are numerous types of the HIV-associated neuropathy classified by onset, putative etiology, pathology of nerve damage, and motor or sensory involvement. The sensory neuropathies associated with HIV (HIV-SN) include distal sensory polyneuropathy (DSP) due to the viral infection and antiretroviral toxic neuropathy (ATN) due to the medical treatment of the viral illness. DSP represents the more common of the two disorders. Although these HIV-SNs may represent two distinct entities,[41] the clinical syndrome and pathophysiologic manifestation of the two disorders are practically indistinguishable. The time course of the illness and temporal relation to the commencement of anti-retroviral therapy represent the primary differentiating characteristics. The onset of DSP can occur in either the subacute or chronic phases, or following the development of an AIDS-defining illness. The clinical manifestation of ATN can appear within the first week to 6 months of the initiation of antiretroviral therapy and may subside after its cessation. The painful peripheral neuropathy results from both direct neuronal inflammatory injury to the nerve itself (DSP) and the treatment using HAARTs leading to mitochondrial dysfunction. The clinical features of HIV-SN are dominated by painful dysesthesia, allodynia, and hyperalgesia. Onset is often gradual and most commonly begins with bilateral lower extremity involvement. The neuropathy progresses in a length-dependent fashion with a worsening gradient of disease from distal structures to those more proximal. The dysesthesias commonly first involve the soles of the feet and progress proximally; when the symptoms encompass the dermatomes of the knee the patient will often report finger involvement. The first symptoms noted are often numbness or burning sensation following a diurnal cycle with the pain worse at night. Shortly thereafter, patients will report allodynia and hyperalgesia of the involved structures. As a result, wearing shoes and walking become painful and the patient's gait becomes antalgic. There is minimal subjective or objective motor involvement and it is generally limited to the intrinsic muscles of the foot. Physical examination shows a diminution or loss of ankle reflexes in addition to the sensory findings.

Reactivation of a latent infection of varicella zoster virus (human herpes virus-3) in the trigeminal ganglia or the dorsal root ganglia can result in facial or peripheral pain in the dermatomal distribution of the affected nerves. The resulting condition herpes zoster or "shingles" can be excruciatingly painful and can result in a chronic pain condition called postherpetic neuralgia (PHN). There are approximately 500,000 new cases per year of herpes zoster in the United States and 9% to 35% of these people gone on to develop PHN.[42] Advanced age, greater severity of the rash, and presence and severity of a painful prodrome preceding the rash are well-established risk factors for the development of PHN. The clinical presentation is most common in the thoracolumbar region, following a single or multiple dermatomes with a prodromal period followed by the eruption of a maculopapular vesicular rash. The pain is most often described as burning, stabbing, and/or throbbing and is commonly associated with cutaneous allodynia of the region. Primary prevention of herpes zoster and PHN was achieved in 51% and 66% of people who received the varicella vaccine.[43] Prevention of PHN in patients who had a herpes zoster reactivation was successful in those who received acyclovir. Patients who received amitriptyline within 90 days of rash onset had a reduced incidence of PHN from 35% to 16%.[44]

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) caused by Guillain-Barré syndrome (GBS) is characterized by areflexic and ascending motor paralysis with sensory paresthesias. It is often preceded by an infection, generally an upper respiratory tract infection or gastroenteritis. Most frequently, if an agent is identified, EBV, CMV, *Mycoplasma pneumoniae*, and *Campylobacter jejuni* are found, although vaccines and other viruses have been also associated with GBS.[45] Other rare etiologies include tumors and certain toxins.[46] The onset of symptoms develops over several days, or more frequently, weeks. Pain is a common early symptom; weakness, usually in the legs, may progress to respiratory failure requiring mechanical ventilation. Sensory symptoms include paresthesias often in the presence of decreased sensation in a glove-stocking distribution. Autonomic dysfunction is also commonly evidenced by tachycardia and orthostatic hypotension. Pain may occur in up to 80% of patients. The pain is principally an ache, strain, or deep burning sensation in the thigh or buttocks and can be quite severe. While pain in AIDP may be severe, it is usually transient. Pain is usually worse at night. Nerve conduction studies and lumbar puncture aid the diagnosis. General therapy for AIDP is supportive along with plasmapheresis and IVIG. Glucocorticoids and other immunosuppressants have not been clearly shown to be helpful.

IDIOPATHIC SMALL-FIBER NEUROPATHY

This condition usually presents with painful feet in patients over age 60. Although most often classified as idiopathic, autoimmune mechanisms are largely suspected in those cases. While diabetes and the metabolic/genetic causes above can cause small-fiber neuropathy, it can also be present in the absence of those conditions, and this state has been the subject of thorough review.[47] It can be defined as the presence of paresthesias (usually painful) with the absence of significant large-fiber dysfunction (atrophy, loss of vibratory sense, or loss of reflexes). Diagnosis is often confirmed through tests of autonomic function, quantitative sensory testing, or skin biopsy.

TREATMENT OF NEUROPATHIC PAIN

There has been substantial improvement and development of treatment options over the past decades for patients suffering from neuropathic pain (Table 55-4). A variety of medications are currently available to the clinician, and there has been a continued increase in randomized, double-blind, and placebo-controlled trials evaluating them. Nonetheless, the effectiveness of even the best of these medications is often highly variable, side effects are common, analgesic effects are delayed, and dosing is complicated. Treatment recommendations are continuously evolving to keep pace with the newest therapy options.[48] Additionally, although evidence for the efficacy of various agents as compared to placebo is increasing, there is a lack of studies comparing various agents against one another and assessing the utility of combination therapy. Furthermore, given the inconsistency and variability of most neuropathic conditions and the highly variable genomic contribution among patients, the conclusions from a study of one group of patients with neuropathy will likely not apply to another.

TABLE 55–4 Medications Used to Treat Neuropathic Pain Conditions

Drug	Start Dose	Maximum Dose	Documented Effect	Side Effects
Gabapentin	100–300 mg/day	3600 mg/day	PHN, PDN, HIV, mixed neuropathic pain	Sedation, dizziness, edema
Pregabalin	50–150 mg/day	300 mg/day, (600 mg/day fibromyalgia)	PHN, PDN, mixed neuropathic pain, fibromyalgia, central pain	Sedation, dizziness, edema
Tricyclic antidepressants	10–25 mg/day	50–150 mg/day	PHN, PDN, central pain, mixed neuropathic pain	Cardiac, anticholinergic, sedation
Nortriptyline				
Desipramine				
Trazadone				
Specific serotonergic and noradrenergic reuptake inhibitors	37.5 mg/day 20 mg/day	25–375 mg/day 60 mg/day	PHN, PDN, fibromyalgia	Sedation
Venlafaxine				
Duloxetine				
Carbamazepine	300 mg/day	1200–1800 mg (1/3 higher dose for oxcarbazepine)	Trigeminal neuralgia	Sedation, dizziness, ataxia, blood dyscrasias
Tramadol	50–150 mg/day	400 mg/day	PHN, PDN	Sedation, dizziness, seizure
Lamotrigine	25 mg/day	400–600 mg/day	Trigeminal neuralgia, poststroke central pain, HIV	Sedation, tremor, rash
Opioids	5–10 mg/day; titrate and substitute with long-acting opioids	Variable, 100–200 mg (OME)/day	PHN, PDN, post–amputation pain	Sedation, dizziness, tolerance, drug abuse, misuse
Lidocaine patch	5%	3 patches/day	PHN, traumatic nerve injury	Allergic reaction
Capsaicin cream	0.025% and 0.075%		PHN, PDN, HIV	

PHN, postherpetic neuralgia; PDN, peripheral diabetic neuropathy; HIV, human immunodeficiency virus; OME, oral morphine equivalents.

Diagnosing and assessing neuropathic pain can often be challenging as well. Given that it often coexists with other types of pain related to its etiology (e.g., musculoskeletal dysfunction, orthopedic deformities) and that it can produce psychological and psychiatric sequelae ranging from sleep disturbances, anxiety, to major depression and suicidal ideation, a multifactorial and often even multispecialty approach might be warranted. Clearly, some of the medications used to treat neuropathic pain might also bring symptomatic relief by alleviating co-factors, such as a tricyclic antidepressant for a patient suffering from neuropathic pain and depression.

One of the most thoroughly studied group of medications employed for the treatment of peripheral neuropathic pain are the antidepressants.[49] In this group, there are three major subgroups that have shown benefits in treatment: tricyclic antidepressants (TCAs), selected serotonin norepinephrine reuptake inhibitors (SNRIs), and selected serotonin reuptake inhibitors (SSRIs). There are no head-to-head studies to date concerning efficacy in peripheral neuropathy and neuropathic pain, but it appears that of these three groups, TCAs (amitriptyline, nortriptyline, desipramine, imipramine) are the best studied and most efficacious, followed by SNRIs (duloxetine, venlafaxine) and then SSRIs (citalopram, paroxetine).[50] The side effect profile of the TCAs, primarily anticholinergic effects, limits their widespread application, especially in patients with autonomic neuropathy, glaucoma, cardiac arrhythmias, and urinary hesitation.

Anticonvulsants are also used very frequently and successfully. Among these, gabapentin and pregabalin, structural analogs to gamma-aminobutyric acid (GABA), are considered first-line agents and are used in the treatment of a multitude of neuropathic pain syndromes including radiculopathy, CRPS Type I and II, diabetic neuropathy, postherpetic neuralgia, and mixed neuropathic pain conditions. In addition to having shown efficacy in numerous randomized controlled studies, they are generally well tolerated, with sedation, dizziness, GI complaints, and lower extremity edema among the more frequently noted side effects.[51] Other antiepileptics such as lamotrigine, lacosamide, and valproic acid have been shown to bring symptomatic relief such as in HIV neuropathy (lamotrigine), painful diabetic neuropathy (lacosamide), and postherpetic neuralgia (valproic acid), but these results were inconsistent and could not always be reproduced in subsequent studies. Levetiracetam, another anticonvulsant, has not been effective in the treatment of neuropathic pain.[52] Other oral medications that have shown beneficial effects, but are generally employed in refractory cases or as second-line agents, include opioids such as morphine or tramadol. Other treatment options that have shown improvement in neuropathic pain include topical agents such as lidocaine patches (postherpetic neuralgia, post-traumatic neuralgia) or in experimental studies, high-concentration (8%) capsaicin creams (HIV neuropathy, postherpetic neuralgia).[53]

In a recent randomized controlled trial, the combination of nortriptyline and gabapentin was found to be produce greater analgesia than either alone.[54] Importantly, these positive results were observed in patients receiving substantially lower dose of each medication than what is commonly used when they are administered as monotherapy. Patients receiving combination therapy received very good analgesia while experiencing dramatically fewer side effects than those in monotherapy groups. Although, as the authors report, they did not have the appropriate design to establish drug-drug synergism, their results are highly supportive of a synergistic analgesic response.

Sympatholytic agents have been proposed for both the diagnosis and treatment of peripheral neuropathic pain, based on the concept of expression of α-adrenoreceptors in damaged peripheral nerves. Analgesic response to intravenous phentolamine infusion may be predictive of response to regional sympathetic ganglion blockade[55]; however, this has fallen out of common practice due to high false-positive rates and placebo response. The α2-adrenergic agonist clonidine has been reported as a useful analgesic in treating neuropathic pain.[12]

Corticosteroids both systemically and by peripheral application have been used based on empirical response. When injected perineurally (but not systemically), corticosteroids reduce the spontaneous ectopic discharge rate seen in nerve injuries and neuromas, possibly by a membrane stabilizing effect. They also have been found to have a short-lasting suppressive effect on transmission in normal C-fibers, but more recent studies on peripheral nerve injury models in the rat confirm that local application of steroid on the area of injured nerve may produce an analgesic effect by suppression of peripheral ectopic sites.[56]

Historically, neuropathic pain has been considered "opioid resistant."[57] But in recent years, this notion has been challenged as more evidence emerges showing that opioids are potent treatment modalities for neuropathic pain. Studies have demonstrated that there is significant improvement in pain symptoms, either in monotherapy or in combination with other treatment options.[58] Perhaps they would even be considered first-line agents if their usefulness were not limited by the many concerns that are associated with their application. The addictive properties, the development of tolerance, the misuse and abuse, and the significant side effects including constipation and nausea appropriately decrease the routine use of these medications for neuropathic pain. Additionally, there have been concerns that with long-term management for neuropathic patients that these patients could develop hypogonadism, paradoxic hyperalgesia, and impairment of the immune system.[59]

Even with broad usage of the above-mentioned medications and treatment choices, there still remain a substantial number of patients—often cited to be greater than 50%—without significant relief of their neuropathic pain. In these circumstances, various alternative options exist, including sympathetic nerve blocks, neurolytic sympathetic blocks, spinal cord stimulation (SCS), deep brain stimulation (DBS), transcutaneous electrical nerve stimulation (TENS), and repetitive transcranial magnetic stimulation (rTMS). Because TENS and rTMS are noninvasive therapy options, the 2006 Task Force of the European Federation of Neurological Societies deemed them suitable as preliminary or add-on therapies.[60] Although more invasive options such as deep brain stimulation do show benefit, given the extent of intervention needed, this method still requires more research before it can be adopted on a larger scale.[61] The use of spinal

cord stimulation is well established in neuropathic pain conditions including postlaminectomy syndrome, CRPS Type I, and diabetic peripheral neuropathy.[62–65]

KEY POINTS

- Neuropathic pain arises from disorders of the peripheral nervous system. Although there are many etiologies of peripheral neuropathy, not all of which always produce pain, the most prominent and common is diabetic neuropathy.
- Many mechanisms have been proposed for the pain that occurs in peripheral neuropathic states. They can be categorized into peripheral and central. Peripheral mechanisms proposed include: formation of ectopic foci, formation of ephapses (unlikely), release of neuropeptides with neurogenic inflammation, and increased expression of α-adrenoreceptors.
- Central mechanisms of neuropathic pain proposed include: loss of large-fiber pain inhibition, downregulation of opioid and GABA receptors, reduction of GABA release, death of inhibitory interneurons, A-β fiber sprouting, A-β fiber phenotypic switching, and cholecystokinin upregulation.
- History and physical examination remain the mainstay in evaluating and following peripheral neuropathic pain. EMG provides evidence of large-fiber changes but rarely will alter therapeutic decisions, while QST may aid in diagnosing subtle aspects of peripheral neuropathy and allow monitoring for scientific study. Skin biopsy can be a useful diagnostic tool.
- Pain in diabetic neuropathy may have a strong central component, given that evidence supports a reduced sensory input in those patients suffering from pain. There are specific syndromes within the class of painful diabetic neuropathy that have profound components, which include rapid onset of symptoms, and significant motor components. It is important in painful diabetic neuropathy not to overlook the development of Charcot's joints, which can also be painful and progress to significant deformity if not addressed.
- The treatment of neuropathic pain typically involves the use of antidepressants, anticonvulsants, and sodium channel stabilizers. Nortriptyline, desipramine, duloxetine, gabapentin, and pregabalin are considered first-line agents and used in a multitude of neuropathic pain conditions. Opioids have been shown to be effective, but considering their side effect profile and potential for abuse and dependence, should be used cautiously. Sympathetic nerve blockade may also be useful in selected cases. Combination therapy of gabapentin and nortriptyline may represent a novel approach to the treatment of a wide range of neuropathic pain conditions.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 56

Entrapment Neuropathies

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There are a number of anatomic locations where nerves are vulnerable to compression or entrapment. The entrapment syndromes that result have been well described and are a common cause of pain. Table 56-1 lists major nerves, possible anatomic sites of entrapment (shown in Figs. 56-1 and 56-2), and resulting entrapment syndromes with eponyms. We review six of these syndromes in detail: carpal tunnel syndrome, ulnar neuropathy at the elbow, thoracic outlet syndrome, meralgia paresthetica, tarsal tunnel syndrome, and Morton's neuroma. We have chosen to concentrate on these six because they are both common and often present with complaints of pain. There are other common entrapment neuropathies that do not usually cause pain, such as peroneal palsy at the fibular head, and therefore we will not highlight those here.

Patterns of weakness and sensory loss can identify which nerves are injured and localize the site of injury. Provocative maneuvers, which briefly increase pressure at a site of compression, aid diagnosis by re-creating or exacerbating symptoms.

When an entrapment neuropathy is clinically suspected, electrodiagnostic testing should be performed to confirm the diagnosis and exclude other neurologic disorders. If electrodiagnostic testing suggests that the site of compression or entrapment is not typical, such as the median nerve compressed in the forearm rather than at the carpal tunnel, then magnetic resonance imaging or ultrasonagraphy should be performed to identify the source of compression. Imaging can miss smaller compressive lesions and, if clinically appropriate, surgical exploration may be necessary.

Diagnosis of one entrapment neuropathy does not exclude another. It is not uncommon for an individual to have two neuropathic lesions in the same limb involving the same nerves at different sites, such as carpal tunnel syndrome and cervical radiculopathy. This phenomenon is called a "double crush." Symptoms and signs can overlap. Electrodiagnostic testing can identify multiple lesions as well as comment on the severity of each. This aids in forming proper expectations for various treatment options. For example, paresthesia may persist after successful carpal tunnel release if a concomitant radiculopathy has yet to be treated.

Electrodiagnostic testing can also provide prognostic information. Electrodiagnostic testing can often differentiate myelin dysfunction from axon damage. When a compressive lesion causes only focal demyelination, the injury is called neurapraxic, and carries a better prognosis for quick and complete recovery. If axon loss has occurred, then recovery will be slower and perhaps incomplete.

CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome is the most common and most studied entrapment neuropathy. It may occur in as many as 1 in 1000 people in the general population, and even more frequently in high-risk groups.

PATHOLOGY

The median nerve can be compressed as it passes through the carpal tunnel. The tunnel is at the base of the hand. The carpal, or wrist bones, form the floor of the tunnel and the flexor retinaculum forms the roof. Nine flexor tendons also pass through the tunnel. Due to this crowded arrangement, any tenosynovial proliferation, fluid collection, or arthritic deformity can lead to carpal tunnel syndrome. Pressure in the tunnel increases several fold with wrist extension or flexion. In those with carpal tunnel syndrome, pressures can reach over 100 mmHg in flexion or extension, pressures high enough to impede flow to the arteries supplying the nerve, causing epineural ischemia. At somewhat lower pressures, venous return can be reduced, resulting in venous stasis and intraneural edema.

SYMPTOMS

Classically, patients report numbness on the palmar surface of the thumb and index, middle, and half of the ring finger. However, in practice, reports of numbness often involve only a portion of the median distribution, especially the middle or index finger. Patients are often not aware of the true distribution of numbness and may report that all five fingers are involved. However, if patients are specifically asked to observe which fingers are involved, they will observe that the fifth finger is spared.

Carpal tunnel syndrome can cause pain. The pain can be both distal and proximal to the site of compression. Patients can report pain in the hand, wrist, elbow, and shoulder. Carpal tunnel syndrome should be considered in any obscure complaint of pain in the arm.

Pain and numbness may increase when the wrist is flexed or extended. For this reason patients often report symptoms at night when they awake after sleeping with their wrists in flexion. Many patients will report needing to shake their hand on waking to relieve their numbness. This is sometimes called the "flick sign." Driving is another common situation in which the wrist may be in flexion for an extended period of time and provoke carpal tunnel syndrome symptoms.

Patients usually do not complain of weakness. They may report dropping things or having difficulty with certain motor activities like doing up buttons or opening a jar. These complaints are probably the result of a combination of mild thenar weakness and sensory loss.

PHYSICAL FINDINGS

The median nerve after it exits the carpal tunnel supplies sensation to the palmar surface of the thumb and index, middle, and half the ring finger. It also supplies the dorsal tips of these same fingers. The palmar branch of the median nerve, which supplies sensation to the proximal portion of

TABLE 56–1 Major Nerves, Possible Sites of Entrapment, and Resulting Entrapment Syndromes with Eponyms

Nerve	Site of Entrapment	Syndrome
Upper Extremity		
Brachial plexus	Anterior and medial scalene muscle	Anterior scalene syndrome
	Subclavius muscle	Costoclavicular syndrome
	Pectoralis minor and coracoid process	Hyperabduction syndrome
	Cervical rib or band, medial antebrachial cutaneous nerve	Thoracic outlet syndrome
Long thoracic		"Rucksack" palsy
Suprascapular	Transverse scapular ligament, scapular notch or foramen	
	Spinoglenoid ligament or notch	
Musculocutaneous	Coracobrachialis muscle	
	Brachial fascia, lateral antebrachial cutaneous nerve	
Axillary	Quadrangular foramen or lateral axillary hiatus (long head of triceps, teres major and minor)	Quadrilateral space syndrome
Radial	Lateral intermuscular septum	"Saturday night" palsy, "honeymooners'" palsy
	Arcade of Frohse (supinator), leash of Henry (brachioradialis, extensor carpi radialis brevis), Monteggia lesion	Supinator syndrome, posterior interosseous syndrome, radial tunnel syndrome, tardy radial palsy, "tennis elbow," "frisbee flinging"
	Superficial branch	Cheiralgia paresthetica, Wartenberg's disease, "hand-cuff" or "wristwatch" neuropathy
Median	Ligament of Struthers (supracondylar process: medial epicondyle)	
	Pronator teres muscle, sublimis bridge (flexor digitorum sublimis), lacertus fibrosis	Pronator syndrome, flexor digitorum sublimis syndrome
	Gantzer's muscle (flexor pollicis longus)	Anterior interosseous syndrome, Kiloh-Nevin syndrome
	Transverse carpal ligament	Carpal tunnel syndrome
	Transverse metacarpal ligament	Intermetacarpal tunnel syndrome, "bowlers' thumb"
Ulnar	Arcade of Struthers (internal brachial ligament, medial head of triceps, medial intermuscular septum)	
	Epicondylo-olecranon ligament, cubital tunnel retinaculum, arcuate ligament of Osborne	Cubital tunnel syndrome
	Humeroulnar aponeurosis (flexor carpi ulnaris)	"Tardy" ulnar palsy
	Deep flexor-pronator aponeurosis	
	Guyon's canal (piso-hamate ligament, volar and transverse carpal ligament)	Ulnar tunnel syndrome, "cyclists'" palsy (Radfahrerlahung)
	Deep branch	Piso-hamate hiatus syndrome
	Transverse and oblique heads of adductor pollicis	
Lower Extremity		
T2–6 posterior rami		Notalgia paresthetica
L5 spinal	Iliolumbar ligament (fifth lumbar: wing of the ilium)	Lumbosacral tunnel syndrome
Ilioinguinal	Transverse abdominis muscle	
Genitofemoral	Inguinal canal	
Lateral femoral cutaneous	Inguinal ligament at anterior superior iliac spine	Meralgia paresthetica, Roth's meralgy, Bernhardt's syndrome
Femoral	Iliopectineal arch	Iliacus tunnel syndrome
	Hunter's canal (vastus medialis, adductor longus, sartorius), subsartorial canal	
	Infrapatellar branch of saphenous nerve	Gonyalgia paresthetica, "housemaids' knee"
Obturator	Obturator canal	Howship–Romberg syndrome
Sciatic	Pyriformis muscle	Pyriformis syndrome
	Greater and lesser sciatic foramens, sciatic notch, Gibraltar of the gluteus	
Common peroneal	Fibular neck, peroneus longus muscle	"Cross leg" palsy
	Crural fascia, superficial branch	
	Inferior external retinaculum (ligamentum cruciforme)	(Anterior) tarsal tunnel syndrome

(Continued)

TABLE 56–1 Major Nerves, Possible Sites of Entrapment, and Resulting Entrapment Syndromes with Eponyms—cont'd

Nerve	Site of Entrapment	Syndrome
Posterior tibial	Canal calcaneen de Richet (ligamentum laciniatum)	(Posterior) tarsal tunnel syndrome
	Medial plantar nerve	"Joggers' foot," abductor hallucis tunnel syndrome
	Medial plantar proper digital nerve	Joplin's neuroma
	Transverse metatarsal ligament	Morton's neuroma (metatarsalgia)

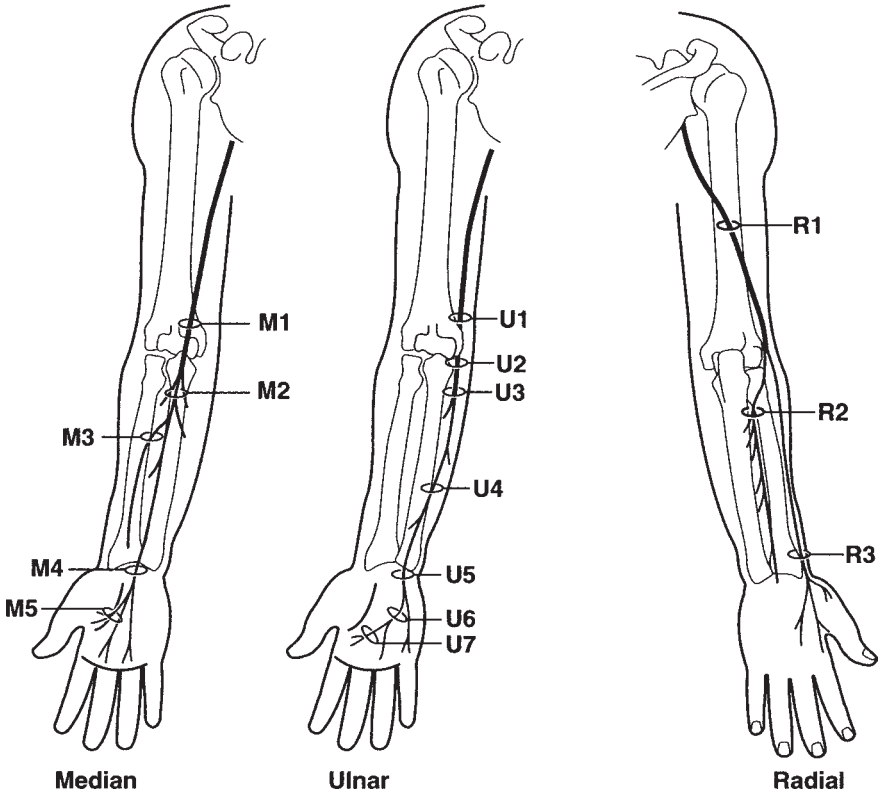

FIGURE 56-1 Sites of possible entrapments of the median, ulnar, and radial nerves (see Table 56-1 for details).

the palm and thenar eminence, does not go through the carpal tunnel, and is therefore spared in carpal tunnel syndrome. Two-point discrimination and pinprick testing will often elicit sensory deficits in parts of the median sensory territory. Often these deficits are only noted when direct comparisons are made with the unaffected hand.

The median nerve after exiting the carpal tunnel innervates a number of intrinsic hand muscles. Those of the thenar eminence, especially the abductor pollicis brevis, are the easiest to test. To test the strength of the abductor pollicis brevis, the patient should place the thumb perpendicular to the plane of the hand and then resist as the examiner attempts to push the thumb into the plane of the hand. In most patients, weakness will only be appreciated when compared to the unaffected hand or to the flexor pollicis longus muscle of the affected side.

Symptoms can also be provoked by transiently increasing the pressure in the carpal tunnel. Phalen's maneuver increases pressure by putting the patient's wrist in hyperextension or hyperflexion. Most patients with carpal tunnel syndrome will report numbness, tingling, or pain within 60 sec of the wrist being placed in extension or flexion. Tinel's sign involves tapping over the carpal tunnel to elicit brief symptoms. It should be noted that brief symptoms can be elicited in anyone if the tapping is vigorous enough.

ELECTRODIAGNOSIS

Electrodiagnostic testing is very sensitive for confirming a diagnosis of carpal tunnel syndrome. Some studies report sensitivity as high as 95%. The hallmark of electrodiagnosis is a delay in the distal latency of median nerve conduction. This suggests a conduction delay through the carpal tunnel. Electrodiagnosis is also useful to rule out other disorders with similar symptoms, such as cervical radiculopathy, thoracic outlet syndrome, and diffuse peripheral neuropathy.

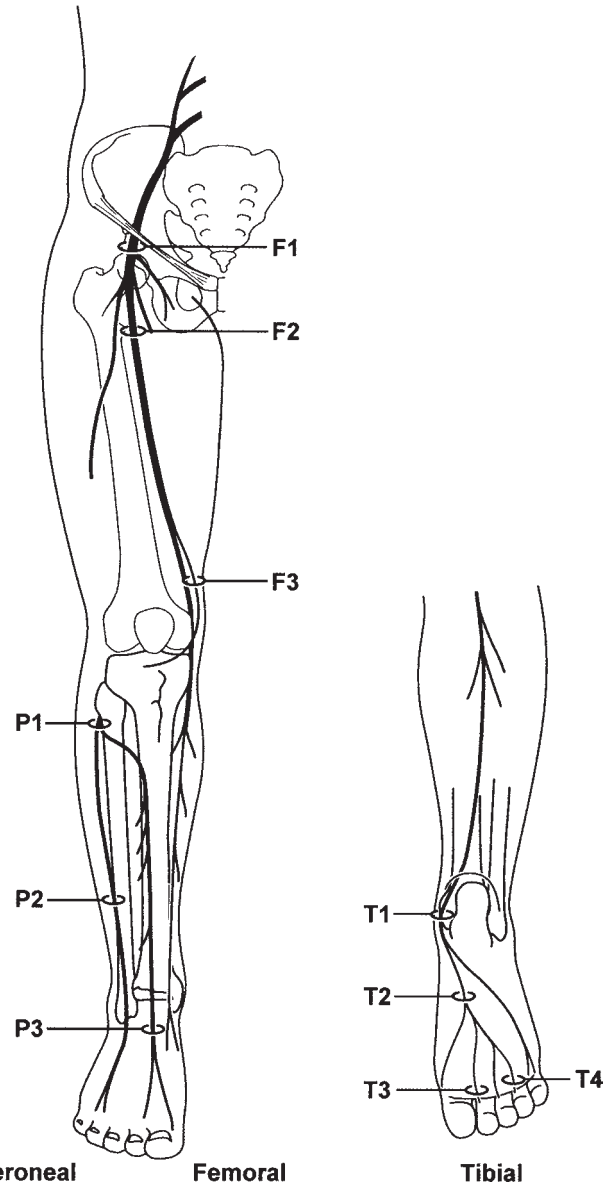

FIGURE 56-2 Sites of possible entrapments of the peroneal, femoral, and tibial nerves (see Table 56-1 for details).

TREATMENT

The first line of treatment for carpal tunnel syndrome is splinting to maintain the wrist in a neutral position and thereby minimize the pressure in the carpal tunnel. Splints should be worn both day and night. Anti-inflammatory treatments including steroid injection benefit some select patients. Should conservative measures fail, then surgical decompression is indicated.

RISK FACTORS

Carpal tunnel syndrome is well known as one of the repetitive stress injuries that occur with computer use. Indeed any occupation that requires repeated flexion and extension at the wrist can put an individual at risk for carpal tunnel syndrome. Other risk factors include obesity, arthritis, diabetes, and hypothyroidism.

The shape of the wrist can also be a risk factor for carpal tunnel syndrome. Square wrists, that is, those whose dorsal-volar distance is close to the medial-lateral distance with a ratio greater than 0.7 are at increased risk for developing carpal tunnel syndrome. Perhaps this is why carpal tunnel syndrome is often present in both hands. This may also be why many patients have a positive family history for carpal tunnel syndrome.

ULNAR NEUROPATHY AT THE ELBOW

Ulnar nerve entrapment at the elbow is the second most common neuropathy in the upper extremity. Entrapment can occur either at the ulnar groove or at the cubital tunnel. Terminology can be confusing as some refer to all lesions of the ulnar nerve near the elbow, even those at the ulnar groove, as cubital tunnel syndrome.

PATHOLOGY

The ulnar nerve is particularly vulnerable to compression or stretch as it crosses the elbow and passes through the cubital tunnel. Compression or impingement of the nerve can occur by a number of mechanisms and it can occur anywhere over several centimeters across the ulnar groove into the cubital tunnel.

The ulnar groove is formed by the medial epicondyle and the olecranon process. The ulnar nerve runs through this groove as it crosses the elbow. The groove is easily palpable when the arm is extended at the elbow. As the elbow is bent, the groove disappears and the ulnar nerve is relatively superficial. Chronic leaning on a bent elbow can compress the ulnar nerve. An acute blow to a bent elbow can compromise the ulnar nerve, as most people have experienced when they "hit their funny bone." The nerve is also vulnerable to impingement if there is a bony deformity or scar formation. Patients with a remote history of supracondylar fracture can develop such a bony deformity and nerve impringement in what has been called "tardy ulnar palsy." In some individuals, when flexing the elbow, the ulnar nerve can sublux out of the ulnar groove medially over the medial epicondyle, where it will be more susceptible to trauma.

Just distal to the elbow, as the ulnar nerve leaves the ulnar groove, it travels under a ligamentous band that stretches from the medial epicondyle to the olecranon of the ulna and then blends into the aponeurosis of the two heads of flexor carpi ulnaris muscle. This humeroulnar aponeurotic arcade or cubital tunnel can be from 0.5 centimeter to 2 centimeters distal to the medial epicondyle, or end of the ulnar groove. Pressure in the cubital tunnel can increase as the elbow is flexed.

SYMPTOMS

Intermittent numbness and tingling in the distribution of the ulnar nerve is usually the first symptom of ulnar palsy. Patients can wake up with elbow pain radiating into the fifth digit. There can be cramping and aching in the hypothenar eminence. Symptoms can be exacerbated by flexion of the elbow. Patients may complain about a generalized loss of strength in the hand or loss of dexterity.

PHYSICAL FINDINGS

The ulnar nerve supplies sensory fibers to the fifth finger, both palmar and dorsal surfaces, and usually half of the ring finger. Sensory deficits that split the ring finger are classic for an ulnar nerve injury. However, in some individuals the ulnar nerve may supply the whole ring finger and even part of the long finger. In these individuals it may be difficult to distinguish ulnar sensory loss from that of a C8 root lesion. Light touch and two-point discrimination are often more sensitive for detecting ulnar sensory deficits than pinprick or temperature testing.

The ulnar sensory territory ends proximally at about the wrist crease. The ulnar half of the forearm is supplied by the medial antebrachial cutaneous nerve, a branch of the brachial plexus. This area should not be involved in ulnar lesions at the elbow.

Ulnar injury can weaken grasp and pinch strength. However, the easiest muscles to test directly are the first dorsal interosseous and the abductor digiti minimi. The hands are placed on a flat surface and the patient is asked to spread the fingers apart and resist the examiner's attempt to bring the fingers closer together. Atrophy of the hypothenar eminence and the first dorsal interosseous can often be seen. Clawing of the ring and little finger is common in chronic cases.

Palpation of the ulnar groove and over the cubital tunnel can often elicit tenderness and help to localize the ulnar lesion. Flexion of the elbow beyond 90 degrees can often provoke sensory complaints or pain.

ELECTRODIAGNOSIS

Electrodiagnostic testing is necessary to confirm a diagnosis and to exclude other causes including brachial plexopathy, cervical radiculopathy, and an ulnar entrapment at the wrist. Nerve conduction studies will usually show slowing across the elbow and sometimes a drop in response amplitude across the elbow. Inching techniques can sometimes localize the site of compression to the ulnar groove or the cubital tunnel.

TREATMENT

Mild cases of ulnar palsy at the elbow can be successfully treated with an elbow pad to reduce trauma to the nerve or by avoiding prolonged flexion at the elbow. More severe cases may require surgery. The precise site of entrapment will determine the surgical procedure, which can include transposition of the nerve, decompression at the aponeurosis, or even medial epicondylectomy.

RISK FACTORS

Resting a bent elbow on a hard surface is a behavior that can provoke ulnar palsy. For example, truck drivers can develop a left ulnar palsy from resting their elbow on the window of the truck while driving. Long-distance airline passengers have developed palsies from resting on an armrest. Those confined to bed can develop ulnar palsy when sitting up and resting on their elbows. Direct trauma including elbow fractures can cause acute ulnar nerve injury. Delayed or tardy ulnar palsies can result from bony deformities that develop after trauma or fracture.

THORACIC OUTLET SYNDROMES

There are many structures that can compress or impinge the brachial plexus as it enters the arm. Vascular structures can also be compressed in the same way. Various positions of the shoulder can also compromise both vascular and neural structures in the thoracic outlet. This has led to much confusion and disagreement concerning what is called thoracic outlet syndrome. In our opinion, it may be better to consider the thoracic outlet as being the site of several syndromes, vascular, neurogenic, and positional, that are not mutually exclusive.

PATHOLOGY

Various structures in the thoracic outlet can be the source of compression or impingement. A cervical rib is the most discussed source of compromise in thoracic outlet syndrome, but this may be because it is easily identified by x-ray, where as other structures are not as easily imaged. An anomalous fibrous band from the transverse process of the last cervical vertebra to the first rib is a common cause of impingement. Entrapments by the scalenes, subclavius, and pectoralis minor muscles have all been reported. Hyperextension injuries of the neck can lead to intrascalene muscle hemorrhage and swelling with resultant scar formation in the muscle or around the brachial plexus. Most commonly in neurogenic thoracic outlet syndrome the lower trunk of the brachial plexus is most involved. Vascular syndromes usually involve compromise of the axillary and subclavian vessels. Flow studies can be useful to confirm a vascular component and better localize the site of compression.

SYMPTOMS

The symptoms of thoracic outlet syndromes depend on whether they are primarily arterial, venous, or neurologic and can vary with shoulder position.

In the arterial form, symptoms are ischemic in nature and include pain, paresthesias, coldness, and color change. Some patients complain of fatigue and soreness in the arm. Venous symptoms can include swelling, and cyanosis, as well as pain and paresthesias.

Initial neurologic symptoms often include numbness of the medial forearm and ulnar side of the hand. This can be followed by an aching pain, poorly localized in the arm and anterior chest. Later patients may complain of clumsiness or weakness in the hand and fingers. Atrophy of both the thenar and hypothenar eminences can be seen.

Anterior flexion of the shoulders can elicit symptoms. For this reason some patients who sleep on their side may wake up with symptoms that resolve on repositioning. Abduction and supination of the arm can also elicit symptoms. Certain activities that affect shoulder position can exacerbate the symptoms, such as carrying a heavy briefcase, combing one's hair, or using a mouse.

PHYSICAL FINDINGS

True neurogenic thoracic outlet syndrome usually affects the lower trunk of the brachial plexus first, which results in sensory deficits on the ulnar side of the hand with weakness and atrophy of the thenar eminence. As the syndrome progresses, sensory loss can involve all five fingers. True neurogenic thoracic outlet syndrome initially causes weakness of median innervated hand muscles and later ulnar innervated muscles. Atrophy of both thenar and hypothenar eminences can occur.

Vascular compression alone usually does not cause loss of strength, but arm and hand muscles may fatigue with use. Vascular compression can cause diffuse but usually only subjective sensory deficits. Swelling, color changes, and temperature differences can all be seen.

Provocative tests can often elicit symptoms. Adson's maneuver involves extending the arm at shoulder height to the side and supinating the hand. The manuever can elicit both signs, that is, loss of radial pulse, and an increase in sensory symptoms. The Elvey maneuver stresses the brachial plexus by again extending the arm to the side and then tilting the head to the opposite side. This maneuver stretches the plexus on the side of the extended arm and in neurogenic thoracic outlet syndrome will provoke symptoms on that same side. It should be noted that the diagnostic value of such provocative tests is limited by their poor sensitivity and specificity. For example, even some healthy normals can lose their radial pulse during Adson's maneuver.

ELECTRODIAGNOSIS

Early neurogenic thoracic outlet syndrome often presents with a normal electrodiagnostic study. One of the first electrodiagnostic abnormalities seen is a reduction in the amplitude of the medial antebrachial cutaneous sensory response. Later ulnar sensory responses in the hand will be diminished. Late responses such as F-waves will become prolonged and conductions across the plexus will be slowed as plexopathy progresses. Needle examination may elicit denervation changes in both median and ulnar innervated hand muscles in advanced cases.

TREATMENT

Correction of shoulder posture can improve if not completely eliminate the symptoms of thoracic outlet syndrome in many cases. Exercises that strengthen the rhomboid and trapezius muscles can improve shoulder posture. Clavicle straps can help maintain correct shoulder posture.

Surgery to open the thoracic outlet was popular during the last century, but its efficacy is controversial. There are indeed certain patients who improve with surgery, but selection of appropriate surgical candidates can be difficult. The most common surgical procedures are resection of cervical rib and fibrous band, and scalenectomies. Both procedures carry significant morbidity.

The injection of botulinum toxin into the scalene muscles has been shown to be effective in some cases of thoracic outlet syndrome. Other muscles, including subclavius, pectoralis minor, trapezius, and levator scapula also have been injected with good results in some patients. Potential complications of botulinum toxin injections in this area include dysphagia, dysphonia, and muscle weakness.

RISK FACTORS

Activities that promote poor shoulder posture can provoke thoracic outlet syndrome. This is seen in professional musicians who play string instruments, nursing mothers, and computer users, especially on the side that operates the mouse. Bony deformities from clavicular fracture, cervical ribs, and sloped shoulders all predispose one to thoracic outlet syndrome. Recent trauma to the shoulder or neck, even without fracture, can predispose a patient to thoracic outlet syndrome.

MERALGIA PARESTHETICA

Entrapment of the lateral femoral cutaneous nerve of the thigh has been well described for over 100 years. It is often called *meralgia* from the Greek *meros* meaning "thigh" and *algo* meaning "pain."

PATHOLOGY

The lateral femoral cutaneous nerve of the thigh arises from upper lumbar roots, travels through the pelvis, and exits into the leg at the upper lateral end of the inguinal ligament. The nerve is usually trapped as it passes under or through the inguinal ligament. Blunt trauma to this area can cause damage to the nerve. More chronic episodic external compression from tight-fitting clothes, a holster, or tool belt can provoke meralgia. However, entrapment most often is related to increased intra-abdominal pressure from weight gain or pregnancy. Mass lesions, including lipomas and fibroids, have been reported in some cases.

SYMPTOMS

Patients complain of unpleasant sensations and numbness in the lateral thigh. Light touch in the area can be unpleasant. Even clothing or touching the area can be unpleasant. Walking, standing, or lying flat can sometimes exacerbate symptoms.

PHYSICAL FINDINGS

The lateral femoral cutaneous nerve is a purely sensory nerve that supplies just the lateral thigh. Therefore, findings are completely sensory. Sensory loss can be identified in a portion of the distribution of the nerve, usually the area that the hand touches when it's in the pants pocket. Should sensory deficits be found outside of this distribution or if there are any motor findings, then other diagnoses should be considered.

ELECTRODIAGNOSIS

It can be technically difficult to elicit sensory responses from the lateral femoral cutaneous nerve in normal individuals. This makes interpretation of a lost

or diminished response suspect. Electrodiagnosis is better suited to ruling out other possible diagnoses such as lumbar radiculopathy.

TREATMENT

Pain control with medication is the standard treatment. Reduction of risk factors, such as weight loss or looser clothing, can be beneficial. Symptoms resolve within 6 months for the vast majority of patients using only these conservative measures. Nerve blocks have been successful in some cases. There are also some reports of successful treatment with pulsed radiofrequency. The utility of surgical intervention remains limited.

RISK FACTORS

Obesity, pregnancy, diabetes, and tight-fitting clothes all increase the risk for meralgia paresthetica. Pelvic osteotomy and use of stabilization devices during spine surgery have also put people at greater risk for meralgia.

TARSAL TUNNEL SYNDROME

The term *tarsal tunnel syndrome* is typically used to describe entrapment of the posterior tibial nerve at the medial ankle. However, some people also use the term to describe entrapment of the peroneal nerve as it enters the foot anteriorly.

PATHOLOGY

The tarsal tunnel is formed by the ankle bones and the flexor retinaculum. Through the tunnel passes the posterior tibial nerve, tendons of the foot and toe flexors, and the posterior tibial artery. Increased pressure in the tunnel brings on the syndrome. This can occur from an ankle fracture or sprain, arthritic changes, tenosynovitis, or fluid collection. Mass lesions in the tarsal tunnel like ganglion cysts or convoluted blood vessels, can also lead to compression of the posterior tibial nerve.

SYMPTOMS

The primary complaint is foot pain, often described as burning. Many patients will isolate the burning to the sole of the foot. Painful numbness will often disturb sleep. Walking and standing can exacerbate symptoms.

PHYSICAL FINDINGS

The posterior tibial nerve has three branches: calcaneal, medial plantar, and lateral plantar. Not all the branches may be affected, so some or all of the sole of the foot may lose sensation. Intrinsic foot muscles primarily toe flexors and abductors, can be affected but clinical testing of these muscles can be difficult. Motor findings, including weakness and atrophy, are therefore usually evident only late in tarsal tunnel syndrome. Pressure over the affected tarsal tunnel is usually painful. Eversion and dorsiflexion can also provoke symptoms.

ELECTRODIAGNOSIS

Nerve conduction studies can reveal both motor and sensory slowing through the tarsal tunnel. The syndrome is usually unilateral so comparisons with the unaffected side make electrodiagnosis easier. Needle examination of intrinsic foot muscles can be misleading. Some 10% to 20% of normal intrinsic foot muscles may demonstrate denervation changes, that is, fibrillations and positive waves, as a result of direct muscle trauma from walking.

TREATMENT

Anti-inflammatory medication can be useful in certain cases in which tenosynovitis or arthritis is suspected. Surgical decompression is highly effective.

RISK FACTORS

Ankle trauma even if remote is common in tarsal tunnel syndrome. Rheumatoid arthritis and diabetes mellitus both increase the risk for tarsal tunnel syndrome.

INTERDIGITAL NEUROPATHY (MORTON'S NEUROMA)

Pressure on an interdigital nerve in one of the intermetatarsal spaces can cause pain and numbness in the distal foot and toes. This was described by Morton in the 19th century and may be the first entrapment neuropathy to be described.

PATHOLOGY

The interdigital nerves are distal branches of the lateral and medial plantars. These distal nerves are vulnerable to chronic pressure and trauma between the metatarsal heads, against the transverse metacarpal ligament. At times, an actual scar, or neuroma, will form. This most commonly occurs between the third and fourth metatarsal heads but can involve other interdigital nerves.

SYMPTOMS

The primary complaint is burning pain in the ball of the foot that radiates to one or two toes. The corresponding toes may feel numb. Pain will be worse with weight bearing.

PHYSICAL FINDINGS

Pain can be elicited by pushing on the ball of the foot over the affected interdigital nerve. At times altered sensation can be demonstrated on the adjoining sides of the affected toes, though this can often be difficult or nonreproducible. A neuroma can often be visualized with magnetic resonance imaging or ultrasound.

ELECTRODIAGNOSIS

Electrophysiologic studies of the interdigital nerves are difficult and often unreliable. Both orthodromic and antidromic sensory or mixed nerve studies using both surface

electrodes and near-needle electrodes have been described, but none are routinely performed. However, electrodiagnosis is very useful for excluding other neuropathologies that also manifest with foot pain and numbness, in particular tarsal tunnel syndrome, lumbosacral radiculopathy, and generalized peripheral neuropathy.

TREATMENT

Conservative measures including physical therapy, orthotics, and avoiding offending footwear are often successful. Interdigital anesthetic nerve blocks, often with corticosteroids, have been effective in some patients. A variety of surgical interventions have been used, all with some success. Morton himself in the late 19th century advocated removal of the metatarsal head, which had a surprisingly good success rate for the time. Now neurolysis of the interdigital nerve or removal of the neuroma (neurectomy) are the most common surgical options. The larger the neuroma, especially if it is greater than 5 mm across, the more likely neurectomy is to be successful. Surgical risks include permanent loss of sensation and recurrent neuroma.

RISK FACTORS

Activities that increase trauma to the foot can all increase one's risk for interdigital neuropathy. Ill-fitting shoes, especially high heels, also predispose one to develop Morton's neuroma.

KEY POINTS

- When an entrapment neuropathy is clinically suspected, electrodiagnostic testing should be performed to confirm the diagnosis and exclude other neurologic diseases including "double crushes."
- Pressure in the carpal tunnel increases with flexion and extension of the wrist, often provoking symptoms.
- The ulnar nerve is most vulnerable to impingement at the humeroulnar aponeurotic arcade, also called the cubital tunnel, or just a few centimeters proximally across the ulnar groove.
- The thoracic outlet is the site of several syndromes, including vascular, neurogenic, and positional, which are not mutually exclusive.
- Mapping the sensory deficit to the territory of the lateral femoral cutaneous nerve is diagnostic of meralgia paresthetica.
- The diagnostic value of the provocative tests such as Adson's maneuver and Tinel's sign is controversial because of poor specificity.
- There are two types of tarsal tunnel syndrome: entrapment of the deep peroneal nerve at the ankle (anterior) and tibial nerve at the ankle (posterior). The latter is the more common entrapment.

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CHAPTER 57

Chronic Pain Management in Children and Adolescents

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Chronic pain in children is an undertreated entity and happens to be ignored in most cases. A recent survey of Chicago middle schools demonstrated the presence of headaches in a large percentage of all school children.[1] This chapter will address the assessment of pain in children and common pain syndromes in children along with their diagnosis and management.

ASSESSMENT OF PAIN

The assessment of pain in children and adolescents is a complex clinical endeavor that ideally involves a multidisciplinary approach specifically tailored to the biomedical, psychological, and social elements of each patient and family. Hence, the measurement of pediatric pain conventionally falls into three common categories: (1) patient self-report; (2) healthcare provider or parent observational scores; and (3) physiological parameters.[2] The Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT) working group (http://www.immpact.org) formulated recommendations for core outcome domains and measures that should be considered by investigators conducting clinical trials for pediatric acute and chronic pain. The FACES Pain Scale-Revised (FPS-R) and the visual analogue score seemed to have greater validity in recording and reporting chronic pain in children.[2]

The Varni-Thompson Pediatric Pain Questionnaire (PPQ)[3] is a patient self-report instrument that is age-specific for a young child (5–7 years), a child (8–12 years), or an adolescent (13–18 years). The PPQ is a valid and reliable tool for measuring pediatric self-reported chronic pain intensity in children as young as 5 years old.[4]

ASSESSMENT OF FUNCTIONAL IMPAIRMENT

Recurring episodic or persistent chronic pain frequently has a major adverse effect on the daily lives of children and adolescents.[5] Our main goal is to increase the functional ability of the child and adolescent and to improve their participation in common daily activities. Common tools used with children are the functional disability inventory and the child activity limitation questionnaire.

The *Functional Disability Inventory (FDI)* was originally developed by Walker and Greene (1991)[6] to assess illness-related activity limitations in children and adolescents with a variety of chronic medical conditions. The patient self-report FDI consists of 15 items addressing physical and psychosocial functioning, including common activities, such as playing with friends, during the previous two weeks.[6] The FDI has been widely applied to assess functional impairment in pediatric patients suffering from chronic pain.

Pediatric Quality of Life Inventory (PedsQL™) (http://www.pedsql.org) is a tool aimed at recognizing clinical outcomes, including pain intensity, health-related quality of life, impact of the health-related condition on the family, and parents' satisfaction with the treatment. This has been used successfully for the treatment of childhood migraine.[7]

QUANTITATIVE SENSORY TESTING

Quantitative sudomotor axon reflex test (QST) is a noninvasive computer-based method to assess transmission of thermal sensation through A-delta fibers and unmyelinated C fibers, as well as vibration sensation transmitted by A-beta fibers.[8] QST values were reported in pediatric patients with CRPS type 1, and when compared to normal controls did not demonstrate a significant difference except for temperature detection thresholds.[9] Therefore this assessment, although frequently used in adult medicine, may not be a reliable marker for child and adolescent pain assessment.

MULTIDISCIPLINARY PAIN CLINICS

The introduction of multidisciplinary pain clinics for managing pain in children has allowed children to be seen in a single office visit by a number of consultants who are able to provide the service for the child and come up with a comprehensive plan for their management. Our clinic composition includes an anesthesiologist specialized in pain management, child psychologist with a special interest in pain, physical therapist, complementary medicine including massage therapy and acupuncture therapy, as well as biofeedback. The comprehensive approach has allowed our patients to get better care with the least amount of disruption to their lives.

Common chronic pain diagnoses in children include CRPS type 1, headaches, abdominal pain, chest wall pain, back pain, and cancer pain (Table 57-1). We will address each one of these conditions with specific emphasis on the accepted current therapy.

COMPLEX REGIONAL PAIN SYNDROME (CRPS)

CRPS type 1, or reflex sympathetic dystrophy as it was originally called, is a complex syndrome consisting of pain, allodynia, hyperalgesia, and potential loss of function. Although considered rare, it is a fairly common referral to a pediatric pain clinic. It is seen more commonly in the lower extremity, and in females more than in males.[10]

TABLE 57–1 Common Chronic Pain Syndromes

Headaches
CRPS type 1
Abdominal pain
Chest pain
Pelvic pain
Back pain
Cancer-related pain

Most of these children usually have sustained a mild injury. There are three distinct presentations based on their time course: (i) an acute phase where the limb may be swollen and painful; (ii) a dystrophic phase where the limb may have decreased blood supply with potential vasomotor and sudomotor changes including loss of hair and color changes; and (iii) an atrophic phase where the limb may atrophy and have loss of muscle mass. The pain in CRPS may be sympathetically independent or sympathetically mediated. The main focus of the treatment and management is to improve function and to get the child back to his or her normal daily activities. In addition, other psychological co-morbidities including depression and anxiety may be overriding the diagnosis of CRPS.

DIAGNOSIS AND MANAGEMENT

The diagnosis is made by physical examination. The presence of allodynia and hyperalgesia along with other symptoms including weakness and muscle atrophy are similar to the adult with CRPS type 1. Quantitative sensory testing (QST) is not reliable for the diagnosis of CRPS.[9] Bone scintigraphy has been used for recognizing and diagnosing CRPS; however, this is not very sensitive and, although performed in several centers, is not a gold standard for the diagnosis of CRPS.[11] Sympathetic blocks have been used for the diagnosis and management of CRPS type 1.

The management of CRPS is to provide ample physical therapy; this has been shown to provide the maximum benefit to children and adolescents with CRPS type 1. Management techniques are performed to facilitate physical therapy. In addition, complementary medicine has been used as an adjuvant to provide physical therapy (Fig. 57-1). Pharmacotherapy is used in addition for pain relief. Cognitive behavioral therapy is one of the mainstays in the management of CRPS in children. A variety of different techniques have been introduced with successful therapy provided toward functional improvement. Multiple psychological interventions have been used for the management of pain including visual guided imagery, hypnosis, relaxation therapy, and biofeedback therapy.[12,13] Physical therapy is aimed towards adequate functional ability of the child. Active and passive physical therapy methods, including the use of magnet and temperature modulated physical therapy is provided. Transcutaneous electric nerve stimulation (TENS) is used extensively in children with CRPS as a first modality for providing pain relief following initial injury or diagnosis of CRPS.[14,15]

Pharmacological Therapy

Tricyclic antidepressants are used initially for the management of pain.[16] A screening ECG is obtained to determine if there is a prolongation of the QT interval.[17] Amitriptyline may result in sedation and hence it is our practice to use nortriptyline, which seems to have less sedative and anticholinergic side effects. It is uncommon to see the use of imipramine or desimipramine in a pain center used solely for the purpose of pain relief.

Anticonvulsant drugs have been used for several years for the management of neuropathic pain. Carbamazepine and oxcarbazepine have been used extensively for neuropathic pain.[18,19] However, the introduction of gabapentin and more recently the introduction of pregabalin have revolutionized the world of pain medicine.[20] There are no controlled trials in children to demonstrate the efficacy of either drug but the voltage gated calcium channel blockers seem to have an effect to decrease pain effectively. More controlled trials have to be conducted to determine the dosing as well as the efficacy of this class of drugs in children with CRPS. One of the important side effects that we have noted in our clinic setting is the potential for increased somnolence as well as a potential for gaining weight. This has to be taken into consideration especially while treating adolescent females who happen to be the majority of this cohort.

Although there is no proven efficacy of the use of selective serotonin reuptake inhibitors (SSRIs) in the management of pain in children and adolescents, they are used to treat psychological co-morbidities including depression associated with pain.[21] More recently, the introduction of SNRIs has allowed this class to be used for neuropathic pain with reasonable relief especially when combined with psychological co-morbidities.[22]

Regional anesthesia although used extensively in adults for the diagnosis and management of CRPS is usually introduced in children after all cognitive behavioral management has been exhausted. Sometimes, regional anesthesia is introduced for the potential to introduce a physical therapy regimen. We will discuss the various regional techniques that are used in children for managing CRPS. The choice of regional anesthesia is based on a simple algorithm that we have devised for our practice.

A central neuraxial block is used especially if the child is in severe pain to facilitate the introduction of physical therapy. An indwelling catheter in the lumbar or cervical area is used with low concentration local anesthetic solution. We find that this allows for better cooperation from the patient and the parents for introducing a physical therapy regimen even in the child with severe pain and allodynia.[23]

Bier block is used for mild to moderate cases of CRPS as a first modality for the provision of analgesia and a sympathetic blockade. Although a variety of substances have been used for providing a Bier block, the use of a local anesthetic in combination with either an α-2 agonist or an NSAID seems to have better results. In our series of children who received an IVRA with lidocaine and ketorolac, we demonstrated a marked improvement of symptoms and the ability to perform physical therapy.[24]

The use of peripheral nerve blocks as to facilitate physical therapy, while providing a sympathectomy, has become

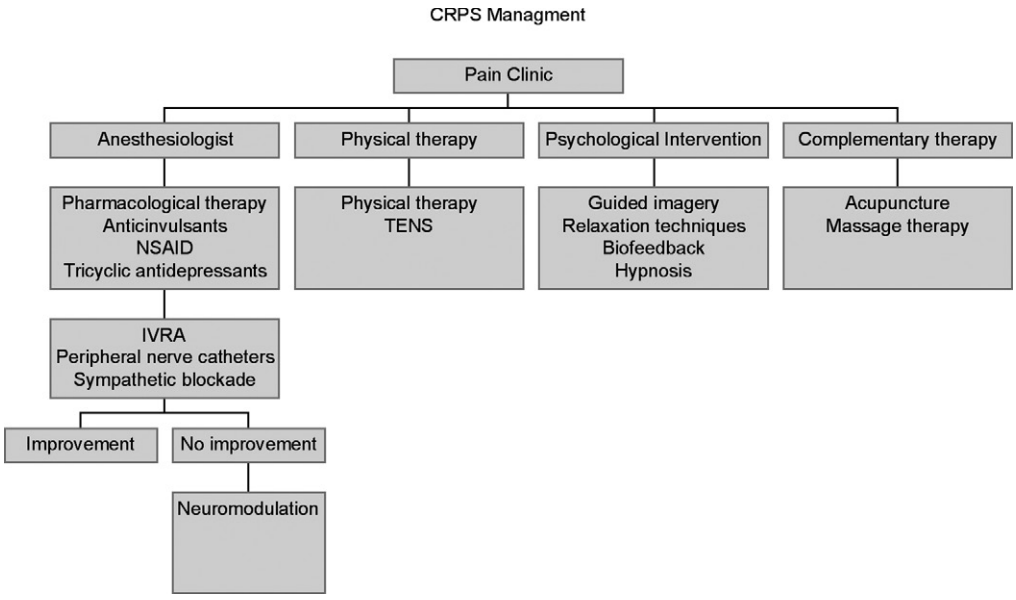

FIGURE 57-1 Management of CRPS type 1

plausible especially with the use of ultrasound guidance.[25] Continuous nerve catheters are utilized to provide analgesia. A dilute solution of local anesthetics is used with the view of providing analgesia while allowing physical activity. We prefer popliteal fossa blocks for the lower extremities and interscalene or infraclavicular brachial plexus blocks for the upper extremities.

Sympathetic blockade is utilized in children and adolescents after exhausting the above techniques. A stellate ganglion block is performed under ultrasound guidance for upper extremity CRPS and a lumbar sympathetic blockade is performed under fluoroscopic guidance for lower extremity CRPS. A crossover trial of fluoroscopic-guided lumbar sympathetic blocks demonstrated a decrease in allodynia and pain intensity when compared to intravenous lidocaine injection in adolescents with CRPS.[26]

Although commonly used in adults for refractory cases of CRPS, this is very rarely used in the pediatric setting.[27] The use of peripheral nerve stimulators is gaining ground in the pediatric setting and may be of benefit in refractory CRPS.

HEADACHES

Headaches are a common presentation in children and adolescents. A 2010 survey of two middle schools in the Chicago area demonstrated a high incidence of headaches in children.[1] Most headaches in children can be classified into organic and nonorganic types and can be deemed as acute or chronic based on the duration of the headaches. Few physicians discussed headaches in children until 1873 when William Henry Day, a British pediatrician, devoted a chapter to the subject of headaches in his book *Essays on Diseases in Children*. In 1967 Freidman and Harms published much of the available data in the book *Headaches in Children*.[28] These early works have given a lot of impetus to the many subsequent papers dealing with headaches in children.

The classification of headaches is based on the presumed location of the abnormality, its origin, its pathophysiology, or the symptom complex with which the patient presents. The International Headache Society has recently updated its classification. By plotting the severity of a headache over time, headaches can be classified into five major categories

A thorough questionnaire should be routinely used to evaluate headaches in children. Other specific questions about neurologic symptoms such as ataxia, lethargy, seizures, or visual impairments are asked. Other important medical problems such as hypertension, sinusitis, and other emotional disturbances must be evaluated. A history of a severe headache without a previous history of headache, pain that awakens a child from sleep, headaches associated with straining, change in the headache pattern, or the presence of a headache with associated symptoms such as nausea or vomiting suggests a more pathological etiology of the headache and must be very carefully evaluated. The following information is obtained at the time of the visit:

- Neurological status including a complete neurological examination.
- Physical status of the patient (i.e., is the patient actively mobile?).
- Does the headache prevent the child from performing his or her normal activities (e.g., interacting with others, participating in sports)?
- Is there school absenteeism?
- What is the child's interaction with the parents and siblings at home?
- Are there any relieving factors for the headache?
- Has the child been placed on any medications for pain?
- Has there been any improvement at all in the clinical characteristic of pain?

Migraine Headache

There is usually a strong family history of migraine along with symptoms that include aura and prodrome. Usually migraine headaches are managed by neurologists and are

referred to us only for management of the refractory cases. We have intervened with providing peripheral nerve blocks for headaches. A trigeminal nerve block for frontal headaches and occipital nerve blocks for persistent occipital pain have been shown to be effective for managing pain.[29]

Tension-type Headaches

This is perhaps the most common type of headache that we see in our pain clinic. Most of these patients have normal lifestyles and have debilitating fronto-temporal or fronto-parietal headaches. The headache is due to contraction of the temporalis muscle and the tension on the scalp muscles.[30] Management is the use of relaxation techniques as well as biofeedback. Routine use of nonsteroidal agents usually helps allay the pain in patients with tension-type headaches.

Persistent Neuropathic Headaches

Patients who have had former surgery or have had decompression for Chiari malformation may continue to experience headaches in the postoperative period. This applies to patients who have ventriculo-peritoneal shunts who have headaches following shunt revisions. After cognitive behavioral therapy is utilized, we have attempted to use serial peripheral nerve blocks for these patients (Fig. 57-2). This includes trigeminal nerve blocks for frontal headaches and occipital nerve blocks for occipital headaches. A newer ultrasound-guided approach to the occipital nerve may allow easy access to the C2 nerve root, thereby providing a more robust blockade as opposed to a peripheral subcutaneous injection.[31] Local anesthetic injection with or without a small dose of steroids is used for providing analgesia.

ABDOMINAL PAIN

Abdominal pain is a common painful problem in infants, children, and adolescents. Recurrent abdominal pain, a commonly used terminology in the past, is now called functional abdominal pain. Most important, it is imperative that all organic causes are eliminated. Once a diagnosis of functional abdominal pain is established, cognitive behavioral measures along with family centered therapy have been shown to be effective. The use of amitriptyline for managing functional abdominal pain has been demonstrated to be effective in children, although in a randomized prospective trail there was no difference between control and amitrtiptyline.[32] In addition, we have demonstrated the efficacy of serial nerve blocks in children with abdominal pain particularly if they develop neuropathic pain after abdominal surgery. The use of ultrasound-guided rectus sheath blocks or transversus abdominis plane (TAP) blocks performed serially has decreased abdominal pain in our cohort[33] (Fig. 57-3). By blocking the thoracolumbar nerve roots, we are able to provide complete analgesia of the anterior abdominal wall.

Ilioinguinal neuralgia following hernia repair is present in more individuals than is reported.[34] Although rare in infants, it is often seen in older adolescents following surgery. The symptoms are seen more often in older children and in obese children following major dissection for their hernia repair. A TENS unit may be helpful for managing pain, but in most instances the use of peripheral nerve blocks have been demonstrated to be effective. Ultrasound-guided ilioinguinal nerve blocks are effective for managing pain. Serial blocks have been demonstrated to be effective.[35] Occasionally, with severe pain, we may leave a catheter in place for managing pain.

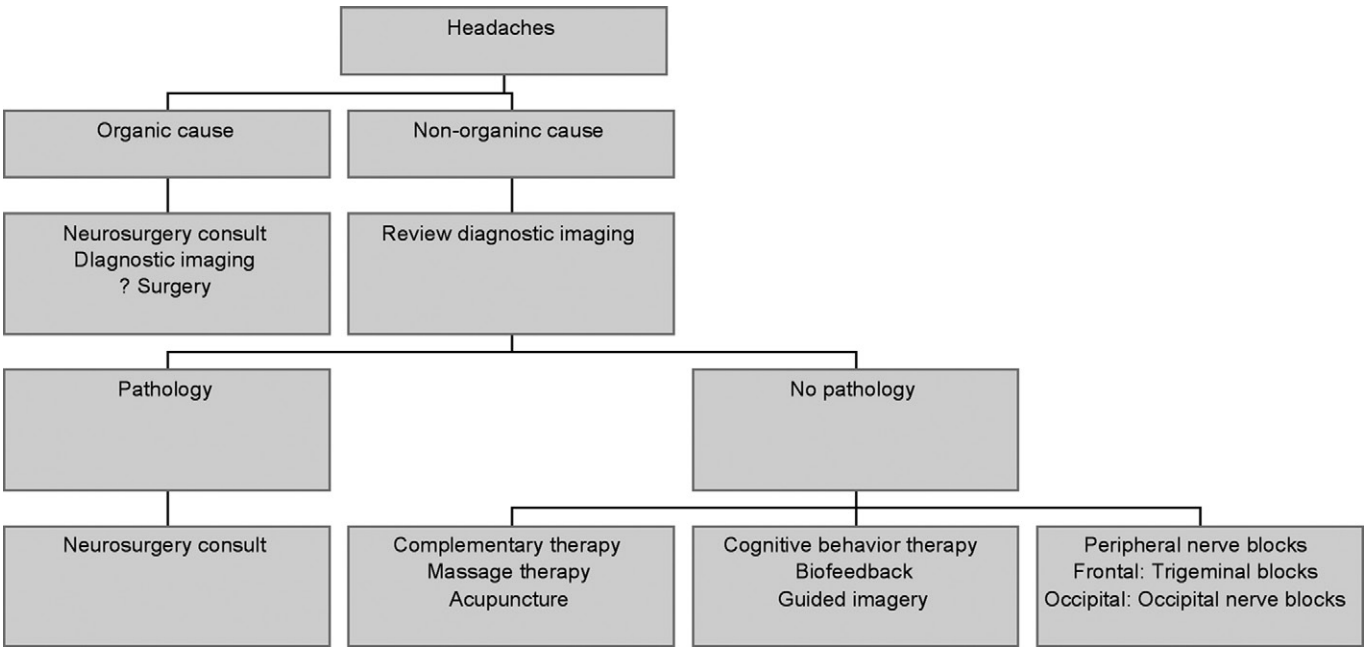

FIGURE 57-2 Headache management.

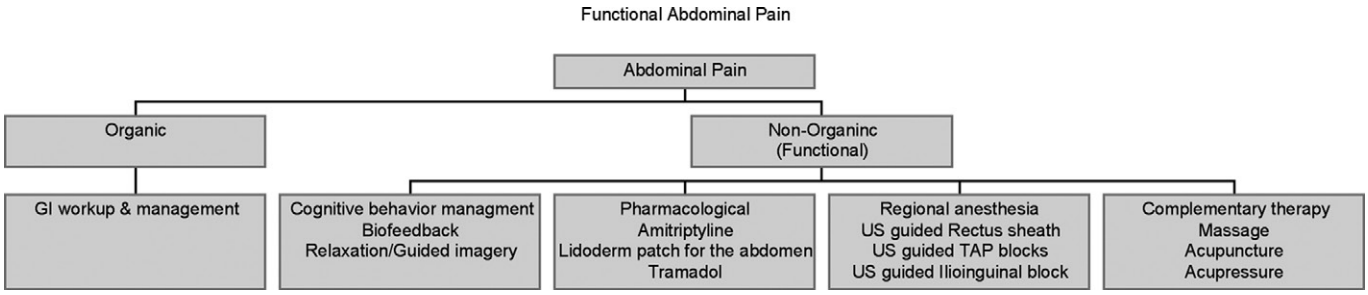

FIGURE 57-3 Abdominal pain management.

CHEST PAIN

This is a common symptom especially in older children and adolescents. The most common presentation is tightness of the chest with pain that is usually lateral to the sternum. In a study of 96 patients, it was noted that 37% had idiopathic chest pain with a mean age of 13 years. A significant life event, such as a family divorce or a heart attack in a family member, was a crucial factor predisposing to chest pain in over 30% of all these children.[36] After cardiac causes are ruled out with an ECG and a careful physical examination, other causes for chest pain should be considered[37] (Table 57-2). Other causes of chest pain, including, but not limited to, drug toxicity, functional anxiety, gastrointestinal illness, asthma, and musculoskeletal problems, should be ruled out. The management of all chest wall pain is usually with reassurance and nonsteroidal anti-inflammatory drugs. In addition, with severe, recurring chest wall pain, we have attempted to place intercostal nerve blocks under ultrasound guidance with very good relief. Serial blocks are performed with adequate resources available for biofeedback and massage therapy to allay the anxiety associated with recurrent chest wall pain. We have now used acupuncture as a modality for pain control in intractable chest wall pain before regional techniques are utilized.

CANCER PAIN

This is one of the areas where pediatric sub-specialization in pain management can help. Cancer in children is different from adults; most cancer is blood dyscrasias with a potential for good recovery. In addition, solid tumors in children are almost always resected. The prognosis in children is not very different except for some of the blood dyscrasias, yet the family expectation and the potential for medical intervention is inevitable despite the outcomes. As a result, there is a greater need for palliative care and increased need for pain medications in the child while understanding the pharmacokinetics and pharmacodynamics of the drugs in children. It has been shown that parents who see their child in pain may want to hasten their death if this became the underlying problem in their child.[38,39] Cancer pain in children is due to several reasons: (i) cancer-related pain (e.g., solid tumor or bony metastatic tumors); (ii) pain caused by treatment (e.g., mucositis pain and surgical pain); and (iii) neuropathic pain either secondary to surgery or caused by tumor invasion. Management of pain must be individualized, and we attempt to accommodate the family needs in the entire process. Patient-controlled analgesia is used extensively with good results. In addition, it may be important to recognize the side effects of opioid administration including constipation, itching and pruritus, and somnolence. There is also a distinct possibility of developing opioid tolerance, and this needs to be addressed effectively.

TABLE 57–2 Chest Pain in Children and Adolescents

Costochondritis
Trauma, muscle overuse
Precordial catch or Texidor's twitch
Tietze's syndrome (after minor trauma)
Slipping rib-cage syndrome
Xiphoid cartilage syndrome
Herpes zoster
Fibromyalgia

ADVERSE EFFECTS OF LONG-TERM OPIOIDS

Constipation is a common side effect of opioids and is seen frequently in children especially if they are devoid of enteral feeding. As this side effect can be painful, we have attempted to use stool softeners as well as increase fiber intake if enteral feeding is still a possibility. In certain cases, especially after major abdominal surgery, we think that the use of an oral μ-opioid agonist may decrease the incidence of ileus and constipation.[40] A dose of 20 to 40 μg/kg naloxone is utilized for treating constipation. Newer drugs including methylnaltrexone have been shown to be effective in adults although no studies have been performed in children.[41]

Opioid tolerance is a major problem in children and infants who have been exposed to long-duration analgesia with opioids.[42] As treatment possibilities for tumors increase, the number of children with opioid tolerance has been increasing, and proactive steps to decrease tolerance must be set in place from the time of initiation of opioids. A simple algorithm that we have developed is effective in dealing with opioid tolerance (Fig. 57-4).

Complementary Therapy: The use of complementary therapy for managing pain dates back several thousand years. In ancient India, yoga and massage were practiced for improving the quality of life and subsequently for decreasing symptoms associated with disease. In ancient

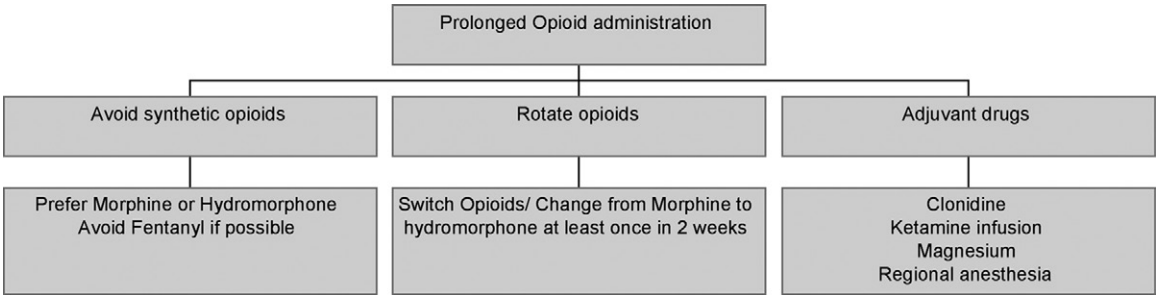

FIGURE 57-4 Opioid tolerance management

China, the use of acupuncture was used for curing all sorts of ailments. The comprehensive use of these techniques has led to a better understanding of some of these ancient techniques with its application to pain control. A study looking at massage therapy in children with chronic pain demonstrated the effectiveness of massage in decreasing pain symptoms and the well being of the patient.[43] Acupuncture has been used to treat severe headaches and neuropathic pain symptoms.[44,45] As more studies are conducted with results supporting these types of treatments, it is our hope that adequate reimbursements of procedures performed for chronic pain in children will follow.

CONCLUSIONS

Chronic pain in children and adolescents is a real entity. Early diagnosis and intervention are helpful for most chronic painful problems. The use of a dedicated cognitive behavioral therapy program helps the families and the children enormously. Complementary therapy including massage, acupuncture, and yoga can be used to reduce pain and reduce the need for additional pain medication. A dedicated pain treatment center can facilitate adequate and early management of pain in children with rapid return to normal function. Future research, especially in the paradigms for managing pain in children with a variety of pain syndromes, must be conducted using multicenter trials to provide norms for managing these very difficult patient problems.

KEY POINTS

- The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recently recommended outcome domains and measurement tools for research on pediatric acute and chronic pain.
- The management of complex regional pain syndrome includes physical therapy, regional blocks, pharmacological management, and psychological interventions.
- Several characteristics of headache suggest a pathological or more serious etiology.
- The management of headache include pharmacological management, nerve blocks, psychological techniques, and complementary therapy.
- Functional abdominal pain is best treated cognitive behavioral measures, antidepressants, and serial rectus sheath or TAP blocks.
- Noncardiac chest pain is treated with NSAIDs, reassurance, and acupuncture. Nerve blocks may be tried in severe and recurring chest pain.
- The management of cancer pain is individualized and based on the family needs.

REFERENCES

Access the reference list online at http://www.expertconsult.com.

CHAPTER 58

Geriatric Pain

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The goal of this chapter is to focus on the unique aspects of pain physiology in older adults and how age affects the assessment and treatment of persistent pain. With advancements in medical interventions and pharmacology, the increasing number of people living past the age of 65 will place significant demands on the treating physician. By the year 2030, the number of older adults will double that in 2000, increasing from 35 million to 71.5 million, representing close to 20% of the total U.S population.[1] Since 25% to 50% of older adults have persistent pain,[2] the prevalence of pain conditions in aging Americans will increase exponentially and health-care professionals will need to be adept at their management. This chapter highlights the characteristics of older adult pain patients that distinguish them from younger patients with persistent pain and that mandate a unique management approach.

PRESENTATION OF DISEASE

Unlike younger patients who often manifest a uniform set of signs and symptoms indicative of a particular disease, older adults may present more atypically. Practitioners should be guided by two overarching principles when evaluating the older adult with pain. First, the rules of multiplicity rather than Occam's razor should drive the assessment of the causes and contributors to pain. That is, pain should be conceptualized as a syndrome potentially "caused by a multiplicity of pathologies in multiple organ systems."[3] Low back pain in older adults, for example, is commonly contributed to by hip osteoarthritis, fibromyalgia syndrome, and myofascial pain.[4] Myofascial pain may be contributed to by axial spondylosis, degenerative scoliosis, leg length discrepancy, and anxiety. The second principle follows in that the symptom with which a patient presents may represent the weakest link, but not necessarily the treatment target.[5] In older adults with delirium, for example, the brain is the weakest link, but the treatment targets are most commonly infections and adverse drug reactions. Similarly, the treatment target in the older adult with low back pain may be vitamin D deficiency or Parkinson's disease rather than degenerative disease of the lumbar spine. Similarly, pain may present subtly as loss of function, or change in mood or cognition. Treatment focused exclusively on analgesia in the vulnerable older adult often fails. Treatment may require targeting biomechanics, insomnia, depression, and/or other long-standing chronic disease often coexisting with persistent pain to optimize function and quality of life.

COMMON COMORBIDITIES

Studies have revealed associations between mental health disorders and persistent pain conditions in older adults. Older patients with persistent pain conditions, although more psychologically robust than their younger counterparts, should be screened routinely for concurrent mental health conditions (e.g., depression, anxiety, and dementia) and vice versa. Failure to treat comorbid psychiatric illness will likely result in ineffective analgesia. Findings in Bonnewyn et al.[6] confirmed previous studies examining the relationship between depression and pain in older adults. In this cross-sectional analysis of a large cohort of older adults, the presence of a painful symptom (back or neck, headaches, or any other persistent pain problem) was found to be greater in subjects diagnosed with major depressive episodes than those without.

Other diseases common in older adults that may cause or exacerbate pain include osteoporosis and osteoarthritis, diabetes, cancer, cardiovascular disease, and dementia. In particular, Alzheimer's disease (AD) may pose a significant challenge to the treating practitioner for a number of reasons: (1) Patients with AD may have difficulty communicating their pain.[7] (2) Anxiety/fear of pain may amplify the experience and expression of pain in patients with AD, thus the most appropriate treatment may be uncertain. (3) Patients with AD may perseverate on, but not suffer from, their pain, thus use of pain self-report as the gold standard for guiding treatment becomes complicated. (4) As dementia progresses, patients with AD may lose treatment expectancy[8] that may compromise analgesic efficacy.

AGING AND DISABILITY

The risk of disability increases with aging. According to some estimates, four out of five people who are 80 years old will report some form of disability.[9] Risk factors for the development of disability include a high burden of medical comorbidities, depression, sensory impairments related to vision and hearing, and musculoskeletal disorders such as arthritis. Smoking, level of alcohol use, inactivity, and lack of social support also contribute significantly.[10] While musculoskeletal disorders are the largest contributor to persistent pain and functional impairment in older adults,[11] all contributors to disability require treatment to optimize outcomes.

AGING-ASSOCIATED PHYSIOLOGY AND PATHOLOGY

Aging is associated with a number of physical and physiologic changes, described here, that can impact the expression and experience of pain as well as its treatment. Knowing how to distinguish aging-associated from disease-associated changes allows the pain practitioner to appropriately prescribe treatment and minimize the risk of adverse effects. Some key considerations are provided.

NEUROLOGIC

Although changes within the nervous system vary across individuals, aging is associated with a number of morphologic and functional changes in the peripheral and central nervous system that may impact pain processing such as a

decline in the number of myelinated and unmyelinated fibers, an increase in the number of damaged nerve fibers, slowed nerve conduction velocity, loss of serotonergic and noradrenergic neurons in the dorsal horn, and a reduction in serotonergic receptor density in the anterior cingulate and prefrontal cortex, among others.[7] Neuropsychological performance (NP) also declines with age and brain volume loss, senile plaques, and neurofibrillary tangles occur in the absence of AD.[12] Persistent pain itself is associated with deterioration of NP above and beyond that associated with normal aging[13] and evidence indicates that pain reduction is associated with improved NP.[14]

Because provider–patient communication is an essential component in the treatment of pain, impairments in vision and hearing may alter treatment efficacy and require modified assessments. *Vision and hearing* change both structurally and functionally with age. Common eye diseases (e.g., cataract, glaucoma, macular degeneration, and diabetic retinopathy) associated with aging may result in moderate to severe vision loss. Presbycusis, defined as the loss of hearing with age, is estimated to affect one-third of patients over the age of 65 and half over the age of 85. Assistive technologies such as hearing aids and a frequency modulation (FM) device for those patients with speech recognition difficulty, may be helpful when practitioners evaluate these patients, as they afford the opportunity to engage in more meaningful conversation and improved care.[15,16]

Postural control abnormalities also become more prevalent leading to an increased risk of falls.[3,17,18] An estimated one in three community-dwelling older adults falls repeatedly,[19] and recent evidence indicates that pain adds to this risk,[20] in addition to acute pain, which can result from a fall. Thus assessment of balance should be a routine part of assessing the older adult with pain.

MUSCULOSKELETAL

Common changes in the musculoskeletal system include sarcopenia (i.e., progressive loss of lean body mass associated with muscle cell atrophy and infiltration of fat),[21] degenerative arthritis, and decreased bone density.[16] Pain practitioners need to be acutely aware of the fact that radiographic evidence of degeneration without pain is exceedingly common. Over 90% of pain-free older adults have degenerative disc and facet disease of the lumbar spine.[22] An estimated 21% of pain-free people over age 65 have moderate to severe lumbar spinal stenosis.[23] Over half of older adults with radiographic evidence of hip osteoarthritis (OA) are without hip pain.[24] Thus, the history and physical examination should provide strong evidence of disease before imaging is ordered to avoid unnecessary procedures such as injections and surgery that carry the potential for morbidity. It has been found that the majority of older adults with chronic low back with or without leg pain have a combination of pathologies responsible for their symptoms (e.g., hip OA, fibromyalgia, iliotibial band pain), and that half of those with neurogenic claudication indicative of lumbar spinal stenosis also have other potential contributors to their symptoms.[4] Vertebral compression fractures may occur in the absence of acute pain,[25] but as kyphosis develops, they may contribute to pain in the upper and lower back. In addition to its role in osteoporosis, vitamin D deficiency is common in older adults and may contribute to muscular pain and falls. Assessment of serum 25-OH vitamin D may be considered as part of pain assessment in older adults and correction of insufficiency a routine part of treatment.

DRUG METABOLISM

A number of physiologic changes associated with aging, summarized in Table 58-1,[26] may lead to alterations in pharmacokinetics and pharmacodynamics. Common doses for multiple classes of pain medications are listed in Table 58-8 and must be adjusted as described in the following sections. The pain practitioner must be cognizant of these changes to optimize analgesia while minimizing adverse effects.

ANALGESICS AFFECTED BY ALTERED PHARMACOKINETICS

Medications that have a high hepatic extraction ratio may undergo decreased clearance and experience a longer half-life in older adults because of diminished liver size and blood flow. Meperidine (contraindicated in older adults because of its renally cleared active metabolite that can cause seizures) and morphine are high extraction ratio analgesics whose first-pass effect and clearance is reduced with age. The following long half-life nonsteroidal anti-inflammatory drugs are hepatically metabolized and their clearance may be reduced in older adults: celecoxib, diflunisal, naproxen, oxaprozin, prioxican, salsalate, and sulindac. The opioids levorphanol and methadone may be similarly affected.

Analgesics that are affected by aging-associated decline in renal function include codeine, duloxetine, gabapentin, meperidine, pregabalin, propoxyphene, salicylate, tramadol, and the opioids morphine, oxycodone, hydromorphone, fentanyl, and methadone. Recent consensus guidelines recommended the dosing schedule shown in Table 58-2 for gabapentin by renal function.[27]

Geriatricians widely use the Cockcroft-Gault equation, shown below, to estimate creatinine clearance (CrCl) that helps to guide dose adjustment of renally cleared medications.[28,29]

$$\mathrm{CrCl} = \frac{(140 - \mathrm{age}) * (\mathrm{Wt\ in\ kg}) * (0.85\ \text{if female})}{(72 * \mathrm{Cr})}$$

ANALGESICS AFFECTED BY ALTERED PHARMACODYNAMICS

Pharmacodynamics refers to tissue sensitivity and how a drug interacts with its end organ. The body's response to medications may be therapeutic or adverse. The effectiveness of a medication may be influenced by age-related changes in receptors and signal processing, that is, the target organ's sensitivity.[16] Opioid sensitivity increases with associated decline in mu opioid receptor density and increase in opioid affinity.[30] Thus older adults may respond to opioid doses that are significantly smaller than those in younger individuals.

TABLE 58–1 Physiological Changes Associated with Aging and Frailty That Can Impact on Pharmacokinetics and Pharmacodynamics of Drugs

Pharmacokinetics			
Absorption	**Distribution**	**Metabolism**	**Elimination**
Remains unchanged	↓ Plasma albumin[a,c]	↓ Liver volume[a,b,c]	Measurable and predictable decline in renal function with age[a,c]
↑ Gastric pH[a]	↓ Protein affinity	↓ Hepatic blood flow[a,b,c]	↓ Glomerular filtration rate[a]
↓ Secretory capacity[a]	↑ α_1-acid glycoprotein[a]	↑ Interindividual variability with age[a,c]	↓ Renal plasma flow[a]
↓ GI blood flow[a]	↓ Total body water[a,c]	↓ First-pass metabolism[c]	
	↑ Expression and activity of P-glycoprotein in liver[a]	↓ Phase I metabolism[a,b]	
		{ReversReact} Phase II metabolism[a,b]	
		↓ Phase II metabolism in frail	

Pharmacodynamics	
Body Composition	**Central Nervous System**
↑ Body fat[a]	↓ Blood supply to brain[a]
↓ Lean and total body mass[a,c]	↓ Baroreceptor activity[a]
Cardiovascular Function	**Renin-Angiotensin-Aldosterone System**
↓ Resting heart rate, stroke volume, and cardiac output[a]	↓ Plasma renin[a]
	↓ Urine aldosterone[a]

[a] *Human/clinical studies.*
[b] *Animal studies.*
[c] *Pharmacokinetic and/or pharmacodynamic change is accentuated in the frail.*
Source: Mitchell SJ, Hilmer SN, McLachlan AJ: Clinical pharmacology of analgesics in old age and frailty. Rev Clin Gerontol *19:103–118, 2009.*

TABLE 58–2 Gabapentin Dosing by Renal Function

Estimated Creatinine Clearance	Maximum Gabapentin Dose (mg)
30–59	600 mg bid
15–29	300 mg bid
<15	300 mg qd

Source: Hanlon JT, et al: Consensus guidelines for oral dosing of primarily renally cleared medications in older adults. J Am Geriatr Soc *57:335–340, 2009.*

COMPREHENSIVE PAIN ASSESSMENT

Pain assessment in older adults requires a comprehensive understanding of the social, psychological, and biophysical factors that contribute to the persistence of pain in the older patient. The purpose of pain assessment is twofold: (1) to identify contributors to pain that are usually multiple, and (2) to identify outcome measures to follow during the course of treatment, that is, each patient's individual "pain signature."[31] Tables 58-3 and 58-4 suggest approaches for assessing pain and outcome measures to follow during pain treatment.

Pain assessment should be an ongoing process to measure change in pain over time as this will affect any necessary modifications in the treatment course. Assessment of pain alone is not sufficient; providers should inquire about changes in appetite, sleep, and/or mood, loss of mobility, and diminished activity level. Finally direct assessment of pain intensity, discomfort, or change in health status is necessary. Older adults may be less likely to state when they are experiencing pain due to possible beliefs that pain is a normal part of aging and fears about addiction to pain medications and cognitive impairments.[32] Caregivers, family members, or friends of the patient may be able to give valuable information if they have noticed any abrupt or subtle changes in the patient's daily activities that may indicate an underlying problem.

KEY ASSESSMENT TOOLS FOR THE OLDER ADULT WITH PAIN

Abnormalities in traditional vital signs such as abrupt changes in respiratory rate or heart rate may be indicative of an acute pain event. In the future, measurement of heart rate variability may have potential clinical application in examining autonomic nervous system dysfunction and pain severity associated with certain persistent pain conditions.[33–35] Measurement of pain intensity is now included among the standard vital signs. For cognitively intact older adults, there are many pain rating tools from which to choose. Numeric rating scales (NRS) and verbal descriptor scales (VDS), are used most commonly.[36] NRSs such as the 0–10 scale are sensitive to change and very feasible in clinical settings.[37] In addition to collecting vital signs, all older adults who present to the pain practitioner should undergo assessment of their mobility function and cognition.

Screening for mobility function is essential because, as noted previously, both aging and pain increase the risk of falls. Many of the medications used to treat these

TABLE 58–3 Brief Pain Impact Assessment for Verbal Patients

How strong is your pain (right now, worst/average over past week)?
How many days over the past week have you been unable to do what you would like to do because of your pain?
Over the past week, how often has pain interfered with your ability to take care of yourself, for example, with bathing, eating, dressing, and going to the toilet?
Over the past week, how often has pain interfered with your ability to take care of your home-related chores such as going grocery shopping, preparing meals, paying bills, and driving?
How often do you participate in pleasurable activities such as hobbies, socializing with friends, travel? Over the past week, how often has pain interfered with these activities?
How often do you do some type of exercise? Over the past week, how often has pain interfered with your ability to exercise?
Does pain interfere with your ability to think clearly?
Does pain interfere with your appetite?
Does pain interfere with your sleep? How often over the past week?
Has pain interfered with your energy, mood, personality, or relationships with other people?
Over the past week, how often have you taken pain medications?
How would you rate your health at the present time?

Source: Weiner DK, Herr K, Rudy TE: Persistent pain in older adults: an interdisciplinary guide for treatment, *New York, 2002, Springer.*

individuals, such as opioids, tricyclic antidepressants, gabapentin, and pregabalin may additionally enhance fall risk. Thus in the older adult who is at increased risk for falls, it is prudent to optimize mobility (e.g., by referring the patient to a physiatrist or physical therapist for instruction in using the appropriate assistive device and gait/balance training) prior to prescribing medications that may further increase this risk. Although many mobility tests exist; there are currently no gold standards amongst screening tests. For additional resources, please see the American Geriatrics Society (AGS) practice guidelines on the *Prevention of Falls in Older Persons* released in 2010.[38]

Assessment of cognitive function is critical for the reasons outlined previously. Many high-functioning older adults with good social skills may be able to hide dementia in casual conversation. Thus, all practitioners must overtly screen for it. The Mini-Cognitive Assessment Instrument (Mini-Cog) shown in Table 58-5[39] is a useful screening tool that takes no more than 2 min to perform and can be administered by the nurse who collects other vital signs.

If there is evidence of dementia on this test, in addition to treating the patient's pain, the provider should refer the patient for neuropsychological testing or to a specialist who can address this important problem such as a geriatrician or neurologist.

SPECIAL CONSIDERATIONS FOR PAIN ASSESSMENT IN COGNITIVELY IMPAIRED PATIENTS

Cognitively impaired older adults are at increased risk of pain undertreatment because of the belief among many health-care workers that their pain ratings are unreliable. In fact, patients with mild to moderate cognitive impairment can reliably report pain using verbal descriptor scales.[37,40] In patients with more advanced dementia who have difficulty using self-report instruments, caregivers rely on behavioral cues to determine the presence and severity of pain (Table 58-6). Facial grimacing is one of the most sensitive and reliable behavioral indicators of pain in patients with dementia or poor verbal communication.[41] Other common pain behaviors include guarding, bracing, rubbing and sighing.[42] Although a number of pain behavior instruments have been developed, a recent consensus statement concluded that there is "insufficient evidence of reliability and validity at this time to recommend any one tool for broad use across populations and settings" in patients with dementia.[7,37] For these patients, there is no substitute for a knowledgeable caregiver's observations as to whether and how much pain a patient is experiencing.

TABLE 58–4 Assessing Functional Response to Treatment of Persistent Pain in Older Adults: Suggested Outcome Measures

Domain Functional	Parameters	Comments
I. Physical	Basic and instrumental activities of daily living (ADL, IADL)	Look at the degree of assistance needed. Decreased activity, such as the diminished participation in advanced activities of daily living (AADL) in the community dweller, or decreased ability to participate in AM care in the nursing home resident may indicate pain.
	Mobility/activity level	
	Sleep	Ask about pain awakening from sleep, difficulty falling asleep because of pain, time spent in bed during the day.
	Appetite	Many persistent pain patients experience appetite suppression from pain. Follow caloric intake and weight.
	Pain intensity	In nursing home residents, use pain thermometer, behavioral indicators of pain, and rate of prn analgesic ingestion. In community dwellers, use numeric or verbal scales.
II. Psychosocial	Mood	Anxiety and depression may coexist and worsen in patients with pain. Reclusiveness and/or irritability/agitation may occur. In nursing home residents, tone of interactions with staff, family, and other residents may be helpful.
	Interpersonal interactions/ behavior	
III. Cognitive	Mental status	Consider pain as causative in the patients who experience decline in mental status or delirium. The Mini Mental State Examination may not be sensitive enough to detect subtle changes.
	Beliefs and attributions	Note if the patient has changed orientation from a "fix-me" mentality to a "teach-me" mentality.

Source: Weiner DK, Herr K, Rudy TE: Persistent pain in older adults: an interdisciplinary guide for treatment, *New York, 2002, Springer.*

TABLE 58–5 Mini-Cognitive Assessment Instrument (Mini-Cog)

Step 1	Ask the patient to repeat three unrelated words, such as "ball," "dog," and "television."
Step 2	Ask the patient to draw a simple clock set to 10 min after 11 o'clock (11:10). A correct response is a drawing of a circle with all of the numbers placed in approximately the correct positions, with the hands point to the 11 and 2.
Step 3	Ask the patient to recall the three words from Step 1. One point is given for each item that is recalled correctly.

Interpretation

Number of Items Correctly Recalled	Clock Drawing Test Result	Interpretation of Screen for Dementia
0	Normal	Positive
0	Abnormal	Positive
1	Normal	Negative
1	Abnormal	Positive
2	Normal	Negative
2	Abnormal	Positive
3	Normal	Negative
3	Abnormal	Negative

Source: Scanlan J, Borson S: The Mini-Cog: receiver operating characteristics with expert and naive raters. Int J Geriatr Psychiatry *16:216–222, 2001.*

TABLE 58–6 Common Pain Behaviors in Cognitively Impaired Elderly Persons

Facial expressions
Frown; sad, frightened face
Grimace, wrinkled forehead, tightened eyes

Verbalizations, vocalizations
Sighing, moaning, groaning, grunting
Calling out, asking for help
Noisy breathing; verbally abusive

Body movements
Rigid, tense body posture; guarding, fidgeting
Pacing, rocking; restricted movement
Gait or mobility changes

Changes in interpersonal interactions
Aggressive, combative, resisting care
Decreased social interactions, withdrawn
Socially inappropriate, disruptive

Changes in activity patterns or routines
Refuses food, appetite change
Sleep, rest pattern changes
Sudden cessation of common routines

Mental status changes
Crying, tears
Increased confusion
Irritability or distress

From AGS Panel on Persistent Pain in Older Persons: Management of persitent pain in older persons. J Am Geriatr Soc *50:S205–S224, 2002.*

RED FLAGS

For all patients presenting with pain ruling out serious conditions (i.e., red flag symptoms) that require immediate attention is paramount. Examples of red flag symptoms in the older adult include but are not limited to: fever, sudden unexplained weight loss, acute onset of severe pain, neural compression, loss of bowel or bladder function, jaw claudication, new headaches, bone pain in a patient with a history of malignancy or that awakens the patient from sleep, and sudden pain in an extremity that is associated with pallor, pulselessness, and paresthesias.[43]

TREATMENT

After determining the older adult's pain signature, multifaceted treatment should be designed accordingly. For the older adult with depression and difficulty walking because of deconditioning, an antidepressant, cognitive behavioral therapy, and physical therapy may be the most appropriate components of the treatment regimen. For the older adult with dementia and excessive fear of pain because of social isolation, placement in an assisted living facility may most effectively improve quality of life. If the practitioner determines that pain itself requires treatment, a stepped care approach should be utilized. Because of the risk of medication nonadherence, and drug–drug and drug–disease interactions,[44] pain treatment should almost always start with nonpharmacologic or nonsystemic pharmacologic modalities, as described below.

EXERCISE

It is well established that exercise is beneficial for many reasons and that inactivity promotes pain-related disability.[45] Results from both observational and randomized controlled trials demonstrate that participation in regular exercise improves psychological well-being, reduces pain, and increases functional capacity in older adults with persistent pain.[46] A combination of endurance, resistance, balance, and flexibility exercises may yield important health benefits. One randomized controlled trial demonstrated that well-structured exercise with appropriate resistance training resulted in improved overall function in walking and muscle strength in frail older adults.[47] When exercise is prescribed for treating osteoarthritic pain, individualized programs should be created to meet the patient's unique needs. It has been demonstrated in older adults with knee OA that both low-intensity and high-intensity stationary bicycling for 25 min three times a week promote decreased pain and improved function.[48] Overweight patients with knee OA benefit from both weight loss and exercise.[49] Additionally, aquatic therapy may be effective for pain relief in

patients with arthritis and low back pain, among others.[50] Practitioners caring for the older adult in pain should encourage exercise as tolerated by the patient and weight loss for overweight patients suffering from arthritic pain.

PHYSICAL THERAPY

Physical therapy alone may be adequate to manage pain. As with exercise, therapy tailored to the specific needs of the patient is crucial. For example, physical therapy for the treatment of lumbar spinal stenosis, myofascial pain, and fibromyalgia syndrome require very different approaches. It is critical, therefore, that the practitioner ask the older adult who has previously had an unsuccessful course of physical therapy, about the specifics of the regimen prescribed. Reducing pain, optimizing fitness, and promoting functional dependence should be the goals of treatment. It is critical that the patients view themselves as taking an active role in treatment rather than as a passive recipient. In addition to being committed to maintaining a home exercise program, learning how to pace activities and self-manage pain flares are key to successful pain rehabilitation.

Medications can be used in combination with exercise and physical therapy and should be viewed as a means to facilitating compliance with rehabilitation efforts. In the frail older adult whose pain is limiting, the practitioner should consider prescribing an analgesic 30-60 min prior to exercise or physical therapy.

ASSISTIVE DEVICES

Assistive devices for older adults with pain serve the following purposes: (1) pain relief, (2) enhancement of mobility and stability, and (3) modification of painful activities. Assistive devices such as canes and walkers exert their analgesic effect by reducing load (e.g., canes for lower extremity arthritis, walkers for low back pain).[51] The patient's living environment must be considered before prescribing an assistive device. Only experienced providers who know how to fit and tailor the assistive device to the patient's impairments and environment should prescribe mobility aids. For complex patients, referral to a physiatrist should be considered. Canes are generally used for those patients with mild to moderate mobility impairment; walkers tend to be prescribed for those patients with "generalized weakness, extreme inability for lower-limb weight bearing, debilitating conditions or poor balance control."[51] Mobility devices should be prescribed with caution in susceptible individuals as some reports have suggested an increase in falls with use of walking aids.[52] Upper extremity assistive devices can help to modify painful activities. Reachers, jar openers, button aids, and zipper pulls are often prescribed for patients with osteoarthritis. Even older adults who live independently and are able to complete their activities of daily living may benefit from these devices, which may reduce pain-related functional interference.

TOPICAL THERAPIES

Topical therapies for pain are an attractive option for older adults given their mild side effect profile, less systemic absorption compared to oral medications, and ease of application. Those recommended for pain management include capsaicin cream and a topical lidocaine patch 5% for joint and low back pain, postherpetic neuralgia, and other neuropathic symptoms; diclofenac gel for osteoarthritis; and a topical diclofenac epolamine patch for acute pain associated with minor strains and sprains. Typical side effects include local irritation or rash and a burning sensation, the latter occurring most commonly with capsaicin cream.[53,54] In addition, compounded topicals can be formulated and individualized.

INJECTION THERAPIES

Injection therapies may be preferable to oral medications, depending upon the extent of the patient's pain and the comparative risk/benefit ratio. In patients with pauciarticular joint pain associated with inflammatory and noninflammatory arthritides, intra-articular corticosteroid and/or hyaluronic acid injections may be beneficial.[55,56] In patients with neuropathic pain (e.g., postherpetic neuralgia) nerve blocks may aid in reducing pain but their benefits are typically short-lived, lasting only a few days or weeks.[3,57] Trigger-point injections with local anesthetic have proven effective in alleviating myofascial pain when combined with other treatment approaches, although the therapeutic element of these injections is thought to be a result of the local twitch response obtained rather than the medication injected.[58,59] Epidural steroid injections (ESI) have been used to treat pain conditions associated with lumbar spinal stenosis involving the central and/or lateral canal. Patients with herniated discs, spondylolisthesis, scoliosis, and degenerative disc disease may see benefits following ESI, although a recent Cochrane review highlights the lack of high-quality evidence demonstrating their efficacy for any disorder.[57] Patients may also benefit from continuous drug infusions or external mechanisms that deliver various modalities of medications reaching steady-state drug levels.[3] Although promising in some patient subgroups, more research is needed regarding these interventions for older adults.

ORAL ANALGESICS

The practitioner who determines that oral analgesics are needed must begin with a careful medication history that includes concomitantly used over-the-counter analgesics, herbal and dietary supplements, vitamin preparations, illicit drugs, and alcohol. Any analgesics included in the Beers list last updated in 2003 (i.e., medications that are contraindicated in older adults because of their unacceptably high risk of adverse effects[60]) should be discontinued. Table 58-7 is a modified version of the Beers list of analgesics and additional pain medications, which are contraindicated in older adults.

The AGS revised its comprehensive persistent pain management guidelines in 2009.[61] These guidelines focus on the treatment of patients over age 75 because of their increased frailty and, therefore, increased risk of adverse drug reactions compared to younger and

TABLE 58–7 Beers List: Pain and Pain-Related Medications

Drug	Adverse Effects
Propoxyphene (Darvon) and combination products (Darvon with acetylsalicylic acid, Darvon-N, Darvocet-N)	No analgesic advantages over acetaminophen, yet has other opioid adverse effects.
Indomethacin (Indocin and Indocin SR)	Most central nervous system–adverse effects of all NSAIDs.
Pentazocine (Talwin)	Opioid analgesic that causes more central nervous system–adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs.
Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol), and perphenazine-amitriptyline (Triavil)	Strongest anticholinergic and sedative properties of any tricyclic antidepressant.
Doxepin (Sinequan)	Strong anticholinergic and sedative properties.
Meperidine (Demerol)	Renally cleared active metabolite may cause seizures and death.
Ketorolac (Toradol)	Gastrointestinal toxicity.
Long-term use of full-dosage, longer half-life, non-COX selective NSAIDs; naproxen (Naprosyn, Avaprox, and Aleve), oxaprozin (Daypro), and piroxicam (Feldene)	Have the potential to induce GI bleeding, renal failure, hypertension, and congestive heart failure.
Daily fluoxetine (Prozac)	Long-half of drug and risk of producing excessive central nervous system stimulation, sleep disturbances, and increasing agitation. Safer alternatives exist.
Skeletal muscle relaxants (methocarbamol, carisprodol, cyclobenzaprine, chlorzoxazone, metaxalone)	Effects may be nonspecific, and adverse effects outweigh the benefits.

Sources: Fick DM, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med *163:2716–2724, 2003; American Geriatrics Society Panel: Pharmacological management of persistent pain in older persons.* Pain Med *10:1062–1083, 2009; Hanlon JT, et al: Evolving pharmacological management of persistent pain in older persons.* Pain Med *10:959–961, 2009.100. Hanlon JT, et al: Evolving pharmacological management of persistent pain in older persons.* Pain Med *10:959–961, 2009.*

healthier individuals. Table 58-8 from the guidelines provides recommendations regarding analgesic starting doses for older adults.[61] These recommendations should be considered in light of several caveats discussed in subsequent sections.

DRUGS FOR THE TREATMENT OF NOCICEPTIVE PAIN

NONOPIOID ANALGESICS

NSAIDs and Acetaminophen: Two of the most commonly used medications in the older adult with mild to moderate pain are acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen is considered first-line treatment in patients with osteoarthritis and other types of musculoskeletal pain. Although acetaminophen is relatively safe in older adults, the increase use of over-the-counter medications containing acetaminophen may pose a risk of unintentional acetaminophen overdose (i.e., >4000 mg/day) in older adults who take these medications in addition to their prescription medications such as combination opioid-acetaminophen products. This scenario reinforces the importance of taking a comprehensive medication history.

In patients with inflammatory pain (e.g., gout, pseudogout), NSAIDs may be indicated for short-term use although intra-articular corticosteroid injections may be used when one or two joints are involved. Because of their relative safety compared with traditional NSAIDs, nonacetylated salicylates (e.g., salsalate, choline magnesium trisalicylate) should be tried first. Chronic use of NSAIDs may be fraught with a number of risks including congestive heart failure,[62] exacerbation of hypertension,[63] renal insufficiency,[64] and gastrointestinal bleeding.[65] According to the American College of Rheumatology, risk factors for GI bleeding are age 75 and older, peptic ulcer disease, GI bleed, and use of glucocorticosteroids. Risk factors associated with renal insufficiency include age 75 and older, diabetes mellitus, hypertension, and use of angiotension-converting enzyme inhibitor or diuretics.[49] Some authorities recommend avoiding NSAIDs in patients with congestive heart failure due to the possibility of exacerbation and in patients with renal dysfunction who have serum Cr concentration over 150 μmol or glomerular filtration rate of less than 50 ml/hr.[66]

Corticosteroids: Corticosteroids are commonly prescribed in older adults with inflammatory disorders (e.g., giant cell arteritis, polymyalgia rheumatica, rheumatoid arthritis). They also are indicated for pain associated with malignancy because they reduce tumor-associated edema that can cause spinal cord compression, brain herniation, and compressive neuropathy. In the early stages of use patients may note improved appetite and mood; however, with prolonged use common side effects include glucose intolerance, hypertension, psychosis, and osteoporosis, to name a few. Long-term steroids should be avoided unless absolutely necessary in older adults because of their broad side effect profile.[66,67]

OPIOID ANALGESICS

The AGS guidelines[61] encourage physicians to consider using opioids for the treatment of moderate to severe pain (both nociceptive and neuropathic), earlier in the course of disease than previously recommended to avoid the multiple potential toxicities associated with NSAIDs.[68] Despite this recommendation, providers continue to carry reservations regarding their potential for abuse, side effect profile, and lack of long-term studies performed specifically in older adults with noncancer pain. A general rule is that long-acting opioids should never be initiated in the older adult who is opioid-naïve. A short-acting preparation should always be initiated and once the total daily dose requirement is determined, the patient can then be

TABLE 58–8 Recommended Drugs for Persistent Pain in Older Adults

Drug	Recommended Starting Dose*	Comments
Nonopioid Analgesic		
Acetaminophen (Tylenol)	325–500 mg every 4 hr or 500–1000 mg every 6 hr	Maximum dose usually 4 g daily. Reduce maximum dose 50% to 75% in patients with hepatic insufficiency or history of alcohol abuse.
Choline magnesium trisalicylate (Tricosal, Trilisate)	500–750 mg every 8 hr	Long half-life may allow daily or twice-daily dosing after steady state is reached. Minimal antiplatelet effect.
Salsalate (e.g., Disalcid, MonoGesic, Salflex)	500–750 mg every 12 hr	In frail patients or those with diminished hepatic or renal function, it may be important to check salicylate levels during dose titration and after reaching steady state. Minimal antiplatelet effect.
Celecoxib (Celebrex)	100 mg daily	Higher doses associated with higher incidence of gastrointestinal, cardiovascular side effects. Patients with indications for cardioprotection require aspirin supplement; therefore, older individuals will still require concurrent gastroprotection.
Naproxen sodium	220 mg 2 times daily	Several studies implicate this agent as possessing less cardiovascular toxicity.
Ibuprofen	200 mg 3 times a day	Food and Drug Administration indicates concurrent use with aspirin inhibits aspirin's antiplatelet effect, but the true clinical import of this remains to be elucidated, and it remains unclear whether this is unique to ibuprofen or true with other NSAIDs.
Diclofenac sodium	50 mg 2 times daily or 75 mg extended-release daily	Several studies implicate this agent as possessing less cardiovascular toxicity.
Nabumetone (Relafen)	1 g daily	Relatively long half-life and minimal antiplatelet effect are associated with this agent (>5 days).
Ketorolac		Not recommended. High potential for adverse gastrointestinal and renal toxicity; inappropriate for long-term use.
Opioid		
Hydrocodone** (Lorcet, Lortab, Norco, Vicodin, Vicoprofen)	2.5–5 mg every 4–6 hr	Useful for acute recurrent, episodic, or breakthrough pain; daily dose limited by fixed-dose combinations with acetaminophen or NSAIDs. Prescribers need to consider the amount of nonopioid agent in each of these preparations—they are not all the same—and other acetaminophen or NSAID-containing preparations the patient is taking, including over-the-counter medications.
Oxycodone†		
(OxylR, Percocet, Percodan, Tylox, Combunox)	2.5–5 mg every 4–6 hr	Useful for acute recurrent, episodic, or breakthrough pain; daily immediate-release dose limited by fixed-dose combinations with acetaminophen or NSAIDs. Immediate-release oxycodone is available without added coanalgesics. Prescribers should specify which oxycodone preparation they want for their patient to avoid confusion or co-analgesic toxicity.
(OxyContin)	10 mg every 12 hr	Usually started after initial dose determined by effects of immediate release opioid or as an alternative to a different long-acting opioid because of indications for opioid rotation. Although intended for 12-hr dosing, some patients only get 8 hr of effective analgesia, whereas some frail older patients get 12 to 24 hr of relief.

TABLE 58–8 Recommended Drugs for Persistent Pain in Older Adults—cont'd

Drug	Recommended Starting Dose	Comments
Morphine		
Immediate release (MSR, Roxanol)	2.5–10 mg every 4 hr	Available in tablet form and as concentrated oral solution, which is most commonly used for episodic or breakthrough pain and for patients unable to swallow tablets.
Sustained release (Avinza, Kadian, MSContin, Oramorph SR)	15 mg every 8–24 hr (see dosing guidelines in package insert for each specific formulation)	Usually started after initial dose determined by effects of immediate-release opioid or as an alternative in a different long-acting opioid due to indications for opioid rotation. Toxic metabolites of morphine may limit usefulness in patients with renal insufficiency or when high-dose therapy is required. Continuous-release formulations may require more-frequent dosing if end-of-dose failure occurs regularly. Significant interactions with food and alcohol toxicity.
Hydromorphone (Dilaudid, Hydrostat)	1–2 mg every 3–4 hr	For breakthrough pain or for around-the-clock dosing.
Methadone (Dolophine)		Use recommended only by practitioners knowledgeable in its pharmacology and experienced in its use. Highly variable half-life and nonlinear dose equivalencies when switching from other opioids. Not recommended as first-line agent.
Oxymorphone		
Immediate release (Opana IR)	5 mg every 6 hr	Typical opioid side effects. Significant interactions with food and alcohol toxicity.
Extended release (Opana ER)	5 mg every 12 hr	Usually started after initial dose determined by effects of immediate-release opioid or as an alternative to a different long-acting opioid because of indications for opioid rotation.
Transdermal fentanyl (Duragesic)	12–25 mcg/hr patch every 72 hr	Started after initial dose determined by effects of immediate-release opioid or as an alternative to a different long-acting opioid because of indications for opioid rotation. Current available lowest-dose patch recommended for patients who require <60 mg per 24-hr oral morphine equivalents. Peak effects of first dose take 18 to 24 hr. Duration of effect is usually 3 days but may range 48 hr to 96 hr. May take two to three patch changes before steady-state blood levels reached.
Adjuvant Drug		
Tricyclic Antidepressant*		
Desipramine (Norpramine), Nortryptyline (Aventyl, Pamelor), Amitriptyline (Elavil)	10 mg at bedtime	Significant risk of adverse effects in older patients. Anticholinergic effects (visual, urinary, gastrointestinal); cardiovascular effects (orthostasis, atrioventricular blockade). Older persons rarely tolerate doses greater than 75 to 100 mg per day.
Other Antidepressant*		
Duloxetine (Cymbalta)	20 mg daily	Monitor blood pressure, dizziness, cognitive effects, and memory. Has multiple drug-drug interactions.
Venlafaxine (Effexor)	37.5 mg daily	Venlafaxine associated with dose-related increases in blood pressure and heart rate.
Milnacipran (Savella)	50 mg 2 times daily/starting dose 12.5 mg once a day. See package insert for titration recommendations. Discontinuation requires tapering.	Caution in renal insufficiency with creatinine clearance less than 30 ml/min, reduce dose by 50%. Common reactions include nausea, constipation, hot flashes, hyperhidrosis, palpitations, dry mouth, hypertension. Contraindicated with monoamine oxidase inhibitors and narrow-angle glaucoma.

Continued

TABLE 58–8 Recommended Drugs for Persistent Pain in Older Adults—cont'd

Drug	Recommended Starting Dose	Comments
Anticonvulsant		
Carbamazepine (Tegretol)	100 mg daily	Monitor hepatic transaminases (aspartate transaminase, alanine transaminase), complete blood count, creatinine, blood urea nitrogen, electrolytes, serum carbamazepine levels. Multiple drug-drug interactions.
Gabapentin (Neurontin)	100 mg at bedtime	Monitor sedation, ataxia, edema.
Pregabalin (Lyrica)	50 mg at bedtime	Monitor sedation, ataxia, edema.
Lamotrigine (Lamictal)	25 mg at bedtime	Monitor sedation, ataxia, cognition. Associated with rare cases of Stevens-Johnson syndrome.
Antiarrhythmic		
Mexiletine (Mexitil)	150 mg twice daily	Monitor electrocardiogram at baseline and after dose stabilization. Avoid use in patients with conduction block, bradyarrhythmia.
Other Drugs		
Corticosteroids (prednisone, methylprednisolone, e.g., Deltasone, Medrol dose pak Liquid Pred, Orasone)	Example: 5 mg prednisone daily and taper as soon as feasible.	Use lowest possible dose to prevent steroid effects. Anticipate fluid retention and glycemic effects in short-term use and cardiovascular and bone demineralization with long-term use.
Lidocaine (topical) (Lidoderm 5%)	1–3 patches for 12 hr per day	Monitor for rash or skin irritation.
Muscle Relaxants		
Baclofen (Lioresal)	5 mg up to 3 times daily	Monitor muscle weakness, urinary function, cognitive effects, sedation. Avoid abrupt discontinuation because of central nervous system irritability. Older persons rarely tolerate doses greater than 30 to 40 mg per day.
Tizanidine (Zanafex)	2 mg up to 3 times daily	Monitor muscle weakness, urinary function, cognitive effects, sedation, orthostasis. Potential for many drug–drug interactions.
Clonazepam (Klonopin)	0.25–0.5 mg at bedtime	Monitor sedation, memory, complete blood count.
Cannabinoid		
Nabilone (Cesamet)	1 mg 1 or 2 times daily	Monitor ataxia, cognitive effects, sedation. High incidence of dizziness or drowsiness. Cardiovascular effects with tetrahydrocannabinol or cannabidiol. Older persons may be prone to postural hypotension. Nabilone is approved for nausea and vomiting but may help with some pain syndromes.
Dronabinol (Marinol)	2.5 mg 1 or 2 times daily	Dizziness, somnolence, cognitive impairment, dysphoria.
Dual-Mechanism Drug		
Tramadol (Ultram/Ultram ER)	12.5–25 mg every 4–6 hr	Mixed opioid and norepinephrine or serotonin reuptake inhibitor mechanisms of action. Monitor for opioid side effects, including drowsiness, constipation, and nausea. Risk of seizures if used in high doses or in predisposed patients. May precipitate serotonin syndrome if used with selective serotonin reuptake inhibitors.
Tapentadol (Nucynta)	50 mg every 4–6 hr by mouth (equivalent to oxycodone 10 mg every 4–6 hr by mouth)	Clinical trials of tapentadol suggest lower incidence of gastrointestinal adverse events than comparator opioids.

Note: This table is intended to highlight common agents for the purposes of illustrating potentially underappreciated features of particular drugs. This table is not an endorsement of any therapeutic agent, nor is it intended to reflect a hierarchy of treatment. Similarly, it is not meant to be an exhaustive listing. Doses listed should be checked with manufacturer's recommendations.

[*] *Lowest starting dose should be considered in frail older persons with a history of sensitivity to central nervous system–active drugs.*

[**] *Only available in combination with acetaminophen or nonsteroidal anti-inflammatory drug (NSAID); see guideline for dose limitations based on coanalgesic.*

[†] *Available with or without acetaminophen or NSAID: see guideline for dose limitations based on coanalgesic.*

Source: American Geriatrics Society Panel: Pharmacological management of persistent pain in older persons. Pain Med *10:1062–1083, 2009.*

switched to a long-acting preparation, supplemented with an as-needed short-acting drug for breakthrough pain.

The risk of opioid abuse appears to be less problematic in older adults than younger individuals.[69] It is important, however, to be vigilant regarding potential abuse. Screening tools have been developed, although most of these instruments have been validated only in younger individuals.[70,71] As an initial screening tool, the AGS panel[61] suggested using the Opioid Risk Tool,[72] which provides a concise office-based instrument for detecting potential for abuse or deviant behavior (Table 58-9).

In addition to ascertaining the potential for abuse before starting opioids, it is very important to counsel patients about the risk of adverse effects. Those of particular relevance to older adults are discussed here. The risk of constipation is substantial, although it does not occur uniformly. Patients should be instructed to be vigilant for its development and at the first sign of constipation a regular bowel program should be established. Educating patients prior to starting opioids about the risk of falls and fractures is critical. In a cohort study of more than 2000 people over age 60, use of opioids at morphine equivalent doses 50 mg/day or more doubled the risk of fracture compared to those no longer taking opioids (hazard ratio [HR]= 2.00, 95% confidence interval [CI] = 1.24–3.24).[73] For older adults with mobility impairment, prescription of an assistive device should be considered prior to prescribing opioids. Other potential side effects especially relevant for older adults include urinary retention (e.g., in the patient with prostatic enlargement) and delirium. Long-term studies regarding the risk/benefit ratio associated with opioids are lacking. Thus the true potential for development of immunologic changes, hypogonadism, and/or hyperalgesia when older adults use opioids indefinitely is unknown.[74]

Buprenorphine has been shown to be both effective and well-tolerated in patients with cancer and nonmalignant persistent pain such as neuropathic pain outside of the United States.[75,76] These studies have studied primarily transdermal buprenorphine, currently unavailable in the United States. Fentanyl patches have been used increasingly to treat persistent pain in the older adult; while it appears that transdermal buprenorphine may have a better side effect profile, therapeutic index, and ease of titration, inadequate data exist to support recommending its use in older adults. Patients with opioid dependence, myasthenia gravis, respiratory depression, and delirium tremens should not be prescribed buprenorphine.

Methadone is not included in the AGS guidelines. It may be underprescribed in older adults, although it is not without risks. Given its low cost, long-acting properties, and efficacy when used in small doses in frail older adults, methadone may be very useful.[77] It is metabolized by CYP 3A4 and CYP 2B6 into inactive metabolites, which pose no threat of neurotoxicity as do morphine and meperidine. However, use of methadone is not without risks given its very long and variable half-life. In addition to having all of the same potential adverse effects as the other opioids, patients on methadone may suffer from QTc prolongation[78] and sleep-disordered breathing.[78,79] Recent guidelines suggest that patients being started on methadone should receive an EKG at baseline, 30 days after initiating methadone, and then annually.[80] Since QT prolongation is dose dependent, it is recommended that an EKG be repeated 30 days after dose titration as well. Because of

TABLE 58–9 Predicting Aberrant Behaviors in Opioid-Treated Patients: Preliminary Validation of the Opioid Risk Tool

Item	Mark Each Box That Applies	Item Score If Female	Item Score If Male
1. Family history of substance abuse			
Alcohol	[ ]	1	3
Illegal drugs	[ ]	2	3
Prescription drugs	[ ]	4	4
2. Personal history of substance abuse			
Alcohol	[ ]	1	3
Illegal drugs	[ ]	2	3
Prescription drugs	[ ]	4	4
3. Age (mark box if 16–45)		1	1
4. History of preadolescent sexual abuse	[ ]	3	0
5. Psychological disease			
Attention deficit disorder, obsessive-compulsive disorder, bipolar, schizophrenia	[ ]	2	2
Depression	[ ]	1	1
Total		—	—
Total score risk category			
Low risk: 0–3			
Moderate risk: 4–7			
High risk: ≥8			

Source: Webster LR, Webster RM: Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med *6:432–442, 2005.*

the lack of research on methadone specifically in older adults, it should not be used as a first line treatment in the older adult for whom a long acting opioid is indicated. Transdermal fentanyl may be preferred as it has similar properties to methadone and has been studied in older adults.[81]

DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

The aging of the population, the number of people living with chronic disease, and the improvements in treating cancer and other diseases have contributed to the increased prevalence of neuropathic pain.[82] The International Association for the Study of Pain, Neuropathic Pain Special Interest Group, has created evidence-based treatment guidelines for neuropathic pain.[74]

For the vast majority of patients (with notable exceptions) the following classes of medications were recommended as first-line treatment: antidepressants with both norepinephrine and serotonin reuptake inhibition properties (SNRIs), calcium channel α2-δ ligands, and topical lidocaine. Second-line agents included opioids and tramadol.[74] The most commonly studied SNRI antidepressants for treating neuropathic pain are duloxetine and venlafaxine. Both have evidence of efficacy for painful diabetic neuropathy.[83,84] Venlafaxine had also been used in cases of painful polyneuropathies, although caution should be exercised in patients with cardiovascular disease.[84] Treatment of trigeminal neuralgia is different from that of other neuropathic pain states. For this disorder, carbamazepine or oxcarbazepine are recommended as first line.[85]

Older adults are well-represented in studies of neuropathic pain, demonstrating the efficacy of gabapentin, pregabalin, and tricyclic antidepressants for postherpetic neuralgia.[86] Tertiary amines (amitriptyline, imipramine, trimipramine, doxepin, clomipramine) should be avoided in older adults because of their anticholinergic side effects (sedation, delirium, urinary retention, constipation, glaucoma exacerbation, and dizziness). Secondary amines have been shown to have more tolerable side effect profiles (nortriptyline, desipramine, protriptyline, amoxapine). Because of their potential for QT prolongation, a baseline EKG should be obtained prior to starting a tricyclic antidepressant and monitored periodically with dose titration.

Limited data have been published on using opioids (morphine, oxycodone, transdermal fentanyl and buprenorphine, and methadone) as second- or third-line options for the treatment of neuropathic pain.[76] However, opioids have proved efficacious in patients with postherpetic neuralgia and painful peripheral neuropathy.[87] Tramadol, a weak μ-opioid receptor agonist that also inhibits the reuptake of norepinephrine and serotonin, may fare better in older adults at reducing neuropathic pain.[88]

Benzodiazepines have been used to treat muscular spasms, neuropathic pain, and anxiety related to pain crises. Given their large therapeutic index, adverse effects are uncommon in younger patients. These medications should generally be avoided in older adults for the treatment of neuropathic pain because of the risk of symptomatic rebound, dizziness, falls, and confusion. Even brief courses of benzodiazepines for persistent pain can be detrimental.[53,89]

DRUGS FOR THE TREATMENT OF WIDESPREAD PAIN

Fibromyalgia is one of the more common chronic nonmalignant widespread pain problems in older women with symptoms occurring for longer than 3 months varying from morning stiffness, fatigue, and nonrestorative sleep to headaches, myofascial pain, and pelvic pain.[90] Treatments for fibromyalgia that have strong efficacy evidence include low-dose tricyclic antidepressants, cyclobenzaprine, aerobic exercise, cognitive behavioral therapy, or a combination of these treatment methods.[91] Duloxetine, pregabalin, and milnacipran are Food and Drug Administration (FDA) approved for the treatments of fibromyalgia. Outcomes used to monitor treatment efficacy in patients with fibromyalgia include pain intensity and physical and emotional functioning. In patients who are unresponsive to traditional treatment options, consideration of complementary or alternative therapies may be beneficial.

COMPLEMENTARY AND ALTERNATIVE MODALITIES

The use of complementary and alternative medicine (CAM) approaches to persistent pain has increased steadily over the past decade. Meditation, vitamin and mineral supplements, herbs, and chiropractic medicine are commonly used in older adults with back pain, arthritis, and mental illness. The evidence base for the efficacy of CAM in older adults is accumulating slowly. Preliminary data suggest that mindfulness meditation (MM) helps older adults with chronic low back pain (CLBP). Specifically, MM appears to exert its effect in part by decreasing the interference of pain with performing daily activities.[92] Lumbar percutaneous electrical nerve stimulation (PENS) also has been studied in older adults with CLBP. A large randomized controlled trial demonstrated that both lumbar PENS and a control procedure using a briefer duration of electrical stimulation significantly reduced pain and improved function and that these beneficial effects persisted for 6 months.[93] Periosteal stimulation facilitated by acupuncture needles also has undergone preliminary investigation, with demonstrated efficacy for older adults with advanced knee OA and persistent pain.[94] Given the multiple potential toxicities and ineffectiveness of many traditional treatment approaches, additional research is essential regarding the effectiveness of CAM for older adults. A critical review on mind and body interventions focused on eight common behavioral modalities in treating persistent pain in older adults.[95] The following modalities were reviewed: biofeedback, progressive muscle relaxation, meditation, guided imagery, hypnosis, tai chi, qi gong, and yoga. The benefits of complementary therapies such as these improve not only the self-reported pain but also pain-related comorbidities such as depression, anxiety, and disability. The authors encouraged more research regarding these techniques in older adults with persistent pain conditions so that clinicians can better implement these treatments in their routine therapeutic approach.

INTERDISCIPLINARY TREATMENT

Geriatrics as a medical discipline originated before the 1950s, although the practice of caring for the older adult continues to involve dynamic paradigms. In its initial phase of development, emphasis was placed on promoting an interdisciplinary approach and maintaining the functional status of the older adult with early detection and management of disability.[96] Similarly, interdisciplinary treatment programs are effective for the treatment of persistent pain conditions, and preliminary data indicate that older adults respond to these programs as well as younger individuals.[97–100]

The practice of interdisciplinary pain medicine should be conceptualized broadly for the older adult. Not only is there a role for physical therapy, occupational therapy, and psychology in treating many of these patients, a number of different physician specialists also may be needed to optimize care. In the practice of pain medicine, it is important to consider geriatricians, geriatric psychiatrists, physiatrists, rheumatologists, neurologists, and endocrinologists as important potential collaborators in the care of frail older adults with complex conditions.

CONCLUSION

The older adult with persistent pain presents multiple diagnostic and therapeutic challenges. Pain and aging is a field with many unanswered questions and few if any gold standards regarding treatment. Over the past decade, expert panels of clinicians comprising diverse specialties have emerged to provide systematic approaches for practitioners caring for the geriatric patient. As a field that is constantly evolving, practitioners caring for the older adult in pain must remain vigilant for new diagnostic and therapeutic developments to optimize their patients' quality of life.

KEY POINTS

- As the number of older adults living with chronic conditions continues to increase physicians in all disciplines will need to be adept at the management and treatment of the older patient in persistent pain.
- Pain may present subtly in older adults as changes in mobility or activity level, mood, sleep, and/or appetite. These symptoms constitute the older adult's pain signature and represent pain treatment outcomes.
- Effective pain treatment requires differentiating the weakest link from the treatment targets.
- To optimize function and quality of life, all contributors to pain and disability must be addressed.
- Given aging-associated changes in pharmacokinetics and pharmacodynamics and the common occurrence of multiple medical comorbidities in older adults, treatment should start with nonpharmacologic or nonsystemic pharmacologic treatment approaches such as exercise, physical therapy, assistive devices, and complementary and alternative treatments.

REFERENCES

Access the reference list online at http://www.expertconsult.com

Interventional Techniques for Pain Management

CHAPTER 59

Joint Injections

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Interventional management of musculoskeletal and joint pain may include injection either into the joint space (intra-articular), around the joint space (periarticular) or within specific soft tissue structures. The choice of medication and number of injections are determined by the indication and treatment goal, that is, diagnostic or therapeutic.[1] Injections may be with corticosteroid, local anesthetics, or viscoelastic supplementation.

In this chapter we will discuss common injections into the shoulder, hip and knee joints, their indications, the various techniques including those with imaging modalities and their complications.

SHOULDER JOINT

Shoulder pain is a very common clinical problem in the general population[2] and is associated with high societal cost and patient burden.[3] It is defined as chronic when it has been present for longer than 6 months. Common conditions that can result in chronic shoulder pain include rotator cuff disorders, adhesive capsulitis, shoulder instability, and shoulder arthritis.[4] Persistent shoulder pain can also result from bursitis, tendonitis, impingement syndromes, avascular necrosis, other causes of degenerative joint disease, or traumatic injury. Rotator cuff disorders, adhesive capsulitis, and glenohumeral osteoarthritis are common causes of persistent shoulder pain and account for about 20% of all shoulder pain. Joint injection should be considered after failure of conservative interventions such as nonsteroidal anti-inflammatory drugs and physical therapy.[3] Physical examination plays a key role in aiding with diagnosis. Imaging studies including plain radiographs, magnetic resonance imaging, ultrasonography, and computed tomography scans may be indicated either when the etiology is unclear or if findings would change the management. For example, the diagnosis of shoulder instability, and shoulder arthritis may be made with plain radiographs although magnetic resonance imaging and ultrasonography are preferred for rotator cuff disorders.

GLENOHUMERAL JOINT

JOINT ANATOMY

The glenohumeral joint is a multiaxial ball-and-socket synovial joint. As the humeral head is larger than the glenoid fossa, only part of the humeral head can be in articulation with the glenoid fossa at any given joint position, thus making it relatively unstable. The glenoid labrum is a rim of fibrocartilaginous tissue that surrounds the glenoid fossa thereby deepening the articular cavity. Additionally, it protects the bony edges and provides lubrication to the joint. The tendons of the long head of the biceps brachii and triceps brachii muscles further strengthen the labrum.[5] The joint itself is surrounded by a thin loosely fitting capsule that attaches medially to the margin of the glenoid fossa beyond the labrum and laterally to the anatomical neck extending slightly below the shaft of the humerus. While the capsule contributes little to the overall stability of the joint, it is the ligaments and the attachment of the muscle tendons of the rotator cuff that is vital to the maintenance of structural integrity of the joint. Superiorly, the joint is supported by the capsule in conjunction with the coracohumeral ligament, anteriorly, by the glenohumeral ligaments and the attachment of the subscapularis tendon and posteriorly, by the attachment of the teres minor and infraspinatus tendons. Inferiorly, however, the capsule is thin and weak and contributes little to the stability of the joint.[5] The inferior part of the capsule is subjected to considerable strain as it is stretched tightly across the head of the humerus when the arm is elevated. The tendon of the long head of the biceps brachii muscle is situated in the intertubercular groove, and then becomes intracapsular. It is particularly prone to injury at the point where it arches over the humeral head and at the junction of bony cortex with articular cartilage.[5]

INDICATIONS

Indications for glenohumeral joint injection include osteoarthritis, adhesive capsulitis, and rheumatoid arthritis. Patients with glenohumeral osteoarthritis present with gradual onset of pain and loss of motion. Adhesive capsulitis, also known as frozen shoulder, typically occurs after prolonged immobility of the arm.[6] Clinical presentation includes diffuse shoulder pain with the inability to abduct at the shoulder more than just a few degrees in any direction. Shoulder examination reveals diffuse pain with palpation and reduced active and passive range of motion in all planes. Adhesive capsulitis can be associated with diabetes and thyroid disorders. Remarkably, findings on radiography will often be normal.[6]

TECHNIQUE

The accuracy of blind injections has been shown to vary significantly and may be as low as 30%. Both ultrasound guidance (USG) and fluoroscopy markedly improve the accuracy to 65% to 90% depending on the approach. The USG resulted in fewer attempts and shorter procedure duration compared to fluoroscopy.[7]

The glenohumeral joint can be injected from an anterior or posterior approach. Rutten et al. compared the anterior and posterior approaches and did not find any advantage of either approach.[7] However, in a cadaveric study, Chung et al. found that the anterior stabilizing structures of the glenohumeral joint are often traversed by the needle when the anterior approach is used, which may cause distortion of the healthy anatomic structures.[8] Thus a modified anterior approach or injection into the rotator cuff interval has been described to avoid injury to the subcoracoid bursa, subscapularis muscle and tendon or the inferior glenohumeral ligament.[9,10] In the blind technique, it is recommended that for easy access of the joint the patient be comfortably seated with his arm at the side, and the shoulder externally rotated for the anterior approach (i.e., palm facing out or forward). By externally rotating the arm, more anterior articular surface of the humeral head is exposed. Additionally, it ensures that the long head of the biceps tendon is removed from the injection tract. On the contrary, internal rotation of shoulder is preferred in posterior approach with the forearm across the body and the ipsilateral hand touching the contralateral elbow.[3,11]

Blind Anterior Approach: The needle should be placed just medial to the head of the humerus and 1 cm lateral to the coracoid process. The needle is directed posteriorly and slightly superiorly and laterally to avoid the cephalic vein, brachial plexus and axillary artery located medial to the coracoid. When the needle hits the bone (humeral head), it should be withdrawn slightly into the joint space (Figs. 59-1 and 59-2).[3,11,12]

Blind Posterior Approach: The needle should be inserted 1 to 2 cm inferior and medial to the posterolateral corner of the acromion and directed anteriorly in the direction of the coracoid process[3,11] (Figs. 59-3 and 59-4).

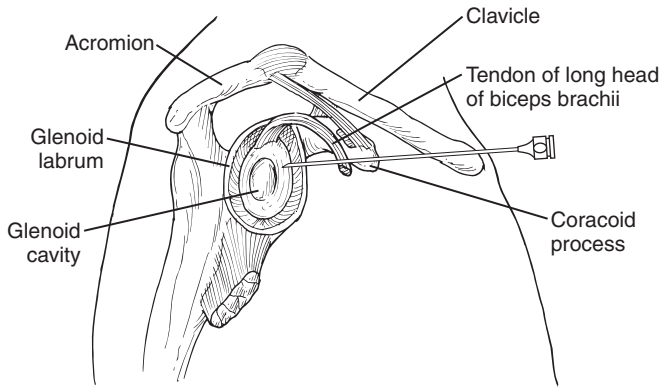

FIGURE 59-1 Illustration showing the glenohumeral joint anatomy and the needle direction for the anterior approach. *(Reprinted with permission from Elsevier.)*

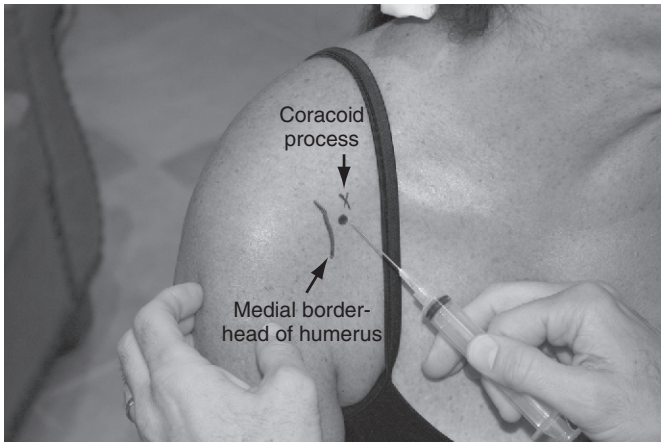

FIGURE 59-2 Glenohumeral joint injection—the anterior approach. *(Reprinted with permission from Elsevier.)*

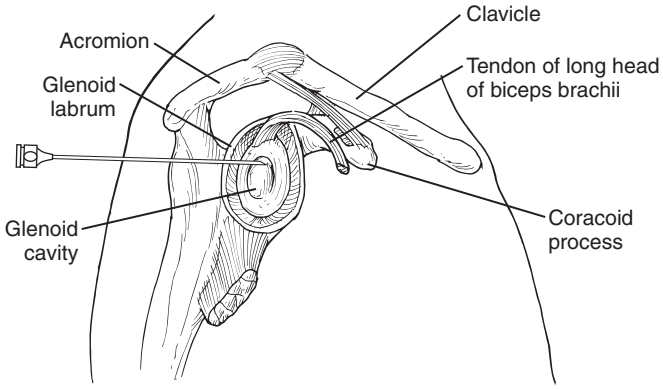

FIGURE 59-3 Illustration showing the glenohumeral joint anatomy and the needle direction for the posterior approach. *(Reprinted with permission from Elsevier.)*

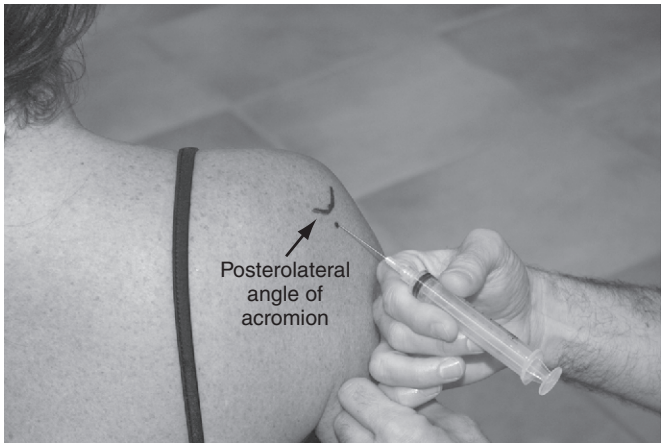

FIGURE 59-4 Glenohumeral joint injection—the posterior approach. *(Reprinted with permission from Elsevier.)*

Fluoroscopically Guided Anterior Approach: The injection is performed with the patient supine and the shoulder slightly externally rotated. After the skin is prepped and draped, the injection site is infiltrated with local anesthetic. A 22-gauge needle is directed in the AP view under fluoroscopic control

at the junction of the middle and lower thirds of the medial part of the humeral head.[13] If resistance to injection is encountered, the needle tip is most likely in the cartilage and should be redirected by rotating or slightly withdrawing it away from the humerus. The needle should not be withdrawn more than few millimeters, otherwise the needle tip will be in the subacromial-subdeltoid bursa. If needle manipulation does not yield the desired result, the needle should be gently directed medially, while exercising caution not to advance the needle into the glenoid labrum. Contrast material may be injected to confirm intraarticular placement with spread of contrast between the glenoid and the humerus.

Fluoroscopically guided injection into the rotator cuff interval. The rotator cuff interval has been described as a triangular space on the superomedial aspect of the humeral head.[10] It is a right triangle, the base of which is formed by the superior border of the subscapularis muscle up to the anterior border of the glenohumeral joint, the height is formed by the lateral border of the coracoid process from the superior border of the subscapularis tendon to the edge of the supraspinatus tendon, and the hypotenuse is formed by the inferior border of the supraspinatus tendon. The apex of the triangle is at the intersection of the base, and the hypotenuse is represented by the bicipital groove. Within this triangle are the biceps tendon, glenohumeral capsule, coracohumeral ligament, and glenohumeral ligament. This triangle serves as a site for glenohumeral joint injection.

External rotation of the humerus may avoid injection into the long head of the biceps tendon. However, if patient cannot tolerate it, the arm may be in neutral position (i.e., palm facing the thigh). The fluoroscopy tube is positioned perpendicular to the table, and the point of entry is marked over the upper medial quadrant of the humeral head close to the articular joint line. With intermittent fluoroscopy, we then advance the needle parallel to the x-ray beam or with a slight medial angulation until it came in contact with the humeral head. Injection of contrast may be used to confirm the intra-articular position of the needle.[10]

Fluoroscopically Guided Posterior Approach: The injection is performed in prone position with the symptomatic shoulder slightly raised until the glenohumeral joint is seen tangentially. After the skin is sterilely prepped and draped, the injection site is infiltrated with local anesthetic. With the shoulder in a neutral position or slightly internally rotated, the needle is aimed at the inferomedial quadrant of the humeral head and advanced vertically under fluoroscopic guidance to the cartilage of the humeral head.[8,14]

Ultrasound-Guided Posterior Approach: The patient is positioned either lying obliquely prone on the contralateral shoulder or sitting upright with the back to the physician and the ipsilateral hand on the contralateral shoulder there by internally rotating the shoulder. The injection may be performed with a 7.5- to 14-MHz linear array transducer. After the skin and transducer are sterilely prepared and drape, the injection site is infiltrated with local anesthetic. The probe is positioned at the myotendinous junction of the infraspinatus muscle inferior to the spine of the scapula. The larger size and the superior location of the infraspinatus muscle and its longer tendon differentiates it from the teres minor muscle. The lateral humeral head, posterior glenoid rim and medial triangular shaped labrum should be identified as hyperechoic areas. The needle is inserted in-plane, that is, from lateral to medial, parallel to the long axis of the transducer and advanced in the joint between the humeral head and the posterior glenoid labrum. Upon piercing the ligament, a "pop" or loss of resistance will be felt. After negative aspiration, the joint should be injected. However, if resistance is felt, the needle should be repositioned as it is most likely in the cartilage.[15–18]

Ultrasound-Guided Rotator Cuff Interval Approach (Modified Anterior Approach): The transducer is placed cephalad to the greater and lesser tuberosities of the humerus with visualization of the intra-articular course of the biceps tendon between the supraspinatus and subscapularis tendons (Fig. 59-5). The superior glenohumeral ligament is visualized between the biceps and subscapularis tendon while the coracohumeral ligament is between the biceps and supraspinatus tendons. The needle is advanced in-plane between the biceps tendon and the subscapularis tendon.[15–18]

ACROMIOCLAVICULAR JOINT INJECTION

JOINT ANATOMY

The acromioclavicular joint is a synovial joint between the small, convex oval facet on the lateral end of the clavicle and a concave area on the anterior part of the medial border of the acromion process of the scapula (Fig. 59-6). The articular surfaces are such that the joint line is oblique and slightly curved. This joint curvature permits the acromion, and thus the scapula, to glide forward or backward over the lateral end of the clavicle. This movement of the scapula keeps the glenoid fossa continually facing the humeral head.[5] The joint contributes to total arm movement in addition to transmitting forces between the clavicle and the acromion. The acromioclavicular joint has a capsule and the upper aspect of the joint is strengthened by the superior acromioclavicular ligament. The major ligamentous structure stabilizing the joint and binding the clavicle to the scapula is the coracoclavicular ligament. Although this ligament is placed

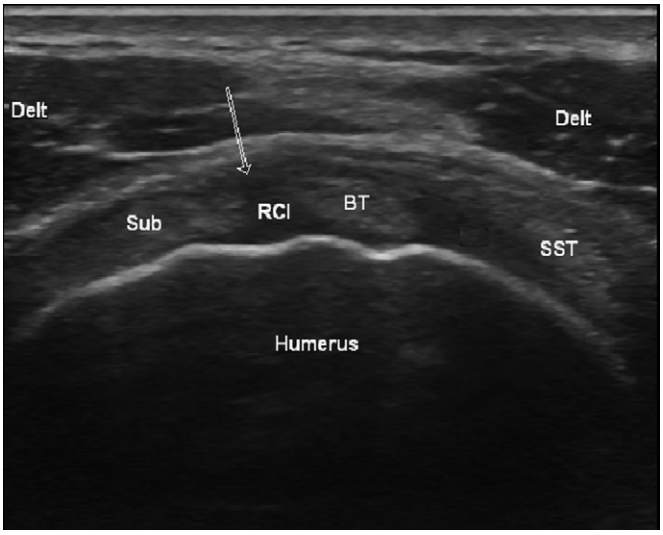

FIGURE 59-5 Sonogram showing the rotator cuff interval (RCI) approach as delineated by the arrow. BT, biceps tendon; Sub, subscapularis; SST, supraspinatus tendon; Delt, deltoid.

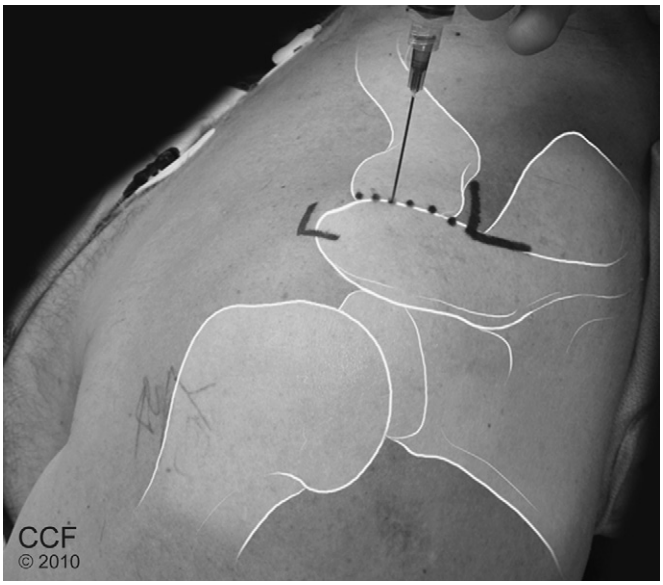

FIGURE 59-6 The acromioclavicular joint. *(Reprinted with permission from Cleveland Clinic.)*

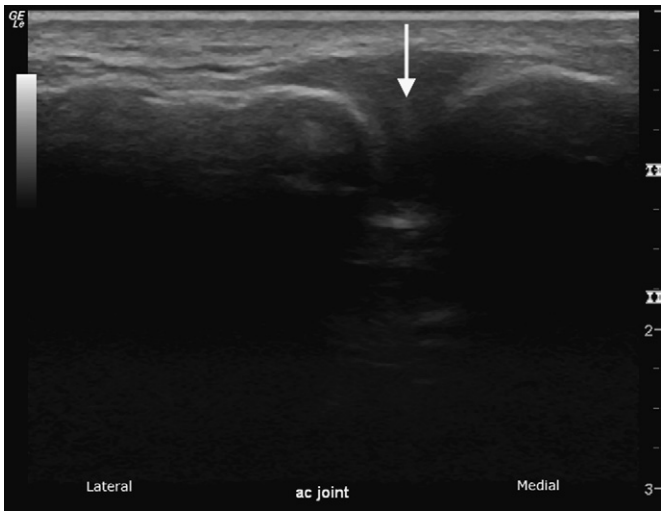

FIGURE 59-7 Long axis sonogram showing the acromioclavicular joint (*arrow*). It is the gap between the clavicle medially and the acromion process laterally.

medially and is separate from the joint, it forms the most efficient means of preventing the clavicle from losing contact with the acromion.[5]

INDICATIONS

Indications for injection of the acromioclavicular joint include osteolysis of the distal clavicle and osteoarthritis.[3] Osteolysis of the distal clavicle is a degenerative process that results in chronic pain, particularly with adduction movements of the shoulder and is typically seen secondary to traumatic injury or in persons who perform repetitive weight training involving the shoulder. Osteoarthritis also may develop in the acromioclavicular joint and typically develops secondary to previous trauma or injury. History and physical examination are important in making the diagnosis of osteolysis of the distal clavicle or osteoarthritis. In each condition, patients usually have insidious onset of pain. On physical examination, there is tenderness to palpation of the acromioclavicular joint, and pain with active or passive adduction (reaching the arm across the body) of the shoulder. Pain can be exacerbated by having the patient hold the opposite shoulder and pushing the elbow toward the ceiling against resistance. Radiographs of the acromioclavicular joint will confirm the diagnosis of osteolysis or osteoarthritis.[3] Acromioclavicular joint injections can be used for diagnostic or therapeutic purposes. As a diagnostic tool, a local anesthetic is injected into the joint to confirm the origin of pain. In some cases, it may be difficult to differentiate pain from acromioclavicular joint pathology from other shoulder pathology, particularly rotator cuff impingement syndrome.

TECHNIQUE

The acromioclavicular is a small diarthrodial joint with a variable anatomy regarding inclination of the articulating bones. This, in addition to arthritic changes, especially local osteophytes may alter the three dimensional perception of the acromioclavicular joint with palpation. Accuracy of blind needle placement for acromioclavicular joint injection was found to be about 40%.[19] However, in a cadaveric study by Partington et al. involving 24 subjects, acromioclavicular joint injection was successful in 67% (16 shoulders), although half involved other structures.[20] In another cadaveric study by Pichler et al., a total of 76 acromioclavicular joints were injected with a methylene blue and subsequently dissected to distinguish intra- from periarticular injection. The overall frequency of periarticular injection was 43% (33 of 76). Twenty subjects were further injected with fluoroscopic guidance with 100% accuracy.[21]

Blind Approach: Patients are placed in the supine or seated position with the affected arm resting comfortably at their side. To identify the acromioclavicular joint, palpate the clavicle distally to its termination at which point a slight depression can be felt at the joint articulation. The needle is inserted from the superior and anterior approach into the acromioclavicular joint and directed inferiorly. Injection of the acromioclavicular joint should be carried out by positioning the needle almost perpendicular to the joint.

Fluoroscopic Approach: With fluoroscopy the patient is positioned supine and the image intensifier should be placed in an anteroposterior direction and the needle is advanced with intermittent fluoroscopy.[21]

Ultrasound Approach: The acromioclavicular joint can be visualized using a high frequency linear ultrasound transducer. The transducer should be placed vertically over the superior aspect of the acromioclavicular joint area and adjusted until the joint space is visualized (Fig. 59-7). Using an in-plane technique, a needle is advanced into the joint space. After injection, the intra-articular placement may be verified by noting widening of the joint space.[22]

HIP JOINT

In the National Health Interview Survey by the Centers for Disease Control and Prevention in 2006, knee pain was reported by 18% of respondents, and hip pain by 7% of respondents. The most common cause of hip pain in people

over the age of 50 is osteoarthritis of the hip joint. Other causes of hip pain include inflammatory arthritides such as rheumatoid arthritis and psoriatic arthritis, and trauma, infection, and avascular necrosis. True intra-articular hip pathology typically presents as pain localized to the groin, exacerbated by internal rotation.

Evaluation of hip pain is particularly challenging as the hip joint cannot be palpated and it is important to be aware of referred pain from a hernia, back (spinal stenosis), or from trochanteric bursitis. Intra-articular hip injections are a valuable tool from both diagnostic and therapeutic perspectives. Aspiration of joint fluid for analysis is commonly done for diagnostic purposes. Therapeutic joint injections typically with a combination of local anesthetic and corticosteroids are used to provide analgesia and improve functionality.

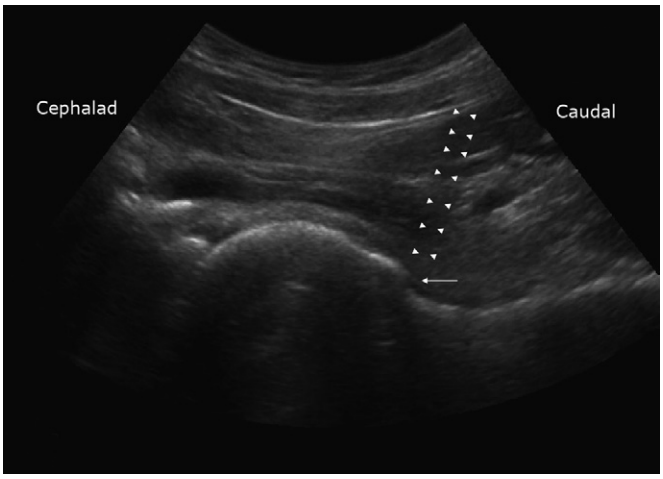

FIGURE 59-8 Long axis sonogram showing the needle path (arrow heads) towards the junction of the femoral head and neck (arrow).

HIP: INTRA-ARTICULAR INJECTION

ANATOMY

The hip is a ball-and-socket joint that exhibits a wide range of motion in all directions. The femoral head articulates with the pelvis to form the hip joint. The greater and lesser trochanters of the femur function as sites for muscle attachment. The spherical acetabular socket covers most of the femoral head except for the acetabular notch inferomedially where it is deficient. This deficient portion of the acetabulum is transversed by the acetabular ligament. The anatomic relationship between the femur and the acetabulum, with the acetabular cup oriented anterolaterally relative to the pelvis and the femoral neck directed posteriorly, contributes to the overall stability of the joint.[12] A thin layer of hyaline cartilage covers the surfaces of both the femoral head as well as the acetabulum allowing smooth movement of the joint. Just like the ball and socket joint of the shoulder, the hip joint also has a labrum, which is a circular layer of cartilage that surrounds the outer part of the acetabulum. This deepens the socket, thereby providing more stability. The joint capsule is a thick ligamentous structure with circular and longitudinal fibers that surround the entire joint and is lined by a synovial membrane. The head of the femur fits into the acetabulum, where it is held firmly by a thick capsule, which is divided into thickened layers forming the iliofemoral, pubofemoral, and ischiofemoral ligaments. The iliofemoral ligament connects the pelvis to the femur in the front of the joint. It is Y-shaped and stabilizes the hip by limiting hyperextension (Fig. 59-8). The pubofemoral ligament connects the pubis to the femur while the ischiofemoral ligament strengthens the posterior aspect of the capsule by attaching to the ischium and between the two trochanters of the femur. There are numerous muscles that attach to or cover the hip joint including gluteals, quadriceps, hamstrings, iliopsoas, and the groin muscles.

INDICATIONS

Intra-articular hip injections are performed for diagnostic and therapeutic purposes. Arthrocentesis of the hip is performed to diagnose the presence or absence of pyarthrosis. Intra-articular injection of the hip is used to determine the likelihood of achieving pain relief after hip arthroplasty. Therapeutic hip injections, although less commonly performed than knee injections, are usually indicated for the treatment of arthritic symptoms in patients who are not considered good surgical candidates.[23]

TECHNIQUE

Intra-articular hip injections are challenging because the joint cannot be easily palpated as well as its proximity to the femoral nerve, artery, and veins anteriorly. The anterior and lateral approaches are the most commonly used techniques. However, neither technique can be reliably used without radiologic guidance although the lateral approach is thought to be safer than the anterior approach. There was 60% success rate with the anterior approach and 80% success with the lateral technique. There was danger of injury to the femoral nerve in the anterior approach where there was actual impaling or contact of the nerve in 27% of anterior injections or were within five millimeters of the femoral nerve in 60% of attempts. Additionally, the anterior approach resulted in greater likelihood of injury to both the femoral artery and the lateral femoral cutaneous nerve than the lateral approach.[27] Thus image guidance is typically recommended either with fluoroscopy or with ultrasonography. Although fluoroscopy facilitates intra-articular needle placement under direct visualization and confirmation of correct placement with contrast injection, it requires additional equipment, and exposes both the operator and the patient to ionizing radiation. It also fails to visualize important neurovascular and soft-tissue structures.[24]

Fluoroscopic Anterior Approach: Fluoroscopy is used to visualize anatomical landmarks including the anterior superior iliac spine and the pubis. The femoral artery is palpated half-way between these points and the femoral nerve is about 1 cm lateral to the artery. The needle entry site is lateral to this point to avoid femoral nerve injury. Skin is prepped and draped and local anesthetic infiltrated into skin. The needle is advanced toward the junction of the femoral head and neck just inferior to the acetabular

lip. An arthrogram is then performed to confirm the placement of the needle inside the hip joint.[25]

Ultrasound Approach: In general, a low-frequency transducer is preferred as it allows for better depth penetration and wider field of view especially in obese patients. Patient is positioned supine with the hip neutral or slightly internally rotated. The anterior–superior iliac spine (ASIS) is palpated, and the transducer is oriented in a sagittal plane with the superior end just medial to the ASIS. While maintaining this orientation, the transducer is moved medially until the femoral head is visualized as a hyperechoic rounded surface. The transducer is then rotated into the transverse plane and moved medially to visualize the femoral nerve and vessels. After confirming the position of the neurovascular structures, the transducer is moved back to the anterior hip joint in the sagittal plane. The inferior end of the transducer is then rotated laterally while maintaining the superior portion on the femoral head to obtain a long-axis femoral head-neck view. The skin at the inferior end of the transducer is marked and the area is prepared in the usual sterile manner, and local anesthesia is injected. A 22-gauge spinal needle is advanced under direct ultrasound visualization to the junction of the femoral head and neck. A slight increase in resistance is appreciated as the needle reaches the iliofemoral ligament. A "pop" is felt as the needle passes through the ligament to enter the joint. Intraarticular placement is verified by visualizing the needle tip and injecting 1 to 2 ml of local anesthetic while observing the capsular distention with ultrasound. Fluid appears anechoic on ultrasound, and therefore as the hip is injected, the relatively hyperechoic iliofemoral ligament and anterior hip capsule can be visualized separating away from the femoral neck and head. In contrast to local anesthetic, corticosteroid crystals are hyperechoic and can be clearly visualized spreading between the femoral head–neck junction and the overlying capsule.[24]

HIP: GREATER TROCHANTERIC BURSA INJECTION

Greater trochanteric pain syndrome (GTPS), previously known as greater trochanteric bursitis, is a very common condition resulting in pain over the greater trochanter.[6] The incidence of greater trochanteric pain is reported to be approximately 1.8 patients per 1000 per year[26] with the prevalence being higher in women and patients with coexisting low back pain, osteoarthritis, iliotibial band tenderness, and obesity. Symptoms include pain in the lateral hip radiating along the lateral aspect of the thigh to the knee and occasionally below the knee. Physical examination reveals point tenderness over the greater trochanter. Most cases of GTPS are self-limited with conservative measures, such as physical therapy, weight loss, and nonsteroidal anti-inflammatory drugs. Other treatment modalities include bursa or lateral hip injections performed with corticosteroid and local anesthetic. More invasive surgical interventions have anecdotally been reported to provide pain relief when conservative treatment modalities fail.[27] Corticosteroid injections can provide considerable relief in most patients who fail to respond to conservative treatment as well as a greater chance of long-term recovery compared with patients who had not had an injection.[26]

ANATOMY

The trochanteric bursa is located over the lateral prominence of the greater trochanter of the femur. Three bursas (two major and one minor) surround the greater trochanter. Major bursas are the subgluteus medius bursa (posterior and superior to the proximal edge of the greater trochanter) and the subgluteus maximus bursa (lateral to the greater trochanter). The minor bursa is the subgluteus minimus bursa (above and slightly anterior to the superior surface of the greater trochanter).[6]

INDICATIONS

Indications for greater trochanteric bursa injection include acute and chronic inflammation associated with osteoarthritis, rheumatoid arthritis, repetitive use, and other traumatic injuries to the area.[28] Imaging studies indicate that the pain can be from gluteus minimus or medius injury or inflammation of the bursa itself. It is often idiopathic but may result from running, local trauma, and gait disturbances. The pain can be severe, radiate to the buttock or anterior thigh, and be exacerbated by standing or sleeping on the affected side. Patients often describe "hip" pain; however, true intra-articular hip pain usually radiates to the groin. Trochanteric bursitis only rarely is caused by infection. On examination, palpation over the greater trochanter reproduces the pain.[6]

TECHNIQUE

Fluoroscopically guided trochanteric bursa injections are not associated with better clinical outcomes compared with injections guided by anatomic landmarks alone in patients with greater trochanteric pain syndrome.[26]

Blind Approach: The patient should be in the lateral decubitus position with the affected side up. It is recommended to flex the hip 30 to 50 degrees and flex the knee 60 to 90 degrees to improve patient comfort as well as for stabilization of the hip. The greater trochanter is identified by palpating the femur proximally from the midshaft until the bony protrusion is felt. The point of maximal tenderness or swelling is identified and marked. A 22- or 25-gauge, 3.5-inch spinal needle is inserted perpendicular to the skin. In very obese patients, a longer needle may be required. The needle should be inserted directly down to bone and then withdrawn 2 to 3 mm before injecting.[28]

Fluoroscopic Approach: The patient is placed in the lateral position with the affected side up. The most painful area is marked over the anticipated site of the bursa. Using fluoroscopy, a 22-gauge 3.5-inch spinal needle should be advanced into the bursa over the greater trochanter. 0.5 to 1 ml of contrast may be injected to confirm intrabursal spread.[26]

Ultrasound Approach: Ultrasonography made greater trochanteric bursa injection even easier. A lateral approach is generally used as with the blind approach. A high-resolution or low-resolution transducer can be used depending on body habitus and the needle can be introduced either in plan or out of plane towards the burse site and injection is made under real-time sonography.[29]

KNEE JOINT

Osteoarthritis of the knee is the most common form of arthritis and the major cause of disability and reduced activity in people older than 50 years. Thirty percent of people older than 50 years have radiographic evidence of osteoarthritis of the knee, which increases up to 80% after age 65. While men have more knee osteoarthritis before age 50, its incidence increases in postmenopausal women such that by age 65, the prevalence is twice as high in women as in men.[30]

KNEE: INTRA-ARTICULAR INJECTION

ANATOMY

The knee joint is the largest joint in the body and consists of four bones, namely the femur, the tibia, the fibula, and the patella, and an extensive network of ligaments and muscles. The knee joint is made up of two functional joints, the femoral-tibial and the femoral-patellar joint.[28] The main movements of the knee joint occur among the femur, patella, and tibia, which are each covered by articular cartilage designed to decrease the frictional forces as movement occurs between the bones. The patella lies in the intercondylar groove at the distal end of the femur. A thick ligamentous joint capsule lined by synovial membrane surrounds the entire knee joint, which secretes synovial fluid to reduce friction and facilitate movement. The frictional forces are additionally reduced by the infrapatellar fat pad and bursae. The primary stabilizers of the knee are the anterior and posterior cruciate ligaments, the medial and lateral collateral ligaments, and the capsular ligaments.[28] The medial collateral ligament is a band that runs between the inner surfaces of the femur and the tibia. It resists valgus forces acting from the outer surface of the knee. The lateral collateral ligament traverses from the outer surface of the femur to the head of the fibula and resists varus forces from the inner surface of the knee. The cruciate ligaments are so called because they form a cross in the middle of the knee joint. The anterior cruciate ligament (ACL) travels from the anterior of the tibia to the posterior the femur and prevents the tibia moving forward. It is one of the most important structures in the knee, and is most commonly injured in twisting movements. Injury to it may require extensive surgery and rehabilitation. The posterior cruciate ligament (PCL) travels from the posterior surface of the tibia to the anterior surface of the femur and in doing so wraps around the ACL. Each knee joint has two crescent-shaped cartilage menisci. These lie on the medial and lateral borders of the upper surface of the tibia and are essential components, acting as shock absorbers for the knee as well as allowing for correct weight distribution between the tibia and the femur.

INDICATIONS

Indications for knee joint injection include delivery of viscoelastic supplementation for advanced osteoarthritis as well as corticosteroid for other noninfectious inflammatory arthritides such as rheumatoid arthritis, gout, or calcium pyrophosphate deposition disease.[28] At present, there is no evidence that medical intervention alters the rate of deterioration of the articular surfaces of an affected joint. Most current therapies are directed toward minimizing pain and swelling, maintaining joint mobility, and reducing associated disability.

TECHNIQUE

While intra-articular knee injections are not complicated procedures, it could be difficult to assess whether the tip of the needle is in the joint space or in intra-articular soft tissue structures.[31] In a cadaver study, Esenyel et al. evaluated the accuracy of intra-articular needle placement using four different approaches: the anteromedial (AM), anterolateral (AL), lateral midpatellar (LMP), and medial midpatellar (MMP) in 156 knees of 78 fresh cadavers. Accuracy rate was the highest (85%) in the AL injection and lowest in the MMP (56%). However, the results were not statistically significant when compared to AM and LMP approaches.[32] In a series of 240 consecutive knee injections in patients without clinical knee effusion, the lateral midpatellar approach led to intra-articular injection in 93% of cases and was more accurate than the anteromedial or anterolateral approaches.[33] In a survey to determine the preferred approach for knee arthrography, 64% reported using the lateral approach.[34] Various approaches have been described in the literature for knee injections (Fig. 59-9).

Midpatellar Approach: The patient is positioned supine with the knee extended and a pillow or roll beneath the popliteal fossa. For the lateral midpatellar approach, lines are drawn along the lateral and proximal borders of the patella. The needle is inserted into the soft tissue between the patella and femur near the intersection point of the lines, and directed at a 45-degree angle toward the middle of the medial side of the joint. Medial midpatellar approach; the needle enters the medial side of the knee under the middle of the patella (midpole) and is directed toward the opposite patellar midpole.

Anterior Approach (Infrapatellar): The knee is flexed 60 to 90 degrees, and the needle is directed either medially or laterally to the inferior patellar tendon and cephalad to the infrapatellar fat pad. This technique is useful when the knee cannot be extended. Also, it avoids injury to the articular cartilage.

Suprapatellar Approach: This approach is more common in large effusion as the suprapatellar pouch will be expanded. However, it is rarely done nowadays especially with the introduction of ultrasound-guided suprapatellar recess injection.

Fluoroscopic Approach: Fluoroscopic guidance may be indicated in obese patients or when it is expected to have difficulty accessing the intra-articular space.

Ultrasound Suprapatellar Approach: Patient is positioned supine with the knee flexed 20 to 30 degrees and is supported by a pillow in the popliteal space. A linear-array high-resolution transducer is placed longitudinally such that it is parallel to the tendon of quadriceps femoris muscle. The distal femur, the superior pole of the patella, suprapatellar fat pad and the suprapatellar recess can be visualized. Minimal pressure should be applied on the transducer to avoid compressing the suprapatellar bursa. The transducer

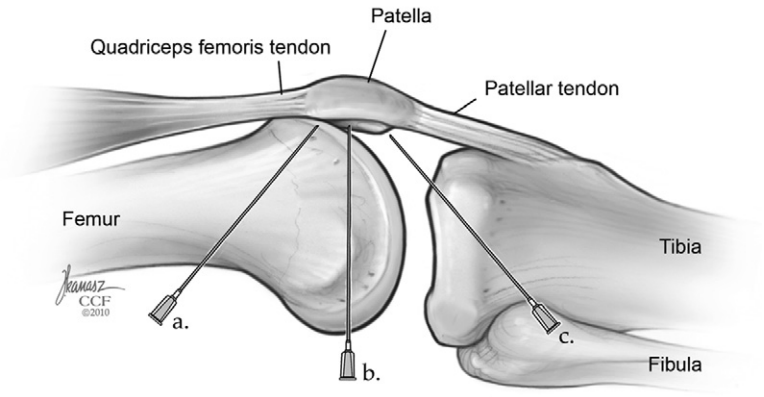

FIGURE 59-9 Illustration demonstrating various portals for knee joint injection. *A*, Suprapatellar approach. *B*, Midpatellar approach. *C*, Infrapatellar approach. *(Reprinted with permission from Cleveland Clinic.)*

is then rotated to the axial plane, and tendon of quadriceps femoris, suprapatellar fat pad, and the suprapatellar bursa should be reidentified.[31] The largest dimension of the synovial recess is identified and is the target for the injection. After the skin is sterilely prepped and draped, a 22-gauge, 3.5-inch spinal needle is advanced in-plane to the suprapatellar recess. Aspiration of synovial fluid confirms proper needle placement. During the injection, a fluid jet may be visualized distending the suprapatellar recess.

Ultrasound Infrapatellar Approach: The infrapatellar approach is more commonly performed blindly with surface landmark technique as described above. The authors prefer the suprapatellar recess approach as ultrasound-guide infrapatellar approach is technically difficult.[31]

COMPLICATIONS

With use of proper technique and patient selection musculoskeletal injections are safe, comfortable, and a valuable tool in the management of musculoskeletal pain. Adverse effects from either the technique or the medications used are rare.[6,30] Infection, the most serious complication, is extremely rare. The risk of septic arthritis from intra-articular injections is less than 0.03%.[6] However, it is strongly recommended to follow strict aseptic technique and avoiding injections in patients with suspected cellulitis, infectious arthritis or bursitis, bacteremia, or in severely immunocompromised patients.[6] The risk of hyperglycemia in patients with diabetes is also very small and transient, even for longer-acting corticosteroid preparations. Risk of hemarthrosis is small even in those taking antiplatelet or anticoagulation agents, although it is recommended that these agents be discontinued prior to elective injections. The role of repeated intra-articular corticosteroids in osteoarthritis is controversial due to reports of steroid-induced arthropathy developing after multiple injections.[30] Intra-articular corticosteroid injections do not lead to the progression of osteoarthritis. Postinjection inflammation is caused by intra-articular injection of corticosteroid crystals causing synovitis and can mimic septic arthritis, however, septic arthritis usually differs in timing and duration, occurring later than postinjection inflammation and lasting much longer.[6] It is a rare complication that begins shortly after the injection and usually subsides within a few hours, rarely continuing for 2 to 3 days. Treatment is conservative and includes ice at the site of injection and oral analgesics until the reaction abates. In a few patients, it may be severe enough to require joint aspiration again to relieve the pain.[30] Capsular (periarticular) calcifications at the site of the injection have been reported in rare cases on radiographs taken after treatment. They usually disappear spontaneously and have no clinical significance. Careful technique and avoiding leakage of the steroid suspension from the needle track to the skin surface prevent or minimize these problems. Additionally, it is recommended that small amounts of local anesthetic or normal saline be used to flush the needle before it is removed to reduce this complication.[30] Other rare complications may include localized subcutaneous or cutaneous atrophy (2.4%), depigmentation (0.8%), localized erythema and warmth (0.7%), and facial flushing (0.6%).[6]

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Access the reference list online at http://www.expertconsult.com.

CHAPTER 60

Pulsed Radiofrequency, Water-Cooled Radiofrequency, and Cryoneurolysis

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BACKGROUND AND TECHNIQUE

CONVENTIONAL RADIOFREQUENCY

The use of radiofrequency (RF) electrical currents to create quantifiable and predictable thermal lesions has been practiced since the 1950s.[1] The first reported use of RF in the treatment of intractable pain appeared in the literature in the early 1970s, and it involved the use of conventional radiofrequency currents (CRF) to create thermal lesions.[2] The CRF lesions for pain control are created by the passage of RF currents through an electrode placed adjacent to a nociceptive pathway to interrupt the pain impulses and thus to provide the necessary pain relief. The application of RF currents imparts energy to the tissues immediately surrounding the active electrode tip and raises the local tissue temperature, whereas the electrode itself is heated only passively. During CRF application the RF current is switched off once the desired electrode temperature is reached and the repetition of the cycle maintains the selected tissue temperature. Temperatures above 45° C have been known to be neurodestructive,[3] and although selective destruction of unmyelinated C- and A-delta fibers has been suggested,[4] further studies showed indiscriminate destruction of all nerve fiber types during thermal RF application.[5] Therefore, during CRF the tissue temperatures are typically raised well above the neurodestructive levels, but below the point of tissue gas formation (80° C to 90° C). In order to avoid thermal injury to the motor and sensory nerve fibers and the complications of weakness, neuritis, and deafferentation pain, the use of high-temperature CRF has generally been restricted to facet denervation. However, lower temperature CRF, in the range of 55° C to 70° C, has been arbitrarily selected for dorsal root ganglia (DRG) lesioning.[6]

PULSED RADIOFREQUENCY

In a CRF study of DRG lesioning, no difference in the clinical results was found between the CRF lesions made at 40° C and 67° C.[7] The authors of this study theorized that the electrical currents rather than the temperature determined the outcome. This observation generated immense interest among pain physicians, as the risks of weakness and deafferentation pain could now be obviated by the use of lower temperature CRF. Based on these assumptions, pulsed radiofrequency (PRF) was introduced, which attempted to maximize the delivery of electrical energy by using higher voltage RF currents, while concomitantly minimizing the risk of thermal tissue injury by keeping the tissue temperatures well below the neurodestructive range (42° C). These conflicting goals were achieved by applying the RF currents in a pulsatile manner to allow time for the heat to dissipate in between the RF pulses.[8]

Sluijter et al.[8] assumed that, because the tissue temperature was kept below the thermal destructive range, thermal tissue injury was avoided. By using mathematical calculations, they further showed that the high-density electrical currents generated at the electrode tip stressed the cellular membranes and biomolecules and caused altered cell function, leading to cell injury. Later investigators, however, suggested a combined role of electrical and thermal tissue injury from PRF application.[9,10] These authors also ascertained that the slow response time of the temperature-measuring devices used during PRF could not reliably exclude the possibility of brief high-temperature spikes and the likelihood of thermal tissue injury. Although some laboratory studies showed evidence of neuronal activation,[11,12] cellular stress,[13] and cellular substructure damage[9] after PRF application, others showed that the observed PRF effects were predominantly a function of set temperature,[14,15] and thus undermined the role of the electrical currents in causing tissue injury. Thus, despite the several claims of its clinical efficacy, the exact mechanism of the clinical effects of PRF hitherto remains unclear, and currently no evidence of the interruption of the nociceptive pathway in response to PRF application exists.

Similarly to CRF, PRF is applied via an electrode placed in the vicinity of the target nociceptive structure. However, unlike CRF, juxtapositioning of the electrode parallel to the target nerve is deemed unnecessary, as the electrical currents, and not the thermal lesion, are considered the source of neuronal dysfunction. During typical PRF application, the RF currents are applied for 20 milliseconds, at 2 Hz, for a total duration of 120 seconds. Therefore, for most of the lesion duration—480–500 milliseconds—no RF currents are applied. The current voltage is controlled in a manner that the maximum electrode temperature achieved remains below 42° C.[8] Variations from this standard PRF protocol have been infrequent, with the exception of longer lesion duration: PRF has been applied for 4, 8, and 20 minutes in some clinical studies.[16]

WATER-COOLED RADIOFREQUENCY

Although water-cooled radiofrequency (WCRF) ablation has been used in cardiac electrophysiology[17] and tumor ablation[18] for some time, its use in the treatment of pain is fairly recent. The basic principle of pain relief during WCRF application is similar to the CRF—a thermal lesion is created by the application of RF energy through an electrode placed in the vicinity of the target neural structure. However, WCRF is applied by using a specialized multichannel electrode that is actively cooled by the continuous flow of water at ambient temperature (Fig. 60-1). The active cooling prevents the electrode from acquiring the high surrounding tissue temperatures and allows the continued

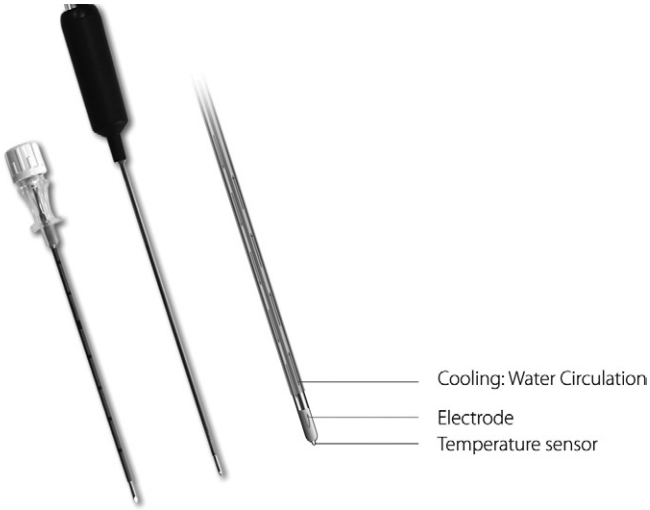

FIGURE 60-1 Multichannel water-cooled electrode. *(Courtesy Baylis Medical Inc. Montreal, Canada)*

flow of the RF current, with the consequent heating of a larger tissue volume and the creation of a larger thermal lesion.[17–19] The resulting WCRF lesion is consequently comprised of a few millimeters of cooled tissue immediately surrounding the electrode, which is surrounded by spherical isotherms of increasing tissue temperature, which in turn are surrounded by lower temperature isotherms at increasing distance from the electrode (Fig. 60-2).[20] Similar to CRF, the size of the WCRF lesion is dependent on the probe size, the electrode temperature, and the duration of RF current applied. If a 50° C isotherm is used as a criterion for the lesion's edge while using an 18-gauge electrode with a 6-mm active tip with the electrode temperature raised to 55° C to 60° C and RF currents applied for 150 seconds, the lesion created would be 8 to 10 mm in diameter.[19,21] Even though a spherical area of tissue heating is expected,[21] several factors may influence the symmetry of the WCRF lesion created in vivo.[20] Active heat sinks such as cerebrospinal fluid flow in the thecal sac and blood flow in the epidural venous plexus, and passive heat sinks such as the osseous and muscular spinal structures, may determine the eventual shape of the heated tissue.[20]

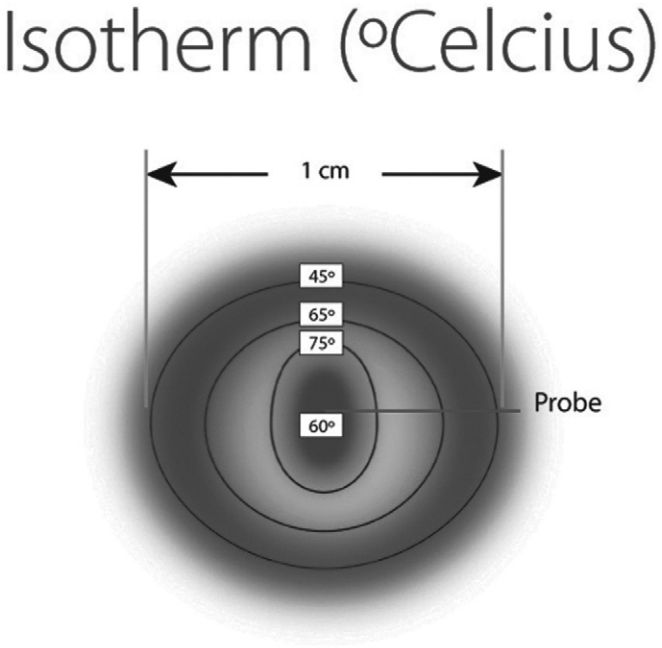

FIGURE 60-2 Morphology of water-cooled radiofrequency lesion. *(Courtesy Baylis Medical Inc. Montreal, Canada)*

The larger area of neural destruction with WCRF application increases the probability of successful denervation of a pain generator with numerous and/or variable afferent nociceptive innervation.[19,21] The preliminary review of the literature on the clinical use of WCRF identified two distinct forms of WCRF techniques, monopolar and bipolar WCRF lesioning. These WCRF lesioning techniques were applied exclusively for the treatment of sacroiliac joint dysfunction (SJD) and discogenic pain (DP), respectively. The unipolar WCRF in the treatment of SJD was applied to S1, S2, and S3 lateral branches and either two or three monopolar lesions were created lateral to each sacral foramen (see Chapter 47).[22,23] These lesions were created by using a 17-gauge specialized electrode with a 4-mm active tip. The RF current was applied for 150 seconds, and the electrode temperature was raised to 60° C. Due to the larger anticipated lesion size, the introducer needle was kept at a "safe distance" from the sacral nerve roots—8 to 10 mm from the lateral edge of posterior sacral foramen.[23] To avoid injury to the segmental spinal nerve, WCRF was not applied to the L4 and L5 dorsal rami, and CRF was used instead.[22] For the treatment of DP, bipolar WCRF was applied to the posterior-lateral disc annulus by placing two 17-gauge introducer needles and specialized RF electrodes (Fig. 60-3).[24,25] The electrode temperature was raised to 55° C over 11 minutes, and this temperature was maintained for an additional 4 minutes.

CRYONEUROLYSIS

Cryogenic nerve injury is not associated with neuroma formation, hyperalgesia, and deafferentation pain, which are the attributes typical of nerve injury by other physical modalities such as surgical nerve sectioning, thermal radiofrequency lesioning, or chemical neurolysis. Trendelenberg first demonstrated that freezing of the peripheral nerves caused nerve disruption without the risk of neuroma formation.[26] Later, Carter et al.[27] and Beazley et al.[28] showed that peripheral nerve injury from extreme cold caused axonal and myelin sheath disintegration and led to Wallerian nerve degeneration without disruption of the endoneurium, perineurium, and epineurium.

The mechanism of cryogenic nerve injury appears to emanate from damage to the vasa nervorum, the resulting endoneural edema and increased endoneural pressure, and consequent axonal disintegration. An autoimmune response triggered by the release of sequestered neural elements has also been implicated in the long-term effects of cryoablation.[29] The spared connective tissue elements and the Schwann cell basal lamina provide a ready substrate for nerve regeneration from intact proximal axons. The axonal regeneration typically occurs at a rate of about 1 to 1.5 mm

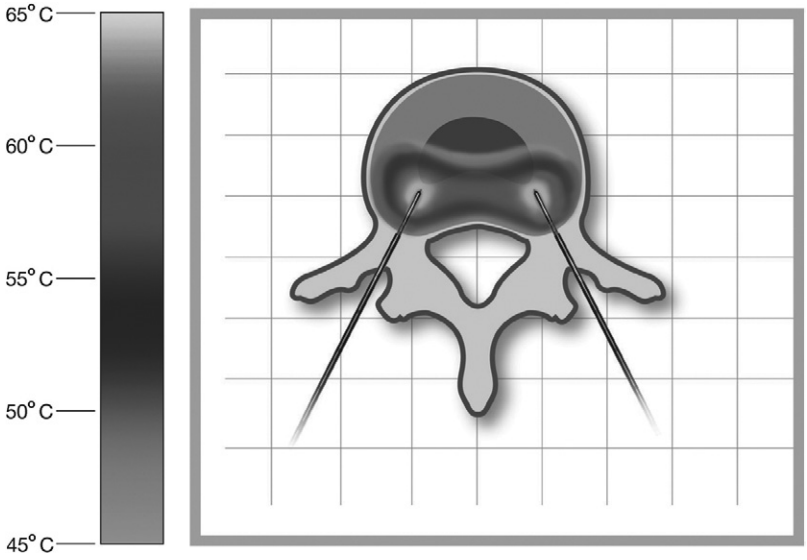

FIGURE 60-3 Water-cooled radiofrequency application for discogenic pain. *(Courtesy Baylis Medical Inc. Montreal, Canada)*

per week, and the duration of analgesia from cryoablation depends on the time taken by the proximal axons to reinnervate the end organs (typically weeks to months).[30] Although the local anesthetic-like properties of cold have been known since ancient Egyptian times,[31] tissue temperatures must be lowered to critical levels for adequate duration for the disintegrative nerve changes to occur—a distinction analogous to the difference between cold, numb fingers and frostbite. The critical temperature required to cause such disintegrative nerve changes has been shown to be –20° C.[32] Additionally, the degree and the duration of analgesia is proportional to the severity of the cryogenic nerve damage.[33] It is therefore crucial that the tissue temperatures are maintained below the critical levels for adequate duration during cryolesioning. In addition, the extent of freezing, and therefore the likelihood of the target nerve injury, depends on the probe size, the proximity of the probe to the target nerve, the freezing duration, and the number of freeze cycles applied. Repeat freeze and thaw cycles increase the size of the eventual ice ball formed.

The first cryoneedle, which used liquid nitrogen as refrigerant and lowered the needle tip temperature below –190° C, was developed in 1962.[34] In 1967, the currently used cryoprobe needle (Fig. 60-4) that used the Joule-Thompson enclosed gas expansion principle and lowered the probe tip temperature to between –50° and –70° C was developed.[35] The contemporary cryoprobe is a double lumen aluminum tube that connects to a gas source by flexible tubing, and either nitrous oxide or carbon dioxide is delivered at a pressure of approximately 42 kg/cm^2 (600 lb/in^2 [psi]) to the inner cryoprobe lumen. The gas under pressure escapes through a small orifice from the inner lumen near the cryoprobe tip and returns to the console through the outer cryoprobe lumen (Fig. 60-5). The drastic drop in the pressure at the probe tip (from 600–800 psi to 10–15 psi) allows gas expansion and consequent cooling. Heat absorbed from the tissues surrounding the probe tip lowers their temperature and creates an ice ball around the probe tip. Currently available cryoprobe sizes include a 14-gauge (2-mm) probe that roughly forms a 5.5-mm ice ball, and an 18-gauge (1.4-mm) probe that forms 3.5-mm ice ball.

Meticulous localization of the target nerve is necessary to increase the likelihood of the target nerve disruption. Most currently used cryoprobes are therefore equipped with a built-in nerve stimulator function that allows both motor (2 Hz) and sensory (100 Hz) testing. The probe also has a thermistor incorporated into the tip to precisely monitor the target tissue temperatures. The console unit is equipped with the nerve stimulator controls, temperature and gas pressure gauges, and a gas regulator switch that allows precise control of the gas flows. To ensure safe and effective cryoablation, the gas flows must be precisely regulated—inadequate gas flows are ineffective in lowering tissue temperatures below critical levels, while excessive gas flows may lead to tissue freezing proximally along the probe length and may cause unintended freeze lesions such as skin burns. The cryoprobe should be withdrawn only after the ice ball has thawed, because withdrawing the

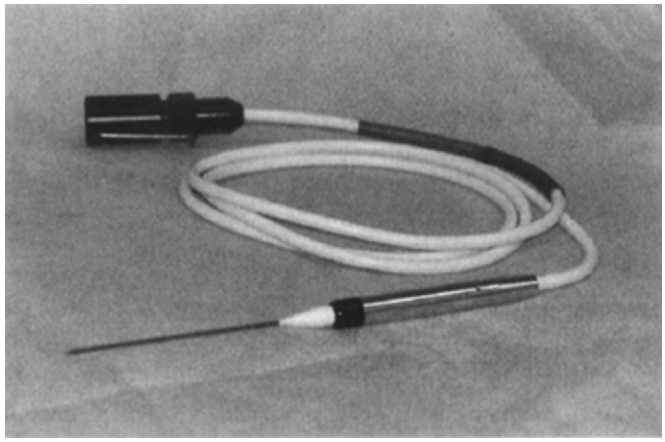

FIGURE 60-4 Cryoprobe needle.

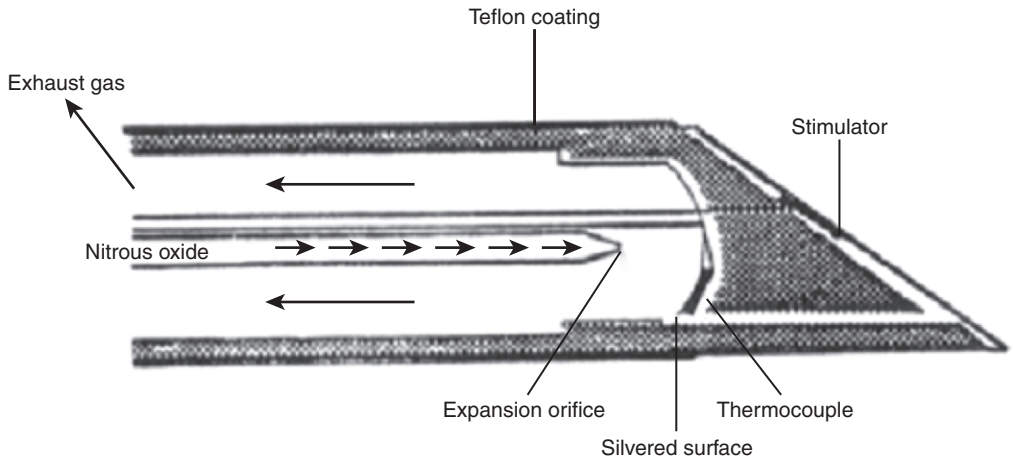

FIGURE 60-5 Schematic design of cryoprobe needle.

probe with the ice ball still present may cause local tissue injury and avulse the nerve segment.

The use of an introducer, such as a large-gauge intravenous catheter, is often recommended during cryoprobe placement. The sharper introducer tip facilitates the placement of the less rigid cryoprobe and affords additional skin protection during cryolesioning of the superficial nerves. Typically, a 12-gauge intravenous catheter is used for the 2.0-mm probe, and a 14- to 16-gauge catheter is used for the 1.4-mm probe.

CLINICAL USES

PULSED RADIOFREQUENCY

Although PRF has been employed in the clinical practice fairly recently, its use is relatively widespread and it is used for both painful and also for some nonpainful conditions.[16] The growing popularity of PRF is likely due to its perceived safety and clinical efficacy. PRF has been applied to the DRG at all spinal levels in the treatment of multiple pain syndromes, including radicular pains, post-herpetic neuralgia, herniated intervertebral disc, post-amputation stump pain, and inguinal herniorrhaphy pain.[16] It is also applied to a wide variety of peripheral nerves for the following pain syndromes: it is applied to the medial branch nerve for facet syndrome, the suprascapular nerve for shoulder pain, the intercostal nerves for postsurgical thoracic pain, the lateral femoral cutaneous nerve for meralgia paresthetica, the pudendal nerve for pudendal neuralgia, the dorsal penile nerves for premature ejaculation, the splanchnic nerves for chronic benign pancreatic pain, the sciatic nerve for phantom limb pain, the obturator and femoral nerves for hip pain, the glossopharyngeal nerve for glossopharyngeal neuralgia, the occipital nerve for occipital neuralgia, and the genitofemoral, ilioinguinal, and iliohypogastric nerves for groin pain and orchialgia.[16] It has also been applied to various central nervous system and autonomic ganglia, including the gasserian ganglion for trigeminal neuralgia, the sphenopalatine ganglion for head, neck, and facial pain, and to the lumbar sympathetic chain in the treatment of complex regional pain syndrome.[16] In some reports, the target neural structure for PRF application has been unclear, such as the sacroiliac joint for sacroiliac joint dysfunction, intradiscally for discogenic pain, myofascial trigger points for myofascial pain, scar neuromas for postsurgical scar pain, the spermatic cord for testicular pain, and intra-articularly for arthrogenic pain.[16]

WATER-COOLED RADIOFREQUENCY

Currently, the use of WCRF is confined to pain syndromes in which the pain generator is considered to have numerous and variable sources of innervation. The reported clinical use of WCRF is currently limited to four recently published articles in peer-reviewed journals.[22–25] In two of these studies,[22,23] WCRF was used for the treatment of SJD, and the remaining two[24,25] pertained to the treatment of DP. However, due to its ability to precisely deliver thermal energy to larger tissue volumes, WCRF may be effective where more traditional forms of neuroablation have failed, and its use may be extended to other pain syndromes.

CRYONEUROLYSIS

The reported use of cryoablation in the literature is most prevalent for the treatment of post-thoracotomy pain.[36–51] Cryolesioning for this clinical indication was typically performed intraoperatively under direct vision on the individual intercostal nerves in the intercostal groove. All the intercostal nerves that were likely to be involved in a patient's pain—from one to two segments above the upper limit of the incision to one to two below the lower limit of the incision or the chest drain—were typically treated. The cryoablation experience with post-thoracotomy pain led to its use in other chronic pain conditions of the chest wall, including postoperative neuroma, costochondritis, post-herpetic neuralgia, and rib fractures.[52–53]

In the head, neck, and facial region, cryolesioning of several regional nerves is reported in multiple studies. These nerves have included inferior alveolar, mental, lingual, buccal, inferior dental, auriculotemporal, supraorbital, and infraorbital nerves.[54–66] The painful head, neck, and facial conditions treated with cryoablation included trigeminal neuralgia, post-herpetic neuralgia, atypical facial pain, and various

postsurgical neuralgias. In the majority of these studies, the craniofacial nerves were exposed by open dissection for cryolesioning; however, in a few studies the cryoprobe was placed by a closed technique, either percutaneously or transmucosally. There is one study of cryoablation in the region of tonsillar fossa, in post-tonsillectomy patients, where the exact target neural structure is less clear.[66]

Cryoablation has also been used in the treatment of spinal and extremity pains. Its use is reported frequently for the treatment of lumbar facet syndrome, where it was applied to the lumbar medial branches.[67–69] For extremity pain, its use is reported for the treatment of intermetatarsal space or Morton's Neuroma.[70] Cryolesioning of the ulnar, median, sural, occipital, palmar branch of the median and digital nerves has also been performed for mostly traumatic nerve injuries and for carpal tunnel syndrome.[71]

Cryoablation has also been used for the treatment of several painful conditions of the abdomen, pelvis, and perineum. The most frequent application in this region has been for the treatment of post-inguinal herniorrhaphy pain, where it was applied to the iliohypogastric and ilioinguinal nerves.[72–75] It has been applied to the lower sacral nerve roots for intractable perineal pain,[76] to the ilioinguinal and iliohypogastric nerves for corresponding neuralgiform chronic abdominal pain,[77] and to the ganglion impar for intractable rectal pain.[78] Its use is also described for pregnancy-related and post-partum pain in women, cryolesioning of the ilioinguinal nerve was performed for late-pregnancy abdominal pain,[79] it was applied to the sacral extradural canal for severe post-partum sacrococcygeal pain,[80] and it was applied to the symphysis pubis for pregnancy-associated symphysis pubis diastasis pelvic pain.[81] Cryolesioning of the iliac crest has been performed for donor site pain.[82]

CLINICAL EFFICACY

PULSED RADIOFREQUENCY

PRF has been used most frequently for the treatment of lumbar or cervical radicular pains. Seven of the nine studies reporting this PRF use have been observational and reported its successful use.[16] There are five randomized controlled trials (RCTs) on PRF (Table 60-1). There is one

TABLE 60–1 Controlled Trials of Pulsed Radiofrequency

Author and Date	Methodology, Patients and Comparison Gps	Follow-up and Outcome measures	Results and Author Conclusions	Study Analysis
Van Zundert et al, 2007[83]	RCT, DB, SCT 23 patients with CRP, 11 had PRF to one level DRG, 12 had ST.	For 3 mos, only patients having favorable response followed for 6 mos. VAS, GPE, SF-36, AU. Success defined as > 50% Δ in GPE and > 20 Δ in VAS	At 3 mos, SS success reported in 9/11 (82%) patients in the PRF group and in 4/12 GPE (33%) and 3/12 VAS (25%) in the ST group. AC: PRF provided SS pain relief compared to ST at 3 mos	High-quality trial: This study provides evidence of short-termed efficacy of PRF for cervical radicular pain.
Simopoulos et al, 2008[84]	RCT 76 patients with LRP, 37 had PRF of DRG, 39 had combined PRF and CRF (maximally tolerated temperatures).	2 mos and monthly thereafter; up to 8 mos. VAS. Success defined as reduction in 2 points in VAS for 8 weeks.	Similar decline in VAS scores between the 2 Gps at 2 mos. Similar loss of analgesic effect between 2 and 4 mos and return of pain to baseline by 8 month. AC: PRF of DRG was safe and resulted in short-term benefit; the additional application of CRF did not offer any additional benefit	Low-quality trial: Significant methodological flaws and the use of unconventional RF techniques makes the results of this trial irrelevant.
Tekin et al, 2007[85]	RCT, DB, SCT 60 patients with LFS, 20 had CRF, 20 had PRF and 20 ST.	Followed at 6 hrs, 6 mos and 1 year after the procedure. VAS, ODI	At 6 hrs, SS lower VAS and ODI scores for CRF and PRF Gps compared to ST. At 6 mos and 1 yr. the lower scores maintained only in CRF Gp. AC: CRF and PRF are both useful interventions in the treatment of chronic facet joint pain	High-quality trial: This trial only provides evidence of the efficacy of PRF at 6 hours after RF facet neurotomy. Its results were therefore regarded as irrelevant in assessing LT pain relief.
Kroll et al, 2008[86]	RCT, DB 26 patients with LFS, 13 patients had CRF and 13 had PRF	For 3 mos. VAS, ODI	No SS difference between the CRF and PRF Gps in relative improvements in either VAS or ODI scores at three mos. AC: As above.	High-quality trial: No difference in the results of PRF and CRF at 3 mos for facetogenic pain.
Erdine et al, 2007[87]	RCT, DB 40 patients with TN; 20 had PRF and 20 CRF.	For 3 mos, noncomparative follow-up for 6 mos. VAS, PSS, AU	At day 1 and 3 mos all patients in CRF had SS improvement in VAS and PSS. Only 2/20 patients in PRF Gp at day 1 and none at 3 mos had SS improved VAS or PSS. AC: Unlike CRF, PRF is not an effective treatment for idiopathic TN.	High-quality trial. This study provides evidence of lack of efficacy of PRF compared to CRF in the treatment of TN .

CRP, Cervical Radicular pains; ST, Sham Treatment; RCT, Randomized Controlled Trial; DB, Double-Blinded; SCT, Sham Controlled Trial; VAS, Visual Analogue Scale; GPE, Global Perceived Effect; AU, Analgesic Usage; AC, Author's Conclusions; SS, Statistically Significant; TN, Trigeminal Neuralgia; PSS, Patient Satisfaction Scale; LFS, Lumbar Facet Syndrome; ODI, Oswestry Disability Index; LRP, Lumbar Radicular Pain

RCT of 23 patients with chronic cervical radicular pains that compared PRF applied to the DRG in 11 patients with a similarly performed sham intervention in 12 patients.[83] The results of this trial showed statistically significant improvement in pain and patient satisfaction scores at 3 months in the PRF group. However, this was a small sized trial, and it reported only short-term results at 3 months. There is one RCT of 76 patients with lumbar radicular pains that compared PRF to combined PRF and CRF application to the involved DRG.[84] In both the study groups, the patients experienced significant pain relief at 2 months, but experienced significant loss of analgesic effect after 4 months, and a complete return of pain after 8 months. Although the study results concluded that the PRF of the DRG led to short-term pain relief and no additional benefit was gained by CRF application, this trial compared PRF to a combined PRF and CRF technique not used clinically: CRF was applied until the patient felt radicular pain. As a result, the CRF lesion temperatures and durations were inconsistent.

The second most commonly reported PRF application is in the treatment of facet syndrome (FS). There are two RCTs and three observational studies available on this topic.[16] In one RCT of 60 patients with chronic lumbar FS, the effects of CRF, PRF, and sham treatment were compared.[85] The three equal study groups were evaluated immediately and at 6 and 12 months after the procedure. The patients in both the CRF and the PRF groups had lower pain and disability scores immediately after the procedure, compared with the sham group. However, this pain relief and functional improvement was maintained only in the CRF group at 6 and 12 months. The significance of the lower pain scores in the immediate postprocedural period in the PRF group in terms of long-term pain relief, however, is unclear. The second RCT was of 50 patients with lumbar FS of more than 1 month's duration.[86] Only 26 patients, of which 13 received CRF and 13 PRF, completed their follow-up evaluations. No significant difference in the pain and disability scores was found at 3 months between the two groups. Several limitations of this trial make its results inconclusive in terms of long-term pain relief: a large dropout rate of 48%, a small study size of 26 patients, short-term results at 3 months, the lack of a placebo control group, and patients with pain duration of only 1 month were included in the trial. The three available observational studies of PRF application for FS all reported its efficacy.[16]

There is one RCT of PRF use: in 40 patients with idiopathic trigeminal neuralgia, the effects of PRF were compared with CRF, both applied to the gasserian ganglion.[87] At 3 months, patients in the PRF group reported no significant pain relief or improved satisfaction, compared with the CRF group. The results of this study concluded that PRF was not an effective method of treatment for idiopathic trigeminal neuralgia. One criticism of this trial is that multiple CRF lesions were performed in the CRF group, compared with only one PRF application in the PRF group. This trial also lacked a sham treatment group. One additional case series reported the efficacy of PRF in the treatment of trigeminal neuralgia.[16]

Successful application of PRF to the suprascapular nerve for shoulder pain has been reported in four case reports or case series.[16] A case report and a prospective case series reported successful application of PRF to the sphenopalatine ganglion for head, neck, and facial pain.[16] The use of PRF for the remaining clinical conditions described earlier is based on a single case report or case series; almost all of these reports described the successful use of PRF for the condition.[16]

Thus, although the observational studies almost universally support the use of PRF, the available controlled data is suboptimal and showed variable efficacy for the reported conditions. The efficacy of PRF reported in these RCTs for various clinical conditions was at best short term.

WATER-COOLED RADIOFREQUENCY

Of the four available clinical studies of WCRF, only one is an RCT. In this RCT of 28 patients with SJD,[22] 14 patients received WCRF in the treatment group, while 14 patients in the control group received the placebo treatment (the electrodes were placed similarly to those in the treatment group, but no RF current was applied). Although statistically significant lowered pain and disability scores were reported for the patients in the treatment group, the comparative analysis of the two study groups was performed at one month only. The second study of WCRF for SJD was a retrospective analysis of 27 patients, and it reported the successful use of WCRF.[23] One study of WCRF use in the treatment of DP is a prospective case series of 15 patients,[24] and the second publication is a single-patient case report.[25] Both the studies reported the success of bipolar WCRF in the treatment of DP. Thus, currently the evidence for the clinical efficacy of WCRF is in early rudimentary stages.

CRYONEUROLYSIS

The RCTs of cryoablation pertain mostly to its use after thoracic surgery for the relief of postoperative pain (Table 60-2).[36–46] Although the majority of these trials were published in the 1980s and 1990s, some were published as recently as 2008.[45] The comparisons made in these trials varied significantly, some comparing cryoablation with no intervention,[36–40] with local anesthetic blockade,[36] with continuous intravenous narcotic infusion,[41,42] and with epidural analgesia.[43–45] Of the five trials that compared cryoablation with no intervention, three[36,37,40] reported statistically significant reduced narcotic usage and pain scores after the cryoablation, while two showed no such advantage.[38,39] The two trials that compared cryoablation with intravenous narcotic infusion showed no advantage of cryoablation.[41,42] There are three trials comparing epidural analgesia to cryoablation.[43–45] The results of one trial showed that patients in the epidural analgesia group had significantly better pain scores and pulmonary function tests compared with the cryoanalgesia group.[43] Results of the other two such trials showed that cryoablation provided postoperative analgesia comparable to the epidural analgesia; however, cryoablation increased the incidence of post-thoracotomy neuropathic pain, and the

TABLE 60–2 Controlled Trials of Post Thoracotomy Pain

Author, Date, and Location	Number of patients and Comparison Gps	Methodology	Follow-up and Outcome Measures	Results	Conclusions
Katz et al, 1980[36] USA	24 patients, 9 in CA Gp, 9 received either LA intercostals block or no block.	Not blind, randomization only partial; 18 patients; random number selection table.	For up to 5 PODs. 10 point pain measurement scale, AC, PFTs.	CA Gp had SS less pain (student's T test: < 0.001 for day 1, < 0.05 for day 3, and < 0.01 for day 5) and less narcotic usage $p < 0.01$. No difference for PFTs. Pain relief in CA Gp lasted for 2–3 wks and no AEs at 6 mos.	CA has definite advantages over other forms of therapy for PTP.
Glynn et al, 1980[37] UK	58 patients, 29 received CA and 29 did not.	Patients were matched; not randomized or blind.	Narcotic usage and time to mobilization and discharge.	CA patients SS less narcotic usage $p < 0.005$. No difference for other 2 parameters.	Patients who received CA required fewer narcotics after surgery than those in the control group.
Roxburgh et al, 1987[38] UK	53 patients, 23 had CA and 30 did not. Patients in both the Gps had lumbar epidural catheter and epidural methadone.	Randomized and blind	Comparative analysis performed until discharge (14 days). Linear analogue pain scale and AC.	No SS difference at the 5% level between the Gps for either measure.	Addition of CA to standard postoperative regimen produced no significant reduction in postoperative pain or analgesic consumption.
Müller et al, 1989[39] Austria	63 patients, 30 CA and 33 CGp.	Randomized and double-blind	For 7 PODs. 0-4 pain scale, AC and PFTs.	None of the measured variables were SS different between the two Gps. In CA Gp 6 patients (20%) had neuralgic pain 6 wks after the operation, which continued for up to 4 wks.	CA provided inadequate pain relief after thoracotomy and advised against its use.
Pastor et al, 1996[40] Spain	100 patients; 55 had CA while 45 patients in the CGp did not.	Randomized and double-blind	For 7 PODs. 0-5 pain scale, AC and PFTs	Pain was SS lower in CA Gp; $p<0.001$, amount of analgesics required was SS lower in the CA Gp; $p<0.001$). No difference in the PFTs between the Gps.	The authors advocated the use of CA.
Orr et al, 1981[41] UK	45 patients. 3 Gps; 15 each. Control, CA, and morphine infusion	Randomized and blind	VAS and analgesic usage	Infusion and CA Gps had similar pain relief p,0.08 and analgesic usage	This trial did not distinguish between the cryoprobe and morphine infusion.
Gwak et al, 2004[42] Korea	50 patients in whom thoracic epidural was not considered. 2 Gps included CIVA and CIVA+CA	Randomized and double-blind	For 7 PODs. Visual analogue pain scale, AC and PFTs. Patients also followed for 6 mos for PTP.	No SS difference for the 2 Gps for pain, AC, PFTs, and PTP.	CA was not effective in reducing the incidence of PTP.
Brichon et al, 1994[43] France	120 patients, control, epidural and CA Gp	Randomized	Until discharge or up to 12 days. Linear visual analogue pain scale, AC and PFTs	. Patients in the epidural group had significantly better scores and PFTs than those in the control and CA Gps.	Epidural analgesia led to the best pain relief and restoration of pulmonary function after thoracotomy.
Yang et al, 2004[44] Korea	90 patients, 45 patients each in Gp; T epidural and T epidural + CA Gp.	Randomized	For 7 PODs. Visual a nalogue pain scale, AC and PFTs. Patients also followed for 6 mos for PTP.	Epidural-CA patients had less pain on the 7^{th} POD (P, 0.036) and less AC on 6^{th} (P, 0.044) and 7^{th} (P,0.018) POD. Δ in FVC on 7^{th} POD was greater in epidural+CA Gp than the epidural Gp (P, 0.024). The incidence of PTP was similar in the two Gps during the 6-mo follow-up.	CA+epidural had less pain, AC and improved PFTs after surgery. However, it failed to decrease the incidence of PTP. In view of its long-term morbidity, CA+thoracic epidural is not recommend in patients undergoing thoracotomy.
Ju et al, 2008[45] China	107 patients. T-Epidural Gp and in CA Gp; a subcutaneous catheter placed in the upper back +IVPCA.	Randomized and double-blind	For 3PODs. , NRS pain scale, PS. Ts. Patients also followed for 6 mos for PTP.	No SS Δ in NRS scores and PS between the Gps at 3 PODs. Higher incidence of allodynia-like pain in CA Gp. with SS on 6^{th} and 12^{th} mos ($P < 0.05$).	Although CA combined with subcutaneous and IV morphine provided comparable pain control to T Epidural, it could not be recommended due to neuropathic PTP.
Miguel et al, 1993[46] USA	45 patients, 4 study Gps: 14 CA, 10 EA (morphine- lumbar), 10 intrapleural analgesia, and 11 CIVA (morphine).		For 5PODs. VAS and PFTs. Patients also followed for 12 wks by telephone.	Epidural morphine provided superior pain relief than the other modalities. No difference in PFTs was found between the Gps. The number of patients was insufficient to draw definitive conclusions.	PTP is best relieved with epidural morphine, compared to intrapleural analgesia, CA and CIVA.

CA, Cryoanalgesia; AC, Analgesic Consumption; SS, Statistically Significant; PTP, Post-thoracotomy pain; AEs, Adverse Effects; VAS, Visual Analogue Scale; CGp, Control Group; POD, Post-operative day; CIVA, continuous intravenous analgesia; PS, Patient Satisfaction; EA, Epidural Analgesia

authors recommended against its use.[44,45] In one controlled trial of four treatment groups, cryoablation was compared with epidural analgesia, continuous narcotic infusion, and intra-pleural analgesia.[46] The results of this trial showed epidural analgesia to provide the best relief of the postoperative pain; however, due to the insufficient number of patients enrolled in this trial, the results failed to reach statistical significance. Overall, of the 11 available controlled studies pertaining to the use of cryoablation for the relief of post-thoracotomy pain, only three favored its use.[36,37,40] This lack of efficacy of intercostal nerve cryoablation has been attributed to unaltered sensitivity of the visceral pleura and the large thoracic wall muscles, such as the latissimus dorsi and serratus anterior.[39]

Although multiple reports of cryoablation in head, neck, and facial region pain have been published,[47–66] only one study is a controlled trial.[66] In this RCT, cryoablation was applied to the tonsillar fossa after tonsillectomy. It reported statistically significant reduced postoperative pain scores in patients receiving cryoablation without evidence of additional complications.

There are three controlled trials of cryolesioning for postoperative pain after herniorrhaphy.[73–75] In two such trials, isolated cryolesioning of the ilioinguinal nerve was performed at the end of the hernia surgery.[73–74] One of these trials reported reduced postoperative analgesic usage in the cryoanalgesia group,[73] while the other trial reported no difference in the pain scores and analgesic consumption between the treatment and the control groups.[74] In the third trial, cryolesioning of both the ilioinguinal and iliohypogastric nerves was performed intraoperatively and no statistically significant difference in pain scores and analgesic usage was reported between the treatment and the control groups.[75] This trial also reported increased incidence of sensory disturbances in the patients in the treatment group, and the authors recommended against the use of cryoablation for postherniorrhaphy pain.

SIDE EFFECTS AND COMPLICATIONS

Although bleeding, infection, and nerve damage from needle placement and burns from the incorrect placement of the grounding pad have been reported,[88] no noticeable side effects or complications have been directly attributable to PRF use.

Apart from local transient post-procedural discomfort, none of the four clinical studies of WCRF reported any significant complications.

Despite the claims of reduced risk of neuroma formation and nerve regeneration after cryoneurolysis, the most significant reported adverse effect of cryoneurolysis has been neuropathic pain characterized by hypersensitivity and allodynia.[44,45,75] Other reported complications from cryoneurolysis are rare and include local tissue injury from the placement of the large-gauge introducer catheter or cryoprobe needle. Patients may report numbness in the territory of the involved nerve, which may be distressful for some patients. A diagnostic local anesthetic block performed prior to the cryoneurolysis allows the patient to experience this numbing effect and judge its tolerability. Alopecia, depigmentation, or hyperpigmentation at the lesion site have also been reported and may especially be of concern when cryolesions are performed in proximity to the face.[89]

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Access the reference list online at http://www.expertconsult.com

CHAPTER 61

Spinal Cord Stimulation

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Spinal cord stimulation (SCS) describes the use of pulsed electrical energy near the spinal cord to control pain.[1] This technique was first applied in the intrathecal space and finally in the epidural space as described by Shealy in 1967.[2] This technique has notable analgesic properties for neuropathic pain states, anginal pain, and peripheral ischemic pain. The same technology can be applied in deep brain stimulation, cortical brain stimulation, and peripheral nerve stimulation.[3–5]

MECHANISM OF ACTION

Neurostimulation began shortly after Melzack and Wall proposed the gate control theory in 1965.[6] This theory proposed that nonpainful stimulation of large myelinated Aβ fibers could impede painful stimuli carried by C-fibers and lightly myelinated Aδ fibers. As an application of the gate control theory, Shealy implanted the first spinal cord stimulator device for the treatment of chronic pain.[2]

Although the gate theory was initially proposed as the mechanism of action, the underlying neurophysiologic mechanisms are not clearly understood. Recent research has given us insight into effects occurring at the local and supraspinal levels, and through dorsal horn interneuron and neurochemical mechanisms.[7,8] Experimental evidence points to SCS having a beneficial effect at the dorsal horn level by favorably altering the local neurochemistry in that zone thereby suppressing the hyperexcitability of the wide dynamic range interneurons. Specifically, there is some evidence for increased levels of gamma-aminobutyric acid (GABA) and serotonin, and perhaps suppression of levels of some excitatory amino acids including glutamate and aspartate. In the case of ischemic pain, analgesia seems to be obtained through restoration of a favorable oxygen supply and demand balance—perhaps through a favorable alteration of sympathetic tone.

TECHNICAL CONSIDERATIONS

SCS is a technically challenging interventional/surgical pain management technique. It merits extensive training and understanding of neuroanatomy, surgical techniques, and perioperative patient care. Collaboration between the pain physician and spine surgeon is advocated for optimal success with neurostimulation.

There are several options in hardware selection. Electrodes are of two types: percutaneous versus paddle (Fig. 61-1). The paddle leads are flat and wide with insulation on one side and electrical pads on the other. This has the advantage of directing the current in one direction. Paddle leads must be placed via laminotomy or laminectomy. Percutaneous leads are cylindrical catheters placed via a needle. Contacts are cylindrical and generate a less eficient electric field circumferentially around the catheter.

Electrodes are connected to an implanted pulse generator (IPG) or an RF unit (Fig. 61-2). The power source options are of three types: primary cell, rechargeable, and RF. Primary cells tend to be larger and have a short life span of 4 years, but have low maintenance because they do not require charging. Rechargeable IPGs contain Li-ion cells with a life span of 9 years. RF units are not limited by battery life but require an external power source, which is inconvenient and may result in skin irritation. Currently three companies produce neurostimulation devices: Boston Scientific Inc., Medtronic Inc., and St. Jude Medical Inc. (see list at the end of this chapter). There is variability in how the devices work but there has not been any study suggesting superiority of one device over another.

A stimulator trial is conducted under fluoroscopy with sterile conditions. A lead is introduced into the epidural space with the standard epidural needle placement (Fig. 61-3). The lead is steered under fluoroscopic imaging into the posterior paramedian epidural space up to the desired anatomic location. Sedation is kept light, and copious local anesthetic is used so that the patient can be awakened after lead placement for evaluatoin of parasthesia coverage over the area of pain. The needle is withdrawn, an anchoring suture placed into the skin, and a sterile dressing is applied. When the patient returns after a trial of several days the dressing is removed, the suture clipped, and the lead removed and discarded regardless of the success of the trial. When the patient returns for implant, a new lead is placed in the location of the trial lead and connected to an implanted IPG. Alternatively, trial leads can also be implanted with tunneled extensions exiting the skin such that, during permanent implantation, only the extensions are discarded and the original trial leads can be used to connect to the generator. This method has the advantage of retaining the same lead position in a successful trial, but on the other hand, it adds an incision that increases postoperative pain confounding trial interpretation. Furthermore, implanted leads may have a greater risk for infection than the straight percutaneous method.[9] In both cases, perioperative antibiotic use is controversial but common.

A careful trial period of 5 to 7 days is advocated to decrease the risk of a failed implant. Patients are encouraged to pursue normal activities with the exception of aggressive bending or twisting to prevent lead migration. In spite of advances in patient selection and improved, redundant multilead systems, clinical failures of implanted neurostimulator devices remain too common and pain practitioners must critically evaluate their own outcomes and adhere to strict selection criteria.

Most consider 50% or more pain relief to be indicative of a successful trial, although the ultimate decision also should include other factors such as activity level and medication intake. If the trial succeeds, the patient returns

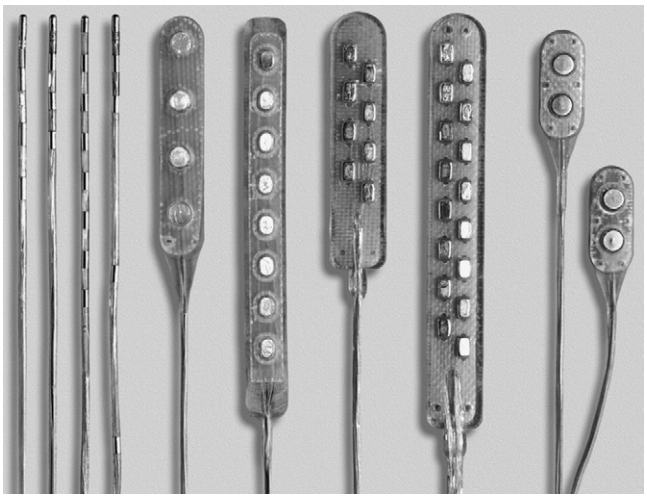

FIGURE 61-1 Neurostimulator leads: (left to right) percutaneous type to paddle type. *(Courtesy of SJM Inc.)*

for permanent lead and generator placement. The technical challenges of permanent lead placement depend on (1) proper fixation and (2) lead redundancy. Consistent and reliable stimulation depends on fixing an electric field over a small area of the spinal cord. Leads have a limited capacity for stretch, and certain body movements can stretch leads significantly and prompt lead migration. Whereas sclerotic changes in the tissue surrounding the implanted system stabilizes the leads over the long-run, during the acute phase, proper anchoring is a major factor in successful lead placement (Fig. 61-4). In the event of minor lead migration, electrode redundancy is used to accommodate for minor shifts by using alternative leads to accommodate the desired electric field. The generator unit is generally implanted in the lower abdominal area or in the posterior superior gluteal area (Fig. 61-5). For cervical or occipital leads, generators are often placed in between the scapula. Generally, generators should be in a location the patient

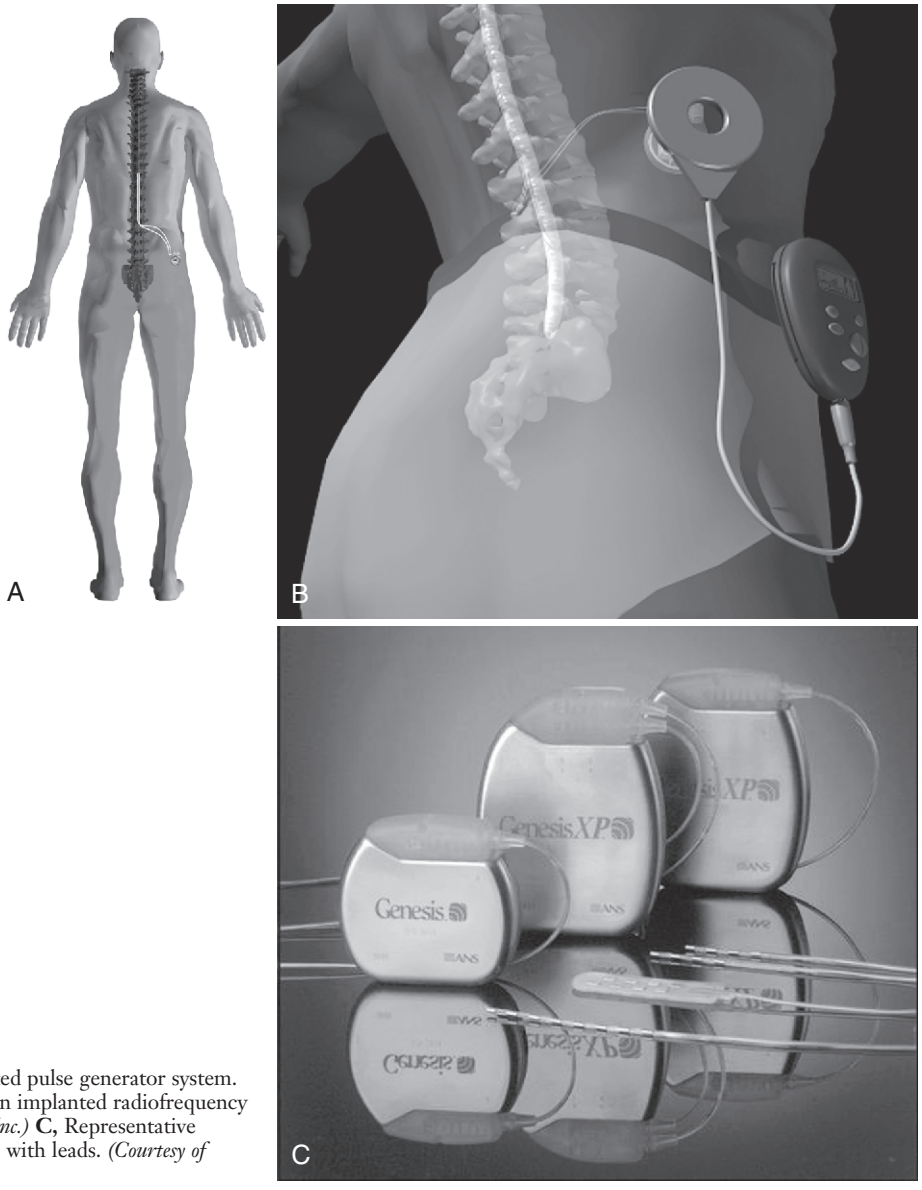

FIGURE 61-2 **A,** Schematic view of an implanted pulse generator system. *(Courtesy of Medtronic Inc.)* **B,** Schematic view of an implanted radiofrequency spinal cord stimulation system. *(Courtesy of SJM Inc.)* **C,** Representative implanted pulse generator neurostimulation units with leads. *(Courtesy of SJM Inc.)*

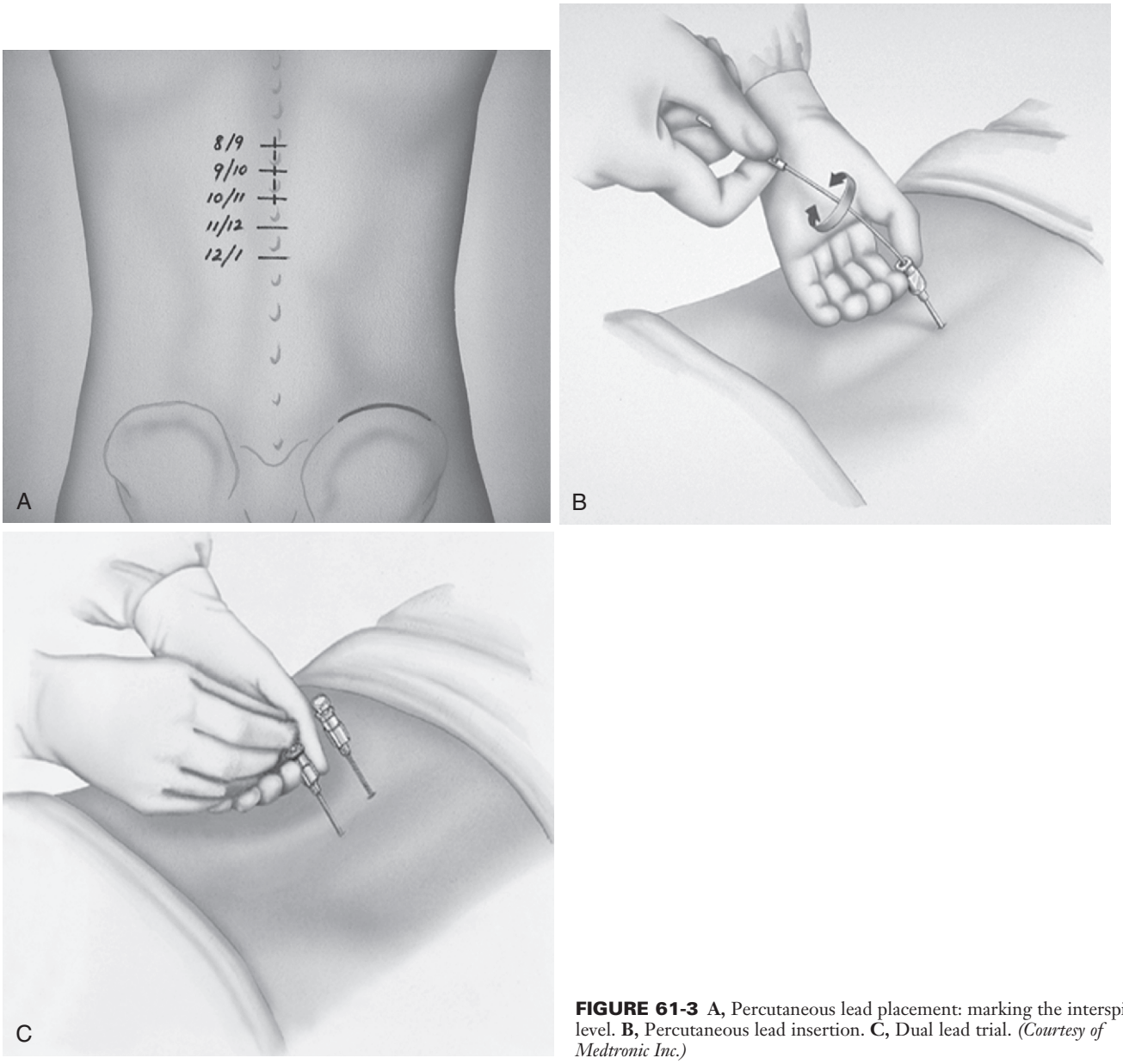

FIGURE 61-3 **A,** Percutaneous lead placement: marking the interspinous level. **B,** Percutaneous lead insertion. **C,** Dual lead trial. *(Courtesy of Medtronic Inc.)*

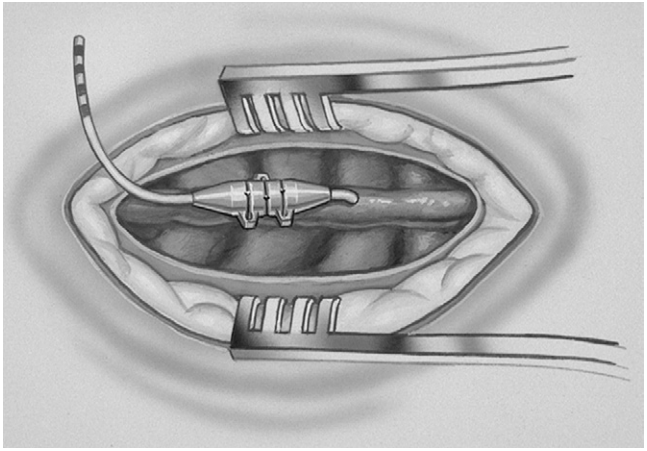

FIGURE 61-4 Anchoring the lead. *(Courtesy of Medtronic Inc.)*

can access with his or her dominant hand for adjustment of settings or charging.

PATIENT SELECTION

Appropriate patients for neurostimulation implant must meet the following criterion: the patient has a diagnosis amenable to this therapy (i.e., neuropathic pain syndromes), the patient has failed conservative therapy, significant psychological issues have been ruled out, and a trial has demonstrated pain relief.[10] However, pure neuropathic pain syndromes are relatively less common than the mixed nociceptive/neuropathic disorders including failed back surgery syndrome (FBSS) (Fig. 61-6). In addition, many patients with chronic pain will have some depressive symptomatology, and psychological screening can be extremely helpful to avoid implanting patients with major

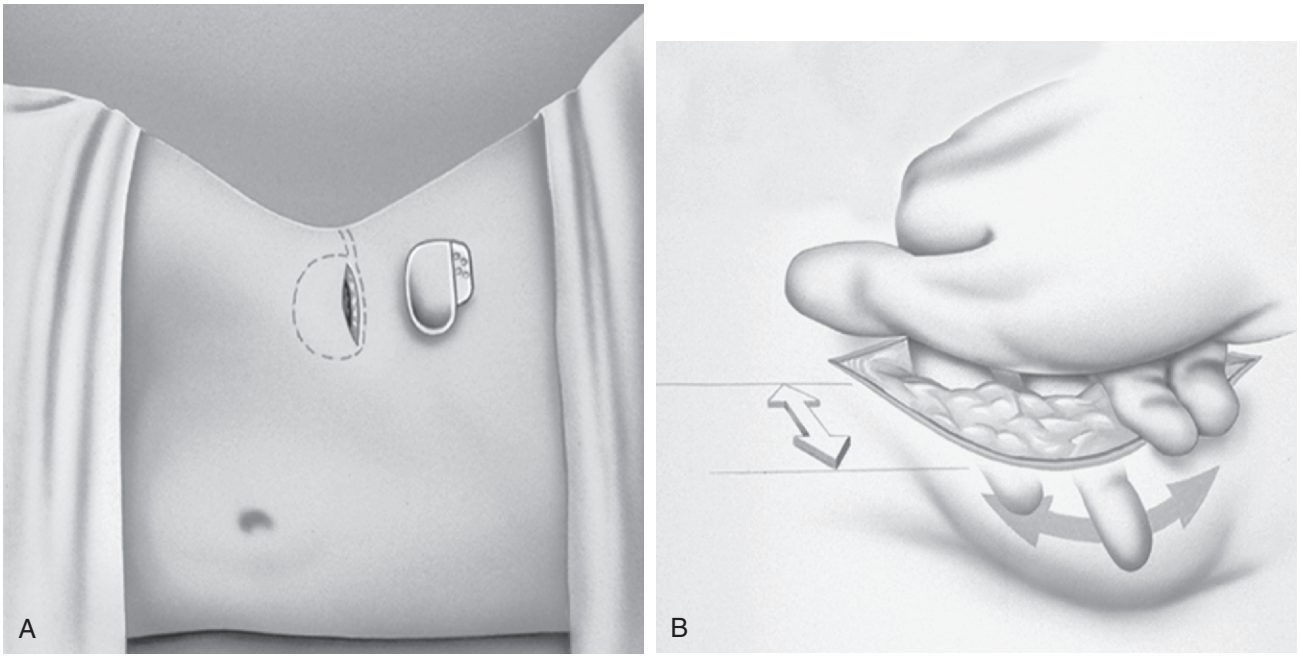

FIGURE 61-5 **A, B,** Permanent implant: pulse generator internalization. *(Courtesy of Medtronic Inc.)*

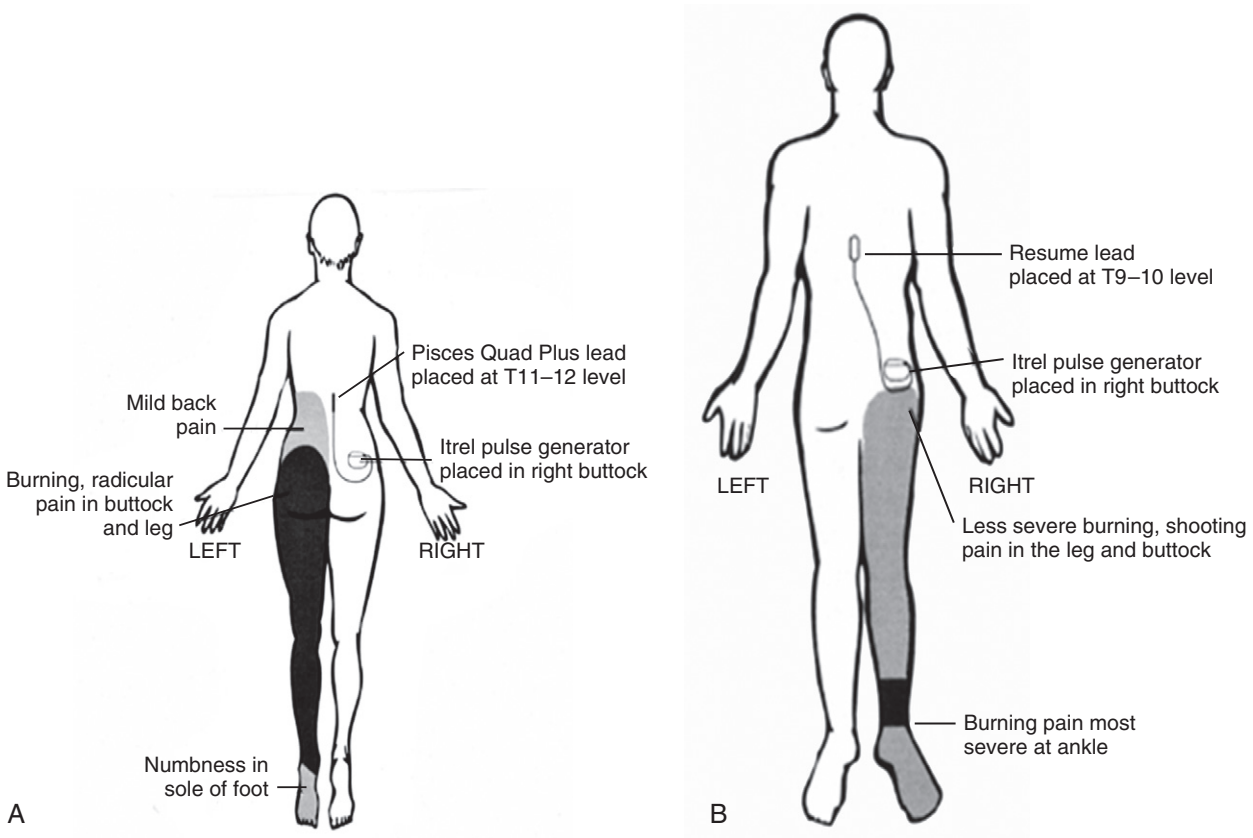

FIGURE 61-6 **A, B,** Ideal candidates: failed back surgery syndrome/complex regional pain syndrome. Note the radicular versus axial pain pattern. *(Courtesy of Medtronic Inc.)*

psychological disorders. An interesting study by Olson and colleagues revealed a high correlation between many items on a complex psychological testing battery and favorable response to trial stimulation.[9] There are numerous standardized psychological screening tools available for preoperative evaluation. It is recommended that holistic evaluation and support for patients are ensured prior to implementing an invasive procedure.

Whereas implantable devices show improvements in pain, they lack evidence for improvements in functional outcomes.[10] One confounder may be psychological well-being prior to SCS implantation; Olson and colleagues revealed a high correlation between many items on a complex psychological testing battery and favorable response to trial stimulation.[9] To maximize the probability of improvements in functional outcomes as well as pain, part of the preoperative evaluation is establishment of functional goals. Doing so will reinforce to the patient that improvement in pain is not the primary endpoint, but rather it is return to functional activity.[11] Patients are often fearful that pain is indicative of damage and that behavior may limit their rehabilitation even after pain improves.[12]

COMPLICATIONS

Complications with SCS range from simple problems, such as lack of appropriate paresthesia coverage, to devastating complications, such as paralysis, nerve injury, and death. Overall complication rates from spinal cord stimulation range from 28% to 42%.[10,13] In a recent systemic review, the most common complication was found to be lead migration or breakage, which occurred in 22% of implanted cases.[14] Studies by Barolat and May reported lead revision rates due to lead migration of 4.5% and 13.6% and breakage of 0% and 13.6%, respectively.[15,16] The generator can also be a source of revision if changes in body habitus affect the source position.

Studies have demonstrated superficial infectious rates ranging from 2.5% to 7.5%, but fortunately only the rare case progressed into more serious infections (<0.1%).[10,15,17,18] To avoid infectious complications, the patient should be instructed on wound care and recognition of signs and symptoms indicative of infection. Many superficial infections can be treated with oral antibiotics, but more serious infection may require surgical exploration and removal of the device. Although less common, abscess of the epidural space can lead to paralysis and death if not identified quickly, so a high index of suspicion is warranted. *Staphylococcus aureus* is the predominant pathogen for percutaneous epidural catheters.[18] While there is no standard to avoid infection, prophylactic intraoperative antibiotics are often used, as well as oral antibiotics for 3 to 5 days postoperatively.

PROGRAMMING

There are four basic parameters in neurostimulation, which may be adjusted to create stimulation paresthesias in the painful areas thereby mitigating the patient's pain (Fig. 61-7). They are amplitude, pulse width, rate, and electrode selection.[19]

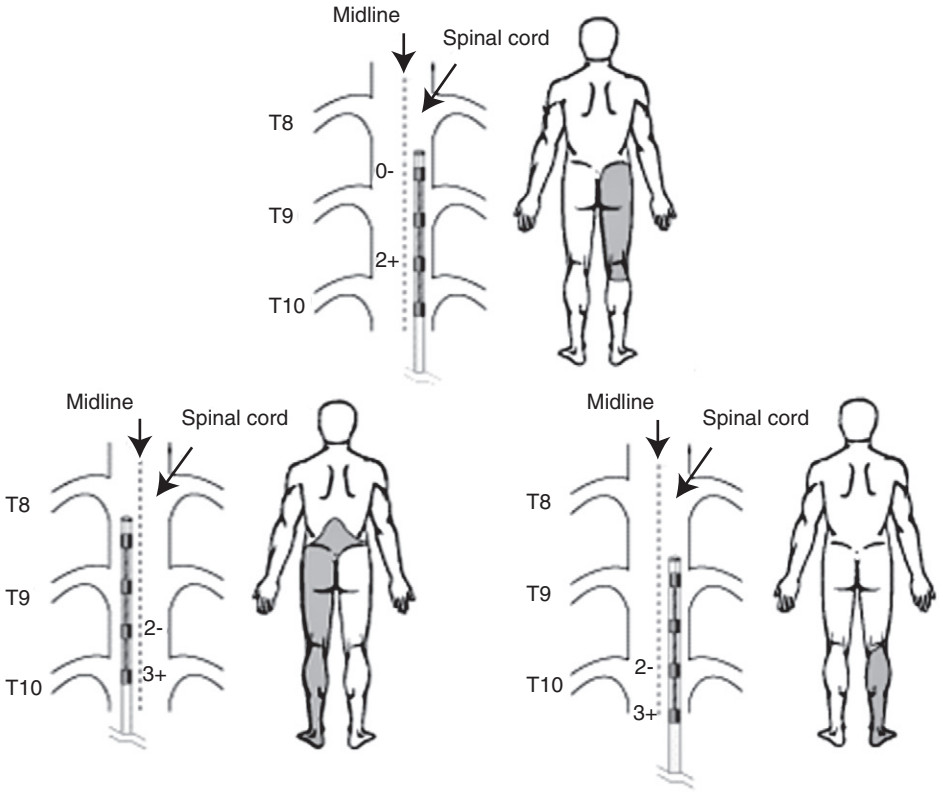

FIGURE 61-7 Typical patterns of coverage using different anodal and cathode combinations. *(Courtesy of Medtronic Inc.)*

Amplitude is the intensity or strength of each individual pulse and can be controlled by voltage (V) or current (ohms). There is no evidence of superiority for voltage or current control, however, theoretically, current-control systems are more immune to changes in electrical resistance in the tissue due to sclerosis and patient positional changes. As such, mathematical modeling predicts more even paresthesia.[20] Amplitudes are variable even for an individual patient, but typical initial settings are 60% to 90% of motor threshold.[21]

Pulse width is the duration of a pulse measured in microseconds (msec). It is usually set between 100 and 400 msec. Similar to increasing the amplitude, a larger pulse width delivers more energy per pulse and typically broader coverage. Common initial settings are 0.2 msec.[21]

Rate is measured in hertz (Hz) or cycles per second, between 20 and 120 Hz. At lower rates, the patient may feel myoclonic vibrations, whereas at higher frequencies, the feeling is more of a buzzing sensation. Very high frequencies (>500 Hz) are suggested to increase blood flow and decrease vascular resistance.[22]

Electrode selection is a complex topic. Barolat and colleagues provided mapping data of coverage patterns based on lead location in 106 patients.[23] Most patients' stimulators are programmed with electrode selection until the patient obtains anatomic coverage, then the pulse width and rate are adjusted for maximal comfort.

The lowest acceptable settings on all parameters are generally used to conserve battery life. Other programming modes that save battery life include a cycling mode during which the stimulator cycles full on/off at patient-determined intervals (minutes, seconds, or hours). The patients' programming may change over time and reprogramming needs are common. Both neurostimulator manufacturing companies are very helpful to clinicians with patient reprogramming assistance. Many busy pain practices designate a stimulator nurse to handle patient reprogramming needs.

OUTCOMES

Outcomes research for spinal cord stimulation is rapidly evolving. Whereas improvements have led to decreased morbidity and much greater probability of obtaining adequate paresthesia coverage with subsequent improved outcomes[24] greater research is needed to hone the technology, pursue increased efficacy, and limit complications. Most of the current evidence falls within the level IV (limited) or level V (indeterminate) categories due to the invasiveness of the modality and inability to provide blinded treatment. The trend has been promising, however. In a level II review study Turner et al. with FBSS patients from 1966 to 1994 reported less positive outcomes than Barolat's level IV FBSS study in 2001.[15,25] The authors believe this represents the effect of improving technology.

FAILED BACK SURGERY SYNDROME

Within the literature, there are two randomized controlled trials on SCS for FBSS. North and colleagues selected 50 FBSS patients as candidates for repeat laminectomy. Exclusion criteria included severe spinal canal stenosis or other instability major neurologic deficit, untreated narcotic dependency, major psychiatric comorbidity, and the presence of any significant or disabling chronic pain problem. Crossover between groups was permitted after the 6-month follow-up. Of the 26 patients who had undergone reoperation, 54% (14 patients) crossed over to SCS. Of the 24 who had undergone SCS, 21% (5 patients) opted for crossover to reoperation. For 90% of the patients, long-term (3-year) follow-up evaluation showed that SCS continues to be more effective than reoperation, with significantly better outcomes by standard measures and significantly lower rates of crossover to the alternate procedure. Additionally, patients randomized to reoperation used significantly more opioids than those randomized to SCS. Other measures assessing activities of daily living and work status did not differ significantly.

The second randomized controlled trial (RCT) was a multicenter international study that randomized 100 FBSS patients with neuropathic radicular leg pain to SCS plus conventional medical management (SCS group) or conventional medical management (CMM) for 6 months. Primary outcome was 50% or greater reduction in pain. Secondary outcome measures included quality of life indicators, functional capacity, pain medication use, satisfaction, and complications. Crossover was permitted at the 6-month interval with an intention-to-treat model and patients were followed for an entire year. The results showed a statistically significant advantage of SCS over CMM for the primary ($p<0.001$) and secondary ($p\leq0.05\%$) outcomes. After the study midpoint, 5/50 SCS patients crossed over to CMM versus 32/50 CMM to SCS. At the study conclusion, however, 32% of SCS patients had experience with device-related complications.[27]

There have been three systematic review articles on neurostimulation of chronic pain of spinal origin.[25,28,29] Turner completed a meta-analysis from the articles related to the treatment of FBSS by SCS from 1966 to 1994.[25] Pain relief exceeding 50% was experienced by 59% of patients with a range of 15% to 100%. Based on this review, however, the authors concluded that there was insufficient evidence from the literature for drawing conclusions about the effectiveness of SCS relative to no treatment or other treatments. North and Wetzel's review consisted of case-control studies and two prospective control studies.[28] They concluded that if a patient reports a reduction in pain of at least 50% during a trial, as determined by standard rating methods, and demonstrates improved or stable analgesic requirements and activity levels, significant benefit may be realized from a permanent implant. The review by Bala et al.[29] focused more on cost-efficacy and reviewed one RCT, one retrospective cohort study, and 13 case series.[29] It was concluded that SCS is effective for treatment of FBSS and less costly over the long-term.

COMPLEX REGIONAL PAIN SYNDROME

Research of high quality regarding SCS and complex regional pain syndrome (CRPS) is limited, but existing data are overwhelmingly positive in terms of pain reduction, quality of life, analgesic usage, and function. Kemler and colleagues[30] published a prospective, randomized, comparative trial of SCS versus conservative therapy for CRPS.

Patients with a 6-month history of CRPS of the upper extremities were randomized to undergo trial SCS (and implant if successful) plus physiotherapy versus physiotherapy alone. At a 6-month follow-up assessment, the patients in the SCS group had a significantly greater reduction in pain, and a significantly higher percentage was graded as much improved for the global perceived effect. However, there were no clinically significant improvements in functional status. The authors concluded that in the short-term, SCS reduces pain and improves the quality of life for patients with CRPS involving the upper extremities.

Several important case series have been published on the use of neurostimulation in the treatment of CRPS. Calvillo[31] reported on a series of patients with advanced CRPS whom were treated with either SCS, PNS, or both. After a 3-year period follow-up, patients with SCS had a statistically significant reduction in pain score and improvement in return to work. The authors concluded that in late stages of CRPS, neurostimulation (with SCS or PNS) is a reasonable option when alternative therapies have failed. Another case series reported by Oakley[32] is remarkable in that it used a sophisticated battery of outcomes tools to evaluate treatment response in CRPS using SCS. The study followed 19 patients and analyzed the results from the McGill Pain Rating Index, the Sickness Impact Profile, Oswestry Disability Profile, Beck Depression Inventory, and Visual Analog Scale. After an average 8 months of follow-up, all scales showed statistical benefits after SCS and all patients received at least partial relief, with 30% receiving full relief. A literature review by Stanton-Hicks[33] of SCS for CRPS consisted of seven case series. These studies ranged in size from 6 to 24 patients. Results were noted as "good to excellent" in greater than 72% of patients over a time period of 8 to 40 months. The review concluded that SCS proved to be a powerful tool in the management of patients with CRPS.

Even in failed cases, there is evidence that more aggressive stimulation, that is only possible with RF generators, can still have a benefit. A retrospective, 3-year, multicenter study of 101 patients by Bennett[34] evaluated the effectiveness of SCS applied to CRPS I and compared the effectiveness of octapolar versus quadripolar systems, as well as high-frequency and multiprogram parameters. The authors concluded that SCS is effective in the management of chronic pain associated with CRPS I. For 15% of patients, pain control was attainable only with use of dual-octapolar systems with multiple-array programming capabilities, and high-frequency stimulation (>250 Hz). These settings are not available with standard implantable devices.

PERIPHERAL ISCHEMIA AND ANGINA

Cook[35] reported in 1976, that SCS effectively relieved pain associated with peripheral ischemia. This result has been repeated and noted to have particular efficacy in conditions associated with vasospasm, such as Raynaud disease.[36] Many studies have shown impressive efficacy of SCS in treating intractable angina.[37] Reported success rates are consistently greater than 80% and these indications, already widely used outside of the United States, are certain to expand in the United States. This is an active area of research with a quickly expanding body of literature. Interested readers are encouraged to evaluate the literature as it is beyond the scope of this chapter.

COST EFFECTIVENESS

Cost effectiveness of SCS in the treatment of chronic back pain was evaluated by Kumar and colleagues[38] in 2002 and again by Bala et al.[29] in 2008. Kumar prospectively followed 104 patients with FBSS. Of the 104 patients, 60 were implanted with an SCS using a standard selection criterion. Both groups were monitored over a period of 5 years. The stimulation group's annual cost was $29,000 versus $38,000 in the control group. The authors found 15% of subjects returned to work in the stimulation group versus 0% in the control group. The higher costs in the nonstimulator group were in the categories of medications, emergency center visits, radiographs, and ongoing physician visits. As already discussed, Bala's group conducted a systematic review of the literature to identify RCTs (two studies found), controlled observation studies (1 retrospective cohort study found), or case series with more than 50 patients and at least 1-year follow-ups (13 qualifying case series). The beneficial effects of SCS were consistent in all studies. Of the three studies that fulfilled inclusion criteria for cost-effectiveness evaluation, all consistently showed higher initial costs, but overall long-term cost effectiveness is greater than conventional medical management.

Bell[39] performed an analysis of the medical costs of SCS therapy in the treatment of patients with FBSS. The medical costs of SCS therapy were compared with an alternative regimen of surgeries and other interventions. Externally powered (external) and fully internalized (internal) SCS systems were considered separately. No value was placed on pain relief or improvements in the quality of life that successful SCS therapy can generate. The authors concluded that by reducing the demand for medical care by FBSS patients, SCS therapy can lower medical costs and found that, on average, SCS therapy pays for itself within 5.5 years. For those patients for whom SCS therapy is clinically efficacious, the therapy pays for itself within 2.1 years.

Kemler[40] performed a similar study by looking at "chronic reflex sympathetic dystrophy (RSD)" using outcomes and costs of care before and after the start of treatment. This essentially is an economic analysis of Kemler's RSD outcomes paper discussed previously. During 12 months of follow-up, costs (routine RSD costs, SCS costs, out-of-pocket costs), and effects (pain relief by visual analog scale, health-related quality of life improvement by a validated quality-of-life instrument) were assessed in both groups. SCS was both more effective and less costly than the standard treatment protocol. As a result of high initial costs of SCS in the first year, the treatment per patient is $4000 more than control therapy. However, in the lifetime analysis, SCS per patient is $60,000 cheaper than control therapy. In addition, at 12 months, SCS resulted in pain relief and improved health-related quality of life. The authors found SCS to be more effective and less expensive when compared with the standard treatment protocol for chronic RSD.

PERIPHERAL, CORTICAL, AND DEEP BRAIN STIMULATION

Besides stimulation of the spinal cord, neurostimulation can successfully be used at other locations in the peripheral and central nervous systems to provide analgesia. Peripheral nerve stimulation was introduced by Wall, Sweet, and others in the mid-1960s.[41] This technique has shown efficacy for peripheral nerve injury pain syndromes as well as CRPS, with the use of a carefully implanted paddle lead using a fascial graft to help anchor the lead without traumatizing the nerve.[42]

Motor cortex and deep brain stimulation are techniques that have been explored to treat highly refractory neuropathic pain syndromes including central pain, deafferentation syndromes, trigeminal neuralgia, and others Fig. 61-8.[43] Deep brain stimulation has become a widely used technique for movement disorders, and much less so for painful indications, although there have been many case reports of utility in treating highly refractory central pain syndromes.[44]

FUTURE

There are many projected innovations that will continue to make SCS an attractive option for treatment of pain. Modern implants have a life span of 2 to 10 years but battery capacity and microprocessor power consumption have improved rapidly, which will eventually prolong the life span, decrease the maintenance requirements, and reduce costs of future implantable devices. Current stimulators are contraindicated for use within magnetic resonance imaging (MRI) due to the risk of magnetically generated currents heating the leads and causing neural injury; manufacturers are developing MRI-compatible leads. There is ongoing research that demonstrates synergistic effects of intrathecal medications with spinal cord stimulation. As the physiologic understanding of dorsal column stimulation improves, newer modes of pulse waveforms and neuroanatomic distribution of currents can substantiate novel therapeutic roles. Closed-loop biofeedback innovations that record neural responses to spinal cord stimulation could play a role in improving the effects of SCS.[45]

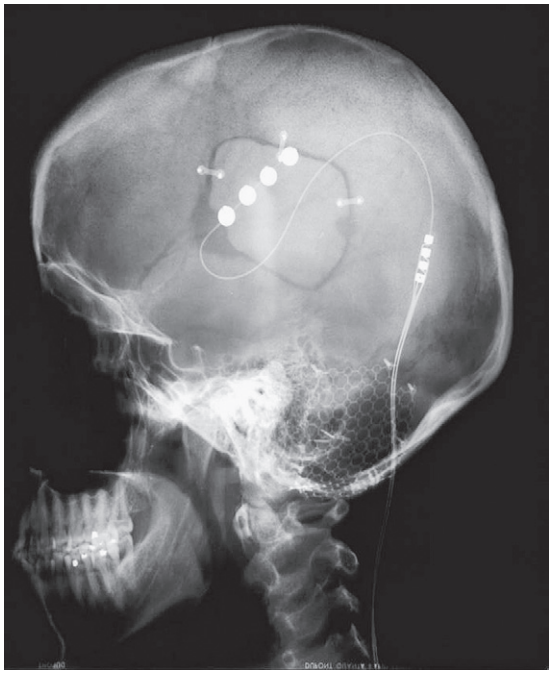

FIGURE 61-8 Radiograph of motor cortex stimulation. *(Courtesy of Ali Rezai, M.D., Cleveland Clinic Foundation.)*

CONCLUSION

Spinal cord stimulation is an invasive, interventional surgical procedure. Linderoth and Meyerson[46] wrote some principles of neurostimulation that are cornerstones of SCS theory and practice (Box 61-1). The difficulty of RCTs in such situations is well recognized. Based on the present evidence with two randomized trials, one prospective trial, and multiple retrospective trials, the evidence for SCS in properly selected populations with neuropathic pain states is moderate. Clearly, this technique should be reserved for patients who have failed more conservative therapies. With appropriate patient selection and careful attention to technical issues, the clinical results are overwhelmingly positive.

COMPANIES THAT PRODUCE NEUROMODULATION DEVICES

1. Boston Scientific Inc., One Boston Scientific Place, Natick, MA 01760-1537; 508-650-8000; www.bostonscientific.com.

Box 61-1 Principles of Neurostimulation

SCS mechanism of action is not completely understood but influences multiple components and levels within the central nervous system with both interneuron and neurochemical mechanisms.

SCS therapy is effective for many neuropathic pain conditions. Stimulation-evoked paresthesia must be experienced in the entire painful area. No consistent evidence exists for the efficacy of neurostimulation in primary nociceptive pain conditions.

Stimulation should be applied with low intensity, just suprathreshold for the activation of the low-threshold, large-diameter fibers, and should be of nonpainful intensity. To be effective SCS must be applied continuously (or in cycles) for at least 20 min prior to the onset of analgesia. This analgesia develops slowly and typically lasts several hours after cessation of the stimulation.

SCS has demonstrated clinical and cost effectiveness in FBSS and CRPS. Clinical effectiveness has also been shown in peripheral ischemia and angina.

Multicontact, multiprogram systems improve outcomes and reduce the incidence of surgical revisions. Insulated, paddle-type electrodes probably decrease the incidence of lead breakage, prolong battery life, and show early superiority in quality of paresthesia coverage and analgesia in FBSS as compared to permanent percutaneous electrodes.

Serious complications are exceedingly rare but can be devastating. Meticulous care must be taken during implantation to minimize procedural complications. The most frequent complications are wound infections (approximately 5%) and lead breakage or migration (approximately 13% each for permanent percutaneous leads and 3% to 6% each for paddle leads).

Modified from Linderoth B, Meyerson BA: Spinal cord stimulation: mechanisms of action. In Burchiel K, editor: *Surgical management of pain*, New York, 2002, Theime Medical, pp 505–526.

2. Medtronic Inc., 710 Medtronic Parkway, Minneapolis, MN 55432-5604; 763-514-5604; www.medtronic.com.
3. St. Jude Medical Inc., 6901 Preston Rd, Plano, TX 75024; 972-309-8000; www.sjm.com.

KEY POINTS

- Neurostimulation mechanisms of analgesia are poorly understood, but it appears to interrupt transmission of nociceptive signaling via interneural inhibition at the substantia gelatinosa and modulation of spinal cord neurotransmitters. Neurostimulation is effective for many neuropathic pain conditions but careful patient selection with a multidisciplinary perspective is valuable to ensure higher rates of successful implantation.
- There are multiple choices for leads and power generators. Paddle-type electrodes may provide superior coverage at lower power settings but are more invasive to place. Generators have variable life spans depending on if they are rechargeable, primary cell, or externally powered RF.
- An effective trial is demonstrated by tolerable stimulation-evoked paresthesias in the painful area that inhibits the pain. Programming stimulators are as relevant to successful outcomes as technical operative skills, and the device companies are well versed in assisting physician practices with this.
- Neurostimulation has demonstrated clinical and cost effectiveness in FBSS patients, CRPS patients, peripheral ischemia patients, and angina patients.
- Multicontact, multielectrode systems improve outcomes and reduce the need for surgical revisions due to minor lead migration. Lead migration is the leading cause of system failure.
- Serious complications are rare, but can be devastating. Complete informed consent must be obtained before trial or implant.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 62

Peripheral Nerve Stimulation

Terrence McNamara, DO, MD ❂ **Marc Alan Huntoon,** MD

Chronic intractable neuropathic pain is common and has a significant impact on patients' quality of life.[1] The treatment of these patients can be challenging for pain physicians. For patients who fail initial conservative therapy, neuromodulation may be effective in select populations.[2] Peripheral nerve stimulation (PNS) and spinal cord stimulation (SCS) have evolved in recent decades, with the latter more widely researched and applied. However, recent technical advances have led to growth in PNS for a wide variety of chronic pain disorders such as, but not limited to, limb mononeuropathies, complex regional pain syndrome, cranial neuralgias, headache disorders, and regional pain not amenable to SCS.[2–5] This chapter will focus on PNS for neuropathic pain in the limbs through stimulation of large peripheral nerves.

HISTORY AND PATHOPHYSIOLOGY

Electricity has been used to modulate pain since before the era of modern medicine, through various basic means.[2] The formal application of electricity to specific peripheral nerves began in the latter half of the 20th century.[6] Wall and Sweet used percutaneous stimulation to treat chronic neuropathic pain in subjects and correlated these findings to the gate theory of pain.[7] Despite advances in the understanding of pain pathophysiology since that time, there is no current unifying theory of how neuromodulation affects chronic pain. Theories include direct effects on peripheral pain fibers through excitation failure,[8] selective release of pain-modulating neurotransmitters,[9] and changes in cerebral flow in pain centers.[5] More research is required and may reveal a unitary PNS effect or that a combination of peripheral and central responses generates observed pain relief.

TECHNICAL CONSIDERATIONS

A key factor that has likely caused resurgence in interest among pain physicians in PNS is the increase in using ultrasound (US) as an image-guidance technique for procedures, and the vast improvement in the computer software and probe technology of modern US machines.[10] Recent anatomic feasibility studies suggested one could place conventional spinal cord stimulator electrodes very near target nerves with US in both the upper and lower extremities without significant risk of mechanical neural injury, and that these placements were fairly durable in spite of simulated anatomic movements.[11,12] For each of the limb nerves described in the anatomy sections below there are universal considerations. Sunderland noted significant variability in fascicle number, location, and size within a given nerve trunk.[13] The complex fascicular arrangement of upper extremity nerves is an important consideration when attempting to stimulate a sensory fascicle.[14] Briefly, a peripheral nerve will have one to several internal fascicles that routinely change locations within the nerve topography. Thus, if the desired fascicle is on the medial peripheral aspect of the nerve, it would be ideal to locate the electrodes as close to that area as is feasible. Often, the location of these fascicles is an advantage of the percutaneous approach. An open neurosurgical approach allows only motor testing with a nerve stimulator, unless the operator performs a wake-up test. In Sunderland's key article, the upper-extremity peripheral nerves were mapped as to the variability in the internal structure of the nerves.[13] The key nerves of interest are usually superficial enough to be seen well under US. US also allows visualization of surrounding key soft tissue structures and in each case, care should be taken to not pierce muscle compartments or vascular structures along the needle/lead path to the nerve. For implantation cases, the lead can be anchored to the superficial muscle fascia with a strain relief loop. The nerve will normally translate within the neurovascular compartment as much as several millimeters. This means that a normal nerve may move up to several millimeters between the muscle and surrounding fascia with flexion, extension, and rotation of the extremity. Thus, redundancy of the number of lead contacts in the vicinity of the desired fascicle is important. This underscores the desire to perform intraoperative testing, and to consider placement of more than one percutaneous electrode (Figs. 62-1 and 62-2).

ANATOMY

RADIAL NERVE

The radial nerve is very close to the lateral surface of the humerus, at a point 10 to 14 cm proximal to the lateral epicondyle. Ultrasound scanning usually begins at the elbow and, with the probe in a transverse orientation to the arm, continues proximally until the desired approach is identified (Fig. 62-3).[11] The needle can be advanced from posterolateral to anteromedial to lie between nerve and humerus. Piercing the lateral head of the triceps muscle may be unavoidable. Potential patients could include those with posterior interosseous neuropathies or resistant lateral epicondylitis (tennis elbow) patients. Early problems with lead migration were most prominently noted in the case series with radial nerve placements.[4] Subsequent radial nerve placements have utilized more than one electrode, and a 4-week period of soft arm immobilization to allow the electrode(s) to better fibrose into place.

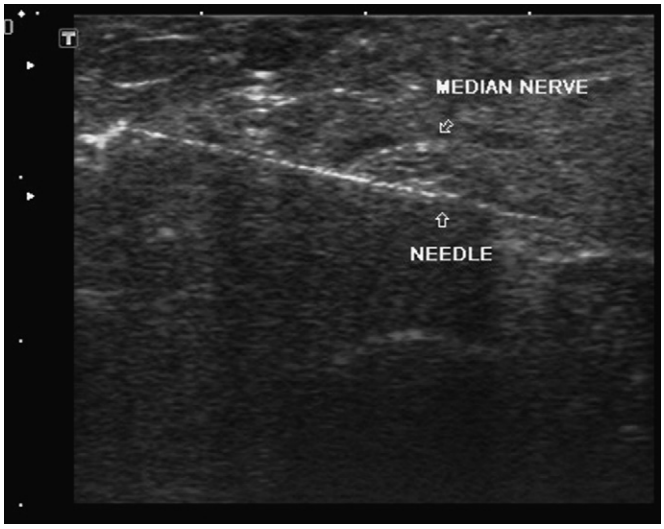

FIGURE 62-1 A short axis view of a 14 gauge stimulator needle passing inferior to the median nerve.

FIGURE 62-2 Final lead placement in a cadaver specimen after similar approach in Figure 62-1, but superficial to the nerve.

ULNAR NERVE

The ulnar nerve is superficial to the medial head of the triceps muscle. In the recent anatomic feasibility studies, the nerve was easily identified at a point 9 to 13 cm proximal to the medial epicondyle in the medial/posterior arm.[11] Ultrasound scanning can commence at the elbow and, with the probe in a transverse orientation to the arm, continue to scan more proximally until the nerve fascicular arrangements can be well identified. The needle may be advanced from posterior to anterior on the medial aspect of the arm to lie between nerve and humerus, staying superficial to the medial head of the triceps. Ulnar nerve placements are perhaps the most facile of all the upper-extremity nerves, as the nerve lies superficial to the medial head of the triceps muscle. Caution is important to avoid injury to the medial cutaneous nerve of the arm, as well as the recurrent ulnar collateral artery.

MEDIAN NERVE

The median nerve enters the antecubital fossa medial to the biceps muscle and its tendon, and next to the brachial artery. The artery serves as a good landmark to scan the neurovascular bundle, identify the median nerve, and continue to scan distally.[11] In the upper forearm at a point approximately 4 to 6 cm distal to the antecubital crease, the nerve passes between the two heads of the pronator teres muscle, and then passes under the sublimis bridge of the two heads of the flexor digitorum superficialis. The common neural fascicular communications between the median and ulnar nerves in the forearm are an important consideration in terms of expected stimulation patterns. Median nerve stimulation may be accomplished either superior to the elbow, or inferior. In some cases, during anatomic testing the ultrasound probe was placed in the longitudinal plane with the nerve to allow more electrode contact.

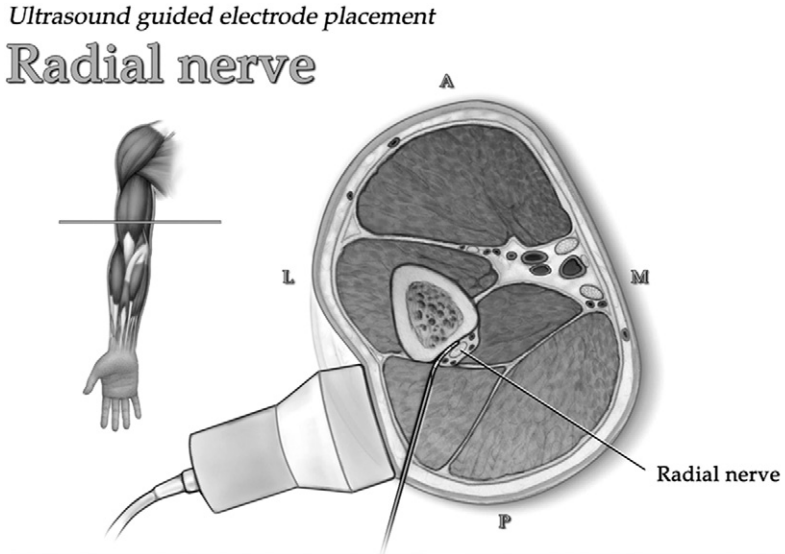

FIGURE 62-3 From reference 12, A cartoon showing placement of a PNS electrode and needle with percutaneous US-guided technique.

POPLITEAL AREA

The common peroneal nerve may be identified at its branch point from the sciatic nerve, a point 6 to 12 cm proximal to the popliteal crease. Ultrasound scanning usually commences at the popliteal crease and, with the probe in a transverse orientation to the limb, continued proximally until the desired nerve is identified (Fig. 62-4).[11] Either transverse or longitudinal placement can be used, with transverse placement being more forgiving of movement, but a greater number of possible electrodes contacting the nerves with longitudinal placement. The needle may be advanced from posterolateral to anteromedial in a slightly oblique plane, attempting to avoid passing through the biceps femoris. In some cases, both the tibial and common peroneal nerves may be approached simultaneously, either at the sciatic bifurcation or more distally (See Fig. 62-4). One must also scan thoroughly to see the sural branches to avoid injury. The popliteal area is highly rich in surrounding adipose tissue. The adipose provides a nice acoustic contrast when performing ultrasound.

POSTERIOR TIBIAL

The posterior tibial nerve can also be approached more distally in the leg. Approximately 8 to 14 cm proximal to the medial malleolus, the nerve is in close proximity to the tibialis posterior muscle, the digitorum profundus, one or two large veins, and the flexor hallucis longus. US scanning begins at the ankle near the medial malleolus, with the probe in a transverse orientation to the leg, and then continued proximally until the desired approach is identified. The needle may be advanced from anterior to posterior along the medial aspect of the ankle to lie just superficial (or deep) to the nerve. The digitorum profundus, tibialis posterior, the tibial bone surface, and surrounding veins and artery make this area highly compact. Operationally, the compactness has meant a very low rate of electrode migration, particularly if the battery pack is implanted superficial to the gastrocnemius fascia.[4] Extremely short distances between the battery and the electrode(s) may be an important feature that lessens risk of migration, as limb movement is likely to cause less "ratcheting" effect on the components.

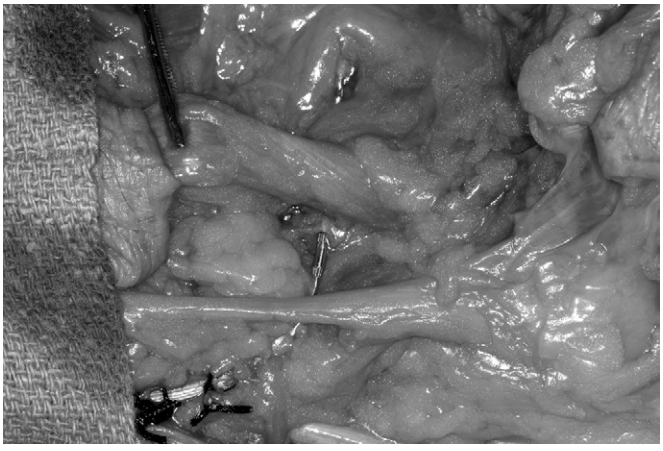

FIGURE 62-4 An electrode has been placed transverse and inferior to the nerves in the popliteal fossa.

CONCLUSION

Peripheral nerve stimulation is a promising frontier in pain medicine. Studies undertaken of a variety of applications have been generally positive, though further trials are warranted as techniques and clinical applications evolve. Key questions that need to be addressed as the field moves forward follow:

- What is the long-term safety and durability of the percutaneous leads relative to flat surgical plate electrodes?
- Do percutaneous leads cause more fibrosis and epineurial scarring due to increased friction?
- What are the optimal programming considerations for the percutaneous leads?
- Would it be preferable to only use the percutaneous leads as a formal trial prior to permanent implantation?
- How close to the nerve do the leads need to be to provide optimal stimulation characteristics?

Pain physicians, with the assistance of ultrasound guidance, have the ability to identify important anatomy and accurately place leads. Future comparative studies and development of new electrodes may be helpful in furthering this minimally invasive technology. Some applications of PNS (lumbar field stimulation) may not require ultrasound, and other references provide appropriate technique descriptions.

KEY POINTS

- Peripheral nerve stimulation systems can be trialed prior to permanent implantation with an ultrasound-guided placement.
- The long-term safety of permanent implants of percutaneous electrodes is not yet known with certainty.
- Although percutaneous ultrasound-guided PNS is similar to peripheral nerve catheter placement for perioperative nerve blockade, the larger size of the needle and potential areas of placement are quite different. These differences mandate a very strict and disciplined approach to implementing these novel techniques into practice.
- When programming the peripheral nerve stimulator system, the lowest frequencies, durations, and amplitudes of stimulation are likely to be safer. In some cases, it may be possible to perform a subthreshold program.[4]
- A thorough knowledge of cross-sectional anatomy is desirable to avoid injury to surrounding structures.
- Adaptation of percutaneous spinal cord stimulation electrodes to PNS is undesirable as a long-term strategy, and necessitates the development of novel technologies.

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Access the reference list online at http://www.expertconsult.com.

CHAPTER 63

Implanted Drug Delivery Systems for the Control of Chronic Pain

Allan Nanney, MD ✪ **Kenji Muro,** MD ✪ **Robert M. Levy,** MD, PhD

While oral, parenteral, and transdermal opioids may be extremely effective analgesic agents; systemic administration may provide inadequate pain relief and cause significant side effects, and long-term use in sufficient doses may result in tolerance and an increased potential for addiction (Table 63-1). The past decade has seen increased recognition of the endocrine, cardiovascular, sexual, and psychological side effects of chronic opioid use. Thus, the control of chronic pain with systemic opioids is often accompanied by a marked reduction in the quality of life.

The discovery of opiate receptors in the substantia gelatinosa of the spinal cord first led to the recognition of opioids having a spinal, as well as supraspinal, analgesic action. Fields and Basbaum[1] in the United States and Besson in France subsequently described and elucidated a descending system of pain inhibition. This pathway begins with projections from the frontal cortex and hypothalamus to the periaqueductal gray (PAG) of the midbrain. PAG fibers then project to the dorsal pons and the posteroventral medulla, where projections then travel via the dorsolateral funiculus to terminate in the substantia gelatinosa of the spinal cord dorsal horn. These efferent projections inhibit the second order ascending nociceptive neurons and thus inhibit pain transmission.

At the spinal level of antinociceptive processing, opiates presynaptically diminish primary afferent terminal excitability and inhibit substance P release. Postsynaptically, opiates act to suppress excitatory amino acid–evoked excitatory postsynaptic potentials (EPSPs) in dorsal horn neurons. Recognition of this spinal antinociceptive mechanism led to the first trials of direct intraspinal administration of opioids, with morphine administered epidurally[2] and intrathecally[3] for the treatment of cancer pain.[4] Since the discovery of opiate receptors in the substantia gelatinosa and the elucidation of their associated spinal antinociceptive systems, intraspinal opioid administration has been used in over 120,000 patients.[5]

Intraspinal pharmacotherapy for pain attempts to largely restrict drug effects to regions associated with the source of noxious input. Systemic side effects are minimized, and a much higher local analgesic concentration is achieved at its site of action, even at comparatively lower doses. Morphine and hydromorphone are particularly well suited for this application, because of their hydrophilicity and resulting slow absorption from the cerebrospinal fluid. As a result, analgesia from intrathecal morphine or hydromorphone not uncommonly lasts up to 24 hours.[2]

The discovery of multiple receptor systems involved in nociceptive transmission and modulation has allowed the testing and application of other receptor selective drugs (Table 63-2) as well as nonreceptor specific agents such as local anesthetics. In fact, the use of multiple agents is now the rule, rather than the exception, to intrathecal drug delivery for the treatment of intractable pain.

PATIENT SELECTION

To achieve optimal results, proper patient selection is crucial. The clinician must carefully consider several factors to indicate or contraindicate the use of chronic intraspinal analgesic therapy (Table 63-3).

FAILURE OF MAXIMAL MEDICAL THERAPY

If a noninvasive treatment program provides satisfactory pain relief without intolerable side effects, then intraspinal drug administration is not necessary. Therefore, patients should have failed a multidisciplinary pain treatment program prior to the consideration of intrathecal drug therapy. Patients should have failed to obtain sufficient relief or developed unacceptable side effects with standard routes of pharmacotherapy including antiinflammatory agents, antidepressants, nonnarcotic analgesics, and systemic narcotics. Physical and psychological therapies should be considered when appropriate. On the other hand, it is important to recognize early the failure of medical therapy in these patients. Hence, patients on increasing oral, transdermal, or intravenous doses of opioids who have already been treated with other nonnarcotic agents should be referred for trial of intraspinal drug administration to limit their suffering and their exposure to extremely high narcotic doses.

FAVORABLE PSYCHOSOCIAL EVALUATION

While most investigators highlight the importance of a favorable psychosocial evaluation in the screening for potential implant candidates, the specific variables, their quantification, and their treatment are not widely agreed upon. As part of this analysis, most advocate evaluating both the patient and his or her support system. Clearly, acute psychotic illnesses and severe, untreated depression or anxiety need diagnosis and treatment prior to surgical consideration. Other psychological issues are less clearly accepted as reasons to delay or contraindicate surgery. Furthermore, deficiencies in social support systems may leave the patient without someone to aid him or her in the event of a pain-related emergency or in the maintenance of the drug administration system.

ABSENCE OF SYSTEMIC INFECTION

The consequences of infection involving the drug administration system range from the need to remove the entire system and thus eliminate, at least for some time, this option

TABLE 63–1 Side Effects from Systemic Administration of Oral, Parenteral, and Transdermal Narcotics

Central Nervous System Effects of Opiates
Analgesia
Mydriasis
Euphoria or dysphoria
Nausea and vomiting
Sedation
Confusion
Cough reflex depression
Respiratory depression
Peripheral Effects of Opiates
Decreased gastrointestinal tract motility
Constipation
Urinary retention
Histamine release
Pruritus
Increased biliary duct pressure

TABLE 63–2 Some Intraspinally Administered Drugs in the Treatment of Intractable Pain

Opiates
Morphine
Hydromorphone
Fentanyl
Sufentanil
Dynorphin
Beta-endorphin
D-ala-D-leu-enkephalin
Methadone
Meperidine
Alpha-Adrenoceptor Agonists
Clonidine
Tizanidine
GABA B Agonists
Baclofen
Naturally Occurring Peptides and their Analogues
Somatostatin
Octreotide
Vapreotide
Calcitonin
Local Anesthetics
Bupivacaine
Ropivacaine
Tetracaine
NMDA Agonists
Ketamine
Other Agents
Ziconotide (SNX I I I)
Midazolam
Neostigmine
Aspirin
Droperidol
Gabapentin

GABA = gamma-aminobutyric acid; NMDA, N*-methyl-*D*-aspartate.*

TABLE 63–3 Indications and Contraindications for Chronic Intraspinal Analgesic Administration

Indications
Chronic pain with known pathophysiology
Sensitivity of the pain to the agent to be infused
Failure of maximal medical therapy
Favorable psychosocial evaluation
Favorable response to trial of intraspinal analgesic agents
Contraindications
Intercurrent systemic infection
Uncorrectable bleeding diathesis
Allergy to agent to be infused
Failure of a trail of intraspinal analgesic agents

for pain control, to the potentially life threatening complication of meningitis. Therefore, any local infection at the surgical site or any systemic infection contraindicates the implantation of drug administration devices. Furthermore, the use of perioperative prophylactic antibiotics is almost universally recommended and postoperative prophylactic antibiotics are often used.

ABSENCE OF COAGULOPATHIC STATES

Coagulopathic states, as a complication of malignancy or as a result of the intentional use of anticoagulant or antiplatelet agents for the prevention of stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolism, present serious potential risks in the patient undergoing implantation of drug delivery systems. Not only can the surgery be made more challenging by intraoperative hemorrhage, but it also can be complicated by the development of subcutaneous, epidural, or intradural hematomas. All efforts should be made to reverse the coagulopathic state prior to both the intrathecal drug trial and implantation of the drug delivery system and to continue this reversal into the postoperative period. Significant uncorrectable coagulopathy contraindicates the implantation of drug infusion systems.

ABSENCE OF DRUG ALLERGY

Allergy to the analgesic agent to be infused obviously and absolutely contraindicates its use. With the availability of multiple intrathecal analgesic agents, however, this has become a less frequent reason to abandon intrathecal drug delivery. Nonallergic reactions to the infused agent, such as urinary retention or pruritus, most often occur only acutely after initial intrathecal exposure to the drug and often resolve with time or respond to specific treatment. These reactions therefore do not represent absolute contraindications to chronic intrathecal drug infusion.

ABSENCE OF OBSTRUCTION OF CSF FLOW

Obstruction of cerebrospinal fluid flow historically has been identified as a relative contraindication to intraspinal drug delivery, depending on the size, location, and cause of the obstruction. In our experience, this has not been a significant problem, and patients may derive excellent

drug benefits despite such an obstruction. More important than the presence of an obstruction to CSF flow is the patient's favorable response to the intraspinal drug trial administered at the level where permanent catheter implantation is intended. It has been suggested, however, that limitations to the regular flow of cerebrospinal fluid may predispose patients to the development of intrathecal granuloma; as such we should be acutely aware of this potential risk in such patients.

LIFE EXPECTANCY GREATER THAN THREE MONTHS

While the expected length of life is not a contraindication to the use of intraspinal drug administration, it does potentially influence the method of drug administration, particularly in light of the potential costs of this therapy. Percutaneous epidural catheter attached to external pumps, internalized passive catheters with reservoirs requiring percutaneous bolus drug administration, patient activated mechanical systems, constant rate infusion pumps, and programmable infusion pumps are all viable options. The choice among these approaches, based upon ambulatory status and life expectancy, is discussed below.

FAVORABLE RESPONSE TO AN INTRASPINAL DRUG TRIAL

Not all patients suffering from chronic pain syndromes will benefit from chronic intraspinal drug administration. Pain relief in response to acute intraspinal analgesic agents is generally regarded as an indicator of long-term efficacy.[6] The inability to achieve sufficient pain relief after such a trial is a contraindication to implantation.

Careful preoperative candidate screening for indwelling drug administration systems can help exclude those who will not benefit from this technology and predict efficacy in others. Unfortunately, bias on the part of both the treating physician and the patient can inappropriately skew the results of subjective or improperly controlled trials. This may lead to drug administration system implantation in patients who will not benefit from chronic intrathecal drug administration.

Several approaches to the trial of intrathecal narcotics have been described, including single versus multiple injections, administration via lumbar puncture versus indwelling catheter, epidural versus intrathecal routes, and bolus versus continuous infusion of the drug. Testing with a single intraspinal dose of an active agent raises the possibility that the strong desire of the physician and other health care personnel to help and the patient's desperation to find some relief from their intractable pain, may lead to a significant placebo response. We have gone so far as to develop a quantitative, crossover, double-blind trial for the pre-implantation screening of candidates for chronic drug infusion therapy.[7] Despite the importance of preoperative trialing of intrathecal drug administration, there is no documented proof of the superiority of one trialing method over another in predicting long-term outcome.

ROUTE OF ADMINISTRATION

While no study has directly compared the relative efficacy of epidural versus intrathecal administration to control intractable pain, observations made by comparing the results of previous studies employing both routes are outlined below (Table 63-4). The equianalgesic epidural dose is roughly 10 times that of an intrathecal dose.[8] As 80% to 90% of an epidural injection is systemically absorbed, this larger dose requirement may lead to greater systemic side effects, including constipation and urinary retention. These higher doses further increase the probability of developing tolerance. Also, the higher dose requirement with epidural infusion to reach equivalent subarachnoid concentration necessitates refilling pump reservoirs on a more frequent basis. In addition, epidural catheter placement has known complication of dural scarring, resulting in catheter failure caused by occlusion, kinking, or displacement.

Although it avoids these complications, intrathecal drug administration carries the disadvantages of potential CSF leak and postural spinal headaches, respiratory depression caused by supraspinal drug redistribution, and meningeal infection or neural injury.

Thus, the major advantage of epidural administration is the theoretically lower risk of serious complication, although they are remarkably uncommon. In addition, epidural catheters can be placed at virtually any level, making it potentially more useful for the treatment of upper body pain. Anderson and colleagues, however, have reported excellent results treating pain of the trunk, neck, and even the head with lumbar intrathecal morphine administration.[9] The advantages of the intrathecal route, including the lower drug dosage requirements leading to increased intervals between pump refills, the lower risk of catheter failure, and

TABLE 63–4 Intrathecal Versus Epidural Administration

	Advantages	Disadvantages
Intrathecal	Lower dosage requirement (10 times more potent than epidural dose) Less systemic effect No dural fibrosis at tip of catheter Possible to sample spinal fluid for culture diagnosis and drug levels	Increased risk of neural injury Increased risk of spinal headaches Increased risk of supraspinal distribution
Epidural	Reduced risk of respiratory depression Reduced risk of spinal headache Reduced risk of neural injury	Greater dose requirement Higher systemic effect Dural fibrosis possible Question of increased tolerance Limited reservoir volume

the infrequent occurrence of potential complications, suggest this is the preferred route for intraspinal drug delivery. As a result, over the past several decades, chronic intrathecal drug administration has become the overwhelming route of choice in clinical practice.

DRUG DELIVERY SYSTEMS

Despite the popularity of implantable programmable drug pumps, there are a number of different methods to accomplish intraspinal drug delivery. These systems include a percutaneous epidural catheters attached to external pumps, internalized passive catheters and reservoirs requiring percutaneous drug administration, patient activated mechanical systems, constant rate infusion pumps, and programmable infusion pumps. In light of the significant expense of implanted programmable drug pumps and the surgery required for their implantation, the choice of drug administration system should be made with careful consideration of the individual benefits of programmability, bolus versus continuous drug infusion, the patient's general medical and ambulatory status and his or her estimated life expectancy.

Several investigators have explored the question of continuous versus bolus infusion. Continuous spinal infusion results in lower peak CSF morphine concentrations and corresponding lower plasma levels than bolus administration, while providing stable steady state levels at the spinal site of action. It has been suggested that continuous infusion may result in a reduced rate of opioid receptor tachyphylaxis[10] and decrease the risk of producing delayed respiratory depression.[11] Clinical studies, however, have not clearly confirmed the superiority of continuous over bolus intraspinal drug infusion. Recently, in fact, there is a suggestion that intermittent bolus intrathecal administration may decrease the risk of intrathecal granuloma formation and may increase the long term efficacy of intrathecal delivery.

Careful consideration should be given to the patient's ambulatory status, general health, and estimated length of life. For patients with a life expectancy of days to weeks, especially those who are bed-bound, a percutaneously implanted tunneled epidural catheter attached to an external drug pump is a viable, inexpensive option. While the risk of infection increases over time, these catheters can be maintained for several weeks to months without complication. Over time, however, the total cost of the external drug pump along with the required nursing and pharmacy services makes this option quite costly. Careful tunneling of the catheter and rigorous hygiene of the catheter and its dressing will help maximize infusion system durability and minimize the risk of infection.

For patients with a similarly limited life expectancy who are ambulatory, an implanted reservoir system attached to an intraspinal catheter is an attractive option. There are subcutaneous reservoirs manufactured specifically for this application; they are rated to withstand hundreds of punctures, while other familiar reservoirs, such as the Ommaya reservoir, are rated only for several dozen punctures. These reservoir systems require daily percutaneous access and are associated with discomfort and increased risk of infection. They do, however, allow the patient unencumbered activity during the day and can be accessed for either bolus administration or for continuous infusion by attachment to an external pump.

Mechanical patient-controlled indwelling drug administration systems are a third option for intraspinal drug therapy. Unfortunately, these devices are not available in the United States.

Two major types of implanted drug pumps are currently marketed. One such device consists of a drug-filled bellows compressed by pressurized gas with its outflow regulated by a high resistance valve. The infused solution is then delivered at a fixed rate; dose changes are made by changing the solution concentration. Thus, there is some increased cost and patient discomfort when dose changes are indicated. Furthermore, changes in temperature and atmospheric pressure subject these devices to small variations in drug delivery rates. Similar pumps with some degree of programmability are currently pending FDA approval.

Somewhat more expensive is the programmable, peristaltic drug pump. This pump can be programmed transcutaneously and sophisticated drug dose regimens can be instituted. Dose changes can be made with noninvasive reprogramming. Because these pumps are battery operated, they require surgical replacement when the batteries expire; under average conditions, the current generation of pumps should last seven years. Both implanted pump types require at an interval dependent upon the size of the drug reservoir, the concentration of the drug to be infused and the rate of drug delivery. The maximum interval between refills of the pump is six months, as drug stability within the pump has been confirmed for up to six months (with rare exception).

Several studies have explored the costs of these drug administration systems over time. In general, it appears that for patients whose life expectancy and intraspinal drug use will exceed three months, it is cost effective to choose a fully implanted drug pump, whereas for patients with shorter life expectancy, a percutaneous catheter or implanted reservoir may be more reasonable.[10,12] Kumar and colleagues[13] recently published their work demonstrating the cost effectiveness of intrathecal drug therapy for the management of failed back syndrome. Of the 67 patients in this study, 23 underwent implantation of a programmable drug delivery pump whereas 44 patients continued with conventional pain therapy. During the five-year follow-up period, the actual cost of care related to failed back syndrome were tabulated. Although the intrathecal drug therapy group incurred a high initial cost because of equipment needs, at 28 months follow-up, the cumulative cost of conventional medical therapy exceeded intrathecal drug therapy. In light of current health care reform and the demands for greater cost containment in medicine, these issues should be considered in every patient who is deemed a candidate for intraspinal analgesic therapy.

INTRATHECAL AGENTS FOR PAIN PHARMACOTHERAPY

Opioids have been long considered the primary agents for intrathecal pharmacotherapy of pain. Their mechanism of action has been detailed above. The field of intrathecal pharmacotherapy for pain has moved generally away from monotherapy with opioids to the adjuvant use of opioids and nonopioid agents.

OPIOIDS

Morphine

Morphine is approved by the United States Food and Drug Administration for intrathecal therapy for chronic pain. Its usefulness lies in the ability to achieve excellent pain control over a long duration at a fraction of the dose required for systemic opioids while avoiding many of the commonly seen side effects of systemic administration. The relative equianalgesic potency between routes of administration has been estimated to be 300 for oral administration, 100 for IV administration to 1 for intrathecal (IT) administration. Doses at the initiation of therapy are almost always below one milligram per day.

Several publications on the efficacy of intraspinally administered morphine are reported; most are case reports and retrospective studies, with few prospective studies (Table 63-5).[14–18] Early data suggest an efficacy of roughly 80% in the setting of cancer pain. Smith and coworkers[18] published an important randomized controlled trial comparing IT opioids plus medical management versus maximal medical therapy alone in cancer related pain. The group receiving intrathecal drug therapy experienced statistically significantly better overall pain control and an improved side effect profile especially with respect to complaints of fatigue and sedation. There was also a trend toward improved survival time in the intrathecally treated group. At the present time, the data concerning intraspinal morphine for pain secondary to cancer appears to be compelling and consistent, with a success rate of approximately 80% to 90% in the first three months and 65% at one year. Success is seen not only with improved pain control, but also with better reported functional status and ability to interact meaningfully with family and friends.

Data concerning its use in the setting of nonmalignant pain is less clear. Deer and coworkers[15] showed that patients' self-perceived disability levels improved significantly 6 and 12 months after the initiation of IT opioid therapy for the treatment of low back pain. Auld and coworkers reported two studies of intraspinal narcotics for the treatment of non-malignant pain; in the first report, 21 of 32 patients demonstrated adequate relief,[19] whereas in the second study, 14 of 20 patients obtained satisfactory pain relief with intraspinal morphine.[20] Other small studies show similar findings. A prospective, randomized, double-blind study evaluated pain relief and opioid related side effects following intrathecal morphine administration in 144 opioid-naive patients versus 25 control patients with nonmalignant chronic back pain. All patients receiving intrathecal opioids reported pain relief compared to only 25% of the control group ($p<0.0005$). Although intraspinal morphine likely provides pain relief in carefully selected patients with intractable pain of nonmalignant origin, further work needs to be done before this should be considered standard therapy.

Hydromorphone

Hydromorphone is a potent opioid with increasing intraspinal "off label" use to treat cancer and nonmalignant pain. Unlike morphine, it is not FDA approved for this application, but hydromorphone has been elevated to a first line therapeutic status along with morphine by expert consensus panels.[21] Hydromorphone is approximately five times more potent, has fewer active metabolites and a smaller supraspinal distribution than morphine; this could account for reports of fewer side effects when compared to morphine.

The most common indication for using hydromorphone appears to be inadequate pain control or intolerable side effects with morphine. Currently, there are no prospective controlled trials evaluating the efficacy and toxicity of hydromorphone. Anecdotally, and also in several retrospective studies evaluating the efficacy of hydromorphone to treat nonmalignant pain ($n = 24$),[22] a high success rate was seen in those who were opioid naïve, as well as in those who had failed IT morphine.

Fentanyl and Sufentanil

Fentanyl and sufentanil are two potent opioids that diffuse rapidly across the blood-brain barrier because of their strong lipophilicity. Fentanyl produces a functionally equivalent effect on pain compared to morphine while binding to fewer, highly potent mu agonist, receptors. Sufentanil may be more useful for segmental rather than diffuse analgesia and may elicit less drug tolerance than morphine. There are prospective studies supporting the efficacy of IT fentanyl. One randomized trial ($n = 60$) showed improved pain control in patients undergoing posterior lumbar spine decompression.[23] Furthermore, both sufentanil and fentanyl have theoretically better side-effect profiles than morphine, including a decreased risk of formation of inflammatory granuloma.

Methadone and Meperidine

Methadone is a racemic mixture of D- and L-opioid isomers and meperidine is a synthetic opioid. Little clinical data regarding their intrathecal efficacy exists in the literature and their intrathecal use is exceedingly rare.

TABLE 63–5 A Comparison of Prospective Studies on Intraspinally Administered Morphine

Authors	Number of Patients	Route	Efficacy
Anderson et al., 1999	22	Intrathecal	11 patients with >25% reduction in nonmalignant pain after 24 months
Kumar et al., 2001	16	Intrathecal	57.5% reduction in pain, best results in deafferentation and mixed pain
Smith et al., 2002	143	Intrathecal	60 of 71 *84.5%) with cancer pain achieved clinical success ($p = 0.05$)
Rauck et al., 2003	119	Intrathecal	Overall success in 83%, 90%, 85%, and 91% at months 1, 2, 3, and 4 for cancer pain
Deer et al., 2004	136	Intrathecal	Oswestry Low Back Pain Disability Scale improved by 47% for patients with low back pain; >31% for patients with leg pain

OPIOID SIDE EFFECTS, WITHDRAWAL, AND TOLERANCE

The most widely recognized side effects of intraspinal narcotics include fatigue, somnolence, nausea, vomiting, urinary retention, pruritus, decreased sexual libido and decreased testosterone levels in men,[24] noncardiac pedal edema, and, rarely, delayed respiratory depression. Respiratory depression is most often seen in opioid-naive patients and results from supraspinal redistribution of the drug. This side effect is both dose dependent and naloxone reversible. A more recently recognized complication, catheter tip granulomas (more properly, catheter tip inflammatory masses), will be discussed in more detail below. These side effects appear to be more prevalent with intrathecal morphine use as compared to other opioids. Fentanyl and hydromorphone have apparently better side effect profiles.

The acute cessation of intrathecal opioid administration presents unique potential risk. Spinal morphine withdrawal syndrome results in hyperalgesia after cessation of morphine and is caused by the release of excitatory neurotransmitters and neuromodulators from primary afferents after long-term exposure to morphine, a type of "rebound" effect.

Clinical experience has demonstrated the development of increasing narcotic requirement to maintain a similar degree of pain control in a significant fraction of patients over time. While this may reflect the development of tolerance at the receptor level, it may also result from a change in the status of the patient's disease. For example, in the setting of pain secondary to a malignancy, tumor progression may involve new areas of pain, invade more pain sensitive structures, or change the nature of the pain from predominantly nociceptive to neuropathic. Furthermore, changes in the patient's psychosocial status may result in the decreased ability to cope, resulting in perceived increase in the degree of pain. Complaints of decreasing drug efficacy over time may also reflect malfunction of the pump and catheter system or the development of a catheter tip inflammatory mass.

Several strategies have been advanced to manage such apparent tolerance. First, one must carefully evaluate for the presence of pump system malfunction or the presence of a catheter tip inflammatory mass. If this is not the case, then simply increasing the drug dose may restore excellent pain control. When this fails, or when the drug dose is escalated to levels that are felt to be potentially problematic, some authors suggest temporarily using systemic analgesics while the pump is turned off for a period of several days to a few weeks, a so-called drug holiday. If the decreased efficacy of intraspinal narcotics is caused by receptor tolerance, this "drug holiday" often results in receptor down regulation and a return of efficacy when intraspinal opioids are reinstituted.

Another strategy involves the use of narcotics active at other opioid receptor subclasses. Like mu receptor agonists, delta receptor agonists appear to work through a G-protein system to hyperpolarize the neuronal membrane through an increase in potassium conductance and thus inhibit neuronal activity. Kappa receptor agonists appear to function differently than mu or delta receptor agonists. These agents appear to activate a different G-protein mechanism, which blocks calcium entry through a voltage-dependent calcium channel. Investigators have had some success with delta receptor agonists or those with mixed receptor subclass activity.

A final strategy is the concomitant administration of another intrathecal pharmacologic agent such as a local anesthetic. The combination of opioids and local anesthetics, alpha-adrenergic agents or ziconotide has been used successfully in patients failing intrathecal opioid monotherapy; algorithms for the use of these agents have been developed and recommended by expert panels (Figure 63-1).[21]

INTRATHECAL LOCAL ANESTHETICS

Bupivacaine is an amide class local anesthetic the role of which, in the intrathecal management of chronic pain, specifically neuropathic pain, has increased profoundly. Hassenbusch and coworkers[25] reported good results lasting over one year in four of seven patients with nonmalignant pain using epidural infusion of morphine sulfate combined with bupivacaine. Du Pen and colleagues[26] examined the efficacy of epidural morphine and bupivacaine in a series of 68 patients who obtained no relief from epidural opioids alone. Sixty-one patients (90%) were considered treatment successes with chronic morphine and bupivacaine infusion.

The data on the effectiveness of intrathecal bupivacaine is mixed. In a 2002 retrospective study of 109 patients, Deer and coworkers[15] showed that opioids plus bupivacaine resulted in significantly better pain control, less oral opioid use, fewer clinic visits, and better patient satisfaction than intrathecal opioids alone. In two prospective studies,[14,27] patients who failed intrathecal therapy with morphine or hydromorphone benefited from the addition of bupivacaine. In one randomized double-blind trial of 24 patients with chronic nonmalignant pain, the addition of bupivacaine to morphine or hydromorphone improved the patients' quality of life, but did not seem to have a significant effect on pain scores.[28] On the contrary, a multicenter, double-blind randomized controlled trial found that the addition of bupivacaine did not provide better pain relief than opioids alone. Bupivacaine was measured against another local anesthetic, ropivacaine, in a randomized controlled trial. An increase of 23% daily ropivacaine was required to produce equivalent pain control, and the cost of ropivacaine was three times higher.

At high doses of local anesthetics, particularly lidocaine, permanent injury can result because local anesthetics injure dorsal and ventral roots by increasing glutamate concentration in the cerebrospinal fluid and produce chromolytic deterioration of motor neurons in the lumbar spinal cord with resultant vacuolation of the dorsal funiculus. In clinically applicable intrathecal doses, however, such side effects are not seen with bupivacaine. Clinically apparent side effects of bupivacaine, seen rarely and at high doses, include transient paresthesias, motor blockade, and gait impairment.

Adrenergic Agonists

Alpha-adrenergic agonists are frequently used second line adjuvant agents in intraspinal pain pharmacotherapy. Alpha-adrenergic receptors exist in the substantia gelatinosa of the

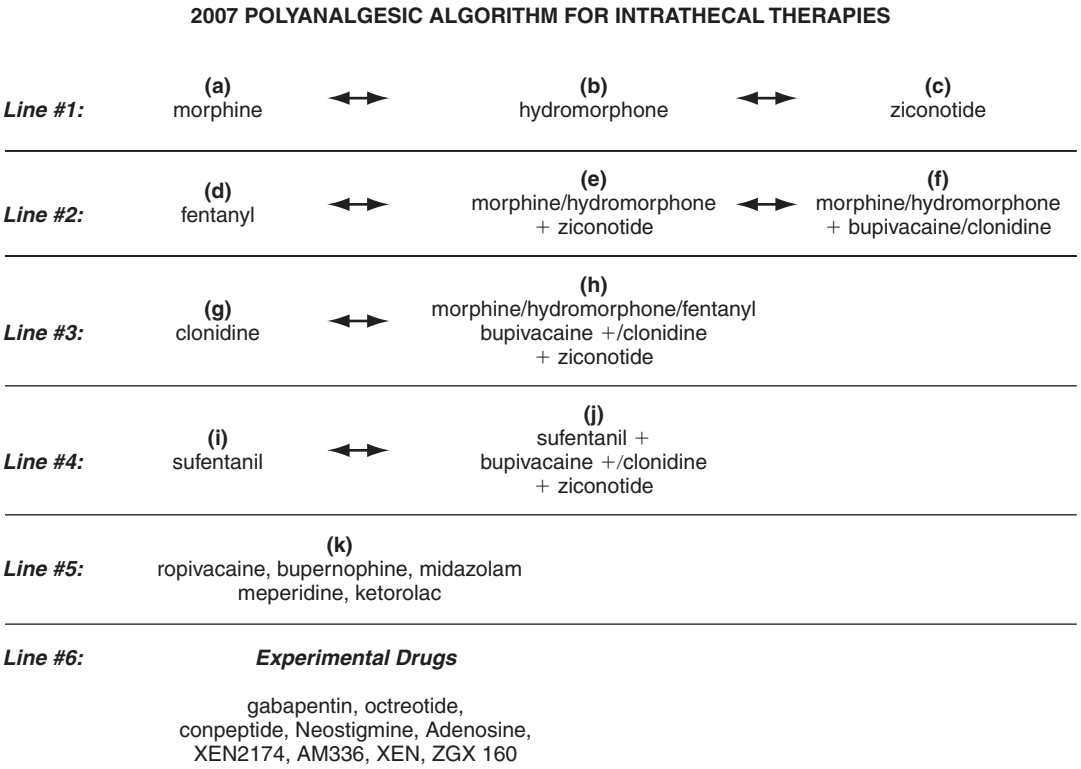

FIGURE 63-1 Recommended algorithm for intrathecal polyanalgesic therapies, 2007. Line 1: Morphine (a) and ziconotide (c) are approved by the Food and Drug Administration of the United States for intrathecal analgesic use and are recommended for first line therapy for nociceptive, mixed, and neuropathic pain. Hydromorphone (b) is recommended based on clinical widespread usage and apparent safety. Line 2: Because of its apparent granuloma sparing effect and because of its wide apparent use and identified safety, fentanyl (d) has been upgraded to a line 2 agent by the consensus conference when the use of the more hydrophilic agents of line 1 (a, b) result in intractable supraspinal side effects. Combinations of opioid plus ziconotide (e) or opioid plus bupivacaine or clonidine (f) are recommended for mixed and neuropathic pain and may be used interchangeably. When admixing opioids with ziconotide, attention must be made to the guidelines for admixing ziconotide with other agents. Line 3: Clonidine (g) alone or opioids such as morphine/hydromorphone/fentanyl with bupivacaine and/or clonidine mixed with ziconotide (h) may be used when agents in line 2 fail to provide analgesia or side effects occur when these agents are used. Line 4: Because of its proven safety in animals and humans and because of its apparent granuloma-sparing effects, Sufenta alone (i) or mixed with bupivacaine and/or clonidine plus ziconotide (j) is recommended in this line. The addition of clonidine, bupivacaine, and/or ziconotide is to be used in patients with mixed or neuropathic pain. *In patients with end of life, the panelists felt that midazolam and octreotide should be tried when all other agents in lines 1-4 have failed. Line 5: These agents (k), although not experimental, have little information available in the literature, and use is recommended with caution and obvious informed consent regarding the paucity of information regarding the safety and efficacy of their use. Line 6: Experimental agents (l) must only be used experimentally and with appropriate Independent Review Board approved protocols. *From: Deer T, Krames ES, Haasebusch SJ, et al: Polyanalgesic consensus conference 2007: Recommendations for the management of pain by intrathecal (intraspinal) drug delivery: Report of an interdisciplinary expert panel. Neuromodulation 10: 300–28, 2007.*

spinal cord, situated on both pre- and postsynaptic terminals of small primary afferents. They appear to mediate antinociception by indirectly decreasing the release of substance P. These agents have the particular advantage over opiates of little or no effect on respiratory centers, largely eliminating the possibility of respiratory depression. Another potential advantage of adrenergic agents is their specific efficacy in the management of neuropathic pain states as documented in both experimental[29] and clinical[20,30,31] settings. Within this category, clonidine is FDA approved for intraspinal use, and tizanidine has been tested in clinical trials.

Eisenach and coworkers[32] used epidural clonidine to treat nine patients with intractable cancer pain tolerant to intraspinal opioids. Patients received between 100 and 1000 micrograms per day; clonidine produced analgesia lasting more than 6 hours but also decreased blood pressure by more than 30%. Hypotension was treatable with intravenous ephedrine. Clonidine also decreased heart rate by 10% to 30% and produced transient sedation at higher doses. There were no opioid-like side effects of respiratory depression, pruritus, or nausea.

Several other studies have reported similar results. In a prospective, randomized trial of adding epidural clonidine to intrathecal morphine in 85 patients with cancer pain,[33] analgesia was achieved more commonly in the clonidine group (45% vs 21%), especially among patients with a component of neuropathic pain. A recent prospective cohort study[31] of ten patients with neuropathic pain treated with the combination of intrathecal morphine and clonidine resulted in a 70% to100% reduction in pain. Furthermore, four of eight patients with concomitant non-neuropathic pain also benefited from the addition of clonidine. In a phase I/II study,[30] 59% of the cohort were considered long-term successes with a mean follow up of 16.7 months.

In contrast to clonidine, the alpha-2-adrenergic agonist tizanidine does not appear to induce hypotension. This

agent has been demonstrated to be an effective analgesic agent when administered intrathecally in experimental[29] paradigms. Tizanidine appears to be particularly useful in the treatment of opioid insensitive neuropathic pain syndromes.

ZICONOTIDE

Ziconotide, originally known as SNX-111 and now marketed as Prialt, is a novel 25 amino acid peptide isolated from marine snail venom. It is a highly selective N-type voltage-sensitive calcium channel antagonist; these channels are found at the presynaptic nerve terminals in the spinal dorsal horn. The putative mechanism of ziconotide induced pain relief is the blockade of neurotransmitter release at the primary afferent nerve terminal.

The FDA and the European Union have approved the use of ziconotide as a nonopioid intrathecal analgesic option for patients with neuropathic pain refractory to conventional treatments. In fact, ziconotide has become the single most intensely studied agent for intrathecal pain therapy and has been recommended by an expert panel as a first line intrathecal agent for the treatment of refractory neuropathic pain. Common causes of neuropathic pain include complex regional pain syndrome (CRPS), HIV-associated neuropathy, postherpetic neuralgia, diabetic peripheral neuropathy, and central neuropathic pain syndromes related to multiple sclerosis, poststroke pain, and spinal cord injury.

Multiple animal studies have shown that ziconotide suppresses tactile and mechanical allodynia in a dose dependent manner. Its effect on hyperalgesia is less clear. More important, pivotal randomized, double-blind placebo controlled trials have been performed to establish the efficacy and safety of ziconotide in patients with chronic malignant, chronic nonmalignant, and severe neuropathic pain.

In one trial, 111 patients with refractory cancer-related pain underwent intrathecal infusion of ziconotide or placebo for five to six days.[34] In another trial,[35] 220 patients were tested using a lower dose and slower titration regimen than the previous studies; these changes were initiated because of the relatively high incidence of cognitive and behavioral side effects during the initial trials. Statistically significant improvement in pain relief was noted with ziconotide as compared to placebo in all trials (malignant pain: 53% ziconotide v. 18% placebo; nonmalignant pain: 31% ziconotide v. 6% placebo; slow titration study: 14.7% ziconotide v. 7.2% placebo). In these studies, the mean reduction in neuropathic pain was 15.7%, 31.6%, and 29.1%, respectively.

Multiple case reports, case series, and randomized controlled trials have demonstrated a relatively high risk of side effects with ziconotide use, which occur in 15% to 99% of ziconotide treated subjects. This is probably related to the fact that ziconotide has a relatively narrow therapeutic window, with a small difference between the dose required for analgesia and the dose required to produce side effects. Reported side effects include dizziness, confusion, gait ataxia, memory impairment, nystagmus, dysmetria, sedation, agitation, hallucinations, nausea, vomiting, urinary retention, somnolence, and coma. Elevated uric acid, lactate dehydrogenase, and creatine kinase levels have also been reported.

These side effects can cause serious psychiatric and neurologic impairment. They seem to occur most often when high doses are used at the initiation of therapy or when dose is increased quickly. On the other hand, ziconotide therapy can be abruptly terminated without withdrawal effects. Despite the severity of the side-effect profile, it has been demonstrated that adverse effects need to resolve fully after the cessation of drug infusion.

To prevent the occurrence of these side effects, it is recommended that infusion start with the lowest possible dose and then is titrated slowly to effect. Ziconotide should not be offered to patients with complicated psychiatric profiles or a history of psychotic episodes. Clinicians should be vigilant for complications of ziconotide in their patients from the time of treatment onset.

As this time, there are no data on the long-term use of ziconotide;[36] nonetheless, it is the most studied intrathecal agent for the management of refractory chronic pain of both malignant and nonmalignant origin. While clinicians must be aware of the limitations of ziconotide (its narrow therapeutic window and high rate of adverse effects), with careful use it has significant efficacy and has been designated a first line intrathecal agent for neuropathic pain.[21]

NEWER DRUGS

Although only morphine, baclofen, clonidine, and ziconotide have been approved by the FDA for chronic intraspinal use, the clinical practice of pain management involves in a majority of cases the "off label" use of agents alone and in combination. Currently, opioids, nonmorphine opioids, nonopioids, and combinations of these drugs are routinely being delivered intraspinally.

Adenosine, baclofen, gabapentin, nonsteroidal anti-inflammatory agents, midazolam, neostigmine, somatostatin[37] and its analogue, octreotide, cholera toxin, botulinum, and a host of conopeptides inspired by the success with ziconotide have all been studied at some level for the intrathecal pharmacotherapy of intractable pain. Many are in the early development phase. Others have shown promise in human subjects. Clearly, our ability to provide relief for patients in pain will be enhanced with the wider availability of multiple intrathecal analgesic agents; however, more careful, controlled trials are needed to establish efficacy, long-term toxicity, and compatibility of these agents before they are introduced to our clinical armamentarium.

COMPLICATIONS

Although implanted drug delivery systems offer a unique method of pain control in selected patients, they are not without significant complications. The risk of infection is common to all implanted drug delivery devices. Percutaneous catheters and implanted reservoirs appear particularly susceptible to infection because of their communication with the skin or frequent access through the skin. Infection may involve the surgical wound or the subcutaneous region surrounding the hardware. This is effectively treated by removal of all implanted hardware and the administration of appropriate intravenous antibiotics;

cure is seldom accomplished without hardware externalization. Re-implantation of the drug delivery system is usually delayed for at least three months after completion of antibiotic therapy.

Infusion of contaminated drug solution is of great concern as this may lead to potentially life-threatening meningitis. The risk of this complication can be limited by the use of an in-line bacteriostatic filter; unfortunately, not all systems allow for or provide such filters. Early recognition and treatment of meningitis is critical.

Erosion of the hardware through the skin is a less common complication, and may occur especially in cachectic, poorly nourished patients. This risk can be limited by placing the implant in a deep pocket, by ensuring the hardware does not lie directly under the incision, and by performing a meticulous multilayer closure.

The most frequently observed complication involves failure of the system itself. Failure of the pump itself is uniquely uncommon but may occur, particularly with the complex electronics of programmable pumps. Catheter problems, however, are most common, reported in 25% of patients; the range of catheter problems is great and some centers have reported catheter complications in 50% or more of patients. These complications include kinking, obstruction, disconnection, or shearing of the catheter. There are several techniques to limit the risk of catheter failure and include the use of fluoroscopy during catheter placement to confirm the absence of loops, partial kinks, or malposition in a dural nerve root sheath. Observation of cerebrospinal fluid flow during each stage of implantation helps detect catheter obstruction during surgery. The paraspinous approach limits the sharp angle of the catheter as it enters and exits the interspinous ligament and guards against shearing at these sites. Securing the catheter with a purse string suture as it exits the interspinous ligament and again with a silastic fixation device also helps prevent cerebrospinal fluid leak and migration of the catheter out of the subarachnoid space. A loop of catheter distal to this point relieves strain on the catheter and prevents catheter migration or dislocation. Finally, dissection of a small space above the fascia in which the catheter comfortably rests will help prevent kinking when the wound is closed.

Despite great care during catheter implantation, these problems may still occur. Patients with drug delivery system failure usually present with increased pain or with subcutaneous fluid accumulation. Initial evaluation includes the comparison of the expected and true residual volume in the pump reservoir; a significant disparity warrants further investigation. Plain radiologic evaluation of the entire system may reveal catheter disconnection and may also demonstrate kinking or migration of the catheter from the subarachnoid space. Occasionally, the instillation and attempted intrathecal delivery of iodinated contrast material via the pump may be helpful in differentiating between catheter or pump failure. Quantitative nuclear medicine studies may also be helpful; the pump can be filled with dilute solutions of radioactive material and the delivery of these materials can be followed over time. Even these diagnostic tests may be equivocal, requiring surgical exploration and revision of the pump or catheter or both. With such a rigorous approach, virtually all such mechanical problems can be corrected and pain relief restored.

Another problem common to all implanted drug delivery systems is the potential for overdose. With an externalized system, this may result from improper setting of the external drug pump or improper dilution of the infusate by the pharmacy. Great care must be used to ensure appropriate drug concentration and delivery. Far more insidious can be the incorrect reprogramming of indwelling drug pumps or injection of the refill volume into the subcutaneous space, as these errors are potentially subtle and not immediately recognized. Such drug overdoses resulting from refill errors, programming errors, or incorrect infusate concentrations have occurred with devastating results.

A further risk is created by the presence, in some pumps, of a side port intended for bolus drug injection or for testing catheter patency. There are two reported deaths resulting from accidental access of this side port rather than the refill port, resulting in the entire refill volume of the drug infusing into the CSF. Modifications have been made to prevent access to the bolus port by needles intended for pump refilling; nonetheless, great care must be exercised to avoid this potentially life-threatening complication.

INTRATHECAL GRANULOMAS (CATHETER TIP INFLAMMATORY MASS)

The development of inflammatory masses (so-called catheter tip granulomas) at the terminal end of the intrathecal catheter within the subarachnoid space has become an increasingly well recognized complication of intrathecal drug infusion systems. While the first reported case was almost 20 years ago, the exact incidence and prevalence of catheter granulomas in patients receiving intrathecal pharmacotherapy is unknown. While initially thought to be an extremely rare event, most recent data suggests that it may occur in as many as one in twenty patients treated with intrathecal opioids. If the intrathecal granuloma becomes sufficiently large, spinal cord and nerve root compression may occur and result in new or worsening neuropathic pain, weakness, numbness, loss of bowel and bladder function, and even paralysis.

It has been postulated that catheter tip granulomas represent indolent, local infections. However, they tend to occur only at catheter tips where drug is infused, rather than along any other part of the catheter length were microorganisms could theoretically be stationed. Furthermore, catheter tips and granulomas have been sent for pathologic and microbiologic studies and only three granulomas have been reported to harbor microorganisms in their center, despite many more being sterile compositions of chronic, inflammatory cells. In two of these three cases contaminants were suspected. Additionally, polymorphonuclear leukocytes (PMNs) are rarely seen in such granulomas.

Some conjecture that granulomas are hypersensitivity reactions to the silicone in catheters. Others suggest granulomas may form in predisposed individuals with prior anatomic damage to neural tissues, previous or simultaneous exposure to other intraspinal devices such as spinal cord stimulators, or as direct result of the surgery necessary for catheter implantation. At this time, however,

the most plausible explanation is that they are local, chronic inflammatory reactions related to dural based mast cell degranulation in response to the very drug infused. They occur where drug is most concentrated at its exit from the catheter lumen before it can disperse throughout the CSF.

Despite the mechanism, there is strong evidence that the regional cerebrospinal fluid flow dynamics play a primary role in granuloma formation. Granuloma formation seems to occur more often in the longest and narrowest portion of the spinal canal, the thoracic spinal cistern. This region has the most stagnant CSF flow during the cardiac cycle and it tends to be the target for the catheter tip in most current pump placement operations. What results is the infusion of drug into the intrathecal space where the highest relative concentration is possible: a tight space with poor flow. If granuloma formation is directly related to drug flow, then the thoracic cord is an ideal candidate.

The risk of catheter-associated granuloma formation is highest with opioids, with the exception of fentanyl. Interestingly, unlike other tested opioids, fentanyl does not cause dural mast cell degranulation. There seems to be a direct relationship between both the concentration of opioid in the infused solution and the rate at which it is infused with the likelihood that a granuloma will form. Interestingly, granulomas have often been seem to form in patients who have poor pain control and require higher daily doses of intrathecal opioids. It was long thought that granuloma formation with intrathecal baclofen was not possible. However, at least two recent case reports demonstrate the contrary. Nevertheless, the paucity of such data does support that baclofen associated granulomas are rare.

Granulomas are more common in patients with nonmalignant pain as opposed to those being treated for cancer pain. They are more often seen in younger patients as well. It could be deduced that because these groups have longer life expectancies, they are exposed to greater concentrations of opioids and subsequently are more likely to develop granulomas. This adds support for the dose-dependent relationship of intrathecal drugs and granuloma formation mentioned earlier.

If granulomas are discovered before they are symptomatic, discontinuation of drug infusion is often all that is necessary. Stabilization and even regression of granulomas has been shown after drug infusion ceases. Another suggested strategy is the infusion of hypertonic saline after discontinuing opioid infusion, and good results are available in the literature. The problem with these management strategies is that they result in the return of pain in nearly all patients. Another option is to replace morphine infusion with another opioid such as hydromorphone. This was reported in one case, and the patient's granuloma remained stable without regression over time. It must be kept in mind, however, that all opioids have the potential for granuloma formation.

Possibly the most common strategy for the treatment of asymptomatic catheter tip granulomas is the withdrawal of the catheter one to two spinal levels. The granuloma frequently resolves and allows for continued analgesic infusion, although at a lesser dose and rate or with another agent less likely to produce catheter tip granulomas.

When catheter tip granulomas enlarge to the size where frank spinal cord compression occurs and when patients have become symptomatic, surgical decompression and resection is often required. The results of surgical therapy, in patients who have already developed a neurologic deficit, are not perfect. While nearly one third of reported patients make a complete recovery and another one third remain ambulatory, one third of patients remain paralyzed or nonambulatory.

The requirement for increasing opioid doses should raise suspicion for the formation of catheter tip granulomas. The appearance of new or altered pain sensations in a dermatomal distribution near the known location of the catheter tip, or new radicular pain or numbness is also suspect. In addition to following a patient's pain, experts recommend close neurological follow up of all patients treated with intrathecal drug administration. Motor examination should be a routine part of every clinic visit. As catheter tip granulomas develop slowly, attention to subtle changes in physical examination may be an indication for MRI imaging or CT myelography. It has also been suggested that routine MRI imaging be instituted in all patients undergoing intrathecal morphine therapy or at least in patients at high risk, including those using high doses or high concentration of intrathecal opioids.

Now that granulomas are well established complications of intrathecal drug infusion and that these complications can be extremely devastating, clinicians should have a low threshold for their development, should take all measures to diagnose them promptly and should use appropriate means to treat them once diagnosis is confirmed.

MORTALITY WITH INTRATHECAL OPIOIDS FOR NONCANCER PAIN

New disturbing data has very recently been published that has demonstrated that both the initial implantation and the routine maintenance of intrathecal drug delivery systems for the treatment of chronic nonmalignant pain carry an increased risk of patient mortality. In February 2006, experts noticed a cluster of three deaths, all seemingly opioid related, that occurred within one day of opioid pump implantation for noncancer pain. Initial review of these pump manufacturers records and those of insurance providers, the Social Security Death Master File, and the Centers for Medicare and Medicaid Services databases identified nine total deaths within three days of pump implantation or pump revision in the four-month period surrounding these three "sentinel cases." The cause of death in all causes was likely the respiratory depressant effect of opioids on the central nervous system.

A more comprehensive age and gender-adjusted comparison of mortality at three days, thirty days, and one year for patients with implantation drug delivery systems was carried out using spinal cord stimulator implantation as a control, as both surgical implantation procedures are similar. For completeness, in-hospital mortality rates after lumbosacral spine surgery in Medicare beneficiaries and after discectomy in a nationwide community hospital sample were also included for comparison.

Mortality within three days after intrathecal opioid system implantation was 0.88 per 1000[38]. This figure is

higher than in-hospital mortality following discectomy operations (0.59 per 1000), but lower than more complex lumbar spine surgery (5.2 per 1000). It is also eight times higher than the reported 0.11 per 1000 deaths seen within three days of spinal cord stimulator implantation. The mortality rates one month and one year after pump implantation remained higher (0.39% at 1 month, and 3.89% at one year) albeit by lower proportions, when compared to spinal cord stimulation implantation.[38]

It can be said with confidence that early death within 24 hours after pump implantation or refill is likely related to opioid overdose and fatal respiratory depression. The cause for late death (thirty days and one year) was more difficult to discern. In many cases, no details or data exist to provide any information about circumstances surrounding the deaths.

The authors suggest that device malfunction can be considered unlikely as a direct cause of death, because safe-guard mechanisms related to device programming may actually decrease drug administration if a pump malfunctions in situ.[38] Logically, however, device malfunction may have resulted in increased oral opioid intake and indirectly caused unintentional overdose because of poor pain control. Of note, they mention that over 90% of delivery devices were not investigated after patients' deaths. They also reject the notion that patients who receive opioid pump systems are sicker, on the whole, than patients who undergo stimulator system placement or lumbosacral surgery and tried to control for this variable. Drug pumps require frequent maintenance, refills, dose changes, and more revision operations compared to stimulator systems. This introduces many potential variables that could result in increased mortality.

In light of this new recognition that pump implantation carries with it a higher risk of death, it must be stressed that every clinician be vigilant in every step of the process after pump initiation or replacement. The lowest possible dose and drug concentration should be used to initiate therapy. The clinician should be an expert in the technological capabilities and limitations of the device they choose, and they should feel comfortable in all steps of device refilling and programming.

FUTURE DIRECTIONS

While tremendous progress has been made in the use of intraspinal analgesics for the treatment of intractable pain, there are several areas that need to be addressed before the technique is more widely accepted and can be of broader clinical use. First, although its efficacy in the treatment of pain secondary to malignancy appears clear, the efficacy of intraspinal drug administration for pain of nonmalignant origin remains to be fully elucidated. Properly controlled, large-scale trials are lacking; until such evidence is available, use in this setting should not be considered routine therapy.

Second, patient selection criteria need to be better defined and validated. In particular, the psychosocial evaluation and specific pain states responsive to this intervention need better characterization. In light of the cost and invasiveness of this approach, we must pay great attention to refining our patient selection criteria to ensure the best chance of obtaining pain relief.

Finally, and perhaps most significantly, further development in analgesic pharmacology needs to be applied to intraspinal drug therapy. Although there are currently dozens of available analgesic agents for oral or parenteral use capitalizing on the complex neurochemistry of pain transmission and modulation pathways, few are validated and FDA approved for intraspinal use. With the development of newer and more specific agents, and with the utilization of agents active at a number of receptor systems involved in pain perception, intraspinal drug administration may help limit the suffering of many more people with otherwise intractable pain.

KEY POINTS

- Intraspinal therapy restricts drug effects to regions associated with the source of the nociceptive input.
- Morphine and hydromorphone are well suited for intrathecal use in view of their hydrophilicity and slow absorption from the cerebrospinal fluid. Morphine, hydromorphone, and ziconotide are the first-line agents in intrathecal drug therapy. The inclusion of ziconotide as a first line drug is secondary to the randomized, double-blind placebo-controlled studies showing its efficacy in cancer-related pain and inadequately managed noncancer pain.
- Bupivacaine is the most commonly used intrathecal local anesthetic. Its addition to intrathecal opioids generally results in better pain control, less opioid use, and improved quality of life.
- Intrathecal granulomas are more common in patients with noncancer pain and younger patients, i.e., patients with longer life expectancies.
- The mortality from intrathecal opioids is higher than in patients who have discectomy or complex spine surgery and in patients who have spinal cord stimulators. The exact causes of the patients' deaths remain to be determined.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 64

Discography

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Discography has been called a "test in search of an indication," and a "solution in need of a problem." Originally employed as a diagnostic tool for herniated discs in the era prior to the advent of advanced imaging, its use in this capacity has been almost completely supplanted by safer, cheaper, and more sensitive modalities such as magnetic resonance imaging (MRI). Yet, discography has continued to persevere, evolving from a defunct imaging tool to the only ostensible means to correlate imaging with symptoms. As a diagnostic and prognostic tool, disc stimulation remains one of the most controversial interventional pain procedures.

SPINAL PAIN OVERVIEW

Pain originating from the spine commonly manifests as pain in the low back and neck, and less frequently as pain in the mid-back. Although many components of the spine are capable of generating pain, its exact source is often elusive. Several factors make the identification of spinal pain generators challenging. First, back pain can originate not only from various spinal column components, but can also be referred from structures adjacent to the spine such as abdominal or pelvic viscera, sacroiliac joints, and so on. Second, pain can be difficult to localize due to multisegmental, predominantly autonomic spinal innervation, with resultant convergence in the spinal cord. The diagnosis of spinal pain is further complicated by the concurrent presence and overlapping clinical features of various spinal disorders, especially degenerative conditions. The lack of diagnostic tests that can reliably identify a spinal pain generator further adds to these challenges. Currently available tests, often based on high-resolution imaging, frequently show abnormal findings in asymptomatic individuals.[1] Due to the frequent spontaneous resolution of symptoms, the high incidence of benign abnormal findings, and the rarity of serious spinal disorders, indiscriminate diagnostic testing of spinal pain patients can lead to inappropriate diagnosis and poor treatment results.

MECHANISMS OF DISCOGENIC PAIN

Although the role played by a herniated nucleus pulposus in causing spinal pain is well-known, the concept of pain originating from the disc itself is less understood. The term *internal disc disruption* (IDD) has been used since the early 1970s to describe a disc that is considered the main source of patient's pain but appears functionally intact on spinal imaging.[2] However, degenerative disc changes seen on spinal imaging are nearly ubiquitous, especially with advanced age.[1] These myriad changes are collectively referred to as degenerated disc disease (DDD) and may represent normal age-related phenomena. Isolated degenerative disc pathology, where one or two discs show profound degeneration in the presence of other relatively normal appearing discs, is less common, and more frequently encountered in younger individuals. Whether IDD and DDD are distinct pathologic entities or represent pathologic progression of the same disease entity is unknown. The term *discogenic pain* (DP) describes a clinical state in which the disc is considered a main source of a patient's spinal pain. For the present discussion, this term appears most appropriate, as it emphasizes the disc as the primary source of a patient's pain irrespective of its pathology (Figure 64-1).

A basic understanding of normal disc physiology is imperative in order to understand the mechanisms responsible for DP. A normal disc is grossly compartmentalized into nucleus pulposus (NP) and annulus fibrosus (AF). Interspersed in an abundant intercellular matrix in the two disc compartments are sparsely present cells. The cells populating the NP are chondrocyte-like, while those comprising the AF are fibrocyte-like.[3] The intercellular matrix in the NP is a "jelly-like" substance containing high concentrations of water and proteoglycans, while the matrix in the AF consists predominantly of Type I and II collagen fibers. These fibers are arranged as 10 to 20 interlacing, concentric lamellae that are firmly attached to the adjacent vertebral bodies.[3] The compressive forces applied to the disc are borne directly by the NP, and are distributed as a tensile force to the annular collagen. The incompressibility exhibited by a normal NP is due to its high water content, which in turn is maintained by the hydrostatic pressure generated by proteoglycans. The normal NP proteoglycan content is a function of the delicate balance between anabolic and catabolic enzymatic activities.

The vascularity of a normal intervertebral disc is limited to the outer third of the AF. In addition, the disc is separated from the vascular vertebral body by avascular cartilaginous end plates.[3] Consequently, the metabolic needs of the NP and inner AF are met almost entirely by diffusion from the capillary plexuses in the adjacent vertebral bodies and outer AF. This process is facilitated by circadian changes in intradiscal pressure; lower nighttime pressure facilitates the flow of fluids into the disc, while higher daytime pressure forces the fluids out of the disc. The end products of the NP cellular metabolic activities are also removed by the diffusion. However, the disc lacks scavenger cells, so that degradative products tend to accumulate over time, which can interfere with normal homeostatic functions.[4]

The innervation of the normal disc is predominantly limited to the outer third of the AF. Disc innervation is mostly in the form of mechanoreceptors, which originate from plexuses along the anterior and posterior longitudinal ligaments. The posterior plexus receives its input from the sinuvertebral nerve and gray rami communicans, while the anterior plexus receives contributions mainly from gray rami communicans. These rich autonomic

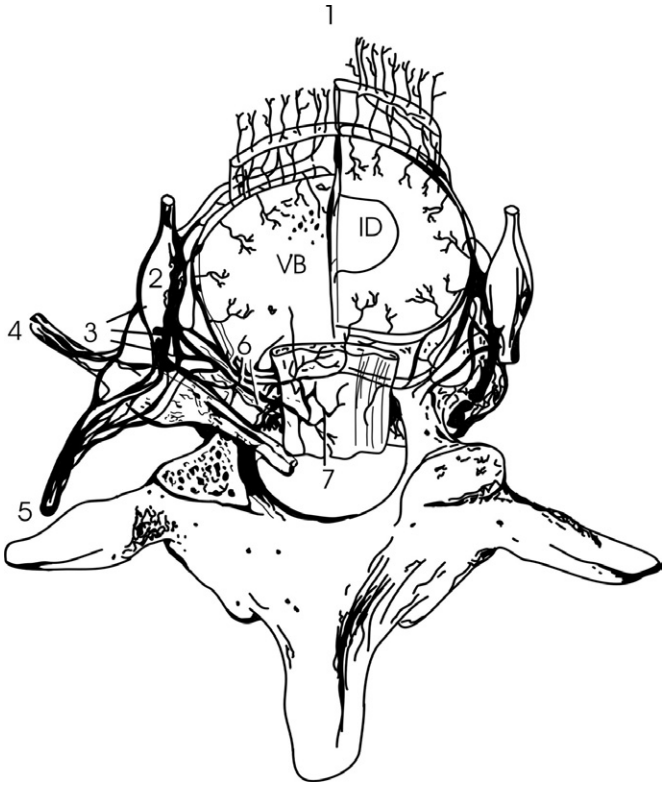

FIGURE 64-1 Schematic drawing of the nerve plexi surrounding the vertebral body (VB) and intervertebral disc (ID). 1 and 7 represent the anterior and posterior plexuses, respectively. The deep, extensive penetration of the nerves indicates degeneration has occurred. 2, sympathetic trunk; 3, rami communicantes; 4, ventral ramus of the spinal nerve; 5, dorsal ramus; 6, sinuvertebral nerves. (Drawing courtesy of Specialist Jennifer Sempsroft, U.S. Army.)

connections may contribute to the vague, poorly localized pain characteristic of IDD.

DDD has been associated with both genetic and acquired factors such as vascular disease, smoking, lifestyle, and obesity.[5–7] It is most likely the result of a decline in the number and function of viable disc cells, enhanced matrix metalloproteinase (MMP) activity, and increased activity of discal cytokines and other proinflammatory mediators.[7,8] These metabolic derangements can result in a reduction of nuclear proteoglycans and loss of discal water content. The diminished NP hydrostatic pressure leads to increased NP compressibility, which exposes the AF to direct compressive forces. In addition to mechanical stress, the AF also undergoes degenerative changes similar to the NP. These combined insults result in the loss of annular collagen, mechanical failure, and the development of annular fissures that spread outward towards the periphery.

Annular fissures are a hallmark of discogenic pain. These tears are zones of highly vascularized and richly innervated granulation tissue. The two types of nerve fibers found in these granulation zones are vasoregulatory nerves that accompany neovascularization, and free nerve endings high in substance P concentration.[9] In addition, annular tears are abundant in mononuclear cell infiltrates, which release nerve growth factors that contribute to nerve in-growth and accelerated degeneration. Disrupted discs also contain high concentrations of pro-inflammatory mediators, which serve to sensitize nerve endings and maintain a state of hyperalgesia. This state has been linked to the painful response associated with minimal pressure elevation, a term denoted as "chemically sensitized."[10] Due to limited repair capacity, a painful disrupted disc may remain a longstanding source of disability.

In the long-term, changes in the disc morphology may alter spinal mechanics, increase stress on adjacent spinal structures, and lead to sclerosis and auto-fusion.[11] This may lead to further disc and vertebral end plate degeneration, sacroiliac and facet joint pathology, and spinal stenosis.

PREVALENCE

Epidemiologic studies evaluating the incidence of spinal pain vary greatly, as the conditions producing back and neck pain are often poorly defined. This is especially true for DP. The lifetime prevalence rate for low back pain (LBP) varies between 50% and 80%,[12] whereas a recent task force on neck pain estimated the 12-month prevalence to range between 30% and 50%.[13] Epidemiologic studies for discogenic pain are uncommon. In an oft-cited study by Schwarzer et al.[14] conducted in 92 patients with chronic, nonradicular LBP and no previous surgery, the authors reported a 39% prevalence of IDD using exact pain reproduction, abnormal computed tomography (CT)–discography imaging, and a negative adjacent control disc as the criteria. In a large-scale study performed in 127 patients with axial LBP who failed facet interventions, Cohen et al.[15] reported a prevalence rate of 65%. In a smaller prospective study conducted in 29 patients with chronic LBP devoid of neurologic symptoms, Collins et al.[16] reported exact reproduction to occur in 13 discs in 12 patients, for a prevalence rate of 41%. Finally, in a large, multicenter epidemiologic study performed in 2374 patients with chronic LBP seen by surgeons at seven medical centers, nonherniated degenerated disc(s) was the final diagnosis in 6.1% of patients.[17]

Studies conducted in the cervical spine tend to yield higher positive rates. In a prospective observational study evaluating 173 cervical discograms, Grubb and Kelly[18] reported at least one positive level in 86% of patients. In a smaller (n = 31) retrospective study by Connor and Darden,[19] the authors found that 84% experienced provocative concordant symptomatology and were considered positive. Neither of these studies required a control disc.

THE CONTROVERSY SURROUNDING DISCOGRAPHY

RATIONALE

The rationale for discography is based on three factors—the high prevalence of spine pain, the high prevalence rate of abnormal MRI findings at asymptomatic levels, and the low success rate for surgical interventions for degenerative spondylosis. The lifetime prevalence of serious LBP episodes ranges from 50% to 80%,[12] while for neck pain, the annual prevalence rates range from 16% to has high as 50%.[13] Confounding matters is that MRI studies conducted in asymptomatic volunteers have consistently demonstrated that a majority of people have abnormalities in the lumbar,

thoracic, and cervical spine regions, with the proportion increasing with age.[1,20,21]

Having an inexpensive, safe, and reliably effective bridge to natural recovery is therefore paramount, yet none exists. Based on systematic reviews, it is clear that surgery performed for axial spine pain is associated with a high failure and significant complication rate, and that most patients will recover without procedural interventions.[12,22] The high prevalence rates for spine pain and coincidental imaging abnormalities, coupled with the absence of any reliable interventional treatment for IDD, augur in favor of an accurate means to correlate symptoms with imaging results.

FALSE-POSITIVE AND FALSE-NEGATIVE RESULTS

Perhaps the main criticism surrounding discography is the high rate of false-positive (FP) results. The first study to quantitatively question the validity of discography was performed by Holt[23] over 40 years ago, who reported an FP rate of 37% in 30 asymptomatic prisoners. Over 20 years later, Walsh et al.[24] performed CT-discography in 10 asymptomatic male volunteers and 7 "control" patients with chronic LBP. In the asymptomatic subjects, CT-discograms were interpreted as abnormal in 17% of the 35 discs injected and half of the 10 subjects. However, none of these patients experienced concordant pain associated with pain-related behavior during the injections.

The bulk of the work on FP discography was done by Carragee and colleagues[25] over a 2-year period. In the first study, eight patients with no history of low back problems who had undergone recent iliac crest bone grafting for reasons unrelated to lumbar spine or hip pathology were studied with provocative discography of their three most caudal discs. Four of the eight study subjects experienced severe LBP similar to the postoperative pain at their bone graft site during injection of at least one disc, with all symptomatic discs having an abnormal morphologic appearance.

In the second study, the authors performed lumbar discography on 10 patients with persistent neck and upper extremity pain after previous cervical spine surgery, 6 patients with somatization disorder, and 10 "control" patients devoid of pain symptoms after successful cervical spine surgery.[26] In the somatization group, 83% of the 6 subjects experienced at least one positive discogram versus 40% of subjects in the chronic cervical pain group and 10% of the control patients. None of the 31 radiographically normal discs provoked significant pain during injection.

In the last study, three-level lumbar provocative discography was performed in 47 individuals who had undergone a single-level disc decompression for sciatica.[27] The study group was comprised of 20 subjects with no recurrent symptoms, while 27 patients with persistent back and/or leg symptoms formed the "control" group. In the asymptomatic participants, positive injections occurred in 40% of the previously operated discs. In the patients with failed back surgery syndrome, concordant pain provocation occurred in 15 of the 27 operative discs (56%). Positive injections were more common in those with concomitant psychopathology, and those with litigation and worker's compensation claims.

The Carragee studies have been criticized on several fronts. The first criticism levied is that one of the hallmarks of modern provocative discography is that the evoked pain must be concordant or similar to a patient's baseline back pain, which is not possible in asymptomatic subjects. Another flaw is that pressure readings were not a determining factor in the designation of a positive disc.

In an attempt to control for some of these factors, Derby et al.[28] performed 43 discograms in 13 volunteers with either no history or infrequent episodes of LBP. In the subjects with occasional back pain, 35% of injected discs were painful, versus 52% in volunteers without LBP. Most discs required high pressures before pain was provoked. No relationship was noted between painful disc injections and radiologic or discographic abnormalities. Controlling for the intensity of response and the pressures at which pain was elicited, the authors concluded the incidence of FP discograms to be less than 10%.

Wolfer et al.[29] performed a systematic review reanalyzing data from five previous studies based on guidelines from the International Association for the Study of Pain (IASP) and the International Spinal Intervention Society (ISIS) for a positive lumbar discogram. Combining all data, the authors found an overall FP rate of 9.3% per patient and 6.0% per disc. In patients without back pain or confounding factors, the FP rates dropped to 3.0% per patient and 2.1% per disc. Chronic pain patients were found to have FP rates per patient and disc of 5.6% and 3.9%, respectively. The highest FP rates per patient and disc were for postdiscectomy patients (15% and 9.1%, respectively) and those with somatization disorder (50% and 22.2%, respectively).

Fewer studies have examined the incidence of FP discograms in the cervical and thoracic regions. In a study by Schellhas et al.,[30] none of 40 cervical discograms done in 10 asymptomatic volunteers elicited reported pain or facial expressions indicative of pain. In a later study done in the thoracic region, the same group of investigators reached slightly different conclusions.[31] Three of 40 discs injected in 10 asymptomatic volunteers provoked intense (>7/10) pain, with two positive responses occurring in one subject.

The issue of "false-negative" discograms has received far less attention, but can lead to inaccurate diagnoses, unnecessary interventions, and withholding beneficial treatment(s) from otherwise good candidates. There are several reasons for this phenomenon, including failure to detect an inadequate rise in intradiscal pressure because of the lack of pressure monitoring, injecting too slow, excessive sedation, overzealous use of local anesthetic, and extensive contrast extravasation in severely degenerated discs. The failure to elicit pain in a degenerated, ostensibly painful disc may be more likely to occur in elderly patients.[32] In a review by Cohen et al.,[33] the authors estimated that between 15% and 25% of degenerated discs fail to elicit concordant pain provocation during stimulation. The proportion of these occurrences that represent false-negative responses versus the accurate reflection of a non–pain generator is a question that remains to be answered.

TABLE 64–1 Clinical Studies Evaluating False-Positive Discography

Study, Year	Region	Subjects	Criteria	Results
Holt, 1964[35]	Cervical	50 male volunteer inmates, 148 discs	Pain provocation + contrast extravasation	All injections provoked severe pain. Contrast extravasation noted in all pts, 93% of discs.
Massie and Stevens, 1967[36]	Lumbar	52 male subjects, 156 discs	NR	FP rate not reported, but stated "injection only occasionally produced symptoms."
Holt, 1968[23]	Lumbar	30 male volunteer inmates, 70 discs (20 failed injections)	Pain provocation	60% FP rate per subject, 37% per disc.
Walsh, 1990[24]	Lumbar	10 male volunteers, 30 discs	3/5 pain provocation + 2/5 pain-related behaviors	0% FP rate per subject and disc.
Schellhas, 1996[30]	Cervical	10 volunteers, 40 discs	7/10 pain provocation + facial expressions	0% FP rate per subject and disc.
Wood, 1999[31]	Thoracic	10 volunteers, 40 discs	7/10 pain provocation + facial expressions	20% FP rate per subject, 7.5% per disc.
Carragee, 1999[25]	Lumbar	8 males who had undergone recent iliac crest bone grafting for problems unrelated to low back pain, 24 discs	3/5 "concordant" pain provocation, + 2/5 pain-related behaviors	50% FP rate per subject, 38% per disc.
Carragee, 2000[26]	Lumbar	6 subjects with somatization disorder, 10 with failed neck surgery, and 10 control pts with no pain after successful cervical spine surgery; 78 discs	3/5 "concordant" pain provocation + 2/5 pain-related behaviors	FP rate per subject: 83% for somatization, 40% for failed neck surgery, and 10% for "control" group. FP rate per disc: 33% for somatization, 23% for failed neck surgery, and 3% for control group.
Carragee, 2000[27]	Lumbar	47 subjects who underwent a single-level discectomy; 20 subjects were "symptom-free" while 27 pts continued to have back and/or leg pain; 138 discs	3/5 pain provocation + 2/5 pain-related behaviors	FP rate per subject: 40% for asymptomatic subjects and 56% for pts with failed back surgery. FP rate per disc: 15% in asymptomatic group.
Derby, 2005[28]	Lumbar	13 volunteers, 43 discs	Criteria not noted; used 0–10 pain rating and 0–4 pain behavior scales along with manometry	Using 6/10 as criteria for a (+) disc, 0% FP rate. Using 4/10 pain at <50 psi, FP rate 23% per subject and 9% per disc.

FP, false-positive; pts, patients.

In summary, FP discograms can occur in all regions of the spine, but are relatively infrequent in unoperated individuals with no confounding factors. A careful consideration of the risks and benefits of discography should be done when considering discography in individuals at high risk for FP results, since many of these factors are also associated with treatment failure. If discography is conducted in these individuals, one should consider obtaining two adjacent control discs, and correlating reported pain with heart rate measurements and/or facial expressions.[24,34] Other factors that may increase the risk of FP discograms include extreme anxiety, performing disc stimulation before allowing previously provoked pain to return to baseline, inadvertent annular injection, contrast-induced irritation of nervous tissue, end plate deflection resulting from suboptimal needle placement, and rapid or over-disc pressurization (Table 64-1).[33]

CORRELATION BETWEEN MRI AND DISCOGRAPHY

Several attempts have been made to correlate imaging with discography results. In one of the earliest studies comparing MRI, the most sensitive test for disc pathology, and lumbar discographic findings, Gibson et al.[37] found agreement in 88% of 50 discograms. Among the 6 discs in which a discrepancy was observed, evidence of IDD was missed in 5 discograms and 1 MRI. Correlation in this study was based solely on radiographic findings and not provocation results. Collins et al.[16] reported similar results. The authors found that discographic and MRI imaging characteristics correlated in 89% of 73 lumbar discograms. In the 8 discordant discs, 4 revealed early evidence of disc degeneration on discography but were normal on MRI, and 4 were discographically normal but demonstrated mild degeneration on MRI. All discs that provoked concordant symptoms were degenerate on both discography and MRI. In a study by Schneiderman et al.,[38] the correlation between MRI and discographic morphology was 99%, with the only discrepancy being noted in a 13-year-old.

However, the relevant question is whether provocation results can be predicted by radiologic imaging. Yoshida et al.[39] investigated the relationship between provocative discography and MR images in 56 discograms done in 23 patients. The authors found the sensitivity, specificity, and positive predictive value and negative predictive value of T2-weighted, gadolinium-enhanced studies in detecting symptomatic discs to be 94%, 71%, 59%, and

97%, respectively. These findings favorably compared to T1-weighted images. In a study by Aprill and Bogduk,[40] the authors found that the presence or absence of a high intensity zone in 118 discograms had a sensitivity, specificity, and positive predictive value for concordant pain provocation in 97%, 63%, and 95% of levels, respectively. Even stronger correlations have been found by Linson and Crowe[41] (94% correlation) and Lei et al.[42]

Not all studies have demonstrated positive results. Zucherman et al.[43] reported a case series of 18 patients with normal MRI and positive discography. In a retrospective study, Sandhu et al.[44] found a poor correlation between vertebral end plate signal changes observed on MRI and the results of provocation discography. Lastly, in an observational study by Horton and Daftari[45] conducted in 25 patients, the authors concluded that significant discrepancies between various findings on MRI and discography necessitated that both be used in surgical planning.

To date, there have been few correlative observational studies performed in the cervical spine. In a study performed in 52 patients (104 discs), Parfenchuk and Janssen[46] found that the sensitivity, specificity, and FP and false-negative rates between MRI and pain provocation to be 73%, 67%, 33%, and 27%, respectively. Schellhas et al.[30] later sought to correlate MRI with disc provocation results in 10 asymptomatic volunteers and 10 patients with chronic neck pain. In the asymptomatic cohort, half of the 40 discs were morphologically abnormal on MRI versus 88% that exhibited abnormalities on discography. However, none of the abnormal discs provoked concordant pain during stimulation. In the symptomatic patients, 29 of the 40 discs exhibited some degree of abnormality on MRI. Among the 11 normal discs, 10 were found to have annular tears discographically, with 8 of these shown to be painful when injected. In summary, whereas a significant correlation between concordant pain provocation and MRI findings has been demonstrated, the high FP and false-negative rates suggest the need for a reliable means to ascertain which abnormalities are pain generators.

EFFECT ON SURGICAL OUTCOMES

SPINAL ARTHRODESIS

The few uncontrolled studies evaluating the impact preoperative discography has on surgical outcomes have been mixed. In the largest study, Colhoun et al.[47] found a strong positive association between disc stimulation findings and fusion results. Among the 137 patients with nonradicular LBP in whom disc stimulation provoked concordant pain, 89% had a favorable outcome at the mean follow-up period of 3.6 years. In contrast, only 52% of the 25 patients whose morphologically abnormal discs failed to elicit symptoms experienced significant benefit. However, later studies failed to replicate these results. Esses et al.[48] retrospectively examined the influence that discography had on predicting external fixation and fusion results in 32 patients with refractory LBP. To summarize their findings, neither concordant pain provocation nor morphologic abnormalities predicted pain relief with external spinal fixation or subsequent fusion. The main flaw in this study is that it was not designed to assess the influence discography had on surgical outcomes; thus, not all patients received preoperative disc injection. The next attempt to correlate discographic findings with spinal fusion outcomes was by Madan et al.,[49] who performed a retrospective analysis in 73 patients with chronic LBP. At the minimum 2-year follow-up, no difference in any outcome measure was noted between the two matched groups. In the only other study evaluating the value of discography as a preoperative screening tool, Derby et al.[10] found that patients with chemically sensitized discs experienced better outcomes following interbody/combined fusion than after other treatments.

In the cervical spine, only one study has evaluated the predictive value of discography in selecting surgical candidates. Kikuchi et al.[50] performed a retrospective study in the pre-MRI era evaluating surgical outcomes on 138 patients with either mechanical ($n = 41$) or radicular ($n = 97$) neck pain who underwent anterior discectomy and fusion based on discography results. One year postprocedure, 80% were either pain-free or experienced only mild discomfort that did not interfere with work. In a control cohort who underwent cervical fusion without the benefit of discography, 60% had favorable outcomes.

Two additional studies have examined the effect of discography in identifying treatment levels in patients already selected for spinal fusion. In a prospective study conducted in 193 patients with neck pain and neurologic symptoms, Hubach[51] evaluated the use of intraoperative discography to select operative levels. In the initial group of patients ($n = 23$) who were fused without discography, 35% developed juxtafusional pain at long-term follow-up. In the ensuing 156 patients in whom the operative levels were based on discography, only 12% developed pain at an adjacent segment. Yet, in a later prospective study conducted in the lumbar spine, Willems et al.[52] failed to demonstrate a benefit for discography in determining fusion levels. In summary, the results are conflicting as to whether pre-operative discography is an effective screening tool in identifying candidates or treatment levels for spinal fusion (Table 64-2).

DISC REPLACEMENT

First reported in the mid-1960s, lumbar disc replacement has been employed to treatment discogenic LBP in Europe since the 1980s, and in the United States since the early 2000s. The indications for lumbar disc replacement include one- or two-level mechanical discogenic back pain without radiculopathy or significant facet pathology. Dozens of studies have been published evaluating lumbar disc replacement outcomes in various contexts that contain wide variations in selection criteria, outcome measures, and follow-up periods. The success rates in these studies range from less 50% to upwards of 90%.[33] Although positive discographic screening was previously considered a selection criterion for lumbar disc replacement, numerous postmarket studies have been published that have not required preoperative discography. Whereas no study has directly compared operative results between surgical candidates selected based on clinical and radiologic studies alone, and those in which patients were chosen using discography results, indirect comparisons have failed to demonstrate any significant differences in outcomes.[33,55]

TABLE 64–2 Comparative Studies Evaluating Effect of Discography on Fusion Outcomes

Author, Year	Spine Region	Study Design	Patients	Results
Colhoun, 1988[47]	Lumbar	Prospective observational	162 pts with nonradicular LBP	89% of 137 pts with positive discogram had favorable outcome vs. 52% of pts in whom discography did not provoke pain. Mean follow-up 3.6 yr.
Esses, 1989[48]	Lumbar	Retrospective study evaluating effect of ESF before spinal arthrodesis	35 patients with chronic LBP, 32 of whom underwent preop discography	Discography results not predictive of ESF or arthrodesis results. Follow-up period not noted.
Derby, 1999[10]	Lumbar	Retrospective	96 surgical candidates with chronic LBP	In pts with chemically sensitized discs (concordant pain at <15 psi above opening pressure), success rates were higher (89%) for interbody/combined fusion than other operations or no surgical Rx. Mean follow-up 28 months.
Madan, 2002[49]	Lumbar	Retrospective	41 pts who underwent fusion without discogr and 32 who had surgery based on (+) discography	81% of pts who had surgery without discogr had satisfactory outcome vs. 76% of pts who underwent arthrodesis based on (+) discography. Mean follow-up 2.4 years in discography group and 2.8 years in MRI/clinical group.
Carragee, 2006[53]	Lumbar	Prospective observational	32 pts with nonradicular LBP and single, (+) low-pressure discgogram who underwent spinal fusion	Approximately 43% of discography pts obtained a "satisfactory" outcome vs. 91% of matched control group with single-level unstable spondylolisthesis who did not undergo discography. Follow-up period 2 years.
Willems, 2007[52]	Lumbar	Prospective observational	82 pts with equivocal indication for fusion who were operated on based on (+) ESF	No difference in outcomes between pts with (+) discogram at an adjacent segment and those with a negative discogram. Mean follow-up 80 months.
Ohtori, 2009[54]	Lumbar	Randomized comparative	42 pts with axial LBP were randomized to provocative discography vs. anesthetic discography	15 pts who underwent fusion based on anesthetic discography had superior outcomes to 15 who were fused based on provocative discography. Follow-up period 3 years.
Kikuchi, 1981[50]	Cervical	Retrospective	138 pts with cervicobrachial pain underwent single-level disc excision and anterior fusion	80% of pts improved 1 year after surgery vs. 39% success rate in 54 pts who underwent fusion without discography.
Hubach, 1994[51]	Cervical	Prospective observational	193 pts with cervical radiculopathy and/or myelopathy who underwent anterior discectomy and fusion	12 of 156 (8%) pts who had fusion based on intraoperative discography, developed adjacent segment pain vs. 35% of 23 pts who underwent fusion without discography. Mean follow-up, 10.4 years.

DDD, degenerative disc disease; discogr, discography; ESF, external spinal fixator; LBP, low back pain; pts, patients.

Unlike the indications for lumbar disc replacement, cervical discs are implanted in patients with or without neurologic symptoms. In the dozens of clinical studies reporting outcomes after cervical disc arthroplasty, over two-thirds of patients generally achieve success at intermediate-term follow-up ranging between 1 and 3 years.[56] However, since no study has routinely used provocative discography as a routine screening tool before disc replacement, no conclusions can be drawn regarding the predictive value of the procedure.

ALTERNATIVES TO PROVOCATIVE DISCOGRAPHY

In an attempt to find a less invasive replacement for discography, Yrjama and Vanharanta[57] developed the bony vibration test (BVT), wherein a blunt, vibrating object is compressed against the skin overlying successive spinous processes in order to provoke pain. In several studies, the authors found the test to have high sensitivity and specificity compared with provocative discography and radiologic imaging. When patients with complete annular tears, herniated discs, and failed back surgery syndrome are excluded, the sensitivity rises above 90%. Later, the authors found that the addition of ultrasonic disc imaging could further enhance accuracy.

Similar to diagnostic tests for other types of spinal pain, several investigators have proposed "analgesic" discography as a replacement or supplement to conventional provocative disc testing. In a study by Kotilainen et al.,[58] the authors found that over 80% of LBP patients who received intradiscal bupivacaine experienced short-term symptomatic improvement. Osler[59] and Roth[60] found that relying on pain relief following the intradiscal injection of local anesthetic resulted in good or excellent results in over 80% of patients who underwent anterior cervical fusion,

an improvement compared to selecting patients with provocation testing. In a more recent randomized study comparing conventional discography to analgesic discography with 0.75 ml of bupivacaine 0.5% in patients being screened for anterior discectomy and interbody fusion, Ohtori et al.[54] found that the 15 patients selected for surgery based on analgesic discography fared better than an equal number selected based on conventional discography. The purported advantage of anesthetic discography is that it may reduce the high incidence of FP results obtained with provocative discography.

INTERPRETATION

EVOKED PAIN RESPONSE

The patient's subjective pain response to intradiscal injection is the most important aspect of discography. Discography is predicated on the fact that normal discs are sparsely innervated, while disrupted discs are relatively richly innervated and have been rendered hyperalgesic from nociceptor exposure to inflammatory mediators. The foundation for discography stems from three premises. The first is that painful stimulation of any kind can provoke symptoms in a chronic pain patient, including pressurization of a nonpainful disc. Therefore, in order to diagnose DP, a control level must be obtained. A true control disc is present only when pressurization fails to elicit a typical pain response in a nontargeted disc. Both the IASP and ISIS consider the presence of two control disc levels in conjunction with one painful disc level to be highly indicative of DP. Pain reproduction in multiple discs with a single positive control disc level is considered to be uncertain or marginal evidence for DP. When pain is provoked in a suspected disc in the absence of any control level, DP can neither be proven nor refuted.

The second assumption is that pain caused by stimulation of a nonpainful disc will be different than the patient's usual pain. Thus, only when an evoked pain response is the same or similar to a patient's typical pain can a disc be considered a likely source of pain. Third, it is assumed that "minor" or nondebilitating pain can be evoked from stimulation of a nonpainful disc. Hence, only generation of significant pain is considered evidence of DP. Such thresholds have been arbitrarily set between 6 to 7 on a 0-to-10 pain scale.[33] However, there are several flaws with this premise. The foremost is that it fails to take into account a patient's baseline pain. For example, reproducing 5/10 pain in a stoic, debilitated patient who rates his pain as 4/10 at baseline would be considered a "negative" discogram, while a somatically focused patient with a baseline pain of 10/10 could be classified as having a positive discogram when disc stimulation provokes 6/10 similar pain. A second limitation is that discography is often done in a sedated patient in a non-functional recumbent position, wherein the distinction between concordant and discordant, and significant and insignificant pain, can be difficult to discern. This is especially relevant when an early disc injection provokes intense pain in a multilevel procedure.

In addition to the quality and magnitude of the evoked response, the amount of pressure needed to evoke pain is considered pivotal to diagnosis. The key rationale behind discography is that pain can be evoked by minimal pressurization of a disrupted disc (akin to allodynia or hyperalgesia), whereas higher intradiscal pressures would be painless in a normal disc. In order to standardize the intensity of disc stimulation, pressure discography was introduced in the lumbar spine. The intradiscal pressure at which the contrast flow is first observed in the disc is the opening pressure, while the maximum pressure achieved during a disc injection is referred to as the peak pressure. Physiologic variations in disc pressures, however, are significant—intradiscal pressures are higher in upright position and lower in the recumbent position. In view of the fact that intradiscal pressures are typically lower in disrupted discs, generating intermediate or high pressures in severely degenerated discs may not be feasible. Manometery essentially quantifies intradiscal pressures at key events (i.e., opening pressure, pain provocation pressure, pressure at which leakage is noted) so that if concordant pain is evoked below a certain threshold, the discogram is considered "positive."

According to most guidelines, asymptomatic lumbar discs are highly unlikely to evoke pain at pressures below 15 psi.[10,33] Therefore, pain evoked at pressure below this level is considered highly suggestive of lumbar DP (i.e., a chemically sensitive disc). At the other end of the spectrum, even a normal disc can provoke pain when the peak pressure is raised too high (i.e., above 90 psi). The implications of pain reproduced at pressures between 15 and 90 psi are less clear. Pain reproduced in a disc at pressures between 15 and 50 psi above the opening pressure suggests that disc is a likely pain generator in the presence of an adjacent control disc; however, the existence of other pain generators cannot be excluded. This is sometimes referred to as a mechanically sensitive disc.[10,33] A disc in which pain is reproduced between 50 and 90 psi is unlikely to be positive, but its contribution to pain cannot be excluded (i.e., an indeterminate disc). Studies evaluating the effect of treatments and patient outcomes based on pressure discography are lacking. In one retrospective study, the results of interbody/combined fusion surgery were superior when performed on chemically sensitive discs.[10] Pressures above 100 psi are considered detrimental to disc integrity, so that one potential advantage of pressure discography may be avoidance of disc injury.

In the cervical and thoracic spine, manometry is not commonly used. In a cadaveric study by Menkowitz et al.,[61] the authors found the median opening pressure to be 30 psi, with the median pressure required to rupture a disc varying between 36.5 psi (C4–C7 discs) to 53 psi in C2–C3, C3–C4, and C7–T1 discs.

VOLUMETRIC MEASUREMENTS

The volumetric measurements made during discography include the amount of contrast injected and the various endpoints. Normal lumbar discs typically accept less than 1 ml of contrast before firm resistance is reached—a firm endpoint. In cervical and thoracic discs, these volumes are approximately 0.25 and 0.5 ml, respectively. Degenerated discs typically accept larger

contrast volumes and only moderate resistance to the injection is encountered—a lower pressure or soft endpoint. In the presence of a complete annular tear where the disc communicates with the epidural space, an unlimited volume of the contrast may be injected with little or no resistance—a volume endpoint. Provocation of significant pain should result in cessation of any disc injection—a pain endpoint. It should be recognized that severely disrupted discs may evoke no pain or resistance on injection.[33]

MORPHOLOGIC DISC EVALUATION

Morphologic patterns of contrast spread in normal and degenerated discs are well described and can be visualized by plain fluoroscopy or CT-discography. In contrast to fluoroscopy, CT-discography allows for the visualization of internal disc abnormalities that are not apparent with fluoroscopy or MRI. The intradiscal contrast spread as seen on CT-discography has been well described by several authors. In one such rating, which has since been revised,[62,33] grade 0 describes a normal lumbar disc in which contrast is limited to the NP; grades 1 to 3 designate discs in which contrast extends to the inner, middle, and outer third of the AF respectively; grade 4 describes a diffusely degenerated disc in which several annular tears extend to the periphery of the annulus; and grade 5 depicts a large tear that results in contrast extending circumferentially to more than 30% of the disc circumference. The pain reproduced on discography has been well correlated to the extent of the annular disruption seen on CT-discography (Figure 64-2). Grade 3 tears usually provoke concordant pain, grade 2 disruptions reproduce pain infrequently, and grade 0 and 1 discs rarely evoke pain.[63] Both IASP and ISIS guidelines require the presence of a significant annular tear in order for a diagnosis of DP to be rendered (Table 64-3).

COMPLICATIONS AND DISC INJURY

The avascular nature of the disc renders it vulnerable to the iatrogenic innoculation of bacteria difficult to treat with antibiotics. These factors make discitis the most feared complication of discography. Whereas procedure-related pain is not uncommon, any patient who experiences a new neurologic finding or continues to complain of persistent pain 1 week postprocedure warrants re-evaluation. At minimum, the postdiscography work-up should include a focused history, physical exam, and laboratory screening tests that include erythrocyte sedimentation rate, C-reactive protein, and white blood cell count.[33] If the erythrocyte sedimentation rate is more than 50, then a high-resolution MRI focusing on the end plates is needed.

Several reviews have been conducted with the aim of determining the incidence of iatrogenic discitis, and whether or not pre-procedure antibiotics should be routinely administered. In a review of 12,770 lumbar discograms performed in 4891 patients without prophylactic antibiotics, Willems et al.[64] found a discitis rate of 0.25% per patient and 0.09% per disc. The authors concluded that there was not enough evidence to support the routine use of prophylactic antibiotics. Similar conclusions were reached by Sharma et al.[65] and Kapoor et al.[66] In their review evaluating 14,133 discograms done in 4804 patients, Kapoor et al.[66] found the rate of infection to be 0.44% per patient and 0.15% per discogram. Among the 21 reported cases, the time to presentation ranged between 3 days and 3 months. If administered, prophylactic antibiotics can be given either parenterally or intradiscally, with studies suggesting comparable efficacy for both routes.[67]

Another controversy surrounding discography is whether the acute elevation of intervertebral disc pressure can worsen back pain or injure the disc. In a biochemical model tested in 69 cadavers, Iencean[68] found the pressure needed

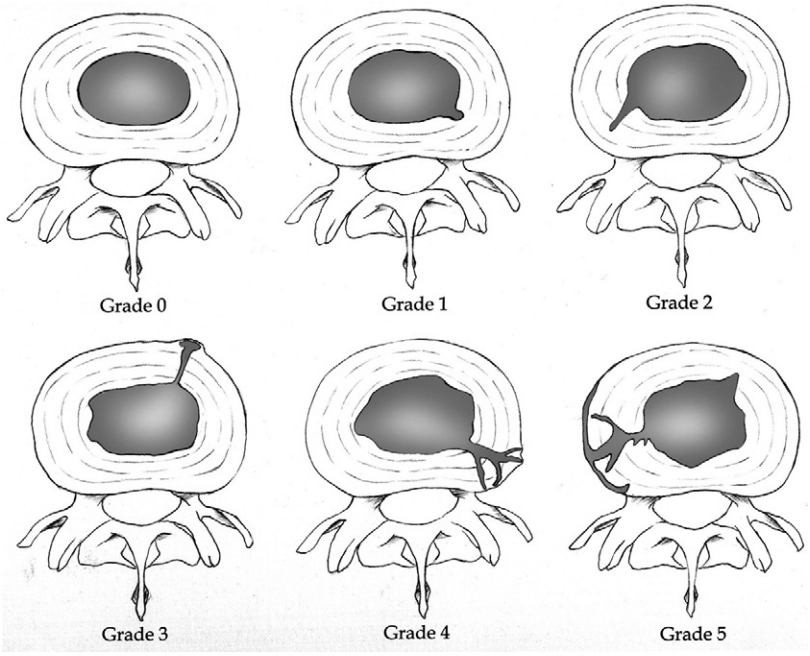

FIGURE 64-2 Modified Dallas discogram scheme for the classification of annular tears by CT-discography. *(From Cohen SP, Larkin TM, Barna SA, et al: Lumbar discography: a comprehensive review of outcome studies, diagnostic accuracy, and principles.* Reg Anesth Pain Med *30:163–183, 2005. Drawings by Jee Hyun Kim.)*

TABLE 64–3 Interpretation of Discography

Diagnosis	Alternate Diagnosis	Manometric Disc Pressure Where Pain Is Evoked	Pain Intensity	Location of Pain Response	Contrast Spread on PDCT	Control Level Injection	Interpretation
Discogenic pain	Unequivocal discogenic pain/ chemically sensitive disc	<15 psi above open pressure	>6–7/10	Concordant to patient's usual pain	>Grade –3 annular tear	No pain >2 control disc levels	The disc is likely the main source of pain.
Presumptive discogenic pain	Probable discogenic pain/ mechanically sensitive disc	Between 15–50 psi above open pressure	>6–7/10	Concordant to patient's usual pain	>Grade –3 annular tear	No pain at >1 control discs OR <5/10 discordant pain at >1 control disc	The disc is likely a source of pain; however, other sources cannot be excluded.
Remote discogenic pain	Indeterminate disc	50–90 psi	>6–7/10	Concordant to patient's usual pain	>Grade –3 annular tear	No pain at >1 control disc OR <5/10 discordant pain at >1 control disc at >50 psi	The disc is unlikely to be a source of pain; however, its presence cannot be excluded.
Normal disc	—	>90 psi	0/10 pain	—	—	—	Normal disc.
Iatrogenic disc injury	—	>100 psi	—	—	—	—	These pressures should be avoided to prevent iatrogenic disc injury.

PDCT, postdiscography computerized tomogram.

to effect disc herniation was inversely proportional to the degree of degeneration, and ranged from 108 to 188 psi. This is consistent with the 100 psi pressure limit imposed by many discographers. In the cervical spine, a cadaveric study found the median pressure required to rupture a disc was 40 psi.[61] However, caution should be exercised even when manometry is utilized, as there are several reports of discography-induced lumbar disc herniation occurring at lower pressures.[69]

The literature is conflicting with regard to whether disc stimulation can have long-term adverse effects. In early studies evaluating the clinical and anatomical sequelae of discography, multiple investigators all found no evidence that discography causes damage to intervertebral discs.[33] However, only one study used MRI to discern interval disc pathology,[70] and the mean follow-up period in this analysis was only 72 days.

A more recent study by Carragee et al.[71] contests the assumption that discography is not associated with long-term sequelae. The authors evaluated repeat MRI scans in 52 asymptomatic or minimally symptomatic individuals who underwent discography 7 to 10 years earlier, and 50 matched control subjects. Upon repeat imaging, they found that those who underwent discography were more likely to have greater disc degeneration, and a 2.5-fold increased likelihood of disc herniation, in injected discs than subjects who did not undergo discography. In an earlier study, Carragee et al.[72] found that painful disc injections and annular disruptions were poor and weak predictors of subsequent LBP in patients without preexisting back symptoms, respectively. Other complications of discography include headache, convulsions attributed to contrast, nausea and vomiting, severe back pain, hematoma, meningitis, arachnoiditis, nerve root injury, paravertebral muscle spasm, vaso-vagal reactions, and allergic reactions.[43]

CONCLUSION

Discography is the only test that purports to correlate symptoms with pathology. In view of the cost, complications, and high failure rate associated with spine surgery, there is a strong need to refine selection criteria. Yet, despite anecdotal evidence supporting the use of discography to select surgical candidates, its ability to improve outcomes remains unproven. One area that has generated intense interest is the use of anesthetic discography, which is based on the same principle as that employed for other diagnostic spinal injections—pain relief. Large-scale clinical trials are needed to determine whether discography, in any form, can enhance surgical outcomes, and whether the benefit derived from the procedure outweighs the potential risks, including but not limited to discitis and accelerated disc degeneration.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 65

Intradiscal Techniques: Intradiscal Electrothermal Therapy, Biacuplasty, Percutaneous Decompression Techniques

David R. Walega, MD

It has long been postulated that annular disruption can be a source of low back pain (LBP). In normal disc anatomy, nociceptive fibers innervate only the outer third of the disc annulus, but in vitro and in vivo studies have shown nerve and blood vessel in growth into deeper layers of the annulus, with high expression of substance P and clinically severe discogenic LBP.[1,2]

Approximately 30% to 50% of all cases of LBP are due to internal disc disruption (IDD).[3] IDD is defined as a "biochemical, biophysical, and morphologic disruption of the nucleous pulposis and annulus fibrosis of the disc,"[3] typically characterized by radial or circumferential fissures extending from the nucleus pulposis into the outer layers of the annulus. These fissures can create a chronic inflammatory response within the disc resulting in neoinnervation, upregulation of nociceptors and overall disc sensitization. The diagnostic criteria for IDD are listed in Table 65-1 (Figs. 65-1 and 65-2).

Traditionally, discogenic LBP, or pain from IDD, has been treated with conservative care: activity modification, opiate and nonopiate analgesic medication, physical therapy, steroidal spine injections, chiropractic care, manual therapy, acupuncture, and other modalities. Surgical arthrodesis or disc replacement may be performed when discogenic LBP remains unresponsive to conservative treatments. There is significant variability in outcome following arthrodesis or disc replacement,[4] and complications can include infection, pseudarthrosis and adjacent segmental instability.

Radiofrequency ablation or thermal neurolytic treatment of the posterior annulus is in theory a plausible technique to ablate nociceptors and modify collagen of the annulus fibrosus of painful discs. Several percutaneous intradiscal techniques have been developed to attempt effective treatment of lumbar discogenic pain. Prospective and randomized controlled trials show percutaeous radiofrequency (RF) disc lesioning with simple monopolar RF electrodes is ineffective or unpredictable in relieving discogenic LBP.[5–9] Intradiscal lesioning of any type remains controversial.

In the late 1990s, intradiscal electrothermal therapy (IDET) was developed on the theory that thermal heating of the posterior and posterolateral disc annulus results in collagen fiber contraction and neurolysis of nociceptors within a painful or sensitized intervertebral disc in addition to enhancement or stimulation of chondrocytes promoting disc repair.[10] In an early study, cadaveric human intervertebral discs were studied in vivo after standard IDET was performed, and disc material was then examined under light and electron microscopy. Extensive collagen disorganization and collagen fibril shrinkage was accompanied by chondrocyte damage in disc material that was treated with IDET when compared to control tissue.[11]

In practice, IDET uses a thermal resistive catheter placed intradiscally at the site of a radial or circumferential annular fissure to deliver RF energy to the posterior intervertebral disc. This RF energy is converted into heat, resulting in a thermal lesion of the disc annulus and neurolysis of upregulated nociceptors. Temperatures at or above 65°C result in consistent shrinkage of unwound triple-helix collagen fibers.[12,13] Clinically this has been verified by disc shrinkage or resolution of disc displacement on MRI occurs following IDET.[14] In an in vivo study of human cadaveric discs, intranuclear pressures and annular stress measurements were assessed before and after a standard IDET procedure. After IDET, the intranuclear pressures decreased by 6% to 13%, whereas in sham procedures there were no differences in these pressures and the majority of treated discs showed decreases in annular stress by nearly 10%,[15] further supporting a biomechanical hypothesis for IDET efficacy.

Although post-IDET annular contraction, thermally induced healing, sealing of annular tears, neurolysis of nociceptors and decreased intradiscal disorder are proposed mechanisms of pain reduction, the exact mechanism of intradiscal RF procedures effecting pain relief remains unclear (Table 65-2).

INTRADISCAL ELECTROTHERMAL THERAPY

TECHNIQUE

The IDET procedure is performed percutaneously, similar to standard disc puncture techniques like discography, using fluoroscopic guidance, a radiolucent table, and strict sterile technique. Parenteral antibiotics are typically delivered to the patient preprocedurally. With the patient positioned prone, local anesthesia is used to anesthetize the skin, subcutaneous tissues, and periosteum at the level at which the IDET will be performed. Conscious sedation is used to ensure patient comfort, though patients must be able to respond to commands and accurately report feelings of dysesthesias or radicular pain during needle placement, catheter placement, and disc heating, if these occur.

Using an extrapedicular approach, an introducer needle is placed into the disc to be treated. Needle entry into the disc is ventral to the superior articular process of the zygophyseal joint at the level IDET is to be performed (Fig. 65-3A, B). The introducer needle tip is precisely positioned halfway between the superior and inferior end plates of the adjacent vertebral bodies, just anterior to the midpoint of the disc on the lateral projection. Either side of the disc can be entered, as this does not appear to have an effect on outcome.[16]

TABLE 65–1 IDD Diagnostic Criteria

Disc stimulation is positive at low pressures (<50 psi).
Disc stimulation produces pain of intensity >6/10 on visual analog scale.
Disc stimulation reproduces concordant pain.
Computed tomography discography shows a grade 3 or greater annular tear (tear extends into the outer third of annulus) (see Figs. 65-1 and 65-2).
Control disc stimulation is negative at one and preferably two adjacent levels.

Source: Karasek M, Bogduk N: Intradiscal electrothermal annuloplasty: percutaneous treatment of chronic discogenic low back pain. Tech Reg Anesth Pain Manage *5:130–135, 2001.*

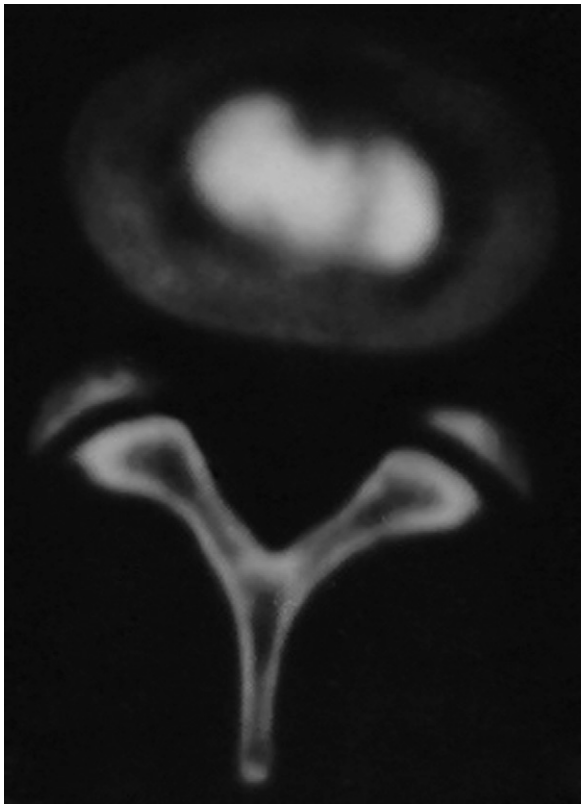

FIGURE 65-1 Axial CT image of a normal L4–L5 intervertebral disc following discography. Note the contrast material held tightly within the nucleus pulposus.

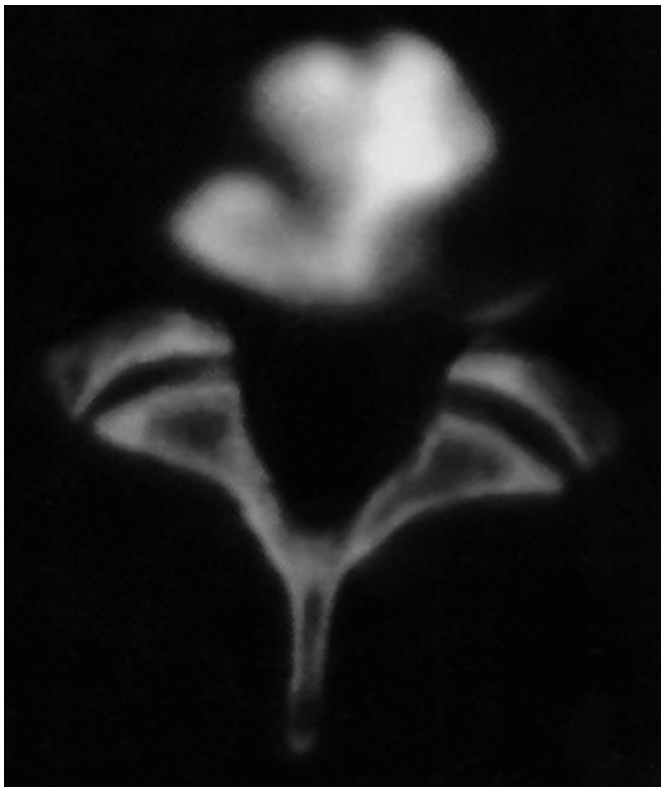

FIGURE 65-2 Axial CT image of an abnormal L4–L5 intervertebral disc following discography. Note the extension of contrast material through a right posterior fissure with slight circumferential spread into the right posterolateral annulus. This is a grade 3 tear. There is no extension of contrast into the epidural space.

TABLE 65–2 Possible Mechanisms of Action for Intradiscal Radiofrequency Procedures

Alteration in spinal segment biomechanics via collagen modification
Thermal nociceptive fiber destruction
Biochemical mediation of inflammation
Stimulation of outer annulus healing process
Cauterization of vascular in-growth
Induced healing of annular tears

Source: Derby R: Intradiscal electrothermal annuloplasty: current concepts. Pain Physician *6:383–385, 2003.*

A thermal resistive catheter is then navigated through the introducer needle to the posterior annulus at the site of the previously diagnosed fissure or tear, as seen in Figures 65-4 and 65-5. CT discography results should be used to plan optimal catheter positioning. Meticulous positioning of the catheter over the pain-generating annular tear improves postprocedural results.[3]

The catheter is then heated to a maximum temperature of 85° to 90° C.[10,17] The avascular disc acts as a heat sink, allowing the disc to retain this delivered heat and effect collagen conformation distal to the catheter without causing nerve root or spinal cord damage. The countercurrent blood flow in the epidural and perineural vessels appear to have a neuroprotective effect, preventing heat from building up within neural tissue when the catheter is appropriately placed intradiscally. Most patients experience their typical LBP during the heating protocol, often with vague aching into the buttocks or legs. This must be differentiated from true radicular pain, specifically if these symptoms are severe and occur early during disc heating. A high index of suspicion should be maintained to prevent thermal injury of the cauda equina or the exiting nerve roots within the neural foramen. If true radicular pain occurs during the heating protocol, the intradiscal catheter must be removed and/or repositioned.

Catheter kinking is known to occur, as is catheter breakage. When breakage occurs, it is typically at the connection of the catheter to the catheter hub, but it can occur along the body of the catheter from damage incurred at the introducer needle tip. Kinking of the catheter can

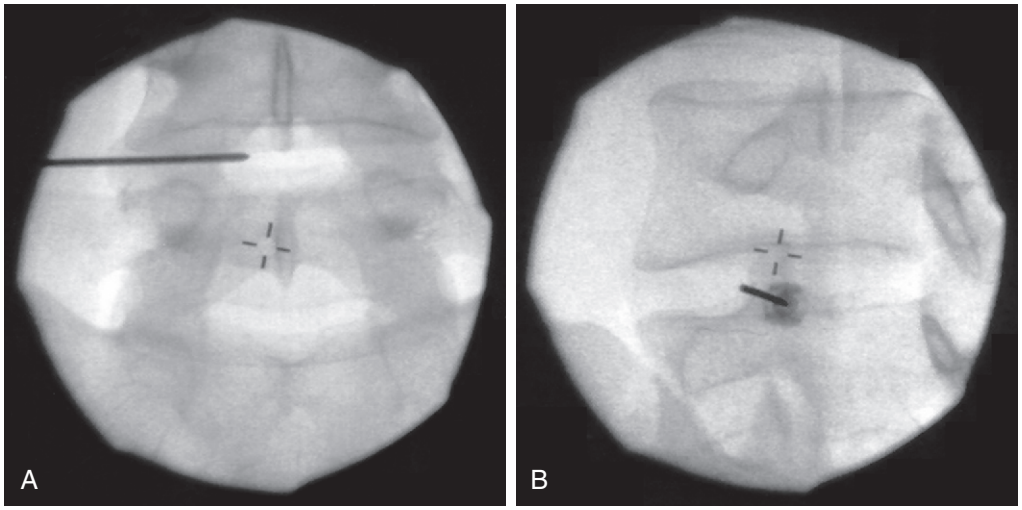

FIGURE 65-3 AP and oblique fluoroscopic views of introducer needle placement via a left extrapedicular approach into the L4–L5 disc. Note how the introducer needle "hugs" the superior articular process on the oblique image, preventing potential for nerve root injury.

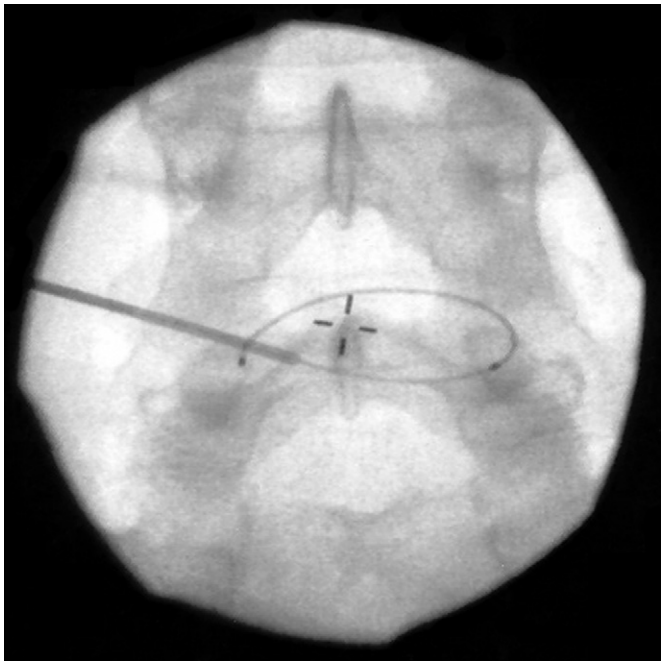

FIGURE 65-4 AP fluoroscopic view of IDET catheter placed into an L4–L5 intervertebral disc. Note the markers on the catheter, delineating the thermal conductive portion of the device.

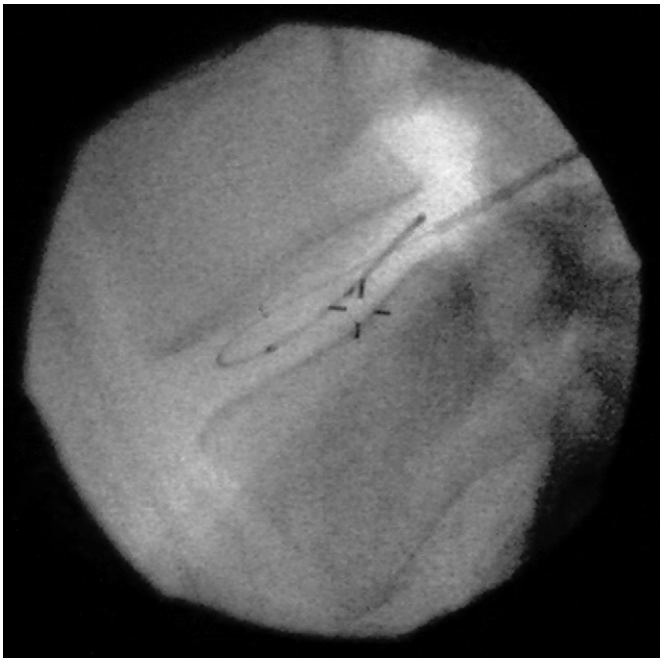

FIGURE 65-5 Lateral fluoroscopic view of IDET catheter placed into an L4–L5 intervertebral disc. The lateral projection is used to confirm that the catheter has not been erroneously placed into the spinal canal or into a foramen. Note that the introducer needle has been pulled back into the outer annulus to prevent heating of the introducer needle.

occur when the tip becomes lodged within a radial fissure or circumferential tear. The catheter should be withdrawn under these circumstances, and the introducer needle moved anteriorly or posteriorly prior to reinsertion of the catheter more optimally. If a catheter is severely bent or kinked, it should be discarded and replaced. If removal of the catheter from the introducer needle is met with resistance, the introducer and catheter should be removed en bloc and then positioned again separately. If the catheter cannot be navigated successfully across the length of a fissure, the introducer needle position can be revised via a contralateral extrapedicular technique with reattempts at optimal catheter placement (Figs. 65-4 and 65-5).

Following the procedure, back bracing is recommended for several weeks, followed by a lumbar stabilization and reconditioning program.

COMPLICATIONS

Rare complications of IDET have been reported in case reports, observational studies, and randomized studies. These include catheter breakage,[10,17,18] post-IDET disc herniation,[19] cauda equina syndrome,[20–22] vertebral end plate osteonecrosis,[23] radiculopathy, headache, foot drop, decreased sphincter tone, fecal incontinence, and discitis.[24,25] In a meta-analysis of 17 reports on IDET, the complication rate was found to be 0.8%.[26]

RESULTS

A series of observational studies showed varying favorable treatment outcomes with IDET in patients with discogenic LBP.[16,17,24,27–34] Subsequently, two randomized trials of IDET were published[25,35] which discounted the more successful clinical outcomes reported in observational studies.

In a double-blind randomized controlled trial (RCT) by Pauza et al., 64 patients were strictly selected and randomized to IDET (32 patients) or a sham procedure (24 patients). Approximately 40% of patients treated with IDET experienced 50% or more pain relief, but 50% of patients experienced no notable improvement whatsoever. Twenty-one percent of the IDET group experienced greater than 80% relief of baseline pain, whereas only 4% of the control group showed similar levels of improvement in pain. A small percentage of the IDET group showed worsening of pain scores on follow-up, whereas 33% of the control group showed similar deterioration. Overall, function remained the same in both treatment groups, even when pain levels improved.[35]

In another RCT, Freeman et al. studied 57 patients with discogenic LBP; 38 patients underwent IDET, and 19 patients had a sham procedure. All were assessed at baseline and at 6 months postprocedure. No statistically or clinically significant differences in outcomes were identified for either treatment group in this study.[25]

Several meta-analyses have been published on IDET with mixed conclusions and recommendations. Mean improvement in the visual analog scale (VAS) after IDET was 3 in one review,[26] and in another, IDET was described as "modestly effective in the treatment of lumbosacral discogenic pain in carefully selected patients."[36] Results of IDET were comparable to those of spinal fusion for discogenic LBP but without the attendant complications of major spine surgery[4] in another review. In contrast, another review found IDET ineffective in treating discogenic LBP.[37] Patients not likely to benefit from IDET include those with multilevel degenerative disc disease,[29] overweight patients,[38] and patients receiving worker compensation benefits.[39] Repeat IDET procedures may be effective in some patients, though improvements may be less notable and shorter in duration.[32]

Based on U.S. Preventive Services Task Force criteria, the evidence for IDET being an effective treatment for discogenic LBP is Level II-2,[40] although in another review, an expert panel from the American Pain Society deferred comment on the efficacy of IDET due to conflicting results of randomized studies.[41]

BIACUPLASTY

Biacuplasty, or intradiscal bipolar water-cooled RF, is a more recent development (TransDiscal System Baylis Medical Company, Montreal, Canada) in discogenic pain management and improves on some of the deficiencies of the IDET procedure. Similar to IDET, biacuplasty deploys thermal energy to the painful upregulated annulus, but in this case delivers *bipolar* RF energy via two stiff adjacent electrode probes placed intradiscally. The electrodes are actively and internally cooled during the ablation procedure with a peristaltic pump unit (Baylis Medical Company, model TDA-PPU-1) that circulates water through the probes to cool the electrodes,[42] allowing bipolar RF energy to heat annular tissue adjacent to and between the two electrodes while the tissue in immediate contact with each electrode probe is actively cooled. Through this active cooling system the bipolar RF energy produces a larger volume of ionic tissue heating with concentrated current in the posterior disc[43–45] and avoids tissue charring which results in rising impedance, unpredictable RF energy delivery, and ineffective intradiscal tissue heating. Peak tissue temperatures are much lower with biacuplasty than those with IDET, offering an additional advantage of better procedural tolerability for patients. The electrode probes are typically placed with greater ease than the IDET coil, a technical advantage over IDET.

TECHNIQUE

The biacuplasty procedure is performed percutaneously, similar to standard disc puncture techniques like discography and IDET. Table 65-3 lists a technique algorithm for intradiscal biacuplasty.

Using an extrapedicular approach, two introducer needles are placed into the disc to be treated. Needle tip placement is in the posterolateral nucleus–annulus junction, half-way between the superior and inferior end plates of the adjacent vertebral bodies. Electrode probes are then placed into the introducer needles, noting the radiodense markers on the electrodes in the posterior annulus. See Figures 65-6 through 65-9 for optimal probe positioning. Bipolar RF heating is then initiated. The temperature of the electrode remains at 45° C, while disc tissue temperature is heated to 55 to 60° C in the inner annulus and 45° C toward the edge of the annulus. Again, the avascular disc, epidural blood vessels, and countercurrent blood flow and the CSF column all act as heat sinks, allowing the disc to retain this delivered heat and effect collagen

TABLE 65–3 Technique Algorithm for Intradiscal Biacuplasty

Obtain informed consent from patient.
Parenteral prophylactic antibiotic delivery.
Perform sterile prep and drape.
Identify level to be treated with fluoroscope.
Anesthetize skin/tissues, and administer light IV sedation as needed.
Confirm status of equipment/functioning biacuplasty electrodes, introducer needles, generator, and water pump.
Place introducer needles into disc to be treated.
Place biacuplasty electrodes, and confirm intradiscal placement with fluoroscopy.
Follow heating protocol; monitor patient for any radicular symptoms.
Remove electrodes.
Administer intradiscal antibiotics.
Remove introducer needles.
Apply dressing to site.
Back brace for 4 to 6 weeks.

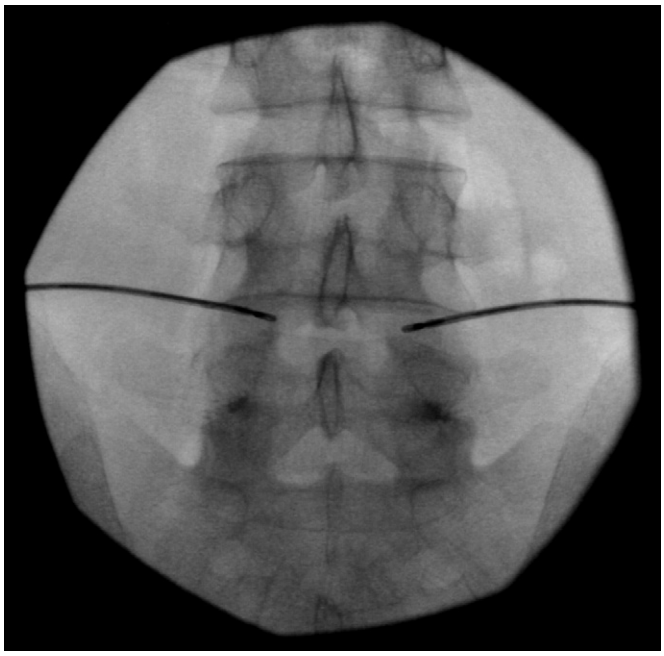

FIGURE 65-6 AP fluoroscopic view of biacuplasty probes placed into the L4–L5 intervertebral disc for treatment of discogenic low back pain. Note the markers on the probes, delineating the conductive portion of the devices.

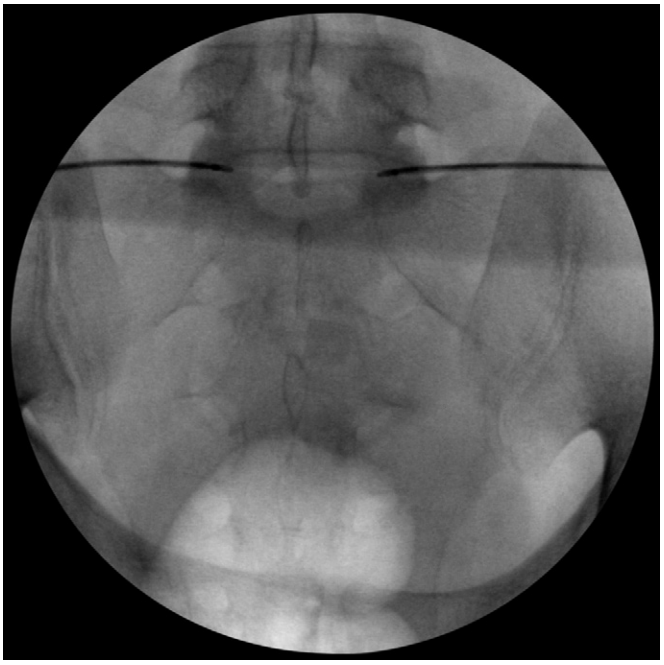

FIGURE 65-8 AP fluoroscopic view of biacuplasty probes placed into the L5–S1 intervertebral disc for treatment of discogenic low back pain. Note the markers on the probes, delineating the conductive portion of the devices.

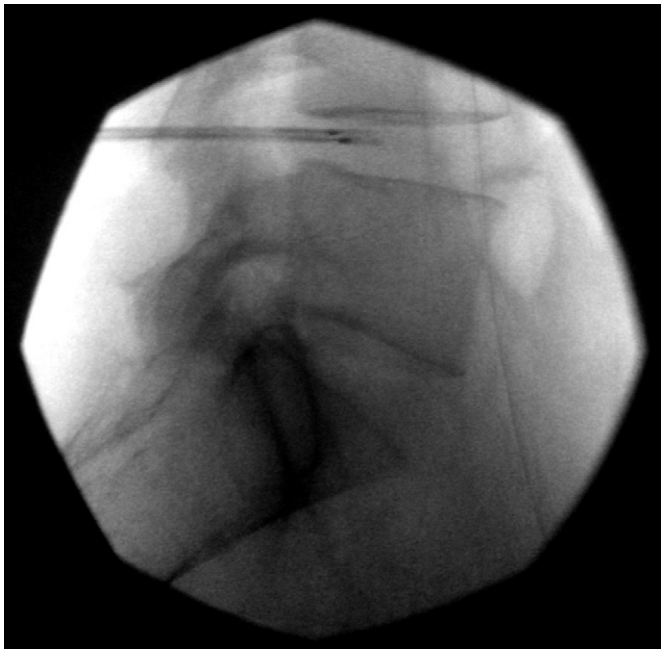

FIGURE 65-7 Lateral fluoroscopic view of biacuplasty probes placed into an L4–L5 intervertebral disc. The lateral projection is used to confirm that the conductive portion of the probes are optimally positioned in the annulus and at least 10 mm from the epidural space or exiting nerve roots.

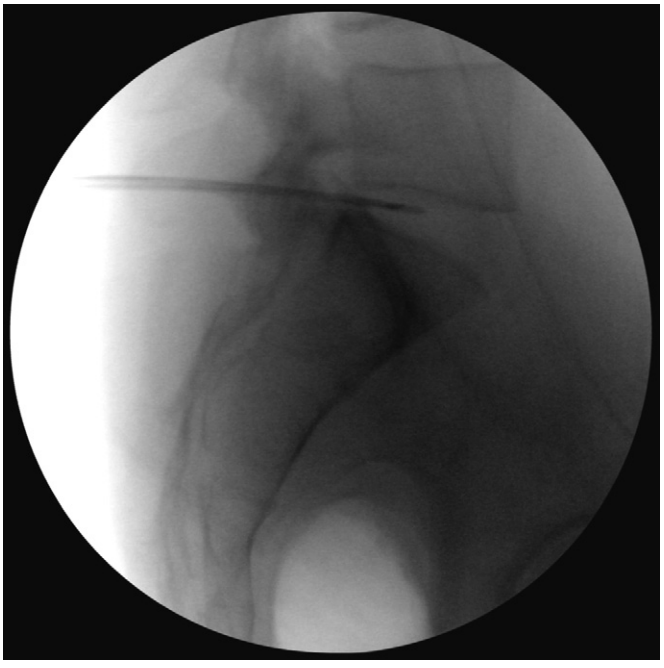

FIGURE 65-9 Lateral fluoroscopic view of biacuplasty probes placed into an L5–S1 intervertebral disc. The lateral projection is used to confirm that the conductive portion of the probes is optimally positioned in the annulus and at least 10 mm from the epidural space or exiting nerve roots.

conformation without causing nerve root or spinal cord damage. Patients may experience mild to moderate LBP during disc heating.

Kapural et al. used human cadaveric models to measure thermal changes within the nucleus, annulus, neural foramen, and epidural space during standard biacuplasty procedures in both normal and degenerated lumbar discs.[42,44] Temperatures reached in the posterior annulus during biacuplasty were greater than required (45° C) for neurolysis and temperatures in the neural foramen and

epidural spaces were low enough to avoid damage to neural structures. On histologic examination following the biacuplasty procedure, no damage to any spinal or neural structure was identified and there was no evidence for heat-induced changes or charring in the posterior annulus. Pauza found similar results of temperature changes within the disc and perineural structures in another human cadaveric study.[45] Petersohn et al. used an in vivo porcine model to confirm that biacuplasty achieves suitable temperatures for intradiscal neurolysis and identified no histological evidence of damage to neural tissues in proximity to the disc.[43]

Thus, there appears to be substantial in vivo evidence that biacuplasty causes intradiscal temperature changes that would allow for thermal neurolysis without concomitant heating of adjacent neural tissues and vascular structures.

RESULTS

There are no published randomized control trials of intradiscal biacuplasty. Two published case reports infer success of the modality.[46,47] A larger observational study of 15 patients with chronic discogenic LBP showed statistically significant improvements in VAS, ODI, and SF-36 scores at 3 and 6 months, though opioid use did not significantly change through the course of the study. Seven out of 13 patients followed over 6 months had more than 50% improvement in their pain scores.[48]

In a follow-up report of this study, it was noted that improvements in function and pain control persisted at 12 months after intradiscal biacuplasty was performed; a large proportion of patients had greater than 50% reduction in pain at the 12-month follow-up, and no complications were detected.[49]

Although these results appear promising, randomized controlled trials of biacuplasty in critically selected patients with discogenic LBP are required to make more definitive statements about treatment efficacy. See Table 65-4 for recommended selection criteria for intradiscal procedures like biacuplasty.

TABLE 65–4 Selection Criteria for Intradiscal Procedures

Low back pain of >6 mo duration
Nonresponsive to conservative treatment
Back pain greater than leg pain
Positive well-performed discography with a negative control
Presence of an annular tear
Disc disease limited to one or two levels
Disc height ≥50% of normal
Body mass index <30
Age <55 yr
No evidence of compressive radiculopathy other than diminished ankle reflexes
Disc bulges ≤5 mm
No prior surgery at the treated level
No symptoms or signs of stenosis
No pending worker compensation or personal injury claims
No significant depression or psychiatric issues on exam or history
No tumor or metastatic disease to the lumbar spine
No systemic infection or localized infection at needle site
No coagulopathy or unexplained bleeding
No progressive neurologic defects
No history of substance abuse
No smoking

Source: Helm S, Hayek S, Benyamin R, Manchikanti L: Systematic review of the effectiveness of thermal annular procedures in treating discogenic low back pain. Pain Physician *12:207–232, 2009.*

PERCUTANEOUS DISC DECOMPRESSION WITH NUCLEOPLASTY

Nucleoplasty is a method of percutaneous intervertebral disc decompression approved by the U.S. Food and Drug Administration in 1999 for selected patients with persistent radicular pain due to small, contained herniated lumbar discs or contained disc bulges unresponsive to conservative, nonsurgical therapy. Percutaneous disc decompression (PDD) is based on the principle that small decreases in volume within an enclosed space will result in a disproportionately higher drop in pressure. Other methods of PDD used in the past include chymopapain nucleolysis, percutaneous manual nucleotomy, nucleotomy via nucleotome use, thermal vaporization via laser, and automated percutaneous lumbar discectomy.[50]

Nucleoplasty uses RF energy delivered through a percutaneous electrode (Perc-DL SpineWand, Arthrocare, Sunnyvale, CA) to create a voltage gradient within the intervertebral disc. A plasma field is then created between an electrode tip within the disc and the surrounding nucleus pulposis, creating a discal temperature rise to 50° to 70° C. This intradiscal transmission of energy excites the surrounding tissues, causing molecular bonds of the nucleus pulposis to break, vaporizing disc material into low-molecular-weight gases (hydrogen, oxygen, carbon dioxide), which then exit the percutaneous needle. Thus, a small volume of the nucleus pulposis is removed, creating a profound decrease in intradiscal pressure. Decreased annular wall stress allows the intact annulus to retract from irritated neural tissue, thereby providing pain relief, as shown in a small in vivo study of cadaveric human intervertebral discs. In this study, Chen et al. further confirmed that younger, healthier, less degenerated discs had a clinically significant drop in intradiscal pressure following nucleoplasty, as opposed to more degenerated or senile discs when nucleoplasty was performed.[51]

TECHNIQUE

Nucleoplasty is performed similar to other intradiscal techniques previously described. After an introducer needle is placed in the disc to be treated under fluoroscopic guidance via an extrapedicular approach, a nucleoplasty electrode is then placed through the introducer needle and advanced across the disc space to the adjacent nucleus-annulus interface at the contralateral, anterior portion of the disc. A total of six channels with 60-degree angulation with each rotation of the probe are

recommended for 3 min. Tissue ablation and coagulation is performed with each "pass" across the nucleus pulposis, creating a single channel within the disc. After making six channels within the disc, a total of 1 cc of intradiscal volume is removed via vaporization, with a significant decrease in intradiscal pressure.[51] Again, patients should be awake and responsive during this procedure. Back bracing is not required following this procedure, nor is a protracted course of physical therapy. Patients are typically able to resume normal activities within 1 to 2 weeks of the procedure.

RESULTS

To date, there are no published studies of placebo-controlled randomized trials of nucleoplasty, and the long-term effects of nucleoplasty on the progression of disc degeneration and the stability of the segmental spine unit are unknown.

Singh et al. reported results of a prospective study of 67 patients who underwent nucleoplasty for low back and/or leg pain due to a contained disc herniation and assessed patients for 12 months after the procedure was performed. Eighty percent of patients had improvements in pain at 12-month follow-up, 56% had greater than 50% relief of pain, and approximately 60% had improvements in functional status. Indices were comparably more favorable at the 3-month follow-up.[50] Sharps et al. reported another prospective analysis of 49 patients with back and/or leg pain due to focal lumbar disc protrusion who had failed to improve with 6 weeks of conservative nonsurgical therapy. VAS, analgesic use, return to work status, and patient satisfaction were measured at 1, 3, 6, and 12 months. Success, rated as a decline of 2 or more VAS points in the protocol, was found in 79% in the study group. At 12 months, the mean VAS was 4.3 versus a preprocedure mean baseline of 7.9.[52] In another prospective study of nucleoplasty, Mirzai et al. included 52 patients with leg pain and MRI results which confirmed a small contained herniation or disc bulge. Thirty-four patients underwent single-level nucleoplasty and 18 patients underwent two-level procedures. At 12 months, VAS dropped from an average of 7.5 to 2.1 and ODI dropped by 50%; 80% of patients were satisfied with their treatment. The authors recommended careful, strict selection of patients with radicular leg pain and small disc herniations to maximize results.[53] Yakovlev et al. reported results of nucleoplasty in 22 patients who were prospectively followed for 12 months after disc decompression. The VAS decreased by an average of 4 points at the 12-month follow-up, 63% of patients returned to work, and 73% decreased their medication use. Sixty-eight percent of patients had at least a 50% reduction in pain.[54,55] Calisaneller et al. reported prospective data on 29 patients who underwent 32 nucleoplasty procedures, with a 6-month follow-up. Only 52% of patients had greater than 50% reduction in pain at the 6-month follow-up, somewhat less than previous studies. Further, MRIs were done prior to and within 24 hours after nucleoplasty was performed and no significant change in disc anatomy or disc displacement following the decompression procedure was found.[56]

In a restrospective analysis by Al-Zain et al., 96 patients with discogenic LBP underwent nucleoplasty with 12-month follow-up data available for 67 patients.

Seventy-three percent of treated patients experienced an improvement of more than 50% in their symptoms in the early postoperative follow-up, but this was reduced to 61% of patients at 6-month follow-up and only 58% of patients at 1 year, but they reported a statistically significant reduction in analgesic consumption and disability following nucleoplasty.[57] In another retrospective nonrandomized analysis of nucleoplasty effect, Reddy et al.[51] reported data on 49 patients with either axial or radicular LBP who underwent nucleoplasty. Follow-up data ranged from less than 6 months to greater than 12 months. They reported a statistically significant improvement in pain scores following the procedure, with an average decrease in VAS of 3.7 at last follow-up.[55]

Very few complications of nucleoplasty have been reported in the literature. Sarjoo et al. assessed 53 consecutive patients for 2 weeks after nucleoplasty was performed. Fifteen percent of patients reported numbness and tingling into the lower extremity 2 weeks following the procedure, and 4% reported an increase in LBP, but no other significant side effects or complications were seen.[59] There is a single case report of perineural fibrosis following nucleoplasty, but symptoms resolved soon after the procedure.[60] Animal cadaveric studies confirmed no significant disc damage other than presence of channels within the disc after nucleoplasty, though no histologic study of surrounding neural tissue was performed.[61] Nau et al. performed nucleoplasty on human cadaveric discs and found transient peaks of 80° to 90° C intradiscally, and temperatures greater than 60° C in areas 3 to 4 mm distal to the introducer needle. This indicates potential for thermal injury to the bony end plates or injury to structures and tissues outside of the nucleus of the disc during the procedure.[62]

OTHER METHODS OF PERCUTANEOUS DISC DECOMPRESSION

Percutaneous disc decompression (PDD) can also be accomplished with a percutaneous disc probe (Dekompressor Stryker, Kalamazoo, MI). In contrast to nucleoplasty the Dekompressor probe *mechanically* removes nucleus pulposus material without RF energy or thermal heat. Disc material collects within a collection hub on this disposable device, and can be objectively measured or objectively analyzed microscopically.

No randomized controlled studies of this device have been published. In a study by Lierz et al., patients with radicular leg pain and a small contained disc bulge or herniation were treated via mechanical disc decompression. The average volume of disc material removed was 1.3 ml (range 0.3–2.3 ml). Patients were followed for total of 12 months. The average VAS score was 7.3 prior to treatment, but dropped to 2.1 at 12 months. There was a reduction in opiate use in 80% of patients and improved activities of daily living (ADLs) in 77% at 12 months. Overall patient satisfaction at 12 months was 77%. Patients who underwent two-level procedures had higher analgesic use, less improvement in ADLs and decreased

satisfaction as compared to patients who underwent single-level procedures. There was no relationship between volume of disc material removed and amount of improvement. The authors recommended single-level procedures and strict selection criteria for best outcomes.[63]

Amoretti et al. reported results of 50 patients who underwent PDD with the Dekompressor device. They found that in 80% of cases, results of pain relief were satisfactory. They found better treatment outcomes in cases of posterolateral or extraforaminal disc herniations and bulges when compared to paracentral disc herniations, indicating that strict selection criteria may improve outcomes.[64]

Few if any complications of this procedure have been published. A single case report of a broken retained intradiscal Dekompressor probe has been reported, necessitating surgical removal from the lumbar region under local anesthesia. No long-term complications were identified in this patient.[65]

In a review of the available literature, Singh et al. reported level III evidence for mechanical percutaneous disc decompression procedures with the Dekompressor device.[66]

In general, studies of other pecutaneous disc decompression procedures are of poor quality or are unrandomized. Based on the available literature for review, Singh et al. found the level of evidence for percutaneous lumbar laser discectomy (PLLD) at II-2 for short- and long-term relief of pain,[67] and Hirsch et al. found the evidence for automated percutaneous lumbar discectomy (APLD) at level II-2,[68] although no randomized controlled or large-scale prospective studies have been published on either technique.

CONCLUSION

Although there is a limited number of high-quality clinical trials of intradiscal procedures available in the literature, patients in prospective studies who meet strict selection criteria for these minimally invasive procedures appear to benefit with reduced pain, decreased analgesic requirements, and improved function. Further investigation is needed on the long-term clinical efficacy, as well as the effects of these procedures on the degeneration cascade of the intervertebral disc and the functional spinal unit.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 66

Osteoporosis, Vertebroplasty, and Kyphoplasty

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There are approximately 700,000 to 750,000 vertebral fractures each year in the United States. Up to 25% of those above 50 years of age will have at least one vertebral fracture in their lifetime and the lifetime risk of vertebral compression fractures in white women is 15.6%.[1,2] Vertebral compression fractures (VCFs) are caused by the inability of the vertebra to sustain internal stresses applied from normal daily load or trauma. The inability of the vertebra to maintain its structure is related to the constant change in its composition. The primary structure of bone is distinguished by cortical, or compact bone, and trabecular bone, otherwise known as cancellous and spongy bone. Cortical bone is generally on the surface and is characterized by its dense composition without cavities. Conversely, trabecular bone has many interconnecting cavities consisting of red blood cells and yellow bone marrow composed of fat cells. Trabecular bone, found in large supply in vertebral bodies, is largely responsible for the majority of the axial forces and inherited extra-axial stress and strains. The extent of the two types of bone varies depending on its location. Bone is also composed of osteoprogenitor cells, osteoblasts, osteoclasts, osteocytes, neurovascular progenitor cells of external origin, and an array of inorganic and organic constituents. In diseases such as osteoporosis, the architecture of trabecular bone becomes altered. In multiple myeloma, there is an imbalance of osteoclasts and osteoblasts (increased osteoclastic activity) that can cause lytic lesions in the absence of osteoporosis.

The majority of vertebral compression fractures are caused by osteoporosis, but other causes include multiple myeloma, metastatic tumor, and hemangiomas. According to Cooper et al., 16% of vertebral fractures are diagnosed radiographically when initial investigation was for another problem.[3] Diagnosis of vertebral fracture is difficult to assess compared to peripheral fractures. Decrease in height and vertebral deformities are indications of vertebral fractures. Most VCFs are asymptomatic, and there is no associated origin of injury.[4] However, when symptomatic, they can be debilitating to the point that any movement will cause severe pain. Most fractures will heal within a few months, but some have pain and disability that fail to respond to conservative therapy. Conservative therapy includes the use of back bracing, bed rest, and pain control with medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), calcitonin, and narcotics. There is no absolute time frame for length of conservative therapy, but adverse consequences such as deep venous thrombosis, pulmonary embolism, pneumonia, and accelerated bone loss can occur with prolonged bed rest.[5] Poor pain control can lead to chronic pain and central sensitization, which is more difficult to treat than acute pain. Other consequences of vertebral compression fractures are height loss and kyphosis.

Initial treatments for painful compression fractures that failed conservative therapies usually revolved around surgery,[6] but outcomes were variable secondary to inherent poor bone quality. Percutaneous vertebroplasty was first reported in 1987 by Deramond and Galibert for the treatment of painful hemangiomas.[7] They noted that injecting polymethylmethacrylate (PMMA) into the painful vertebral body provided significant pain relief. The procedure was then done in Europe for the treatment of pain related to multiple myeloma and metastatic neoplasms.[8] Eventually, the technique was introduced in the United States where its use has been for the treatment of osteoporotic compression fractures.[9] Kyphoplasty was introduced in 2000 to address the additional consequences with vertebral compression fractures that came along with pain (height loss and kyphosis).[10] It involved the addition of inserting and inflating a balloon in the vertebral body prior to cement to restore height and decrease kyphosis.

Both procedures are by radiologists, spine surgeons, anesthesiologists, and interventional pain specialists. Numerous case reports, case series, nonrandomized and unblinded prospective studies have suggested the efficacy of vertebral augmentation in the treatment of osteoporotic fractures, but two recent studies that were randomized, blinded, and placebo-controlled demonstrated no benefit of vertebroplasty over placebo. The data for the use of vertebral augmentation in other causes of painful compression fractures is also based on retrospective and nonrandomized comparative studies. Both methods appear to have a good safety profile.

In this chapter, we discuss the pathophysiology, diagnosis, prevention, and treatment of vertebral compression fractures.

OSTEOPOROSIS

Osteoporosis is the most common debilitating metabolic bone disease, and is marked by a reduction in bone mass per unit volume with normal bone chemical composition, decreased skeletal function, progressive spinal deformity, and vulnerability to fractures. Also dubbed "porous bone disease" or "brittle bone disease," osteoporosis is a universal disease with a common language of improper bone remodeling posing an array of complications.

Bone is a connective tissue that is responsible for hematopoiesis, mechanical and structural support, and mineral storage of inorganic salts and organic material. Bone is constantly broken down and architecturally rebuilt to provide optimal mechanical support for its various functions. If bone turnover, the breakdown and formation of new bone, is unbalanced, then progression of bone loss develops. However, peak bone mass is achieved at 35 years of age and is in decline thereafter; thus, bone loss is expected in adulthood

and consequently in old age. Although various other factors also contribute to progressive bone loss, an increase in bone resorption and a decrease in new bone formation are the hallmarks of osteoporosis. Characteristics of this disease follow:

- It affects more women than men, as women possess 10% to 25% less total bone mass at maturity.
- Caucasian and Asian women are at highest risk of developing an osteoporotic fracture due to low bone mineral density.[11–13]
- In the United States, 35% of women over age 65 years and 15% of Caucasian postmenopausal women are osteoporotic.[14]
- In the United States, this debilitating disease causes fractures in 1 million individuals per year with $14 billion spent for treatment.[15]
- Hip and vertebral fractures occur in women at a rate of 250,000 and 500,000 cases annually, respectively, and an additional 250,000 fractures are experienced by men every year.[16,17]
- Vertebral fractures in women increase as menopause approaches and old age, with a ratio of 2:1 compared to men.[3]

There are two types of osteoporosis, as noted by Riggs and Melton[18] (Table 66-1). The best indication of osteoporosis is low bone mass. However, a slew of secondary causes that affect bone mass must be excluded before rendering a diagnosis of primary, idiopathic, or iatrogenic osteoporosis (Table 66-2).[17] Iatrogenic osteoporosis is caused by prolonged corticosteroid administration, furosemide, thyroid supplements that suppress TSH production, anticonvulstants, heparin, lithium (by causing hyperparathyroidism), and cytotoxic agents.[17]

DIAGNOSIS AND INITIAL EVALUATION

- Medical evaluation requires thorough investigation of family and medical history as well as physical and gynecologic assessment.

TABLE 66–1 Types of Osteoporosis

Type I	Type II
Postmenopausal	Senile
Primarily trabecular bone	Primarily cortical bone
6:1 female to male ages 51–65	2:1 females to males of age ≥75 years
No calcium deficiency	Calcium deficiency, decreased vitamin D, and increased PTH activity
Estrogen deficiency	No estrogen deficiency
Vertebral and Colles' fractures prevalent	Pelvic, hip, proximal tibia, and proximal humerus prevalent
Risk factors: low calcium intake, low weight-bearing regimen, cigarette smoking, and excessive alcohol consumption	Related to low calcium intake

TABLE 66–2 Secondary Causes of Osteoporosis

Paget's disease
Malabsorption syndrome
Hyperparathyroidism
Multiple myeloma
Hyperthyroidism
Prolonged drug therapy
Osteomalacia hypogonadism

- Secondary causes or coexisting diseases may be the catalyst for or exacerbate bone loss.
- A complete blood cell count, serum chemistry group, and a urinalysis including a pH count should be carried out.
- Consider thyrotropin, a 24-hour urinary calcium excretion, erythrocyte sedimentation rate, parathyroid hormone and 25-hydroxyvitamin D concentrations, dexamethasone suppression, acid–base studies, serum or urine protein electrophoresis, bone biopsy and/or bone marrow examination, and an undecalcified iliac bone biopsy if suspected as the underlying cause.
- Dual-energy x-ray absorptiometry (DXA) to evaluate bone mineral density. Plain radiographs are an option, but changes are usually seen after 30% loss of bone mass.[14]

The American Association of Clinical Endocrinologists recommend the following categories receive routing screening by DXA[19]:

- All women 65 years and older
- Any adult with a history of fracture not caused by severe trauma
- Younger postmenopausal women with clinical risk factors for fracture

The Association recommends the lumbar spine (PA) and proximal femur as sites of measurement.

In 1994 the World Health Organization (WHO) established diagnostic criteria to designate the presence of osteoporosis based on DXA measurements.[20] Normal individuals possess a bone mineral density of one standard deviation (SD) of the mean of young adults. Osteopenia is indicated if the SD of bone mineral density is between 1.0 and 2.5 below the mean of a young adult population. If bone mineral density is measured 2.5 or more SDs below the mean of a young adult population, then osteoporosis is present. Furthermore, severe osteoporosis is denoted when one or more accompanying fragility fractures is present. Low body mass index has been associated with an increased likelihood of developing a fracture.[11–13] Based on these criteria, it is estimated that 38% of white females in their mid-seventies will have osteoporosis, and low bone mass will characterize 94% of that population.[2,21–23] These criteria were established by the WHO as a measure of the prevalence of osteoporosis and not intended as a guideline for a therapeutic course.

PREVENTION

Antiresorptive therapy and preventive measures are essential considerations in managing and preventing osteoporotic manifestations. An attempt to slow bone loss is of utmost concern. Bone mass is ever changing with peak levels obtained in the mid-thirties. Since more women are osteoporotic and are at greater risk for developing osteoporosis than men, various factors are at play that account for the variable rates in bone loss. Women lose 3% to 7% of BMD around the onset of menopause followed by a 1% to 2% decline yearly in the postmenopausal period. Men also lose bone with age, but at similar levels as postmenopausal women. Yet men seem to continue to increase the cortical surface by gaining cortical bone through periosteal deposition until age 75 years.[2,24] Numerous factors must be considered before administering an appropriate regimen of preventive and therapeutic measures to combat osteoporosis. Potential options follow:

- Calcium and vitamin D[25]
- Bisphosphonates[26-31]
- Calcitonin[32]
- Selective estrogen receptor modulators[33]
- Parathyroid hormone[34, 35]
- Sodium fluoride[36]
- Exercise[37–39]
- Modifiable risk factors such as cigarette smoking, excessive alcohol consumption, and treatment of potential secondary causes (Table 66-2)

PATHOPHYSIOLOGY

OSTEOPOROTIC FRACTURES

Osteoporotic fractures are more prone to occur at the hip, ribs, wrists, and vertebrae. In 1990, it was estimated that 1.66 million osteoporotic individuals worldwide suffered hip fractures. An increased risk of mortality exists among osteoporotic patients who experience a hip fracture with 25% of patients dying in the first year.[40–45] Of those who survive, 50% are unable to resume their previous independent lifestyle.[18] Such complications as pneumonia, blood clots in the lungs, and heart failure contribute to the complications of an osteoporotic hip fracture. Vertebral compression fractures (VCFs) can decrease height by up to 15 cm and result in the kyphotic deformity called "dowager's hump." VCFs in women result in 15% higher mortality compared to women with no disruption.[46] Furthermore, VCFs increase with age, affecting 40% of women in their eighties.[47]

Vertebral compression fractures occur due to the inability of the osteoporotic vertebra to sustain internal stresses applied by the vertebral load from daily life or from minor or major traumatic events. Trabecular bone is largely responsible for the majority of the axial forces and inherited extra-axial stress and strains. With the cascade of osteoporotic effects and aging, the architecture of trabecular bone becomes altered, characterized with increased spaces, thinness, disorientation, and weakened connectivity. Although trabecular bone network maintains both the horizontal and vertical framework, a decrease in density and loss of structural strength compromise the vertebra's mechanical prowess, integrity, and spinal column stability, predisposing it to trabecular buckling. Therefore, alteration of trabecular bone as seen in osteoporotic individuals and with age is accompanied with a decrease in bone density[48–51]and a propensity for fracture.[52,53]

Multiple VCFs develop a hyperkyphotic or "dowager's hump" at the thoracic level with a stooped posture decreasing abdominal and thoracic cavities. Multiple lumbar VCFs further increase lordosis, creating a protruding abdomen. A decrease in axial height is a result of reduction of intervertebral and vertebral loss of height. Also, developed stooped posture progresses to the point where ribs rest on the iliac crest with circumferential pachydermal skin folds developing at the pelvis and ribs. As this posture becomes more severe, eating is difficult and the patient eats less, feeling full and bloated. The cauda equina or spinal cord related symptoms are uncommon and are secondary to other conditions, such as Paget's disease, lymphoma, primary or metastatic bone tumors, myeloma, and infection.[54] When awakening, the abdomen appears normal, only to distend throughout the day. Nonrestorative sleep or trouble getting to sleep is often the case with patients. Lifestyle changes occur, such as difficulty driving a car, getting dressed, fear of large crowds, and depression. Self-esteem is also compromised as a result of a socially unacceptable body image.[55] After a second vertebral fracture, women report high levels of anxiety due to fear of future recurrences[56,57] and accompanying stress.[58,59] With time and continued osteoporotic problems, signs of depression develop in women.[57,60]

OTHER FRACTURES

Multiple myelomas are the most common primary malignant tumors of the bony spine that rarely affect the posterior elements.[61–63] These tumors are rare radiosensitive lesions occurring in 2 to 3 cases per 100,000. Diffuse multiple myeloma presents reoccurring lesions at previously radiated levels and offers a poor prognosis. Initially, patients report severe pain and disability and are unresponsive to drug treatment. The disease is usually multifocal in nature and surgical consolidation is not advantageous. In spite of this, single-level lesions are treated with vertebrectomy and strut grafting with some success. Nonetheless, radiation therapy alone or as an adjunct to surgery to address the painful manifestation of malignant lesion offers partial or complete pain relief in 90% of patients. However, this pain relief is delayed 10 to 14 days after initial radiotherapy.[64] Also, initiation of spine strengthening begins 2 to 4 months after initial radiotherapy.[64,65] Thus delayed reconstruction predisposes the spine to vertebral collapse and ensuing neural compromise. Vertebral augmentation offers an alternative route for immediate pain relief, bone strengthening, and mobility. Although vertebral augmentation goes some way to restoring the mechanical integrity of the vertebral body and provides a degree of pain relief, tumor growth is not prevented. Therefore radiotherapy accompanying augmentation is appropriate because it does not affect the properties of the bone cement, affects tumor growth, complements pain relief, and effects spine strengthening.[66]

Hemangiomas are benign bony spine lesions whose detection is difficult because of their asymptomatic disposition. Often, hemangiomas are detected during evaluation of back

pain and subsequent routine plain radiographs. Soft tissue extension of the lesion may compress the spinal cord and nerve roots producing neurologic symptoms and even produce epidural hemorrhage.[67,68] If extensive growth of the hemangioma transpires, vertebral integrity may be compensated, resulting in fracture with associated pain at the level of the lesion. Hemangioma aggressiveness is indicative upon clinical symptoms and radiological evaluation. Vertebral collapse, neural arch invasion, and soft tissue mass extensions are signs of the aggressive nature of hemangiomas and their candidacy for vertebral augmentation. Lymphomas and eosinophilic granulomas are also candidates for vertebral augmentation.

Approximately 10% of patients with metastatic tumor develop malignant lesions in the spine in the United States.[69] Ten percent to 15% of 120,000 new patients per year develop symptoms in the form of VCFs.[69] The most common location is the thoracic spine but all levels can be affected and usually more than one level is involved. Every kind of malignant cancer has been described to spread to the spine.[69]

INITIAL EVALUATION OF VERTEBRAL COMPRESSION FRACTURES

The most important aspect of patient evaluation begins with a good clinical history and physical exam. Most vertebral compression fractures (VCFs) are asymptomatic with unknown origin of injury.[4,70]

Patients with symptomatic VCF typically present with acute or subacute back pain with no associated major trauma or precipitating event. The sudden onset of pain is usually described as a moderate to severe, deep ache, at midline location, and exacerbated by any motion. More specifically, pain is experienced when standing from a seated position, bending, lifting, and prolonged sitting and/or standing. Walk is sluggish, but gait is normal. Coughing, sneezing, and bowel exertion exacerbate pain. A succession of VCFs could follow the first initial fracture with discontinued pain between each period of disruption or continually present. However, cluster VCFs have a string of fractures with severe and persistent pain. Pain may be relieved by recumbent positioning and bed rest.

Physical examination will usually find a patient in mild to severe distress depending on the the general conditioning of the patient as well as the location and type of fracture. There is usually tenderness at the site of fracture in the midline, but its absence does not rule out the presence of an unhealed fracture. Kyphosis may also be an important indicator of VCF as loss of more than 4 cm of height is associated with 15 degrees of kyphosis, but measurements of kyphosis are fraught with error.[4] Comprehensive musculoskeletal and neurological exam is imperative to rule out other causes of symptoms, especially myelopathy, radiculopathy, and spinal stenosis.

Diagnosis of VCF is difficult to assess compared to peripheral fractures. Decrease in height and vertebral deformities are indications of vertebral fractures. VCFs maintain an axis of rotation at the middle column. As a result, anterior column disruption is seen with intact middle and posterior columns. Since the neural arch remains intact, neurologic deficits are not as common. Bioconcave VCFs manifest as a central vertebral deformity as a crush fracture involves anterior, posterior, and central aspects. Wedge fractures are the most common VCFs, affecting anterior elements more often than posterior. Whatever the morphology VCFs adopt, fractures occur more often at the thoracolumbar and midthoracic region.[3,71,72] The tendency of VCFs to occur at these regions could possibly be attributed to alterations of stiffness from thoracic spine to the more mobile lumbar region and transitory curvature from kyphosis to lordosis.

Once there is suspicion of VCF or new-onset, moderate to severe back pain not explained by any other cause, radiographic imaging should be ordered. The simplest, most cost-effective initial study is a plain AP and lateral x-ray of the suspected area of the spine. However, if there is a high clinical index of suspicion, it is reasonable to proceed straight to magetic resonance imaging (MRI). MRI is useful in determining acute versus chronic fractures (edema on T2 weighted image) as well as determining any canal compromise or tumor presence. A hypointense T1 weighted image is also suggestive of edema (Fig. 66-1). Short tau inversion recovery (STIR) is a type of MRI that is used to suppress the hyperintensive image readings of substances such as fatty tissue and cerebrospinal fluid. STIR is the most sensitive imaging sequence for visualizing edema, and edema is highly predictive of success with vertebral augmentation (Fig. 66-2).

If MRI is contraindicated, then either bone scan or computed tomography (CT) scan may be useful in determining the acuity of the fracture. Acute or unhealed fractures will take up the injected 99mTc-MDP tracer in higher concentrations on bone scan. Thin-section (≤3 mm) CT is often used in conjunction with MRI reconstructions in order to derive the most accurate visualization of the target vertebral levels. CT has been cited specifically as the best modality for determining whether or not a fracture line has extended through the posterior wall of a vertebral body. CT can also see fracture cavities that should be the targets. Aiming the pedicle needle for fracture cavities increases the success rate. One can also assess size and trajectory of pedicles with 3D CT. In addition, certain fracture

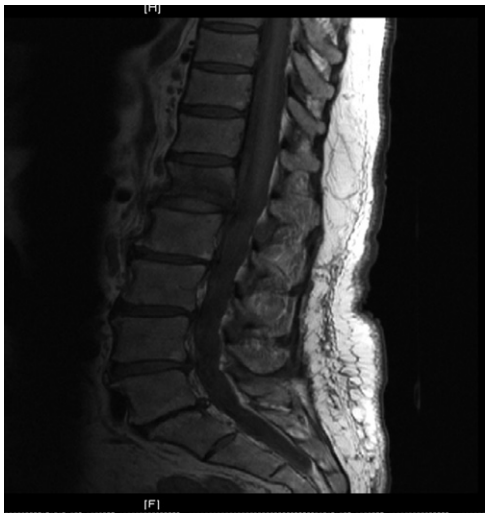


FIGURE 66-1 Sagittal MRI-hypointense lesion at L1 vertebral body on T1 weighted image suggesting acute fracture.

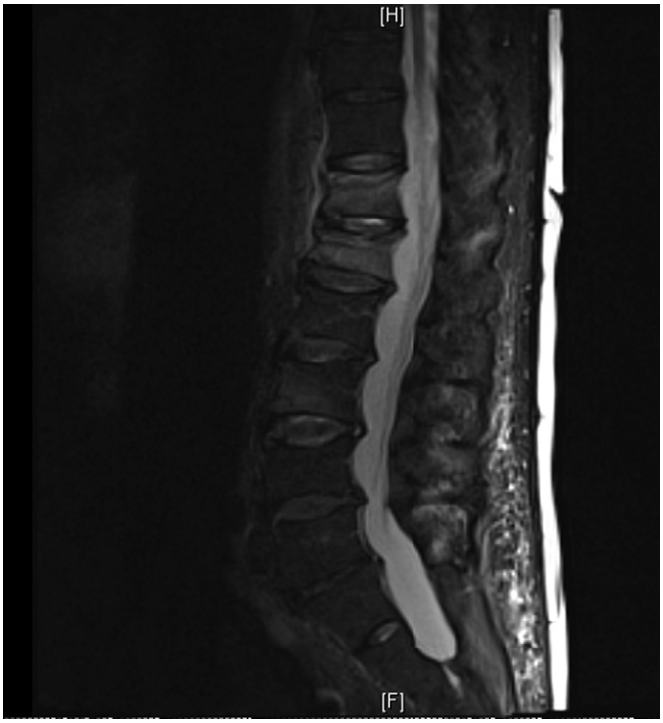


FIGURE 66-2 Sagittal STIR image of acute compression fracture at T12 and L12 with edema and fracture lines visible.

types may be less amenable to vertebral augmentation. This would include a "butterfly"-shaped fracture.

Comprehensive evaluation of the patient should also include other causes of VCFs as described in the osteoporosis section. These studies are listed in Table 66-3.

Once a determination is made that VCF is the cause of the patient's pain, steps should be taken to manage and keep the patient weight bearing and prevent functional decline. Approximately 2% to 10% of patients require hospital admission for pain control.[73–75] Initial modalities include walking aids and lumbar supports, but efficacy of lumbar supports has limited evidence and my cause more harm if used chronically.[76] Exercise programs have demonstrated decreased use of analgesics, improved quality of life and increased bone mineral density along with evidence that 1% of bone loss per year in the spine and hip is prevented or reversed.[77,78] Pharmacologic therapy includes NSAIDs[79] if tolerated, short- or long-acting opioids, and, possibly, calcitonin.[80] Acute pain from VCF can persist up to 12 weeks, while chronic pain is secondary to vertebral deformity, paraspinal muscle spasm, or degenerative arthritis in the region of the fracture. At any time point, if pain is uncontrolled to the extent that the patient cannot perform weight-bearing activities, or has side effects from analgesics, vertebral augmentation should be considered, assuming that proper workup is completed and the VCF is the source of pain. The exact time that interventional therapies should be pursued is controversial as some advocate immediate intervention, whereas others advocate 12 weeks for bone healing.

TABLE 66–3 Laboratory Investigations

Complete blood count
Serum calcium
Serum alkaline phosphatase
Serum creatinine
Urinary calcium excretion
Serum 25-hydroxyvitamin D
Serum protein electrophoresis
Sex steroids
Serum aminotransferase
Serum TSH

Note: Laboratory investigations should be correlated clinically; not all tests are required in all patients.

VERTEBRAL AUGMENTATION

Vertebral augmentation is a procedure that has an excellent safety profile IF it is done properly by experienced physicians who have had appropriate training. Minimum requirements for the procedure include:

- IV access and sedation; possibly general anesthesia.
- Image guidance—usually fluoroscopy, possibly computed tomography or both. Some practitioners advocate using a biplanar fluoroscope to always have an AP and lateral image. This is convenient and saves time, but is not necessary.
- Informed consent.
- IV antibiotic prophylaxis—cefazolin 1 g or clindamycin 600 mg—within 60 min of incision.
- Appropriately padded table for prone positioning.
- Sterile precautions.
- Appropriate bone biopsy needles with opacified PMMA.

Both vertebroplasy and kyphoplasty are similar in the beginning stages of the procedure with regards to local anesthetic and image-guided approach to the vertebral body. There are two different techniques in placing the 11- or 13-gauge needles: transpedicular and parapedicular. Proper placement with either method requires a thorough knowledge of fluoroscopic anatomy. In general, the augmentation of the lumbar and lower thoracic (below T10) spine is usually performed with a transpedicular approach, while the upper thoracic spine (above T8) is done with either route, but usually parapedicular.

Intravenous antibiotics should be given within 60 min of incision. Once the patient is in position and pressure points are padded, the C-arm is brought in to identify the proper level or levels to be augmented. This level is marked and the area is prepped and draped in usual sterile fashion. For the transpedicular approach, there are two methods that can be utilized and can be simply defined as the AP approach (maintaining visualization of the medial and lateral cortex of the pedicle) versus the en face approach (tunnel vision). Regardless of approach, an AP image is first obtained of the appropriate level. The endplates of that level are lined up as best as they can be, but may be difficult because of the deformity. If utilizing the en face approach, the C-arm is then angulated ipsilateral oblique to place the pedicle in the middle of the vertebral body. This may be difficult because of the deformity, in which case the AP method can be used.

For the AP approach, the target needle site is the superior and lateral portion of the pedicle, sometimes described as the 10 o'clock or 2 o'clock for the left and right pedicle on AP view, respectively. If utilizing the oblique view, then the needle should be placed in the center of the pedicle (Fig. 66-3). Local anesthetic is infiltrated intradermally and subcutaneously. A 22-gauge spinal needle is then advanced coaxially to the periosteum of the pedicle. Then 5 to 10 ml of either 2% lidocaine or 0.5% marcaine is injected at the periosteum and during withdrawal of the spinal needle to anesthetize the tract of the larger needle. Then, a small incision is made with an 11-blade scalpel. The needle is advanced to the pedicle in the tract of the spinal needle. After the needle is engaged into bone, either a screwdriver technique or gentle tapping with an orthopedic hammer is used to drive the needle into the pedicle with frequent imaging to confirm that the needle is within the pedicle (see Fig. 66-3C and D). Once properly engaged, an AP view is obtained to confirm that the medial cortex of the pedicle is not violated (Fig. 66-3E). A lateral image is then

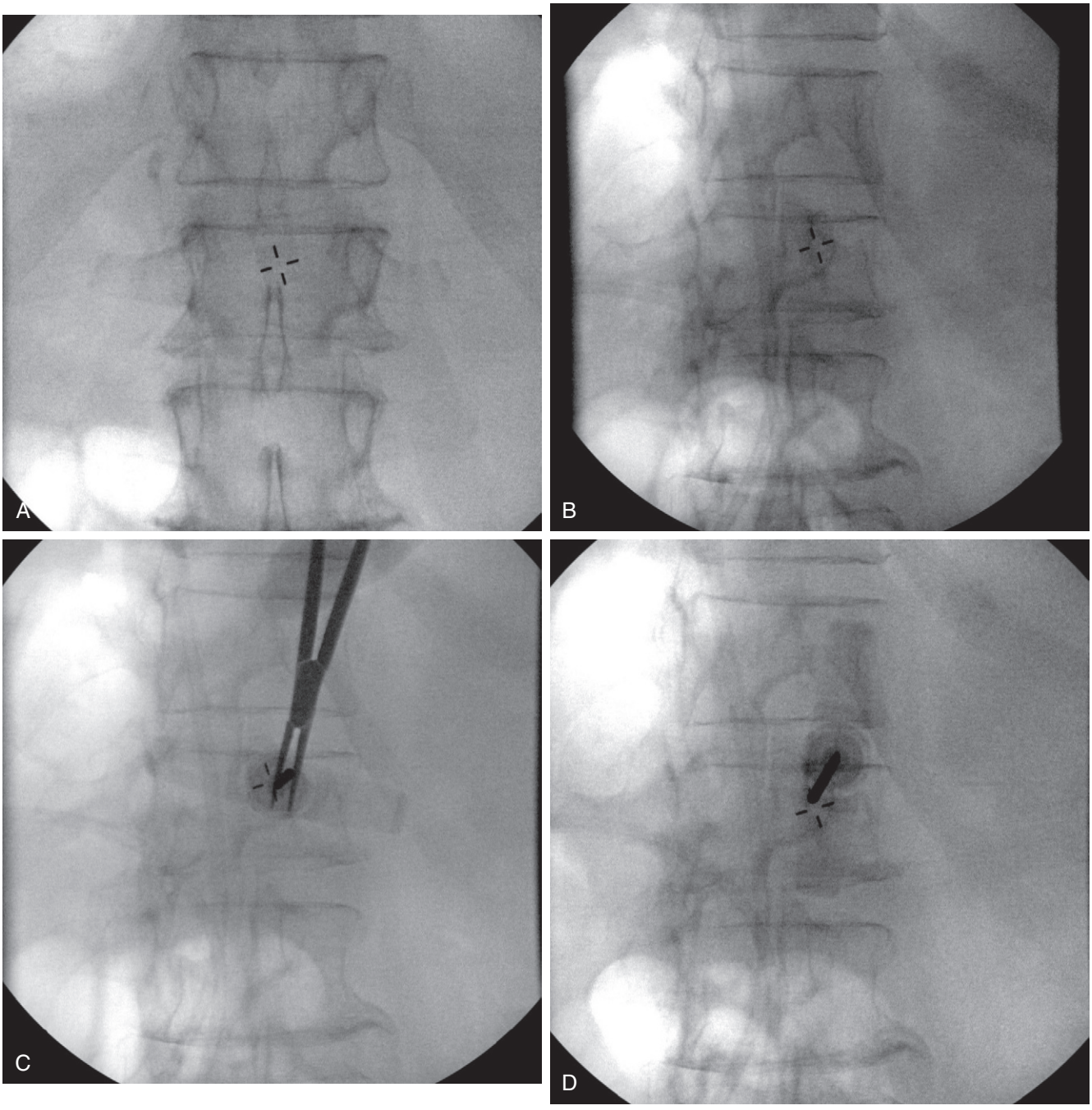
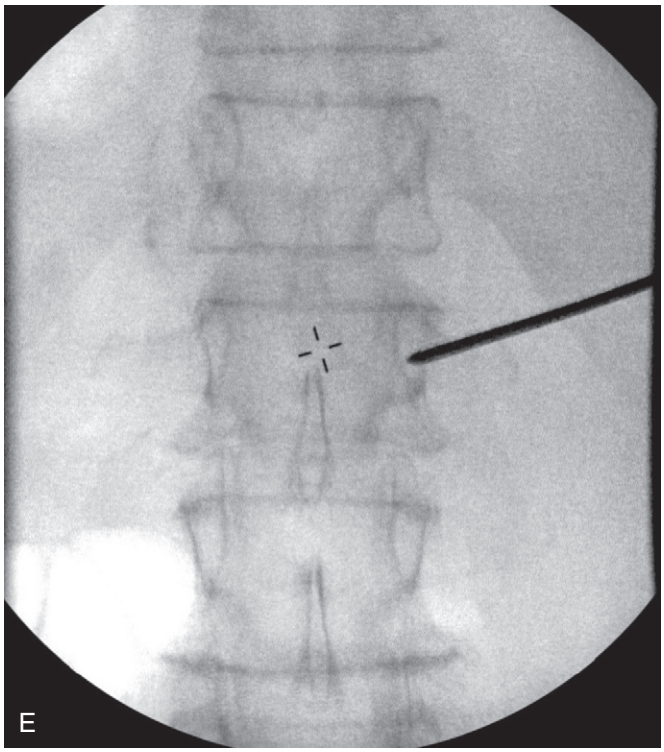
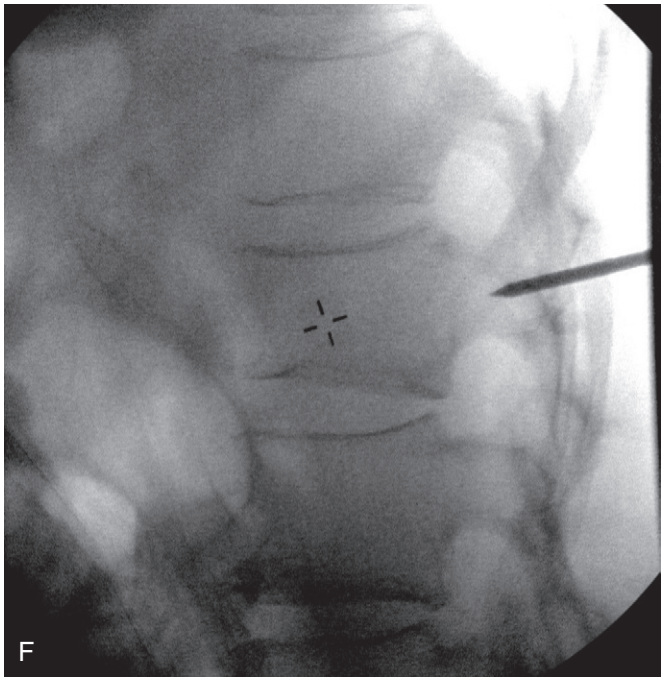


FIGURE 66-3 L1 osteoporotic compression fracture treated with percutaneous vertebroplasty. **A,** AP view of L1 compression fracture. **B,** Oblique view prior to needle placement for the en face or tunnel vision (en face) approach. **C,** Initial trochar or bone biopsy needle placement under oblique view. **D,** Needle engaged into pedicle.





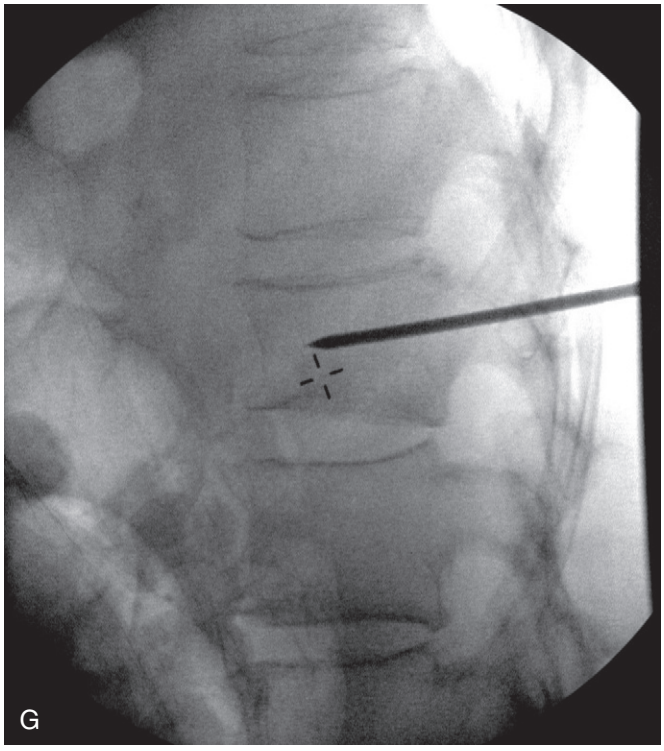


FIGURE 66-3, cont'd E, AP view to confirm that the needle has not passed the medial cortex of the pedicle. This image is important prior to advancing through the pedicle so avoid the spinal canal. **F,** Changed to lateral view to confirm placement of needle into pedicle. **G,** Advancing the needle into the anterior one-third of the vertebral body.

obtained to confirm that the needle is within the pedicle and not cephalad or caudal, in which case a disc or nerve foramen may be entered (Fig. 66-3F). For vertebroplasty, the needle is advanced into the anterior third of the vertebral body, while for kyphoplasty the needle is only advanced into the posterior third (Fig. 66-3G). Again, slow advancement and frequent imaging is recommended to avoid misplacement.

The parapedicular approach involves placing the needle lateral to the edge of the pedicle and advancing along the surface of the pedicle directly into the vertebral body. Initial needle placement is lateral to the lateral cortex of the pedicle. The vertebral body is entered the junction of the pedicle which will appear more anterior on lateral imaging. This method is useful when there is severe collapse leading to poor visualization of the pedicle. More

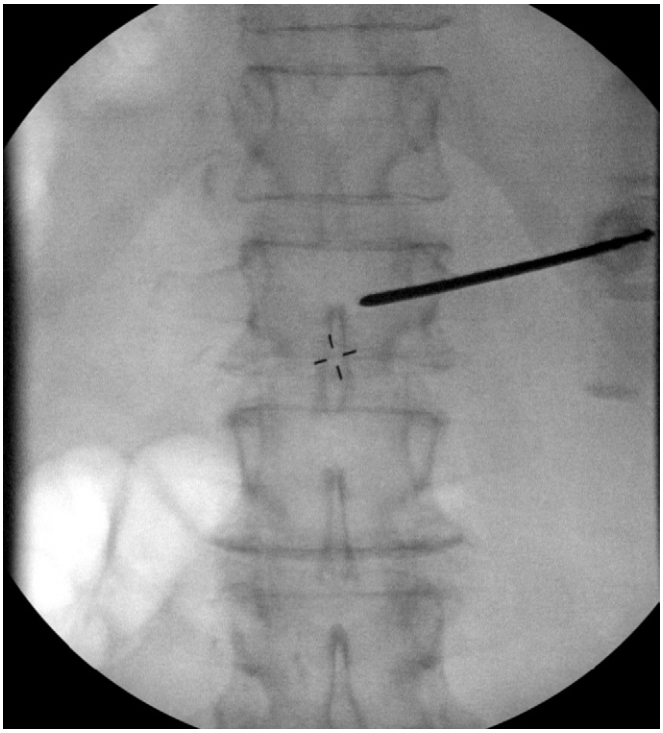


FIGURE 66-4 Confirmation of needle into the vertebral body.

medial placement of the needle in the vertebral body, and thus greater likelihood of a single needle placement, may occur with this approach. This approach may be preferred for treatment of compression fractures above T10 because of the smaller pedicle size.

Either one or two needle techniques may be utilized for vertebroplasty (Fig. 66-4). The goal of augmentation is to have filling of all of the fracture lines. There is no absolute with either approach, but the procedure can begin unilaterally and then be converted if the needle placement is in the lateral portion of the vertebral body, and bilateral filling is not likely to occur or after initial cement placement demonstrates inadequate spread to the contralateral side.

KYPHOPLASTY

As mentioned above, initial needle placement is similar to the vertebroplasty approach except that the needle is not advanced past the posterior one-third of the vertebral body. Also, the introducer system is slightly larger than the vertebroplasty needles. There are a few different options for cannula placement with regards to size and tip. The introducer has a beveled or diamond tip, which allows it to be gently hammered or manually pushed into the vertebral body (Fig. 66-5A). After entering the posterior aspect of the vertebral body, the introducer is removed leaving the cannula in place. A hand-operated drill is advanced to the anterior aspect of the vertebral body taking care not to violate the anterior margin on lateral imaging (Fig. 66-5B). Ideal placement on AP imaging is in the midline. The drill is then removed and the deflated balloon is advanced through the cannula into the cavity created by the drill. A second introducer and balloon should be placed on the opposite side in a similar fashion. Each balloon is attached to a locking syringe that has a digital manometer followed by slow inflation with iodinated contrast. Both manometry and fluoroscopy are used to monitor balloon inflation (Fig. 66-5C-F). Continue inflating the balloon until:

- Maximum pressure (up to 400 psi) or volume is reached.
- The balloon tamp reaches any cortical margin.
- Correction of the kyphotic deformity.
- The balloon is then deflated and removed.

PREPARATION OF POLYMETHYLMETHACRYLATE AND DELIVERY

Some advocate the performance of a venogram at this point to look for any potential venous uptake and potential cement embolization, but there is limited data to support this practice. There are various PMMA mixing and delivery options for both vertebroplasty and kyphoplasty. In general, the PMMA contains a sterile barium sulfate powder to provide radiographic opacity. The systems vary from a premixed powder that is combined with a liquid into a blender versus a spatula and a mixing bowl. After all ingredients are mixed, there is usually a 10- to 20-min working time that varies with the room temperature and formulation.

For vertebroplasty, a cannula from the cement mixer is connected to the needle and the cement is slowly injected under live fluoroscopy in the lateral position. Injection is stopped periodically with intermittent fluoroscopy during "rest" periods to ensure proper control of cement spread and avoid aberrant placement. Newer mixtures may allow for aspirating the cement back into the system. Injection is stopped when the posterior one-third or one-fourth or any other cortical margin is reached. If any margin is not intact, a small amount of cement can be injected to the edge of the margin followed by waiting a few minutes to allow the cement to harden and thus prevent further spread into unwanted areas. The volume of cement does not correlate to success and complete fill of the vertebral body is not required. If there is not midline spread of the cement, a second needle is placed on the opposite side and a similar injection of cement occurs. The stylet must be placed into the needle to complete the injection and not allow the cement in the lumen of the needle to track back in the needle which could cause cement leakage into neural foramen, spinal canal, or paraspinal muscles. The stylet is placed under live or intermittent fluoroscopy to visualize final spread of cement (Fig. 66-6A-D). For kyphoplasty, the cement has a slightly greater viscosity than the one used during vertebroplasty. PMMA is injected using a blunt cannula under live fluoroscopy. Injection is stopped when the cavities are filled along with any potential fracture line outside of the cavity (see Fig. 66-5E). The needle stylet should be replaced under live fluoroscopy to watch for cement extravasation.

After the cement is injected, the delivery system is removed and pressure is maintained on the incision sites. Sufficient time for the cement to harden must be allowed

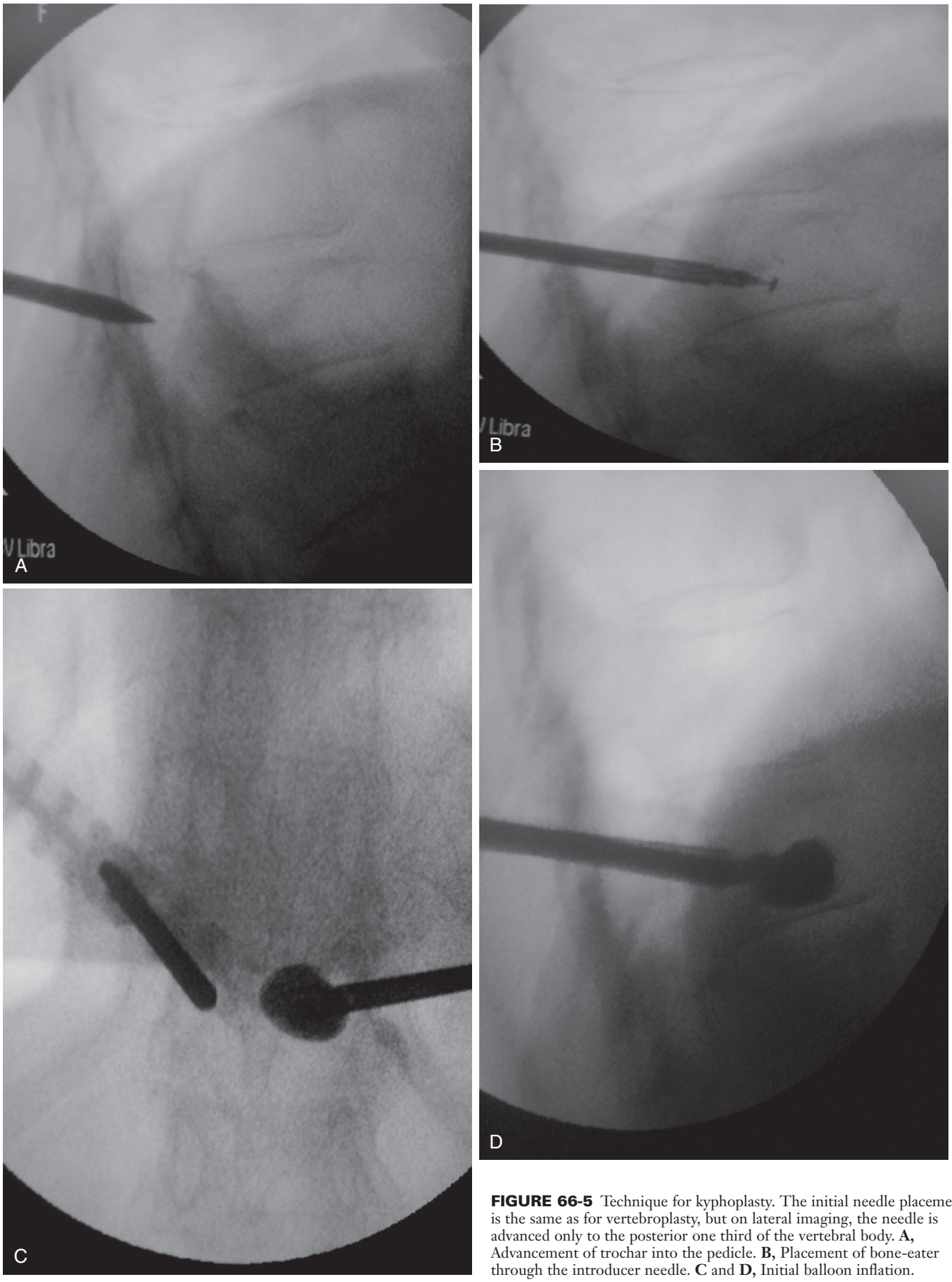


FIGURE 66-5 Technique for kyphoplasty. The initial needle placement is the same as for vertebroplasty, but on lateral imaging, the needle is advanced only to the posterior one third of the vertebral body. **A,** Advancement of trochar into the pedicle. **B,** Placement of bone-eater through the introducer needle. **C** and **D,** Initial balloon inflation.

Continued

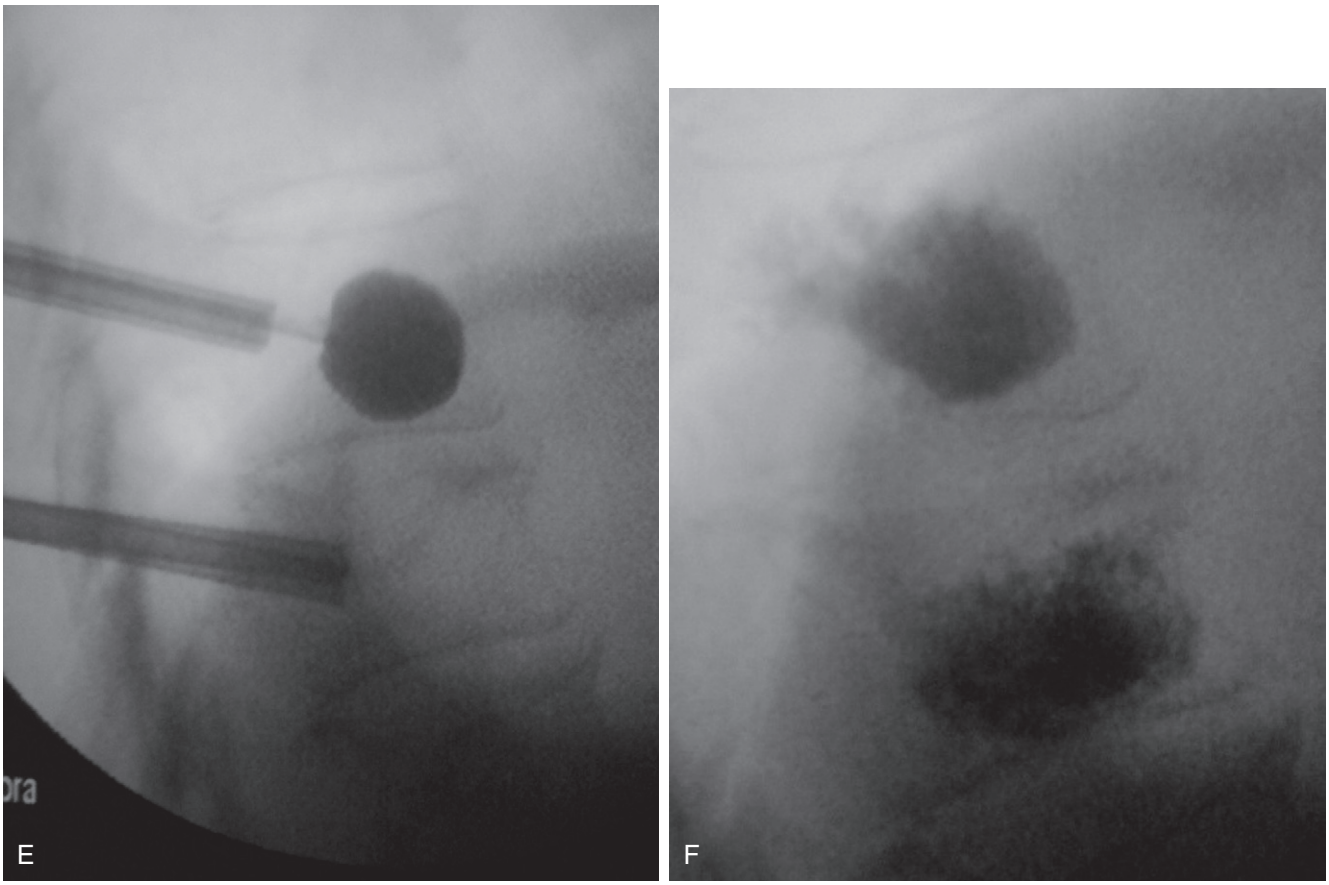


FIGURE 66-5, cont'd E, Final balloon inflation. F, Placement of cement after balloons are deflated and removed.

to prevent extravasation. Approximately 10 to 20 min should suffice, or, more objectively, place a small amount of the PMMA onto a gauze pad away from the patient with the understanding that polymerization occurs more rapidly with higher temperatures. Thus, if the cement is firm at room temperature, it is safe to assume that it is firm at body temperature.

CONTRAINDICATIONS AND COMPLICATIONS

The contraindications to vertebral augmentation have evolved and some are based on the potential complications that have been seen with either procedure. Contraindications for vertebral augmentation are similar to any neuraxial procedure (Table 66-4). The most common complication is cement leakage, but is reduced significantly with kyphoplasty (Table 66-5). One study reported that 3% of leaks in vertebroplasty were symptomatic compared to 0% with kyphoplasty.[81] Most of the leaks are clinically irrelevant and further treatment is not required. Other complications include the following[81–85]:

- Osteomyelitis
- Hematoma (paraspinal or epidural)
- Rib fracture
- Sternum fracture
- Adjacent vertebral fracture
- Pedicle fracture
- Pulmonary embolus of PMMA
- Hypotension
- Cord compression
- Epidural abscess
- Neurologic complications
- Allergic reaction to contrast or PMMA

All of the above complications are based on analysis of numerous case series. Some of the relative contraindications can be overcome with proper vigilance and technique, while most of the complications can be avoided with proper interpretation of pre- and peri-procedural imaging and patient preparation/selection. General anesthesia should be considered if the patient is unable to lay prone secondary to pain. Loss of vertebral height and severe compression fractures such as vertebra plana, gibbus, and H-shape were formerly absolute contraindications, but Peh et al.[86] retrospectively reported on 155 patients who underwent 310 vertebroplasties with any of the above fractures with good efficacy in eliminating or reducing pain in 97% of patients without any clinically significant complications. Previous surgeries and obesity may cause poor visualization of landmarks, while poor pulmonary status may not tolerate the usually asymptomatic PMMA emboli seen in 0.6% of patient who undergo vertebroplasty (0.01% in kyphoplasty). Underlying asymptomatic spinal stenosis may not tolerate any cement leakage into

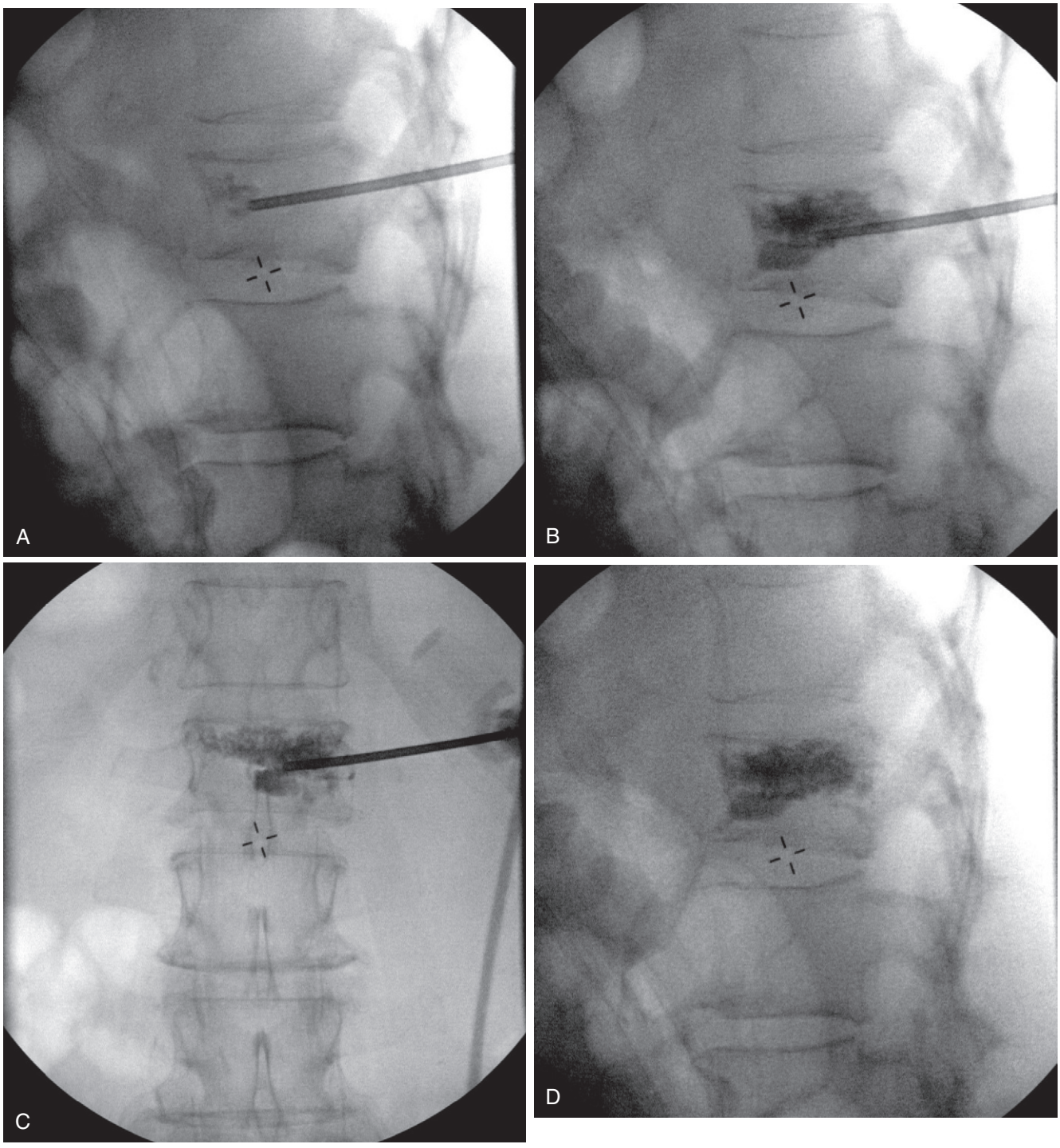


FIGURE 66-6 **A,** Initial injection of cement past the needle tip. This should be done slowly and under live fluoroscopy. **B,** Continued injection of cement noted both cephalad and caudad and posteriorly. Injection should be stopped here to avoid extravasation into the epidural space. **C,** Note bilateral spread of PMMA on AP image. **D,** Final image upon removal of needle. The stylet should be placed into the needle under live fluoroscopy as there is still cement in the needle. If the stylet is not placed, there is risk of tracking the cement into the pedicle and muscle. Keep the patient in this position to allow for the cement to harden. Each manufacturer has their guidelines on how long it takes for this to occur, but usually between 20-30 minutes from the time that the cement was mixed.

the epidural space. Surgical decompression may be required if there is any postprocedural neurologic compromise caused by bleeding or cement leakage into the epidural or foraminal space.

Adjacent vertebral fractures are a significant concern with vertebral augmentation. A vertebral compression fracture causes a focal kyphotic deformity that moves the center of gravity forward, which increases the load onto adjacent vertebrae. Kobayashi et al.[87] found that prophylactic injection of cement in adjacent, nonfractured vertebrae may prevent new compression fractures in osteoporotic patients. Oakland et al.[88,89] noted that under normal physiologic

TABLE 66–4 Contraindications to Vertebral Augmentation

Absolute	Relative
Uncorrectable coagulation disorders	Inability to lie prone
Allergy to PMMA or contrast	Loss of vertebral height ≥66% (vertebroplasty)
Spinal instability	Posterior wall destruction
Myelopathy	≥20% retropulsion with spinal stenosis
Pregnancy	Previous spinal stenosis
Active site infection or sepsis	Vertebra plana
Fractured pedicles	Gibbus
Burst fractures	H-shape
Young age	Multiple previous surgeries
Pain unrelated to fracture	Obesity
Solid tissue or osteoblastic tumor	Poor pulmonary status
	Greater than three compression fractures

TABLE 66–5 Cement Leakage in Vertebroplasty and Kyphoplasty

Location	Vertebroplasty	Kyphoplasty
Epidural	32.0%	11%
Paraspinal	32.5%	48%
Intradiscal	30.5%	38%
Pulmonary	1.7%	1.5%
Foraminal	3.3%	1.5%

Note: Overall incidence of leakage is 41% and 9%, respectively.

Source: Eskey CJ, Hirsch JA, Manchikanti L: Vertebroplasty and kyphoplasty. In Manchikanti L, Singh V, editors: Interventional techniques in chronic spinal pain, *Paducah, KY, 2007, ASIPP Publishing, pp 633–652.*

loads associated with moderate physical activity, there is little evidence to support prophylactic augmentation of adjacent vertebra. Eck et al.[82] performed a meta-analysis and found that vertebroplasty had a slightly higher, but statistically significant, rate of adjacent fracture than kyphoplasty (17.9% vs. 14.1%). Trout et al.[90] reported that there is a 4.62 times greater risk of developing a vertebral fracture adjacent to an augmented vertebrae with vertebroplasty than at a nonadjacent level. The risk of developing an additional VCF after an initial VCF secondary to osteoporosis is 4 times greater than the population with no VCF. Therefore the argument of whether vertebral augmentation predisposes the patient to additional VCF needs to be further studied and there is not enough evidence to support augmenting adjacent vertebra prophylactically.

EVIDENCE

There are two multicenter, randomized, double-blind, placebo-controlled trials to assess vertebroplasty in the treatment of painful osteoporotic vertebral fractures. There are no such studies for kyphoplasty, but there is one prospective, randomized, double-blind study for kyphoplasty that compared augmentation to conventional medical management.

Buchbinder et al.[91] studied 78 patients with 91% of participants following up at 6 months. Study enrollment began in 2004 and commenced in 2008, with goal follow-up of 2 years. They selected patients who had 12 months or less of back pain with the presence of one or two vertebral compression fractures of grade 1 or higher with edema and/or fracture line on MRI. A total of 468 patients were screened with 248 not meeting inclusion criteria and 141 (plus one death) not willing to participate. Of the 78 patients who met inclusion criteria, 38 underwent a vertebroplasty, while 40 underwent a sham procedure. The sham procedure involved the placement of a 13-gauge needle to the lamina, replacement of the sharp stylet with a blunt stylet, and, gentle tapping to simulate vertebroplasty. They also mixed the PMMA so that the smell permeated the room. All participants underwent basic testing as well as "up and go testing," which involved measuring the time required to rise from a standard arm chair, walk 3 m, turn around, return to chair, and sit down again. Subjects were also separated based on acuity of the fractures (less than 6 weeks vs. more than 6 weeks). Primary outcome was

TABLE 66–6 Summary of Advantages and Disadvantages of Kyphoplasty

Vertebroplasty	Advantages	Disadvantages
	Lower cost	42% cement extravasation
	Shorter procedure	Limited correction of lost vertebral Body height
	Decreases pain	Cannot correct sagittal imbalance
	Infrequent clinical sequelae due to cement extravasation	
	Often done under local anesthesia	
	Stabilize and strengthen vertebral body	
Kyphoplasty	**Advantages**	**Disadvantages**
	Lower cement extravasation	Increased cost
	Lower complication rate	Increased procedural time
	Equivalent pain relief	More likely to require general anesthesia
	Vertebral body height restoration	Usually requires overnight hospital stay
	Sagittal imbalance correction	
	Stabilize and strengthen vertebral body	

overall pain score measured on a scale of 0 to 10, while secondary outcomes included quality of life measures, pain at rest and pain in bed at night, and Roland-Morris Disability Questionnaires. Measurements were taken at 1 week, 1 month, 3 months, and 6 months. Mean pain reduction in the vertebroplasty and placebo groups was 2.6 (±2.9) and 1.9 (±3.3), respectively. The authors concluded that at 6 months, there was no beneficial effect of vertebroplasty over a sham procedure at any time point. The authors admit to a selection bias based on the fact that only 78 patients were enrolled while 141 declined to participate. Critics[92] of the study cite multiple additional flaws with the study:

- They note that patients did not require edema, only a fracture line on MRI even though they state that bone marrow edema indicates an acute fracture.
- Also questioned is the definition of "acute" being up to 1 year whereas most would define an acute fracture as 4 to 6 weeks.
- Sham procedure with local anesthetic at the facet joint.
- Primary outcome of pain as overall pain which may not be reflective of back pain because it is a report of overall body pain.
- No report of whether back pain was from fracture by percussing the spinous process systematically in order to find a level of maximal tenderness.
- Not reporting pain severity and functional compromise of the patients who met criteria but refused to enroll.

Kallmes et al.[93] studied 131 patients with one to three compression fractures that were less than 1 year old defined by onset of pain, pain score of at least 3 (0–10), and fractures of uncertain age underwent either an MRI or bone scan to assess for edema. Only the uncertain age of fracture underwent imaging and those who had edema were eligible for inclusion. A total of 1813 patients were screened with 300 patients who the fit criteria but declined to participate. Of the 131 patients enrolled, 68 underwent vertebroplasty and 63 underwent a sham procedure. The sham procedure involved placement of local anesthetic at the skin, subcutaneous tissues, and infiltration of the periosteum of the pedicles with 0.25% bupivicaine. Then, instead of placement of 11- or 13-gauge trochars, verbal and physical cues of pressure were given on the patient's back and the methylmethacrylate monomer was opened. Primary outcomes measured included modified Roland-Morris questionnaire (RDQ) and pain scores at various times over 1 year with the goal to evaluate the outcome at 1 month as the primary outcome. Secondary outcomes included scores on health status questionnaires, and physical and mental component summary of SF-36 version 2, as well as opioid use. At 1 month, the mean pain score of the vertebroplasty and control group were 3.9 (±2.9) and 4.6 (±3.0), respectively. The mean RDQ score was essentially the same for both groups. Forty-three percent of patients who underwent the control procedure crossed over to the vertebroplasty group while only 12% did the reverse (vertebroplasty to control). There was also no significant difference in any of the secondary outcome measures, but there was a trend toward meaningful improvement in pain in the vertebroplasty group compared to the control group (64% vs. 48%, respectively). The authors concluded that there was no significant difference at 1 month between the two groups. The authors cited limitations in their study:

- Crossover at 1 month complicating interpretation of data.
- Did not compare the study groups with respect to medical treatments received that might have affected outcomes.
- Persistence of pain after vertebroplasty or fracture healing may indicate causes of pain other than the fracture.
- Vertebroplasty may only be beneficial for fractures of a certain age or healing stage, which was not accounted for.
- Kyphoplasty was not evaluated.

Critics[92] of the study further cite the following weaknesses:

- Selection bias.
- Poor patient selection criteria by not requiring edema on MRI or bone scan for all patients.
- Not reporting pain severity and functional compromise of the patients who met criteria but refused to enroll.
- Sham procedure being a facet block instead of a dry needle approach.
- No report of whether back pain was from fracture by percussing the spinous process systematically in order to find a level of maximal tenderness.

The results of these studies were quite shocking to the "spine community" as those that have performed vertebral augmentation over the years have clinically seen profound relief of pain in those patients that had acute vertebral compression fractures and numerous large case series, prospective and retrospective, have demonstrated dramatic pain relief. What the studies most demonstrate is that there does need to be improvement in patient selection criteria for vertebral augmentation, and randomized, double-blind, placebo-controlled studies are very difficult to perform on patients in severe pain. Important physical examination findings along with imaging need to be included along with a comparison of the patients outcomes that fit criteria for inclusion but choose not to enroll in the study. This may further be assessed by the authors of the above studies to retrospectively review the patients who chose not to enroll in the above studies, but met inclusion criteria. Future studies should take this into account rather than jump to the conclusion that vertebral augmentation is not any better than placebo.

Taylor et al.[81] performed a systematic review and metaregression to compare the efficacy and safety of kyphoplasty and vertebroplasty for the treatment of vertebral compression fractures and to examine the prognostic factors that predict outcome. They reviewed studies that compared kyphoplasty to conventional medical therapy, vertebroplasty to conventional medical therapy, and vertebroplasty to kyphoplasty. Based on a total of 74 studies,

none of which were randomized, they concluded that there is level III evidence to support vertebral augmentation for osteoporotic fractures refractory to conventional medical therapy. There is a good ratio of benefit over harm for both procedures, with kyphoplasty having a better adverse event profile. They later followed up with a study that demonstrated that patients undergoing kyphoplasty experienced superior improvements in pain, functionality, vertebral height, and kyphotic angle at least up to 3 years after the procedure. They also concluded that there are prospective studies of low bias, with follow-up of 12 months or more, that demonstrate that kyphoplasty is more effective than conventional medical management of osteoporotic vertebral compression fractures and at least as effective as vertebroplasty.

Eck et al.[82] performed a meta-analysis to assess both pain relief and risk of complications associated with vertebroplasty versus kyphoplasty. They included 168 studies that met inclusion criteria. They concluded that vertebroplasty had a significantly greater improvement in visual analog scale (VAS) scores compared to kyphoplasty (mean VAS decrease 5.68 vs. 4.60, respectively), but also had a statistically greater risk of cement leakage and new fracture.

Wardlaw et al.[94] studied 300 patients with vertebral compression fractures by randomly assigning them to receive kyphoplasty or non-surgical care. They used the following inclusion criteria:

- 1-3 VCF from T5 to L5.
- At least one fracture with edema by MRI.
- At least one fracture with greater than 15% height loss.
- Single fractures had to meet both criteria.

The primary outcome was the change in SF-36 score from baseline to 1 month, which was noted to show a decrease in 7.2 points in the kyphoplasty group versus 5.2 points in the non-surgical group. They also noted no difference in frequency of adverse reactions between the groups and concluded that kyphoplasty is a safe and effective procedure for patients with acute VCFs. This is the only prospective, randomized, double-blind study for kyphoplasty with the only negative being that there is no placebo control.

Masala et al.[95] evaluated the efficacy and cost effectiveness of vertebroplasty by comparing 58 patients who accepted and underwent a vertebroplasty versus 95 who refused the procedure and underwent conservative medical therapy. They found that significant reduction in VAS and improvement in ambulation and activities of daily living were observed in both groups at 1 week, 3 months, and 12 months. The results were significantly superior in the vertebroplasty group at 1 week and 3 months and was more cost effective than conventional medical management with regards to VAS and activities of daily living at 1 week. By 3 months, vertebroplasty was more cost effective with regards to ambulation. However, no significant cost difference was noted at 12 months between the two groups.

Kyphoplasty has been touted to restore vertebral body height and restore sagittal alignment. There are only a few retrospective reviews that discuss this benefit. Kim et al.[96] concluded that balloon kyphoplasty after postural reduction and intraoperative kyphotic angle correction is well tolerated and effective for treating severe osteoporotic VCFs.

VERTEBRAL AUGMENTATION IN MULTIPLE MYELOMA AND METASTASES

Studies in patients with multiple myeloma and spinal metastases have also been completed. Fourney et al.[97] retrospectively reviewed 56 patients that underwent vertebroplasty or kyphoplasty (total of 97 procedures) for either myeloma or metastases. He reported complete pain relief in 84% and no change in 9% of procedures. No patient was worse and asymptomatic cement extravasations occurred in 9.2%. Significant improvement in pain scores was noted at 1 year and analgesic consumption was reduced after 1 month. Berenson et al.[98] randomly assigned 134 patients with a variety of cancers and three or less painful VCFs to receive immediate kyphoplasty (n = 70) or nonsurgical supportive care (n = 64). They excluded patients with primary bone tumors, osteoblastic tumors, or solitary plasmacytoma at the fracture site. Primary outcome measure was the Roland-Morris disability questionnaire at 1 month which was found to be significantly improved in the kyphoplasty group (–8.3) versus the nonsurgical care group (–0.1). Secondary measures included VAS scores which were also improved (–4.1 vs. –0.5). There was no significant difference in serious adverse reactions between the groups. The authors concluded that the improvements in disability and pain with kyphoplasty were both statistically and clinically significant without an increase in adverse reactions.

Pflugmacher et al.[99] found that the mean VAS and Oswestry Disability Index significantly improved in patients with lumbar or thoracic VCFs secondary to metastases that underwent balloon kyphoplasty. Sixty-five patients were prospectively followed over 24 months with sustained improvement in both scores noted. They also noted a 12% rate of cement leakage and 8% incidence of vertebral fracture. There were no symptomatic cement leaks.

Other retrospective reviews[100,101] have demonstrated positive results with vertebroplasty in spinal metastases and multiple myeloma with marked pain reduction and decrease in analgesic consumption along with minimal complications.

KEY POINTS

- Osteoporosis and VCFs are a significant public health concern with high morbidity.
- Vertebral augmentation is a safe and efficacious procedure for treatment of painful VCFs that fail conservative therapy.
- Proper technique and vigilance can help avoid serious complications and the procedure should only be performed by those trained and experienced with the procedure.

- Both kyphoplasty and vertebroplasty are efficacious for pain relief, but recent double-blind, placebo-controlled trials suggest that vertebroplasty is no more beneficial than placebo in osteoporotic VCFs.
- There is more evidence to support kyphoplasty in the treatment of multiple myeloma and spinal metastases related to VCFs, but vertebroplasty is also safe and efficacious.
- Patient selection via proper history, physical exam, and imaging is important to the success of vertebral augmentation.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 67

Ultrasound-Guided Sympathetic Blocks: Stellate Ganglion and Celiac Plexus Block

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Cervical sympathetic analgesic and neurolytic blockade were introduced in the mid-1930s. The method was originally described by Leriche, who advocated it for the treatment of angina. The technique was eventually refined by Findley and Patzer, and has remained largely unchanged since then.[1] It is commonly used in the diagnosis and management of sympathetically mediated pain and vascular insufficiency of the upper extremities. In addition, stellate ganglion block has been advocated for treatment of a variety of medical conditions, such as phantom pain, postherpetic neuralgia, cancer pain, cardiac arrhythmias, orofacial pain, and vascular headache.[2] Recently cervical sympathetic blockade has been suggested as an effective method for prevention and treatment of the cerebral vasospasm.[3]

STELLATE GANGLION BLOCKS

The stellate ganglion, also known as the cervicothoracic ganglion, represents a fusion of the inferior cervical and first thoracic ganglions of the sympathetic trunk. It can be found in about 80% of the population. Anatomy and position of the stellate ganglion have been investigated by dissection, magnetic resonance imaging, and computed tomography.[4–8] It is usually situated on the lateral border of the longus colli muscle anterior to the neck of first rib. It lies posterior to the vertebral vessels and is separated from the cervical pleura by the suprapleural membrane inferiorly. It measures 1 to 2.5 cm long, about 1 cm wide, and 0.5 cm thick, and may be fusiform, triangular, or globular.[7]

Although a C7 approach to stellate ganglion has been described,[9] the blockade is routinely performed at the C6 level according to the following anatomic landmarks: prominent anterior tubercle of the transverse process (Chassaignac's tubercle), cricoid cartilage, and carotid artery.[4] Given that only traversing sympathetic fibers or middle cervical ganglia can be found at the C6 level,[10] the procedure should more accurately be called the *cervical sympathetic block*. The middle cervical ganglion or traversing sympathetic fibers are located anterolaterally to the belly of the longus colli muscle.[10] Conceivably such a "convenient" position makes it easy to access the sympathetic chain for either diagnostic or therapeutic blockade.

Cervical sympathetic block is traditionally performed as a "blind" injection, though fluoroscopic guidance is now commonly used. Practitioners are typically taught to palpate Chassaignac's tubercle, to gently retract the carotid artery, and then to insert the needle paratracheally until it contacts a bone, presumably the lateral part of the vertebral body. The needle is then withdrawn by 1 to 5 mm, and a solution injected. This maneuver was presumed to be sufficient to position the needle outside the longus colli muscle, where the stellate ganglion is thought to be situated. However, this essentially "blind" paratracheal injection technique produces unreliable results, and is associated with a variety of side effects and complications such as intravascular injection, formation of hematomas, temporary paralysis of the recurrent laryngeal nerve, discitis, and esophageal injury.[2,11–15]

Narouse at al. further emphasized the risks of a blind approach,[14] pointing out that blind injection at the C6 level on the left side may cause inadvertent esophageal puncture, or may traverse the thyroid. Hematoma formation is likely related to damage to the inferior thyroid artery. Flouroscopic guidance reduces overall risk associate associated with the "blind" technique. It has the advantage of identifying bony anatomy, though the anatomic position of the cervical sympathetic trunk (CST) is confined to the soft tissues (longus colli muscle, thyroid, and esophagus) rather than the cervical vertebrae. Preliminary injection of a contrast agent assists in precise needle placement, though the contrast agent may show aberrant and inconsistent spread. Clearly, neither "blind" nor fluoroscopy-guided injection can ensure reliable results.

Injection of anesthetic at the C6 level has a long history and evolution, but the reliability of achieving blockade of the stellate ganglion was only recently tested. The success or failure of cervical sympathetic block is contingent on precise needle placement for delivery of the anesthetic, and is therefore entirely dependent on the anatomic location of the CST and the thickness of the longus colli muscle. Several clinical and cadaver trials have been performed in an attempt to elucidate the pattern of spread when solutions are injected at the C6 level.[8,16–19] The results of these studies have been conflicting, probably due to differences in study design: cadavers versus live subjects, low volume versus high volume of injectate, and computed tomography versus fluoroscopy control. The results of one cadaver study suggest that only deposition of solution into the prevertebral "interlaminar space" provides reliable spread to the stellate ganglion.[18] The cervical prevertebral fascia is attached to the base of the skull and extends over the prevertebral muscles (longus capitis, rectus capitis, and longus colli muscles) to attach distally at the T4 vertebra, just beyond the longus colli muscle. This positioning of the fascia forms a plane along which the injected fluid can flow.

Although some anatomic and imaging studies indicate a subfascial position,[10,19] textbooks relate the path of the CST to the suprafascial plane.[5,20] It is hoped that two recently published studies will put an end to this discussion. The first research utilized cadaver dissections and human MRI imaging and showed subfascial position of the stellate ganglion. This study described highly variable thickness of the longus colli muscle, which may lead to negative block

results.[21] The second study was designed as a step-to-step methodology validating of a new ultrasound-guided approach (described below); a subfascial position of the sympathetic trunk was discovered by three-dimensional (3D) ultrasonography and confirmed at cadaver dissections. In addition, this study measured thickness of the longus colli muscle at the C6 level, and proved that the muscle is 2 to 10 times thicker than was previously suggested in the regional anesthesia literature. As such, routine injection by the traditional method would have resulted in the intramuscular injection, and the CST will be anesthetized only by overflow or diffusion of the injectate.[22]

Ultrasound guidance is a logical solution to ensure accurate injection when soft tissues are involved. Clear imaging of the muscles, fasciae, blood vessels, viscera, and bone surface makes ultrasonography superior to fluoroscopy for image-guided CST block. In 1995, Kapral et al.[13] described an ultrasound-guided technique and published a case series. Compared with blind injection, these authors found that ultrasound-guided stellate ganglion block used a smaller quantity of local anesthetic (5 ml rather than 8 ml), was not associated with formation of a hematoma (whereas three patients in the blind injection group had a hematoma), and was associated with more rapid onset of Horner's syndrome. However, because tissue visualization was probably not feasible below the C7 level, the authors concluded that a local anesthetic depot was limited to the C4–C7 levels and speculated that the upper extremity sympathetic blockade was not related to blockade of the stellate ganglion per se. Their findings agreed with those published by Hogan et al.,[7] but these observations and conclusions have been refuted by Gofeld et al.,[22] who observed the contrast agent spread between the C4 and T1 levels in all patients ($n = 10$), occasionally reaching the T2 level.

Shibata et al.[23] was the first who suggested that subfascial injection would result in better spread of the injectate and more reliable sympathetic blockade; however, the published image in that study was more consistent with the intramuscular injection. Such injection can be a limiting factor in the onset and spread of blockade. A recently published study[22] confirms that injection of 5 ml of local anesthetic beneath the fascia but above the longus colli muscle ensures reliable spread of the solution to the stellate ganglion.

TECHNIQUE

There are two ultrasound-guided approaches to the cervical sympathetic trunk: the modified "anterior" paratracheal out-of-plane approach, and the newer "lateral" in-plane method. Both techniques can be performed using either low-frequency curvilinear or high-frequency linear ultrasound transducers. Low-frequency sonography provides better visualization of the surrounding structures and facilitates needle entry planning, while high frequency gives better resolution of pertinent anatomy and fascial planes.

ANTERIOR APPROACH

The patient is placed in the supine position. A pillow can be placed under the lower neck to achieve some extension. The head may be slightly rotated contralaterally to the injection side increasing distance between the carotid artery and the trachea and improving sonographic view. After skin preparation and dressing, sterile ultrasonic gel is applied. A transducer is covered by a sterile adhesive transparent dressing or sleeve. Ultrasonography of the anterior neck is performed with initial transducer placement at the level of the cricoid cartilage, anterior to the sternocleidomastoid muscle. Short-axis ultrasonography reveals the typical appearance of the C6 transverse process—the prominent anterior tubercle, the short posterior tubercle, and the exiting C6 nerve root (Fig. 67-1). Scanning caudally and dorsally brings the C7 transverse process into the view. The C7 transverse process has no anterior tubercle. The C7 nerve root is situated just anterior to the posterior tubercle (Fig. 67-2). At the C6 level, the longus colli muscle is seen as an oval structure adjacent to the base of the transverse process and vertebral body (see Fig. 67-1). Sometimes the caudal portion of the longus capitis muscle could be seen as well. The CST is visualized as a spindle-shaped structure (the midcervical ganglion), and typically situated on the posterolateral surface of the longus colli muscle; if the CST cannot be identified, some widening of the tissue plane below the prevertebral fascia can usually be seen. Once the correct level for injection is localized, surrounding anatomical structures should be identified and feasibility of the "anterior" approach is determined.

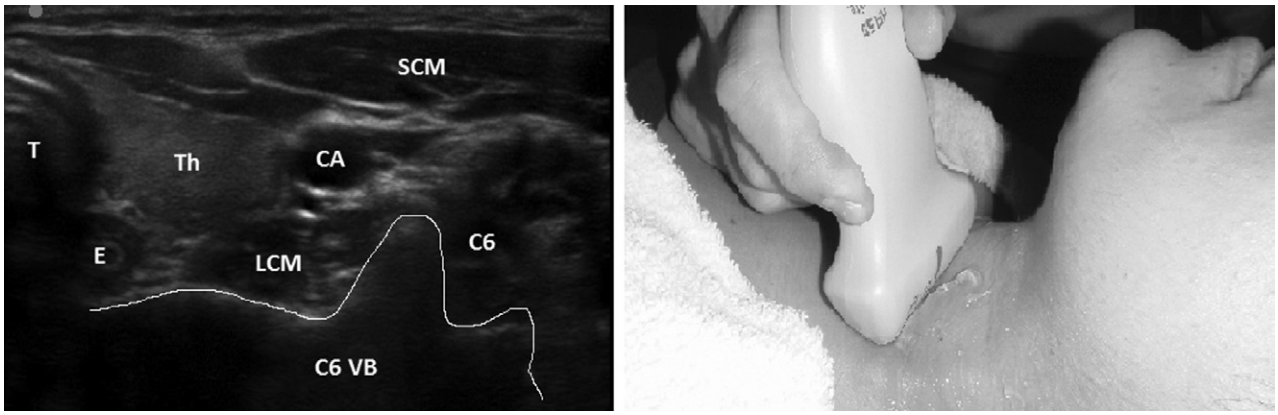

FIGURE 67-1 Linear transducer positioned at cricoid cartilage level (*right*); sonogram of anterior neck (*left*). T, trachea; E, esophagus; Th, thyroid; CA, carotid artery; SCM, sternocleidomastoid muscle; LCM, longus colli muscle; C6, exiting C6 nerve root; C6 VB, C6 vertebral body; *white line*, contours of C6 vertebra.

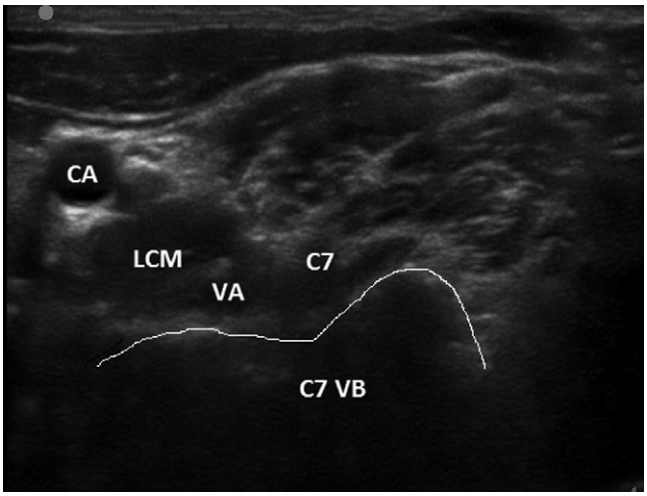

FIGURE 67-2 Sonogram at C7 vertebral level. CA, carotid artery; VA, vertebral artery; LCM, longus colli muscle; C7, exiting C7 nerve root; C7 VB, C7 vetebral body; *white line*, contours of C7 vertebra.

Often the distance flanked by the carotid artery and the trachea is wide enough and, therefore, only thyroid tissue and superficial neck muscles are seen between the needle entry to the surface of the longus colli muscle. Gentle pressure may actually decrease the skin-to-target distance and further separate the carotid artery from the trachea. Additional scanning should be performed to confirm that the inferior thyroid artery is not seen immediately caudad. The injection is performed as a short-axis out-off-plane approach (Fig. 67-3). The skin is anesthetized immediately caudad to the transducer. The injection is performed using a spinal needle (22–25 gauge and 2–3.5 inches long) with a three-way stopcock and extension tubing connecting two syringes, one with NaCl 0.9% and one with local anesthetic. The needle is inserted under continuous ultrasound guidance, directed to the anterior surface of the longus colli muscle using a short-axis out-of-plane approach. When the needle tip is visualized, either directly or indirectly (tissue movement) as approaching the target, 1 to 2 ml of saline is injected to confirm placement of the needle under the prevertebral fascia, facilitating clear separation of the tissue planes (Fig. 67-4). If the injectate is observed above the fascia or within the muscle, the needle must be carefully repositioned. If the spread is appropriate, 5 ml of local anesthetic is injected, and the needle is withdrawn.

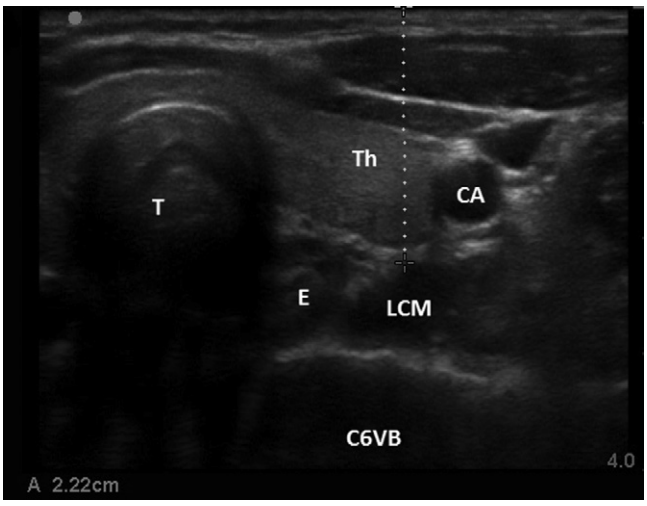

FIGURE 67-3 Sonogram of anterior neck obtained with gentle transducer pressure. T, trachea; E, esophagus; Th, thyroid; CA, carotid artery; LCM, longus colli muscle; C6 VB, C6 vertebral body; *white dotted line*, skin to target distance (2.2 cm).

Note: The "anterior" approach should be abandoned and an alternative "lateral" approach should be attempted if any of the following conditions are present: the anterior sonogram shows narrow distance between the carotid artery and the thyroid, the serpentine inferior thyroid artery cannot be eliminated from view, the esophagus is seen above the longus colli muscle (left side), or thyroid cysts are present.

LATERAL APPROACH

The patient is placed in the lateral decubitus position, with the side to be treated uppermost. Preparation and ultrasonography is performed as previously described. However, the transducer is centered at the C6 transverse process and not at the anterior neck. It is of utmost importance to localize the C6 nerve root and the anterior process. With the transducer placed as shown in Figure 67-5, only the anterior tubercle of the C6 transverse process is visible adjacent to the projected entry point of the needle, and no visceral or neural elements between the entry site and the anterolateral surface of the longus colli muscle. The needle tract should be entirely intramuscular, passing through the sternocleidomastoid muscle, the anterior scalene muscle, or both. Occasionally the internal jugular vein is seen within the projected needle tract, but it can be readily collapsed by light pressure on the transducer.

Skin anesthesia is performed immediately posterior to the ultrasound transducer. Under continuous ultrasound guidance, the previously described needle is inserted using the short-axis in-plane technique (Fig. 67-6). The advantage of the lateral approach, in addition to avoiding the trespass through the thyroid, is in the totally controllable visible progression of the needle from the skin entry point to the target. Verification of the needle position and the rest of the procedure are the same as in the anterior approach (Fig. 67-7).

Injection of 5 ml of a local anesthetic typically results in C3–T1 prevertebral spread and the complete blockade of the cervical sympathetic trunk and the stellate ganglion (Fig. 67-8). If anesthetic blockade of the upper cervical ganglion is not desirable it will be prudent to limit volume of the injectate to 3 ml.

Visualization of the soft tissue, vessels, and cervical sympathetic ganglia makes ultrasound imaging guidance superior to fluoroscopy. Subfascial injection of 5 ml of an injectate reliably produces cervical sympathetic blockade. Ultrasound guidance may prevent complications and adverse outcomes associated with either blind or fluoroscopy-guided techniques.

VISCERAL BLOCKS

One of the commonest causes for morbidity in the general population is chronic visceral pain. Major causes for visceral pain include functional gastrointestinal disorders, visceral malignancies, and chronic pancreatitis. Management options available for these painful conditions are both

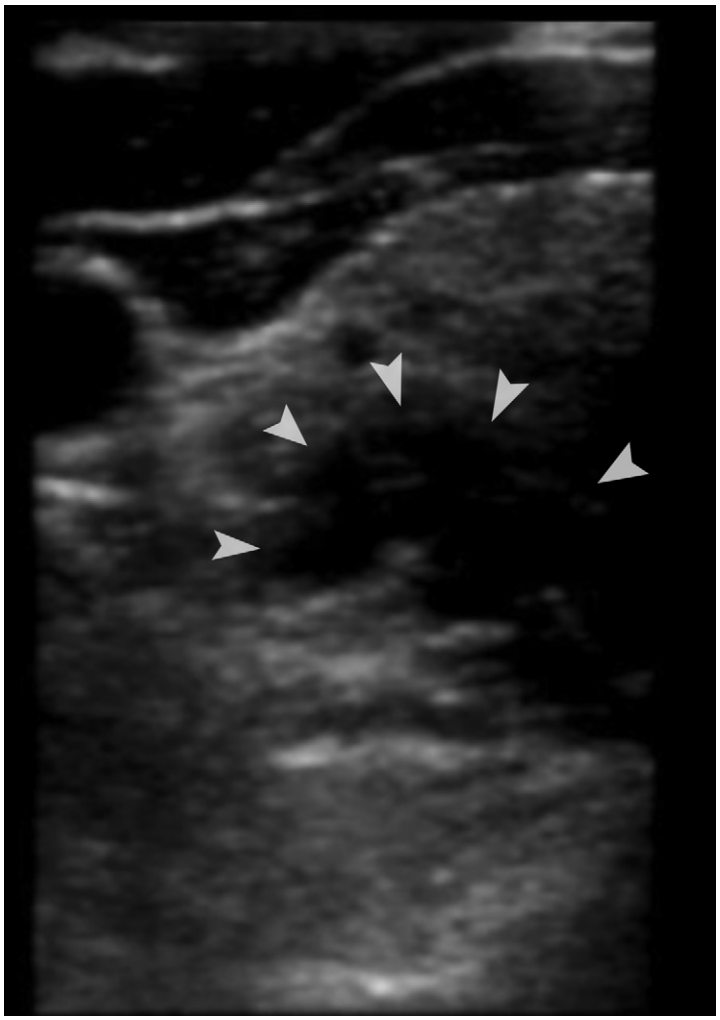

FIGURE 67-4 Needle tip (*circle*) positioned under prevertebral fascia with local anesthetic injected (*arrow heads*). The longus colli muscle is compressed by the injectate and appears "hyperechoic."

pharmacologic and interventional. Chronic visceral pain secondary to cancers of the pancreas, stomach, duodenum, proximal small bowel, besides metastatic tumors in the lymph nodes in this area may be amenable to celiac plexus block (CPB). There are also reports of CPB providing benefit in chronic pancreatitis pain.[24,25] The most commonly studied painful condition ameliorated with neurolytic CPB is pancreatic cancer. Approximately 75% of pancreatic cancer patients suffer from moderate to severe pain, contributing to a significant effect on physical functioning and quality of life. Neurolytic CPB complements medical management. This section will review the anatomy, evidence, and techniques for the performance of CPB specifically focusing on percutaneous ultrasound guidance technique.

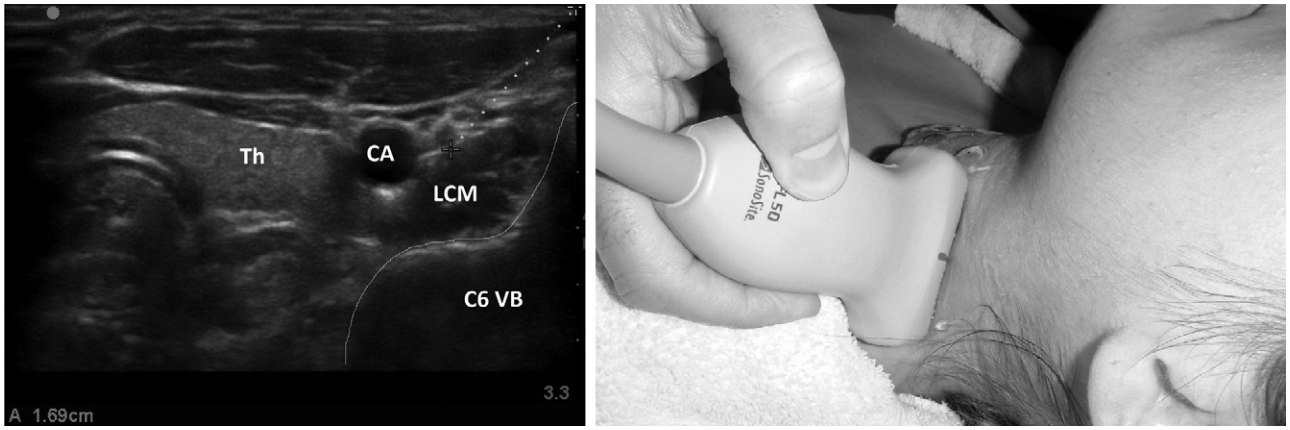

FIGURE 67-5 Linear transducer positioned at C6 vertebral level (*right*), with needle entry point marked; sonogram of anterolateral neck (*left*). Th, thyroid; CA, carotid artery; LCM, longus colli muscle; C6 VB, C6 vertebral body; *white dotted line*, skin to target distance (1.69 cm).

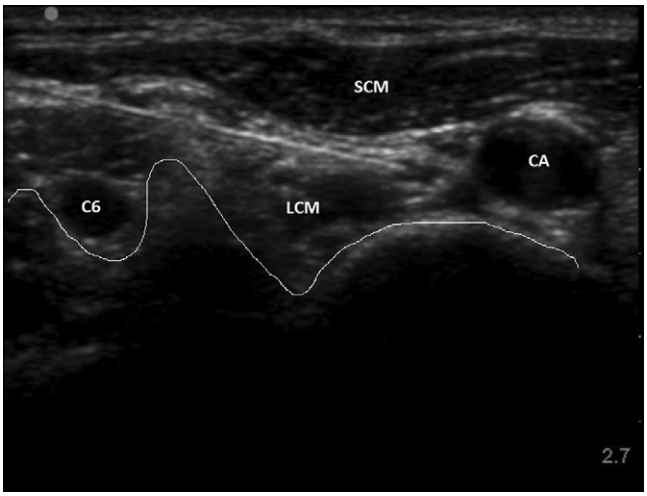

FIGURE 67-6 Sonogram of anterolateral neck with needle positioned under prevertebral fascia. CA, carotid artery; SCM, sternocleidomastoid muscle; LCM, longus colli muscle; C6, existing C6 nerve root; *white line*, contours of C6 vertebra.

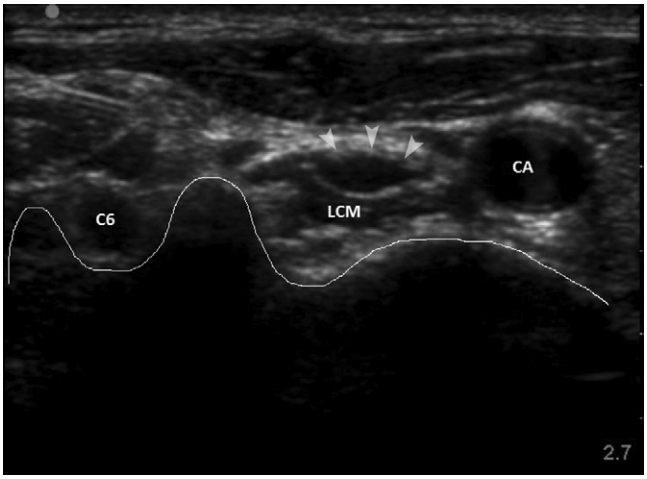

FIGURE 67-7 Sonogram of anterolateral neck with local anesthetic injected (*arrowheads*) under prevertebral fascia. CA, carotid artery; LCM, longus colli muscle; C6, existing C6 nerve root; *white line*, contours of C6 vertebra.

ULTRASOUND-GUIDED CELIAC PLEXUS BLOCK

CLINICALLY RELEVANT ANATOMY

Located approximately at the level of the 12th thoracic and/or first lumbar vertebra, the celiac plexus is composed of two to five celiac ganglia with its network of nerve fibers. The plexus surrounds the celiac trunk and the superior mesenteric artery at its root). It is located in front of the aorta and the crura of the diaphragm, and posterior to the stomach and omental bursa. The presynaptic sympathetic fibers to the plexus are provided by the greater, lesser, and least splanchnic nerves which originate from the paravertebral sympathetic ganglia T5 to T12. The plexus in turn supplies the various abdominal viscera through multiple smaller plexuses and nerve fibers accompanying the arteries. In addition, the plexus also receives

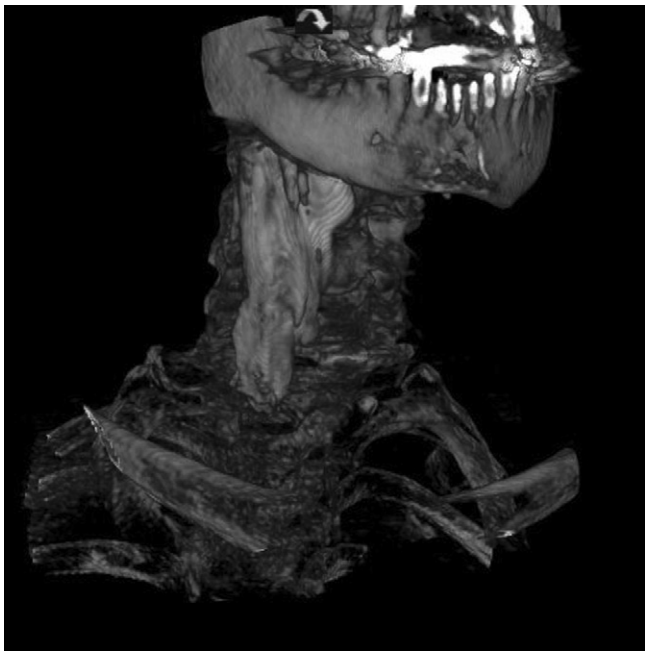

FIGURE 67-8 CT reconstruction shows typical spread of 5 mL of injectate between C2 to T1 levels.

parasympathetic supply from the vagus. The various structures supplied include the diaphragm, liver, stomach, spleen, suprarenal glands, kidneys, the ovaries and testis, the small intestine, and the colon up to the splenic flexure. The celiac plexus also sends branches to the superior and inferior mesenteric plexuses.

INDICATIONS

Neurolytic CPB may provide relief of pain originating from tumors of the stomach, liver, pancreas, spleen, and proximal small bowel beside adrenals. CPB has also been attempted for relief from chronic pancreatitis pain and during biliary interventions.[24–26]

AVAILABLE TECHNIQUES AND APPROACHES

Landmark-based percutaneous CPBs were introduced by Kappis in 1919. With the introduction of fluoroscopy, compute tomography (CT), sonography, and magnetic resonance imaging (MRI), the need for imaging for the safe conduct of CPB became obvious, although there is presently no study comparing the different imaging modalities.[27–29] The various techniques include endoscopic transduodenal ultrasonography-guided CPB, intraoperative CPB, and percutaneous CPB. Anterior and posterior approaches to the plexus have been described.[30] Anterior approach is used intraoperatively, during percutaneous and endoscopic ultrasound-guided CPB. Fluoroscopic, MRI, and landmark-based injections approach the CPB posteriorly. CT-guided CPB may be performed through an anterior or posterior approach, although the posterior approach is commonly preferred. Fluoroscopy and CT carry the risk of increased radiation exposure to the patient and personnel. CT may provide finer details about the plexus, celiac artery, and neighboring structures for

improved safety and better targeting. Fluoroscopy may fail to visualize the soft tissues, posing the hazard of soft tissue damage. CT and MRI require equipment that is costly, not portable, and occupies a lot of space, precluding their utility at the patient's bedside. Open MRI has been used with 57% success for CPB, but may not be completely real time.[31]

Endoscopic ultrasound-guided CPB has been safely performed with clear visualization of the ganglia, but requires the use of other equipment and has its complications and side effects. Endoscopic CPB may be more cost-effective when compared to CT-guided CPB.[25] Percutaneous sonographic guidance has been used successfully for CPB for many years. Ultrasound-guided percutaneous CPB has several advantages. It is low cost, portable, may be performed at the bedside, and lacks the risk of radiation. In addition, the supine position is more comfortable to the patient. It may also avoid entry into the kidney or spinal cord, and the abdominal aorta, the celiac trunk, and the superior mesenteric artery are clearly visualized. It permits real-time visualization of the injectate spread. The disadvantages include poor visualization of deeper structures, including the pancreas, and the interference of the air in the intestinal loops. Similar to CT guidance, it may cause perforation of the stomach, intestine, pancreas, or liver.

A variety of techniques and approaches are described in the literature, including retrocrural, antecrural, transcrural, transdiscal, transaortic, and splanchnicectomy, in addition to single-needle and two-needle techniques.[32–38] Each technique has its proponents and opponents claiming advantages and disadvantages. The cancer spread as seen on CT may sometimes dictate the approach.[39]

Neurolytic CPB is usually performed with either phenol 6% to 10% or alcohol 50% to 100% following a diagnostic local anesthetic injection despite low negative predictive value of the diagnostic block.[40,41]

EVIDENCE FOR THE USE OF CPB

Neurolytic CPB has been shown to be effective in ameliorating pancreatic cancer pain in up to 20% of patients; when combined with other modalities, it is effective in providing substantial pain relief in 80% of patients.[40] The pain relief provided by neurolytic CPB seems to be better when performed at an earlier stage rather than at a later stage.[42,43] A reduction in opioid consumption following neurolytic CPB has also been demonstrated by many authors despite similar VAS scores.[44–46] Changes in survival duration following neurolytic CPB has been disputed, although it is possible that statistically strict criteria may have prevented detection of a small difference in survival.[46,47] The effect of neurolytic CPB on quality of life is still unresolved as some randomized controlled trails report benefit while others do not.[43,47–49] In a more recent retrospective review, a positive outcome following neurolytic CPB was found to correlate with prior lower opioid use.[50]

COMPLICATIONS

Side effects such as orthostatic hypotension and transient diarrhea are known to occur after a CPB in approximately 38% and 44% of patients, respectively. One of the frequently reported complications is pain at the injection site, occurring in about 90% of cases. Other rare complications are retroperitoneal hematoma, injury to the pleura and lung leading to pneumothorax, injury to kidneys and intestines, and paraplegia secondary to neurolytic injection into the epidural or spinal canal or secondary to accidental injection of neurolytic agent into the artery of Adamkiewicz, all of which are reported in less than 1% of cases.[27] Superior mesenteric vein thrombosis has been reported with alcohol CPB.[51] An intravascular injection of neurolytic agent is a potential complication and can cause tremors and convulsions with phenol.[52]

TECHNIQUE OF PERCUTANEOUS ULTRASOUND-GUIDED CELIAC PLEXUS BLOCK

Following informed consent and with the patient supine, American Society of Anesthesiologists monitor guidelines are applied. A peripheral intravenous line is established. The patient may be instructed to control his/her respiration at certain times during the procedure. Typically, a low-frequency, curved-array, 3- to 5-MHz transducer is used. A scout scan is performed starting from the epigastrium and moving caudad to visualize the aorta, vertebral body, and the liver in a transverse view (Fig. 67-9). Once the celiac trunk is visualized, colorflow Doppler is turned on to verify the vessels (Fig. 67-10). Following this, the transducer is turned longitudinally and the celiac trunk and the superior mesenteric artery are visualized (Fig. 67-11). Colorflow Doppler is again used to verify the vessels. The target is the space between the celiac trunk and the superior mesenteric artery. Some would argue that the needle-tip position cephalad to the celiac trunk ensures better spread of the neurolytic agent.[28] The neurolytic spread may be determined more by the cancer spread than the needle position. The scout scan also helps in planning the approach based on the structures in the path of the needle.

Following the scout scan, the area is prepped and draped. With the transducer in a sterile sleeve, the target is once again identified. A 22-gauge, 15-cm-long Chiba needle is advanced to the space between the celiac trunk and the superior mesenteric artery in a longitudinal view. The needle may be advanced in plane or out of plane depending on the size of the needle, the safest path to the target area and personal preference of the physician. An extension set is connected to the needle following proper positioning. After negative aspiration, a test dose of 3 ml of lidocaine with epinephrine is injected real-time to rule out any intravascular uptake. Subsequently, real-time injection of the neurolytic agent in 5-ml increments is done. The typical volume of injectate used varies from 10 to 50 ml. The concentrations of alcohol used vary from 50% to 100%. With phenol, the concentration ranges from 6% to 10%. The needle is flushed with 1 ml of local anesthetic at the end of the procedure to flush the needle track of remaining neurolytic agent. This may decrease the pain secondary to subcutaneous infiltration of the neurolytic agent.

An alternative two-needle technique has also been described in which the celiac trunk is visualized in a transverse view, and the needles are introduced from the lateral

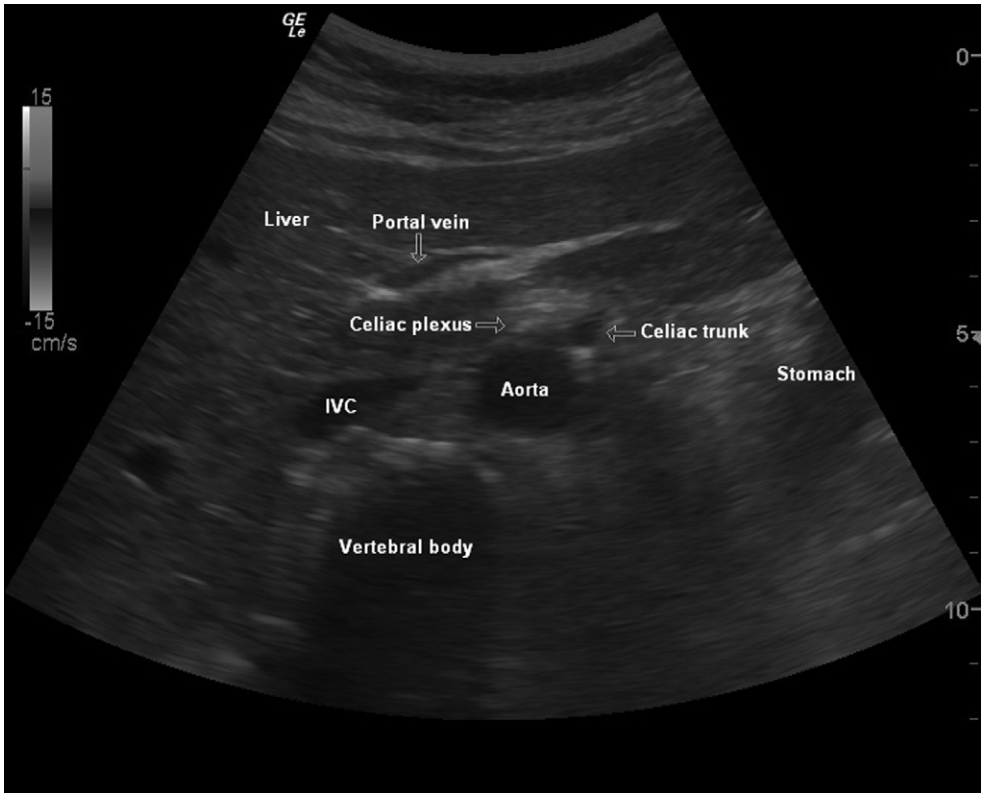

FIGURE 67-9 Transverse ultrasound picture over the hypogastrium showing the various structures in relation to the celiac trunk. *IVC*, Inferior vena cava.

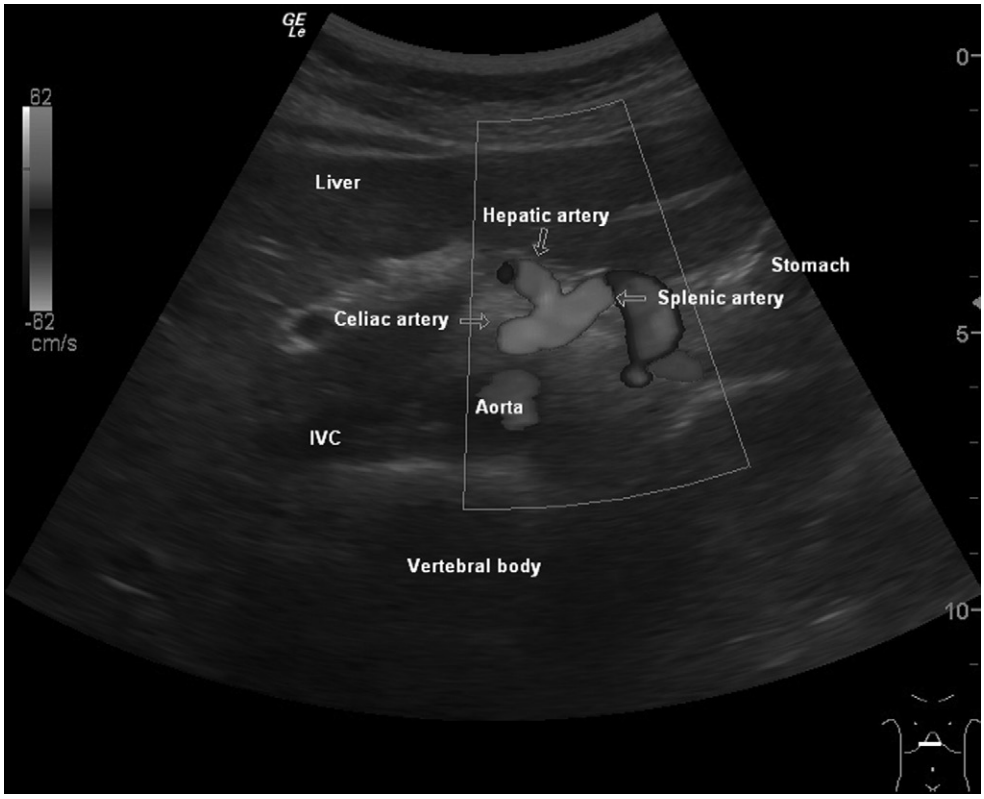

FIGURE 67-10 Transverse ultrasound view of the celiac trunk with colorflow Doppler. *IVC*, Inferior vena cava.

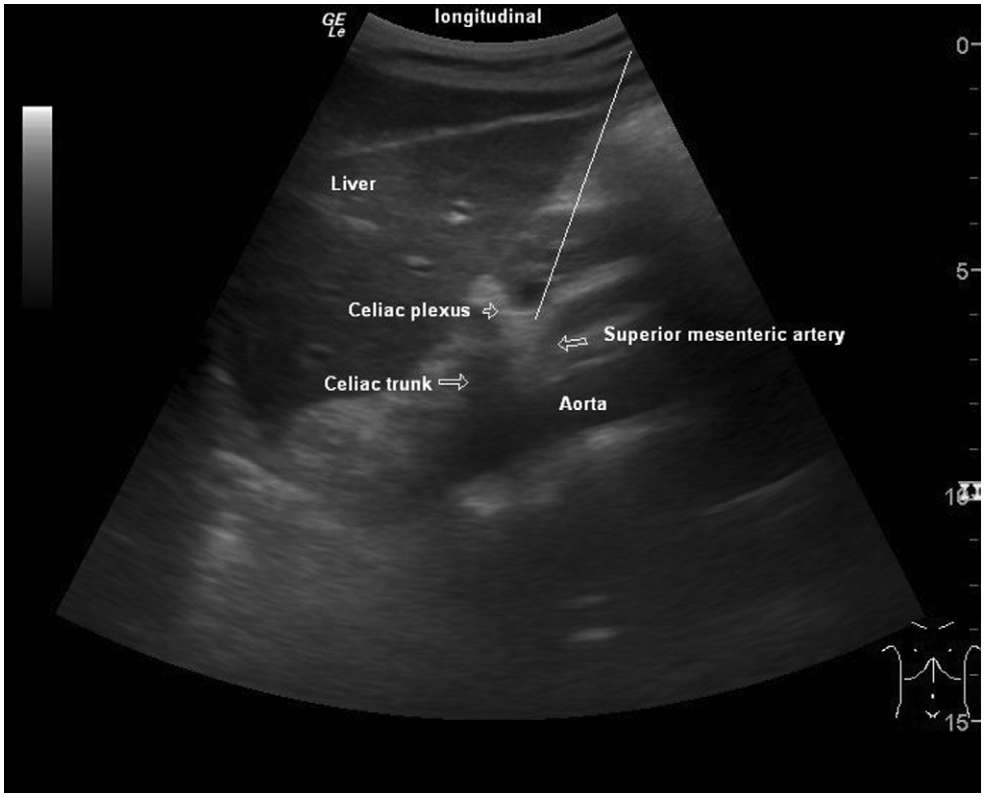

FIGURE 67-11 Longitudinal ultrasound view of the celiac trunk and superior mesenteric artery with a line showing the path of the needle.

sides of the transducer. The authors claim better visualization of the injectate with this approach.[53]

CONCLUSIONS

Ultrasound-guided CPB is safe, real time, and may be performed at the bedside using an anterior approach. It may be especially useful in patients who have difficulty lying prone. The technique is easy to learn, and success with ultrasound-guided techniques has been demonstrated.

KEY POINTS

- Celiac plexus is supplied by the greater, lesser, and least splanchnic nerves originating from the T5–T12.
- Celiac plexus is made up of a few ganglia and interconnecting nerves and is located adjacent to the junction of the celiac artery and the aorta.
- Ultrasound guidance for the performance of neurolytic celiac plexus block permits an anterior approach with relative safety and without radiation.
- Ultrasound guidance is real time and may avoid accidental neurolytic injection into the posterior structures including neuraxis.
- The target is the space between the origins of celiac trunk and the superior mesenteric artery and may be performed in a longitudinal view.
- Neurolytic celiac plexus block provides substantial pain relief in chronic visceral pain, specifically pain in pancreatic cancer.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 68

Fluoroscopy and Radiation Safety

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The use of fluoroscopy has revolutionized interventional pain management. Fluoroscopy is required in the advanced procedures where precise needle placement is required. These procedures include interventions for back pain such as epidural steroid injection, facet joint injection, facet nerve block and rhizotomy, sacroiliac joint injection, discography, placement of spinal cord stimulator and the newer interventional procedures such as biaculoplasty, nucleoplasty, and vertebroplasty. Fluoroscopy is also used in lumbar paravertebral sympathetic blocks as well as visceral sympathetic blocks such as celiac plexus block, superior hypogastric plexus block, and ganglion impar block. Blocks outside the vicinity of the spine also benefit from fluoroscopic guidance and include trigeminal nerve block and gasserian ganglion block.

Several studies on epidural steroid injections have shown the usefulness of fluoroscopy. Anatomic landmarks can be difficult to recognize especially in obese, elderly, or arthritic patients.[1] Access to the epidural space is not always straightforward, especially in the sacral region where surface landmarks are not clearly delineated in the adult patient. In addition, fluoroscopy can inform the physician of important details not clearly known to the patient. For example, a patient who was treated by one of the authors had a history of a laminectomy and fusion and presented with a right L1 radiculopathy (Fig. 68-1). She did not realize that she had a bone stimulator in situ that was placed at the time of surgery. As the device was clearly evident on x-ray imaging, a right paramedian epidural steroid injection was safely performed with the needle insertion a distance from the bone stimulator (Fig. 68-2).

In a nationwide survey done in the United States in 2002, investigators found that there was a wide variability in the use of fluoroscopy. Private practitioners used fluoroscopy more than those in academic centers. In the cervical region 73% of private practitioners used fluoroscopy compared to only 39% in academic institutions.[2] The transforaminal approach to epidural injections were employed in patients who had previous laminectomy by 61% of private practitioners compared to 15% of those in academic institutions.[2] For transforaminal epidural steroid injections, confirmation of correct needle placement and spread of the dye in the anterior epidural space can only be demonstrated by fluoroscopy.

One of the earlier studies on epidural steroid injections showed that blind placements were accurate in 83 of 100 patients.[1] In this study in which 85% of the injections were performed in the lumbar area, the anesthesiologists who performed the interlaminar epidural placements were well-experienced, and yet the incidence of inaccurate placement was 17%. Another study in which the epidurals were again placed by experienced anesthesiologists and an orthopedic surgeon showed a 75% success rate with blind epidural placements.[3]

In cervical epidural placements, a study noted that there was a 47% success rate on the first attempt of needle placement.[4] In 63% of the placements (24 of 38 epidurals), a second attempt was required. The lack of reliability of the loss-of-resistance technique may be partially due to the lack of continuity of the ligamentum flavum in the cervical area.[5] Another finding in the study[4] was a 51% incidence (19 of 38) of unilateral spread of contrast, although the authors inserted their needle slightly lateral to the midline. In addition to the slight lateral insertion of the needle, the unilateral spread may also be caused by the plica mediana dorsalis, a thin septum dividing the posterior epidural space. The presence of the plica mediana dorsalis has not been demonstrated in the cervical region, but in the lumbar and thoracic levels the plica mediana dorsalis has been shown to divide the posterior epidural space into compartments hindering the free flow of the injected solution.[6–8] Knowledge that the contrast spread is unilateral can allow for readjustment of the needle tip. One of the more interesting findings in the study by Stojanovic et al.[4] is the spread of the contrast in the ventral epidural space in only 28% of the patients (11 out of 38 epidurograms). The spread of the injectate in the anterior epidural space is important since this is the location of the herniated intervertebral disc and the interface between the herniated disc and the nerve root. The placement of the drug in the anterior epidural space is the rationale for transforaminal epidural steroid injections (see Chapter 45).

Caudal epidural steroid injections are ideally performed under fluoroscopic guidance. Without image guidance, experienced radiologists incorrectly place the caudal needle 38% of the time.[9] Renfrew et al.[9] showed that the experience of the physician improved the success rate of blind epidural placements. Physicians who performed fewer than 10 epidurals had a success rate of 48% compared to 62% by experienced physicians.[9] Another study showed that senior physiatrists successfully placed the caudal needle in 74% of their initial attempts.[10] Their success rate improved to 88% when landmarks were identified easily. It appears that the most common site of incorrect needle placement is in the subfascial plane posterior to the sacrum.[10] Correct placement of the caudal needle is intuitively improved when fluoroscopy is utilized. In a study of 116 caudal steroid injections done under fluoroscopy, radiologists found that the success rate was 97%.[11] In this study[11] it was found that the injection of 9- to 15-ml volume reached the mid to upper lumbar spine except in those patients with a severely stenotic spinal canal.

In patients who had a previous laminectomy, it was noted that the mean number of attempts to place the needle in the epidural space successfully is 2 ± 1.[12] The difficulty in placing the epidural needle may be due to fibrosis and adhesions within the epidural space making the loss-of-resistance technique equivocal. In 25 of 48 patients, the

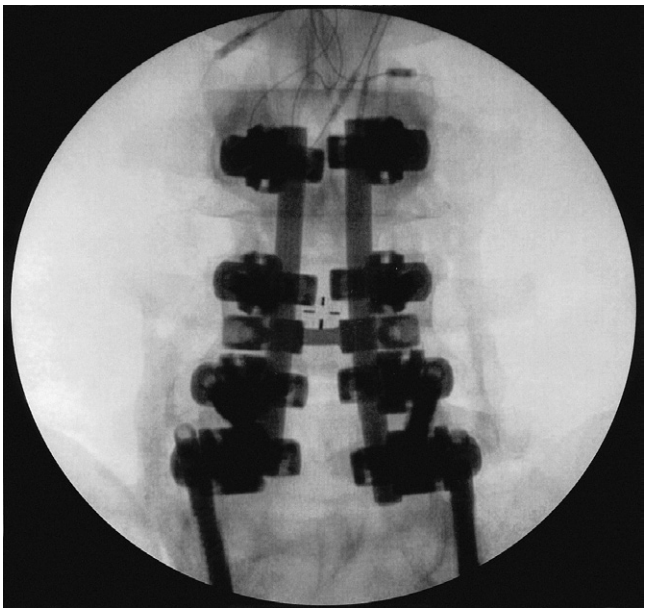

FIGURE 68-1 Fluoroscopic image of a patient who had a lumbar laminectomy and fusion. In addition, a bone stimulator was placed.

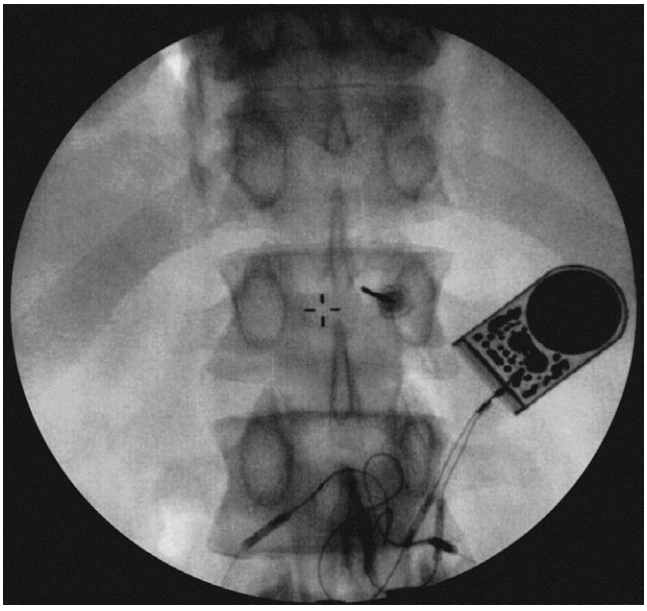

FIGURE 68-2 Fluoroscopic image of the patient wherein a right T12–L1 paramedian epidural steroid injection was performed; the needle was inserted close to the bone stimulator. A lead wire is seen obscuring the L1–L2 interspace.

Touhy needle and epidural catheter were placed one or two intervertebral spaces above or below the desired level. The lack of reliability of surface landmarks may be due to the surgical removal of the posterior spinous process making the count of the vertebral levels difficult. When 5 ml of contrast medium was injected, the contrast reached the level of pathology in only 26% (12 of 47) of the patients. It has been postulated that this is due to postoperative adhesions that hindered the spread of the dye.[12] The success rates of needle placements in the studies[1,3,4,9–12] are shown in Table 68-1.

Machikanti et al.[13] emphasized the necessity of using fluoroscopy in epidural steroid injections. The low incidence of the dye reaching the level of pathology requires the use of fluoroscopy to eliminate the question of incorrect needle placement with blind injections. Documentation of the spread of the dye can be correlated with the response of the patient. It should be noted, however, that there are differences in the flow characteristics between the contrast media and the steroid solution and that the flow of the dye may not completely predict the flow of the steroid injectate. The steroid solution may be more limited in its distribution because it tends to precipitate in its diluent which is typically either a local anesthetic or saline.

In addition to confirmation of correct needle placement, the other advantage of using fluoroscopy is the determination of the needle tip in an inadvertent location prior to injection. Unintentional intravascular or intrathecal injection may occur in spite of negative aspiration of blood or cerebrospinal fluid, respectively, through the needle. The vascular uptake of the dye can be detected when live fluoroscopy is used during contrast injection or can be suspected when there is immediate contrast disappearance after injection. Intravascular injection would be especially hazardous via the transforaminal route as arteries entering the foramen supply the exiting nerve roots as well as the spinal cord depending on the level involved. Smuck et al.[14] performed a prospective observational study on the incidence of simultaneous epidural and vascular injection during cervical transforaminal epidural injections. They found that vascular-only injection had a 13.9% incidence where as a vascular and epidural injection occurred in 18.9% of their study patients. They recommended live injection fluoroscopy for contrast injection. They performed a similar study on the lumbosacral level.[15] Although the incidence of vascular and vascular plus epidural injection was much lower than at the cervical level, they made the same recommendation for live fluoroscopy for these procedures. Digital subtraction angiography (DSA) can further increase sensitivity of live fluoroscopy for intravascular detection. McLean et al.[16] found that with live fluoroscopy alone, intravascular injection occurred 17.9% in their study population. When DSA was employed, the rate rose to 32.8%.

Although not typically as catastrophic as injection into an artery, intrathecal injection of injectate needs to be detected as well. For example, 3 ml of lidocaine 1% into the intrathecal space inadvertently is enough to cause a significant motor and sensory block with the accompanying hemodynamic alterations. In addition, as the injectate is not placed in the intended epidural space, the intended effect will be lacking. Recognizing the characteristic spread of contrast intrathecally can help to avoid this complication. One may look for a distinctive contrast-fluid level seen on lateral imaging with the patient in the prone position (Fig. 68-3).

There are several reasons for not utilizing fluoroscopy in epidural steroid injections. These include the avoidance of radiation; costs associated with the fluoroscopic equipment, its maintenance and technicians; inconvenient scheduling; location of the x-ray facility; and allergy to contrast agents. However, the substantial potential for

TABLE 68–1 Success Rates in Epidural Placements

Route	Blind/Fluoroscopy	Physician	Experience/Faculty	Success Rate (%)	Reference
Cervical	Fluoroscopy	Anesthesiologists	Faculty/house staff	100*	4
Lumbar**	Blind	Anesthesiologists	Experienced	83	1
Lumbar	Blind	Anesthesiologists and orthopedic surgeons	Experienced	75	3
Lumbar, s/p surgery	Blind	Anesthesiologists	Attending	92	12
Caudal	Blind	Radiologists	Attending	48–62†	9
Caudal	Blind/fluoroscopy	Radiologists	Attending	74–88	10
Caudal	Fluoroscopy	Radiologists	Attending	97	11

**Up to four attempts were made in successfully placing the needle in the epidural space.*
***Eight-five percent of the injections were in the lumbar area.*
†Experienced radiologists had a success rate of 62% compared to 48% for inexperienced anesthesiologists (see text).

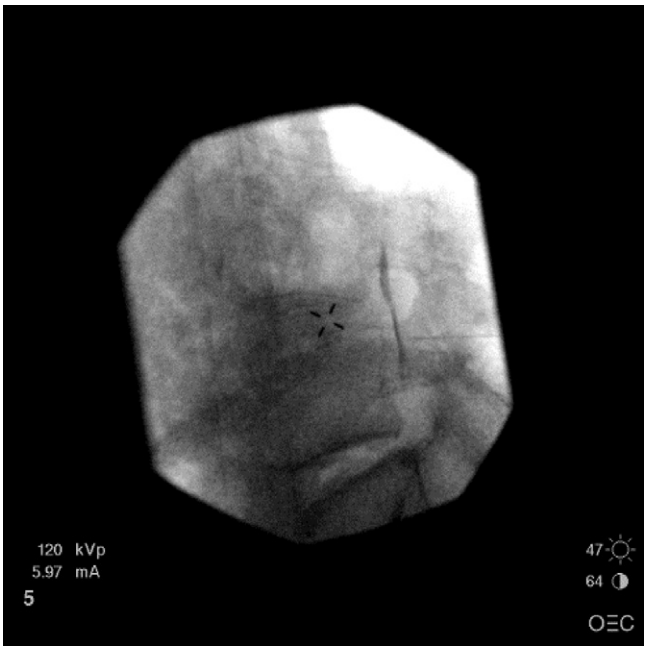

FIGURE 68-3 Lateral fluoroscopic view showing placement of 25-gauge spinal needle intrathecally in a patient in the prone position. The contrast has a characteristic appearance in which the contrast border is uneven dependently (i.e., anteriorly) and essentially straight posteriorly at the contrast–CSF interface.

incorrect needle location makes fluoroscopy desirable in epidural steroid injections. The added benefits of fluoroscopy include the documentation of the spread of contrast whether it is unilateral, located in the ventral epidural space, or whether it reached the desired level of pathology. The documentation of correct needle placement and ideal spread of the injectate eliminates technical factors as a cause of lack of response of the procedure in the patient. For these reasons, the use of fluoroscopy and contrast epiduroscopy is becoming the standard of care in epidural steroid injections as well as other spinal procedures. In addition, the *Practice Guidelines for Spinal Diagnostic and Treatment Procedures* published by the International Spine Intervention Society (ISIS) mandate the use of fluoroscopy for the performance of transforaminal epidural steroid injections as well as medial branch blocks.[17,18] One final factor in using fluoroscopy to guide spine procedures will likely include reimbursement. For example, in January 1, 2010, the established Current Procedural Terminology (CPT) codes for medial branch blocks were removed and replaced with codes that bundle together both the medial branch block(s) and use of fluoroscopy for needle guidance. There is no longer a separate billable code for a medial branch block that has not been performed with x-ray guidance.

FLUOROSCOPY MACHINE

For medical imaging purposes, x-radiation can be produced with the aid of electricity. A current, which is measured in milliamperes (mA), passes from an electrically heated negatively charged filament (the cathode) to an anode under a high voltage (kilovolt peak, kVp) within an x-ray tube.[19] The anode is typically tungsten which has a high melting point.[20] As the electrons interact with the anode, energy is released as both heat and photons called x-rays. These x-rays will then exit the tube and either become absorbed by or pass through the patient. The energy that passes through the patient will enter an image intensifier where it is converted to a visible image that is displayed on a monitor screen and can be saved as a permanent record.

The important parts of the fluoroscopy machine include the x-ray tube, image intensifier, C-arm, and the control panel (Fig. 68-4).[21] The x-ray tube fires the beam of electrons through a high-voltage vacuum tube, forming x-rays that are emitted through a small opening. The image intensifier collects the electromagnetic particles and translates them into a usable image that can be viewed on a television monitor. The C-arm allows for the x-ray source and recording source (i.e., the image intensifier) to be on opposite sides of the patient. By its design, it will also facilitate the positioning of the fluoroscope for the physician to easily obtain anteroposterior, oblique, and lateral views of the patient. The control panel (Fig. 68-5) contains the controls for the technician to make adjustments either to the image itself or the settings used to create the x-ray image. For the latter, typically the "automatic brightness control," or ABC, system is employed (see below). Also located in the control panel are the controls for magnification and collimation of the image. Many machines also have the software required for DSA, which is useful to detect for inadvertent vascular placement. The quality of image contrast depends

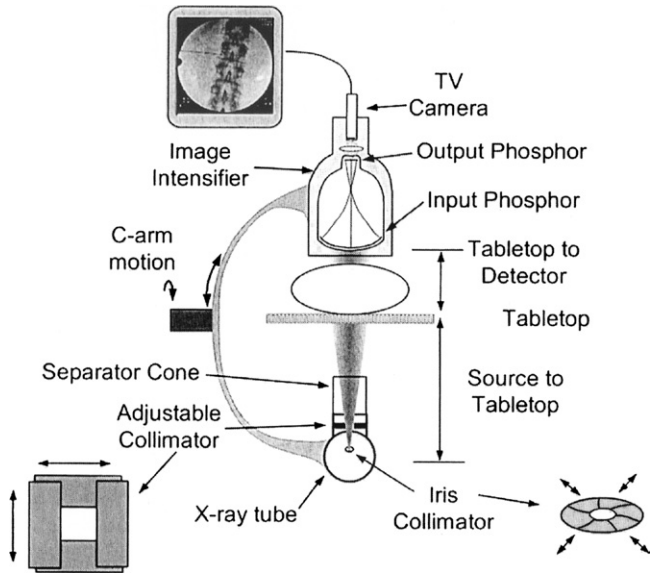

FIGURE 68-4 *Reprinted from Fishman SM, et al: Radiation safety in pain medicine,* Reg Anesth Pain Med *27:296–305, 2002, with permission from the American Society of Regional Anesthesia and Pain Medicine.*

on the balance between the tube voltage (or kVp) and the tube current.[21] The kVp is the voltage through which the electron beam passes in the x-ray vacuum tube. Increasing the kVp increases the penetrability of the x-ray beam through the patient and thereby decreases its absorption. This will act to produce brighter, more exposed images but then also to decrease the contrast. The fluoroscopic examination of the spine of a normal sized adult starts with the kVp set at ~75; larger patients require a higher kVp. The typical settings are 80 to 100 kVp for the back, 50 kVp for the hands, and 70 kVp for the abdomen. Broadman[19] recommends the highest kVp setting that produces the adequate contrast or grayscale ordering to minimize x-ray exposure for the patient and personnel. The tube current reflects the number of electrons fired through the high-voltage vacuum tube. Higher tube currents mean more x-rays are produced and emitted. The tube current is set between 1 and 5 mA; lower settings are adequate for most interventional fluoroscopy procedures.

The image contrast is obtained by balancing the tube voltage or kVp against the tube current.[19] Higher kVp settings reduce the number of x-rays absorbed and decrease exposure time. However, if the kVP settings are too high, the image will lack the necessary contrast for a useful image. In terms of the resulting image, it can be likened to a photograph taken with an inappropriately bright flash in which all objects appear overexposed and the ability to distinguish features falters. A nice component of fluoroscopy machines is the ABC system in which the computer automatically analyzes the image contrast and makes the appropriate tube current adjustments balancing image contrast and patient safety. It is recommended that the interventional pain physician leave the machine on the ABC system during the performance of most interventional procedures.

RADIATION SAFETY

The increasing use of fluoroscopy implies that the pain physician is aware of radiation safety to limit the radiation exposure to the patient and personnel.[22] A review article, book chapters, monographs, and government publications are available to help the interventional pain physician better understand the concept of radiation safety.[19,21,23–27]

Radiation is the process by which energy, in the forms of waves or particles, is emitted from a source.[21] Radiation includes x-rays, gamma rays, ultraviolet, infrared, radar, microwaves, and radio waves. Radiation absorbed dose (rad) is the unit of measure that expresses the amount of energy deposited in tissue from an ionizing radiation source. Units of gray (Gy) are preferred, instead of rad, in

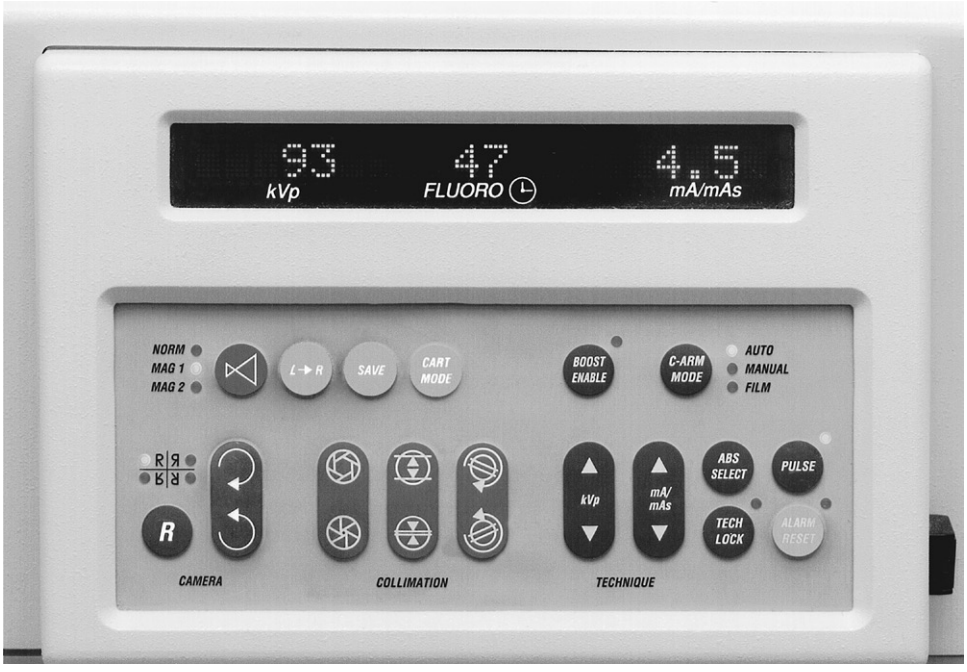

FIGURE 68-5 Control panel of the fluoroscopy machine.

the International System (SI) of units. A gray is defined as the quantity of radiation that results in an energy deposition of 1 joule per kilogram (1 J/kg) within the irradiated material; 1 Gy is equivalent to 100 rad and to 1,000 mGy.

Different types of radiation may have similar absorbed doses but produce different biologic effects.[21] To predict occupational exposure from x-radiation, the term radiation absorbed dose (rad) is converted to radiation equivalent man (rem) in a 1:1 ratio. The unit of dose equivalent to rem in the SI system is the sievert (Sv); 1 rem is equivalent to 1 rad and 100 rem is equivalent to 1 Sv.

RADIOBIOLOGY

The biologic effects of radiation are caused by either the direct disruption of macromolecules such as DNA, or by the ionization of water molecules within cells, producing highly reactive free radicals that then damage macromolecules. Acute effects (nonstochastic or deterministic) occur at relatively high dose levels such as those given during radiotherapy treatments or in accidents. The term *acute* refers to not only the short time course but also to the high dosage involved. Chronic effects are the results of long-term, low-dose effects. The severity of these effects is unrelated to the dose as there is a threshold effect. Hence chronic effects are termed stochastic or nondeterministic. Doses lower than 1 Gy generally do not cause noticeable acute effects other than slight cellular changes. However, there is increased probability of induced cancer or leukemia in the exposed individual. A radiation dose equivalent of 25 rem (0.25 Sv) may lead to a measurable hematologic depression.[21,25] A whole body total radiation dose exceeding 100 rem (1 Sv) may lead to nausea, fatigue, radiation dermatitis, alopecia, intestinal disturbances, and hematologic disorders. The average annual radiation dose from medical x-rays is only approximately 40 mrem (0.4 mSv).[21,25]

MAXIMUM PERMISSIBLE DOSE

The maximum permissible dose (MPD) is the upper limit of allowed radiation dose that one may receive without the risk of significant side effects. The annual whole-body dose limit for physicians is 50 mSv. Table 68-2 shows the annual maximum permissible dose per target area.[21] For the fetus, the annual maximum permissible dose is 0.5 rem or 5 mSv. Assuming proper techniques and well-functioning equipment, the scattered radiation dose to the patient and the medical personnel should be less than the above radiation doses. Reduction of the amount of radiation implies selection of the type of examination and imaging modality to minimize the dose to the patient and personnel. These include knowledge of the value of the radiologic examinations and the views that are necessary, selection of the equipment to be as dose-efficient as possible, and proper installation and regular maintenance of the equipment. The principle involved in reducing the amount of radiation dose is ALARA (as low as reasonably achievable) or ALARP (as low as reasonably practicable). This implies that in the process of obtaining good, usable images for the procedure, all steps are taken to minimize extraneous radiation exposure.

TABLE 68–2 Annual Maximum Permissible Radiation Dose by Target Organ

Organ/Area	rem	mSv
Whole body	5	50
Lens of eye	15	150
Thyroid	50	500
Gonads	50	500
Extremities	50	500

Source: Fishman SM, Smith H, Meleger A, Sievert JA: Radiation safety in pain medicine. Reg Anesth Pain Med *27:296–305, 2002, with permission.*

RADIATION PROTECTION OF THE PATIENT

Several precautions should be employed to minimize the exposure of the patient to radiation. The beam-on time should be reduced since radiation exposure increases linearly with time, and total exposure is equal to the exposure rate multiplied times the time. It is recommended that the fluoroscopy machine be equipped with a laser pointer, which is attached to the image intensifier (Fig. 68-6). The laser pointer allows the technician to "mark" the area of interest externally before an image is taken. This will reduce the number of scout fluoroscopy views required before the actual area of interest is encountered. The x-ray tube should be kept as far away from the patient as possible. Increasing the distance between the x-ray tube and the patient reduces radiation to the patient. It will also necessarily move the patient closer to the image intensifier, leading to a sharper and higher quality image. It has been recommended that the x-ray tube be at least

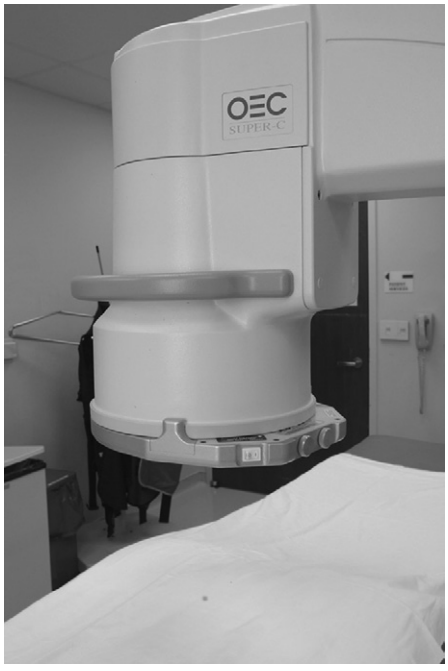

FIGURE 68-6 A laser pointer is attached to the image intensifier. The red dot corresponds with a target (such as an "X") on the fluoroscopic image.

30 cm away from the patient. The image intensifier should be positioned as close to the patient as possible while still maintaining the room required to perform the procedure. Collimation should be used to reduce the area being irradiated thereby reducing the amount of x-rays received by the patient. Collimation may also increase the quality of the image by a reduction in radiation scatter. The use of live fluoroscopy should be minimized; freeze frames should be relied on as frequently as possible. Many machines have the capacity to use pulsed, live fluoroscopy. This will create a choppier moving image as opposed to a smooth image from continuous fluoroscopy. Some machines also have a low-dose mode which provides for grainier images that lack the fine detail that would be provided if a higher dose of radiation were used (Fig. 68-7). These settings may be used in those circumstances in which a high quality or smooth moving image is not required. Finally, magnification should be limited since magnifying the image by a factor of 1 increases the amount of radiation 2.25 times while magnifying the image by a factor of 2 increases the amount of radiation 4 times.[21]

As stated, the MPD to the fetus is 5 mSv per year. An old theory is the "10-day rule" wherein it was thought that x-ray examination of the abdomen of a woman of childbearing age should be carried out within 10 days of the onset of menstruation because this time represents the least likelihood of conception taking place. If conception took place, the embryo would be most sensitive to the effect of radiation. The "10-day rule" is probably erroneous. The fetus is relatively insensitive to the effects of radiation in the early stages of pregnancy. The period when the fetus is most sensitive to radiation is between 8 to 15 weeks' gestation, when the rate of proliferation of DNA within the brain is at a maximum.[23] Any significant deleterious effect of radiation during conception is likely to lead to spontaneous abortion.

RADIATION PROTECTION OF PERSONNEL

The factors affecting radiation exposure to personnel include the time or duration of x-ray exposure, distance from the source of the x-rays, and protection from the radiation. It should be noted that the major source of radiation to the personnel is the patient or fluoroscopy table, which serves as a conduit for scattered radiation. The radiation dose to the patient and subsequent scatter can be reduced by using the lowest tube current (mA) compatible with a good x-ray image. The beam-on time should be kept to a minimum; there is a 5-minute alarm in most fluoroscopy machines. Only necessary personnel should be present in the fluoroscopy room. The personnel should be notified each time before fluoroscopy is on. The personnel should step back from field whenever possible when the fluoroscopy machine is turned on. The intensity of ionizing radiation decreases exponentially as the distance from the source is increased. The inverse-square law states that the radiation is inversely proportional to the square of the distance (the space between the individual and the x-ray source). Therefore, as the distance is doubled, the exposure rate is reduced by one fourth.[21] Finally, barriers or screens can be employed; these are utilized mostly in the orthopedic, urology, and radiology suites.

UNDERCOUCH AND OVERCOUCH FLUOROSCOPY

The conventional undercouch fluoroscopy arrangement occurs when the x-ray tube is located beneath the fluoroscopy table and the image intensifier is above the table (Fig. 68-8). In this arrangement and with the table horizontal, most of the scattered radiation is in the downward direction and absorbed in the floor or the side panels of the table. In the overcouch fluoroscopy arrangement, the position of the x-ray tube and image intensifier is reversed or the oblique and lateral views are employed. In this arrangement it is difficult to get adequate shielding to the medical personnel.

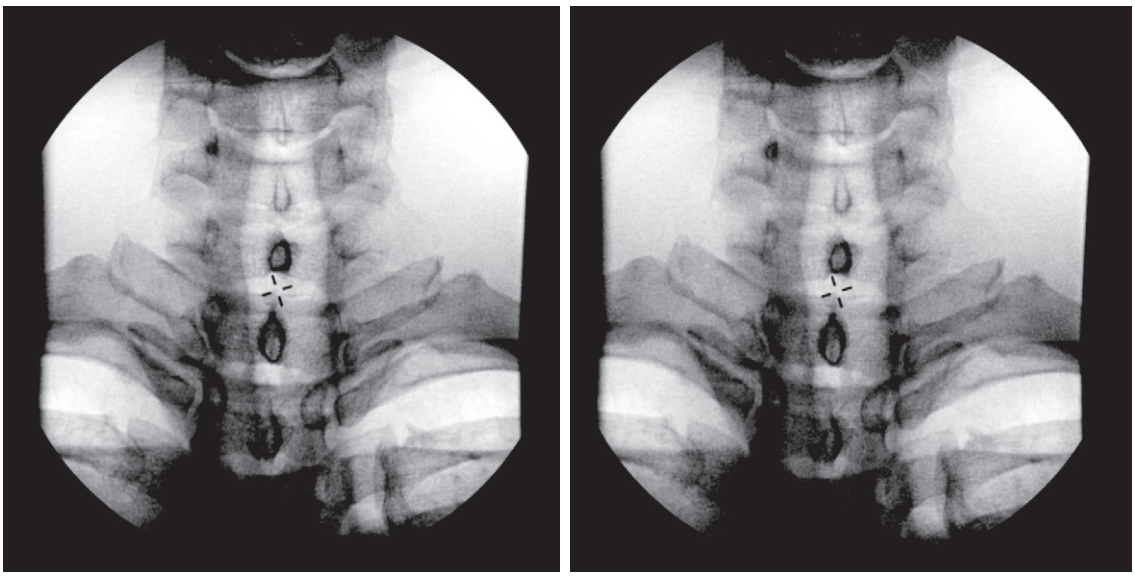

FIGURE 68-7 On the *left* is an image using the standard ABC setting (kVp 71, 2.2 mA); on the *right* is an image using the low-dose setting (kVp 75, 0.84 mA). The differences in this image are subtle with the low-dose image differing notably by a blurring of edge margins.

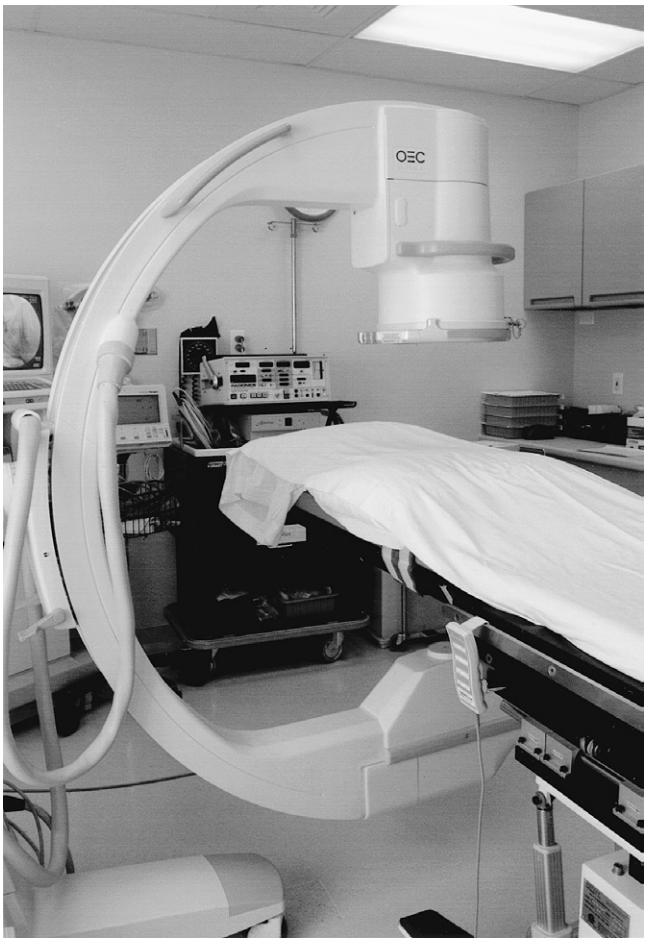

FIGURE 68-8 A conventional undercouch fluoroscopy arrangement wherein the x-ray tube is located beneath the fluoroscopy table and the image intensifier is above the table.

The maximum amount of scattered radiation is normally backwards from the entrance surface of the radiation and the side of the patient receiving most of the primary beam (i.e., the side of the x-ray tube). Scattered radiation is 2 to 3 times higher at the side of the x-ray tube. The physician should preferably stand on the side of the image intensifier when lateral views are taken; care must be taken to make sure that the x-ray tube and image intensifier are at the same level, and not above, the level of the patient. Also, the image intensifier has a lead–plastic apron attached to its edge, which serves to absorb much of the scattered radiation that emerges from the patient and shielding the physician from some of the scattered radiation.

BARRIERS AND SHIELDING

Shielding refers to radiation protection afforded by equipments that absorb x-rays. The categories of shielding include fixed, mobile, and personal shielding.[23] Fixed shielding includes the thickness of walls, which should have a lead equivalence of 1 to 3 mm, the doors, and protective cubicles. Mobile shielding is appropriate during fluoroscopy procedures in which a member of staff needs to remain near the patient. Personal shielding includes lead aprons, gloves, thyroid shields, and glass spectacles.

Lead Aprons: For reasons of weight, lead aprons generally have shielding equivalence equal to a 0.25- to 0.5-mm lead barrier and will only attenuate the radiation. Lead aprons absorb 90% to 95% of scattered radiation that reaches them (Table 68-3). "Wrap-around" lead aprons are useful when the medical personnel spend a lot of time with their backs turned away from the patient. When wrap-around aprons are not used, the personnel wearing them should not turn unshielded backs toward the x-ray beam. Lead aprons should be worn properly and stored properly. They should not be folded or thrown on the floor since it may produce creases that develop into breaks in the protective barrier. The integrity of lead aprons should be assessed annually.

Lead Rubber Gloves and Leaded Glasses: Lead rubber gloves usually have a minimum lead equivalence of 0.25 mm since thicker leaded gloves make manipulations that require dexterity difficult. The protection offered by "radiation-resistant" gloves may not be significant and the gloves may only give a false sense of security. The use of leaded gloves may actually increase the x-ray exposure when the fluoroscopy machine is in the ABC mode. In this scenario the machine senses the poor contrast between the bones of the gloved hand and the surrounding soft tissue and the ABC system automatically adjusts the tube current setting to produce a better contrast but a higher radiation dose.

The use of leaded glasses with side shields may reduce the risk of cataract formation. However, the effectiveness of glass spectacles may be overrated and ordinary eyeglasses may give adequate reduction in the radiation dose that reaches the eye. A single dose of 200 rem (2 Sv) or a total exposure of 800 rem (8 Sv) has been related to cataract formation and the latent period between the radiation exposure and the appearance of cataracts is approximately 8 years.[21,25]

MINIMIZING AND MONITORING RADIATION

Wagner and Archer recommended 10 measures to reduce risks from fluoroscopic x-rays (Table 68-4).[27] Federal and state regulations in the United States require that anyone who works in a station where he or she may receive over 25% of the allowable quarterly limit (1.25 rem or 1250 mrem) must be supplied with monitoring equipment or a radiation badge or film badge. A radiation badge is a pack of photographic film that measures radiation exposure for personnel monitoring. It measures the quantity and the

TABLE 68–3 Percentage Primary x-ray Beam Transmission for Kilovoltages and Lead Aprons, Single-Phase Generator (1 or 2 Pulse)

Lead Thickness (mm)	75 kVp	100 kVp	125 kVp
0.22	4.5	12.1	12.8
0.44	0.7	3.7	5.1
0.5	<0.1	3.1	4.4
0.72	<0.1	1.4	2
1	<0.1	0.3	0.6

Source: Robinson A: Diagnostic protection and patient doses in diagnostic radiology. In Grainger RG, Allison D, editors: Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging, *New York, 1997, Churchill-Livingstone, pp 169–189.*

TABLE 68–4 Ten Measures for Minimizing Risks from Fluoroscopic x-rays

1. Dose rates are greater and dose accumulates faster in larger patients.
2. Keep the tube current as low as possible.
3. Keep the kVp as high as possible (and mA as low as possible) to achieve the appropriate compromise between image quality and low patient dose.
4. Keep the patient at maximum distance from the x-ray tube.
5. Keep the image intensifier as close to the patient as possible.
6. Do not overuse geometric or electronic magnification.
7. If the image quality is not compromised, remove the grid during procedures on small patients or when the image intensifier cannot be placed close to the patients.
8. Always collimate down to the area of interest.
9. Personnel must wear protective aprons, use shielding, monitor their doses, and know how to position themselves and the machines for minimum dose.
10. Keep beam-on time to an absolute minimum.

Source: Wagner LK, Archer BR: Minimizing Risks from Fluoroscopic x-rays, ed 3, Woodlands, TX, 2000, RM Partnership.

quality of radiation (beta or gamma radiation). It is read with a densitometer and the amount of darkening of the film is proportional to the amount of radiation absorbed by the film. The film inside the badge is easily damaged by pen or moisture and the badge cannot be used for periods exceeding 8 weeks because the image fades.

There are usually two badges worn by the physician during the fluoroscopy procedure. The "collar badge" is worn outside the apron on the upper portion of body, usually on the upper edge of the thyroid shield. This badge approximates radiation exposure to the lens of eye. The "behind the apron" badge is worn behind the apron, usually on the waist of the physician. The x-ray reading in this badge represents the actual dose to the gonads and the major blood-forming organs. The film badges should be placed correctly and worn consistently. It is not uncommon for the physician to interchange the placement of the badge, resulting in a gross error in the interpretation of the x-ray risk to the physician.

The badges should be returned on time: old badges give inaccurate results. It should be realized that all the radiation badges from all departments in the hospital (e.g., radiology, cardiology, operating rooms, etc.) are sent for readings at the same time and that a delay in returning the badges from one department unnecessarily delays the reading of all the badges. The reports are issued in the form of monthly computer printouts (Fig. 68-9).

ORGANIZATION OF RADIATION PROTECTION

Each hospital has a radiation safety office. The office usually has a clinical director, a radiation adviser, and a radiation protection supervisor.[23] The clinical director is usually a radiologist or clinician responsible for establishing protocols and procedures for the examination of patients and is involved in the selection of equipment as well as day-to-day decisions. The radiation protection adviser (RPA) is usually an experienced physicist who gives advice on the design of x-ray rooms, monitoring of doses to patients and staff, and performs calibration and safety checks on radiology equipment. The radiation protection supervisor (RPS) is usually an experienced full-time member of the radiology staff who will, in collaboration with the RPA, write local rules and ensure their compliance by the staff, ensure that the staff wear radiation monitoring devices, and report to the department chair, administration, or RPA any incident in the hospital that is related to radiation safety.

RADIOLOGICAL CONTRAST MEDIA

Iodine is the only element that has proved satisfactory for general use as an intravascular radiological contrast medium. Its radio-opacity is conferred by its high molecular weight. The maximum recommended concentration of iodine is 300 mg iodine per ml and the maximum recommended dose is 3 g of iodine. The absorption of iodine is variable. Its mean half-life is 12 hr and 80% to 90% is excreted via the kidneys within 24 hr. There are two kinds of contrast media with respect to their osmolality: the high-osmolality contrast media (HOCM) and the low-osmolality contrast media (LOCM) (Table 68-5).[28,29] The HOCM are ionic monomers and include various concentrations of sodium, meglumine, or sodium-meglumine salts of diatrizoic and iothalamic salts. They are also called first-generation agents. These media provide 3 iodine atoms for 2 ions, giving an iodine:particle ratio of 3:2; their osmolalities range between 433 mOsm/kg and 2400 mOsm/kg.[28] The LOCM are nonionic monomers, that is, a molecule that does not dissociate in solution. They are also called second generation agents, and are by far the most common type of contrast agent used today. The LOCM provide an iodine:particle ratio of 3:1 and their osmolalities range between 411 mOsm/kg and 796 mOsm/kg.[28] The LOCM cause less nausea and vomiting, produce less pain on peripheral arterial injection, and are associated with a lower incidence of mild, moderate, and severe adverse reactions compared to the HOCM. (The incidence of adverse reaction rate with LOCM is 0.03% compared to 0.36% with HOCM.) There are formulations of LOCM that are Food and Drug Administration–approved for intrathecal use (e.g., Isovue-M 200 and 300, Omnipaque 180 and 210). Only these agents should be used for spine procedures, as any planned injection may be inadvertently in the intrathecal space.

ADVERSE REACTIONS TO CONTRAST MEDIA

The concerns regarding the use of contrast media include adverse reactions. Patients considered at greater risk of an adverse reaction to the contrast media are listed in Table 68-6.[28] Patients who have a history of allergic reaction to the radiologic contrast media should be premedicated. Greenberger and Patterson[30] recommended that the patient be given three doses of oral prednisone 50 mg at 13, 7, and 1 hr before the procedure. It has also been recommended that oral diphenhydramine (Benadryl) 50 mg be given 1 hr before injection of the contrast.[27] Lasser et al.[31] recommended two oral doses of methylprednisolone 32 mg given at 12 and 2 hr before the procedure.

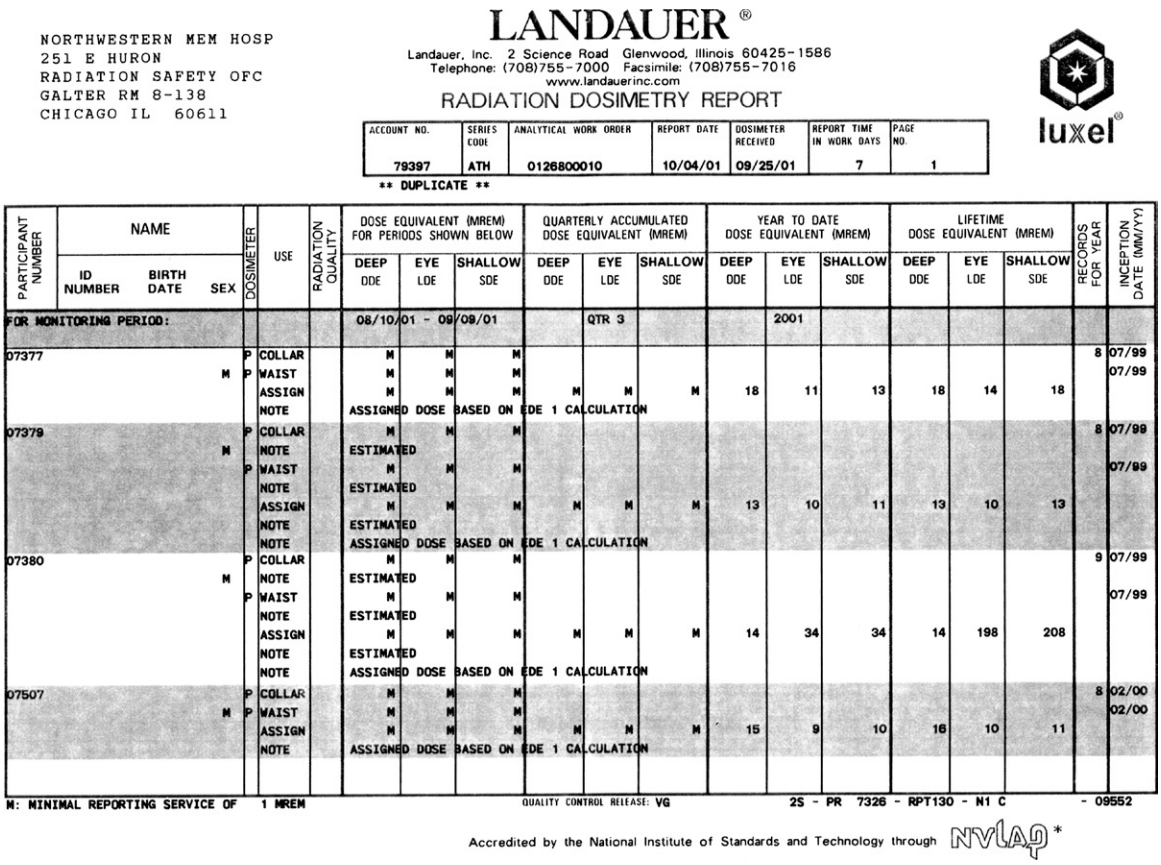

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FIGURE 68-9 Printout sample of radiation exposure of medical personnel.

TABLE 68–5 Contrast Media, Iodine Concentrations, and Osmolalities

Contrast Medium	Iodine (mg/ml)	Osmolality
HOCM		
Diatriazoate Na (Hypaque)	300	1522–1550
Diatriazoate Na (8%)-meglumine (52%) (Renografin)	292	1422–1539
Iothalamate meglumine (60%) (Conray)	282	1400
LOCM		
Iohexol (Omnipaque)	300	709
Iopamidol (Isovue)	300	616
Ioversol (Optiray)	320	702
Ioxaglate sodium (19.6%)-meglumine (39.3%) (Hetabrix)	320	600

Source: Drug reviews from the formulary. Intravascular contrast media. Hosp Pharm *26:275–278, 1991.*

TABLE 68–6 Patients at Greater Risk of a Severe Adverse Reaction to Radiologic Contrast Media

Patients with history of a previous adverse reaction to radiologic contrast media (excluding mild flushing, nausea)
Asthmatic patients
Allergic and atopic patients
Cardiac patients with decompensation, unstable arrhythmia, recent MI
Renal failure, diabetic nephropathy
Feeble infants and the elderly
Patients with severe general debility or dehydration
Patients with metabolic hematologic disorders

Source: Grainger RG: Intravenous contrast media. In Grainger RG, Allison D, editors: Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging, *New York, 1997, Churchill-Livingstone, pp 35–45.*

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Access the reference list online at http://www.expertconsult.com

Cancer Pain

CHAPTER 69

Approach to the Management of Cancer Pain

William M. Mitchell, MD ❁ **Charles F. von Gunten,** MD, PhD, FACP

Pain is one of the most prevalent and distressing symptoms reported by patients with cancer.[1] It is also under-reported by patients, under-recognized by health-care providers and consequently undertreated. In its report *Ensuring Quality Cancer Care*, the Institute of Medicine identified management of cancer-related pain as a fundamental element of quality cancer care.[2]

ASSESSMENT OF CANCER PAIN

Effective pain management must begin with comprehensive pain assessment. Because pain perception is inherently subjective, the gold standard for assessing pain is the patient's self-report.[3] Patients with chronic cancer pain may fail to display any signs of adrenergic stimulation such as tachycardia and hypertension even though the patient reports severe pain. Thorough assessment includes report of location, type, temporal profile, and severity of each significant pain.

TYPE

Cancer pain can be classified as nociceptive, neuropathic, or a combination of the two.[4] Each type typically presents with a number of relatively distinct qualities.

Nociceptive pain results when pain-sensing neuronal pathways are stimulated and function normally. Specialized receptors at the distal end of neuronal axons, termed nociceptors, detect noxious mechanical, chemical, and thermal stimuli and generate neuronal electrical activity. These signals are transmitted normally along neuronal pathways to the brain.

Nociceptive pain can originate from somatic or visceral sources, or both. Somatic pain originates from skin, muscle, bone, and fascia. It is mediated by the somatic nervous system. As innervation is highly specific, localization of the pain is precise. Somatic pain is often described as sharp, aching, or throbbing. Visceral pain originates from internal structures. It is mediated by the autonomic nervous system. As there is a lack of specificity of innervation, and considerable neuronal crossover, visceral pain is typically difficult for the patient to localize or describe, and may encompass an area that is much larger than might be expected for a single organ. Visceral pain is often characterized as crampy.

Neuropathic pain has been defined as a primary lesion or dysfunction of the pain-sensing nervous system.[5] The lesion can be either peripheral in the somatic or visceral nervous system, or central. The nerves themselves may be subject to damage from compression, infiltration, ischemia, metabolic injury, or transection.[6] The myelin sheath that insulates one nerve from another may also be damaged. Alternatively, neuropathic pain may also be caused by dysfunction of the nervous system, as in central facilitation or "wind-up"[7] where an event that is normally not painful, such as the pressure from a bed sheet or clothing on the chest of patient with recurrent breast cancer, causes pain.[8] Neuropathic pain is often described as burning, shooting, stabbing, or electric-like, and may be associated with numbness, tingling, and/or sensory deficits.

TEMPORAL PROFILE

The temporal profile of a pain will provide further clues to its etiology.[3] The patient should be asked about the duration of the pain. When did it first start? How long has it been present? Did it come on slowly, or suddenly? One can ask what the baseline or background pain is like. Does it vary over time, such as worse at night? Is the patient ever pain-free? Are there times when the pain gets much worse? What factors exacerbate or relieve the pain, such as by activity, touch, clothing, cold/heat, procedures, and so on. As an example, spontaneous pain of short duration could be the paroxysmal firing of a neuroma. Back pain that occurs only with weight bearing could indicate a spinal bony metastasis. Most cancer pain is continuous over time with some variation in intensity, particularly at night. Without intervention, it rarely disappears completely. Cancer pain is also frequently associated with intermittent paroxysms of pain that occur with activity (e.g., movement, chewing, swallowing, breathing, defecating, urinating, dressing, touch, etc.) or during a procedure.

SEVERITY

Sequential measurement of severity using a validated severity assessment scale will provide an indication of the changing intensity of the pain experienced by a given patient over time. It will also guide analgesic management. In a given patient, the same tool should be used for each assessment.

A numerical analog scale is the simplest. The patient is asked to indicate the severity of the pain on a 11-point scale where 0 represents "no pain" and 10 represents the "worst possible pain."

Alternatively, a visual analog scale can provide more visual cues, and be more reliable. The patient is asked to indicate the severity of the pain by marking a 100-mm line at a point that indicates the intensity of her/his pain (delimited by the descriptors "no pain" at one end (usually the left) and "worst possible pain" at the other end). A few patients will find it easier to understand a vertical line in which "no pain" is at the bottom and "worst possible pain" is at the top. For children, and adults who do not understand numeric or visual analog scales, the Wong-Baker or other faces scales are similarly reliable assessment tools.

To understand how the pain varies over time, one can ask about the intensity of the continuous pain now, the worst it has been in the last 24 hr, the best it has been in the last 24 hr, and the intensity of intermittent pain at its peak.

TOTAL PAIN

Together with a careful physical examination and select laboratory and imaging studies, it is usually possible to identify the relevant pathophysiology leading to a pain state. However, a particular pain syndrome is part of a whole person's experience. The concept of "total pain" emphasizes that multiple nonphysical factors can also contribute to pain, that is, psychological factors (e.g., anxiety, depression), social factors (e.g., familial estrangement), and spiritual or existential factors (e.g., loss of meaning in life, fear of death). It may not be possible to control pain successfully without also addressing each of these other sources of suffering.[9]

TREATMENT OF CANCER PAIN

WORLD HEALTH ORGANIZATION THREE-STEP LADDER

In 1988 the World Health Organization (WHO) first promoted the Canadian three-step ladder for cancer pain management (Fig. 69-1).[10] Recent pain guidelines from the Royal College of Physicians and the European Association for Palliative Care both use the WHO guidelines as a basis.[11,12] Today, it is the cornerstone for the WHO's public health initiative to treat cancer pain worldwide.

The ladder provides a clinically useful strategy for classifying the available analgesics, and guiding initial analgesic selection based on the severity of the patient's pain. If the pain is mild (1/10 to 3/10), an analgesic can be chosen from step one. If it is moderate (4/10 to 6/10), one can start with an analgesic from step two. If it is severe (7/10 to 10/10), one can start with an opioid from step three. At any step, adjuvant analgesics can be added to optimize pain control.[13]

Step One: Acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (ASA) are the mainstay of step one of the WHO analgesic ladder for the management of mild pain. They obey first-order kinetics and may be dosed up to recommended maximums (Table 69-1). Many are available without prescription.

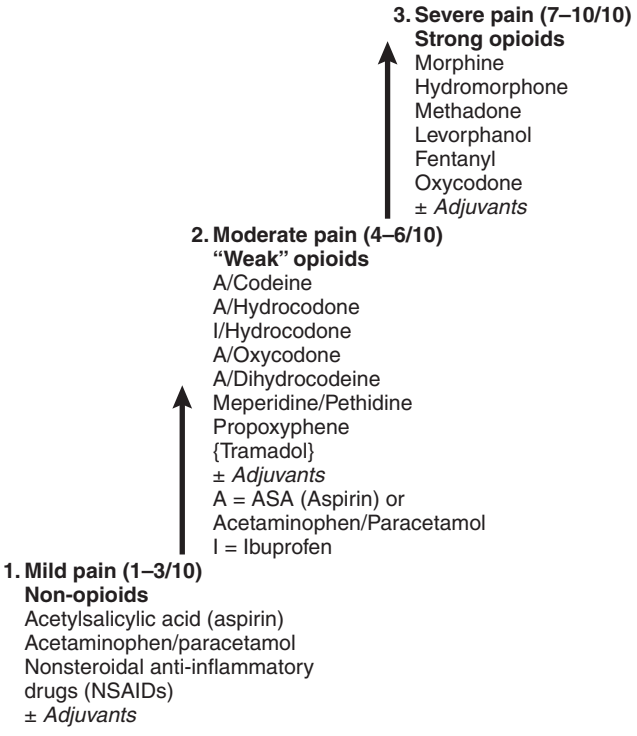

FIGURE 69-1 World Health Organization three-step ladder.

Sustained-release preparations or NSAIDs with longer half-lives (e.g., piroxicam) that require less frequent dosing may encourage adherence. When pain is more than mild, step-one analgesics can be combined with opioids at steps two and three.

TABLE 69–1 Selected Step-One Analgesics

Drug	Suggested Maximum Dose
Acetaminophen (APAP, Tylenol)	650 mg PO q4h
Acetylsalicylic acid (ASA, aspirin)	650 mg PO q4h
Ibuprofen (Motrin)	800 mg PO qid
Choline magnesium trisalicylate (Trilisate)	1500 mg PO tid
Celecoxib (Celebrex)	100 mg PO qd
Diclofenac (Cataflam)	50 mg PO qid
Diclofenac, extended release (Voltaren)	75 mg PO tid
Diflunisal (Dolobid)	500 mg PO tid
Etodolac (Lodine)	400 mg PO tid
Indomethacin (Indocin)	50 mg PO qid
Ketoprofen (Orudis)	75 mg PO qid
Nabumetone (Relafen)	1 g PO bid
Naproxen (Naprosyn)	500 mg PO tid
Oxaprozin (Daypro)	1800 mg PO qd
Rofecoxib (Vioxx)	25 mg PO qd
Sulindac (Clinoril)	200 mg PO bid
Salsalate (Disalcid)	1500 mg PO tid
Ketorolac (Toradol)	60 mg IM/IV then 30 mg IV/IM q6h; 10 mg PO qid; not to exceed 5 days

Step Two: Several opioid analgesics are conventionally available in combination with acetaminophen, ibuprofen, or ASA and are commonly used to manage moderate pain. They are listed in Fig. 69-1 under step two of the WHO analgesic ladder. With the exceptions of propoxyphene (that truly has weak analgesic activity), tramadol (that has a unique combination of weak opioid activity with other analgesic properties), meperidine, and codeine (methylmorphine, which has one-tenth the potency of morphine), the opioids in this class are close in potency to morphine (mg for mg).[14] However, they have been called "weak" opioids because, in combination, they have a ceiling to their analgesic potential due to the maximum amounts of acetaminophen or ASA that can be administered per 24 hr (e.g., 4 g acetaminophen per 24 hr).[15]

The combination medications of step two all obey first-order kinetics and may be dosed up to recommended maximums (Table 69-2). The potential adverse effects are those of the component drugs.[16,17]

Frequently, patients are simultaneously given prescriptions for several step-two drugs even though pain is poorly controlled. This usually occurs when physicians are reluctant to prescribe a step-three opioid. Aside from propoxyphene, there is no evidence that maximal dosing of any "step-two" medication is better than another and trials of several step-two medications are likely to prolong the patient's pain. In addition, when a step-two drug inadequately relieves pain, patients may combine two or more medications, or take more than the prescribed amount in an attempt to obtain pain relief. In doing so they may unknowingly put themselves at increased risk for significant toxicity from either the acetaminophen or ASA component of the medication. If pain persists, or increases, despite a maximum dose of a step-two drug, a step-three drug should be prescribed instead.

Step Three: The pure agonist opioid analgesics comprise step three of the WHO analgesic ladder. Morphine is the prototypical drug because of its ease of administration and wide availability. Other widely prescribed opioids are listed in step three of Fig. 69-1. Many patients with chronic pain are best managed with an appropriately titrated strong opioid that is combined with one or more coanalgesics. In contrast with the step-one and step-two analgesics, there is no ceiling effect or upper limit to the dose of opioids when titrating to relieve pain.

TABLE 69–2 Selected Step-Two Analgesics

Drug	Suggested Maximum Dose
Codeine	60 mg PO q4h
Codeine 30 mg/325 mg APAP (Tylenol #3); codeine 30 mg/325 mg ASA (Empirin #3)	2 PO q4h
Hydrocodone 5 mg/500 mg APAP (Vicodin)	2 PO q6h
Hydrocodone 10 mg/650 mg APAP (Lortab)	1 PO q6h
Hydrocodone 7.5 mg/200 mg ibuprofen (Vicoprofen)	1 PO q4h
Oxycodone 5 mg/325 mg APAP (Percocet); oxycodone 5 mg/325 mg ASA (Percodan)	2 PO q4h
Tramadol 50 mg (Ultram)	2 PO q6h

"Step Four": Several studies of the WHO three-step ladder have demonstrated that its application results in the adequate control in up to 90% of patients with cancer pain.[3] Several authors have informally invoked "step four" to indicate approaches that should be reserved for patients whose pain is not controlled by competent use of the analgesic approaches outlined in the first three steps. In general, "step four" involves invasive approaches for pain relief that can be summarized as follows.

Subcutaneous (SC) or intravenous (IV) administration of opioid analgesics and coanalgesics may be required for patients in whom oral (PO), buccal mucosal, rectal (PR), or transcutaneous approaches are not possible or practical, or in whom doses of oral opioids lead to undesirable adverse effects. Adverse effects may be minimized as a result of the uniform delivery of the drug parenterally, the change in route of administration, or the reduction in first-pass metabolite production.

- Intraspinal administration of opioid analgesics either epidurally or intrathecally may be required in selected patients.
- Intraventricular application of opioid analgesics and other drugs has been investigated for selected central pain syndromes.
- Neuroablative techniques such as peripheral neurolytic blockade, ganglionic blockade, cordotomy, and cingulotomy may be appropriate in highly selected patients.

COMMON ANALGESICS

ACETAMINOPHEN

Despite its wide use, the precise mechanism of action remains unclear. Although it is analgesic and antipyretic, it is not anti-inflammatory, at least systemically. Its analgesic activity is additive to other analgesic agents, including the NSAIDs and opioids.

Acetaminophen is associated with significant liver toxicity. It is generally recommended that the total dose not exceed 4 g per 24 hr for routine dosing of patients with normal liver function.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, INCLUDING ACETYLSALICYLIC ACID

Normally, the enzyme cyclooxygenase (COX) catalyzes the conversion of arachidonic acid to prostaglandins and thromboxanes. These inflammatory mediators sensitize nerve endings to painful stimuli and stimulate a group of silent nociceptors that only fire in an inflammatory milieu. In the spinal cord, COX plays a role in setting up the dysfunctional signaling pattern involved in neuropathic pain.

NSAIDs are potent anti-inflammatory medications that inhibit the activity of COX and decrease the levels of these inflammatory mediators. As a result, there is less sensitization of nerve endings, less recruitment of silent nociceptors, and less risk of central "wind-up." Although primary analgesia may be achieved at low doses, for their

anti-inflammatory effects maximum doses should be used. As they act through an alternate mechanism to opioids and other adjuvant analgesics, NSAIDs may be combined with other analgesics to achieve better pain relief than is possible with a single medication.

The morbidity and mortality associated with NSAIDs, including ASA, are significantly higher than for any of the other analgesics. The adverse effects of NSAIDs are related to their mechanism of action. Inhibition of COX leads to inhibition of platelet aggregation and microarteriolar constriction/decreased perfusion, particularly in the stomach and kidneys. In the stomach the relative ischemia compromises the production of gastric mucus by the chief cells, and significantly increases the risk of gastric erosions and bleeding. In the kidneys the relative ischemia increases the risk of renal papillary necrosis and renal failure.

COX exists in two forms: a constitutive form, COX-1, and a form that is inducible under conditions of inflammation, COX-2. There are both COX-2-selective and nonselective NSAIDs that target both forms of COX. Whereas renal insufficiency is a risk of both nonselective and COX-2-selective NSAIDs, the risk of gastropathy and platelet inhibition is significantly decreased with COX-2-selective NSAIDs.

Patients (particularly the elderly) who are dehydrated, malnourished, cachectic, or have a history of nausea, gastritis, or gastric ulceration with NSAIDs are at increased risk for adverse effects from NSAIDs. However, the dyspepsia and abdominal pain that limit use of the NSAIDs in some patients do not correlate with significant gastric erosions and gastrointestinal bleeding.

To minimize the risk of ischemia, the patient should be well hydrated. The use of an H_2 blocking antacid (e.g. cimetidine or ranitidine) to treat NSAID dyspepsia and abdominal pain does not prevent gastric erosions and gastrointestinal bleeding. Only misoprostol, a prostaglandin-E analog that reverses the effect of NSAIDs on the microarteriolar circulation of the stomach, and the proton-pump inhibitors (such as omeprazole, pantoprazole) have been shown to heal gastric erosions and reduce the risk of significant gastric bleeding.

The nonacetylated salicylates (choline magnesium trisalicylate and salsalate), nabumetone, and the COX-2 inhibitors do not significantly affect platelet aggregation. They may be useful in patients who are thrombocytopenic and for whom other NSAIDs are contraindicated. Sulindac is thought to be least likely to induce renal failure because of its minimal effect on prostaglandin synthesis at the level of the proximal renal tubule.

In contrast to the opioids, the NSAIDs and acetaminophen have a ceiling effect to their analgesic potential, do not produce pharmacologic tolerance, and are not associated with physical or psychological dependence.

OPIOIDS

Opioid analgesics act by binding to opioid receptors of three subtypes (mu, kappa, and delta) both peripherally and centrally. The central receptors in the spinal cord and brain are most important for mediating analgesia. The opioid analgesics in common usage may be divided into those that are full agonists, partial agonists, and mixed agonist–antagonists. The pure agonist drugs are the most useful in chronic cancer pain.

OPIOIDS TO AVOID

The mixed agonist–antagonist opioids (such as pentazocine, butorphanol, and nalbuphine) and the partial agonist opioids (such as buprenorphine) are poor choices for patients with severe pain. They have no advantages over the pure agonist opioids. Besides having a ceiling effect to the analgesia they produce, they have the significant disadvantage that, if combined with a pure opioid agonist, they may precipitate acute pain and opioid withdrawal symptoms.

Meperidine (Demerol) is a synthetic pure agonist opioid that was widely used in the postoperative management of acute pain. However, its continued use has been questioned for three reasons. First, because of its short duration of action in comparison with morphine or other pure agonist opioids, it must be dosed too frequently to provide convenient, adequate analgesia. Second, because its oral absorption is unpredictable, a reliable oral dose cannot be prescribed that corresponds to parenteral doses. Third, and most significant, the major liver metabolite normeperidine, which has a longer half-life (approximately 6 hr) than meperidine (approximately 3 hr), accumulates with repeat dosing q3h for analgesia and frequently causes significant subclinical or clinical toxicity, including impaired concentration, restlessness, agitation, excessive dreams, hallucination, myoclonic jerks, or even seizures. This accumulation is particularly accentuated in patients with compromised renal function. The assertions that meperidine is associated with less constipation or spasm of the sphincter of Oddi are not supported by evidence. Its use is best limited to small doses (25 to 50 mg) parenterally to treat rigors associated with fever, drugs, or blood product transfusions.

ROUTES OF ADMINISTRATION

The oral route of administration is preferred for the management of cancer pain. It provides the simplest, least expensive way to manage most cancer pain. When it is not available, analgesics can be administered buccally and rectally before resorting to more invasive and expensive routes of delivery. In a small number of patients (<5%) subcutaneous, intravenous, or intraspinal administration may be required. The time to peak serum concentration (C_{max}) correlates with time to peak effect, and this occurs in 1 hr for an oral or rectal dose of a short-acting opioid. Subcutaneous doses reach peak effect in 30 min and IV doses reach peak effect in 8 min.

ACHIEVING INITIAL PAIN RELIEF

In a patient with severe pain, opioids should be dosed frequently until the patient achieves pain relief or undesirable side effects. This is accomplished by administering a single dose and reassessing after the dose has reached peak effect (time to C_{max}: 1 hr for an oral dose, 30 min for a subcutaneous dose, and 8 min for an IV dose). If the patient remains in severe pain, the dose should be doubled and the patient observed again until peak effect. This should be

repeated with careful observation until the pain is no longer severe or the patient experiences side effects. For example, if a patient continues to have severe pain and no unacceptable side effects 8 min after a single 4-mg intravenous dose of morphine, the patient should receive an additional 8 mg of morphine intravenously. If the patient remains in severe pain, 8 min later a 16-mg dose should be administered.

ROUTINE DOSING FOR CONSTANT PAIN

One should distinguish between constant and intermittent pain. For constant, ongoing cancer pain, analgesics should be prescribed on a regular schedule at doses sufficient to keep the pain controlled. For patients with constant pain, dosing solely on an "as needed" or "prn" basis guarantees that the patient will frequently return to pain and may increase both the patient's anxiety and the total dose required to control the pain.

Most of the short-acting drugs used for analgesia, particularly acetaminophen, the NSAIDs including ASA, and the opioids, follow first-order kinetics. When prescribing them on a routine schedule, they should be administered once every half-life in order to achieve steady state and maintain constant serum levels, such as q4h for oral opioid dosing. Methadone, with its longer half-life, is administered every 8 to 12 hr.[18–20]

TITRATION

When initiating, titrating, or changing analgesic therapy, drugs that follow first-order kinetics take 5 half-lives to reach pharmacologic steady state. Changes in dosages should only be made once the serum level has reached steady state, such as once every 20 to 24 hr when morphine is given PO, or even SC. Waiting longer will not improve pain control or safety. Increasing scheduled dosages before steady state is reached may lead to unnecessarily high serum levels and undesired adverse effects.

SUSTAINED-RELEASE PRODUCTS

Sustained-release medications should not be used alone to adjust or titrate a patient's uncontrolled pain. Using them for titration unduly prolongs the process to bring the pain under control, because they can be titrated only once every 5 half-lives (roughly 60 hr). However, once the pain is controlled, changing to a sustained-release product may enhance the patient's quality of life and improve compliance and adherence due to the decreased frequency of dosing (e.g., q8h, q12h, q24h, etc.).

Sustained-release preparations of morphine and oxycodone are available for PO administration and should be administered in accordance with the instructions of the manufacturer.

Transdermal fentanyl patches are convenient when patients are receiving stable opioid dosing, but should not be used to titrate unrelieved pain. Approximately 12 to 18 hr are needed for significant serum levels of fentanyl to accumulate, so appropriate doses of opioids need to be maintained during this window of time. Fentanyl patches may be changed every 72 hr, although a small number of patients may need to have their patch(es) changed every 48 hr. Titration may be done every other day.

BREAKTHROUGH OR RESCUE DOSING FOR INTERMITTENT PAIN

Changes in pain severity may occur spontaneously because of activity (e.g., movement) or a procedure (e.g., venipuncture, wound dressing change). If the duration and severity of the change are sufficient, extra short-acting doses of the same or similar medication (breakthrough or rescue doses) on an "as needed" or "prn" basis may be appropriate. If a patient regularly requires more than 2 to 4 breakthrough doses per 24 hr, then the routine scheduled dose should be adjusted upwards. For intermittent pain of short duration (seconds to a few minutes), breakthrough dosing, particularly of the opioids, may lead to undesired adverse effects without increased analgesia.

Breakthrough doses of an analgesic can be given safely with a frequency equivalent to the time required to reach C_{max}. Again, this is 1 hr for an oral dose, 30 min for a subcutaneous dose, and 8 min for an IV dose. Making the patient wait any longer when the pain is not controlled simply prolongs the time required to establish optimal pain control.

The size of the breakthrough dose should be related to the routine dose. For the strong opioids such as morphine, hydromorphone, and oxycodone, a simple rule-of-thumb follows: for the oral route, administer 10% of the total 24-hr dose per breakthrough dose every 1 hr as needed. For the intravenous route, administer 50% to 100% of the hourly infusion rate every 5 to 10 min as needed. The dose is then adjusted as the routine dose changes or as the intensity of the intermittent pain requires.

Oral transmucosal fentanyl is available in several preparations including a candy matrix lozenge on an applicator stick that is twirled against the buccal mucosa, as an orally dissolving tablet that is absorbed transmucosally, or an adherent film. Additionally, other preparations will likely be commercially available soon including nasal sprays, inhalers and active transdermal patches. Relatively quick onset and offset make these preparations useful to treat short-lived breakthrough pain. Dosing of fentanyl preparations must be individualized: it cannot be calculated as an equianalgesic dose.[21,22]

EQUIANALGESIC DOSING

The relative abilities of opioid analgesics to relieve pain have been correlated (Table 69-3). These relationships are not scientifically precise, as there is significant interpatient variability. Further, the data from which these equivalencies are derived are often obtained in clinical settings other than chronic cancer pain. Nevertheless, the equianalgesic tables are useful to approximate the dose of a new analgesic when changes are contemplated. The dose should then be adjusted based on patient response.[23]

When changing between opioids, there is incomplete cross-tolerance. To correct for this when pain is controlled, some advocate reducing the dose of the new medication by 25% to 50% after calculating the equianalgesic dose.[24]

TABLE 69–3 Equianalgesic Dosing

Oral Dose (mg)	Analgesic	IV/SC/IM (mg)
150	Meperidine	50
100	Codeine	60
15	Hydrocodone	–
15	Morphine	5
10	Oxycodone	–
4	Hydromorphone	1.5
2	Levorphanol	1
–	Fentanyl	0.050

Methadone, an opioid with a half-life that ranges from 15 to 40 hr or more, is an important exception.[25] Its apparent equianalgesic efficacy varies with the dose of opioid. In acute dosing, or at low doses, it appears to be a 1:1 ratio of methadone to morphine. For doses of morphine less than 500 mg/day, the relative potency of methadone to morphine is about 5:1. For patients taking between 500 and 1000 mg of morphine per day, the relative potency of methadone becomes 10:1. For patients taking greater than 1000 mg of morphine per day, the relative potency could be from 15:1 to 20:1. Because of its long and variable half-life, care must be taken when switching from one opioid to methadone and while titrating to an effective dose. Because of its long half-life, adverse effects may appear several days after doses are adjusted. Without continuous review these may be serious: methadone is the opioid most associated with respiratory depression when dosed on a regular basis.[26,27]

Attempts have been made to correlate the relative analgesia provided by acetaminophen, the NSAIDs, and the opioids. Ketorolac 10 mg orally seems to be roughly equivalent to the combination tablet 60 mg codeine/650 mg acetaminophen PO or 6 to 9 mg morphine PO in cancer pain. Transdermal fentanyl 25 μg/h is approximately 50 mg morphine PO q24h.

When changing routes of administration, differences in opioid metabolism (e.g., less first-pass catabolism IV/IM/SC compared to PO) necessitate adjustments to the opioid dose as indicated in Table 69-3. For example, an equivalent dose of morphine IV/IM/SC will be one-half to one-third that given by mouth.

CLEARANCE BUILDUP

Most opioids are conjugated in the liver and more than 90% of the metabolites excreted renally. Although most of the opioid metabolites are inactive, some (such as morphine 6-glucuronide) have analgesic activity and several (such as morphine 3-glucuronide) may be responsible for observed adverse effects (e.g., central nervous system excitation).[28] Mild elevation in transaminases should not have a significant impact on opioid dosing. Patients with severe liver failure should have their opioid doses decreased and/or dosing intervals increased.

Impaired renal excretion will reduce opioid clearance,[29] leading to buildup of metabolites, prolonged analgesia and increased risk of adverse effects. To reduce these risks, patients receiving morphine should be well hydrated and maintain adequate urine output. If renal function is impaired, morphine doses should be decreased and dosing intervals increased. The patient with anuria may require very little or no extra morphine to maintain analgesia. Routine dosing should be discontinued.

Methadone and fentanyl are not renally excreted, and fentanyl does not have active metabolites.

OPIOID ADVERSE EFFECTS

Common and uncommon adverse effects of opioid analgesics are listed in Table 69-4. Common adverse effects of the opioid analgesics are easily managed.[30] In the majority of patients, pharmacologic tolerance develops to all of the common adverse effects, except constipation, within 1 to 2 weeks. Consequently, nausea and vomiting may be treated expectantly with antiemetics for the short period that these symptoms are problematic. If nausea and/or vomiting persist, changing the opioid or the route of administration may resolve the problem.

Similarly, patients should be counseled that the drowsiness they experience when initiating an opioid will usually dissipate after the first week or so. Patients can often tolerate a little drowsiness if they are assured that it will not persist for the entire time they are taking opioid analgesics. In fact, once a stable dose of an opioid has been reached, drowsiness will likely settle completely, and function will normalize. Most patients on a stable dose of opioid who have no adverse effects may safely drive a car. Persistent somnolence may be managed by ensuring adequate hydration and renal clearance, changing to a sustained-release product to minimize peak effects, changing the opioid, changing the route of administration, or by adding a psychostimulant (such as methylphenidate).

As patients given opioid analgesics will not develop tolerance to constipation, they should be treated with stimulant laxatives (e.g., senna or bisacodyl), osmotic laxatives (e.g., magnesium salts or lactulose), or prokinetic agents (e.g., metoclopramide) on a routine basis. Constipation refractory to usual laxatives can be treated with methylnaltrexone, a peripherally acting μ-opioid antagonist. Simple stool softeners (e.g., sodium docusate) are usually ineffective. Fiber-containing products can worsen opioid-induced constipation in patients with poor oral intake.

Persistent adverse effects from opioids seem to be somewhat idiosyncratic to the drug and individual. Simply changing to an alternative opioid at an equianalgesic dose will often resolve the problem.

TABLE 69–4 Adverse Effects of Opioid Analgesics

Common	Uncommon
Constipation	Dysphoria/delirium
Nausea/vomiting	Bad dreams/hallucinations
Drowsiness	Pruritus/urticaria
Dry mouth	Urinary retention
Sweats	Myoclonic jerks/seizures
	Respiratory depression

The uncommon adverse effects of the opioids are also manageable. The dysphoria and confusion that occasionally occur may be managed by ensuring adequate hydration and renal clearance (thereby minimizing metabolite buildup), lowering the opioid dose, changing the opioid analgesic, or by adding low doses of a neuroleptic drug such as haloperidol, chlorpromazine, or risperidone.

The pruritus and urticaria that occur with opioids are not immune mediated, but a nonspecific release of histamine from mast cells in the skin. This may be managed with long-acting antihistamines, doxepin 10 to 30 mg PO qhs, or by changing to an alternative opioid analgesic. True allergy presenting as bronchospasm leading to anaphylaxis is extremely rare. Most patients who report allergy have had poorly managed adverse effects (usually nausea/vomiting and/or constipation) or too much medication too fast (leading to drowsiness and/or confusion).

The risk of respiratory depression from opioid analgesics in patients with pain is frequently misunderstood. This side effect occurs at relatively higher doses than those that produce other forms of toxicity, such as sedation. Patients develop pharmacologic tolerance to the respiratory depressant effects of opioids over the same time course as other adverse effects. Too frequently opioids have been withheld or underdosed because of unsubstantiated fear of respiratory depression or the mismanagement of adverse effects. In the patient with uncontrolled pain, opioid analgesics can be judiciously but expeditiously and safely titrated until adequate relief is obtained or intolerable adverse effects encountered.

OPIOID EXCESS/OVERDOSE

In the setting of pain management, opioid excess presents first as mild drowsiness, proceeds to persistent somnolence, then to a poorly arousable state, and finally to respiratory depression. These changes may be associated with increasing restlessness, agitation, confusion, dreams, hallucinations, myoclonic jerks, or even sudden onset of seizures.

When assessing a patient for respiratory depression, it should be remembered that a respiratory rate of 8 to 12 per minute is frequently normal, particularly at nighttime. One should first check for arousability: the patient may be sleeping. If early, or even moderate excess is present without major compromise, the opioid can be held and normal metabolism will clear the excess opioid, particularly if the patient is adequately hydrated. Naloxone reversal is not normally necessary.

If the patient is not arousable, has a respiratory rate less than 6 to 8 per minute or there is significant hypoxemia or hypotension present, opioid reversal with naloxone may be warranted. A 0.4- or 1.0-mg ampule of naloxone can be diluted with 10 ml of saline and 0.1 to 0.2 mg IV boluses administered every 1 to 2 min. SC or PO administration is not appropriate. Because naloxone has a high affinity for opioid receptors, titration any faster, or with larger boluses, may precipitate opioid withdrawal that presents as an acute pain crisis, psychosis, or severe abdominal pain and precipitates pulmonary edema or even myocardial infarction. Only if several 0.1- to 0.2-mg boluses are ineffective should the bolus size be increased.

Naloxone has a high affinity for lipids and will redistribute itself into adipose tissue within 10 to 15 min of administration. Any improvement frequently disappears within this time frame and signs of toxicity return. Repeated naloxone dosing may be necessary to sustain the reversal until the patient has cleared sufficient of the opioid to be out of danger. If the overdose is severe and considerable naloxone is required, a continuous infusion of naloxone may be required until the crisis is over.

If a patient who has been well managed on a stable dose of opioid for some time suddenly develops signs of overdose, the opioid should be stopped and sepsis, renal failure, or other causes should be ruled out. It is unlikely that the opioid alone will be the cause of the "effective overdose."

ADDICTION AND PHYSICAL DEPENDENCE

Addiction, the psychological dependence on a drug, is a vastly overrated and misunderstood consequence of using opioid analgesics.[3] In patients with chronic cancer pain, the incidence of addiction is less than 1:1000 and is usually related to pre-existing dependency.

Physical dependence alone, meaning the development of a withdrawal syndrome upon abrupt discontinuation of the drug, is not evidence of addiction. Physical dependence occurs over the same time course as tolerance develops to the adverse effects of the opioid analgesics and is the result of changes in the numbers and function of opioid neuroreceptors in the presence of exogenous opioid.

If opioid analgesics are tapered instead of abruptly withdrawn, withdrawal symptoms do not occur. Usually the opioid dose can be reduced by 50% to 75% every 2 to 3 days without ill effect. Occasionally a small dose of a benzodiazepine (e.g., 0.5 to 1.0 mg of lorazepam) or of methadone (with its longer half-life) may be necessary to settle the feeling of slight uneasiness or restlessness that accompanies a rapid tapering process. If restlessness or agitation is anything more than very mild, the rate of tapering should be slowed.

ADJUVANT PAIN MEDICINE

Adjuvant analgesics are used to enhance the analgesic efficacy of opioids, treat concurrent symptoms that exacerbate pain, and/or provide independent analgesia for specific types of pain. They may be used at all stages of the analgesic ladder. Some of the adjuvants, such as acetaminophen, the NSAIDs, the tricyclic antidepressants, and perhaps the antiepileptics, have primary analgesic activity themselves and may be used alone or as coanalgesics.

Two cancer pain syndromes bear particular mention in this regard. Bone pain from bone metastases is thought to be, in part, prostaglandin mediated. Consequently, the NSAIDs and/or corticosteroids may be particularly helpful in combination with opioids. Spinal cord compression should always be considered if back pain is severe, increasing quickly, or associated with motor, bowel, or bladder dysfunction.

Neuropathic pain is rarely controlled with opioids alone. The tricyclic antidepressants, antiepileptics, and corticosteroids are often required in combination with the opioids

to achieve adequate relief. Commonly used agents are listed below with a few comments about their use.

- NSAIDs and/or acetaminophen may be added to the opioids for adjuvant analgesia, particularly when inflammatory or peripheral mechanisms are thought to be responsible for the painful stimulus.
- Corticosteroids provide a range of effects including anti-inflammatory activity, mood elevation, antiemetic activity, and appetite stimulation. They reduce pain both by their anti-inflammatory effect of reducing arachidonic acid release to form prostaglandins as well as decreasing swelling and pressure on nerve endings. Undesirable effects such as hyperglycemia, weight gain, myopathy, infection, and dysphoria or psychosis may complicate therapy.[31–33]
- Anticonvulsants (such as gabapentin, pregabalin, levetiracetam, carbamazepine, valproate, and lamotrigine) are used either alone or in addition to opioids or other coanalgesics to manage neuropathic pain. They have been particularly advocated for neuropathic pain with a shooting or lancinating quality (such as trigeminal neuralgia or nerve root compression).[34–38]
- Tricyclic antidepressants (such as amitriptyline, desipramine, imipramine, and nortriptyline) are useful in pain management in general, and neuropathic pain in particular. They have innate analgesic properties and are effective through mechanisms that include enhanced inhibitory modulation of nociceptive impulses at the level of the dorsal horn. If the anticholinergic adverse effects of tertiary amine tricyclics (amitriptyline, imipramine) are undesirable or troublesome, the secondary amine tricyclics (nortriptyline, desipramine) may be effective analgesics and produce fewer adverse effects. The selective serotonin reuptake inhibitor class of antidepressants has not been shown to be useful in similar ways to the tricyclic antidepressants. Selective norepinephrine and serotonin reuptake inhibitor antidepressants (such as duloxetine and venlafaxine) may have a role in management of cancer pain, but have not been well studied.[39,40]
- Bisphosphonates (such as pamidronate and zoledronate) and calcitonin have been used as adjuvant analgesics in the management of bone pain from bone metastases.[41] In cancer, bone pain is caused in large part by osteoclast-induced bone resorption rather than the direct effects of the tumor on periosteal or medullary nerve endings. Both the bisphosphonates and calcitonin inhibit osteoclast activity on bone and have been reported to reduce pain significantly in at least some patients.

Neuroleptic medications (such as haloperidol, chlorpromazine, or risperidone) and anxiolytics (such as lorazepam) are used for the management of specific psychiatric disorders that complicate pain management such as delirium, psychosis, or anxiety disorders. With the exception of methotrimeprazine and clonazepam, none have been shown to have intrinsic analgesic activity.

N-methyl-D-aspartate (NMDA) receptor antagonists, such as dextromethorphan, ketamine, and methadone, may affect the spinal neural circuitry that leads to a neuropathic pain state resistant to high-dose opioids.[42] Clinical studies with dextromethorphan and ketamine have shown some mild pain effects but have been significantly limited by dose-related adverse effects, particularly drowsiness. Methadone, however, is inexpensive and well tolerated. It exists as a racemic mix of levo and dextro isomers. The levo form binds at opioid receptors, whereas both forms can block the NMDA receptor. It is hypothesized that its NMDA receptor antagonist activity explains the variable potency observed when changing from other opioids to methadone. Recent studies have shown QT prolongation as a potential side effect of methadone and electrocardiogram monitoring is recommended in patients treated long term.

Local anesthetics, such as systemic lidocaine, that are nonselective inhibitors of sodium channels have also been utilized to treat neuropathic pain.[43,44] Oral anesthetics such as mexiletine have also been used in neuropathic pain, but clinical trials to date have not been definitive. Topical lidocaine patches have been approved for use in postherpetic neuralgia. Research has identified many subtypes of Na channels. In the future it may be possible to block a specific subset involved in mediating pain transmission.

Alpha-2-adrenergic agonists such as clonidine can also be effective adjuvant analgesics for both nociceptive and neuropathic pain.[45] They act at the level of the spinal cord in two ways. First, they act in a mechanistically similar way to the opioids. They act on the same neurons in the cord and lead to the same intracellular events but act through a different receptor. Thus, it is likely that they can enhance the nociceptive effects of opioids. Second, researchers believe α-2-adrenergic agonists also decrease sympathetic outflow, which is involved with neuropathic pain. Clonidine can be given systemically or delivered intraspinally. Systemic delivery may be limited by the adverse effects of lethargy, dry mouth, and hypotension.

ADDITIONAL CONSIDERATIONS

Although this chapter reviews the pharmacologic management of cancer pain, medications are not the only important component of comprehensive cancer pain management. In an attempt to simplify the subject of cancer pain management, pathophysiologic processes have been separated from psychological, social, and spiritual factors. This has led to the unfortunate labeling of the former as "real" pain and the latter as "not real" pain. It has also led to the inappropriate extrapolation of research on acute pain, particularly in laboratory animals, to the management of chronic pain, and to the general avoidance of emotional, psychological, social, and spiritual issues by physicians trained in the scientific method. Optimal pain control may not be possible unless suffering in these other dimensions is addressed. Appropriate referral to allied health-care providers, such as counselors, social workers, chaplains, or hospices, may be required.

CONCLUSIONS

Although cancer pain is a prevalent and severe problem there are a multitude of effective tools to treat nociceptive, neuropathic, and mixed pain syndromes. The opioids

remain the first-line therapy for moderate to severe pain. However, when unsuccessful or limited by adverse effects multiple classes of adjuvant analgesics are available to help optimize pain control. If one class alone is insufficient to control pain or is limited by adverse effects, it is rational to try combining classes. This combination may result in synergistic treatment of pain and may allow individual doses to be decreased thus lowering the risk of adverse effects. Using these guidelines and keeping in mind the concept of total pain, most cancer pain can be controlled with oral drugs.

KEY POINTS

- Successful treatment of cancer pain is possible most of the time.
- The cancer pain syndrome should be determined: nociceptive, neuropathic, or mixed.
- Cancer pain should be assessed and managed within the dimensions of suffering that a patient and his or her family experience: physical, psychological, social, and spiritual.
- Daily evaluation includes an assessment of the location, type, temporal profile, and severity of each significant pain.
- The World Health Organization's three-step approach to cancer pain management using systemic analgesics has been demonstrated to be effective at managing pain in 90% of patients worldwide.
- Opioids are essential for the management of moderate to severe cancer pain. Familiarity with pharmacokinetics of each opioid, equianalgesic dosing, adverse effects, and cost are necessary for their safe, effective, and cost-efficient use.
- Adjuvant analgesics combined with opioids will improve cancer pain control, especially in neuropathic and mixed pain syndromes.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 70

Management of Pain at End of Life

Judith A. Paice, PhD, RN

Pain is a serious problem for people with life-threatening illnesses. In studies exploring symptoms experienced near the end of life, pain, dyspnea, anxiety, and depression are common.[1–3] Cancer pain has been well characterized, representing a wide array of syndromes. These range from acute episodes related to procedures, such as bone marrow aspiration, to chronic syndromes emanating from direct tumor involvement or cancer therapies. Although it may be common during advanced disease, cancer pain can be relieved in 80% to 90% of patients.[4] Less is known about pain occurring in persons with other life threatening illnesses ordinarily seen in palliative care or hospice, such as congestive heart failure, end-stage renal disease, or neuromuscular disorders. An awareness of the most common syndromes in these populations, specific assessment techniques, as well as therapies used to treat these conditions is essential to providing relief.

Until recently experimental models that analyzed the neurobiology of pain due to cancer or other life-threatening illnesses did not exist, limiting our understanding of the unique mechanisms of these phenomena. The development of rodent models of bone pain[5] and chemotherapy-induced neuropathies[6] will provide insights into the neurobiology of cancer pain, eventually leading to the development of targeted, mechanism-based therapies. Furthermore, greater understanding of cancer pain biology may enhance knowledge related to other symptoms common in end of life care. For example, initial evidence surrounding the role of inflammatory cytokines suggests a common biological mechanism between pain, fatigue, depression, and other symptoms.[7] These investigations will be critical to complete our understanding of symptom management for those in palliative care or hospice.

PALLIATIVE CARE AND HOSPICE

All health-care professionals, regardless of their specialty area, are responsible for care of the dying, and, therefore, must gain necessary knowledge and skills to care appropriately for those patients. Pain and symptom management, along with advance care planning, are key elements of this care. Resources, such as palliative care services and hospices, are available to assist clinicians as they provide care to these patients and their families.

Palliative care is the "active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social, and spiritual problems is paramount. Palliative care affirms life and regards dying as a normal process."[8] Palliative care is best integrated into the patient's care early in the course of the disease, rather than being segregated to the last days or weeks of a person's life. Palliative care is often provided through consultation services, inpatient units, outpatient clinics, home care, day programs, and other creative models.[9]

Hospice care in the United States is a philosophy of care with similar tenets to palliative care. Goals include attention to alleviation of physical and emotional suffering, along with focus on the patient and family as the unit of care. Most hospice care in the United States is provided within the home, although a few free-standing units exist for patients unable to be cared for in the home. Hospice is reimbursed through the Medicare hospice benefit. Qualified patients must be certified as having a life expectancy of 6 months if the disease takes its natural course.[10]

PAINFUL SYNDROMES IN CANCER AND OTHER LIFE-THREATENING ILLNESSES

Awareness of the painful syndromes seen in those with cancer and other life-threatening illnesses promotes accurate diagnosis and management. Other chapters in this book describe a variety of pain syndromes that, although primarily seen in the general population, also may occur in people with life-threatening illnesses. However, several syndromes occur uniquely in those with cancer or other advanced diseases.

CANCER

Cancer pain syndromes can be grouped in a variety of categories: acute versus chronic, somatic versus neuropathic, and disease versus treatment related[11] Acute pain is generally due to invasive procedures, such as diagnostic or surgical interventions, and is not unlike the experience of patients with nonmalignant disease. Examples of treatment-related acute pain unique to individuals with cancer are noted in Table 70-1. Chronic pain syndromes often include involvement of bone, soft tissue, the viscera, and the nervous system. Bone metastases are common sources of pain, particularly in patients with breast, lung, or prostate cancers. Lymphedema, occurring in approximately 20% of women who undergo axillary node dissection, is an example of soft tissue pain associated with significant physical and psychological morbidity.[12] Visceral pain may arise from involvement of tumor within the liver, intestine, kidney, peritoneum, bladder, or other organs. Neuropathic pains can evolve from numerous causes, may be difficult for patients to describe, and are often complex to treat (see Table 70-2).[13–15] Finally, many people with cancer experience syndromes unrelated to the cancer or its treatment, such as osteoarthritis.

OTHER LIFE-THREATENING ILLNESSES

The prevalence and types of pain experienced by patients with specific nonmalignant diseases at the end of life have not been fully characterized. Examples include neuropathic pain associated with multiple sclerosis, chest pain due to

TABLE 70–1 Acute Cancer Pain Syndromes

Chemotherapy
Arthralgia and myalgia induced by paclitaxel
Cold allodynia induced by oxaliplatin
Headache due to methotrexate or L-asparaginase
Mucositis commonly due to pre-transplant chemotherapy regimen
Pain due to infusion of chemotherapy into peritoneum or bladder
Growth Factors
Myalgia, bone pain, fever, headache
Hormonal Therapy
Flare syndrome (myalgia, arthralgia, and headache) in prostate or breast cancer
Immunotherapy
Myalgia, arthralgia, and headache due to interferon
Radiation
Bone pain flare (due to radionuclides)
Enteritis and proctitis
Mucositis
Myelitis when spinal cord is irradiated

Adapted from Koh M, Portenoy RK: Cancer pain syndromes. In Bruera E, Portenoy RK, editors: Cancer pain: assessment and management, *ed 2, Cambridge, 2010, Cambridge University Press, pp 53–85.*

TABLE 70–2 Chronic Neuropathic Pain Syndromes Seen at End of Life

Cancer-Related
Brachial, cervical, or sacral plexopathies
Chemotherapy-induced neuropathy
Cisplatin
Oxaliplatin
Paclitaxel
Vincristine
Vinblastine
Cranial neuropathies
Postherpetic neuropathy
Postradiation plexopathies
Surgical neuropathies
Phantom pain
Postmastectomy syndrome
Post-thoracotomy syndrome
Noncancer Causes of Neuropathies
Alcohol-induced neuropathy
Brachial plexus avulsion (trauma)
Carpal tunnel syndrome
Complex regional pain syndrome
Diabetic neuropathy
Fabry's disease
Failed back syndrome
Guillain-Barré syndrome
HIV-associated neuropathy
Viral involvement
Antiretrovirals
Poststroke pain
Trigeminal neuralgia
Vitamin deficiencies

Sources: Koh M, Portenoy RK: Cancer pain syndromes. In Bruera E, Portenoy RK editors: Cancer Pain: Assessment and Management, *ed 2, Cambridge, 2010, Cambridge University Press, pp 53–85; Paice J: Mechanisms and management of neuropathic pain in cancer.* J Support Oncol *1:107–120, 2003; Mendell JR, Sahenk Z: Clinical practice. Painful sensory neuropathy.* N Engl J Med *348:1243–1255, 2003.*

end-stage cardiac disease, and pain due to pressure ulcers or immobility in those who are debilitated (Table 70-3).

ASSESSMENT OF PAIN AT THE END OF LIFE

The assessment techniques described in other chapters should be applied to patients with cancer or other life-threatening illnesses. Intensity, location (or often, multiple locations), quality, temporal nature of the pain, and factors that alter the pain are critical to ascertain.[11] As with all other pain syndromes, a thorough history is followed by a comprehensive physical examination, with particular emphasis on the neurologic evaluation.[16] Radiographic, laboratory, and other diagnostic techniques may be indicated, although in caring for those at the end of life, treatment decisions may be made empirically to avoid uncomfortable scans or invasive procedures.

When patients are unable to verbalize or describe their pain, clinicians can use the furrowed brow as a proxy measure of pain.[17] If there is no response to adequate doses of opioids or other analgesics, additional sources of distress (e.g., distended bladder or fecal impaction) should be explored.

While the general assessment of pain is universal, several additional dimensions are critical at end of life. A psychosocial assessment is indicated, directed towards the meaning of the pain as well as the effect of pain on the patient and their caregiver. The findings of this assessment may suggest the need for education, to mediate fears of addiction, for example. The results of this questioning may also prompt referral to social workers, chaplains, or others who are trained to address the existential distress or suffering experienced by the patient or their family.[18,19]

Pain does not exist in isolation and symptom clusters are common, particularly at end of life. Several instruments have been designed to measure clinically multiple symptoms, including the Edmonton Symptom Assessment Scale (ESAS),[20,21] the M.D. Anderson Symptom Inventory (MDASI),[22] the Memorial Symptom Assessment Scale (MSAS),[23] and others. Another tool, the Distress "Thermometer," is a vertical visual analog scale designed to look like a thermometer, with 0 meaning "no distress" and 10 (at the top of the thermometer) indicating "extreme distress."[24] Accompanying the distress scale is a checklist of various physical, psychological, practical, family support, and spiritual/religious concerns. These are brief, clinically useful tools that quantify the intensity of a variety of symptoms common at end of life (see Table 70-4). The specific needs of people enrolled in hospice are addressed in the Brief Hospice Inventory (BHI). The BHI assesses

TABLE 70–3 Pain Syndromes Seen in People with Noncancer Diagnoses at End of Life

Disorder	Pain Syndromes
Cardiovascular Disease Cardiomyopathy Congestive heart disease Peripheral vascular disease	Chest pain Ischemia
Cirrhosis	Abdominal pain due to portal hypertension, esophageal varices
Debility	Myalgias due to immobility Painful pressure ulcers Abdominal pain due to constipation, impaction Suprapubic pain due to distended bladder
End-Stage Renal Disease	Painful pruritus
HIV	Abdominal pain due to infectious gastrointestinal disorders Chest pain from pneumocystis pneumonia Headaches Herpetic neuropathy Myalgia Neuropathies due to antiretrovirals and the virus
Neuromuscular Disorders ALS Multiple sclerosis (MS) Spinal cord injury	Painful spasticity Lower extremity dysesthesias Periorbital pain and trigeminal neuralgia (MS)
Pulmonary Disease Embolism Infection Pneumothorax	Chest pain Dyspnea

outcomes of hospice patients, including physical and psychological symptoms, patient's perceptions of hospice care, as well as ratings of their quality of life.[25] Each statement is measured using an 11-point scale.

Benefits of these instruments include the systematic assessment of pain and other symptoms. These data inform the clinician as a treatment plan is developed, particularly when managing complex pain syndromes that occur at the end of life.

COMPLEX PAIN SYNDROMES AT END OF LIFE

The management of pain in palliative care and hospice incorporates the same analgesics, routes, and principles described in the chapter on cancer pain and in monographs.[26] The majority of patients will obtain relief from these therapies or with the addition of interventional techniques. Unfortunately, a small percentage of patients will experience complex syndromes that do not respond to traditional approaches, such as bone pain, intractable neuropathic pain, or malignant bowel obstruction, or will develop severe opioid-induced toxicity.

MALIGNANT BONE PAIN

Bone pain is often difficult to treat, in that patients may obtain good relief of movement-associated pain from higher-dose opioid therapy, yet will be extremely sedated when they stop moving or placing pressure on the bone. Patients at risk include those with cancers that frequently metastasize to bone, including breast, lung, prostate, or multiple myeloma.[5] Table 70-5 lists treatment options.

INTRACTABLE NEUROPATHIC PAIN

Neuropathies can be difficult to treat. Standard therapies include opioids and adjuvant analgesics, including corticosteroids (Table 70-5).[16,27] Additionally, nerve blocks and other interventional techniques can be useful.[28] In more refractory cases intravenous lidocaine infusions are used to treat intractable pain.[29] Using techniques and protocols originating from pain clinics, intravenous lidocaine 1 to 2 mg/kg is given over 15 to 30 min. If effective, a continuous infusion of 1 to 2 mg/kg/hr is started. The analgesic effects can be as prolonged as weeks of relief. Perioral numbness is an early warning sign of potential

TABLE 70–4 Pain and Other Symptom Assessment Tools Used in Palliative Care

Assessment Tools	Description
Edmonton Symptom Assessment Scale (ESAS)	Consists of nine symptoms; can add one to individualize Measures severity using a 0 to 10 visual analog or numeric scales Sum of nine symptoms = distress Valid and reliable[21,49] (See www.palliative.org for instructions)
M.D. Anderson Symptom Inventory (MDASI)	Consists of 13 items; ranked from 0 "not present" to 10 "as bad as you can imagine" Includes 6 interference items; ranked from 0 "did not interfere" to 10 "interfered completely" Valid and reliable[22] (See www.mdanderson.org/departments/prg)
Memorial Symptom Assessment Scale (MSAS)	Measures 32 physical and psychological symptoms using Likert scales Evaluates prevalence, severity, and distress Total score is average of all 32 symptoms Valid and reliable[23,50,51] Pediatric versions available[52,53] (See www.promotingexcellence.org)
Distress Thermometer	Measures distress using a vertical visual analog designed to look like a thermometer Zero (0) indicates "no distress" and 10 (at the top of the thermometer) indicates "extreme distress" Includes a checklist of physical, psychological, practical, family support, and spiritual/religious concerns (See www.nccn.org)

TABLE 70–5 Management of Complex Pain Syndromes at End of Life

Malignant Bone Pain[5,54,55]
Dexamethasone 8–20 mg PO, IV, SQ every morning (not to be used in conjunction with NSAIDs)
Opioids
Bisphosphonates such as pamidronate or zoledronic acid
Radiation therapy (may be given as single fraction in some cases)
Radionuclides such as strontium-89
Orthotics for braces or slings
Physical or occupational therapy for assistive devices
Intractable Neuropathic Pain[16,27,29,47,56,57]
Dexamethasone 8–20 mg PO, IV, SQ every morning (not to be used in conjunction with NSAIDs)
Opioids can be effective but higher doses are indicated (methadone may provide additional benefit over other opioids)
Anticonvulsants
Antidepressants, including novel or atypical agents such as venlafaxine
Local anesthetics (e.g., LidoDerm patch, intraspinal infusions in combinations with opioids or parenteral infusions)
Malignant Intestinal Obstruction[30]
Dexamethasone 8–20 mg PO, IV, SQ every morning to reduce inflammation and nausea (not to be used in conjunction with NSAIDs)
Opioids
Octreotide 20 μg/hr IV or SQ to decrease intestinal secretions; increase dose as needed
Scopolamine transdermal patches (1.5 mg, up to 2 patches) may reduce secretions
Nasogastric tube or venting gastrostomy if consistent with patient goals

toxicity. Hepatic dysfunction and significant cardiac conduction abnormalities are relative contraindications to the treatment, viewed in balance with the patient's goals of care and prognosis.

MALIGNANT INTESTINAL OBSTRUCTION

Bowel obstruction is common in progressive gynecologic and colorectal malignancies. The majority of patients with bowel obstruction will die within 6 months. Palliation can include surgery in selected cases, or, more commonly, intravenous or subcutaneous octreotide, nasogastric tube suction, and venting gastrostomy, in addition to analgesics and antiemetics.[30] Table 70-5 lists specific treatment options.

OPIOID NEUROTOXICITY

The neuroexcitatory effects of opioids include myoclonus, hyperalgesia, delirium, and grand mal seizures. These toxicities have been reported in association with morphine, hydromorphone, hydrocodone, fentanyl, methadone, and oxycodone.[31,32] The 3-glucuronide metabolites are implicated as contributing to these neuroexcitatory effects.[33] Both morphine-3-glucuronide (M3G) and hydromorphone-3-glucuronide (H3G) are believed to produce myoclonus and seizures.[34] Renal failure appears to be a significant, but not absolute, risk factor, as patients are unable to clear the metabolite.[35] Case reports suggest that H3G plasma levels are greatly increased in the presence of renal failure, with the ratio of H3G to the parent compound four times higher than the ratio seen in patients with normal renal function.[35]

The treatment of mild myoclonus generally includes switching to another opioid, lowering the dose of the opioid, and adding a benzodiazepine. Clonazepam 0.5 mg orally twice daily with upward titration may be effective. If the patient is unable to swallow, midazolam or lorazepam may be used. Hyperalgesia frequently is misdiagnosed and the first response by well-meaning clinicians often is to increase the opioid dose. This generally results in greater pain, with potential progression to delirium and possibly seizures.

When these more severe neurotoxicities occur, the opioid dose should be reduced by at least 50%. Some advocate stopping the opioid altogether, since the half-life of these metabolites is long and the patient is unlikely to experience the abstinence syndrome.[36] Naloxone appears to be ineffective in reversing this toxicity. In select cases, spinal delivery of analgesics can be effective in relieving pain and reducing systemic opioid exposure. Should seizures occur, first- and second-line therapies include phenytoin and benzodiazepines, such as diazepam or lorazepam.[37] In some cases the seizures will progress in frequency and intensity, advancing to status epilepticus.[38] Refractory status epilepticus treatment may require midazolam, barbiturates, and propofol.[39]

- Midazolam is particularly useful in palliative care due to its rapid onset and short duration, as well as its ability to be given subcutaneously, intravenously, orally, buccally, sublingually, or rectally. Furthermore, its only known drug incompatibility is with corticosteroids, particularly betamethasone, dexamethasone, and methylprednisolone.[39]
- The standard dose of phenobarbital in the management of seizures is 20 mg/kg intravenous infusion, with a maximum rate of 50 to 100 mg/min.

- The recommended dose of propofol to treat refractory status epilepticus is 1 to 2 mg/kg via intravenous injection over 5 min and repeated if necessary. A maintenance intravenous infusion of 2 to 10 mg/kg/hr is then started, using the lowest dose needed to suppress seizure activity.[39]

OTHER SYMPTOMS COMMON AT END OF LIFE

Dyspnea, anxiety, depression, and other symptoms are common in the face of advanced illness. Palliation of these symptoms, which are frequently linked with pain, can result in improved pain control and enhanced quality of life.

DYSPNEA

Dyspnea, or air hunger, can occur as a result of a variety of illnesses, including cancer, congestive heart failure, or pulmonary diseases.[2] Opioids are the first drug of choice, often in small doses that do not cause sedation.[40] Short-acting anxiolytics are indicated in the face of severe anxiety. Simple measures such as bedside fans can provide additional comfort.

ANXIETY

Anxiety is highly correlated with unrelieved pain.[41] Additionally, many medications commonly used in palliative care, such as corticosteroids, neuroleptics (including metoclopramide), bronchodilators, antihistamines, digitalis, and occasionally benzodiazepines (which can cause a paradoxical reaction in elderly patients), can result in motor restlessness and agitation. Abrupt withdrawal from alcohol, opioids, benzodiazepines, and nicotine also produce agitation. Hypoxia, pulmonary embolus, sepsis, hypoglycemia, thyroid abnormalities, and heart failure are associated with anxiety, as are certain tumors, including pheochromocytomas, and some pancreatic cancers. Primary or metastatic lung cancers and chronic cardiopulmonary conditions can lead to dyspnea, which can also produce anxiety.

Pharmacologic treatment of anxiety usually consists of benzodiazepines, particularly lorazepam as it has a short duration of action and produces fewer adverse effects. A typical initial dosage is 0.5 to 2 mg orally 3 or 4 times daily. Lorazepam can be placed sublingually, which is useful when patients have difficulty swallowing, or given parenterally as a bolus or infusion. Haloperidol is frequently used for short-term management of severe anxiety and as an antipsychotic, with initial dosage starting at 0.5 to 1 mg orally twice daily.[41] Frank discussion of patients' fears in a supportive environment, along with the use of relaxation strategies, such as audiotapes, breathing exercises, and guided imagery, may alleviate anxiety.[42]

DEPRESSION

Depression is often poorly recognized in people at end of life.[43] Diagnosis may be difficult in advanced disease, as the usual physical symptoms of depression (fatigue, anorexia, and sleep disturbance) can result from the disease itself or its treatment. Psychological symptoms suggestive of depression in the patient with life-threatening illness include loss of self-worth, unremitting sadness and hopelessness, and suicidal ideation. There is evidence that a simple screening question "Are you depressed?" or "Are you sad?" is the most valid measure of a patient's depression.[44] Supportive psychotherapy may be of benefit, although limited life span may be a barrier. Antidepressant medications, such as serotonin-specific reuptake inhibitors (SSRIs), such as citalopram, fluoxetine, paroxetine, and sertraline, are usually well tolerated. However, the 2 to 4 weeks required for the drug to take effect is often too long for patients with advanced disease and a very short life span. Newer, "atypical antidepressants" (bupropion, mirtazepine, and venlafaxine) have a relatively rapid onset of action and few reported side effects. However, for patients with a very limited life span, stimulants such as methylphenidate and pemoline provide rapid relief, usually within hours to days.[45,46]

CONCLUSION

Pain, dyspnea, anxiety, and depression are serious symptoms experienced by people with life-threatening illnesses. All health-care professionals are responsible for care of the dying, and, therefore, must be aware of the most common syndromes occurring in this population, able to conduct specific assessment techniques, and knowledgeable about the therapies used to treat these symptoms. Resources, such as palliative care services and hospices, can assist physicians as they provide care to these patients and their families.

KEY POINTS

- All physicians, regardless of specialty, are responsible for care of patients with life-threatening illnesses.
- Assessment of pain and other symptoms at end of life requires knowledge of common syndromes, as well as skill to conduct a thorough history and physical examination, with particular attention to the neurologic evaluation.
- Complex pain syndromes require novel drug therapies, in addition to standard nonopioid, opioid, and adjuvant analgesics.
- Adequate pain control in those with life-threatening illness requires attention to related symptoms such as dyspnea, anxiety, and depression.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 71

Neurolytic Visceral Sympathetic Blocks

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Pain associated with cancer may be somatic, visceral, and neuropathic in origin, and about 50% of all cancer patients have a combination of pain types at the time of diagnosis. When visceral structures are stretched, compressed, invaded, or distended, a poorly localized noxious pain is reported. Patients experiencing visceral pain often describe the pain as vague, deep, squeezing, crampy, or colicky in nature. Other signs and symptoms include referred pain, such as shoulder pain that appears when the diaphragm is invaded with tumor, and nausea/vomiting.

Visceral pain associated with cancer may be relieved with oral pharmacologic therapy that includes combinations of nonsteroidal anti-inflammatory agents, opioids, and coadjuvant therapy. Neurolytic blocks of the sympathetic axis are also extremely effective in controlling visceral cancer pain. Thus, neurolysis of the sympathetic axis should be judged as an important adjunct to pharmacologic therapy for the relief of severe pain experienced by cancer patients. As such, these blocks can rarely eliminate cancer pain, because patients also frequently experience coexisting somatic and neuropathic pain. Thus, oral pharmacologic therapy must be continued albeit at lower doses. The goal of performing a neurolytic block of the sympathetic axis is to (1) maximize the analgesic effect of opioid and nonopioid analgesics, and (2) reduce the dosage of these agents to alleviate untoward side effects.

Neurolytic techniques have a narrow risk–benefit ratio. Thus, sound clinical judgment and complete patient understanding are essential to minimize undesirable effects. The detailed description of the techniques for these blocks is beyond the scope of this review. Thus, the reader is directed to other publications for this purpose.[1]

CELIAC PLEXUS BLOCK

The celiac plexus is situated retroperitoneally in the upper abdomen. It is at the level of the T12 and L1 vertebrae, anterior to the crura of the diaphragm. It surrounds the abdominal aorta and the celiac and superior mesenteric arteries. The plexus continues inferiorly to form the superior and the inferior mesenteric plexus.

The celiac plexus is composed of a network of nerve fibers, both from the sympathetic and parasympathetic systems. It contains one to five large ganglia, which receive sympathetic fibers from the three splanchnic nerves (greater, lesser, and least). The thoracic splanchnic nerves lie above and posterior to the diaphragm, anterior to the T12 vertebra. The celiac plexus also receives parasympathetic fibers from the vagus nerve, and provides autonomic supply to the liver, pancreas, gallbladder, stomach, spleen, kidneys, intestines, and adrenal glands, as well as to the blood vessels.

INDICATIONS

Neurolytic blocks of the celiac plexus have been used for malignant and chronic nonmalignant pain. In patients with acute or chronic pancreatitis it has been used with significant success.[2] Likewise, patients with cancer in the upper abdomen who have a significant visceral pain component have responded well to this block.[3]

TECHNIQUE

There are multiple posterior percutaneous approaches to block nociceptive impulses from the viscera of the upper abdomen. These include the classic retrocrural approach, block of the splanchnic nerves, the anterocrural (or transcrural) approach, and the transaortic approach. With the common posterior approaches, the two needles are inserted at the level of the first lumbar vertebra, 5 to 7 cm from the midline. The tip of the needle is then directed toward the body of L1 for the retrocrural and anterocrural approaches and to the body of T12 for neurolysis of the splanchnic nerves. The left needle is positioned just posterior to the aorta and the right needle is advanced 1 cm deeper with a retrocrural or splanchnic nerve approach. Fluoroscopy reveals spread of contrast anterior to the vertebral body and posterior to the diaphragm. The needles must be advanced through the diaphragm using the anterocrural approach. This is relatively easy on the right side, but more difficult on the left side, because of the position of the aorta. Two solutions have been described: confirmation with computed tomography (CT) scan[4] and use of a single-needle, transaortic injection on the left side.[5] The left needle is inserted closer to the midline and placed anterolateral to the aorta with CT scan, or into and through the aorta with the transaortic approach. Figs. 71-1 to 71-3 illustrate the final position of the needles and the expected spread of contrast medium after successful placement. More recently, CT[6] and ultrasound[7] techniques have allowed pain specialists to perform neurolysis of the celiac plexus via a transabdominal approach. This approach is frequently used when patients are not able to tolerate either the prone or lateral decubitus position, or when the liver is so enlarged that a posterior approach is not feasible.

DRUG AND DOSING

For neurolytic blocks, 50% to 100% alcohol, 20 ml per side, is utilized. Smaller volumes may be more appropriate for retrocrural approaches. When injected by itself, alcohol can produce severe pain. Thus, it is recommended to first inject 5 to 10 ml of 0.25% bupivacaine 5 min prior to the injection of alcohol, or to dilute 100% alcohol by 50% with local anesthetic (0.25% bupivacaine). Phenol in a 10% final concentration may also be used, and it has the

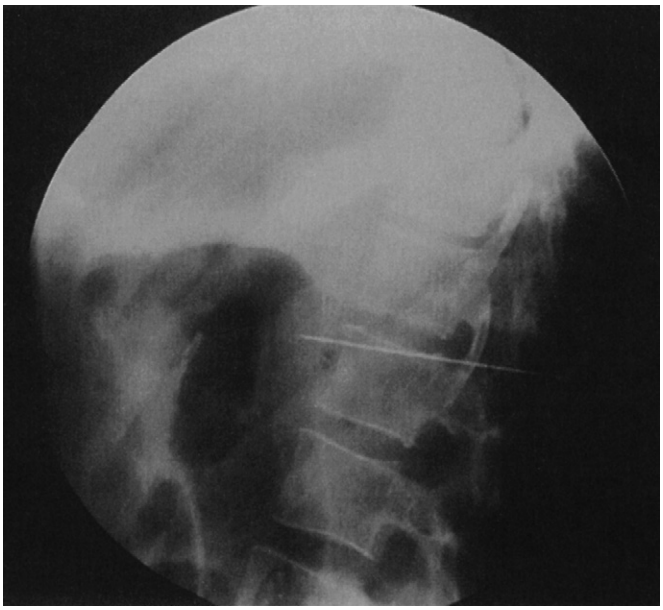

FIGURE 71-1 Lateral radiograph showing placement of the needle tip 1.0 to 1.5 cm anterior to the body of the L1 vertebra.

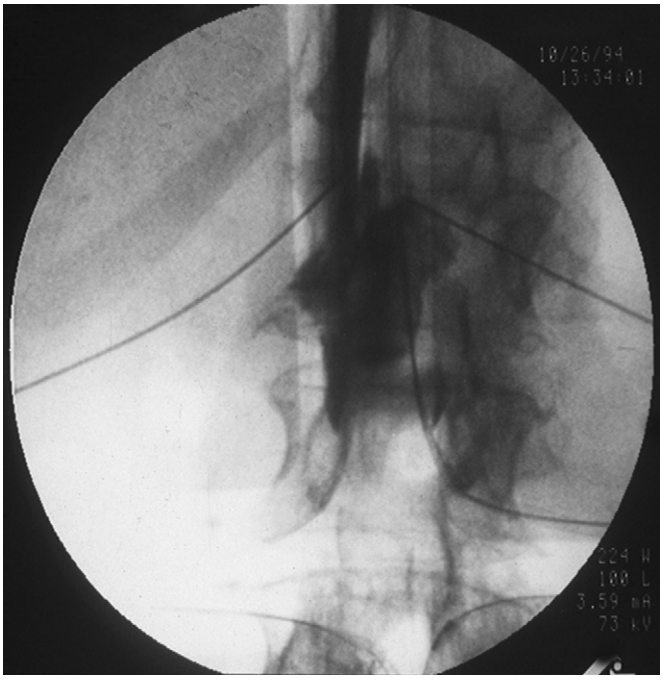

FIGURE 71-2 Posteroanterior radiograph showing bilateral caudad spread of contrast medium through the right-sided needle, which is anterocrural, and unilateral cephalad spread through the needle on the left side, which is retrocrural.

advantage of being painless on injection. Both agents appear to have the same efficacy.

COMPLICATIONS

Complications associated with celiac plexus blocks appear to be related to the technique used: retrocrural, transcrural,[4,8] or transaortic.[5] In a prospective, randomized study of 61 patients

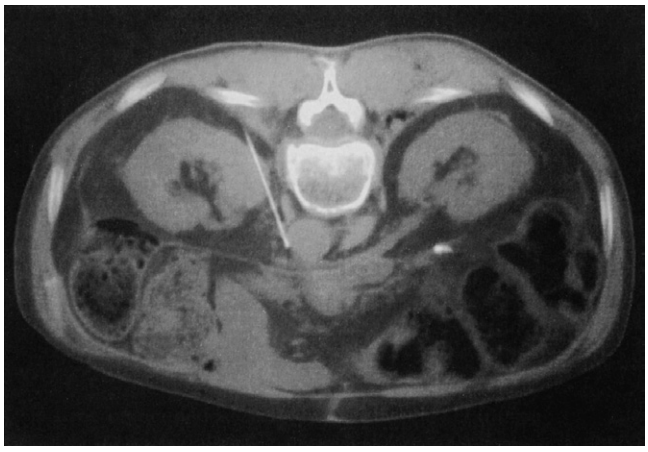

FIGURE 71-3 Computed tomographic (CT) scan showing the needle adjacent to the lateral wall of the aorta, anterior to the crura of the diaphragm.

with cancer of the pancreas, Ischia et al.[3] compared the efficacy and the incidence of complications associated with three different approaches to celiac plexus neurolysis. Orthostatic hypotension was more frequent in patients who had a retrocrural (50%) or splanchnic nerve block technique (52%) than those who underwent an anterocrural approach (10%). In contrast, transient diarrhea was more frequent in patients who had an anterocrural approach (65%) than those having a splanchnic nerve block technique (5%), but not the retrocrural approach (25%). The incidence of dysesthesia, interscapular back pain, hiccoughing, or hematuria was not statistically different among the three groups.

The incidence of complications from neurolytic celiac plexus blocks was recently determined by Davis[9] in 2730 patients having blocks performed from 1986 to 1990. The overall incidence of major complications, such as paraplegia and bladder and bowel dysfunction, was 1 in 683 procedures. However, the report does not describe which approach or approaches were utilized for the performance of the blocks.

Important aspects in the diagnosis and management of specific complications include:

1. Malposition of the needle should always be ruled out with radiologic imaging prior to the injection of a neurolytic agent, as the needle's tip may be intravascular, in the peritoneal cavity, or in a viscus. Imaging techniques currently used include biplanar fluoroscopy, CT, or ultrasound guidance. However, no study has evaluated the superiority of one technique over the others. Wong and Brown[10] suggested that the use of radiologic imaging does not alter the quality of the block or the incidence of complications, based on a retrospective study of 136 patients with pancreatic cancer pain treated with a celiac plexus block with or without radiologic control of the position of the needle's tip. However, it is not clear how many of those patients had radiologic imaging. Assuming that half of the patients did not, the upper 95% confidence limit for complications is 5%.[11]

2. Orthostatic hypotension may occur in 1% to 3% of patients after the block for up to 5 days. Treatments include bed rest, avoidance of sudden changes in position, and fluid replacement. Once compensatory vascular reflexes are fully activated, this side effect disappears. Wrapping of the lower extremities from the toe to the upper thighs with elastic bandages has been used with success in patients who developed orthostatic hypotension and needed to ambulate during the first week after the block.
3. Backache may result from (a) local trauma during the needle placement resulting in a retroperitoneal hematoma, (b) alcohol irritation of the retroperitoneal structures, or (c) injury to the lumbar plexus. Patients with a backache should have at least two hematocrit measurements at a 1-hour interval. If there is a decrease in the hematocrit, radiologic imaging is indicated to rule out a retroperitoneal hematoma. A urine analysis positive for red cells suggests renal injury.
4. Retroperitoneal hemorrhage is rare but has also been reported. Thus, in patients who present with orthostatic hypotension, one must rule out hemorrhage before assuming that it is a physiologic response to the block. Patients who present with backache and orthostatic hypotension after a celiac plexus block should be admitted to the hospital for serial hematocrit monitoring. If a low or a decreasing hematocrit is demonstrated, patients should undergo radiologic evaluation to rule out injury to the kidneys, the aorta, or other vascular structures. A surgical consult should be obtained as soon as feasible.
5. Diarrhea may occur due to sympathetic block of the bowel. Treatment includes hydration and antidiarrheal agents. Oral loperamide is a good choice, although any anticholinergic may be used. Matson et al.[12] have reported near-fatal dehydration from diarrhea after this block. Thus, in debilitated patients, diarrhea must be treated aggressively.
6. Abdominal aortic dissection has also been reported.[13,14] The mechanism of aortic injury is direct damage with the needle during the performance of the block. As expected, the anterocrural approach is more frequently associated with this complication. Thus, if there were evidence of atherosclerotic disease of the abdominal aorta, it would seem appropriate to avoid this approach.
7. Paraplegia and transient motor paralysis have occurred after celiac plexus block.[15–21] Current thinking is that these neurologic complications may occur due to spasm of the lumbar segmental arteries that perfuse the spinal cord.[21] In fact, canine lumbar arteries undergo sustained contraction when exposed to both alcohol and phenol.[22] The magnitude of the response to phenol was directly related to concentration, while the alcohol-induced response was inversely related to concentration. Low concentrations of ethanol produce significant contractile effects in human aortic smooth muscle cells by increasing the intracellular concentration of ionized calcium.[23] Thus, it may be empirically suggested that alcohol should not be used if there is evidence of significant atherosclerotic disease of the aorta, suggesting that the circulation to the spinal cord may also be impaired. However, there is also a report of paraplegia after phenol use,[15] suggesting that other factors, such as direct vascular or neurologic injury or retrograde spread to the spinal cord, may come into play. These complications further support the use of radiologic imaging during the performance of the block.

EFFICACY

There are four randomized controlled trials[3,24–26] and one prospective study[27] evaluating the efficacy of celiac plexus neurolysis in pain due to cancer of the upper abdomen. One of the studies evaluated the efficacy of three different approaches to celiac plexus neurolysis in pancreatic cancer in a prospective, randomized fashion.[3] In this study, 48% (29 of 61 patients) experienced complete pain relief after the neurolytic block, while 52% (32 of 61 patients) required further therapy for residual visceral pain. This was attributed to technical failure in 15 patients (20%) and to neuropathic/somatic pains in 17 patients (28%). The second study[24] compared the procedure with oral pharmacologic therapy in 20 patients. The author concluded that celiac plexus neurolysis resulted in an equal reduction in visual analogue pain scores as therapy with a nonsteroidal anti-inflammatory drug (NSAID)–opioid combination. However, opioid consumption was significantly lower in the group of patients who underwent neurolysis, when compared to the group receiving oral pharmacologic therapy, during the 7 weeks of the study. Moreover, the incidence of side effects was greater in the group of patients receiving oral pharmacologic therapy when compared to those in the block group. The third randomized controlled trial[25] also compared the procedure with drug therapy in 24 patients. Celiac plexus block was associated with better short-term pain relief, and transient diarrhea and hypotension. There were no persistent analgesia benefits when compared to the patients using drug therapy alone, but the block patients had lower analgesic consumption and fewer side effects such as nausea, vomiting, and constipation. The fourth controlled study of 100 patients randomized to CPN vs. sham injection showed that at 6 weeks, there was a significant decrease in pain in those who received CPN. No differences in opioid use, opioid adverse effects, quality of life, or survival were appreciated.[26]

In one prospective, nonrandomized study,[27] 41 patients treated according to the World Health Organization (WHO) guidelines for cancer pain relief were compared with 21 patients treated with a neurolytic celiac plexus block. The authors concluded that this technique could play an important role in the management of pancreatic cancer pain.

A recent retrospective statistical analysis showed that patients receiving a daily morphine equivalent dose per day of less that 250 mg and those not receiving sedation for the procedure were more likely to achieve successful outcome from celiac or splanchnic neurolysis.[28]

The results of a meta-analysis that evaluated the results of 21 retrospective studies in 1145 patients concluded that adequate to excellent pain relief can be achieved in 89% of the patients during the first 2 weeks after the block.[29] Partial to complete pain relief continued in approximately 90% of the patients who were alive at the 3-month interval and in 70% to 90% until death, even if beyond 3 months after celiac plexus block. Moreover, the efficacy was similar in patients with pancreatic cancer and in those with other intra-abdominal malignancies of the upper abdomen. However, it is important to recognize that these results are based on retrospective evaluations, which may not yield reliable information or may be subject to publication bias. In addition, statistical techniques used for the analysis must account for the heterogeneity produced by the patient selection criteria, technical differences in the performance of the blocks, choice of neurolytic agents and doses, diversity in the tools for the evaluation of pain, and goals of therapy.

The efficacy of celiac plexus neurolysis appears to be related to the site and extent of pancreatic tumor involvement. Rykowski and Hilgier[30] demonstrated that sustained, effective pain relief occurred in 92% (33 of 36) of patients with cancer of the head of the pancreas but in only 29% (4 of 14) of patients with cancer of the body and tail of the pancreas. Block failure in 13 patients appears to be explained by the extent of tumor growth around the celiac axis, which was confirmed by CT scan.

As previously discussed, oral pharmacologic therapy with oral opioids, NSAIDs, and coadjuvants is frequently used for the treatment of cancer pain. However, there is evidence to suggest that chronic use of high doses of opioids may have a negative effect on immunity.[31] Thus, analgesic techniques that lower opioid consumption should have positive effects on patient outcomes. Lillemoe et al.[32] showed in a prospective, randomized trial that patients with nonresectable cancer of the pancreas receiving splanchnic neurolysis had a longer survival than patients that did not. These findings may be the result of lower opioid use in the group of patients randomized to neurolysis, resulting in (1) better preserved immune function and (2) lower incidence of side effects, such as nausea and vomiting, that allows patients to eat better. In contrast, a prospective study did not demonstrate a survival benefit.[27]

SUPERIOR HYPOGASTRIC PLEXUS BLOCK

Cancer patients with tumor extension into the pelvis may experience severe pain unresponsive to oral or parenteral opioids. Moreover, some patients may complain of excessive sedation or other side effects that limit the acceptability and usefulness of oral opioid therapy. Thus, a more invasive approach may be needed to control pain and improve quality of life.

Both pelvic pain associated with cancer and that seen with chronic nonmalignant conditions may be alleviated by blocking the superior hypogastric plexus.[33–36] Analgesia to the organs in the pelvis is possible because the afferent fibers innervating these structures travel with the sympathetic nerves, trunks, ganglia, and rami and are accessible for neurolytic block. Thus, a sympathectomy for visceral pain is analogous to a peripheral neurectomy or dorsal rhizotomy for somatic pain. Another study has suggested that, even in advanced stages, visceral pain is an important component of the cancer pain syndrome experienced by patients with cancer of the pelvis.[34] Thus, it appears that percutaneous neurolytic blocks of the superior hypogastric plexus should be offered more frequently to patients with advanced stages of pelvic cancer.

The superior hypogastric plexus is situated in the retroperitoneum, bilaterally, extending from the lower third of the fifth lumbar vertebral body to the upper third of the first sacral vertebral body.

TECHNIQUE

Patients are placed in the prone position with a pillow under the pelvis to flatten the lumbar lordosis. Local infiltration of the intervening muscle planes can be performed. Needle insertion sites are 5 to 7 cm lateral to the midline, depending on patient's height and girth, at the level of the L4–L5 interspace. Two 7- to 9-inch, 22-gauge short beveled needles are inserted with the bevel directed medially, 45 degrees mesiad and 30 degrees caudad, so that the needle tips lie anterolateral to the L5–S1 intervertebral space. Aspiration is important to avoid injection into the iliac vessels. If blood is aspirated, a transvascular approach can be used.

Biplanar fluoroscopy is used to verify accurate needle placement. Anteroposterior (AP) views should reveal the tip of the needle at the level of the junction of the L5 and S1 vertebral bodies. Lateral views will confirm placement of the needle tip just beyond the vertebral body's anterolateral margin. The injection of 2 to 3 ml of water-soluble contrast medium is used to verify accurate needle placement and to rule out intravascular injection. In the AP view, the spread of contrast should be confined to the midline region. In the lateral view, a smooth posterior contour corresponding to the anterior psoas fascia indicates that the needle is at the appropriate depth. Figs. 71-4 and 71-5 show adequate needle placement and contrast medium spread prior to neurolysis of the superior hypogastric plexus. A transdiscal approach has been described through the L5–S1 disc.[37] An approach similar to that used for L5–S1 discography is used; however, the needle is advanced just anterior to the disc.

For a prognostic hypogastric plexus blockade; a volume of 6 to 8 ml of 0.25% bupivacaine through each needle is recommended. For therapeutic purposes, a total of 6 to 8 ml of 10% aqueous phenol or 80% alcohol can be injected through each needle.

COMPLICATIONS

Potential complications include retroperitoneal hematoma formation and acute ischemia of the foot, due to the dislodgement of an atherosclerotic plaque from the iliac vessels. A combined experience of more than 200 cases from the Mexican Institute of Cancer, Roswell Park Cancer Institute, and M.D. Anderson Cancer Center has

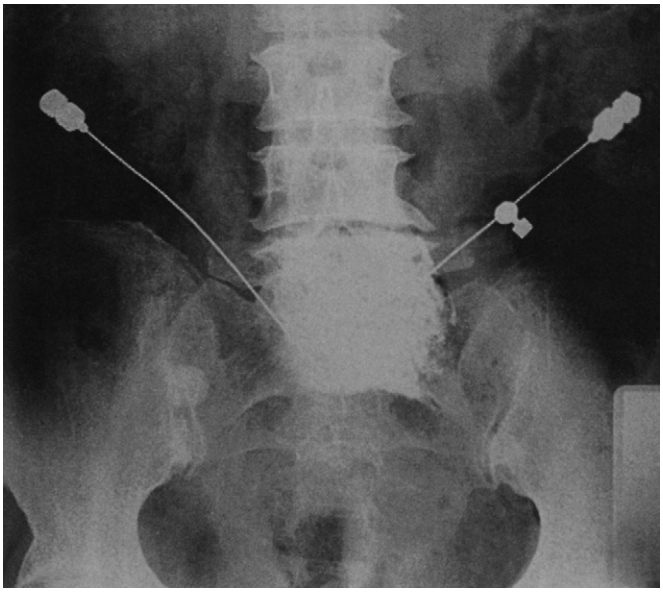

FIGURE 71-4 Posteroanterior radiograph demonstrating bilateral correct needle placement and adequate spread of the contrast medium.

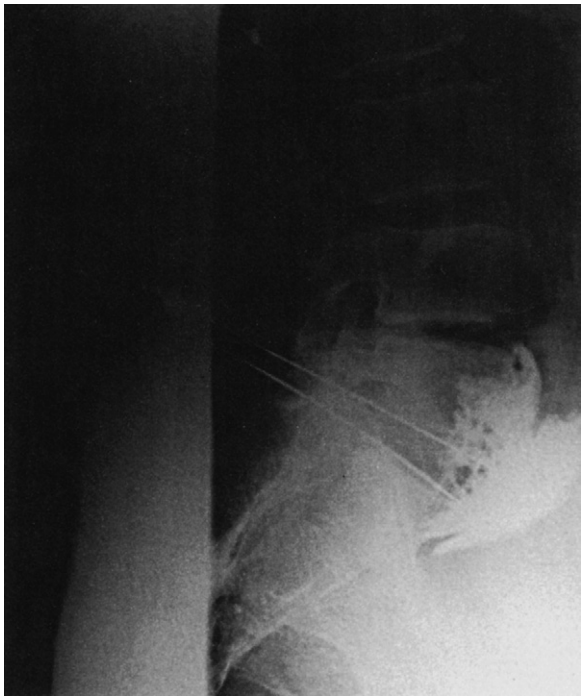

FIGURE 71-5 Cross-lateral radiograph demonstrating correct needle placement and adequate spread of the contrast medium.

failed to detect neurologic complications associated with this block.[35]

EFFICACY

The effectiveness of the block was originally demonstrated by documenting a significant decrease in pain scores via a visual analog pain scale (VAS). In this study, Plancarte et al. showed that this block was effective in reducing VAS scores in 70% of the patients with pelvic pain associated with cancer.[33] The great majority of the patients enrolled had a diagnosis of cervical cancer. In a subsequent study 69% of the patients experienced a decrease in VAS scores. Moreover, a mean daily morphine dose reduction of 67% was seen in the success group (736 ± 633 to 251 ± 191 mg/day), and 45% in the failure group (1443 ± 703 to 800 ± 345 mg/day).[34] In a more recent multicentric study, 159 patients with pelvic pain associated with cancer were evaluated. Overall, 115 patients (72%) had satisfactory pain relief after one or two neurolytic procedures. Mean opioid use decreased by 40% from 58 ± 43 to 35 ± 18 equianalgesic mg/day of morphine, 3 weeks after treatment in all of the studied patients. The decrease in opioid consumption was significant for both the success group (56 ± 32 to 32 ± 16 mg/day) and the failure group (65 ± 28 to 48 ± 21 mg/day).[35] Success was defined in these two studies as the ability to reduce opioid consumption by at least 50% in the 3 weeks following the block and a decrease in the pain scores below 4/10 in the VAS.[34,35] Thirty patients randomized to either transdiscal versus classic posterior approach showed the transdiscal group to have a significantly shorter procedure time (24.4 vs. 67.9 min). There was no difference in pain scores or morphine consumption between the groups, and the transdiscal group had no evidence of discitis or disc herniation.[37]

Three important conclusions may be drawn from the results of these studies. First, reductions in pain scores and in opioid consumption are significant even in advanced stages of pelvic cancer. This suggests that visceral pain may be an important component of cancer pain even in the late stages of the disease, when differentiation of somatic pain from visceral pain is very difficult. Second, neurolysis is not as effective in the presence of significant retroperitoneal lymph node involvement (20% vs. 70% response rate). This lack of success may reflect involvement of nerve tissue or tumor spread to somatic structures within the pelvis. However, patients with extensive retroperitoneal pelvic involvement who showed a confluence of contrast material in the midline, on PA fluoroscopic views, experienced good results in one of the studies.[34] Third, use of this neurolytic block early in the management of pelvic visceral pain associated with cancer may be economically sound, based on the opioid reduction experienced by patients in both the failure and the success groups.[34,35]

In a case report Rosenberg et al.[36] reported on the efficacy of this block in a patient with severe chronic nonmalignant penile pain after transurethral resection of the prostate. Although the patient did not receive a neurolytic agent, a diagnostic block performed with 0.25% bupivacaine and 20 mg of methylprednisolone acetate was effective in relieving the pain for more than 6 months. The usefulness of this block in chronic benign pain conditions has not been adequately documented.

GANGLION IMPAR BLOCK

The ganglion impar is a solitary retroperitoneal structure located at the level of the sacrococcygeal junction. This ganglion marks the end of the two sympathetic chains.

Visceral pain in the perineal area associated with malignancies may be effectively treated with neurolysis of the ganglion impar (the ganglion of Walther).[38,39] Patients who will benefit from this blockade will frequently present with vague and poorly localized pain, which is burning in character and frequently accompanied by sensations of urgency. However, the clinical value of this block is not clear because the published experience is limited.

TECHNIQUE

This block may be performed with the patient in the left lateral decubitus position with the knees flexed, in the lithotomy position, or in the prone position. The initial technique employs a 22-gauge, 3.5-inch spinal needle that is manually bent to facilitate placement of the needle tip anterior to the concavity of the sacrum and coccyx. The needle is introduced through the anococcygeal ligament with its concavity oriented posteriorly and, under fluoroscopic guidance, is directed along the midline to contact bone at or near the sacrococcygeal junction (Fig. 71-6). Contrast dye confirms retroperitoneal spread; on the lateral view, it is shaped like a comma.

An alternative, transcoccygeal approach is performed with the patient in the prone position. This approach has been reported to be both effective and safe.[40] A 20-gauge, 1.5-inch needle is inserted through the sacrococcygeal ligament in the midline. The needle is then advanced until the tip is placed posterior to the rectum. For diagnostic blocks, 4 to 8 ml of 1% lidocaine or 0.25% bupivacaine is selected; for neurolytic block, 4 (to 8) ml of 10% phenol is used. Although the technique is relatively straightforward, care is needed to prevent perforation of the rectum and injection into the periosteum.

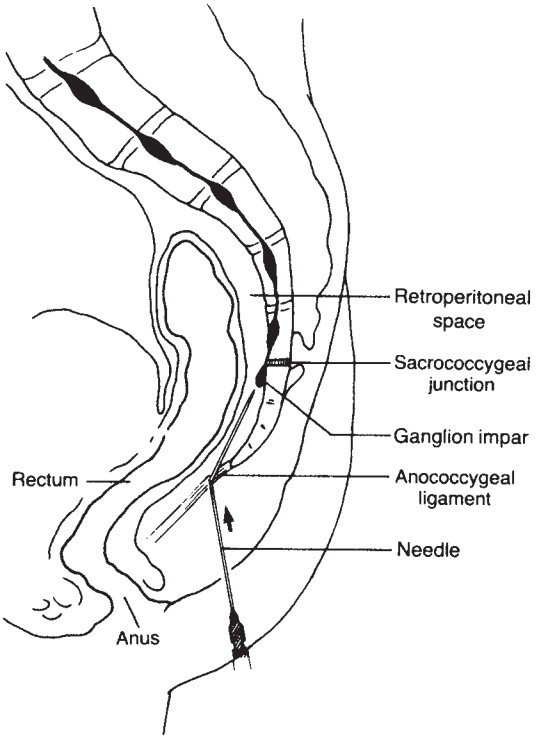

FIGURE 71-6 Lateral schematic view of correct needle placement for blockade of the ganglion impar.

COMPLICATIONS

No complications or side effects have been reported with this block.

CONCLUSIONS

Neurolysis of the sympathetic axis is a safe and cost-effective way to treat visceral pain associated with cancer. The benefits are not limited to improved analgesia but also include a decrease in opioid consumption. These results may have both economic implications and additional important clinical effects due to the actions of high-dose chronic opioid therapy in the immune and gastrointestinal systems. The knowledge and refined techniques, currently used to perform these blocks, allow patients to undergo these procedures in a safe and expeditious manner. Thus, pain practitioners should consider them as adjuvant therapy for the successful treatment of cancer pain.

KEY POINTS

- Neurolytic blocks of the sympathetic axis are an important adjunct to pharmacologic therapy for the relief of severe visceral pain experienced by cancer patients. The goal of performing these blocks is to maximize the analgesic effect of opioid and nonopioid analgesics while reducing their dosage to alleviate untoward side effects.
- Neurolytic celiac plexus block for patients with pancreatic cancer pain results in excellent analgesia, reduced opioid utilization, and decreased side effects such as nausea, vomiting, and constipation when compared to systemic analgesic therapy.
- In one study, patients with nonresectable cancer of the pancreas receiving splanchnic neurolysis had longer survival than patients not blocked. This may result from their lower opioid use, resulting in better-preserved immune function as well as improved nutrition due to fewer opioid side effects.
- Complications of neurolytic celiac plexus block include diarrhea, postural hypotension, back pain, aortic injury, hemorrhage, and paraplegia.
- Neurolytic superior hypogastric plexus block has proven effective, with minimal complications, in reduction of pain and opioid consumption in patients with advanced pelvic cancer, suggesting that a significant component of visceral pain is present even with advanced disease.

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Access the reference list online at http://www.expertconsult.com.

CHAPTER 72

Central and Peripheral Neurolysis

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Chemical neurolysis is a modality that has been used for pain control for almost a century. Multiple agents have been evaluated through the years, but only a few are still clinically relevant. Glycerol is used for the treatment of trigeminal neuralgia. Phenol and ethyl alcohol are the only two agents commonly used in the epidural or intrathecal space, as well as for sympathetic plexus neurolysis. The decision to use neurolytic agents usually is made after many other modalities have failed to provide benefit. Chemical and surgical neurolysis potentially have very serious side effects. Their use is primarily limited to patients with pain associated with terminal malignancies. These procedures provide the most benefit in the oncology patients in whom more conservative measures were unsuccessful, possessed too high a side effect burden, or unable to be performed. In patients in extremis, neurolysis represents a palliative measure to provide pain relief while maintaining the patient's ability to interact with family and friends in their final days to months of life. This can be preferable to systemically delivered opioids, which may interfere with the patient's mental status enough to diminish meaningful communication with family and friends. Neurolysis is an alternative to allow patients the ability to control their pain with less systemic medication, significantly improving their quality of life.

PATIENT SELECTION

Once a patient is deemed to have a pain pattern or pathology that is appropriate for neurolytic therapy (Table 72-1), it is imperative to clearly explain the specific goals and expectations. Neurolysis can provide substantial analgesia, and will usually allow a significant reduction of systemic pain medications. The limitations and complication profile of this modality are not insignificant and are an important part of the decision process for the patient and provider. Although neurolysis can provide analgesia in the dermatomal distribution affected by the block, it will not necessarily provide pain relief from an expanding tumor or new metastasis. In addition, the effects of this therapy can be temporary, and will diminish over time, requiring readministration of the neurolytic agent. Although these agents usually provide good to excellent pain relief, sometimes the level of analgesia expected by the patient is inadequate, or the duration of pain relief is too short. There have also been reports of limb weakness and loss of bowel or bladder tone. Typically, the patient subset chosen for epidural or intrathecal neurolysis has been escalated through the World Health Organization (WHO) analgesia ladder (Fig. 72-1A) without relief, and they are experiencing pain that cannot be adequately controlled by standard analgesics, or the analgesic doses are producing intolerable side effects. These patients will also fall into a category in which advanced interventional pain medicine strategies have been tried, but without inadequate analgesia, or the patient possesses contraindications to these procedures (Fig. 72-1B). Patients with complaints of neuropathic pain will not get the desired results compared to those with visceral or somatic pain. Due to the nature of neurolytic administration, it is ideal for controlling unilateral pain in the trunk and focused to a few adjacent dermatomes. However, in the presence of an intraspinal tumor, the effectiveness of these techniques will decrease, making these patients unsuitable candidates. Neuraxial neurolytic therapy is ideal for patients with advanced or terminal malignancy and unilateral somatic pain.[1]

TABLE 72–1 Intrathecal Neurolysis: Indications for Neurolytic Spinal Blockade

Intractable cancer pain (advanced or terminal malignancy)
Failure of medical and interventional analgesic therapy
Intolerable side effects of current therapy
Unilateral pain
Pain restricted to one to four dermatomal levels
Pain located in the trunk, thorax, abdomen
Primary somatic pain mechanism
Absence of intraspinal tumor spread
Effective analgesia with local anesthetic block
Informed consent of patient
Realistic expectations and family support

PATIENT PREPARATION

Prior to attempting any neurolytic block, it is essential to have a clear and accurate pain diagnosis, and the location needs to be accurately mapped with a dermatomal chart (Fig. 72-2). Multiple modalities are available to achieve an accurate diagnosis, and should be utilized to ensure an effective block that is appropriate for the underlying condition.[2] Once a definitive plan is established, informed consent should be explained in detail to the patient, outlining all the risks associated with the particular procedure. A thorough neurologic examination before any invasive techniques are attempted is vital not only for assessing the effectiveness, but it can provide a baseline assessment in the event of any potential complications. In an ideal treatment scenario, a member of the patient's multidisciplinary cancer team will perform these blocks, with all providers aware of the status and progression of the primary and metastatic malignancies throughout the treatment period. The patient and primary oncology team should be aware that in cases of rapidly growing tumors, expanding tumor growth may compromise the efficacy of a block. Before any neurolytic agents are used, it is advisable to perform a diagnostic blockade with a local anesthetic that reproduces the planned intervention. This diagnostic maneuver helps

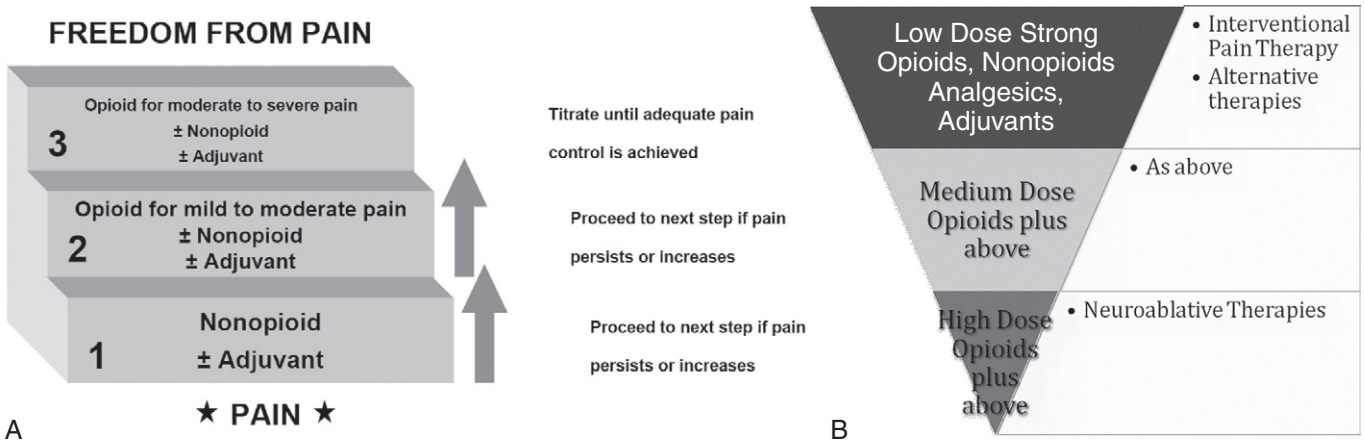

FIGURE 72-1 *Adapted from WHO Cancer and Palliative Care 2011. In Figure A, escalation of treatment is represented by moving up the figure, whereas in figure B escalation of treatment is represented by moving down the diagram.*

to confirm needle placement and can provide information about the level of effectiveness of the neurolysis.[3] Patient and practitioner should be aware that the agents used for neurolysis have a longer time to onset of pain relief compared with local anesthetics, and that the effects may not be as profound or immediate. The choice of neurolytic agent is based on the location of needle placement, the ability of the patient to get in the required position, and the volume of injectate required (Table 72-2). Baricity may play a role in determining which neurolytic agent to use for the patient. Phenol is a hyperbaric agent that would be more appropriate for pelvic and saddle blocks compared with a hypobaric agent such as ethanol.

NEUROLYTIC AGENTS

ALCOHOL

Ethyl alcohol (ethanol) is one of the classic neurolytic agents, and was first reported by Dogliotti in 1931 for intrathecal injection.[4] Anhydrous ethyl alcohol is commercially available in the USA in undiluted (100% concentration) 1-ml and 5-ml ampules. Although commercial preparations are undiluted, exposure to the atmosphere will cause dilution via absorption of water. Ethyl alcohol injections perineurally are associated with burning dysesthesias running along the course of the nerve. This sensation is often extremely unpleasant for the patient, and can last from a few minutes to a few weeks. To alleviate this known effect, most practitioners inject a local anesthetic preceding the use of ethyl alcohol. The use of this initial dose of local anesthetic can also provide guidance on the correct location of the injectate. The neurolytic action of alcohol is produced by the extraction of neural cholesterol, phospholipids, and cerebrosides, and the precipitation of mucopeptides.[5] These actions result in sclerosis of the nerve fibers and myelin sheath, leading to demyelination.[1] The basal lamina of the Schwann cell sheath remains intact, allowing for new Schwann cell growth, thereby providing the framework for subsequent nerve fiber growth. This framework encourages the regeneration of axons, but only if the cell bodies of these nerves are not completely destroyed.[6] The pathway of degeneration is nonselective, and can be observed in peripheral nerves and spinal nerve roots following intrathecal injection. Areas of demyelination can be seen in posterior columns, Lissauer's tract, and the dorsal root, followed by Wallerian degeneration to the dorsal horn.[7] Intrathecal alcohol injection results in rapid uptake of alcohol and variable injury to the surface of the spinal cord. Ethyl alcohol is quickly absorbed from the cerebrospinal fluid (CSF) so that only 10% of the initial dose remains in the CSF after 10 min and only 4% after 30 min.[8] The rapid spread from the injection site means larger volumes are required than for phenol, which in turn may result in local tissue damage.[9] In the case of celiac plexus blocks, alcohol is rapidly absorbed into the bloodstream. It has been shown that serum ethanol levels up to 54 mg/dl can occur after a celiac plexus block.[10] Even though these levels are lower than those required, they could result in systemic effects or legal consequences, which should be factored in when considering the additive effects of sedatives and central nervous system (CNS) depressants. However, following intrathecal administration of alcohol, it is unlikely that there will be significant vascular uptake. The use of ethanol as a neurolytic agent has been associated with a disulfiram-like effect, known as acetaldehyde syndrome. Case reports of the disufiram-like effect include patients taking moxalactam, a beta-lactam antibiotic that inhibits aldehyde dehydrogenase; another patient taking 1-hexyl carbamoyl-5-fluororuracil, an anticancer drug, experienced similar symptoms.[11] The patients experienced flushing, hypotension, tachycardia, and diaphoresis within 15 min of alcohol administration. The symptoms resolved 4 to 6 hr later, and efforts were undertaken to stabilize hemodynamics. Both cases occurred after celiac plexus blocks. It is important for the pain practitioner to recognize medications that may cause disulfiram-like effects after peripheral neurolytic blocks with alcohol, such as chloramphenicol, beta-lactams, metronidazole, tolbutamide, chlorpropamide, and disulfiram.[12] Ethyl alcohol has a specific gravity of less than 0.8, and CSF has a specific gravity of slightly greater than 1.0. Within the CSF, alcohol is hypobaric and will move against gravity, "floating" upward. Therefore, positioning of the patient is an extremely important factor to consider when planning the procedure. The administration of ethanol for the

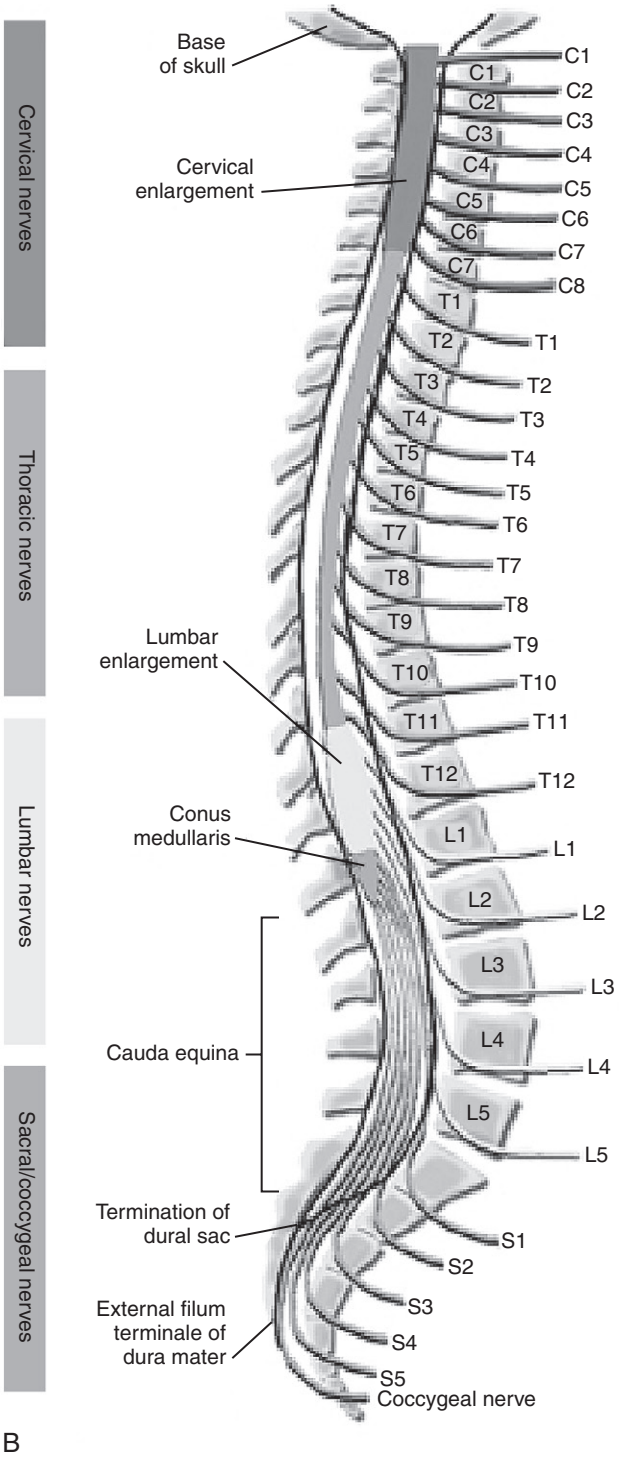

FIGURE 72-2 Lateral, midline view of the spinal cord, vertebral bodies and nerve roots.

purpose of neurolysis can have catastrophic consequences. It has been associated with both transient and permanent paraplegia in both celiac plexus and intrathecal blocks. It has been postulated that these effects are secondary to vasospasm of the spinal arteries by the direct action of alcohol.[9] In the case of transient effects, paraplegia developed within 22 min and resolved within 90 min. The patient had good pain relief for several weeks after his injection, suggesting good needle placement, and frequent negative aspirations during injection indicated that no intravascular injection of the alcohol had occurred. In the permanent paraplegia case, the patient received an intrathecal block, and symptoms did not develop until 12 hr after the procedure. This patient also had good pain relief; however, she did not regain the use of her lower extremities. She died several weeks later secondary to her primary condition.[13]

TABLE 72–2 Characteristics of Neurolytic Agents

	Alcohol	Phenol
Physical properties	Low water solubility	Absorbs water on air exposure
Stability at room temperature	Unstable	Stable
Concentration	100%	4–7%
Diluent	None	Glycerin
Relative to cerebral spinal fluid	Hypobaric	Hyperbaric
Patient position	Lateral	Lateral
Added tilt	Semiprone	Semisupine
Painful side	Uppermost	Most dependent
Injection sensation	Burning pain	Painless, warm feeling
Onset of neurolysis	Immediate	Delayed (15 min)
Cerebrospinal fluid uptake ends	30 min	15 min
Full effect	3–5 days	1 day

INTRATHECAL ALCOHOL

A neurolytic intrathecal block should be performed at the level where the target dorsal root leaves the spinal cord, and not at the level where it passes through the intervertebral foramen. The latter is not recommended due to mismatch of the spinal cord level and vertebral bone level (especially as one progresses from high thoracic levels to low lumbar). An accurate determination of the level to be blocked should be evaluated according to dermatome and sclerotome charts, as well as selective local anesthetic blockade.[14] The patient should be positioned laterally so that the rootlets (dorsal root entry zone [DREZ]) are above the injection site.[15] This positioning is necessary given that alcohol will float in the CSF due to its greater specific gravity that renders it hypobaric, as previously described.[16] It is not uncommon for the patient to have difficulty moving into the correct position and maintaining it without undue levels of pain. The judicious use of pillows, towels, and tape, and maximizing table positioning is prudent to ensure the patient is not at a level of discomfort that would require movement before the block is completed. The patient should also be turned 45 degrees toward the prone position. This will raise the DREZ horizontally so it will be superior to the ventral nerve rootlets.[15] After proper patient positioning, correct needle depth must be obtained. A short, beveled needle is placed slowly into the predetermined location until arriving at the epidural space. This is best-confirmed using loss of

resistance to air. Due to patient positioning, the hanging drop technique may be difficult to perform. After ascertaining that the epidural space has been reached, the needle should be advanced slowly while aspirating continuously until it reaches the intrathecal space. Once the needle is in the intrathecal space, adjust the bevel so it is anterior to the arachnoid mater.[17] Depending on the institution and practitioner, placement may be verified with radiographic imaging (Figs. 72-3A and B) and contrast dye administration. The practitioner may then inject the alcohol, or it may be preceded by a low-volume injection of local anesthetic. Without the use of local anesthetic, significant discomfort can occur during the procedure. Whether needle placement is confirmed by local anesthetic or by the burning sensation of the alcohol injection, if the patient reports pain areas that are not covered by the primary needle placement, additional locations may require local anesthetic. Using a tuberculin syringe, the alcohol is injected in 0.1-ml increments, with at least 60 seconds (preferably 90 sec) between repeat administrations. Total alcohol volume should not exceed 0.5 to 0.7 ml.[17] After injection, the patient should remain in the same position for 15 to 30 min. This immobilization allows the alcohol to exert its maximal effect at the desired location, with minimal spread to adjacent levels. After the 30-min time period, a neurologic examination should be performed. Three to 5 days after the alcohol injection, the patient's pain should be evaluated to assess effectiveness of the technique and determine whether repeat injections are required.

PHENOL

Phenol is a benzene ring with one hydroxyl group substituted for a hydrogen atom. It is usually prepared by the hospital pharmacy because it is not commercially available in premixed liquid form. Phenol is poorly soluble in water and, at room temperature, forms only a 6.7% aqueous solution. Consequently, phenol is frequently prepared with contrast dyes and either sterile water, saline or glycerin. When phenol is exposed to room air, it undergoes oxidation and turns a reddish color; however, it has a shelf life of approximately 1 year if refrigerated and shielded from light exposure. When phenol is prepared with glycerin, it has limited spread, and, hence, injections are well localized. In rats, the aqueous solution of phenol has greater ability to penetrate the perineurium and produce greater endoneurial damage than glycerin preparations, but there is no difference in results following intraneural injection.[18] Unlike alcohol, phenol injection has an initial local anesthetic effect. It is not associated with localized burning, but instead, creates a sensation of warmth and numbness. The distribution of this sensation can help the practitioner verify proper needle placement. Concentrations of 4% to 10% are typically used for neurolysis. When phenol is prepared in glycerin, it has a specific gravity of 1.25, making it hyperbaric. Preparations of phenol in glycerin are highly viscous, which may make administration through a spinal needle difficult. Warming the injectate in a warm water bath before drawing it up into a tuberculin syringe may facilitate the ease of injection.[15] Careful patient positioning to allow phenol to settle into the desired location is important, and contrary to the concepts associated with patient positioning for alcohol neurolysis. Putnam and Hampton first used phenol as a neurolytic agent in 1936. Mandl used it for a sympathetic ganglion block in animals in 1947.[19] Phenol was first used as a medication in an intrathecal injection in humans in 1955.[20] Originally, it was surmised that phenol had a selective effect on small-diameter, unmyelinated nerve fibers, such as C-fiber afferents and A-g afferents. Subsequent studies have shown that phenol concentrations determine the type and extent of nerve disruption. Dilute intrathecal phenol can produce a transient local anesthetic blockade, while increased concentrations can produce significant neural damage.[21]

Phenol concentrations have a direct relationship with the extent of neural damage. At concentrations less than 5%, phenol instigates protein denaturation of axons and surrounding blood vessels. At concentrations greater than 5%, phenol can produce protein coagulation and nonselective segmental demyelination.[9] The nonselective effects of phenol were confirmed by Nathan using histologic studies combined with evidence of electrophysiologic changes to Aα- and Aβ-fibers.[22] Smith has shown that

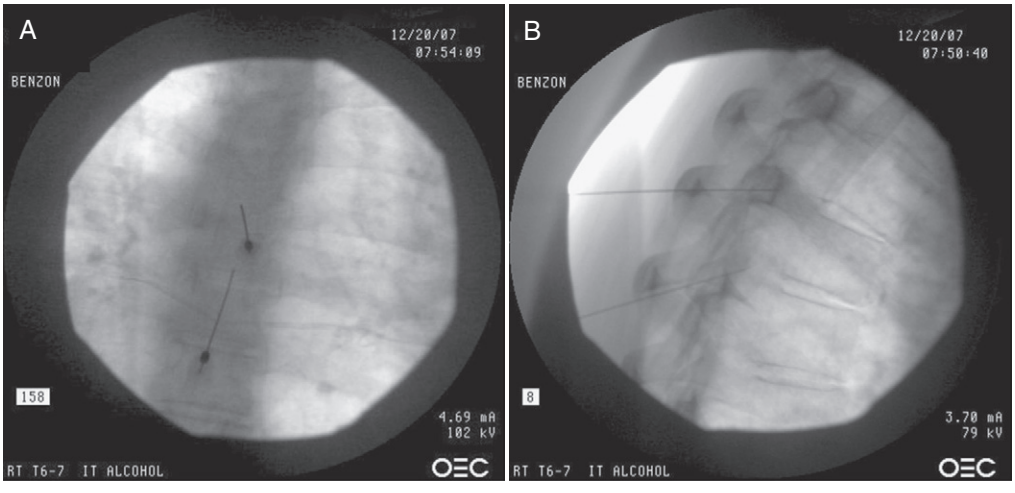

FIGURE 72-3 Anterior/posterior **(A)** and lateral **(B)** fluoroscopic images of needle placement for neurolysis.

intrathecal phenol injections in cats and humans primarily destroyed axons in dorsal rootlets and in the dorsal columns of the spinal cord. It was also noted to exert some effects on the ventral root axons.[23] Maher and Mehta noted that motor blocks by phenol were possible at concentrations greater than 5%, while intrathecal injections of less than 5% produced mostly sensory blocks.[24] At higher concentrations, the extent of damage can increase quite significantly, with the potential of axonal nerve root damage and spinal cord infarcts. Injections of high-concentration phenol have also been associated with arachnoiditis and meningitis.[25]

When compared to alcohol, phenol seems to facilitate axonal regeneration in a shorter period of time. Electrophysiologic studies comparing peripheral nerve destruction in cats showed that those injected with phenol had returned to normal by 2 months, while at the end of the same time period, those injected with alcohol still demonstrated depression of compound action potentials.[26] However, another study by Smith suggests regeneration is not completed until approximately 14 weeks after the administration of phenol.[23] It was once thought that phenol's neurolytic effects might be due to local ischemia because of its greater affinity for vascular tissue compared to neural tissue.[27,28]

Racz found that unlike epidural injection, tissue destruction resulted after intrathecal injection even though the vasculature was intact in the areas of spinal cord destruction.[29] This finding points toward direct neurotoxic effects rather than effects secondary to local ischemia. Phenol's effects may be a combination of direct neurotoxic and ischemic effects.[30] Romero-Figuero and colleagues demonstrated that vascular thrombosis is likely due to a caustic effect of phenol on the endothelium.[31] The vascular effects of any of the neurolytic agents are salient, particularly when these agents are injected in close proximity to prosthetic vascular grafts. The effect of neurolytic agents on prosthetic grafts seems to depend on the type of graft itself. Gore-Tex grafts appear to be able to withstand exposure to neurotoxic agents unharmed, while Dacron grafts show diminished tensile strength after a 72-hour exposure to either 6% phenol or 50% alcohol.[32] Systemic doses of phenol in excess of 8.5 g are associated with toxic side effects. These effects initially are convulsions, followed by CNS depression, and, finally, cardiovascular collapse. Chronic long-term exposure may be associated with renal toxicity, skin lesions, and gastrointestinal effects. However, phenol is not classically used in long-term settings, and the customary doses of less than 100 mg are unlikely to produce any systemic effects.[1]

INTRATHECAL PHENOL

The considerations that should be taken into account prior to the injection of alcohol also apply to the administration of phenol. The pain location should be determined with dermatome and sclerotome mapping, and preferably isolated with a diagnostic injection of local anesthetic or contrast dye under fluoroscopy. The site must be cleaned thoroughly, and standard sterile techniques applied. There are two fundamental differences between alcohol and phenol administration. When using phenol, the patient's targeted anatomy must be facing down, the patient leaned 45 degrees supine, and the spinal needle diameter must be larger due to the increased viscosity. The hyperbaric nature of phenol in glycerin requires positioning much different than in intrathecal alcohol administration. The "sinking" of phenol into its area of effect requires the targeted rootlets to be under the site of administration. Although positioning can be challenging, a common technique involves elevating the head of bed slightly, with the bed under the target flexed, and the patient turned 45 degrees supine. Turning the patient optimizes the dependent positioning of the nerve rootlets.

As with the use of alcohol, it is imperative to optimize the patient's comfort once the desired position has been achieved. Utilizing supporting devices such as pillows, towels, and foam can facilitate a reasonable level of comfort to prevent failure of the technique due to patient movement. Close monitoring of the patient as the neurolytic agent takes effect and throughout the cycle is essential because of the serious complications associated with these procedure. The feeling of warmth from the phenol is fleeting, and may provide some pain relief, but neurolysis is slower to manifest than with alcohol. The phenol can take 15 min before it starts to exert its effect. Although there is less outward diffusion with phenol compared to alcohol, the patient should be maintained in position for 30 min after phenol administration. The full effect of phenol manifests over approximately 24 hrs; if the block is incomplete, the injection can be repeated. A short, 20-gauge needle should allow the thick phenol solution to be injected in most situations. However, if this proves difficult, warming the injectate in a warm water bath before drawing may ease the flow of the injection. Like alcohol, phenol is injected in 0.1-ml increments, with 60 to 90 s between subsequent injections. Phenol is injected up to a total dose of 0.5 to 0.7 ml.

EPIDURAL NEUROLYTIC BLOCK

An epidural neurolytic block provides bilateral pain relief; however, its analgesia effects may not be as complete as intrathecal neurolysis. Epidural neurolysis is used for abdominal cancer pain of both visceral and mixed somatic and visceral origin.[33] Epidural neurolysis remains popular, not only due to its increased safety index and the ease for repeated injections, but also for its greater efficacy on thoracic and cervico-thoracic junction pain. Although the traditional technique is described below, a recent study demonstrated that the use of a transforaminal approach when necessary provided excellent results.[33] Selecting the appropriate size needle depends on the agent used. The use of phenol in glycerin requires a large-bore needle, while the use of aqueous phenol, phenol in saline, or alcohol permits the use of a much smaller needle, in which case an epidural needle or catheter may be used. With an epidural catheter, repeated injections can be performed without accessing the epidural space multiple independent times; however, the catheter can be a nidus for infection. The catheter is a soft, nonkinking, styletted version that can be maneuvered with precision, and allows confirmation of position with the injection of a small amount of local anesthetic.

Unlike the intrathecal administration of neurolytic agents, needle or catheter tip location should be chosen near the vertebral levels that correspond to the dermatomal

levels manifesting in the patient's pain area in order to deposit the medication over the appropriate nerve roots. The injections should be performed under sterile conditions. Many expert providers recommend repeated injections over the course of several days, so making a consistent location choice can improve efficacy and outcome. Once needle and patient positioning have been established, the use of contrast-enhanced fluoroscopic imaging and a local anesthetic test dose can be performed to confirm proper needle depth and location. The appropriate volume of injectate depends on the level of the neurolysis being performed. Doses ranging from 2 to 5 ml are usually adequate, with doses increasing as location moves more caudally. As stated earlier, recommendations are that injections be performed daily until satisfactory results are achieved. Racz and colleagues endorse daily injections until noticeable changes in pain levels no longer occur or the patient is pain-free after 24 hr. For up to 3 days after the initial placement of an epidural catheter 3 to 5 cm into the epidural space, ethyl alcohol can be injected daily. Before each daily administration, they reaffirmed placement with a local anesthetic test dose, which also reduced the negative sensations associated with alcohol.[34] Using 0.2-ml increments, they dosed the catheter with 3 to 5 ml of alcohol over a period of 20 to 30 min. Although initial relief was achieved in all cancer patients, results were less significant in patients with chronic nonmalignant pain.[35] In four studies, the results of thoracic epidural neurolysis revealed significant improvement of cancer pain.[6] Pain relief, ranging from 65% to 100%, was achieved in 80% of patients. Pain relief varied among populations, and reflected the severity of disease; nonetheless, many patients were pain-free until the time of their death. In the patients who survived, the duration of pain relief varied from less than 1 month to in excess of 3 months.

Although ease of administration is a factor, there does not appear to be increased margin of safety of epidural neurolysis versus intrathecal neurolysis. A study done by Katz showed that 2 weeks after the lumbar epidural injection of phenol in a group of primates, predominant posterior nerve root damage was noted, in addition to anterior nerve root and spinal cord damage. These test subjects also demonstrated lower extremity motor weakness on physical examination.[36] In a patient who died 24 days after a series of three thoracic alcohol injections by Hayashi, the laminar structure of the dura was destroyed at the outer third. However, there was no abnormality to the spinal nerve root or the spinal cord.[37]

COMPLICATIONS ASSOCIATED WITH INTRATHECAL AND EPIDURAL NEUROLYSIS

Complications with neurolysis range in frequency from 1% to 14%, and in severity from incomplete block to limb weakness or bladder/rectal paresis.[1] Like most interventional pain procedures, the most common complication is failure of the procedure to provide significant pain relief. Poor pain relief can have numerous etiologies. It is not unusual for patients to have high expectations for pain relief and have those expectations not met by neurolysis. Therefore, it is important for the pain practitioner to have clear communication with the patient prior to the procedure to prevent these disappointments. Another cause of inadequate pain relief may be as simple as an incomplete block that can be remedied with a repeat dose. If tumor growth is extensive or crosses several dermatomes, neurolysis may be less effective.

Unfortunately, there is always the possibility that the block works well, but that local spread of the neurolytic agent may have produced peripheral damage. There are complications due to entry into the anatomic space where these medications are administered. They include postdural puncture headaches, meningitis, arachnoiditis, and neural damage due to trauma. Postdural headaches usually resolve quickly, within 1 to 5 days. Complications related to neurolytic agents include loss of motor function due to neurolysis of the ventral rootlets, loss of touch and proprioception, and loss of sphincter tone. Of these potential complications, loss of bowel or bladder sphincter tone is relatively common. The complications caused by the neurolytic agents are usually transient. According to Gerbershagen, who observed the duration required for resolution of neurolytic complications, 28% resolved within 3 days, 23% within 1 week, 21% within 1 month, 9% within 4 months, and 18% longer than 4 months.[38]

Complication rates appear to be similar between alcohol and phenol, as shown by Swerdlow, who analyzed complications in a series of 145 patients.[39] Complications can be specific to location along the spine where the neurolysis is performed. At the cervical level, damage can occur to the brachial plexus, most often manifesting as limb paresthesias. Complications at the thoracic level are the least common relative to the cervical and lumbar level. Below the L1 spinal level, injections may travel into the cauda equina, where anterior and posterior roots are not separated. This factor that may make the degree of motor or sensory effect difficult to predict.

Hollis documented that patients with complete obstruction of the intrathecal space have different risks of neurologic deterioration, depending on the location of penetration. Punctures performed above the site of complete obstruction at C1-2 had no incidence of neurologic deterioration, while punctures below the site of obstruction in the lumbar region resulted in neurologic deterioration in 14% of patients.[40] This complication may be due to downward spinal coning after the removal of CSF below the lesion, and should be considered when performing neurolytic blocks. Changes in opioid use may occur after a neurolytic block. Patients who have typically been on high doses of opioids for long periods of time will have reduced requirements for pain control with a successful block. Rapid discontinuation of opioids will cause withdrawal side effects; without pain as a stimulus, preneurolysis opioid doses may produce excessive sedation and respiratory depression. Careful observation of the patient in the hours to days after successful neurolysis can circumvent these problems.

PERIPHERAL NEUROLYSIS IN CANCER PAIN

Peripheral neurolysis is a controversial subject. Although some argue that it has no real use in cancer pain management, it has found a role in intercostal neurolytic blocks.

The use of peripheral neurolysis follows successful diagnostic blocks using local anesthetics. Peripheral neurolytic blocks are frequently associated with neuritis and deafferentation pain, in addition to postinjection dysesthesias. While these complications are unpleasant, they may be preferable to the patient's current pain, or the patient may succumb to their primary disease before these complications fully manifest.[3] Neurolytic intercostal blocks may help with pain that originates from the thoracic wall, abdominal wall, or parietal perineum. Intercostal blocks are performed by "walking the needle off" the inferior border of the rib. Proper needle placement should be verified using fluoroscopy and paresthesias. Typically, phenol is the agent of choice. Phenol is injected in 1- to 2-ml doses of 5% phenol. Its effects are notable, and repeat dosing over several days is common. Most complications are associated with the agent or the location. As noted before, neuritis, dysesthesias, and pain are relatively common side effects. Pneumothorax is a potential complication, but can be minimized by careful technique.

ADDITIONAL TECHNIQUES OF NEUROLYSIS

Techniques on cryoanalgesia and surgical approaches to pain management are discussed in other chapters.

KEY POINTS

- Neurolytic therapy should only be considered after other pain modalities have been exhausted. These therapies are usually reserved for patients with terminal disease. Very clear therapeutic goals and limitations need to be communicated between patient and practitioner.
- Neurolytics can offer patients the ability to decrease their systemic pain medications that can improve their quality of life and allow them the opportunity to clearly communicate with loved ones during difficult times.
- Alcohol and phenol are the primary agents used in intrathecal and epidural neurolysis. Alcohol is associated with burning upon injection, so it is preceded local anesthetic injection. Phenol injection is relatively painless and is associated with a feeling of warmth.
- Pain location should be pinpointed with sclerotome, dermatome mapping, and radiologic survey. Patient positioning for injection is determined by patient comfort and by which agent is to be injected. Alcohol is hypobaric and "floats" in CSF while phenol is hyperbaric and "sinks" in CSF.
- The most common complication is poor pain relief. Proper location is paramount. Often, pain relief may require several injections. Other complications related to intrathecal or epidural neurolytics are loss of motor function, loss of touch or proprioception, and loss of bowel or bladder sphincter tone.

REFERENCES

Access the reference list online at http://www.expertconsult.com

Nerve Blockade

CHAPTER 73

Head and Neck Blocks

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Nerve blocks of the head and neck are key components of an anesthesiologist's and pain management practitioner's skill set. From an anesthesiologist's perspective, some of the blocks can be used for regional anesthesia and postoperative pain control. From a pain practitioner's standpoint, these blocks can be used for diagnostic and therapeutic purposes and are generally indicated when pharmacological therapy is partially effective or ineffective in alleviating a patient's chronic pain. Detailed knowledge of the relevant anatomy is key as this will theoretically improve efficacy and minimize complications.

Specific indications will be listed with the individual blocks. Informed consent prior to the block should be obtained. Absolute contraindications include patient refusal, local infection and sepsis, and increased intracranial pressure (trigeminal ganglion block). Relative contraindications are coagulopathy, anticoagulant therapy, history of facial trauma, and pre-existing neurologic deficits. Allergy to medications used can be absolute or relative depending on the severity of the allergy.

TRIGEMINAL NERVE AND GANGLION

ANATOMY

The trigeminal ganglion resides in the middle cranial fossa.[1–3] It is situated in a fold of dura mater that forms an invagination around the posterior two-thirds of the ganglion. This region is referred to as Meckel's cavity and contains cerebrospinal fluid. The ganglion is bound medially by the cavernous sinus and optic and trochlear nerves; superiorly by the inferior surface of the temporal lobe of the brain; and posteriorly by the brain stem. The ganglion is formed by the fusion of a series of cell bodies that originate at the mid-pontine level of the brainstem. The ganglion has three major divisions: ophthalmic (V1), maxillary (V2), and mandibular (V3). The ophthalmic division is located dorsally, the maxillary branch intermediate, and the mandibular branch ventrally. The ophthalmic division leaves the ganglion and passes into the orbit through the superior orbital fissure. It further divides into the supraorbital, supratrochlear, and nasociliary nerves which innervate the forehead and the nose.[3] The maxillary division exits the middle cranial fossa via foramen rotundum, crosses the pterygopalatine fossa, and enters the orbit through the inferior orbital fissure. Branches include the infraorbital, superior alveolar, palatine and zygomatic nerves which carry sensory information from the maxilla and overlying skin, the nasal cavity, palate, nasopharynx and meninges of the anterior and middle cranial fossa.[3] The mandibular division exits through foramen ovale and divides into the buccal, lingual, inferior alveolar and auriculotemporal nerves. These nerves carry sensory input from the buccal region, the side of the head and scalp, and the lower jaw including teeth, gums, anterior two-thirds of the tongue, chin, and lower lip.[3] The motor component of V3 innervates the several muscles including the masseter, temporal, and medial and lateral pterygoids. The ganglion interfaces with the autonomic nervous system via the ciliary, sphenopalatine, otic, and submaxillary ganglia. It also communicates with the oculomotor, facial, and glossopharyngeal nerves.[4]

PROCEDURES

MAXILLARY NERVE BLOCK

Diagnostic and therapeutic blocks of the maxillary nerve are performed similarly. Fluoroscopy is not always necessary, but may be used when external landmarks are not easily palpated or when a neurolytic technique is planned. The most common indication for this block is regional anesthesia for surgery of the upper jaw, but is also effective for acute postoperative pain control. In the pain management arena, it is indicated for the diagnosis and treatment of chronic pain in the distribution of the maxillary division of the trigeminal nerve. Place the patient in the supine position. Palpate the mandibular notch located below the zygoma and anterior to the temporomandibular joint. Under sterile conditions, anesthetize the skin over the notch. Insert the block needle (usually a 22-gauge, 8–10 cm, short-bevel or a same-size curved, blunt needle) in a horizontal plane through the mandibular notch until bone (lateral pterygoid plate) is touched (typically 4–5 cm) (Fig. 73-1). If a blunt needle is used, an 18-gauge, 1.25-inch angiocatheter is inserted first. Withdraw the needle and redirect it anteriorly and superiorly through the pterygomaxillary fissure into the pterygopalatine fossa. Advance the needle approximately 0.25 to 0.5 cm at which depth a paresthesia is usually perceived in the upper lip or teeth.[5] If performed under fluoroscopy, the needle is angled toward the superior

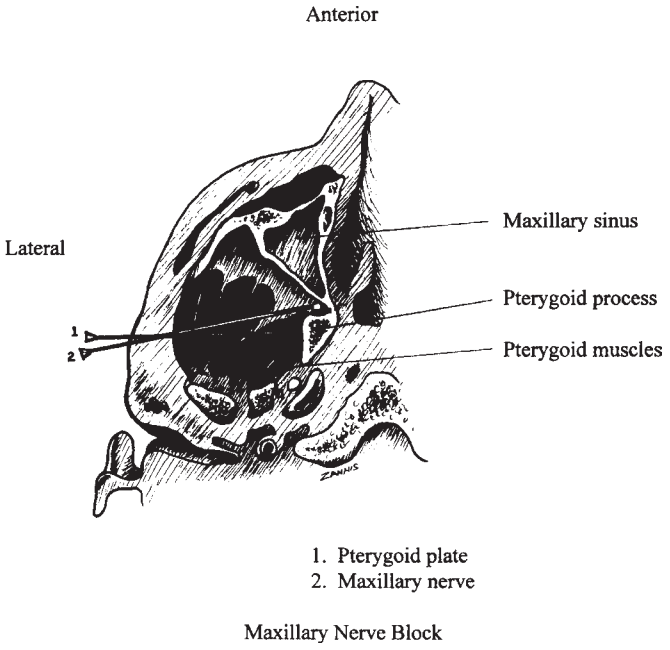

FIGURE 73-1 Maxillary nerve block, transverse section.

portion of the pterygopalatine fossa, which appears as a "V" on the lateral image. On an anteroposterior image, the needle tip should be above the level of the middle turbinate. Inject 3 to 5 ml of local anesthetic. If fluoroscopy is used, 0.5 to 1.0 ml of contrast can be injected first to rule out intravascular placement of the needle. Remove the needle and apply an ice pack to the cheek. Neurolytic blocks can be done with 6% phenol or absolute alcohol. After appropriate placement of the needle, up to 1.0 to 1.5 ml of the neurolytic solution is injected in 0.1-ml aliquots. The needle should then be flushed with 0.5 ml of saline prior to removal. Pulsed radiofrequency lesioning can also be performed after a successful diagnostic block. Sensory stimulation is performed at 50 Hz, 1 V. Paresthesia in the upper teeth should be perceived at less than 0.3 V. Once confirmed, two or three 120-sec pulsed radiofrequency cycles are administered at 45 V.

MANDIBULAR NERVE BLOCK

Diagnostic and therapeutic blocks of the mandibular nerve are both performed in the same manner. Fluoroscopic guidance is not a necessity, but is encouraged when a therapeutic block is planned as it can facilitate needle positioning. Indications are similar to those for the maxillary nerve block except the area to anesthetize or treat pain is the lower jaw and tongue. The procedure is performed identically to the maxillary nerve block except for the following: once the lateral pterygoid plate has been touched with the block needle, withdraw it and redirect in a slightly caudal and posterior direction until a paresthesia is produced in the lower lip, lower jaw, or ipsilateral tongue or ear (Fig. 73-2).[6] The depth should not be more than 0.1 to 0.25 cm beyond the depth at which the lateral pterygoid plate was contacted.[7] The total distance should not exceed 5.5 cm. If a paresthesia is not elicited at a depth of 5.5 cm, the needle should be withdrawn and redirected. After

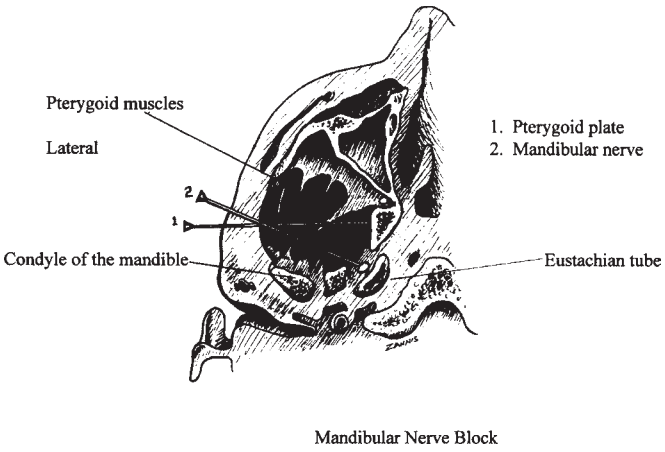

FIGURE 73-2 Mandibular nerve block, transverse section.

proper positioning, inject 2 to 3 ml of local anesthetic, remove the needle, and apply an ice pack to the side of the face. If using fluoroscopy, start with a lateral view and proceed using the same technique as described above. Since this technique involves blocking the nerve as it exits the foramen ovale, a submental, oblique view can be obtained (described in the trigeminal ganglion block section of this chapter) in order to verify the position of the needle tip in relation to foramen ovale. The needle tip should be adjacent to, or overlie, the shadow of the foramen ovale. To rule out intravascular or intrathecal injection, instill 0.5 to 1.0 ml of contrast. If negative, inject the aforementioned volume of local anesthetic. Chemical neurolysis can be achieved using 6% phenol, 50% glycerol, or absolute alcohol. After a successful diagnostic block and after proper positioning of the needle, up to 1.0 ml of the neurolytic solution is injected in 0.1-ml increments. Flush the needle with 0.5 ml normal saline before removing it. For pulse radiofrequency lesioning, perform sensory and motor stimulation at 50 Hz, 1 V, and 2 Hz, 2 V, respectively, to check needle position. Paresthesia should be obtained at less than 0.3 V, and masseter contraction should be apparent at less than 0.6 V. Two to three 120-sec pulsed cycles should be carried out at 45 V.

TRIGEMINAL GANGLION

Tic douloureux is the most common indication for trigeminal ganglion blockade.[8] The block is indicated for patients who have failed conventional pharmacologic therapy. Secondary trigeminal neuralgias from injury to the major divisions or the distal branches of the ganglion are a frequent indication.[4] Palliation of cancer-related pain has successfully been accomplished through blockade of the trigeminal ganglion or its divisions. This block has also found a niche in the treatment of chronic, intractable cluster headaches.[9–13] Persistent idiopathic facial pain (formerly atypical facial pain) also responds to ganglion blockade and neurolysis.[14] As with most current fluoroscopically guided block techniques, the original description of the trigeminal ganglion block utilized external landmarks and a blind approach. Since the use of fluoroscopy is stressed in this chapter to improve the accuracy and success of the block as well as decrease the chance of complications, the blind

approach will not be discussed. The description of this block will focus on the use of a 20- to 22-gauge, curved, blunt needle, but sharp spinal or block needles are also acceptable. Obtain intravenous access. Place the patient on the table in the supine position with the head slightly extended. Light sedation with midazolam and fentanyl is usually required. Sterilely prepare and drape the appropriate side, leaving the eye exposed. Utilizing continuous or pulsed fluoroscopy, locate foramen ovale by rotating the C-arm image intensifier obliquely away from the nose approximately 20 to 30 degrees, and then angle the C-arm image intensifier approximately 30 to 35 degrees in the caudocephalad direction to bring the foramen ovale into view. Subtle adjustments of the C-arm angles may be necessary. Raise a skin wheal directly over the shadow of the foramen which will be approximately 2 to 2.5 cm lateral to the corner of the mouth. Insert a short, 16- or 18-gauge angiocatheter through the skin wheal and advance to the hub. Insert a gloved finger into the oral cavity to confirm that the buccal mucosa has not been breached. Re-glove before proceeding. Insert a 20- or 22-gauge, curved, blunt block needle through the angiocatheter and advance a few centimeters. Obtain a fluoroscopic image to check the trajectory of the needle. The goal is to advance the needle in a coaxial fashion toward the foramen ovale (Fig. 73-3). Corrections in trajectory can be made by turning the needle tip in the appropriate direction. With respect to external landmarks, the trajectory of the needle will be in a plane slightly superior to the external auditory meatus and medially toward the pupil in the midline. Advance the needle in 1- to 2-cm increments until bone is touched. Obtain a lateral image to check the position of the needle. If the foramen has not been traversed, adjust the needle tip (usually posterior) and advance through the foramen a distance of 0.5 to 1.0 cm (Fig. 73-4). The depth of the needle tip is not as important with a local anesthetic block as it is for a neurolytic procedure. After a negative aspiration for cerebrospinal fluid or blood, inject 0.5 to 1.0 ml of nonionic, water-soluble contrast to confirm position and filling of Meckel's cavity. Any vascular runoff requires repositioning of the needle. If cerebrospinal fluid is obtained, the needle tip can be withdrawn until fluid is no longer appreciated. If an abundant cerebrospinal fluid leak is present, the remainder of the procedure should be halted. With a significant leak, a high spinal block can be caused with even low volumes of local anesthetic. A small leak of cerebrospinal fluid may or may not cause a high spinal and if present, the pain practitioner should proceed with caution. Inject local anesthetic in volumes of 0.25 to 0.5 ml at a time, up to 1 to 2 ml, and observe for effect. Remove the needle and apply an ice pack to the cheek to decrease swelling.

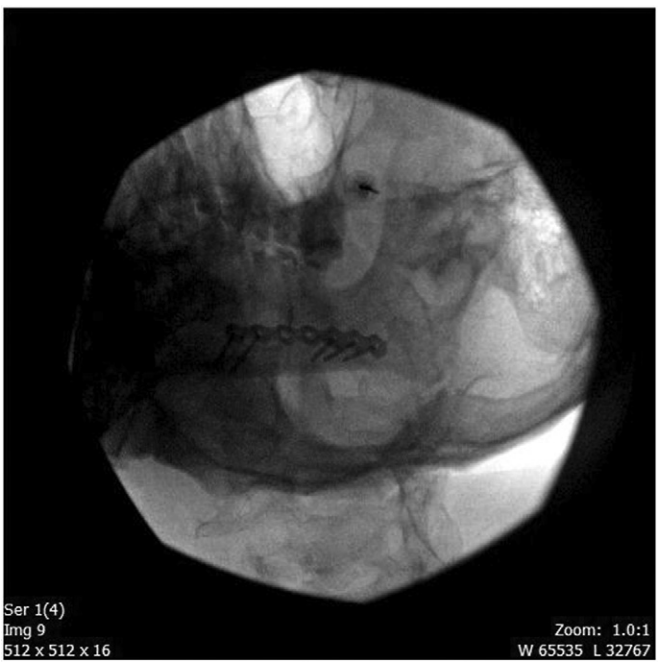

FIGURE 73-3 Submental oblique coaxial fluoroscopic image of the block needle through foramen ovale.

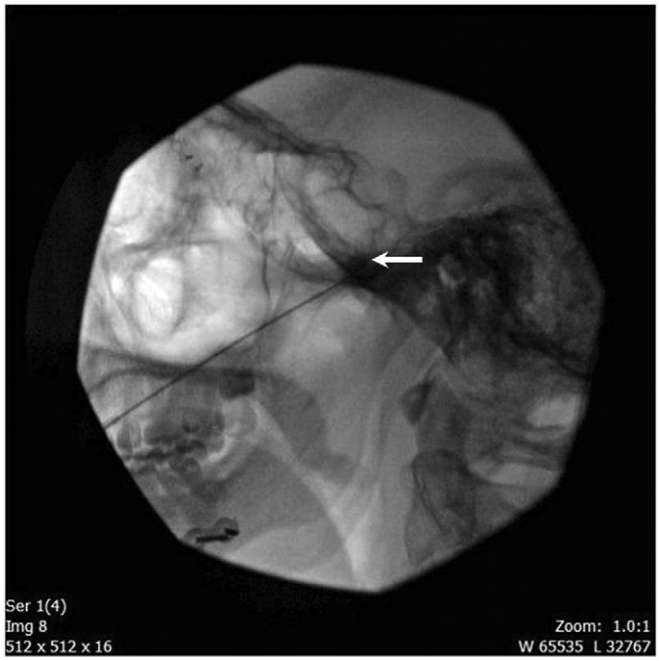

FIGURE 73-4 Lateral fluoroscopic image of the block needle residing in the middle cranial fossa. The arrow indicates the tip of the needle.

NEUROLYTIC TECHNIQUES

After a successful diagnostic block, a neurolytic procedure can be planned. Needle placement for all of neurolytic procedures except balloon microcompression is performed in the same manner as for the local anesthetic block. Heavier sedation may be required for radiofrequency techniques.

CONVENTIONAL RADIOFREQUENCY

For conventional radiofrequency lesioning, a 3- to 5-mm active-tip needle is placed. The target depth of the needle tip depends on the division of the trigeminal nerve that needs to be lesioned. The mandibular division is rostral and lateral; the maxillary division is intermediate; and the ophthalmic division is mostly cephalad and medial. Location of the needle tip on the appropriate division/s is determined by the response to sensory and motor

stimulation (50 Hz, 1 V, and 2 Hz, 2 V, respectively) of the ganglion. Paresthesia should be perceived at less than 0.3 V, with little to no muscle contraction of the masseter muscle at 0.6 to 1.0 V.[4] If no contraction is seen, then the tip of the needle is on the ophthalmic or maxillary divisions. Once the patient senses paresthesia in the painful area, inject 0.5 ml of 0.25% bupivacaine or 0.2% ropivacaine with steroid. Wait 30 to 60 sec and begin lesioning at 60° C for 90 sec. If the patient cannot tolerate the lesioning, stop and wait an additional 30 s, and then try again or add another 0.5 ml of local anesthetic prior to resuming lesioning. If more than one branch of the trigeminal nerve is affected, perform several lesions of the ganglion. Reposition the needle and repeat the stimulation test to get paresthesia in the desired site. For lesioning of the ophthalmic division, assess the corneal reflex during and after each lesion. Lesioning is typically started at temperatures of 55 to 65° C to preserve this reflex. One or two lesions are recommended. If the corneal reflex diminishes, lesioning should be stopped.

PULSED RADIOFREQUENCY

Pulsed radiofrequency is not a temperature-dependent technique. It is a nondestructive method of providing long-term pain relief.[15] After proper positioning of the needle tip, perform two or three pulsed radiofrequency cycles for 120 sec each at 45 V. The temperature of the needle tip rarely exceeds 42° C, thus local anesthetic is not required. If significant masseter contraction is noted during pulsing, inject 1 to 2 ml of local anesthetic to diminish this, or hold the patient's mouth closed with your hand while the cycles are completed.

CHEMICAL NEUROLYSIS

Chemical neurolysis has been performed with phenol and alcohol in the past, but their use is not currently recommended. Glycerol is the chemical neurolytic of choice. Once through the foramen ovale, advance the needle until cerebrospinal fluid is observed returning through the needle. Place the patient in a semi-sitting position with the neck flexed. Inject water-soluble, nonionic contrast solution in 0.1-ml aliquots (up to 0.5 ml) into the trigeminal cistern.[6] Failure of visualization or diffusion of the contrast requires repositioning the needle. Once the cistern is visualized, draw back the contrast material by free flow. The flow of contrast is slower than cerebrospinal fluid. Inject the same amount of glycerol into the cistern. Flush the needle with 0.5 ml of saline prior to removal. Keep the patient in a semi-sitting position for 2 hr. During the procedure, patients often report pain, burning, or paresthesia in the affected division/s.[16]

COMPLICATIONS

With the exclusion of sensory loss (an expected side effect) from the complications considered for all neurolytic techniques, radiofrequency thermal lesioning had the highest number of complications (29.2%) followed by glycerol rhizotomy and balloon compression at 24.8% and 16.1%, respectively.[17] Retrobulbar hematoma is possible if the needle is advanced into the retrobulbar space. Exophthalmus develops secondary to bleeding in the retrobulbar space. Cheek hematoma can occur if a blood vessel is punctured during placement of the needle. Masseter weakness can develop, especially with lesioning of the mandibular division. The incidence is highest with balloon microcompression (66%) and less for radiofrequency lesioning and glycerol rhizotomy (24% and 1.7%, respectively).[6] Loss of the corneal reflex, keratitis, ulceration, and hypesthesia are observed in 3% to 15% of patients after a neurolytic procedure.[8] Keratitis was more likely to occur after radiofrequency lesioning and glycerol neurolysis.[17] Corneal anesthesia was highest for radiofrequency rhizotomy at 7%, and was observed with glycerol rhizotomy and balloon compression at 3.7% and 1.5%, respectively.[6]

Anesthesia dolorosa (deafferentation pain) occurs in up to 4% of patients with radiofrequency, followed by glycerol where it occurs in 2% of cases.[6] Other complications include meningitis, dural arteriovenous fistulae, rhinorrhea, transient cranial nerve deficits, tissue sloughing, and even death.[17,18] Postprocedure trigeminal nerve sensory loss is an expected occurrence after a properly performed neurolytic procedure. The incidence with radiofrequency rhizotomy is as high as 98%, followed by balloon compression (72%) and glycerol neurolysis (60%).[19]

SPHENOPALATINE GANGLION

ANATOMY

The ganglion resides in the pterygopalatine fossa. The fossa is bordered anteriorly by the maxillary sinus; posteriorly by the medial pterygoid plate; medially by the palatine bone; and superiorly by the sphenoid sinus. The pterygomaxillary fissure allows passage of a needle into the fossa, while the pterygopalatine foramen is located medial to the ganglion and is just posterior to the middle turbinate. The fossa is approximately 1 cm wide and 2 cm high and resembles a V-shaped vase on a lateral fluoroscopic image. A large venous plexus overlies the fossa. Foramen rotundum and the pterygoid canal are located on the superolateral and inferomedial aspect of the fossa, respectively. The maxillary artery resides in the fossa. The ganglion is "suspended" from the maxillary nerve by the pterygopalatine nerves and is medial to the maxillary nerve. Posteriorly the ganglion is connected to the vidian nerve which is formed by the deep petrosal (sympathetic from the upper thoracic spinal cord) and greater petrosal (parasympathetic from the superior salivatory nucleus) nerves. The ganglion has efferent branches and forms the superior posterior lateral nasal and pharyngeal nerves. Caudally, the greater and lesser palatine nerves exit the ganglion. Sensory fibers arise from the maxillary nerve, pass through the SPG, and innervate the upper teeth, nasal membranes, soft palate, and some parts of the pharynx. A small number of motor nerves are believed to travel with the sensory trunks.

PROCEDURE

Indications for sphenopalatine ganglion block and neurolysis include sphenopalatine neuralgia, trigeminal neuralgia, migraine headaches, cluster headaches, atypical facial pain,

and cancer of the tongue and floor of the mouth. Other reported, but not yet mainstream therapeutic uses include sinus arrest in postherpetic neuralgia, vasomotor rhinitis, complex regional pain syndrome of the lower extremity, low back pain, and post-traumatic headache.[20–24]

INTRANASAL APPROACH

The intranasal SPG block can be safely performed in an office setting. The location of the SPG in relation to the middle turbinate as well as the lateral nasal mucosa allows absorption of local anesthetic from a cotton-tipped applicator inserted into the nare. Four percent cocaine is the local anesthetic of choice secondary to its inherent vasoconstrictor property. If this is not available or there is a contraindication to using cocaine, 1% to 2% lidocaine or 0.25% to 0.5% bupivacaine or ropivacaine can be used instead. If these are chosen, the practitioner can pretreat the nare/s with neosynephrine to produce vasoconstriction. Place the patient in the supine position. Estimate the depth of insertion by externally measuring the distance from the opening of the nare to the mandibular notch. Place a mark corresponding to this depth on the shaft of the cotton-tipped applicator. Soak the applicators in the local anesthetic for several minutes. Slowly insert the applicator into the nare and advance in a line parallel to the zygoma with the tip angled laterally. Do not advance the applicator in a cephalad direction. The endpoint should be the depth marked on the applicator. Place a second applicator into the nare using the same technique, except advance it approximately 0.5 to 1.0 cm deeper and superior to the first. If resistance is encountered at any time, slightly withdraw and redirect the applicator. The second applicator is not a necessity and the nares of some patients may not accommodate it. Leave the applicator(s) in for 30 to 45 min. Signs of a successful block of the SPG include ipsilateral tearing, conjunctival injection, and nasal congestion. If the SPG is a pain generator or transmitter, analgesia should also be apparent. If after 20 to 30 min there are no signs of a block or the patient has not received any pain relief, additional local anesthetic may be needed and can be trickling down the shaft of the applicator. Remove the cotton-tipped applicators after 45 min even if there are no signs of a block or analgesia. If there are no signs of a block or analgesia, the SPG may be too deep to be blocked by this technique, or is not involved in the transmission of pain. Regardless, the infrazygomatic approach should be performed to rule out both of the aforementioned scenarios.

INFRAZYGOMATIC APPROACH

The infrazygomatic approach to SPG blockade is technically challenging. It can be performed without fluoroscopy, but fluoroscopic guidance is highly recommended as this will anecdotally improve the success of the block, the speed at which it is performed, and will decrease potential complications. Noninvasive monitors should be used to record vital signs. Light sedation with midazolam and fentanyl can be used, but on occasion, deeper sedation may be necessary for radiofrequency lesioning. For pulsed radiofrequency, heavy sedation is not required.

Place the patient in the supine position. Sterilely prep and drape the appropriate side of the face. Obtain a lateral fluoroscopic image. Palpate the mandibular notch and anesthetize the skin. If the notch is not palpable, identify the notch on a lateral fluoroscopic view. Identify the pterygopalatine fossa (appears as a "V") on the lateral image and superimpose the right and left fossae (Fig. 73-5). This is accomplished by manipulating the C-arm or the head. The block can be performed with a 4.5-inch, 22-gauge, short-bevel needle with the distal tip bent at a 30-degree angle, or with a curved, blunt, 10-cm, 20- or 22-gauge needle. The technique description will reflect the use of a blunt needle. Anesthetize the skin and insert a 1.25-inch, 16-gauge angiocatheter through the skin and advance until it is just medial to the ramus of the mandible. This can be checked on an anteroposterior (AP) image. Pass the block needle through the angiocatheter and advance it medial, anterior, and slightly cephalad. Obtain a lateral image to check the direction of the needle. Your target is the mid portion of the pterygopalatine fossa (Fig. 73-5). Get an AP view and advance the needle toward the middle turbinate, stopping when the tip is adjacent to the palatine bone (Fig. 73-6). If resistance is encountered at any point, withdraw and redirect the needle. Given the small size of the fossa, frequent AP and lateral images are may be required to redirect the needle. Once in the fossa, inject 0.5 to 1 ml nonionic, water-soluble contrast, and observe for intravascular spread and/or intranasal placement of the needle. Once correct placement has been confirmed, inject 2 cc of local anesthetic, with or without steroids.

RADIOFREQUENCY THERMOCOAGULATION AND PULSED RADIOFREQUENCY

After a successful diagnostic block, two therapeutic choices are available: conventional radiofrequency lesioning (RFTC) and pulsed electromagnetic field radiofrequency (P-EMF).

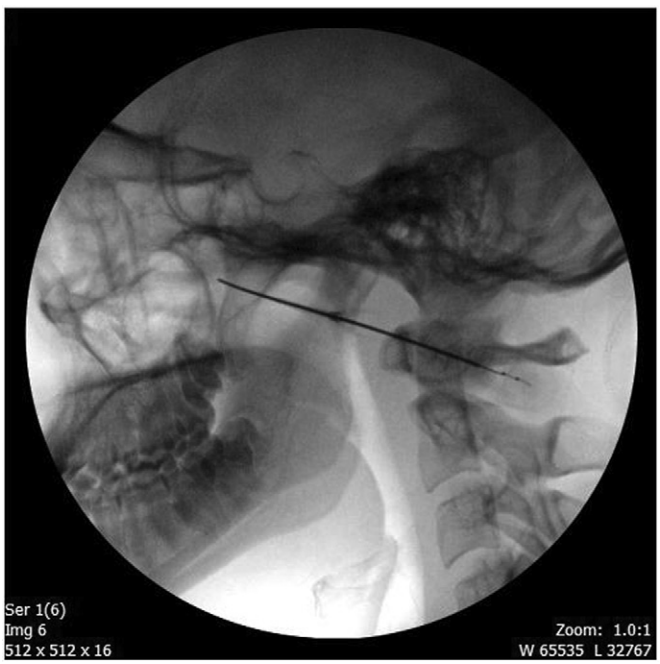

FIGURE 73-5 Lateral fluoroscopic image of the block needle in the midportion of the pterygopalatine fossa.

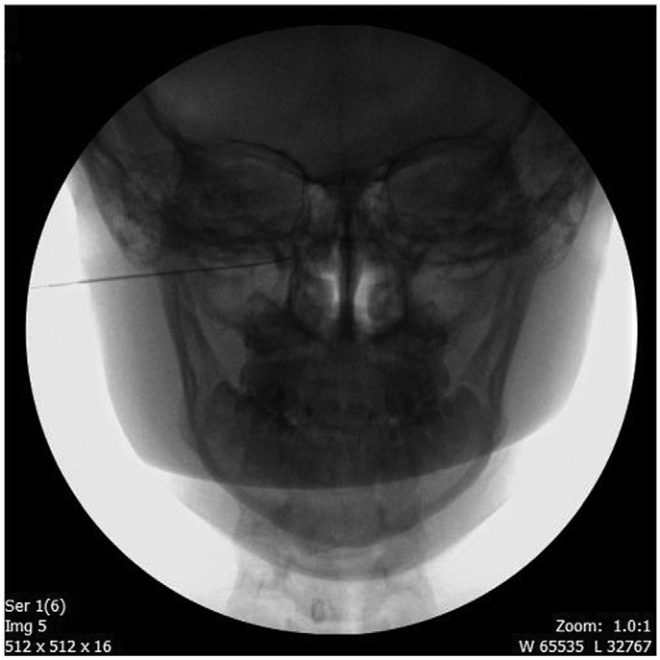

FIGURE 73-6 AP fluoroscopic image of the block needle adjacent to the palatine bone at the level of the middle turbinate.

An insulated RF needle with a 3- or 5-mm active tip is placed using the infrazygomatic approach. Once in place, sensory stimulation is performed at 50 Hz up to 1 V. If the tip of the needle is adjacent to the SPG, the patient should perceive a paresthesia at the root of the nose at less than 0.3 V. If the paresthesia is felt in the hard palate, the needle should be redirected cephalad and medial. A paresthesia in the upper teeth indicates stimulation of the maxillary nerve and the needle should be more caudal and medial. Motor stimulation is not necessary. After appropriate sensory stimulation, RFTC can be performed at 67 to 80° C for 90 sec times two cycles. Before lesioning, 2 to 3 ml of local anesthetic should be injected. To avoid inadvertent lesioning of other nerves around the SPG, a 3-mm active tip is a better choice. For P-EMF, the size of the active tip is not important as the electromagnetic field is projected from the tip of the needle and not from the shaft. With P-EMF lesioning, two to four 120-sec lesions are performed at 45 V. Local anesthetic is not required for P-EMF. The choice of whether to do an RFTC or a P-EMF lesion after a successful block is up to the discretion of the pain practitioner.

COMPLICATIONS

Complications include bruising, bleeding, infection, damage to nerves, proptosis from retrobulbar hematoma, dysesthesias, paresthesias, and/or numbness from RFTC. Bradycardia ("Konen" reflex) has been noted during RFTC and P-EMF, and can be prevented with pretreatment with atropine or glycopyrolate.[25]

OCCIPITAL NERVE BLOCK

Occipital headaches known as occipital neuralgia and can present from multiple sources. Occipital neuralgia was a term initially introduced in 1821 to describe a headache originating from the occipital and suboccipital region.[26,27] The term described an irritation of the greater occipital nerve (GON), and/or the lesser occipital nerve (LON). The International Headache Society defines occipital neuralgia as a paroxysmal jabbing pain in the distribution of the greater or lesser occipital nerves or of the third occipital nerve, sometimes accompanied by diminished sensation or dysesthesia in the affected area. It is commonly associated with tenderness over the nerve concerned and the pain is often relieved with a local anesthetic block.[28] Recognized causes of occipital neuralgia include trauma to the greater and lesser occipital nerves, compression of the greater and/or lesser occipital nerves or C2 and/or C3 nerve roots by degenerative cervical spine changes, cervical disc disease, myofascial pain, referred pain from ipsilateral trigeminal distribution, and tumors involving the C2 and C3 nerve roots.[29] Treatment options vary depending on the etiology of the pain. Management usually begins with conservative treatment such as physical therapy, massage, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, tricyclic antidepressants, and anticonvulsants. When occipital neuralgia has a structural basis then treatment is aimed at the cause and surgery may be warranted such as decompression or resection. Structural lesions are rare and most patients that suffer from occipital neuralgia are usually treated with local anesthetic blocks, botulinum toxin injections, medications, and occipital nerve stimulators. Several authors have reported improvement in pain associated with occipital neuralgia following occipital nerve blocks. Tobin and Flitman performed a literature review and concluded that occipital nerve block is an effective treatment for cervicogenic headache, cluster headache, and occipital neuralgia.[30] Anthony evaluated 796 patients with idiopathic headache, of which 128 were found to be suffering from cervicogenic headache. Injections of depot methylprednisolone into the region of the GON and LON produced complete relief of headache in 169 out of 180 patients with cervicogenic headaches for a period ranging from 10 to 77 days.[31]

ANATOMY

The cutaneous innervation of the posterior head and neck is from the cervical spine nerves. In the treatment of occipital neuralgia, it is essential to understand the course of these cervical nerves as the muscular investment of these nerves may be a source of entrapment leading to compression and irritation. The GON arises from the dorsal ramus of the second cervical nerve and to a lesser extent the dorsal ramus of third cervical nerve. This nerve passes between the inferior capitis oblique and semispinalis capitis muscles and ascends to pierce the semispinalis capitis and the trapezius superiorly. At this point, it travels with the occipital artery to provide cutaneous innervation to the posterior scalp as far anterior as the vertex of the skull. Medially and over the occiput, this nerve communicates with the third occipital nerve (TON) and laterally with the LON. The LON is composed of branches from the ventral ramus of the second and third cervical nerves and ascends toward the occiput by running parallel to the posterior border of the sternocleidomastoid muscle. Near

the scalp it perforates the deep fascia, and is continued superiorly over the occiput where it supplies the skin over the posterior lateral portion of the scalp and above the ear. The TON arises deep to the trapezius from the medial branch of the dorsal ramus of the third cervical nerve. This nerve ascends medial to the GON and is connected to it both over the occiput and as the GON rounds the inferior edge of the inferior capitis oblique. The medial terminal branch of the TON supplies the skin over the rostral end of the neck and the occiput near the external occipital protuberance (Fig. 73-7).[32]

TECHNIQUE

The patient is placed in a sitting position with the head slightly flexed downward. The landmarks are then identified as follows: The occipital protuberance, superior nuchal ridge, occipital artery, and mastoid process. The location of the GON is typically medial to the occipital artery one third the distance between the occipital protuberance and the mastoid process on the nuchal ridge. The LON is often found two thirds the distance from the occipital protuberance and the mastoid process on the nuchal ridge. When the occipital artery is palpated the GON should be located just medial to the artery. However, anatomy may vary and the GON may be located just lateral to the occipital artery. At the nuchal ridge a 1.5-inch, 22- or 25-gauge, B-bevel needle is inserted in the skin at the nuchal ridge and advanced until bony contact is made. The needle is then slightly withdrawn just of the bone and after negative aspiration a total of 3 to 5 ml of local anesthetic is injected. Many authors advocate a fan-like approach when injecting local anesthetics. We recommend avoiding the fan like approach as this can puncture the occipital artery. Instead, withdraw the needle slightly and after negative aspiration inject the local anesthetic. If a diagnostic block is planned a small volume should (1–1.5 ml) be used, to avoid any confusion in distinguishing greater occipital neuralgia from myofascial pain. The LON block is performed in a similar fashion at its location. The most serious complication is piercing the occipital artery and bleeding. Compression of the occipital artery is usually effective in avoiding any significant problems.

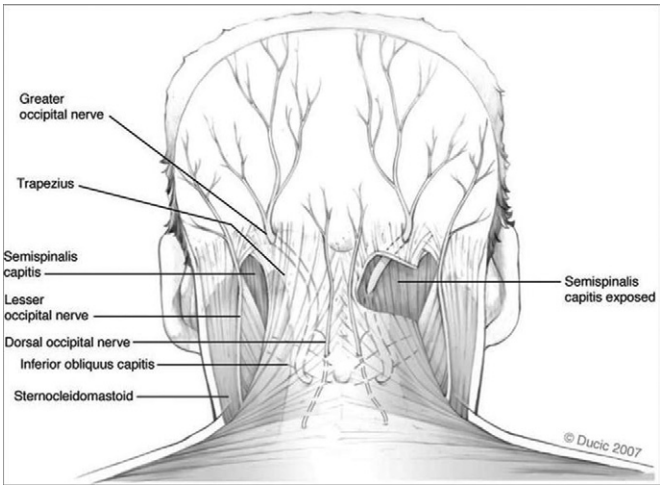

FIGURE 73-7 Occipital triangle cartoon showing the innervation of the occiput by the occipital nerves.

SUBOCCIPITAL COMPARTMENT INJECTION

Numerous causes have been attributed with multiple interventions aimed for the treatment of occipital headaches. However, there is no clear consensus on the best diagnosis and treatment. Treatment for occipital neuralgia is theorized on the basis of neural entrapment within the muscle and fascia investing the suboccipital compartment and the posterior occiput. The traditional approach to blocking the greater occipital nerve has been to infiltrate local anesthetic with or without steroid into the subcutaneous tissue around the course of the nerve after it has penetrated the trapezius muscle. The goal of infiltration at this point along the course of the nerve is the pharmacological blockade of nociceptive transmission. This treatment is effective when the entrapment is superficial, but fails when the entrapment occurs deeper within the suboccipital triangle. Currently other treatment options include conservative medical management, physical therapy, nerve stimulators, C2 gangliectomy, C2–C3 rhizotomy/root decompression, radiofrequency lesioning, and sectioning of the inferior oblique muscle. While many of the aforementioned treatment have shown good results the benefits are usually short lived, lasting weeks to several months. In contrast, procedures such as surgical decompression of the nerves in the suboccipital compartment have proven effective for longer periods of time.[33,34] While surgery has shown better outcomes compared to non surgical treatment there is an increased risks with higher rates of morbidity and mortality. Currently, there is an alternative approach to for treating occipital neuralgia caused by neural entrapments within the suboccipital triangle. The suboccipital compartment injection, introduced in 1980 by Gabor Racz, has become popular over the last 5 years. Recently Justiz et al. performed a retrospective study of 29 patients with confirmed occipital neuralgia using the suboccipital compartment injection. His study showed that the procedure was effective in reducing headaches by numerical rating scale greater than 50% at the 6-month follow-up in 58% of patients. At the 1-year follow-up, 34.5% of patients still showed significant pain relief.[35] Given that this is one of the most common sites of entrapment within the suboccipital triangle this less invasive approach for treatment has been devised without the complications associated with surgery.

ANATOMY

The suboccipital triangle is a region of the posterior cervical neck that has the potential for neural structures to become entrapped at multiple locations. The triangle is composed of bony articulations, ligaments, fibro-fatty tissue and bounded by three different muscles: the rectus capitis posterior major, obliquus capitis inferioris (inferior oblique), and obliquus capitis superioris. The contents of the triangle are the suboccipital nerve, greater occipital nerve, third occipital nerve and the vertebral artery. As these nerves enter and exit the triangle their courses can be tortuous with anatomic variation among individuals.[36] As they travel past the muscles that

enclose the triangle, there is a potential for impingement, especially the greater occipital nerve (GON). The most common site of entrapment within the triangle is the inferior oblique muscle and outside the triangle, the trapezius. Initially the GON begins within the suboccipital triangle and courses downward and lateral in a posterior direction at the lower edge of the inferior oblique muscle where it bends around the muscle and ascends in a superior and medial direction above the rectus capitis toward the head of the semispinalis muscle. Here the nerves form another bend from its upward orientation in a deep to a superficial direction as it begins to move laterally. As the nerve courses upward and lateral it moves between the dorsal aspect of the semispinalis muscle and deep to the trapezius muscle. Here the nerve may pierce the semispinalis muscle or just continue upward until it pierces the trapezius muscle and travels subcutaneously upward toward the base of the occiput.

TECHNIQUE

The patient is placed in a prone position with the neck slightly flexed. The superior nuchal ridge is palpated and the occipital protuberance is identified. Two to three centimeters lateral to the occipital protuberance at the nuchal ridge the skin is anesthetized with 1% lidocaine. Once anesthetized a 22-gauge, 1.5- to 3.5- inch, sharp or blunt Stealth™ (Epimed International) needle is advanced in a posterior-anterior direction perpendicular to the skin toward the arch of C1 (Fig. 73-8). Once the needle is advanced 2 to 3 cm into the tissue a lateral view is obtained. While in the lateral view, the needle is further advanced under live fluoroscopy toward the arch of C1. As the needle is advanced you should experience two to three distinct pops as each muscle fascial layer is penetrated (Fig. 73-9). Once the needle tip is positioned at posterior arch of C1, contrast material is injected in the lateral radiographic view. The contrast spread should be limited around the muscle layers within that enclose the suboccipital compartment and no vascular uptake must be noted (Fig. 73-10). After successful needle position is confirmed, a total of 5 to 10 ml of local anesthetic (0.2% Ropivacaine) and steroid (20 mg Depo-Medrol) is injected. Complications are rare and patients may complain of slight dizziness immediately after the procedure.

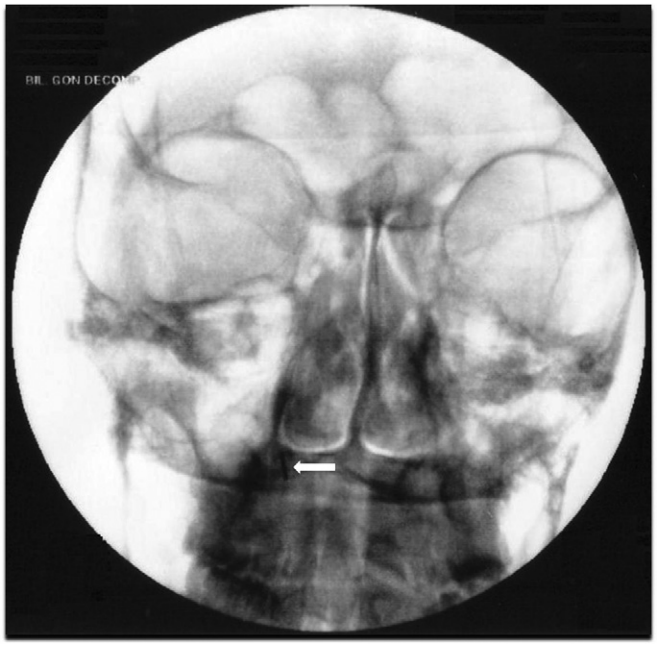

FIGURE 73-8 AP fluoroscopic image of the block needle. The arrow indicates the needle.

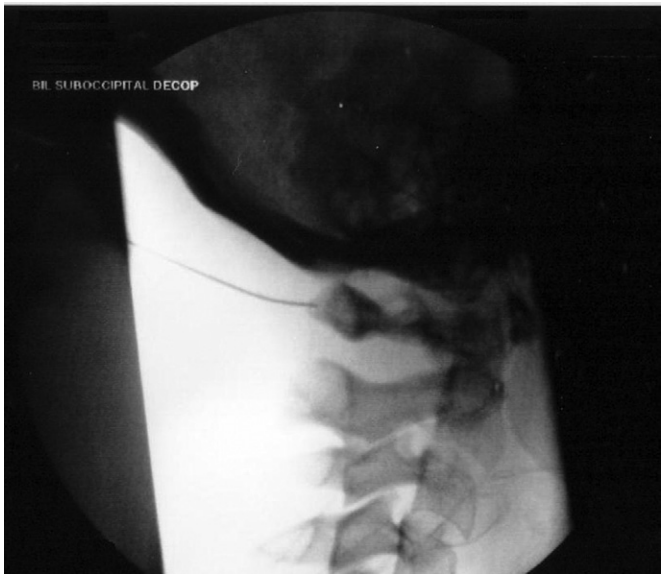

FIGURE 73-9 Lateral fluoroscopic image of the block needle with the tip at the level of the posterior arch of C1.

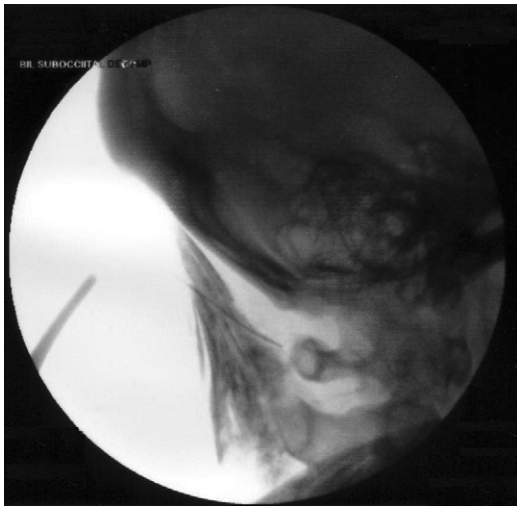

FIGURE 73-10 Lateral fluoroscopic image after injection of non-ionic, water soluble contrast.

GLOSSOPHARYNGEAL NERVE BLOCK

ANATOMY

The glossopharyngeal nerve originates from the cranial part of the medulla oblongata. Its rootlets form one root and course forward and laterally until it reaches the jugular foramen. As it exits the jugular foramen it joins with the

vagus and spinal accessory nerve and passes between the internal jugular vein (IJV) and the internal carotid artery (ICA). It continues to descend anterior to the ICA and dips medially behind the styloid process in close proximity to the vagus nerve, accessory nerve, and IJV emerging beneath the tip of the styloid and continuing to its terminal branches. The glossopharyngeal nerve (GN) is a mixed nerve containing sensory, motor, and autonomic fibers. It provides sensation to the posterior one-third of the tongue, middle ear, palatine tonsils, and mucous membranes of the mouth and pharynx above the vocal cords. Additionally, it innervates the carotid sinus and the carotid bodies. The motor fibers innervate the stylopharyngeus muscle and its autonomic functions are related to the parotid gland via the otic ganglion.[37,38] The glossopharyngeal nerve lies in close relation to the vagus and spinal accessory nerve. Specifically, they are in close approximation until they diverge at the midpoint of the styloid process. There have been reported cases of GN paroxysms with associated bradycardia and asystole. This phenomenon is due to the close connection between the vagus and GN.[39] Lesions arising from the GN can send afferent impulses via the tractus solitarius to the dorsal motor nucleus of the vagal nerves result in reflex bradycardia or asystole.[40] Although there are no reported adverse events associated with the spinal accessory or hypoglossal nerve there can be complications following blockade of the GP nerve. There is a potential of pharyngeal and trapezius weakness due to unwanted blockade of the closely situated nerves.

INDICATIONS

Blockade of the glossopharyngeal nerve has several indications. It is used for the treatment of glossopharyngeal neuralgia. The block can be done with local anesthetics as a diagnostic tool to determine if the patient truly has glossopharyngeal neuralgia or it can be performed with the addition of steroids for therapeutic treatment. The procedure also can be used for surgical anesthesia or as an adjunct to depress the gag reflex in an awake, endotracheal intubation. If a neurolytic procedure is considered, the block can be used prior to neurolysis as a prognostic indicator.

TECHNIQUE

Extraoral Approach: Ensure appropriate monitoring and intravenous access prior to procedure. Two major landmarks must first be identified: the angle of the mandible anteriorly and the mastoid process posteriorly. The patient is placed supine and the head is turned slightly opposite the direction of the affected side. Once in correct position a lateral fluoroscopic view is obtained visualizing the angle of the mandible and the mastoid process. Once identified and marked a line is drawn between those two points inferior to the ear and the styloid process should lie midway between both points. When the target is identified a small skin wheal with 1% lidocaine is applied to the skin and a 22-gauge, 1.5-inch needle is advanced perpendicular toward the styloid process. Bony contact is typically obtained at 3 cm. After contact, the needle is slightly withdrawn and walked off the styloid process in an anterior direction, approximately 0.5 cm. Inject 1 ml of contrast agent under continuous fluoroscopy. This permits real-time imaging of the contrast media to look for any irregular patterns indicating that a vascular structure has been punctured. After injecting the contrast then 2 to 3 ml of local anesthetic (0.2% Ropivacaine) and steroid (4 mg dexamethasone) is injected.[24]

Intraoral Approach: This approach is popular when there is an anatomic distortion externally by previous surgery or tumor. The patient is placed in a supine position with mouth wide open and the tongue is retracted downward and medially using a tongue depressor or a laryngoscope blade. The nerve will be located at the inferior portion of the tonsillar pillar and is accessed via the palatoglossal fold. Once the fold is identified, a topical local anesthetic spray or pledget with 1 ml of saline with epinephrine is applied for hemostasis. A 22- or 25-gauge needle with a slight distal bend (25 degrees) is advanced to a depth no more than 0.5 cm into the mucosa. After negative aspiration, 2 to 3 ml of local anesthetic (0.2% ropivacaine) and steroid (4 mg of dexamethasone) are injected (Figs. 73-11 and 73-12).[41]

COMPLICATIONS

There are multiple complications that can occur with this procedure and care must be taken when performing. Complications will vary depending on the approach used for the blockade. The extraoral approach can be inherently more difficult and lead to complications secondary to the close proximity of relation of the CN IX, CN X, CN XI, and CN XII at the styloid process. There can be accidental puncture of the vessels leading to vessel trauma and hematoma formation. Also inadvertent intravascular injection of the ICA or IJV may lead to seizures or even cardiovascular collapse. With the intraoral approach there is a potential of vessel trauma and neurotoxicity but much less that the extraoral approach. Other complications can occur with unwanted blockade of CN X, CN XI, and CN XII. As mentioned earlier, these complications will

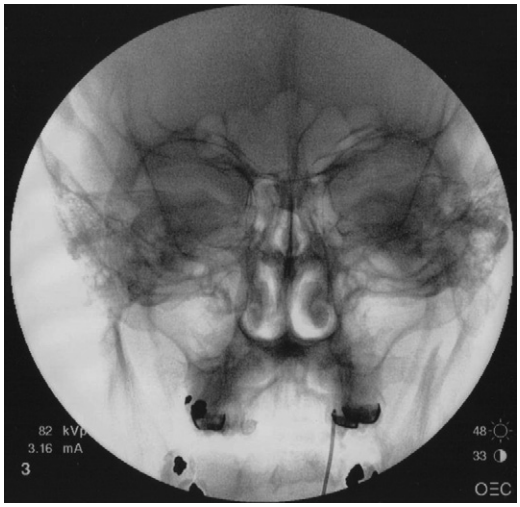

FIGURE 73-11 AP and lateral fluoroscopic images of the block needle in position for a glossopharyngeal nerve block.

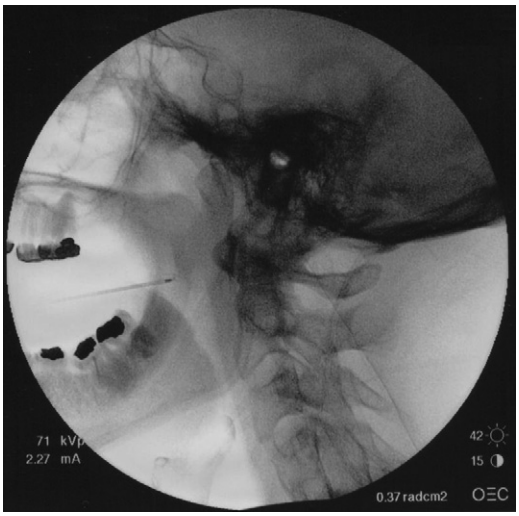

FIGURE 73-12 AP and lateral fluoroscopic images of the block needle in position for a glossopharyngeal nerve block.

vary by approach. With the extraoral approach there is the potential of unwanted blockade of the aforementioned nerves. Blockade of the vagus can lead to bradycardia, asystole, reflex tachycardia, and syncope, as well as dysphonia secondary to ipsilateral vocal cord paralysis. Blockade of CNXI and CNII can result in temporary weakness of the trapezius muscle and the tongue. These complications can minimized with small amounts of local anesthetic but not necessarily avoided. Most complications of the affected nerves will gradually resolve as the local anesthetic wears off.

CERVICAL PLEXUS BLOCK

The cervical plexus block is performed for anesthesia and analgesia involving the head and neck region. The cervical plexus is formed by the anterior divisions of the first four upper cervical nerves (C1–C4) and the lower four nerves (C5–C8) together with the first thoracic ventral ramus (T1) form the brachial plexus. The location of the cervical plexus lies deep to the internal jugular vein upon the levator scapulae, scalene muscles and underneath the sternocleidomastoid muscle. The plexus is divided two separate rami each dividing into an ascending (superficial cervical plexus) and descending (deep cervical plexus) branch forming loops at each level with the corresponding nerves except for the first ramus. The first cervical ramus (suboccipital nerve) is thought to be primarily a motor nerve. Even though it lacks cutaneous innervation it does have some sensory function and communicates sensory information to deeper muscles in the suboccipital region as the suboccipital nerve. The C1 nerve is often not affected by a cervical plexus block due to its posterior and deeper location. The second, third, and fourth cervical nerves leave their respective transverse processes anteriorly and surface lateral to the vertebral artery. The C2 and C3 nerves continue on and emerge at the midpoint of the posterior border of the sternocleidomastoid muscle and travel toward to their destination. The C2 nerve moves upward along the sternocleidomastoid toward the posterior and lateral part of the scalp. It provides cutaneous innervation to the posterior scalp behind the ear, the upper and posterior auricle as well as the mastoid and angle of the mandible as the lesser occipital and great auricular nerve. The C3 nerve bifurcates into an anterior and descending portion. The anterior branch runs in an anterior oblique direction where it gives cutaneous innervation to the lateral neck from the chin to the sternum as the transverse cervicalis. The descending branch continues along the sternocleidomastoid muscle into the posterior triangle of the neck beneath the platysma and deep cervical fascia and joins the fourth cervical nerve. Here these nerves provide cutaneous innervation to the upper trapezius, shoulder and pectoral region as the supraclavicular nerves (Fig. 73-13).[42]

The deep branches of the cervical plexus divide into medial and lateral branches. The medial branches supply the anterior and lateral neck muscles and gives rise to the phrenic nerve via the fourth cervical nerve as the main contributor. The lateral deep branch forms communicating branches between C1 and C2 rami to the vagus and hypoglossal nerves. Additionally, the deep cervical plexus gives rise to several muscular branches. These branches supply the rectus capitus lateralis (C1), rectus capitus anterior (C1, C2), longus capitus (C1–C3), and longus colli (C2–C4). The lateral branches communicate with the spinal accessory nerve and supply the deep surface of the trapezius via the communicating branches. The muscular branches are distributed to the sternocleidomastoid (C2–C4), trapezius (C2, C3), levator scapulae (C3, C4) and scalene medius (C3, C4).[42]

INDICATIONS

The cervical plexus block is a regional technique that is a safe alternative to general anesthesia for procedures involving the anterior-lateral portion of the neck, upper shoulder, and posterior scalp. Its potential indications are many and include superficial neck procedures, neck dissection, thyroglossal and brachial cyst surgery, thyroidectomy, lymph node dissection, cervical node biopsy, carotid endarterectomy, and other head and neck neuralgias. The sensory and motor component of the cervical plexus can each be blocked separately or together. A deep cervical plexus block provides motor and sensory blockade while a superficial plexus block only blocks the sensory component of the plexus.[37] The blockade of the superficial cervical plexus provides anesthesia and analgesia for the posterior and anterior auricular scalp region, lateral and anterior neck, and the upper shoulder region. The superficial cervical plexus block is useful for postoperative pain relief; reduce nausea and vomiting with surgeries involving the tympanic-mastoid region, and for simple superficial procedures such as involved with plastics or superficial biopsies involving the neck. Additionally, this block is sometimes performed for carotid endarterectomy and thyroid surgery. The branches blocked by the superficial cervical plexus block include the lesser occipital, great auricular, transverse cervicalis and the supraclavicular nerves. For blockade of the deeper structures and the motor components a deep cervical plexus block is warranted.

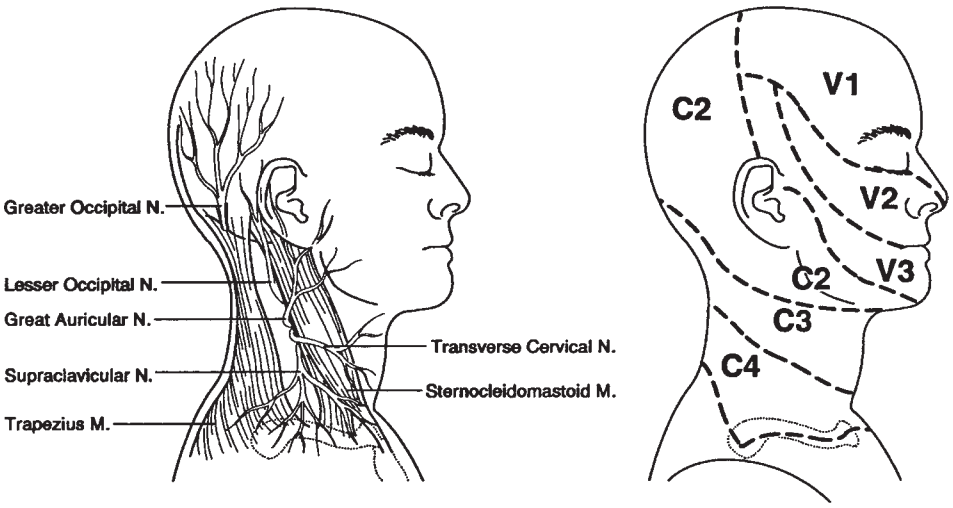

FIGURE 73-13 Peripheral cutaneous (*left*) and dermatomal (*right*) innervation fo the head and neck, including the branches of the superficial cervical plexus and the greater occipital nerve.

Blockade of the deep cervical plexus provides anesthesia and analgesia of the superficial and the deeper muscles within the anterior and lateral neck up to the upper shoulder region. Both the motor and sensory component of the aforementioned regions are interrupted as the nerve roots are anesthetized prior to the motor and sensory components branching. This technique can be used for surgical anesthesia, post operative pain relief and diagnosis and treatment of painful conditions involving the neck, posterior scalp, and upper shoulder region. This block is performed for procedures such as thyroidectomy, tracheostomy, and laceration repairs under local anesthesia or any procedure that require muscle relaxation of the neck. One of the most common indications is for awake carotid endarterectomy. This helps with instant feedback to the surgeon and anesthesiologist in the event of any neurologic compromise and they can act appropriately without delay.[43] One of the more uncommon indications is for the treatment of intractable hiccups as the deep branches innervate the muscle of the diaphragm.

TECHNIQUE

Superficial Cervical Plexus Block: The essential component to performing this procedure lies upon the identification of the sternocleidomastoid muscle. The patient is placed in a supine position with the head turned away from the side that is going to be blocked. Once in correct position, it is important to identify the posterior border of the sternocleidomastoid muscle. This can be done one of two ways. Two landmarks must be identified; the mastoid process and Chassaignac's tubercle at C6. A line is drawn from the mastoid process to Chassaignac's tubercle over the sternocleidomastoid muscle. Alternatively, the patient can lift their head and the sternocleidomastoid muscle will be identified. The drawn line should overly the path of the superficial cervical plexus over the posterior border of the sternocleidomastoid muscle. The position of needle entry will be at the midpoint of line drawn from the mastoid process to Chassaignac's tubercle. This is the site where the branches superficial plexus appear behind the posterior boundary of the sternocleidomastoid muscle. A 22- or 25-gauge, 4- to 5-cm needle is inserted subcutaneously 2 to 3 cm deep at the midpoint of the posterior border of the sternocleidomastoid muscle and 3 to 5 ml of local anesthetic is injected. The needle is then withdrawn and redirected subcutaneously in a superior direction toward the mastoid process while injecting 3 to 5 ml of local anesthetic in a fan-like fashion. The needle is then redirected in an inferior direction subcutaneously toward Chassaignac's tubercle injecting 3 to 5 ml of local anesthetic in a fan-like fashion. This technique should provide adequate blockade of all four major branches of the superficial plexus.

Deep Cervical Plexus Block: The deep cervical plexus block is performed much in the same manner as the superficial plexus block with some distinct differences, the transverse processes of C2 to C4 will be targeted. The patient is placed in a supine position with the head turned away from the side that is going to be blocked. Once in correct position, two landmarks are identified; the mastoid process and Chassaignac's tubercle at C6 (Fig. 73-14). A line is drawn from the mastoid process to chassaignac's tubercle overlying the sternocleidomastoid muscle. Once the sternocleidomastoid is identified then the transverse processes of C2, C3, C4, and C6 must be identified. This is achieved by first identifying the cricoid cartilage. Once identified, a line is drawn from the inferior aspect of the cricoid to the sternocleidomastoid. The point where these two lines intersect at a right angle is the C6 transverse process. Next the thyroid notch and superior cornu is palpated. Once located, a line is drawn to the sternocleidomastoid, and the transverse process of C4 is identified at the point where the two lines intersect. Once the C4 transverse process is located, the transverse processes of C2 and C3 can be easily identified. This is done by taking half the distance between C4 and C6. This measurement will be the distance between the transverse processes at each level. Once the intertransverse process distances are determined it is plotted along the original line drawn from the mastoid to Chassaignac's tubercle. Beginning at the C4 transverse process the distance is plotted upward toward the mastoid process and it should identify the C3 transverse process. The same distance is plotted from C3 to the mastoid and the C2 transverse process will be identified (Fig. 73-14). The intertransverse process distances will typically measure

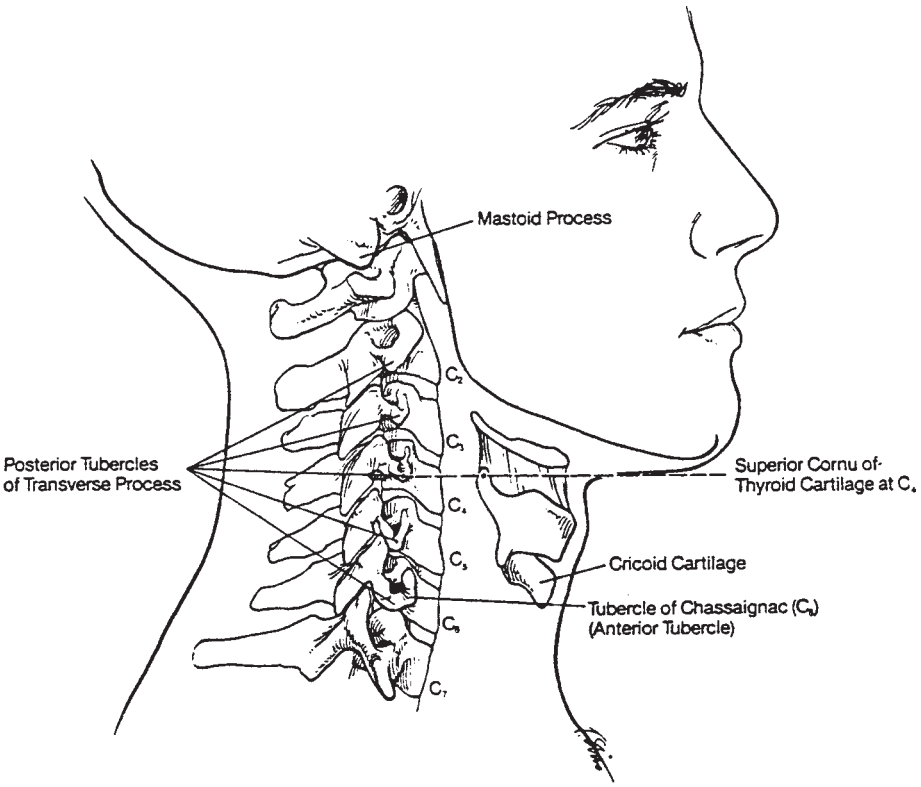

FIGURE 73-14 Bony landmarks for deep cervical plexus block *(From Raj PP, Pai D, Rawal N: techniques of regional anesthesia in adults. In Raj PP (ed): Clinical Practice of REgional Anesthesia. Churchill Livingstone, New York, 1001, p 271.)*

some 2 cm from each other. Some authors advocate drawing a second line 1 cm posterior to the original line from the mastoid to chassaignac's tubercle as the transverse processes may vary in location. After drawing out the points of interest the neck is prepped, cleaned, and draped in sterile fashion.

The block is performed by using a 22-gauge, 1.5-inch needle, the transverse processes are located by entering the skin in a perpendicular fashion. The needle is always directed in a medial caudal direction to avoid any unintentional vertebral artery, epidural, subdural, or spinal injection. The needle is advanced slowly until the transverse process is contacted, which is typically 1.5 to 2.5 cm. The depth of the transverse process will vary with the body habitus of the patient. In general, as you proceed inferiorly, the other transverse processes will appear more superficial. If a paresthesia is obtained the needle should be redirected slightly posteriorly as the spinal nerves are located just in front of the transverse process. When bony contact is made, withdraw the needle 1 cm and after negative aspiration, 3 to 5 ml of local anesthetic is injected slowly. The needle is then removed and the entire procedure is repeated at the other two transverse processes. Failure to contact the transverse process can be a problem with this procedure. When insertion of the needle does not result in bony contact the needle should be withdrawn and redirected in a caudal inferior manner approximately 15 degrees until the transverse process is contacted. If the does not work the needle should be withdrawn and the landmarks reassessed. Never attempt to redirect the needle in a cephalad direction or go deeper than 3 cm as you may risk inadvertently injuring the cervical spinal cord.

CHOICE OF LOCAL ANESTHETICS

There are several choices of local anesthetics depending on the length of surgery and the duration of the blockade desired. For shorter duration procedures 2% lidocaine and mepivacaine may be desired as this may achieve blockade up to 4 hr. For longer procedures ropivacaine or bupivacaine can be used and this may prolong the block up to 8 hr. Higher concentrations of local anesthetic will also prevent required supplemental infiltrations from the surgeon. Umbrain and colleagues showed that 0.75% concentrations of ropivacaine were more effective in duration compared to 0.5% or 0.375%.[44] Onset times will vary with the local anesthetic used. Lidocaine will have faster onset times than mepivacaine, ropivacaine and bupivacaine.[45] Additionally, the neck is a highly vascular area and there is a potential for toxicity that must be considered when performing this block. The total local anesthetic given in superficial plexus block and a deep cervical block will vary depending on each individual block or if combined. A total amount of 0.4 or 0.5 ml/kg (30 ml) is usually considered sufficient to perform either the superficial, deep or a combination of both blocks.[46] Furthermore, toxicity and systemic absorption can be decreased with the addition of epinephrine to the local anesthetics. Epinephrine will decrease systemic absorption of bupivacaine and lidocaine by 20% or more.[47] Another adjunct used with local anesthetic is clonidine. Clonidine use with lidocaine has not been as successful as epinephrine. Adding clonidine 5 mg/ml does not change onset time or block duration and may lead to potential toxicity with lidocaine.[48] However, clonidine use with ropivacaine has been shown to decrease onset time of

block and improve surgical anesthesia in patients undergoing elective carotid endarterectomy.[49]

COMPLICATIONS

Several complications can occur when performing a cervical plexus block. With careful performance and good knowledge of the cervical anatomy this procedure can be performed with minimal complications. If complications do transpire they can be minimized with appropriate care and knowledge of the possible reactions that may occur. As with many interventional procedures there is always a risk of infection when a needle punctures the skin. The risk of infection albeit low is present and can be avoided with strict proper aseptic technique. There is always the risk of hematoma when performing a cervical plexus block. To reduce the risk of arterial puncture you should minimize multiple needle insertions or passes if the initial attempt is unsuccessful. If a hematoma does develop you should hold constant pressure over the site for 5 min and evaluate the airway for possible compromise with an expanding hematoma. If airway compromise does occur, an emergent airway and surgical consultation may be indicated.

Temporary diaphragmatic paresis invariably will occur with the deep cervical plexus block. The blockade of the phrenic nerve cannot be avoided with this block. For that reason this procedure should never be performed in a bilateral fashion. Patient selection when performing this procedure is essential and should be carefully considered in patients that suffer from chronic respiratory disease. These patients may not be suitable candidates as they will experience diaphragmatic hemiparesis and possibly compromise breathing. The superficial plexus block will not cause blockade of the phrenic nerve.

Local anesthetic toxicity is something one should always consider with any type of regional technique, but especially when considering a cervical plexus block due to the high vascularity of the neck region. Intravascular injection may occur either into a vein or artery. Puncturing the vertebral or carotid artery is possible due to their close proximity to the block site. The vertebral artery is typically located 0.5 cm below the tip of the transverse process. Intravascular injection of local anesthetics can lead to central nervous system (CNS) or cardiac side effects. The CNS effects can vary and will most likely consist of perioral numbness, sedation, tinnitus, or even seizures. Cardiac effects can occur but usually happen with higher blood levels of local anesthetics. These complications can be minimized with careful and frequent aspirations prior to injecting the local anesthetic and constant communication with the patient during the procedure to look for signs of CNS toxicity. Nerve injury is another complication that can occur and can be avoided with careful attention while performing the procedure. Try to avoid multiple passes of the needle. After two unsuccessful attempts, reassess the anatomic landmarks prior to proceeding. Also, never inject the local anesthetic if the patient complains of severe pain with injection or if you experience high resistance with injection. This may indicate that the needle has been placed into the nerve or nerve sheath and injection of local anesthetics may lead to nerve ischemia and permanent damage.

Lastly, a high spinal is a potential complication of this procedure. Avoid inserting the needle to deep as there is a possibilty of a cervical cord or intrathecal injection. As mentioned earlier, avoid injecting with high resistance. The injection of local anesthetics within the dural sleeves around the nerves can cause some of the volume to back track into the epidural space and even the subarachnoid space leading to a high spinal. This will present as hypotension and loss of consciousness. Treatment will involve airway control and cardiovascular support until the local anesthetic is metabolized from the CNS.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 74

Brachial Plexus Blocks: Techniques Above the Clavicle

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ANATOMIC CONSIDERATIONS

The brachial plexus is formed by the anterior primary rami of cervical nerve roots C5–C8 and thoracic nerve root T1. The fourth cervical nerve (C4) contributes to about 67% of plexuses, and, if significant, may shift the plexus in a craniad direction ("prefixed plexus"). The second thoracic nerve (T2) contributes to about 33% of plexuses, and may shift the plexus in a caudad direction ("postfixed plexus"). Through a complex series of dividing and reuniting, the principal elements of the plexus interact in a manner analogous to the components of a tree: roots, trunks, divisions, cords, and terminal branches (Fig. 74-1). The roots of C5–C8 and T1 travel along the groove between the anterior and posterior tubercles of the transverse processes of the cervical vertebrae, pass posterior to the vertebral artery (Fig. 74-2), and descend toward the first rib. Along the way, they are enveloped by the posterior fascia of the anterior scalene muscle and the anterior fascia of the middle scalene muscle: the so-called "interscalene space"[1,2] (Fig. 74-3). The anterior scalene muscle arises from the anterior tubercles of the transverse processes of C3–C6 and inserts on the scalene tubercle of the first rib. It separates the subclavian vein and artery (Fig. 74-4). The middle scalene muscle arises from the posterior tubercles of the transverse processes of C2–C7 and inserts on the first rib just posterior to the subclavian groove on the rib.

After arriving at the distal end of their respective transverse processes, the five roots converge to form the three trunks (superior, middle, inferior), which together with the subclavian artery invaginate the scalene fascia to form a "subclavian space."[2] The superior trunk of the plexus is formed by the union of the C5 and C6 nerve roots; the middle trunk is the distal continuation of C7; and the inferior trunk is formed by the union of the C8 and

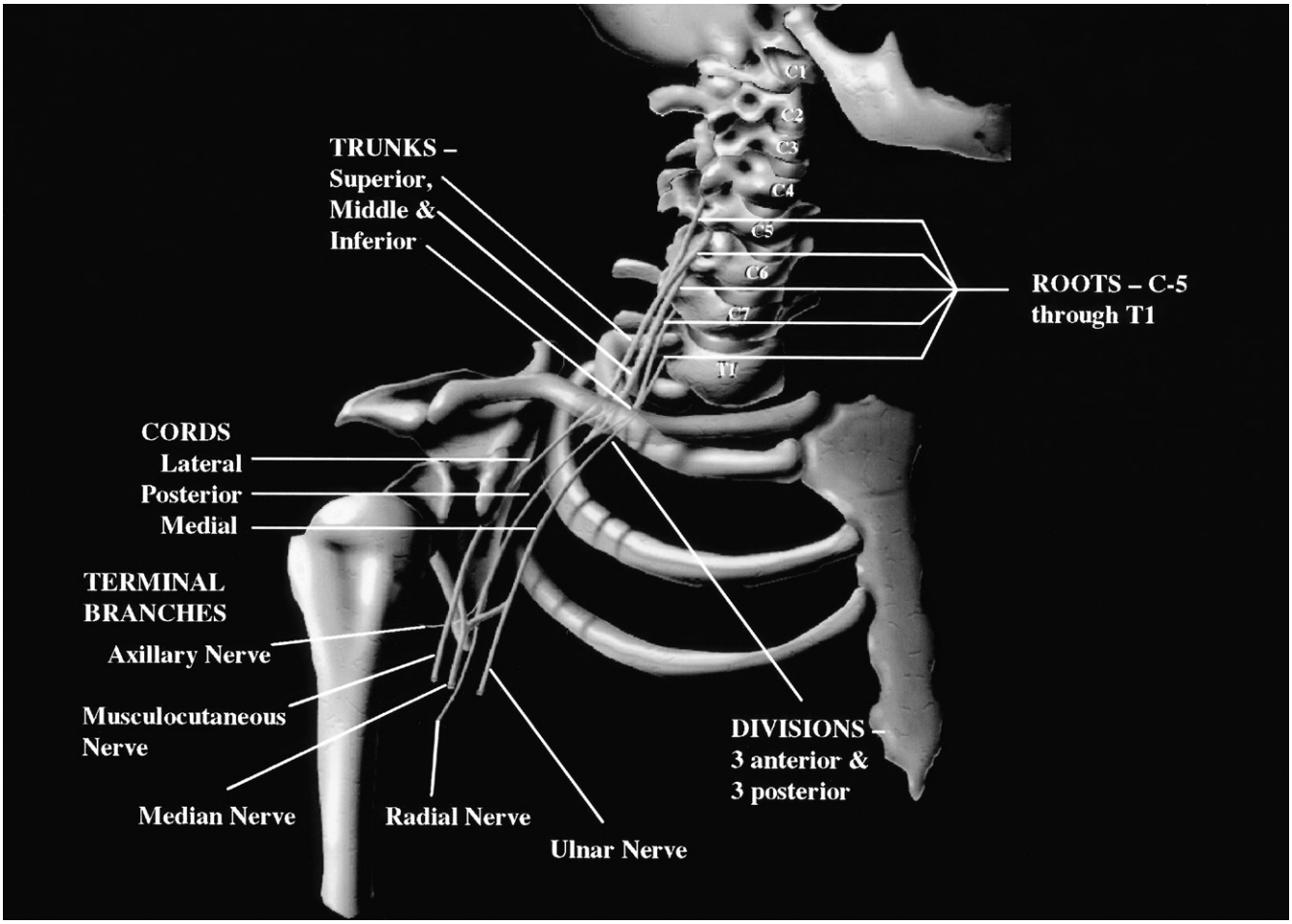

FIGURE 74-1 Anatomy of the brachial plexus: roots (5); trunks (3); divisions (6); cords (3); major peripheral nerves (5).

T1 nerve roots. As these three trunks pass over the first rib and under the clavicle, each divides into an anterior and posterior division (there are a total of six divisions) (Fig. 74-1). It is at this level that separation of fibers destined for the anterior arm (flexor or volar surface of the upper extremity) and the posterior arm (extensor or dorsal surface) occurs. As the plexus emerges from beneath the clavicle, the fibers recombine to form the three cords of the brachial plexus. The lateral cord is formed by the union of the anterior divisions of the superior and middle trunks; the medial cord is simply the continuation of the anterior division of the inferior trunk; and the posterior cord is composed of the posterior divisions of all three trunks (Figs. 74-1 and 74-5).

The medial and lateral cords then give rise to nerves that supply the flexor surface of the upper extremity while those nerves arising from the posterior cord supply the extensor surface of the arm. Each of the three cords of the plexus gives off a branch that contributes to or becomes one of the major nerves to the upper extremity, and then terminates as another major nerve. The lateral and medial cords give off branches that become the lateral and medial heads of the median nerve (C5–C8) (major terminal branch). The lateral cord continues as the musculocutaneous nerve (C5–C7) (major terminal branch), while the medial cord continues on as the ulnar nerve (C7–T1) (major terminal branch). The posterior cord gives off the axillary nerve (C5–C6) (major terminal branch) and then continues on as the radial nerve (C5–T1) (major terminal branch) (Fig. 74-1). When performing brachial plexus blocks above the clavicle, it is important to appreciate several of the less commonly-known anatomic branches from the roots. While not essential to successful brachial plexus anesthesia, these branches may have considerable significance especially when utilizing an electrical nerve stimulator to evoke a motor response prior to injecting local anesthetic solutions.

The long thoracic nerve, arising from C5, C6, and C7, innervates the serratus anterior muscle. Its stimulation may result in contraction of the muscular wall enveloping the ribs, and may be mistaken for diaphragmatic contraction resulting from stimulation of the phrenic nerve (C3, C4, C5). The dorsal scapular nerve, arising from C5 and innervating the major and minor rhomboids and the levator scapulae, may be stimulated, resulting in a contraction of the musculature of the back and shoulder blade. The trunks also supply two branches, the nerve to the subclavius (C5–C6) and the suprascapular nerve (C5–C6). The suprascapular nerve has significance in the performance of brachial plexus blocks above the clavicle, since in addition to motor branches to the supraspinatus and infraspinatus muscles, it also supplies the only sensory fibers (to the

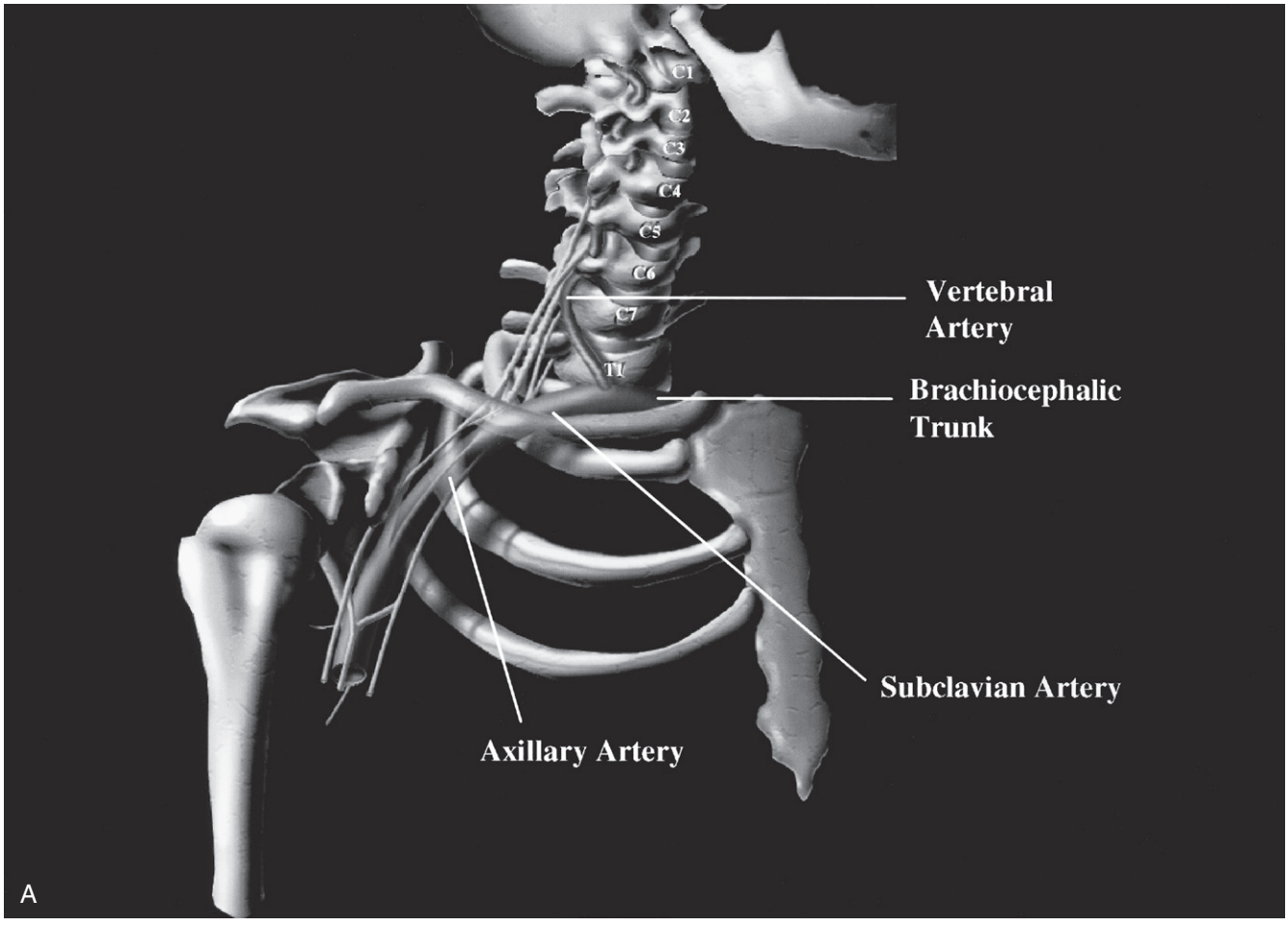

FIGURE 74-2 A, Relationship of relevant arterial structures to the brachial plexus above the clavicle. Note that the brachial plexus is posterior to both the subclavian artery as well as to the vertebral artery.

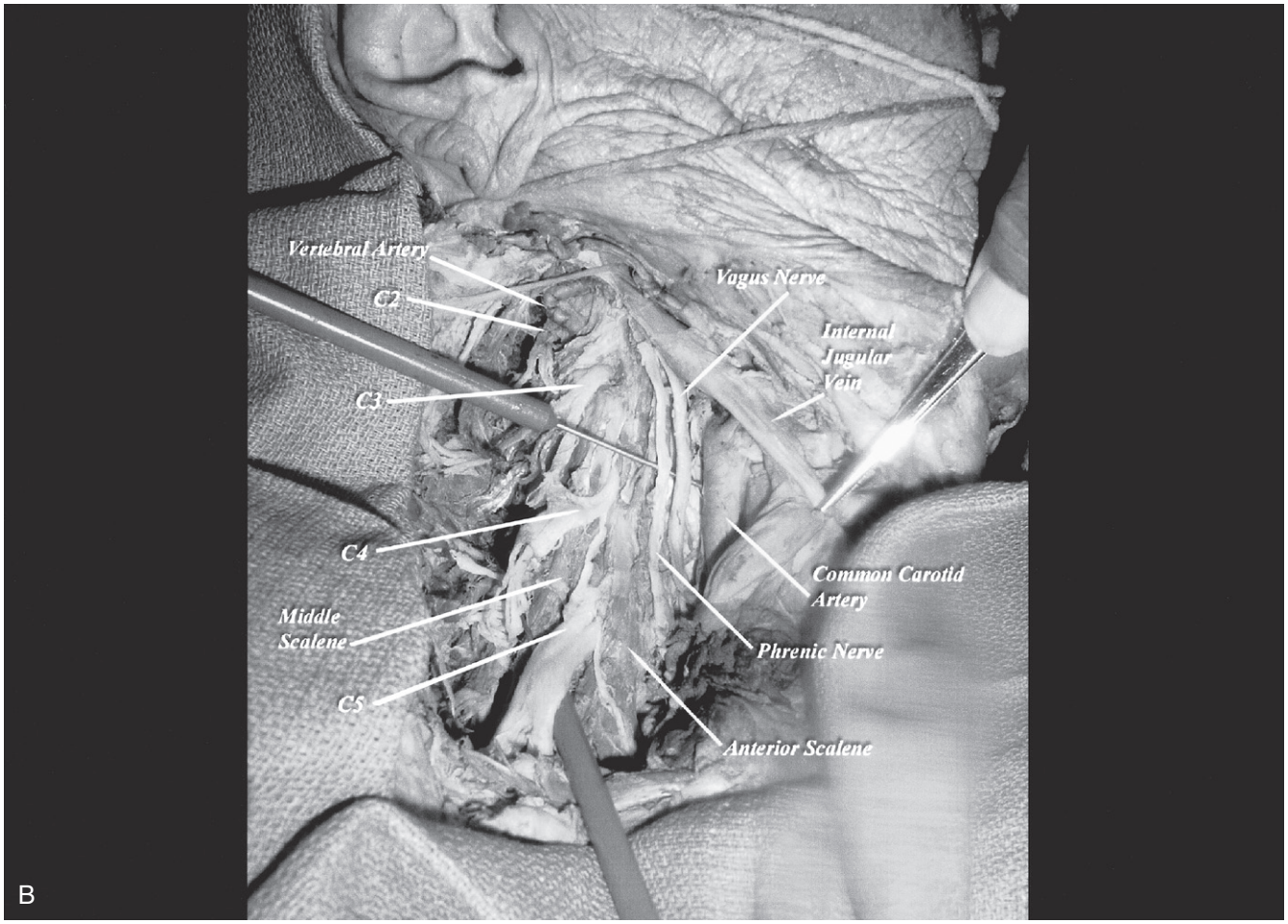

FIGURE 74-2, cont'd. B, Anatomic dissection of the right side of the neck depicting the relationships seen in **A.** Note the proximity of the vertebral artery to the C2 nerve root, and the location of the phrenic nerve sitting on the anterior surface of the anterior scalene muscle. Also note the significant girth of the cervical nerves 4 and 5.

shoulder joint) that arise above the clavicle. Since the nerve may leave the brachial plexus shortly after arising from the superior trunk, a paresthesia resulting from its stimulation is an unreliable indicator that a stimulating needle is correctly placed within the confines of the sheath.[3] As a general rule of thumb when using a nerve stimulator technique, diaphragmatic contraction requires a more posterior reinsertion of the needle (the phrenic nerve is typically located outside the sheath on the anterior scalene muscle) while trapezius or posterior deltoid contraction requires reinsertion of the needle more anteriorly in the interscalene space.

Brachial plexus block, in addition to providing sensory analgesia and anesthesia and motor block, also blocks the sympathetic outflow to the upper extremity. Postganglionic sympathetic nerve fibers reach the nerve roots as gray rami communicantes from the middle and inferior cervical sympathetic ganglia and stellate ganglion (Fig. 74-6), and are subsequently distributed to the upper extremity. Additional contributions may arise from the vertebral artery (fibers given off to C4, C5, C6), and from the nerve of Kuntz (branch from T2).[2] Ultimately, postganglionic fibers to the upper extremity are derived from two potential sources. The first is a distal innervation that is carried to the peripheral vessels by the somatic nerves of the plexus. The second mode is a proximal innervation (not extending beyond the proximal part of the brachial artery) arising from the cervical sympathetic chain, particularly via the stellate ganglion. This supplies the proximal one-third of the extremity.

The distal innervation (distal two-thirds of the arm) mediates vasoconstriction of resistance vessels, implying that brachial plexus block produces vasodilatation of veins of the upper extremity, increases the amount of blood pooling in the distal arm, and increases skin temperature. In a prospective study of 45 subjects undergoing interscalene block (ISB) for elective shoulder surgery, skin temperature was assessed at sites innervated by the median, ulnar, radial, axillary and musculocutaneous nerves following the block.[4] At skin areas innervated by the axillary and musculocutaneous nerves, skin temperature did not rise following successful block. At more distal sites innervated by the median, radial, and ulnar nerves, skin temperature did increase, by 1.9 to 2.1° C at 30 min after injection. However, sensory changes occurred in earlier than skin temperature chanes (56.3%), or at the same time as skin temperature changes (35.2%) or even after skin temperature changes (8.5%) implying that sympathetic block assessment is an imprecise method of assessing the adequacy of ISB.[4] Another study of eleven volunteers wherein Doppler ultrasound of the humeral artery was employed to

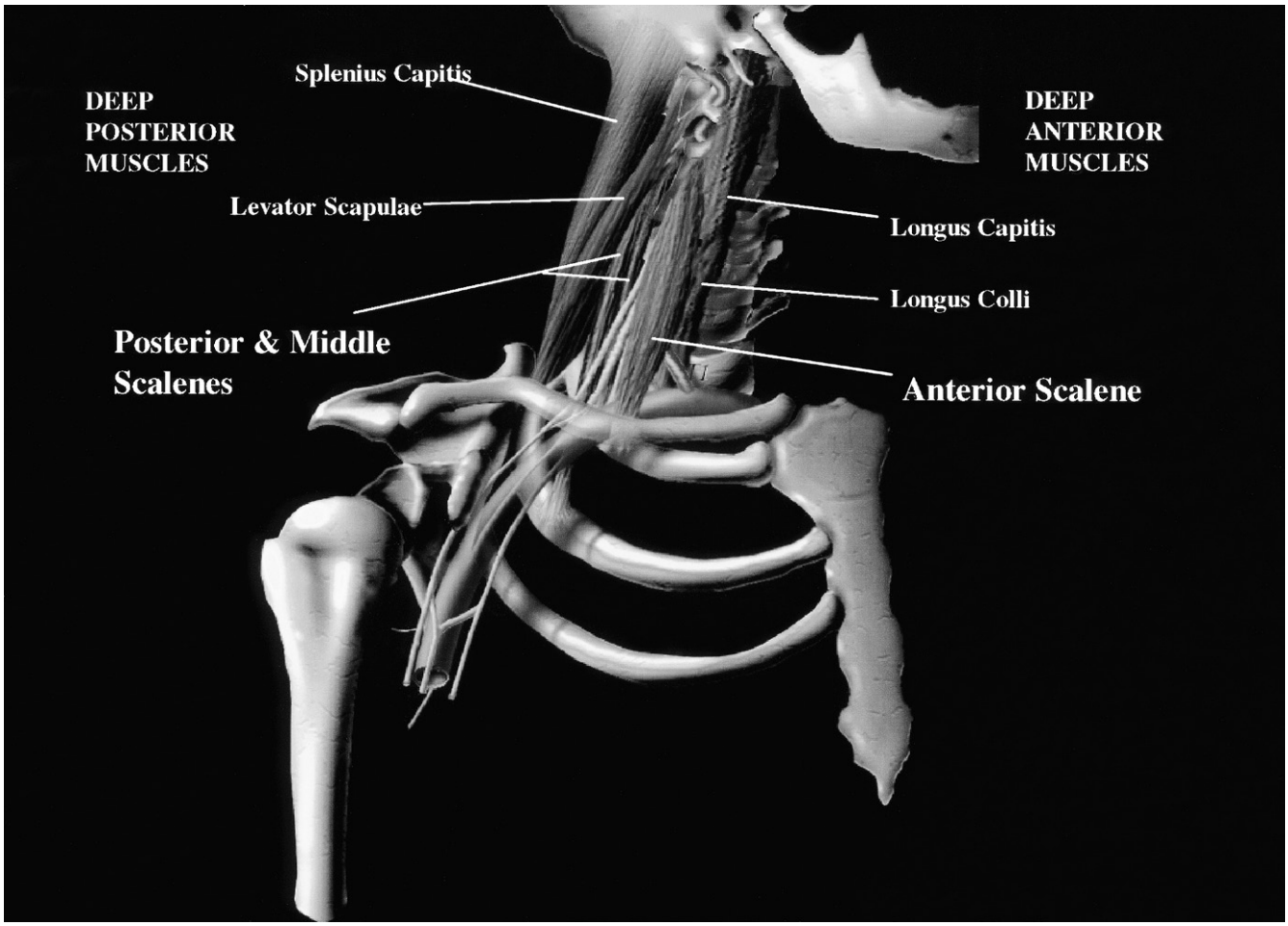

FIGURE 74-3 The brachial plexus above the clavicle is "sandwiched" between the anterior and middle scalene muscles and is enclosed in their respective fascial envelope.

assess arterial blood flow demonstrated that, 30 min after ISB, median humeral blood flow increased from 32 ml/hour to 88 ml/hour due to a reduction in arterial resistance.[5] Techniques for brachial plexus block above the clavicle rely upon anatomic considerations at the root and trunk levels, as opposed to infraclavicular techniques (cords) or axillary approaches (major peripheral branches). Single-injection techniques above the clavicle rely upon the concept of a continuous fascial compartment from the prevertebral fascia of the cervical vertebrae passing distally to (and beneath) the clavicle (Fig. 74-7). Low-volume ISB has even been used to reduce thoracotomy pain in the ipsilateral shoulder.[6]

TECHNIQUES FOR BRACHIAL PLEXUS BLOCK ABOVE THE CLAVICLE

INTERSCALENE BLOCK TECHNIQUES

The block is performed as follows: The patient lies supine with the head turned slightly toward the opposite side and is asked to relax the shoulder and reach with the hand on the affected side toward the ipsilateral knee. The interscalene groove is palpated posterior to the sternocleidomastoid muscle, and the C6 level is estimated by dropping a line laterally from the cricoid cartilage (Fig. 74-8). The external jugular vein typically crosses the interscalene groove at C6, but this occurs with some variability. An "anesthetic line" has been described to locate the plexus along its proximal to distal length, but this appears to nullify the inherent simplicity in locating the scalene muscles as the primary landmark in supraclavicular techniques.[7] With the palpating index and middle fingers straddling and indenting the interscalene groove (to minimize the distance from the skin to the cervical transverse processes), the opposite hand advances a short (1–2 inch) insulated needle into the groove, using nerve stimulator assistance (Fig. 74-9). Although the fingers compress the skin toward the nerve roots and central neuraxis, it should be appreciated that cadaver dissections have demonstrated that the minimum distances from the skin to the C6 foramen and vertebral column are 23 mm and 35 mm, respectively.[8] The direction of the needle should be perpendicular to the skin with a slightly posterior (dorsad), medial (mesiad), and inferior (caudad) direction until a motor response is observed at 0.5 mA or less (Fig. 74-10). A second study in 10 adult volunteers, wherein MRI was used to measure angles to the spinal cord and distances to the intervertebral foramen and cord, demonstrated that the distance from the skin to the foramen could be as short as

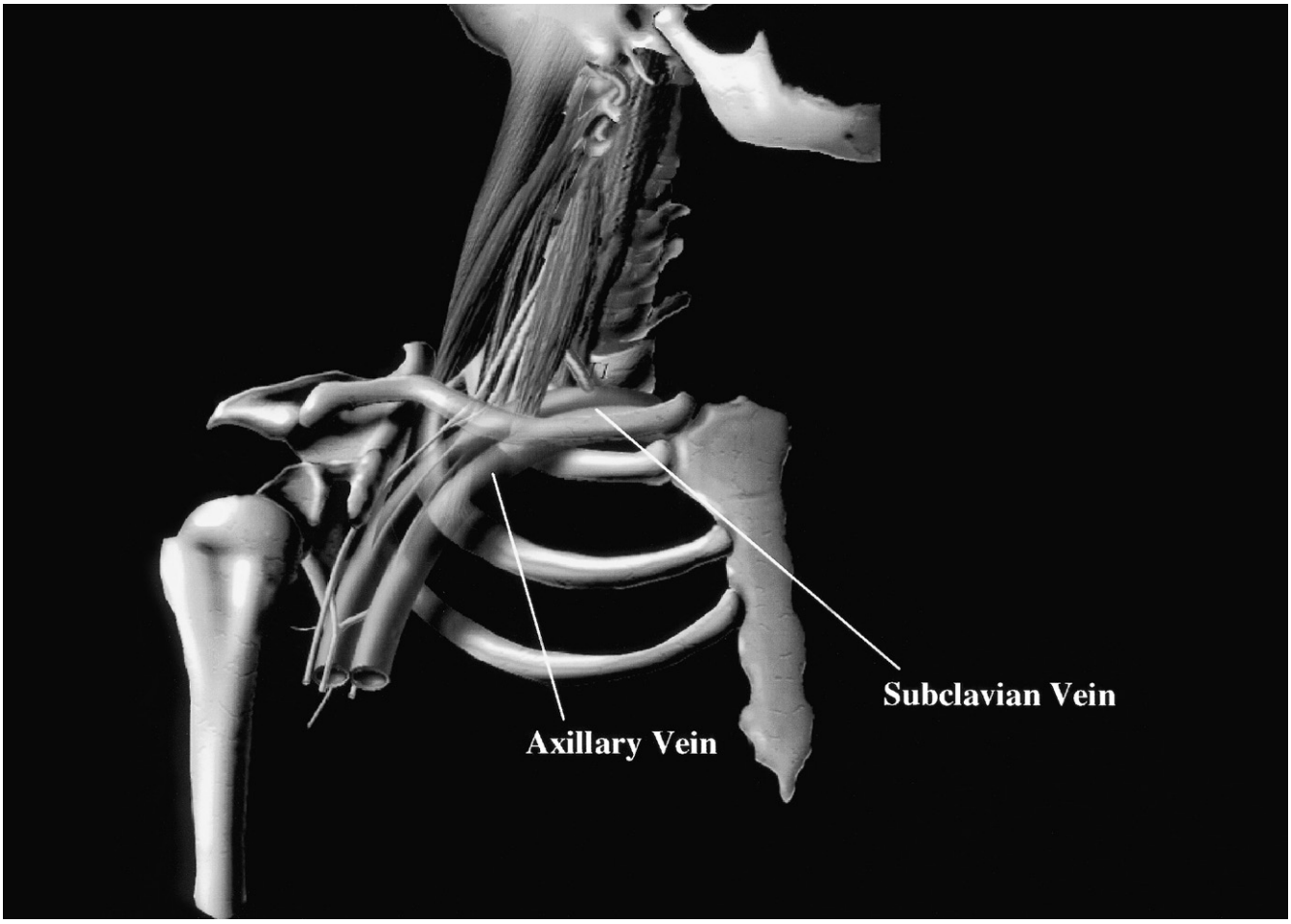

FIGURE 74-4 The subclavian vein and artery separated by the anterior scalene muscle. The artery, then, is within the confines of the perivascular space; the vein is not.

2.5 cm. The authors also noted that the mean optimal angle of approach in a sagittal plane was 61.1 degrees, corroborating Winnie's original description.[9] A cadaver study of four specimens noted that a caudal angulation of the needle was essential in minimizing risk of entering the intervertebral foramen.[10] In obese individuals, or in those with altered anatomy, both ultrasound (US) guidance (see below) and even fluoroscopic guidance[11] have been described as aids to performing proximal brachial plexus blocks successfully. One of the several advantages associated with US use is the identification of anatomic variants in real-time without the requisite exposure to ionizing radiation imposed by fluoroscopic techniques.[12]

When using PNS guidance for ISB, whereas an evoked motor response of the shoulder, elbow, or hand is acceptable prior to injecting local anesthetic, a shoulder paresthesia should not be used as a sole endpoint since it may indicate that the stimulating needle is stimulating the suprascapular nerve, either within or outside the brachial plexus sheath.[3,13] The roots lie slightly closer to the middle than to the anterior scalene muscle, and the needle should therefore be in closer proximity to the middle scalene. Blockade of C8 and T1 may not occur, and resultant anesthesia and analgesia will commonly be in the distribution of the nerve roots C5–C7. This block may provide complete surgical anesthesia for shoulder procedures; and, if the surgeon is performing arthroscopy, where a posterior port is frequently utilized (Fig. 74-11), one may consider injecting at C4 instead of C6.

Although ISB use has been described using a "low" approach (i.e., toward C7) in the interscalene groove for providing lower root block for surgery of the elbow,[14] the primary utility of ISB remains as a component of anesthesia for shoulder surgery. The C4 level can be estimated by moving our lateral line to the interscalene space from the most prominent aspect of the thyroid cartilage, instead of the cricoid (Fig. 74-12). Although palpation of the interscalene groove is more difficult as one progresses more cephalad, it has been found that the groove is easily followed from an inferior (caudad) point upwards on the neck.[15]

Alternatively, C4 may be blocked separately by an additional injection of 5 ml of local anesthetic. A recent study at the author's institution confirmed Kerr's anatomic data indicating that 7% of brachial plexuses have no C4, and only partial C5 contributions to the trunks.[16] Due to the proximity of the phrenic nerve, hemidiaphragmatic paresis and concomitant 25% to 30% reduction in pulmonary function occurs routinely following this technique,[17] which limits its usefulness in patients who cannot tolerate

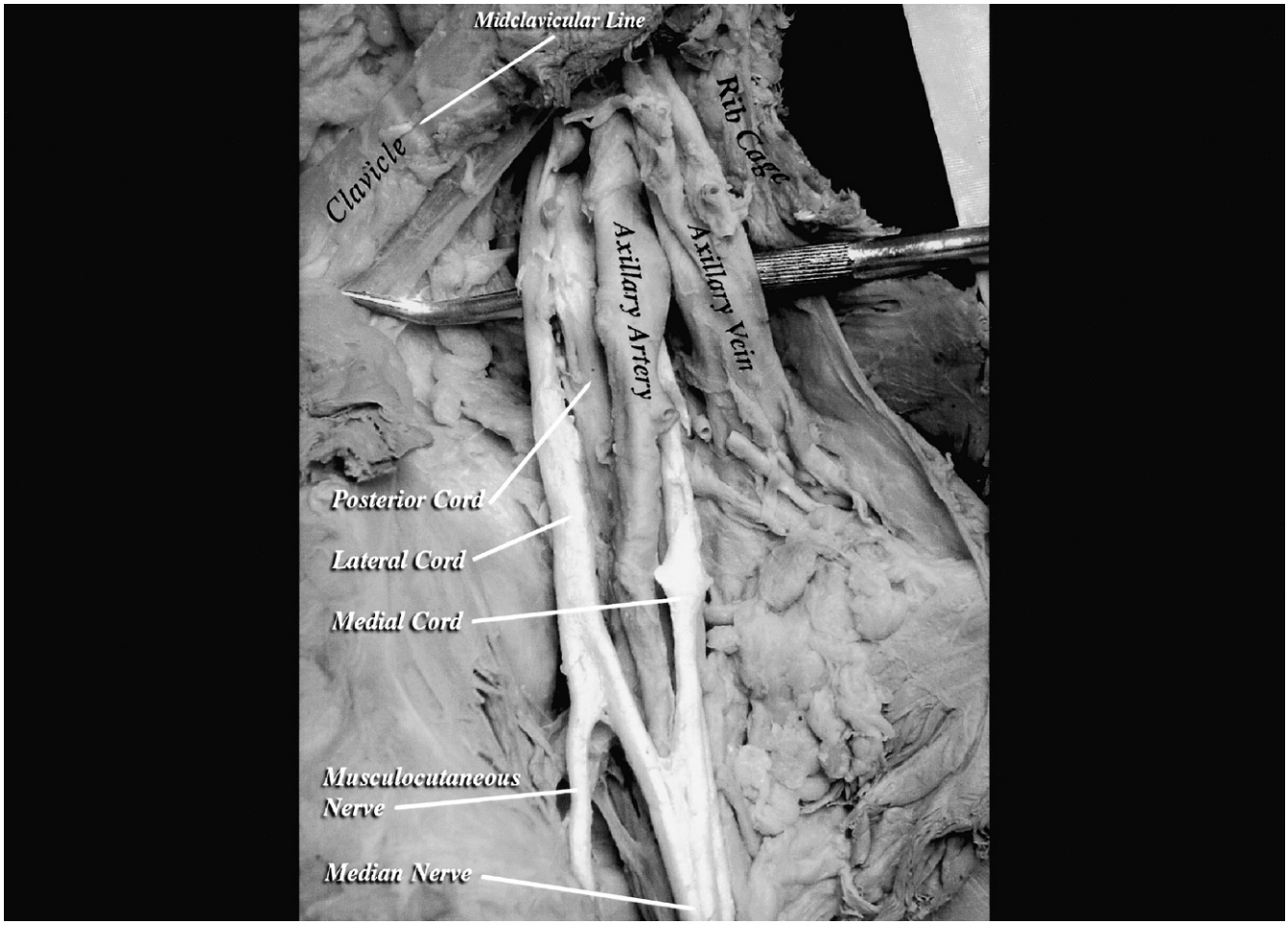

FIGURE 74-5 The three cords (lateral, posterior, medial) of the brachial plexus immediately beneath the clavicle, entwined around the axillary artery.

unilateral, impaired diaphragmatic function. US use has enhanced our appreciation of the phrenic nerve and has offered a possible solution to the formerly described 100% incidence of phrenic nerve block noted above. When US was used to scan the necks of 23 volunteers, the nerve was identified in 93.5% of scans.[18] Interestingly, the phrenic nerve was nearly indistinguishable from the C5 ventral ramus at the level of the cricoid cartilage, the location most often cited as the landmark for performing percutaneous techniques of ISB. The nerve was identified at a mean distance of 1.8 mm from the C5 ventral ramus, with 3 mm of additional separation between the two structures being noted at each subsequent cm of caudal observation.[18]

In a group of 40 patients randomized to receive US-guided ISB using low volume (5 ml) or larger volume (20 ml) ropivacaine 0.5%, the incidence of hemidiaphragmatic paresis was noted to be 45% in the low-volume group versus 100% in the 20-ml group.[19] Additionally, the incidence of forced expiratory volume in 1-s, forced vital capacity and peak expiratory flow using bedside spirometry, 30 min after the ISB was also lower in the 5-ml group, while the block success rate was equivalent between the two groups.[19] Further, there were significantly greater reductions in postoperative oxygen saturations in the higher volume group, than in the 5 ml group.[19]

US guidance for ISB performance has been touted as a means of avoiding hemidiaphragmatic paresis.[20] When 60 patients were randomized to receive either 20 ml of 0.75% ropivacaine for ISB using PNS guidance or US guidance, the group receiving the US blocks had a lower incidence of hemidiaphragmatic paresis (0% vs. 53%) as well as a lower incidence of other respiratory abormalities.[20] Similarly, a prospective evaluation of 30 patients receiving supraclavicular blocks using 10 ml of 0.75% ropivacaine with either using US or PNS guidance also found a reduction of hemidiaphragmatic paresis when US was utilized (13% vs. 93%) while block success rate was essentially equal between the two approaches.[21] Other respiratory parameters were also more abnormal in the PNS group, than they were in the US group.[21]

While these data are compelling, they still do not define the optimal dose or volume of LA. Some have suggested that a larger volume ISB, using combined techniques as described by Winnie and Pippa (proximal cranial needle approach) and employing as much as 70 ml of dilute LA actually results in a greater spread of analgesia to include the medial cutaneous nerve of the arm (in addtion to median, radial, ulnar and musculocutaneous nerves) than does a smaller volume (30 ml).[22] For supraclavicular block (SCB), the minimum effective volume of LA has been suggested to be 23 ml in 50%, and 42 ml in 95% of a group of 21 adults undergoing

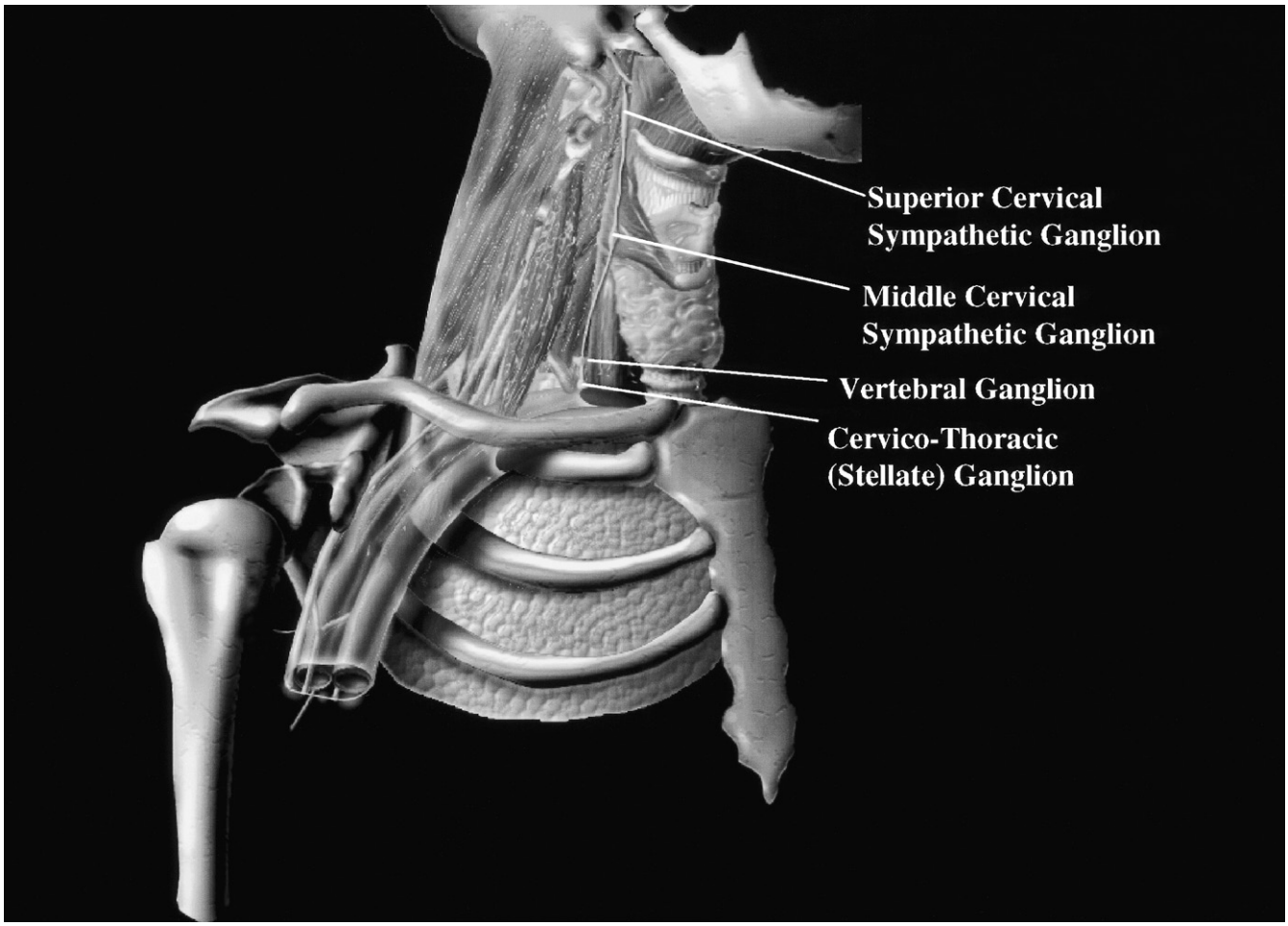

FIGURE 74-6 The relationship of the cervical sympathetic nerves to the roots and trunks of the brachial plexus on the right side of the neck.

US-guided SCB when a 50:50 mixture of lidocaine 2% and bupivacaine 0.5% with epinephrine added.[23] Regarding pharmacokinetics, it has been determined that supraclavicular techniques of BP block (lateral interscalene—Winnie; posterior interscalene—Pippa) produce earlier and higher peak plasma concentrations of 0.75% ropivacaine than do infraclavicular techniques (infraclavicular; axillary). Furthermore, these peaks occur sooner following blocks above the clavicle (13.4 min) than for infraclavicular blocks (25 min).[24]

Ultrasound may be used to localize the brachial plexus and guide the block needle toward the target nerves. There is a suggestion in the literature that the use of US is associated with a cost savings when compared with general anesthesia for patients undergoing upper extremity surgery.[25] For performing US-guided block, the patient is positioned in similar fashion to traditional techniques or in the lateral decubitus position for in-plane needle guidance.[26] When performing US-guided interscalene block techniques, the brachial plexus is identified in the short axis using a high-frequency linear transducer placed at or below the level of the cricoid cartilage in transverse orientation perpendicular to skin and posterior to the sternocleidomastoid muscle[27] (Fig. 74-13). The roots and trunks of the brachial plexus appear as hypoechoic structures between the fascia of the anterior and middle scalene muscles (Fig. 74-14). Once the brachial plexus is identified, the block needle is inserted out-of-plane anterior to the interscalene groove[28,29] or posterior to the US transducer in-plane aiming anteromedially[26,27,30] (Fig. 74-13). When the needle tip is positioned within the interscalene groove, local anesthetic solution is injected incrementally with real-time confirmation of appropriate injectate spread on US.

Common long-acting local anesthetics chosen for single-injection brachial plexus blocks include racemic bupivacaine or levobupivacaine (the S (–) enantiomer of bupivacaine) with or without epinephrine,[31,32] although some patients prefer to avoid the 18 to 30 hr of postblock paresis routinely seen with these agents. In these cases, one can use 1.5% mepivacaine, and additives such as clonidine or buprenorphine 0.3 mg/40 ml can be added to prolong postoperative analgesia.[33–35] Ropivacaine, an aminoamide local anesthetic that is highly protein bound and lipid soluble, may be an alternative anesthetic in institutions without access to levobupivacaine, as it is purported to have less propensity for cardiotoxicity than racemic bupivacaine, while having a similar anesthetic profile (in equipotent concentrations) for brachial plexus anesthesia.[36]

When ropivacaine and bupivacaine were compared in equal volumes and concentrations for ISB (30 ml of 0.5%), although *not equipotent* doses, in a group of 44 patients having shoulder surgery, it was found that the two agents

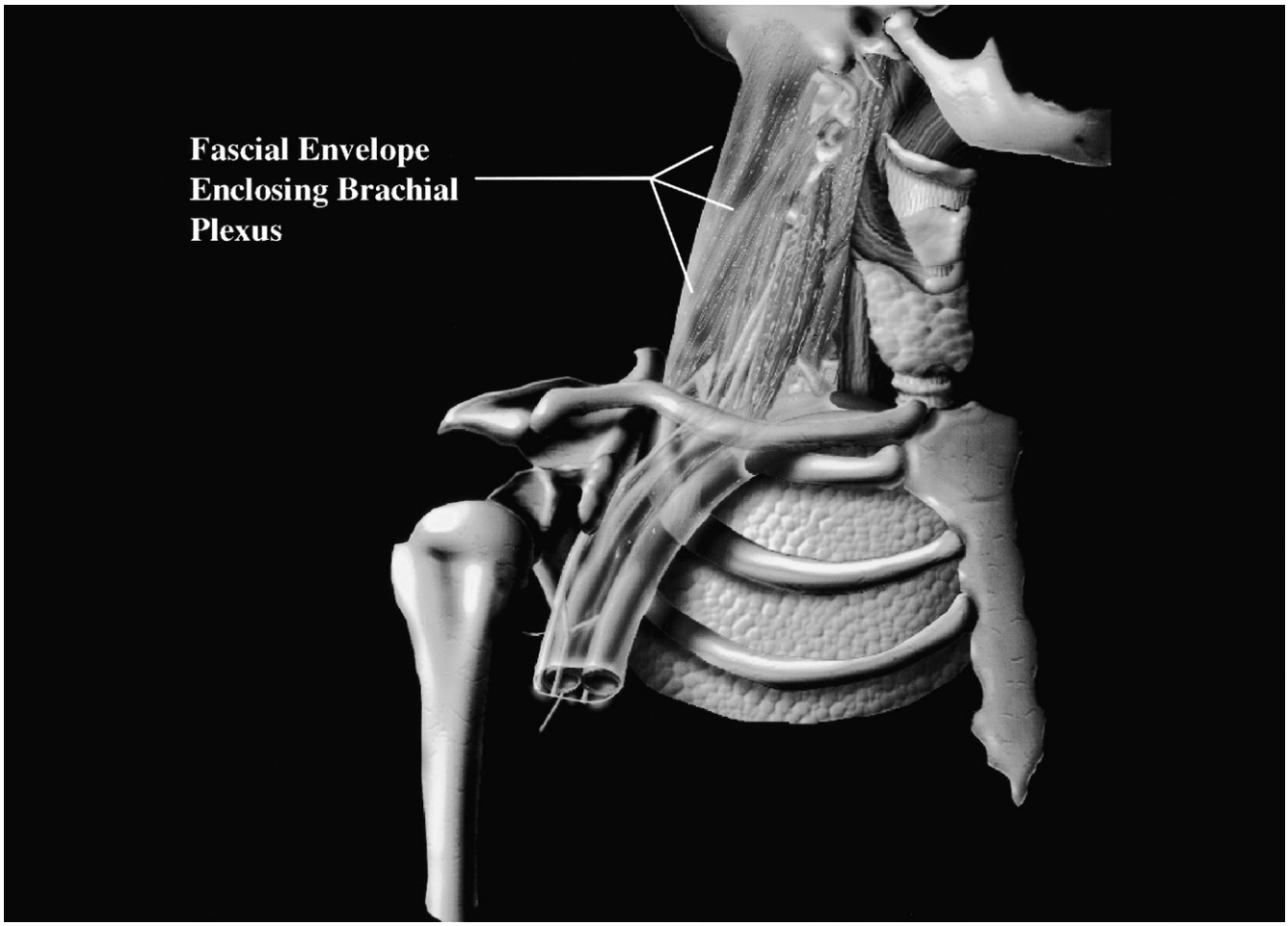

FIGURE 74-7 A continuous fascial compartment from the cervical prevertebral fascia to the distal axilla, enclosing and enveloping all the major elements of the brachial plexus. The "brachial plexus sheath" may be entered at any level (analogous to peridural anesthesia) and forms the foundation for single-injection techniques.

produced blocks that were similar in terms of onset, duration and postoperative analgesia.[37] When comparing 40 ml 0.25% bupivacaine used for ISB, to 40 ml of 0.25% levobupivacaine, both agents provided mean time to sensory block of less than 5 min and mean time to motor block of less than 25 min.[38] There was no apparent effect of increasing body mass index (BMI) on determining the ED50 of 0.5% bupivacaine used for ISB, which was noted in a group of 21 patients of differing BMIs to be 10.8 ml when used for SCB.[39] BMI was also found not to be an independent factor determining successful block in diabetics undergoing SCB wherein it was noted that the incidence of utilizing general anesthesia for failed blocks in these patients was less than in the nondiabetic population.[40]

As for toxicity, it has been established that bupivacaine is more toxic at equipotent doses than is ropivacaine. A recent study of 32 patients scheduled for shoulder surgery under ISB were randomized to receive either 40 ml of 0.5% bupivacaine or 0.5% ropivacaine. Holter monitoring begun the evening prior to surgery and continued for 6 hr after the blocks showed significant prologation of the P-Q interval on ECG commencing 15 minutes after the block and persisting for 1 hr, while other measurements of cardiac electrophysiology were not different between the groups. Total peak LA concentration in both groups occurred between 30 and 45 min after bolus injection of LA.[41] However, the case report of Satsumae et al., wherein an 18-year-old male patient sustained a convulsion following a combined axillary and ISB using a total of 300 mg of ropivacaine highlights the fact that there may be a wide variation and dose associated with systemic toxicity in susceptible individuals.[42]

In terms of hastening ISB onset time, various efforts have been put forth, including using shorter-acting agents followed by potent, highly protein bound and lipophilic amino-amide drugs. A comparison of 3% 2-chloroprocaine plus bicarbonate plus epinephrine immediately followed by bupivacaine 0.5% with epinephrine was made to lidocaine 2% in place of chloroprocaine in a group of 30 patients having ISB performed prior to shoulder surgery. The median time to motor block onset was 90 s for chloroprocaine versus 180 s for lidocaine, and the median time to sensory block onset was 90 s for chloroprocaine vs. 210 s for lidocaine. By 10 min, 15/15 chloroprocaine patients had full motor block versus 10/14 for lidocaine. These data suggest that if speed of onset is a priority, adding 3% 2-chloroprocaine prior to bolus bupivacaine may be efficacious.[43]

Enhanced motor activity of an upper extremity, utilized in an attempt to employ frequency-dependent block principles to rapidly open and close sodium channels, was

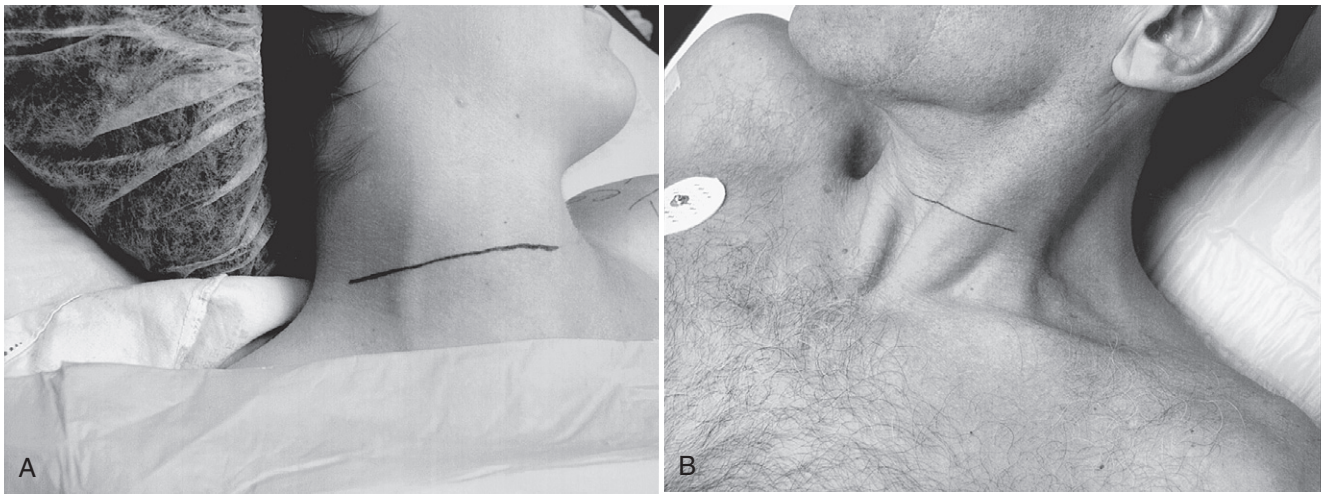

FIGURE 74-8 **A**, Anatomic landmarks for interscalene brachial plexus block on the right side of the neck including the external jugular vein, crossing the interscalene groove at about the level of the cricoid cartilage (C6). **B**, The head has been elevated from the gurney, tensing the sternocleidomastoid muscle. The lateral line at approximately C6 indicates the level of needle insertion for interscalene brachial plexus block (left-side view).

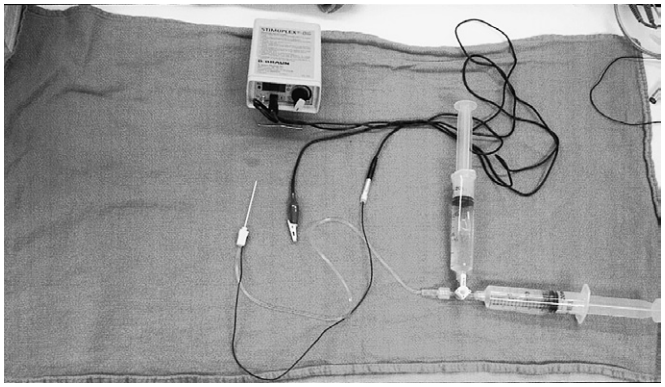

FIGURE 74-9 A peripheral nerve stimulator and insulated 22-gauge block needle. Note the "immobile needle" (extension tubing) that serves to free the operator's hand and isolate the needle from the rest of the syringe system containing the local anesthetic.

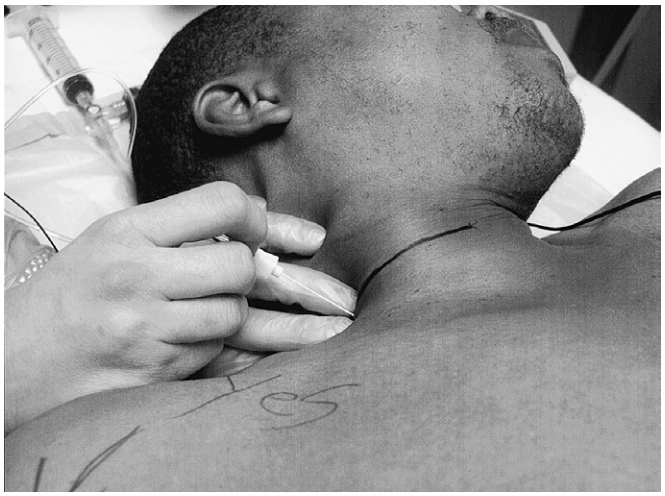

FIGURE 74-10 Insertion of the insulated regional block needle for right-sided interscalene brachial plexus block. The direction of needle insertion is slightly mesiad, slightly dorsad, and slightly caudad.

shown to be of no value in hastening the onset of sensory or motor block for ISB performed using bupivacaine 0.5% with epinephrine.[44] Adjuvants given to augment postoperative analgesia may be administered systemically or as part of the perineural injectate or infusion. For prolonged postoperative analgesia, clonidine 150 μg or buprenorphine 300 μg may be added to the local anesthetic solution, or continuous catheter techniques may be used.[33,34,45] A recent study of the use of clonidine 50 μg added to 40 ml of mepivacaine 1.5% with epinephrine given for ISB in a group of 20 patients undergoing continuous-catheter techniques for providing postoperative analgesia was undertaken. Patients received either ropivacaine 0.2% for patient-controlled regional analgesia (PCRA) after surgery or else the same local anesthetic to which clonidine 2 μg/ml was added. There were no differences in analgesia in either group, implying that while clonidine may be efficacious for single-shot ISB, the use of this adjuvant for perineural infusion is without merit.[46]

Gabapentin, used as a preemptive analgesic and administered in a single 800 mg dose orally before ISB for shoulder surgery did not augment the effects of 0.5% ropivacaine analgesia.[47] Dexamethasone 8 mg added to bupivacaine 0.5% (20 ml) to which was added clonidine (75 μg) plus epinephrine (5 μg/ml) in a group of 88 patients randomized to the treatment group or saline placebo, was noted to prolong sensory and motor block and to reduce numeric pain rating scores (NRS) by 50% for up to 24 hr after surgery.[48]

Another study compared dexamethasone (8 mg) added to 0.5% bupivacaine versus tramadol (2 mg/kg) added to the LA for ISB in upper extremity surgery and noted that the dexamethasone produced a more than doubling of the analgesic effect of bupivacaine compared to tramadol.[49] When 0.5% bupivacaine 30 ml was compared to the same volume to which midazolam 50 μg/kg was added for supraclavicular brachial plexus block (SCB) in a group of 40 adults undergoing upper limb surgery, it was noted that the additive provided a more rapid onset of both sensory

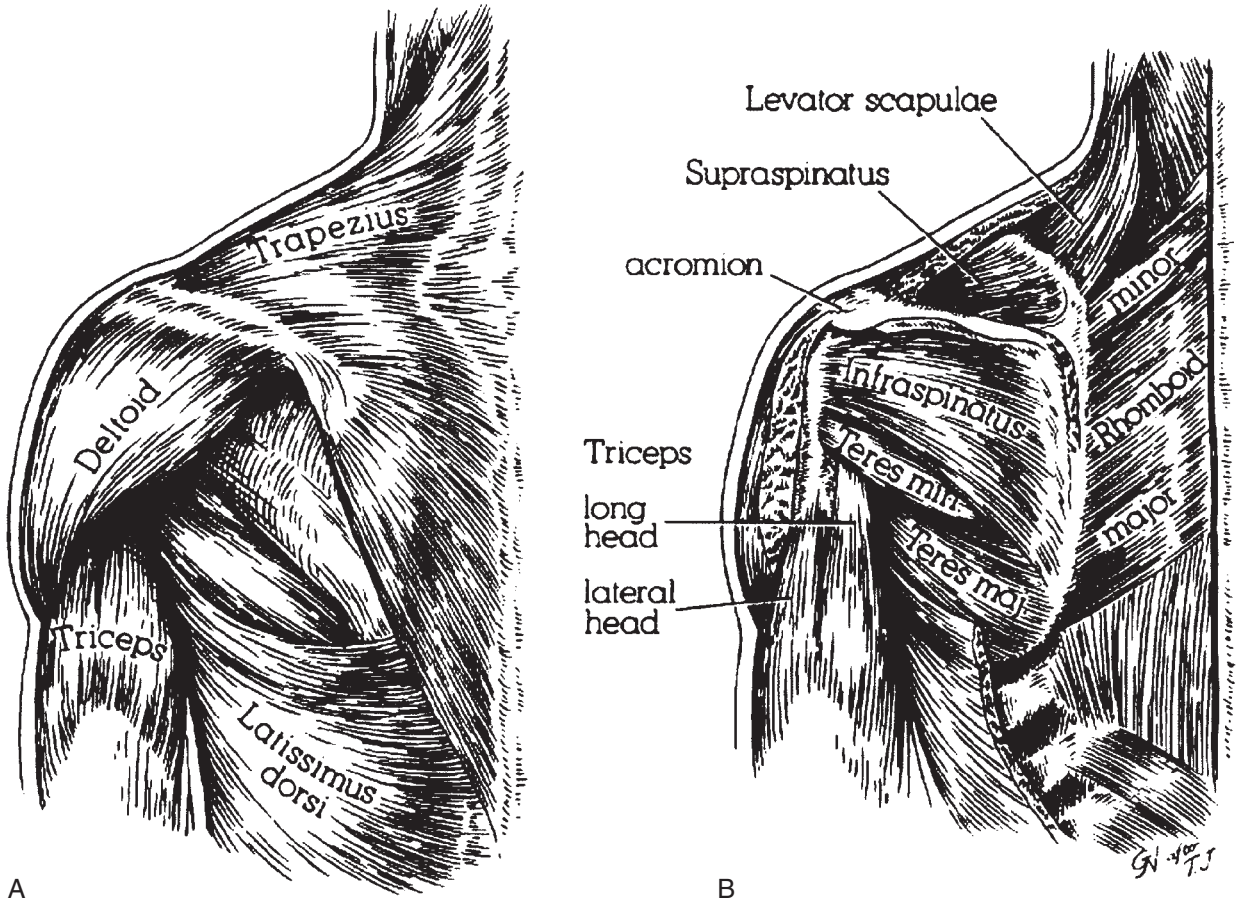

FIGURE 74-11 Posterior view of the left shoulder demonstrating the muscles beneath dermatomes C4–C7, particularly the posterior deltoid and the superior segment of the trapezius.

and motor block and an extended duration of postoperative analgesia compared to the LA alone.[50]

Continuous brachial plexus catheters and subsequent perineural local anesthetic infusion provide many patient benefits (see chapter on continuous peripheral nerve blocks). Challenges involved with interscalene catheter insertion may be overcome by US-guided anterolateral[28] or posterior[26,27,51] approaches. Compared to stimulating techniques, US-guided perineural catheter insertion may be performed in less time.[52,53] Continuous ISB has been compared to single-injection ISB for analgesia following shoulder surgery with more favorable analgesia occurring for up to 24 hr in the catheter group to which an infusion of 0.25% levobupivacaine was administered at 5 ml/hour.[54]

Stimulating catheters have been compared with nonstimulating ones placed using both PNS guidance and US guidance. Pain at rest was improved when stimulating ISB catheters were compared to nonstimulating catheters in a group of 60 patients receiving ropivacaine blocks, although stimulating catheter placement required twice as long (12 min vs. 6 min) as nonstimulating catheters.[55] Stevens et al. demonstrated that stimulating catheter use was associated with a faster onset of motor block after the injection of 40 ml of 1% prilocaine followed by 10 ml of 0.75% ropivacaine followed by an infusion of 0.2% ropivacaine, but noted no improvement in postoperative pain scores compared to conventional catheters, although they did discover significantly improved functional outcome at the 6-week postoperative assessment in the stimulating-catheter group, which defies explanation.[56] A semi-quantitative review suggested that stimulating catheter use was meritorious for some continuous regional techniques but acknowledged a lack of ability to be definitive in many cases.[57]

Continuous ISB catheters placed using US have been used as part of a multimodal home infusion regimen for PCRA during ISB analgesia. Swenson et al. noted that in 190 continuous ISB catheters, there was no evidence of neurologic injury using this approach.[58] As with single-injection techniques, side effects like hemidiaphragmatic paresis, Horner's syndrome, and recurrent laryngeal nerve block are all possible using continuous catheter techniques, as are complications like hematoma, infection, nerve injury, hemopneumothorax, subcutaneous and mediastinal emphysema, and spinal subarachnoid and epidural block.[2] The incidence of side effects like Horner's syndrome, hoarseness, and subjective breathing difficulties related to the spread of local anesthetic to neural structures may be slightly higher following right-sided blocks than it is for left-sided interscalene brachial blocks, but the mechanism for this is unclear. The recurrent laryngeal nerve, on the right side, leaves the vagus nerve and loops around the subclavian artery several centimeters higher than the nerve on the left side, which does not emerge

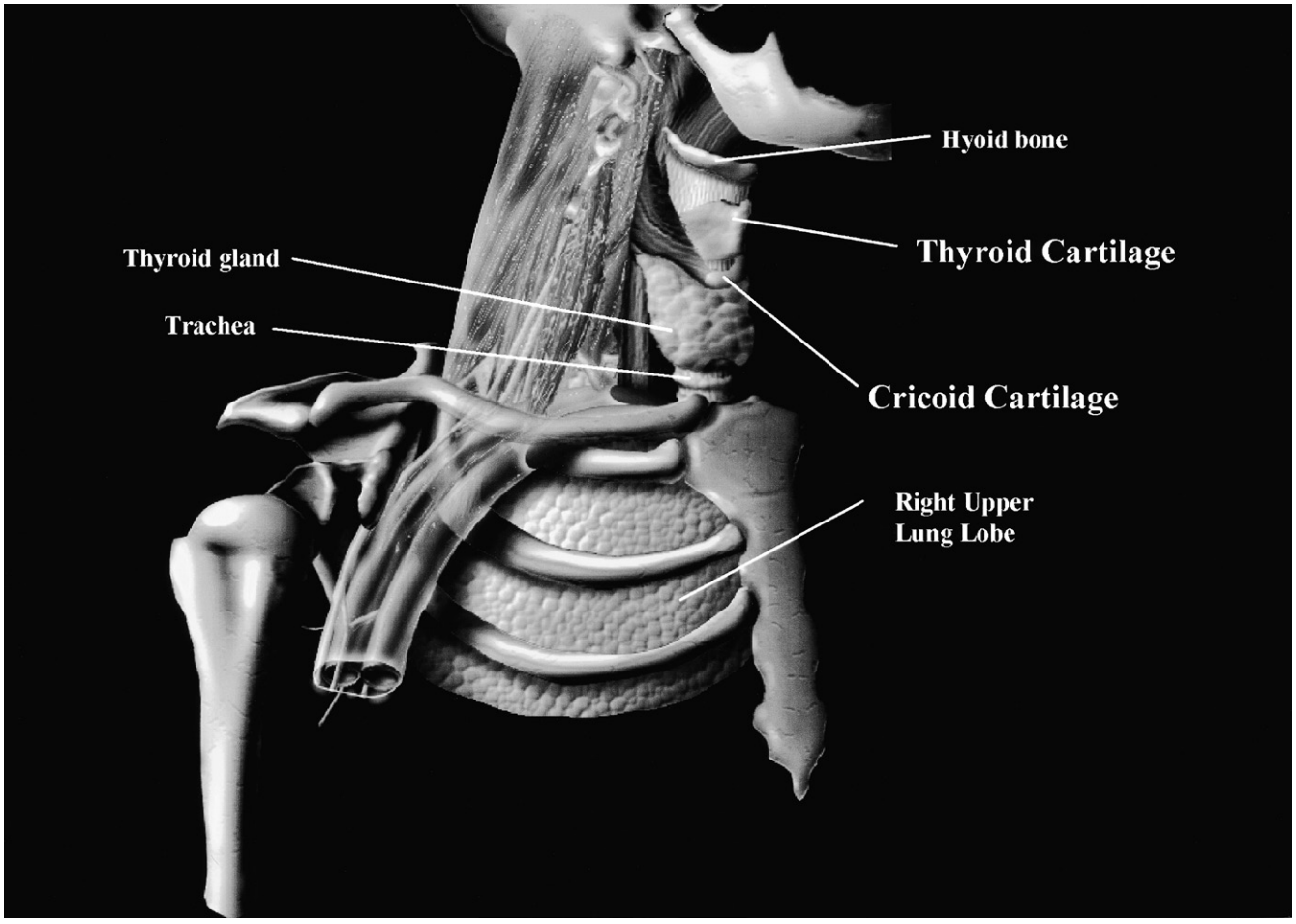

FIGURE 74-12 Distinction between the cricoid cartilage (C6) landmark for interscalene block and the thyroid cartilage (C4) landmark for cervical plexus block.

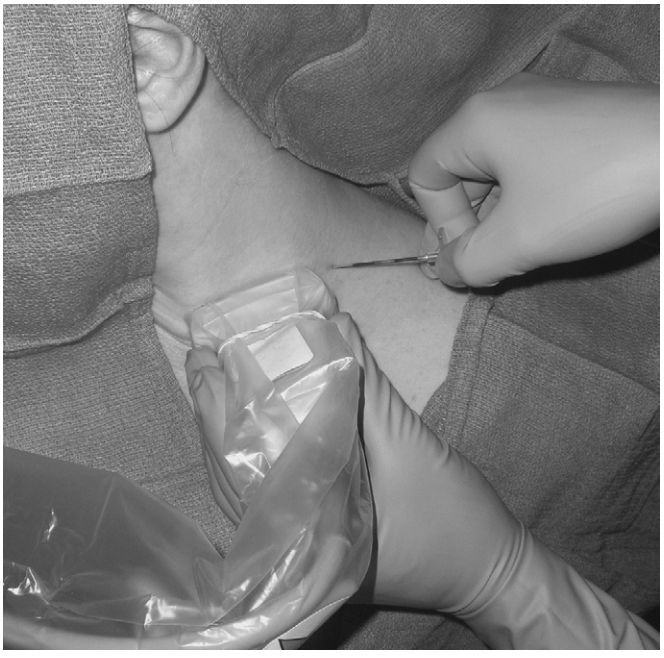

FIGURE 74-13 View of the left neck showing the application of a high-frequency linear ultrasound transducer for ultrasound-guided interscalene block over the interscalene groove with posterior needle insertion in-plane.

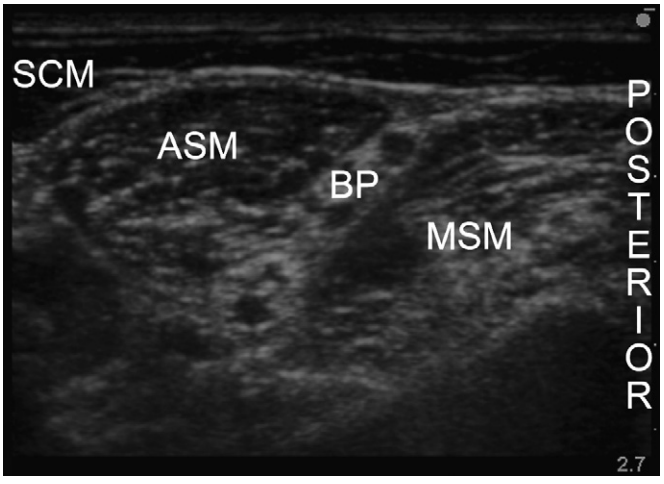

FIGURE 74-14 Sonoanatomy of the interscalene groove and brachial plexus. SCM, sternocleidomastoid muscle; ASM, anterior scalene muscle; MSM, middle scalene muscle; BP, brachial plexus.

until the carotid has joined the aorta lower in the chest[2] (Fig. 74-15). This may explain the higher incidence of hoarseness on the right side versus the left. Alternatively, hoarseness may result from vasodilation of the larynx from local anesthetic spread to cervical sympathetic fibers.

Serious complications such as death, cardiac arrest, and respiratory arrest are rare following interscalene and supraclavicular techniques. A study from France identified two major complications occurring after 5358 total interscalene (ISB) or supraclavicular (SCB) brachial blocks.[59] There was 1 neurologic injury out of 3459 ISBs and 1 seizure out of 1899 SCBs for an overall incidence of 3.7 major complications per 10,000 blocks. The single-injection technique can be used to minimize these complications associated with multiple-injection techniques (reported to be 1.7%).[60–64] The syndrome of sudden hypotension and bradycardia (vasovagal syncope) during shoulder surgery with the patients in the beach-chair position is of continuing concern, and has been attributed to activation of the Bezold–Jarisch reflex, although this remains controversial.[65] The incidence of this complication has been reported to range from 13% to 24% of awake patients in the sitting position who are undergoing shoulder arthroscopy with interscalene brachial plexus anesthesia.[66,67]

SUPRACLAVICULAR BLOCK TECHNIQUES

Brachial plexus block approaches near the clavicle have been associated with an incidence of pneumothorax as high as 6%.[68] Anatomically, the traditional approach, whereby the needle is inserted 1 cm above the midpoint of the clavicle, is flawed since this point frequently does not lie over the first rib (as suggested), thereby negating the protection afforded to the cupola of the lung by the rib. The anatomy of the scalene muscles, and the orientation of the three trunks of the brachial plexus vertically (stacked, one above the other) in the scalene space, lend themselves ideally to approaches whereby the needle is advanced dorsally tangential to the subclavian artery (i.e., directly caudad) when not employing US guidance.

By directing the needle parallel to the borders of the scalene muscles, since these muscles insert on the first rib, the locations of the plexus, subclavian artery, and rib may be located more precisely using this approach than with any of the other described supraclavicular techniques.[69] The nerve stimulator technique based on the approach described by Winnie[2,69] is as follows. The patient lies supine with the shoulder completely relaxed and the head turned slightly toward the opposite side, as noted for

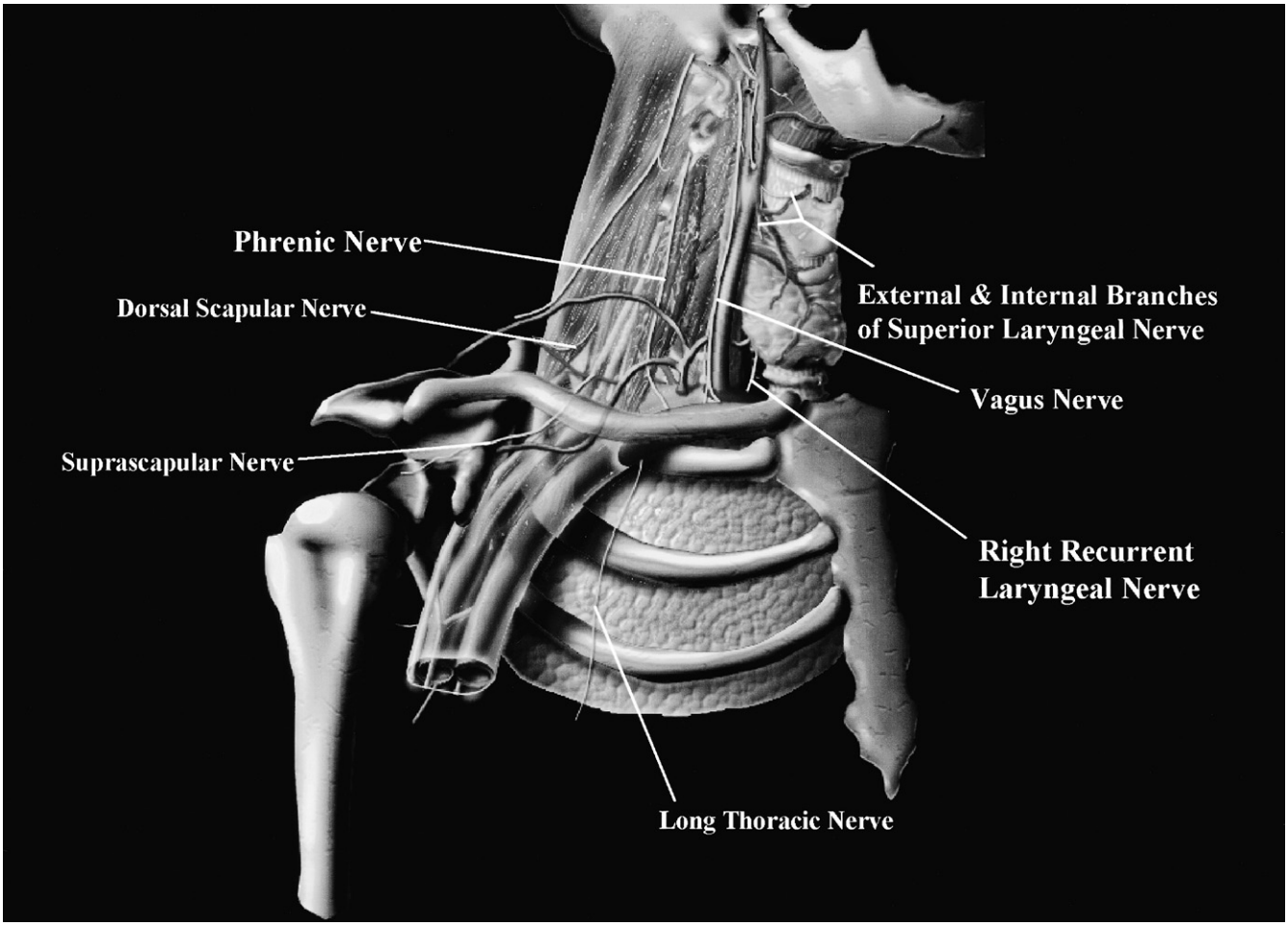

FIGURE 74-15 Relative position of the right recurrent laryngeal nerve and its relationship to the vagus nerve and to the roots and trunks of the brachial plexus.

interscalene block discussed above. The interscalene groove is palpated after the patient elevates the head off the bed to demonstrate the prominence of the clavicular head of the sternocleidomastoid muscle (Fig. 74-16). The palpating finger(s) now sit on the anterior belly of the anterior scalene muscle, and must be rolled laterally toward the middle scalene muscle into the groove between the two muscles. The groove is traced inferiorly until the subclavian arterial pulse is felt, or until the omohyoid muscle (running obliquely and inferiorly across the groove) obscures further palpation (Figs. 74-17 and 74-18). At the approximate level of C6, a short (2-inch) insulated needle is advanced inferiorly (caudad, but not mesiad or dorsad). The needle is now in the longest dimension of the interscalene space (parallel to the scalene muscles), while observing the arm for an appropriate distal motor response at 0.5 mA or less. A total volume of 40 ml of local anesthetic solution is now injected in divided doses. Aspiration of bright red blood through the needle signifies that the needle is situated too far anteriorly (subclavian artery) and needs to be withdrawn and reinserted closer to the middle scalene muscle. The resultant anesthesia and analgesia will be in the distribution of the trunks (superior, middle, inferior).

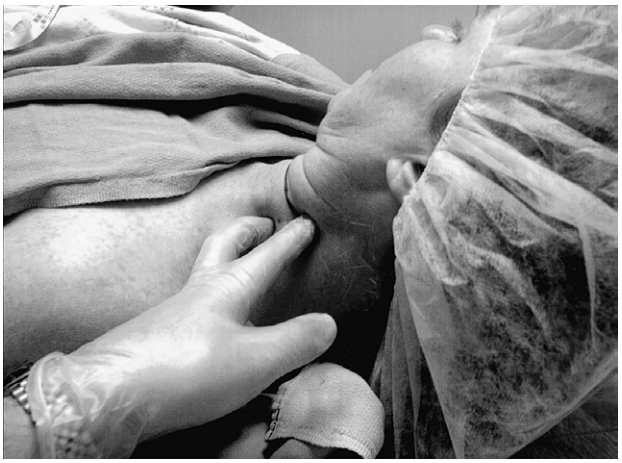

FIGURE 74-16 Initial patient position for left-sided subclavian perivascular brachial plexus block. As for interscalene block, the interscalene groove is the major cutaneous landmark, and is identified by indenting the skin lateral to the clavicular head of the sternocleidomastoid muscle. The fingers are then rolled laterally from the belly of the anterior scalene muscle into the groove between the anterior and middle scalene muscles.

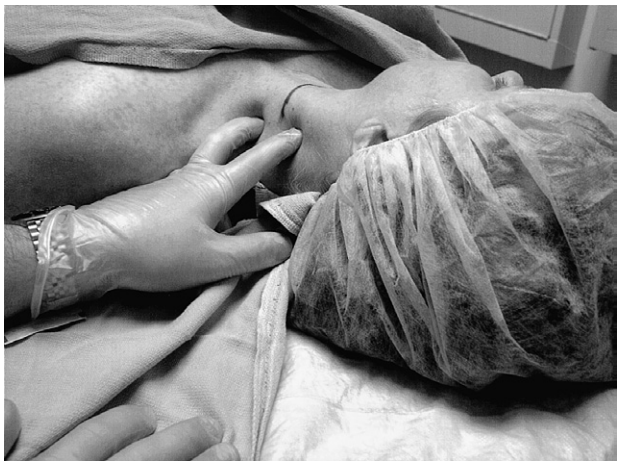

FIGURE 74-17 Palpating fingers appropriately seated in the interscalene groove on the left side.

This block is appropriate for upper extremity surgeries at or below the shoulder. Even though pneumothorax remains the most dreaded potential complication associated with this approach, Franco and Vieira reported no clinically apparent pneumothoraces following 1001 consecutive supraclavicular blocks.[70] This supported earlier work performed at two other institutions where no pneumothoraces were encountered in a combined total of 237 subclavian perivascular brachial plexus blocks.[2]

Anatomically, phrenic nerve block (with resultant hemidiaphragmatic paresis) is less likely with this approach than with interscalene block. Neal et al. demonstrated, in fact, that the incidence of phrenic nerve block following supraclavicular brachial block is about 50%.[71] Interest in US guidance for supraclavicular block stems for the desire to improve block efficacy and minimize the risk of pneumothorax.[72,73] Even so, a report by Bryan et al. of indwelling ISB catheters placed with US guidance presents one case of pneumothorax out of 144 consecutive patients, for an incidence of 0.7%.[74] This emphasizes that US is no guarantee that such complications will be avoided.

For US-guided supraclavicular block, the patient is positioned in similar fashion to traditional supraclavicular block approaches, and a high-frequency linear[72] or curvilinear[73] US transducer is placed perpendicular to skin at the base of the interscalene groove just medial to the clavicle to image the brachial plexus in short axis (Fig. 74-19). The neural elements of the brachial plexus appear posterolateral to the subclavian artery as hypoechoic round structures surrounded by hyperechoic connective tissue (Fig. 74-20). Color flow doppler can be a useful aid in identifying the subclavian artery and distinguishing neural tissue from blood vessels. Once the brachial plexus is identified, the block needle is inserted in-plane either anterior or posterior to the transducer and directed toward the target nerves using real-time US guidance.[75] To ensure blockade of the C8 and T1 divisions for complete distal upper extremity anesthesia, local anesthetic injectate should be deposited in the "corner pocket" between the posterolateral portion of the subclavian artery and first rib.[76]

Compared to nerve stimulation techniques, US guidance may improve procedural speed[77] and minimize the occurrence of phrenic nerve block.[21] Local anesthetic selection for single-injection supraclavicular blocks is similar to that for interscalene blocks. Outcomes data regarding specific continuous supraclavicular block techniques are limited[78] although the subclavian perivascular approach may offer advantages for continuous catheter insertion and maintenance since the catheter may secured flat against the neck. Since the plexus is compartmentalized at this level, continuous catheter techniques may require lower infusion rates to be effective compared to other approaches.[45] Potential side effects and complications are similar to those listed above for interscalene block.

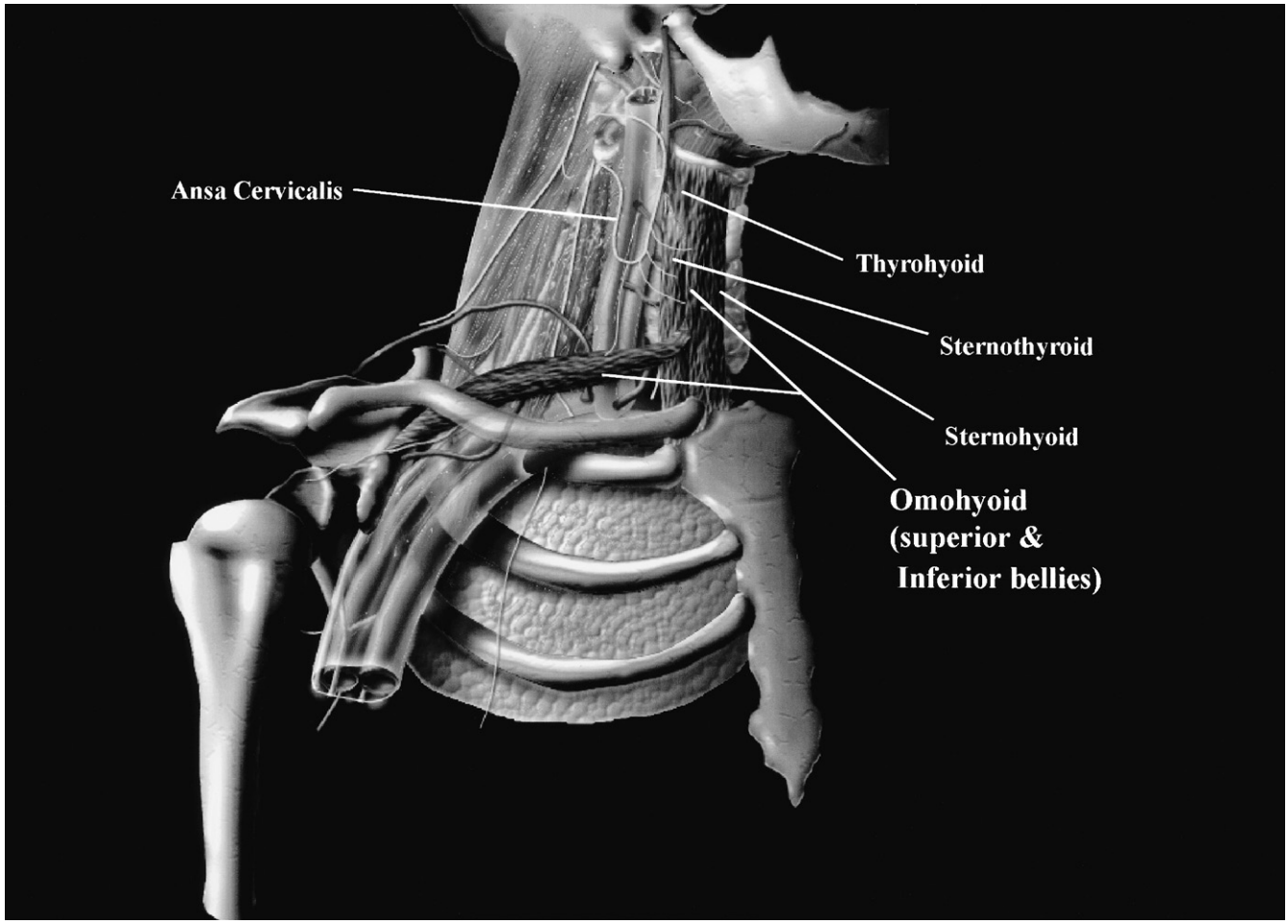

FIGURE 74-18 Demonstration of the obliquely situated omohyoid muscle, an impediment to tracing the interscalene groove inferiorly to the clavicle in some individuals.

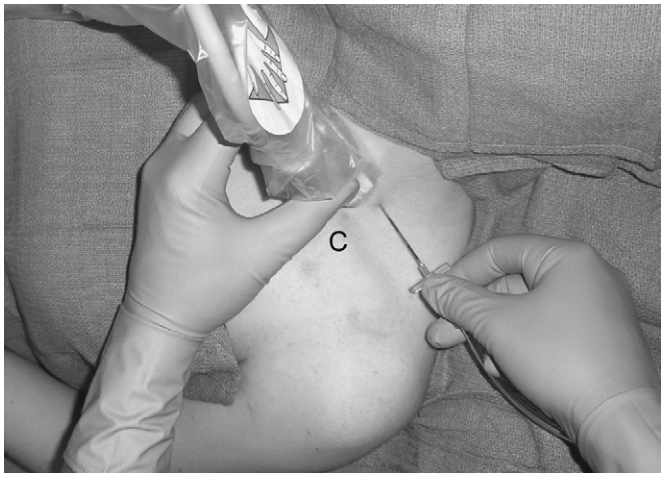

FIGURE 74-19 View of the left neck showing the application of a high-frequency linear ultrasound transducer for ultrasound-guided supraclavicular block medial to the clavicle (C) with posterior needle insertion in-plane.

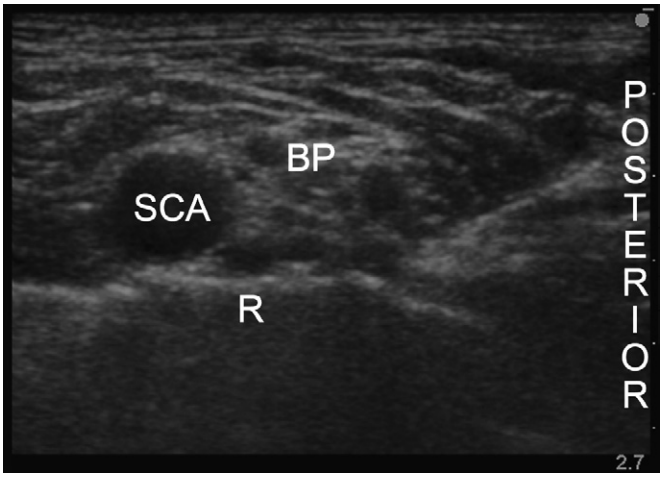

FIGURE 74-20 Sonoanatomy of the brachial plexus during ultrasound-guided supraclavicular block. SCA, subclavian artery; R, periosteum of first rib; BP, brachial plexus.

ALTERNATIVE BRACHIAL PLEXUS BLOCK TECHNIQUES ABOVE THE CLAVICLE

New techniques continue to be sought and developed in the quest to improve on success rates and minimize complications inherent to regional block anesthesia. The parascalene technique of Vongvises and Panijayanond[79] is one of the first of these modifications. They advocate an approach at a site similar to the subclavian perivascular block, but advance the needle in a vertical direction (i.e., perpendicular to the long axis of the body). The technique employs similar patient positioning to that of subclavian perivascular block, including palpation of the sternocleidomastoid muscle to identify the anterior scalene muscle, and hence the groove between it and the middle scalene muscle. At a point 1.5 to 2 cm above the clavicle, a 22-gauge needle is advanced in an anteroposterior direction until a paresthesia is elicited then local anesthetic solution is injected at this point after careful aspiration. The authors state that the first rib acts as a barrier if the plexus is missed by the advancing needle. If, after multiple unsuccessful attempts, no paresthesia can be elicited, the local anesthetic is simply injected along the lateral edge of the anterior scalene muscle above the first rib in a "fanlike manner." The authors report a 97% success rate but recommend a second injection to attain this high percentage.

For pediatric patients, Dalens et al. describe a modified parascalene technique.[80] They determined from pediatric cadavers that the technique of Vongvises and Panijayanond would result in pneumothorax for greater than 50% of pediatric cases. A rolled towel is placed under the child's shoulders with the child in the supine position. The head is turned somewhat to the opposite side, and a line is drawn from the midpoint of the clavicle to Chassaignac's tubercle, which is located either by palpation or by dropping a line drawn laterally from the cricoid cartilage to the lateral border of the sternocleidomastoid muscle. This line is trisected and the needle is inserted at the junction of the lower and middle thirds of the line.

For single-injection blocks, a 22-gauge, short (1 inch) insulated needle is advanced posteriorly, and an appropriate motor response is sought employing an electrical nerve stimulator. Dalens et al. reported a 98% success rate in pediatric patients using this approach, with no major complications. Brown, in 1993,[81] described his "plumb-bob" technique for supraclavicular brachial plexus block. This parascalene approach uses an injection site even lower than the two techniques mentioned above and do not require complex measurements or equipment as described by both Vongvises and Dalens. The patient is placed supine with the head turned to the opposite side. The point at which the lateral border of the sternocleidomastoid muscle joins the superior aspect of the clavicle is marked, and a 22-gauge, 5- to 6-cm blunt needle is inserted at this point (Fig. 74-21) and aimed directly posterior (perpendicular to the bed). The needle is advanced until a paresthesia is elicited, after which the local anesthetic is injected. If the plexus is not contacted initially, the needle is redirected caudad in small steps until a paresthesia is obtained or until a 30-degree angle is reached.

An evaluation of this technique using magnetic resonance imaging (MRI) and needle direction simulation suggests that the direction of the needle in the original description of the technique would have resulted in pleural contact in 60% of volunteers, without prior contact with the subclavian artery or the brachial plexus, but always with subclavian vein contact.[82] Importantly, these investigators found that the plumb-bob trajectory very rarely contacts the brachial plexus, usually passing it by 12 mm. They recommend changing the needle angle more cephalad (45 degrees) than described by Brown.[81] The intersternocleidomastoid approach[83] attempts to minimize the risk of pneumothorax by directing the needle anterior and superior to the dome of the lung toward the distal trunks. Subclavian arterial puncture may occur. Direct pressure over the artery may be difficult because of its position behind the clavicle. The insertion site is at the medial border of the clavicular head of the sternocleidomastoid muscle, 3 cm above the sternal notch. An insulated needle is attached to a nerve stimulator and is directed caudally, dorsally, and laterally toward the midpoint of the clavicle, passing posterior to the clavicular head of the muscle and forming a 45-degree angle with the plane of the operating room table. The goal is to pass the needle deep to the clavicular head of the sternocleidomastoid muscle, pass through the posterior and caudal portion of the anterior scalene muscle, and to approximate the plexus just superior to the first rib. Usually, a 90-mm (3.5-inch) needle is employed versus the shorter needles used in the single-injection interscalene and subclavian perivascular techniques. The needle is advanced until an appropriate motor response is obtained. Injuring or impaling the phrenic nerve as it crosses the anterior scalene muscle may occur with this technique.

COMPLICATIONS

Complications of brachial plexus techniques above the clavicle have been discussed above without providing detail which is now provided. Perioperative nerve injury remains a significant concern following brachial plexus block. In Auroy's retrospective analysis, all neurologic complications of regional anesthesia presented within 48 hr of surgery, and 85% resolved within 3 months.[59] In Cheney's closed claims report, 31% of brachial plexus injuries associated with regional anesthesia followed a paresthesia either during the needle insertion or during the injection of local anesthetic.[84] It has been suggested that perineural hematoma, intraneural edema, tissue reaction, or scar formation may be causative factors in neural injury. Importantly, positioning and surgical trespass, including the use of tourniquets or retractors intraoperatively and the application of casts postoperatively, may be etiological factors in many nerve dysfunction cases that are erroneously attributed to regional anesthesia. The roles of epinephrine-induced neural ischemia, intrafascicular (intraneuronal) injections, and chemical injury due to local anesthetics themselves as anesthetic factors in nerve injury have also been considered.[84]

The types and severity of complications associated with ISB have been reviewed extensively. In a unique retrospective review conducted at the University of Washington Medical Center, 15 years worth of complications was

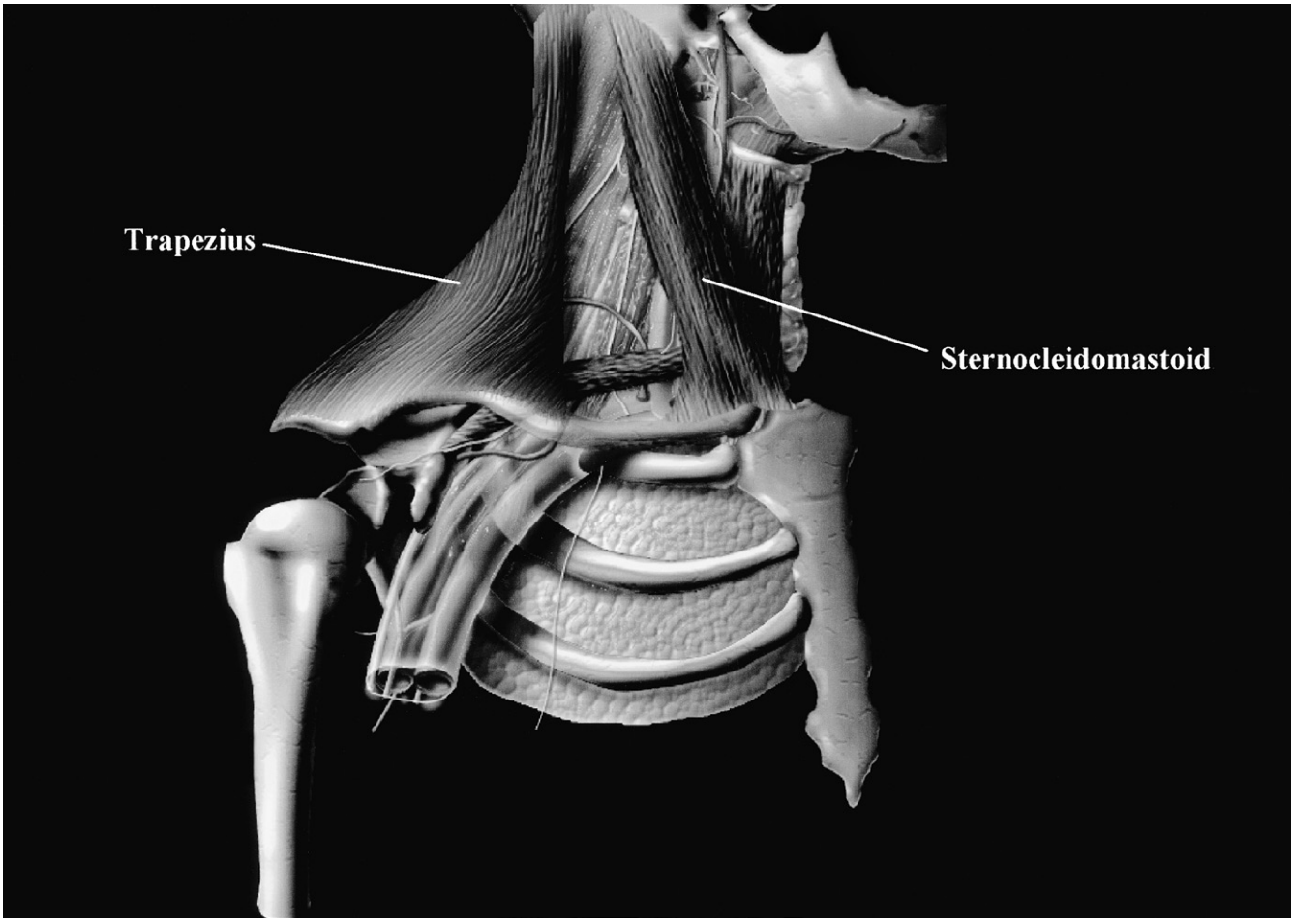

FIGURE 74-21 Major anatomic landmarks for the parascalene techniques of brachial plexus block, including the sternocleidomastoid muscle and midpoint of the clavicle, two important landmarks for Brown's "plumb-bob" technique.[46]

compared with the American Society of Anesthesiologists (ASA) closed claims data to compare their incidence with that published by the Society. Interestingly, the University review noted more peripheral neurologic complications (27) than were reviewed in the Closed Claims Project (20).[85] There have been case reports of quadriparesis (delayed presentation of central extension of the ISB),[86] severe brachial plexopathy after a US-guided ISB (in a patient with multiple sclerosis),[87] persistent hiccups after a failed attempt at an ISB,[88] acute neck cellulitis and mediastinitis after placment of a continuous catheter,[89] and superficial cervical plexus neuropathy (7.7% incidence in a series of 273 consecutive patients).[90] Neurologic complications have been a subject of significant interest in regional anesthesia. Liguori et al. showed that the incidence of postoperative neurologic symptoms (PONS) was equivalent in patients who underwent ISB with either PNS guidance or paresthesia techniques, but the authors used a large volume of local anesthetic rarely employed in most contemporary practices of regional anesthesia (up to 60 ml of 1.5% mepivacaine with epinephrine and bicarbonate).[91] Neurologic symptoms may range from nuisance symptoms to catastrophic and may occur following single-shot blocks or continuous catheter techniques. Faust et al. reported a patient who developed ipsilateral lower limb paresis following the replacement of continuous ISB catheter that entered the intervertebral foramen at C7-T1.[92] Candido and colleagues found that most neurologic sequelae following ISB are transient, lasting up to 16 weeks. Independent risk factors for the development of symptoms included paresthesias during needle placement and bruising at the needle insertion site.[93] In a large, retrospective review of 10 years worth of data wherein 32 studies met the metaanalysis criteria, Brull and associates found that neurologic complications of peripheral nerve blocks tended to be transient, versus those of central neuraxial blocks, which tend to persist. The relative incidences of transient neurologic complications associated with regional anesthesia were: 2.84% for ISB; 1.48% for axillary block; and lower extremity blocks associated with relatively lower rates.[94] It is entirely conceivable that US use will help explain the incidence of neuropathy following PNB. Bigeleisen et al. have suggested that stimulating currents are useful guides to determine neural engagement by block needles when US guidance is used for SCB, but found that the minimum stimulation threshold extraneurally is 0.6 mA compared to 0.3 mA intraneurally, with higher thresholds for both intra- and extra-neural injection occurring in diabetics.[95]

OUTCOMES

ISB may be compared to either general anesthesia in terms of outcome, or it may be compared to intra-articular local anesthetic injection (IAA). Additionally, US may be compared to PNS usage in terms of safety and efficacy.

When compared to IAA, continuous ISB was shown to provide superior analgesia to IAA via a subacromial catheter when both catheters were infused with 0.2% ropivacaine at 5 ml/hour after arthroscopic rotator cuff repair.[96] Following single injections, ISB provided superior analgesia to suprascapular nerve block and IAA when 0.25% bupivacaine was the local anesthetic administered to each of three groups of patients in a prospective, randomized fashion.[97] When catheters were used for ISB and IAA but were removed after performing a third, and final injection one hour after the completion of surgery, again the ISB treatment provided superior pain relief in the PACU compared with the IAA catheter, although there were no differences noted between groups at 24 hr. All patients received 0.5% bupivacaine with epinephrine prior to catheter removal.[98] Finally, during the first 12 hr after surgery, a continuous ISB using 0.2% ropivacaine proved superior, in terms of analgesia, to the analgesia provided to a group of patients receiving a continuous subacromial infusion of the same LA.[99]

For ambulatory surgery, ISB as a single shot or continuous infusion has been shown to provide superior pain relief for rotator cuff repair[100] and for total shoulder arthroplasty[101] than that provided by use of systemic opioids and adjuvant medications. For open shoulder surgery, it appears that 24 hr of continuous catheter PCRA infusion of ropivacaine 0.2% may provide optimal analgesia with diminishing returns past the first day of use.[102]

How does ISB or SCB compare to other PNBs of the upper extremity? In one study of 120 patients randomized to one of two groups, US-guided SCB using mepivacaine and ropivacaine was compared to infraclavicular nerve block (ICNB) using the same LA. The ICNB provided a more rapid onset of "surgical" block at 20 and 30 min following the block, but a poorer block of the axillary nerve, while the SCB group had a poorer block of the median and ulnar nerves.[103] However, another group of 120 patients randomized to receive US-guided blocks using either the SCB, ICNB or an axillary block (AXB) of the brachial plexus found no differences in success rates, total anesthesia-related times, and block-related pain scores.[104]

How does ISB performed using US compare with PNS-assisted blocks? This is clearly a function of which literature one ascribes to, but there evidence which is accruing that suggests a superiority of US guidance in terms of some, but not all parameters. For instance, one study of trainees performing single-injection, US-guided ISB under attending supervision stated a success rate of ISB of 97.3% that did not improve over the time assessed.[105] In contrast, a randomized trainee-based ISB catheter study has demonstrated a higher success rate and shorter procedural duration attributed to a technique employing US alone.[27]

Borgeat has stated that it would require many thousands of patients studied to demonstrate a superiority of US use to the high success rates demonstrated with PNS use alone.[106] Certainly few would argue that US guidance has a prominent role in ISB and SCB performance today. Several studies have shown a reduction in paresthesias when US was compared to landmark-based ISB,[107] a high degree of success regardless of evoked motor response above or below 0.5 mA,[108] an ability to be successful even if no stimulation is attained with a PNS,[109] an improved effectiveness during the first 24 hr when catheters are placed using this technology versus PNS placement,[102] and at least some major controversy when at least one study purported to demonstrate a success rate 8% higher with US (99%) versus PNS-assisted ISB (91%).[110] Other studies have suggested that, when US guidance is utilized for SCB, the use of a PNS is superfluous, although again, the success rates cited (88% with PNS; 90% US alone) were far below what most studies state as being the usual and customary success rates for each of these respective modalities.[111]

The use of US for regional anesthesia continues to evolve and mature. Both positive as well as negative studies provide evidence as to optimal approaches and optimal number of needle insertions for SCB.[112] Expert opinion, however, favors the use of US for regional anesthesia although there is no unequivocal evidence demonstrating benefits in terms of the incidence of nerve injury, local anesthetic toxicity, or the risk of pneumothorax for blocks performed above the clavicle.[113]

SUMMARY AND CONCLUSIONS

Consistent and reliable anesthesia of the upper extremity with either the interscalene or supraclavicular techniques of brachial plexus block can be performed with few complications. These techniques are easy to learn, and subsequently teach, in a busy clinical setting, and have a very high patient acceptance. A variety of approaches utilizing the elicitation of paresthesias, nerve stimulation, US guidance, or a combination have been described. Anatomically, any of these techniques can be expected to result in high success rates since a correctly-placed needle lies within the very narrow interscalene space. Alternatively, parascalene techniques advocate placing the needle across the interscalene space in its narrowest dimension. The slightest movement of the needle, therefore, may result in the needle exiting this space; hence a significant volume of local anesthetic could theoretically be deposited outside the intended fascial compartment. The interscalene block is carried out at the level of the brachial plexus roots, while the supraclavicular block is carried out at the level of the nerve trunks or divisions. The C8 and T1 nerve roots are frequently missed following interscalene block, which is not clinically significant if planned surgery is limited to the shoulder. The risk of pneumothorax (estimated to be 0.5% to 6%) is the most feared complication of the supraclavicular block. However, pneumothorax is unlikely when intended techniques are meticulously followed. Ultrasound guidance in the performance of brachial plexus blocks above the clavicle has emerged as a reliable means of localizing target nerves and may offer some advantages over traditional techniques.

KEY POINTS

- The C4 nerve root contributes to about two-thirds of brachial plexuses and shifts the plexus cephalad (prefixed plexus). The T2 nerve root contributes to about one-third of plexuses and shifts the plexus caudad (postfixed plexus).
- The minimum distances from the skin to the C6 vertebral foramen and to the spinal cord are 23 mm and 35 mm, respectively, implying that inserting a needle for interscalene brachial block to a depth of less than 25 mm may result in nerve root contact.
- The incidence of neural side effects such as Horner's syndrome and hoarseness appears to be greater with right- as compared to left-sided interscalene brachial block.
- The incidence of phrenic nerve block (and hence hemidiaphragmatic paralysis) occurs about one-half as frequently following supraclavicular block as it does following interscalene block.
- The needle trajectory in the original description of the "plumb-bob" technique of brachial plexus block has been demonstrated by an MRI study to contact the brachial plexus elements infrequently and may be improved by changing the angle of insertion to 45 degrees cephalad.
- Needle insertion in the intersternocleidomastoid technique of brachial plexus block through the anterior scalene muscle places the phrenic nerve in jeopardy of being directly contacted.
- Ultrasound guidance may be used for real-time needle guidance and confirmation of injectate spread during brachial plexus blocks above the clavicle and may offer advantages over traditional techniques.

ACKNOWLEDGMENTS

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Access the reference list online at http://www.expertconsult.com

CHAPTER 75

Brachial Plexus Blocks: Techniques Below the Clavicle

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ANATOMIC CONSIDERATIONS

Brachial plexus blocks below the clavicle involve blockade of the cords or peripheral nerves and include the infraclavicular block and axillary block approaches, which may be performed with peripheral nerve stimulation (PNS) or ultrasound (US)-guided, paresthesia-seeking, transarterial, and fascial click techniques. Recent developments in US-guided regional anesthesia now permit blockade of the brachial plexus transitions from the trunks to their respective anterior and posterior divisions, as they cross over the first rib (Fig. 75-1). As the plexus emerges from beneath the clavicle and crosses over the lateral aspect of the first rib the fibers from the anterior and posterior divisions recombine to form the three cords of the plexus (Fig. 75-2). The lateral cord is formed by the union of the anterior divisions of the superior and middle trunks; the medial cord is merely the continuation of the anterior division of the inferior trunk; and the posterior cord is composed of the posterior division of all three trunks. Thus, because of their derivation, the medial and lateral cords give rise to nerves that supply the flexor (volar or anterior) surface of the upper extremity whereas nerves arising from the posterior cord supply the extensor (dorsal) surface of the arm.[1]

Next, each of the three cords of the plexus gives rise to a branch that becomes one of the major nerves to the upper extremity, and then terminates as another major terminal nerve. The lateral and medial cords are the origins of the lateral and medial heads of the median nerve (C5–C8) (major terminal branch). The lateral cord continues on as the musculocutaneous nerve (C5–C7) (major terminal branch), whereas the medial cord continues on as the ulnar nerve (C7–T1) (major terminal branch). The posterior cord gives off the axillary nerve as its branch (C5–C6) (major terminal branch) and then continues on as the radial nerve (C5–T1) (major terminal branch).

The musculocutaneous nerve (C5–C7) is the major terminal branch of the lateral cord (Fig. 75-3). After the lateral cord gives off its contribution to the median nerve, the musculocutaneous nerve leaves the plexus and typically dives into the substance of the coracobrachialis muscle, but may also course in a fascial plane between the biceps brachii and coracobrachialis muscles. Then, it courses down the arm between the biceps and brachialis muscles, sending motor fibers to the powerful flexors of the forearm (Table 75-1). It terminates as the lateral antebrachial cutaneous nerve. Injury to the musculocutaneous nerve typically results in paralysis of the coracobrachialis, biceps, and brachialis muscles with resultant inability to flex the forearm. The musculocutaneous nerve has particular significance in axillary techniques of brachial plexus block that employ a peripheral nerve stimulator, where stimulation of this nerve and resultant flexion of the arm at the elbow often confuse the novice trainee into believing they are safely situated within the confines of the axillary perivascular sheath of the brachial plexus. In reality, the stimulating needle may either be in the coracobrachialis muscle or within the fascial compartment between the coracobrachialis and biceps brachii muscles, and injection of local anesthetic (LA) using this response as an endpoint inevitably results in a partial, or failed, block of the other three nerves within the axillary brachial plexus. Thus, the musculocutaneous nerve must be routinely blocked by a separate injection in either of these locations since the usual takeoff of the nerve is proximal enough that its fibers are not bathed by LA solutions administered at more distal levels in the perivascular sheath.

The median nerve consists of motor fibers originating primarily from C6–C8, with occasional contributions from C5 and T1 (Fig. 75-3). Sensory fibers originate from C6–C8.[1] The lateral cord contributes to the lateral head of the median nerve, which joins the medial head contributed by the medial cord. Thus, this nerve may be considered as a branch of both the cords derived from the anterior divisions. The two contributing divisions of the nerve, at their most cephalad point of origin, straddle the third part of the axillary artery before uniting on its ventral surface. The nerve then continues its course along the brachial artery into the forearm, where it ultimately divides into muscular and cutaneous branches in the hand. The median nerve provides motor branches to most of the flexor and pronator muscles of the forearm (Table 75-1). It also supplies all the superficial volar muscles except the flexor carpi ulnaris, and all of the deep volar muscles except the ulnar half of the flexor digitorum profundus. The motor branches in the hand supply the first two lumbricals and the thenar muscles that lie superficial to the tendon of the flexor pollicis longus. Sensory branches supply the skin of the palmar aspect of the thumb, the lateral two and a half fingers and the distal end of the dorsal aspect of the same fingers. Occasionally, the median nerve may encroach upon the sensory area normally innervated by the ulnar nerve, or that innervated by the radial nerve. Injury to the median nerve results in the so-called "ape hand deformity."

The medial brachial cutaneous nerve is derived from C8–T1. It is the second collateral derivation of the medial cord. It supplies the medial portion of the upper arm as far distally as the medial epicondyle. High in the axilla, part of this nerve forms a loop with the intercostobrachial nerve, with which it shares a reciprocal size and innervation area relationship. The medial antebrachial cutaneous nerve is also derived from C8–T1. It is another branch from the medial cord and arises just medial to the axillary artery. It passes down through the arm medial to the brachial artery to supply the skin over the entire medial aspect of the

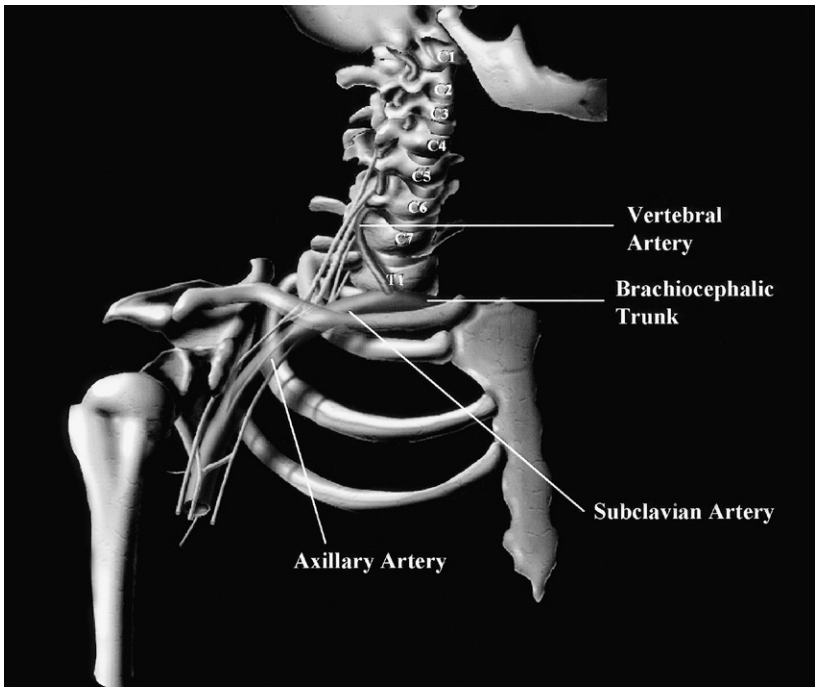

FIGURE 75-1 Relationship of the various elements of the brachial plexus to the bony skeleton. From roots, trunks, divisions, and cords to terminal nerves. Note the relatively isolated location of the divisions of the brachial plexus beneath the clavicle and above the first rib.

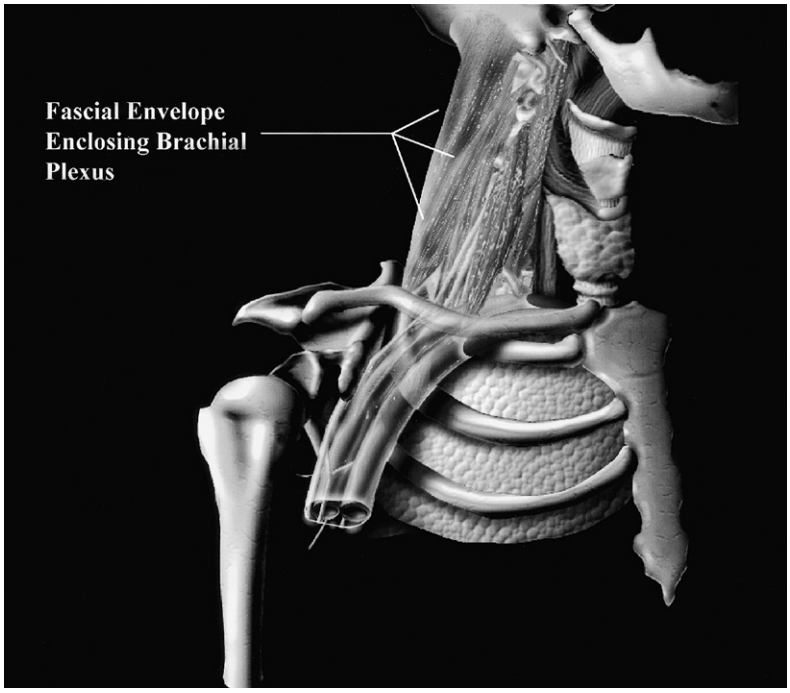

FIGURE 75-2 Anatomic dissection of the right side of the infraclavicular region demonstrating the derivation of the three cords of the brachial plexus.

forearm to the wrist. A segment of this nerve may also innervate the skin over the biceps muscle to the elbow.

The ulnar nerve is the major terminal branch of the medial cord (see Fig. 75-3). It arises from the medial cord after the medial head of the median nerve has branched off the cord at the lower border of the pectoralis minor muscle. It typically lies medial to the axillary artery at its origin and continues down the arm medial to the brachial artery, running parallel to and between the median and medial antebrachial cutaneous nerves. It passes distally through a groove on the medial head of the triceps and passes behind the medial epicondyle. It then passes down the medial aspect of the lower forearm into the hand. Motor branches in the forearm supply the flexor carpi ulnaris and the ulnar head of the flexor digitorum profundus (Table 75-1). In the hand motor branches supply all of the small muscles deep and medial to the long flexor tendon of the thumb except the first two lumbricals. There are no sensory branches in the forearm, but in the hand the skin of the fourth and fifth fingers and the medial half of the hand are usually supplied by the ulnar nerve. Ulnar nerve injury typically results in the deformity known as "clawhand."

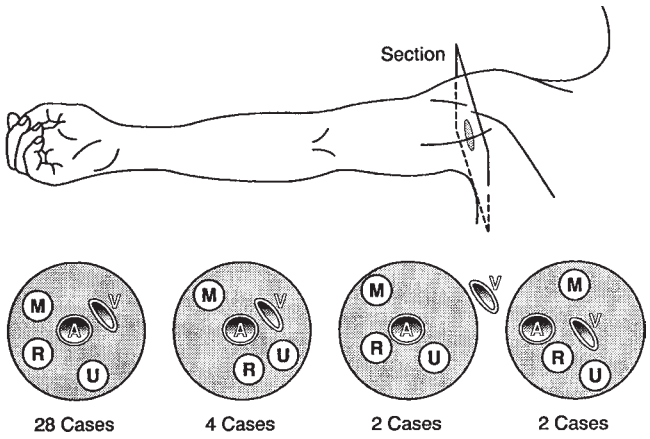

FIGURE 75-3 Anatomy of the brachial plexus. (From Hughes JJ, Desgrand DA: Upper limb blocks. In Wildsmith JAW, Armitage EN, editors: *Principles and practice of regional anesthesia*, ed 2, Edinburgh, 1993, Churchill Livingstone, p 169.)

The posterior cord gives off one major terminal branch, the axillary nerve, before continuing on as the radial nerve. The axillary nerve (C5–C6) leaves the plexus high in the axilla through the quadrilateral space bounded by the surgical neck of the humerus, the teres major and minor muscles, and the long head of the triceps. Its sensory fibers supply the skin overlying the lower two-thirds of the lateral and posterior deltoid, and its motor fibers supply the deltoid and teres minor muscles (Table 75-1). An articular branch supplies the inferior, lateral, and anterior structures of the shoulder joint. Injury to the axillary nerve results in an inability to abduct the arm. The radial nerve is the largest terminal branch of the entire plexus and is the terminal continuation of the posterior cord. It accompanies the profunda brachii artery as they course behind and around the humerus in the musculospiral groove. Recent studies using a combination of US and peripheral nerve stimulation indicate that the radial nerve is most often located posterior (dorsal) and medial to the axillary artery. Motor branches supply the triceps (the powerful extensor of the forearm), the anconeus, and the upper portion of the extensor-supinator group of muscles. The motor branches of the radial nerve that supply the triceps muscles are typically located more superficially in the axillary perivascular compartment, and are separated from the main trunk of the radial nerve by the ulnar nerve and in some patients, by the axillary artery. This anatomic location potentially affects the success of peripheral nerve stimulation–guided techniques, where acceptance of a proximal radial nerve–evoked motor response (EMR) (arm extension at the elbow) decreases the success of axillary blocks for hand and wrist surgery compared to more distal radial nerve–EMR (wrist extension). The major sensory branches include the dorsal antebrachial cutaneous nerve that innervates the posterior aspect of the forearm as far as the wrist, as well as the posterolateral aspect of the upper

TABLE 75–1 Motor Innervation of the Upper Extremity

Nerve	Muscle Group(s)	Function/Action
Axillary nerve (C5–C6)	Deltoid	Abducts arm; flexes and medially rotates arm (anterior fibers); extends and laterally rotates arm (posterior fibers)
Musculocutaneous nerve (C5–C6)	Teres minor	Rotates arm laterally, adduction
	Coracobrachialis	Flexes, adducts arm
	Biceps (long head)	Flexes arm and forearm
	Biceps (short head)	Supinates hand
	Brachialis	Flexes forearm
Radial nerve (C5–C8)	Triceps (long head)	Extends, adducts arm
	Triceps (lateral head)	Extends forearm
	Triceps (medial head)	Extends forearm
	Brachioradialis	Flexes forearm
	Extensor carpi radialis	Extends, abducts hand
	Extensor digiti	Extends fingers
	Extensor carpi ulnaris	Extends, adducts hand
	Supinator	Supinates forearm
	Abductor pollicis longus	Abducts, extends thumb
Median nerve (C6–T1)	Pronator teres	Pronates, flexes forearm
	Flexor carpi radialis	Flexes, abducts hand
	Palmaris longus	Flexes hand at wrist
	Flexor digitorum superficialis	Flexes hand, first, and second phalanges
	Flexor policis longus	Flexes hand, phalanges
	Pronator quadratus	Pronates forearm
Ulnar nerve (C8–T1)	Flexor carpi ulnaris	Flexes, adducts hand
	Flexor digitorum profundus	Flexes phalanges, hand at wrist
	Intrinsic hand muscles	Flex, extend, abduct, adduct phalanges

Source: Adapted from Neal J, Hebl J, Gerancher J, et al: Brachial plexus anesthesia: essentials of our current understanding. Reg Anesth Pain Med *27:402–428, 2002.*

arm. Branches to the hand innervate the dorsal aspect of the lateral hand, including the first two and a half fingers as far as the distal interphalangeal joint. Injury of the radial nerve results in "wrist drop."

As axillary and infraclavicular blocks of the brachial plexus block the sympathetic nerves to the arm and hand, recall that a dual system of innervation exists for the upper arm. Postganglionic sympathetic fibers are distributed distally via the somatic nerves of the plexus to the peripheral vessels. About 23% of fibers in a peripheral nerve are sympathetic postganglionic axons, where they are bundled together by Schwann cells.[2] Efferent sympathetic fibers supplying a cutaneous region do not necessarily arrive via the same pathway as the sensory afferents supplying that same area. The proximal sympathetics arise directly from the cervical sympathetic chain, particularly from the middle and inferior cervical sympathetic ganglia. The postganglionic sympathetic fibers pass directly to the subclavian artery and are conveyed in a plexiform manner along the outer coat of the vessel and subsequently into the axillary artery. Whereas the proximal innervation is the mechanism of sympathetic supply to the proximal third of the arm, distal innervation through the sympathetic fibers traveling with the somatic nerves of the brachial plexus control the constrictor impulses to the resistance vessels in the extremity. Blockade of the brachial plexus, then, results in complete blockade of the vasoconstrictor fibers to the capacitance vessels (i.e., the veins), which allows blood to pool peripherally in the arm.

A study showed that there is an increase in skin temperature of the hand by 1.5° C after axillary block, accompanied by an increase in skin blood flow of 73% as determined by laser Doppler flowmetry.[3] Thomas et al.[4] demonstrated that axillary block increased upper limb blood flow by 23% and increased transcutaneous PO_2 from 41 to 54 mmHg in room air. This suggested that the blood flow increase was not all through shunts. Sympathetic block, however, dramatically increased the transcutaneous PO_2 in hyperbaric oxygen, presumably by prevention of vasoconstriction during hyperoxia. A study using strain gauge plethysmography demonstrated that axillary block increased blood flow to the hand by 296% compared with 132% produced by stellate ganglion block.[5] Smaller flow changes were noted in the forearm and no changes were noted in the venous capacitance vessels. Using a simple infrared thermometer in a group of 30 consecutive patients undergoing upper limb surgery under infraclavicular brachial plexus block, it was found that a temperature increase of 1° C at 5 and 10 min corresponded to successful block of the nerve evaluated. When temperature change occurred in all four nerves (musculocuteneous, radial, ulnar, median) at 5 and 10 min, the block was invariably successful at 30 min.[6]

The subclavian artery becomes the axillary artery beneath the clavicle at the lateral border of the first rib (Figs. 75-1 and 75-4). The axillary artery lies central to the three cords of the infraclavicular brachial plexus (medial, lateral, and posterior). The cords are not truly medial, lateral, and posterior with respect to their positions around the axillary artery until they have passed beneath the pectoralis minor muscle just medial to the medial border of the coracoid process. If the topographic anatomic description is viewed from a clinically relevant (parasagittal) point of view in relation to the axillary artery (as they are encountered when performing an infraclavicular block), the posterior cord lies in between the lateral and medial cords. The lateral cord is the most superficially located cord and is typically located superior to the axillary artery. Just deep to the lateral cord is the posterior cord, which is typically located slightly cephalad and deep to the axillary artery. The medial cord is typically located deep and slightly caudal to the axillary artery.

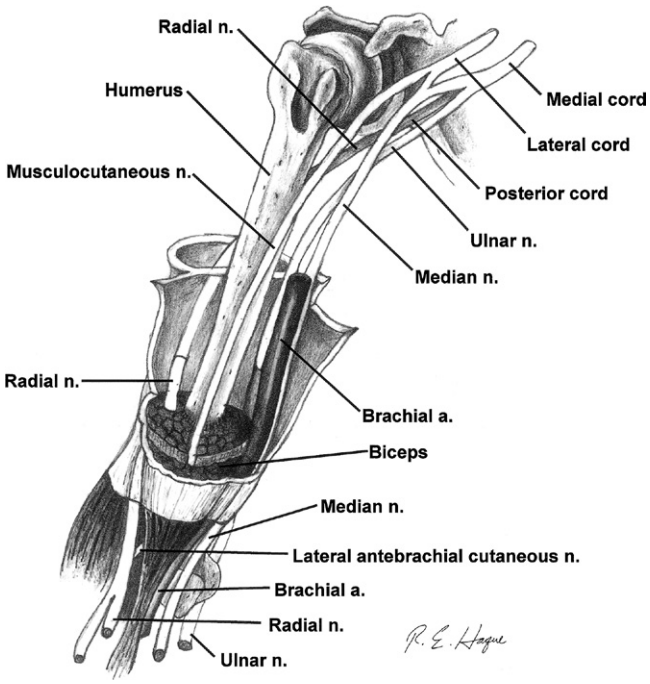

FIGURE 75-4 Evolution of the axillary artery from the subclavian artery. Note the relationship of the arteries to the clavicle and the lateral border of the first rib.

In summary, the contents of the proximal axillary perivascular space are enclosed by two muscles (the biceps brachii and coracobrachialis), and the humeral insertions (the conjoint tendon) of the latissimus dorsi and teres major muscles. These structures surround and envelop two vessels (the axillary vein and artery) and three nerves (median, radial, and ulnar). The axillary sheath, a collection of connective tissue surrounding the neurovascular structures, is a continuation of the prevertebral fascia that separates the anterior and middle scalene muscles (Fig. 75-5). DeJong[7] demonstrated that the axillary perivascular sheath of cadavers accommodated a volume of 42 ml to extend circumferentially to the three major nerves of the axillary brachial plexus as well as to spread proximally high enough to reach the musculocutaneous nerve. This concept has implications for determining the appropriate volume of LA to inject for both axillary, as well as for infraclavicular blocks of the brachial plexus. Within the neurovascular space, the usual relationship of the structures has the axillary vein medial, the median nerve superior, the ulnar nerve anterior and inferior, and the radial nerve inferior and posterior to the axillary artery.

The concept of a "sheath" has not been embraced by all anatomists, however. When US was used in 28 adult

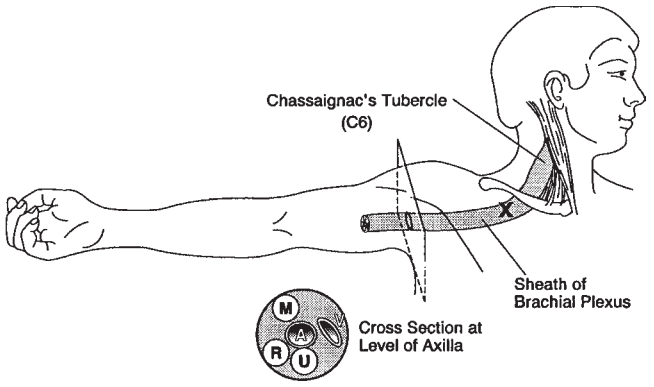

FIGURE 75-5 Derivation of the axillary perivascular sheath. The sheath is derived from the prevertebral fascia of the cervical vertebrae, and extends from the interscalene space to the level of the distal axilla. It may be entered at any level to provide brachial plexus anesthesia using single-injection techniques.

subjects during the performance of infraclavicular block, septae were identified in four or six patients where unilateral LA spread was found. Septae were not observed in 22 patients with unrestricted LA spread after the initial injection.[8] It is likely that each individual nerve has its own "sheath," which may explain the noted failure of single-injection techniques to reliably block all the peripheral components of the brachial plexus when using the infraclavicular or axillary approaches. A cadaver study that utilized 10, 20, and 40 ml of methylene blue injected sequentially into the compartments of the axillary compartment resulted in the finding that septae from the deep surface of the axillary sheath form compartments for each individual nerve. The authors suggested that these septae function as barriers under physiologic conditions.[9]

In contrast, other investigators have emphatically stated that a "sheath" of the brachial plexus does not exist. Cornish et al.[10] used CT-scan axial tomographic dye studies of the axillary brachial plexus and noted that the brachial plexus lies in a tissue plane closely surrounded by the clavicle, scapula, chest wall, and humerus. They suggested that LA injected close to a nerve will travel using the path of least resistance, along a tissue plane, in both directions from the point of injection. A second such study by the same authors was conducted in 10 volunteers with functioning supraclavicular catheters in place. An MRI study in the infraclavicular region just medial to the coracoid process in 20 volunteers demonstrated that the three cords of the brachial plexus were all positioned within 2 cm from the axillary artery approximately within two-thirds of a circle, between the 3 and 11 o'clock position.[11] Using an MRI to evaluate the depth of the brachial plexus in the infraclavicular region, Cornish and associates[12] stated that the plexus, in 21 volunteers used for the study, was found directly inferior to the lateral third of the clavicle, being most often identified exactly 1 cm medial to the coracoid process at a horizontal distance from the skin to the plexus ranging from 2.92 to 5.57 cm. Using an MRI recommendation for needle placement for infraclavicular block (ICB), however, resulted in a high failure rate in the clinical setting. For 160 patients, ICB was performed using the lateral sagittal infraclavicular block technique determined by MRI to place the needle at the epicenter of the cords. This resulted in only a 91% success rate as defined by the presence of blockade of five nerves at 30 min from injection. The authors did note a relatively low incidence of axillary vessel puncture (2%), but otherwise this technique does not appear to offer any benefits over conventional US-guided blocks.[13]

There are multiple variations in the distribution of the three nerves in the inferior segment of the axillary artery. If one conceptualizes the axilla to be divided into 12 sectors of a clock face with the axillary artery at its epicenter (Fig. 75-6), the nerve distribution around it may be somewhat variable.[14] Typically, the median nerve is located superficial and lateral to the axillary artery (between 10 and 11 o'clock), the ulnar nerve is located superficial and medial (between 1 and 2 o'clock), the radial nerve is located deep and medial (between 4 and 6 o'clock), and the musculocutaneous nerve is located (between 8 and 10 o'clock) at an average distance of 1.03 cm lateral to the axillary artery.[15]

AXILLARY APPROACH OF BRACHIAL PLEXUS BLOCK

The authors perform axillary brachial plexus block for surgery of the arm at or below the elbow, including the wrist and hand. The block is also useful for manipulating fractures in adults and pediatric patients.[16] While single-injection axillary block has been shown not to reduce pain at home on postoperative days 1 up to 14 days when compared to general anesthetics, it does reduce nausea and result in faster hospital discharge.[17] Using 20 ml of 2% lidocaine with epinephrine, O'Donnell et al.[18] showed 100% success rates for US-guided block of the axillary brachial plexus, reducing the time to discharge, and bypassing the PACU compared to general anesthesia.

PATIENT AND ARM POSITION FOR AXILLARY BLOCK

The same noninvasive monitoring and safe precautions apply when performing these blocks. The patient lies supine with the arm abducted to approximately 90 degrees and externally rotated to permit the dorsum of the hand to lie flat on the gurney while supported on one or two pillows. The forearm is flexed approximately 90 degrees at the elbow and should be parallel to the long axis of the patient's body. In a prospective, randomized double-blind study, Ababou et al.[19] demonstrated that arm abduction maintained after performance of an axillary block with a triple peripheral nerve stimulation technique resulted in both a shorter onset time to complete the block as well as a prolongation of sensory and motor block, compared to immediately adducting the blocked extremity.

Hyperabduction of the arm beyond 90 degrees is avoided since it tends to obliterate the axillary arterial pulse, a critical landmark in the successful performance of the technique. It has been shown that hyperabduction obliterated the pulse in 83% of individuals.[1] Hyperabduction causes stretching, torsion, and pinching of the subclavian–axillary vessels and the brachial plexus at three distinct locations: where the subclavian vessels and plexus trunks pass between the clavicle

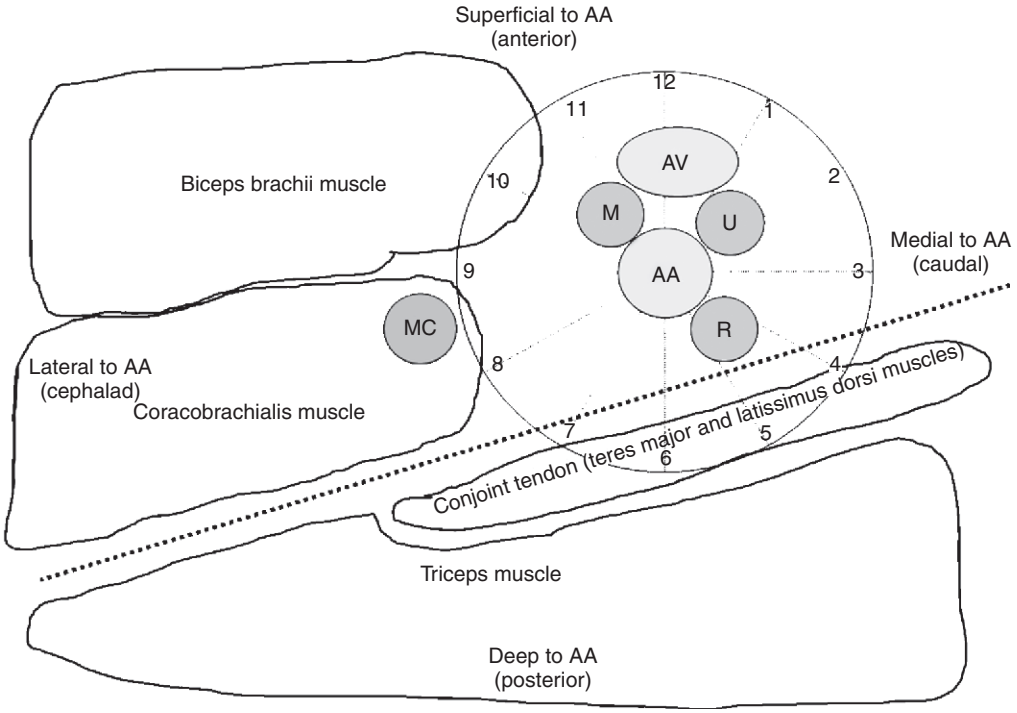

FIGURE 75-6 The topographic anatomic arrangement of the axillary brachial plexus. Note the median, ulnar, and radial nerves surrounding the axillary artery. The radial nerve is deep to the axillary artery and just superficial to the conjoint tendon. The median and ulnar nerves are superficial to the axillary artery. The musculocutaneous nerve is lateral (cephalad) to the axillary artery and typically located within the body of the coracobrachialis muscle.

and first rib, at the point where the cords and vessels pass around the tendinous insertion of the pectoralis minor muscle to the coracoid process, and at the level where both vessels and plexus pass around the head of the hyperabducted humerus.[1] After the axillary arterial pulse has been identified, it is traced proximally as far beneath the pectoralis major muscle as possible, using the index finger of the left hand (for right-sided axillary block), or of the right hand (for left-sided axillary block). A Doppler probe or US may be used to appreciate adequately the pulse in those who are obese or who have poorly palpable peripheral pulses. Reducing the degree of abduction sometimes makes palpation of the pulse easier as one proceeds more proximally. It is important to attempt to trace the pulse as proximally as possible, since injection of LA above the level of the head of the humerus tends to favor cephalad spread of the LA and tends to promote blockade of the nerves (i.e., musculocutaneous and axillary) that leave the plexus high in the axilla. While maintaining continual palpation of the pulse, the opposite hand guides a short-beveled, 22-gauge, 1.5- to 2-inch needle toward the maximally appreciated pulse, superior and tangential to it. For transarterial and peripheral nerve stimulation-guided techniques, the needle should be directed along the long axis of the humerus, and should not be directed perpendicularly, since it will then be crossing the axillary perivascular space in its shortest dimension (i.e., will "bisect" it). The chances for successfully blocking all three major nerves at this level (median, ulnar, radial) are increased by guiding the needle into the perivascular space in the same orientation as the direction of the artery itself.

TRANSARTERIAL TECHNIQUES

The transarterial technique relies on the close anatomic relationship of the terminal nerves to the axillary artery in order to place the needle within the neurovascular sheath. In a case series of 100 consecutive patients, Cockings et al.[20] reported that the transarterial technique was associated with a 99% success rate for axillary brachial plexus block, but other investigators have subsequently reported lower success rates (60% to 90% successful block for each individual nerve).[21] In one retrospective and one prospective study, the transarterial technique was associated with 88% and 94% success rates, respectively.[22,23]

In this technique, the axillary artery is transfixed between the index and middle fingers of the palpating hand, and the artery is intentionally entered using the short-beveled needle. As the needle is advanced, aspiration of bright red blood indicates that the anterior (superficial) wall of the artery has been entered, and the needle should then be advanced through the posterior (deep) arterial wall. Digital pressure applied over the artery should then be released, and the artery is reentered by withdrawing the needle to verify its placement. It is then passed once again through the posterior wall of the artery while maintaining continual aspiration. When continual aspiration ceases to reveal bright red blood, but only a "wisp" of blood, it indicates that the needle has once again passed through the posterior wall of the artery, and it is acceptable to incrementally inject the entire contents of the syringe (typically 40–50 ml) into the perivascular space. Alternatively, half the contents of

the syringe may be injected posteriorly, and the other half anterior to the artery after withdrawing the needle tip back toward the skin.

MULTIPLE INJECTION TECHNIQUES IN THE TRANSARTERIAL APPROACH

Hickey et al.[24] found no overall difference in success rates between single and multiple transarterial injection techniques; however, there was a lower incidence of blockade and a longer latency of median nerve anesthesia in the group receiving a single injection of LA behind the artery. Some have found lower overall success rates (for the single injection technique posterior to the artery), however, when criteria are standardized to include blockade of three or four peripheral nerves of the forearm or hand. When compared to the so-called "fascial click" technique of identifying correct needle placement in the axillary perivascular space, the transarterial approach provided a similar (and low) rate of successful blockade of all four peripheral nerves of the forearm using a single injection.[25] In that study, there was only a 48% successful blocking of all four nerves with the transarterial approach, versus 59% with the single-injection fascial click or paresthesia technique.

Goldberg et al.[26] compared the two-injection transarterial technique to a single-injection paresthesia or single-injection nerve stimulator-guided technique. These techniques resulted in 79%, 80%, and 70% success rates, respectively. There was no statistically significant difference in the number of unblocked nerves among the three approaches. These results were subsequently confirmed by Pere et al.,[27] who compared two-injection transarterial techniques to a single-injection nerve stimulator approach. There was greater spread of contrast media using the transarterial method, as well as better circumferential spread and greater distal and proximal spread within the sheath. However, the spread of contrast did not correlate with block success.

In two studies by Koscielniak-Nielsen et al.[28,29] a two-injection transarterial technique was compared with the four-nerve, peripheral-nerve stimulation technique. In both their studies, the four-nerve method resulted in a higher success rate of complete surgical anesthesia of the forearm (88%, 94%) versus the transarterial, two-injection method (62%, 64%). They also found a shorter latency of onset with the four-nerve stimulator technique but a shorter time to perform the block using the transarterial technique. Since the latency to onset was shorter with the four-nerve stimulating technique, the longer time to perform the block was deemed inconsequential.

PERIPHERAL NERVE STIMULATION TECHNIQUES

The advantages cited with using a peripheral nerve stimulator include a high success rate, the ability to perform the block on sedated or uncooperative patients, the avoidance of paresthesias and the potential for neurologic injury, and the avoidance of arterial puncture and subsequent vascular insufficiency or hematoma formation.[26–30] It has been suggested that the use of the nerve stimulator avoids altogether the possibility of neuropathy from nerve trauma.[31,32] This may not be true, as demonstrated by Choyce et al.[33] They used noninsulated needles and intentionally sought paresthesias. Once obtained, they turned on a peripheral nerve stimulator to obtain an evoked motor response (EMR). In 25% of patients a current of more than 0.5 mA was required to manifest a motor response while 42% required currents of 0.75 to 3.3 mA. The site of the original paresthesia was concordant to the EMR in 81% of patients. This implies that a nerve stimulator response may not exclude neural injury from the unintentional contact of the needle to the nerve.

The use of noninsulated needles by Choyce et al.,[33] however, may be questioned since Ford et al.[34] demonstrated that the use of insulated needles resulted in more precise localization of the needle tip than does use of noninsulated ones. In one randomized, prospective analysis comparing the efficacy and safety of various techniques of axillary block including transarterial, single paresthesia, or nerve stimulator, Goldberg et al.[26] failed to encounter a single case of postoperative neural injury among the three groups. The total number of patients was small (59), so the validity of the results needs to be interpreted cautiously. Fortunately, axillary block may not be associated with as high an incidence of neural injury as other approaches to the brachial plexus. Indeed, Fanelli et al.[35] reported a higher incidence of neural complications (4% vs. 1%) in the interscalene technique versus the axillary approach when both techniques are performed using the peripheral nerve stimulator. In that report complete recovery of neurologic function occurred in all patients within 3 months (range 4 to 12 weeks).

In our technique, the 22-gauge, insulated stimulating needle is connected by a sterile extension tubing set ("immobile needle") to a 20- or 30-ml syringe loaded with LA. Although it has been suggested that a properly placed needle will pulsate, this sign cannot be taken as definitive evidence that the needle is correctly seated. A nerve stimulator response is sought with a current of less than 0.4 mA in the distributions of the median, radial, or ulnar nerves. Riegler,[36] in a retrospective review, suggested that the predominant response elicited by the nerve stimulator during axillary block is finger motion (61% of cases) and wrist movement (flexion, extension, or deviation) (35% of cases). Stimulation of the median nerve, typically located at the superior border of the artery, results in an EMR characterized by pronation of the arm, wrist flexion, finger adduction, flexion of the lateral two fingers, and thumb opposition. Stimulation of the main trunk of the radial nerve, typically located inferior and posterior to the artery, results in wrist extension, supination of the arm, metacarpophalangeal extension, and thumb abduction. In our experience, stimulation of the ulnar nerve is rarely encountered using the nerve stimulator technique. The ulnar nerve is typically situated inferior and anterior to the artery, and its stimulation results in deviation of the wrist in an ulnar or medial direction, metacarpophalangeal flexion, and thumb adduction.

EVOKED MOTOR RESPONSE PATTERNS WITH PERIPHERAL NERVE STIMULATION

It is generally accepted that multiple-injection (EMR) techniques result in increased block success rates compared to single-injection (EMR) techniques for axillary

block. Inberg et al.[37] stated that the success rate of single-injection techniques is much lower than two-injection techniques. Gaertner et al.[38] concurred that a three-nerve injection technique of axillary block was more efficacious than single-injection techniques. Coventry et al.[39] showed a 97% rate of complete anesthesia of all peripheral nerves of the forearm and hand when a three-nerve electrical stimulation technique was used. They stimulated the musculocutaneous, median, and radial nerves. However, there was only a 53% block success rate when only the musculocutaneous and median nerves were electrically stimulated in the same study. Kosceilniak-Nielsen et al.[40] similarly demonstrated improved success, reduced latency, and shortened time to readiness for surgery when comparing three-nerve stimulation versus one-nerve stimulation axillary blocks, even though the three-nerve technique took longer to perform. A meta-analysis using the Cochrane Central Registery of Controlled Trials was undertaken to evaluate the benefit of multiple stimulation for axillary block performance.[41] Twelve trials, including 981 participants, were reviewed. The multiple injection techniques provided decreased primary anesthesia failure, and incomplete motor block, at the expense of increased time to perform the blocks. A more recent investigation compared the efficacy of axillary block for hand surgery when a standard triple-injection technique (EMR with radial, median, and musculocutaneous nerves) was compared to a "selective" single- or double-injection (EMR) technique in the specific distribution of the planned surgery.[42] The selective injection technique had a lower success rate, higher degree of tourniquet pain, and higher intraoperative requirement for sedation and parenteral analgesia administration than did the triple-injection technique. Thus, the triple-injection technique seems preferable to a more selective approach (with fewer injections) even when a limited number of nerves is involved in the surgical field.

When mutiple EMR are utilized, it appears that the specific patterns of EMR play a key role in axillary block success rates. Rodriguez and colleagues[43] noted that radial plus musculocutaneous nerve stimulation produced more extensive anesthesia of the upper limb than did ulnar plus musculocutaneous nerve stimulation in a group of 60 patients randomized to receive the stimulations as described above. However, Rodriguez et al.[44] showed that compared with triple-nerve stimulation, accepting radial plus musculocutaneous nerve stimulation was inferior to radial, median, and musculocutaneous nerve stimulation in terms of ultimate anesthesia and requirement for supplemental block.[44] Other investigators suggest that it is the specific nerve(s) sought, and not particularly the number of nerves stimulated, that influences latency and success. Lavoie et al.[45] found that four- or two-nerve stimulation techniques were equally successful, as long as one of the two nerves being sought in the latter technique was the musculocutanoues nerve. Sia et al.[46] noted that four- and three-nerve stimulation techniques (without searching for ulnar nerve stimulation) were virtually identical in overall success rates (92% vs. 90%). These same investigators noted that during triple-injection axillary block, radial nerve stimulation was superior to ulnar nerve stimulation in terms of latency of onset of block and ultimate efficacy (91% vs. 73%) of complete block.[47] As previous discussed, a distal radial nerve response during triple stimulation is superior to a proximal radial response in terms of success, although obtaining a distal response is associated with a significantly longer duration of time to complete the block. Thus, it is appears that musculocutaneous nerve and radial nerve stimulation play predominant roles in the success of axillary block, although triple-nerve stimulation is still required to produce complete anesthesia of the upper limb. Additionally, since the four-nerve stimulation technique required significantly longer time to perform, the data suggest that it is unnecessary to seek deliberate stimulation of the ulnar nerve.

In summary, multiple-stimulation EMR have increased success compared to single-stimulation EMR techniques, but are more complex and take more time, but are balanced by decreased latency. There appears to be no clinically significant advantage to quadruple EMRs (since the ulnar EMR is the least important) compared to a triple-EMR technique. Thus, a triple-EMR with the distal radial EMR (deep to the axillary artery), the median EMR (superficial to the axillary artery) (in close proximity to the ulnar nerve), followed by specifically targeting the musculocutaneous EMR (within that separate anatomic location from the other three nerves) provides the optimal balance between efficacy and efficiency.

PARESTHESIA AND FASCIAL CLICK TECHNIQUE

Paresthesia elicitation may be associated with neural injury, but there is some controversy regarding this issue. Axonal degeneration and a damaged blood-nerve barrier are inconsistent or absent after needle-tip penetration without injection,[48] or even with the intrafascicular injection of saline.[49,50] The elicitation of paresthesias during axillary plexus block is probably of minimal consequence as long as LA is not injected intrafascicularly, although the clinical data are contradictory.[50,51] Although the intentional elicitation of a paresthesia may represent direct needle trauma and theoretically may increase the risk of neurologic injury, there are no prospective, randomized clinical studies that are able to definitely support or refute these claims.[23,50–54] Selander and colleagues[52] performed one of the early prospective investigations examining the role of paresthesias and nerve injury. They reported a higher incidence of postoperative neurologic complications in patients where a paresthesia was intentionally sought during axillary blockade (2.8%) compared to those undergoing a perivascular technique (0.8%). While the difference was not found to be statistically significant, it bears mentioning that unintentional paresthesias were elicited and injected upon in patients within the perivascular group who experienced postoperative nerve injury. Overall, 40% of patients within the perivascular group reported unintentional paresthesias during performance of the procedure, demonstrating the difficulty of standardizing the technique and analysis of nerve injury. Additionally, a fascial "pop" technique has also been associated with less pain during performance of axillary block compared with PNS use, in a group of 100 patients undergoing upper limb surgery following trauma to the arm. Lastly, Sia et al.[47] noted that their four-nerve axillary technique resulted in significantly shorter time to perform the block,

as well as shorter latency to onset and time to readiness for surgery, than did a multiple paresthesia technique. Complete surgical anesthesia was also more likely (91%) with the nerve stimulator technique than for the multiple paresthesia technique (76%).

ULTRASOUND-GUIDED AXILLARY BLOCK TECHNIQUE

The patient and arm position for US-guided axillary block is similar to that for the peripheral nerve stimulation technique. A high-frequency linear array transducer (3–12 MHz) with a 38- to 50-mm footprint is typically placed within the proximal axilla perpendicular to the long axis of the arm, with lateral side of the transducer oriented cephalad (Fig. 75-7). This placement and orientation will provide a cross-sectional (short-axis) view of the axillary artery, the four terminal nerves, and the surrounding perineural musculature (conjoint tendon and biceps, coracobrachialis, and triceps muscles). The optimal US image will demonstrate the round, pulsatile, and non compressible hypoechoic (will appear dark on the US screen) axillary artery surrounded by the hyperechoic (will appear brighter) median, ulnar, and radial nerves (Fig. 75-8). Decreased pressure on the transducer will typically demonstrate the easily compressible axillary vein(s) located superficial to the axillary artery. The terminal nerves will display a "honeycomb" appearance, representative of the polyfascicular architecture of the brachial plexus nerves below the clavicle. Subtle movements of the transducer (tilting or proximal-to-distal translation) will result in optimal imaging of the musculocutaneous nerve located either in the coracobrachialis muscle or in fascial plane between the biceps and coracobrachialis muscles.

The typical topographic appearance of the terminal nerves in relation to the axillary artery is as follows (Fig. 75-6): the median nerve is located superficial and lateral (between the 10 and 11 o'clock position); the ulnar nerve is located superficial and medial (between 1 and 3 o'clock position); the radial nerve is located deep to the ulnar nerve and axillary artery (between the 3 and 6 o'clock position) and often lies directly over the conjoint tendon, which appears as an obliquely oriented hyperechoic fascial plane located superficial to the teres major and triceps muscles. Although this is the most common sonographic pattern of the axillary brachial plexus, considerable invididual anatomic variations may occur.

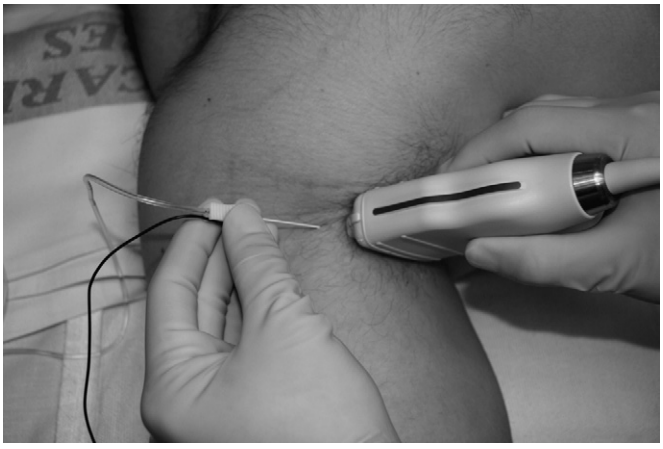

FIGURE 75-7 Illustration of the typical ultrasound transducer and needle placement for an ultrasound-guided axillary block utilizing a short-axis-in-plane technique. The transducer is positioned perpendicular to the long axis of the arm and the block needle is inserted superior (lateral) to the transducer and advanced within the plane of the ultrasound beam.

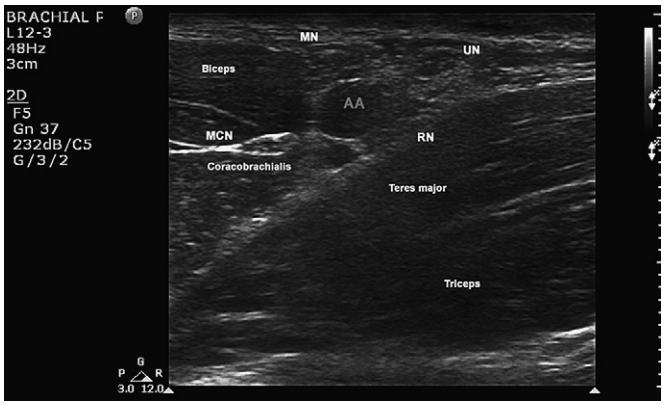

FIGURE 75-8 Ultrasound image demonstrating the typical hyperechoic polyfasicular appearance (honeycomb) of the terminal nerves of the brachial plexus in the axilla. The median, ulnar, and radial nerves are closely related to the axillary artery, while the musculocutaneous nerve is located in between the biceps brachii and coracobrachialis muscles.

We typically utilize an "in-plane" needle approach, where the needle is initially inserted 1 to 2 cm away from the cephalad side of the transducer. A 21-gauge, 100-mm needle (attached to a 20–30 ml syringe via sterile tubing) is advanced from a cephalad to caudad direction (which will translate into a lateral to medial needle direction on the US screen). Given its clincal importance and relatively deeper location, the radial nerve is typically targeted initially by advancing the needle tip deep to the axillary artery, just above the conjoint tendon-triceps muscle. Local anesthetic (10–12 ml) is incrementally injected and a hypoechoic distribution should be seen below the artery and encircling the radial and ulnar nerves. Next, the needle is withdrawn to just below the skin and advanced in a lateral to medial direction toward the median and ulnar nerves located superficial to the axillary artery. The needle then is withdrawn to just below the skin and advanced toward the location of the musculocutaneous nerve. Given the more cephalad (lateral) location of the musculocutaneous nerve, the transducer may require a slight relocation more cephalad over the biceps muscle. The goal for the US-guided technique is complete circumferential spread of LA around the individual nerves ("donut sign"). Although a single needle insertion site is often adequate, the described US technique is by definition a "moving needle multiple-injection" technique not dissimilar to a multiple EMR peripheral nerve stimulation technique.

US use has enhanced the success rate of multiple nerve injection techniques of axillary block. A study of 46 patients undergoing forearm or hand surgery revealed 100% success of blocking four nerves (utilizing an average of 7–10 ml of LA) when US was used, with an average time to perform the block being 5 min and onset of surgical anesthesia within 20 min.[55] Compared to the

transarterial technique, US use in 56 patients undergoing axillary block was shown to reduce time to perform the block (11.1 vs. 7.9 min), but there was no difference in complete sensory or motor block between groups at 30 min. In a large retrospective review, Lo et al.[56] noted that US alone (572 patients), without supplemental verification by PNS use, resulted in improved complete block success rates, reduction in LA volume used, and reduced time to perform the axillary block compared to either transarterial (71 patients) or triple peripheral stimulation (53 patients) techniques.

When US was used to identify the respective neural elements, and then patients were queried as to the presence of paresthesias, or peripheral nerve stimulation use was implemented to assess for EMR, it was found that paresthesias were 38.2% sensitive and PNS use 74.5% sensitive for detection of needle-nerve contact, implying that neither paresthesia or peripheral nerve stimulation was a sensitive indicator of needle tip to nerve proximity.[57] In patients undergoing hand surgery with the radial, median, and ulnar nerves localized with either US or peripheral nerve stimulation techniques, US increased the success rate of complete sensory block and surgical anesthesia, as well as decreased block procedure time compared to peripheral nerve stimulation.[58] In contrast, when axillary block was performed targeting all four nerves separately with either US or peripheral nerve stimulation by experts in both techniques, there was no difference in success rate. However, a secondary finding in this same study demonstrated significantly fewer patients with procedure-related pain with US guidance.[59] A more recent study directly comparing a triple-EMR peripheral stimulation technique to an US-guided multi-injection technique also demonstrated that US is associated with significantly less procedure-related discomfort.[60]

One of the potential benefits of US-guided techniques is a decrease in the minimum effective LA volume for axillary brachial plexus block. O'Donnell et al.[61] demonstrated that very small doses of lidocaine produce successful axillary block when US is used. These authors were able to show that as little as 1 ml per nerve of lidocaine 2% resulted in successful axillary nerve block in a group of five consecutive patients. While use of this exceptionally small volume may appear to be a lofty goal in clinical practice, Marhofer et al.[62] demonstrated that the success rate of axillary block using 4 ml compared to 14.8 ml of mepivacaine 1% was 90% versus 100%, respectively. However, the onset time to complete block was 25.0 min versus 15.8 min, and the duration of sensory block using the small volume averaged 125 min, versus 152 min in the larger volume group.[62] In a small pilot study, Harper et al.[63] showed that it is possible, using US, to surround each nerve of the axillary brachial plexus using LA volumes as low as 2 to 4 ml per nerve.

US may also potentially decrease the incidence of complications associated with peripheral nerve blocks. In a retrospective survey of 5436 consecutive patients undergoing single-injection peripheral nerve blocks (interscalene, axillary, femoral, and sciatic), 3290 were performed with peripheral nerve stimulation alone versus 2146 performed with combined US guidance–peripheral nerve stimulation. There were eight adverse outcomes among patients having nerve blocks guided by peripheral nerve stimulation alone (five seizures and three nerve injuries) compared to none in the combined group. When comparing the incidence of seizures in the 2301 brachial plexus blocks between the two techniques, the associated risk of seizures was statistically higher in the peripheral nerve stimulation only group.[64] Despite the findings of this large retrospective survey, there is not yet enough data to state that US guidance decreases the incidence of severe complications.

LOCAL ANESTHETICS AND ANALGESIC ADJUNCTS

Local anesthetics used for infraclavicular approaches, including axillary approach, demonstrate slower peak and lower peak plasma concentrations than when equivalent doses of ropivacaine are used for supraclavicular blocks. Following axillary block using ropivacaine, peak plasma levels occur on average at 25 min, versus 13.4 min for supraclavicular block.[65] Following aspiration in several quadrants, 40 to 50 ml of LA are injected incrementally with frequent intermittent aspiration tests being performed at least after every 3 ml. Speed of injection seems to be important, with rapid injection (15 ml in 10 s versus over 20 to 30 s) resulting in reduced anesthetic spread and increased axillary block failure rates.[66] Other physical modalities attempting to speed block onset, such as warming the LA prior to performing axillary block, have not been shown to decrease latency of onset.[67] Our LA of choice is levobupivacaine 0.5% with epinephrine, 1:300,000. We found that this provides an acceptable latency of onset. When multiple nerve stimulation techniques are used, even small doses of levobupivacaine provide successful axillary block analgesia. In a study of 110 patients prospectively randomized to receive either 36 ml of 0.1% levobupivacaine, 72 ml of 0.1% levobupivacaine, or 36 ml of 0.25% levobupivacaine, the group receiving the lowest dose had a 94.4% success rate, equivalent to the two other groups.[68]

We add buprenorphine 300 μg/40 ml, or alternatively clonidine 150 μg/40 ml, if we use shorter-acting agents and still desire prolonged postoperative analgesia.[69,70] Liisanantti et al.[71] noted that ropivacaine 0.5% produced slightly better sensory and motor block intensity than the same dose of levobupivacaine in 90 patients randomized to receive one or the other LA agents. Additionally, Gonzalez-Suarez et al.[72] showed that in a group of 86 patients, half of whom received 30 ml of 0.5% levobupivacaine and half 0.33% levobupivacaine, the ropivacaine group demonstrated significantly faster onset of motor block, while the time to be ready for surgery was similar for both groups. Sensory block duration was longer in the levobupivacaine group, as expected. Alternatives to levobupivacaine are racemic bupivacaine or ropivacaine. Plain bupivacaine 0.5% has been demonstrated to provide prolonged anesthesia and analgesia versus plain ropivacaine 0.5% for axillary block.[73] Raeder et al.[74] showed that 0.5% bupivacaine is approximately equivalent to 0.75% ropivacaine for axillary block. Freitag et al.[75] noted that prilocaine 1% alone or in combination with ropivacaine 0.75% was similar in onset of sensory and motor blocks,

but differed in duration of both, without a differential sensory and motor block offset.

The pharmacokinetic behavior of prilocaine appears to be equivalent to those of lidocaine when used for axillary block.[76]

We tend to avoid using mixtures of LAs, agreeing with the opinion of Covino and Wildsmith[77] that these combinations provide few clinically significant advantages. Axillary block with bupivacaine 0.25% was shown by Martin et al.[78] to have a significantly longer duration of action than when it was combined with 1% lidocaine. The uncertainties and complexities of adding chemicals with distinct pKa values, lipid solubilities, and protein-binding qualities to produce an intermediate-onset and intermediate-duration LA are intuitive.

Clonidine has been extensively studied as an adjuvant to LA for brachial plexus block analgesia. A recent meta-analysis of 20 trials published between 1992 and 2006 reviewed the evidence for and against clonidine use. Clonidine (single-shot use) prolonged the duration of postoperative analgesia, sensory block, and motor block. In a group receiving 150 μg clonidine for axillary block, these changes occurred irrespective of whether or not clonidine was added to an intermediate or long-acting LA. However, clonidine also produces clinically significant hypotension, orthostatic hypotension or fainting, bradycardia, and sedation, which may be severe.[79] However, for continuous catheter techniques, evidence is lacking for a beneficial result from the addition of this adjuvant.[80] Use of another α-2 agonist, dexmedetomidine, was recently shown to inhibit lipid peroxidation in the case of anticipated ischemia-reperfusion injury, such as would occur with tourniquet application in cases of upper extremity surgery. This is manifest as a reduction in plasma hypoxanthine production is the ischemic time period and a reduction of plasma malondialdehyde production during reperfusion period.[81]

In addition to buprenorphine and clonidine, several other additives have been used with LA administered for axillary or infraclavicular brachial plexus block. These have included several showing promising results, including naloxone added to lidocaine 1.5% with or without epinephrine[82] dexamethasone added to lidocaine 1.5%[83] and magnesium added to 2% prilocaine.[84]

On the other hand, other adjuvants have not demonstrated efficacy as additives to LA for infraclavicular blocks. Tramadol is an agent demonstrating mixed results when used as an additive. When 100 mg tramadol was added to 0.75% ropivacaine for axillary block, there was no prolongation of sensory or motor block or analgesia.[85] Another tramadol study using two dosing regimens, 100 and 200 mg added to lidocaine 1.5%, showed that there was a prolongation of sensory block after the 200-mg addition, at the expense of a significantly prolonged latency of onset, however.[86]

DETERMINANTS OF SUCCESS

Axillary block success is volume dependent up to 40 to 60 ml unless performed under US assistance, in which case much lower volumes are typically used successfully. Most authorities agree that low-volume block frequently fails to block one or more nerves when US is not used. Vester-Andersen et al.[87] demonstrated that musculocutaneous nerve block was improved following axillary block by increasing the volume of injectate from 20 to 40 ml (52% vs. 75%), as was block of the axillary nerve, but there was no additional improvement by increasing the volume (while maintaining the same total dose of LA) to 80 ml. The same group, in a different study, found that increasing the volume and total dose of 1% mepivacaine from 40 ml (400 mg) to 50 ml (500 mg) to 60 ml (600 mg) had minimal effect on the incidence of sensory or motor block latency or success rates, and, further, that the incidence of musculocutaneous nerve block was similar in all three groups.[88] The same group noted a progressive increase in successful motor block using 40 ml volumes while increasing the concentration (hence, total dose) of LA (mepivacaine with epinephrine).[89] The results of these studies imply that drug mass (i.e., volume ∞concentration) is the most important determinant of block efficacy. The actual volume of injectate should depend upon the patient's size, sex, and age. An amount of 20 ml of LA is probably not a large enough volume to reach consistently the cords of the plexus in most adults, a level indicated by the coracoid process.[1] Some suggest that a volume of 40 ml more consistently spreads cephalad toward the level of the first rib.[1] However, a recent report by Bertini et al.[90] suggested that using a multiple-injection technique, 400 mg mepivacaine, regardless of volume, produces the optimal axillary block. Some advocate placing firm digital pressure just distal to the needle insertion site during and immediately following injection to minimize the likelihood of retrograde flow of LA distally in the axillary perivascular space, but this is of questionable efficacy. Controversy exists regarding the efficacy of using a distally placed tourniquet or applying digital pressure distal to the regional block needle.

Whereas Eriksson advocated using a tourniquet, Winnie demonstrated that this was an ineffective means of minimizing distal spread of local and enhancing cephalad spread.[1] Lang et al.[91] verified that digital pressure, and not the use of a distally placed tourniquet, prevented distal spread of LA. Yang et al.[92] suggested that this maneuver did not improve sensory block following axillary block. Successful blockade of the musculocutaneous nerve was not improved using digital pressure distal to the needle.[93]

With either the transarterial or nerve stimulator techniques, once the injection of the appropriate volume of LA has been accomplished, the needle is withdrawn until it lies in the subcutaneous tissue directly over the artery, and its orientation is changed so that it runs from the biceps to the triceps. At this point, 3 to 5 ml of LA are deposited. This is to block the intercostobrachial nerve and the medial brachial cutaneous nerve, if it lies outside the sheath. This supplemental block is suited for those individuals who require a tourniquet placed on the upper arm. The intercostobrachial nerve supplies cutaneous analgesia to the superior portion of the axilla, and often extends distally to the anterior border of the axilla and to the anterior shoulder. As soon as the subcutaneous injection has been made, the needle should be withdrawn while maintaining the digital pressure, and the arm is brought down alongside the body to reduce the obstruction imposed by the humeral head to central spread of the LA.[1] Yamamoto

et al.[94] showed that adduction of the arm to 0 degrees increased central flow of LA after axillary block, but there was no effect on sensory block when using this maneuver. They did note, however, that there was improved motor block of the radial nerve using arm adduction. Other approaches to block peripheral branches of the brachial plexus below the clavicle have been developed. The midhumeral approach of Bouaziz et al.[95] was compared to conventional axillary block. The midhumeral approach had a higher success rate of blocking four nerves of the hand and forearm compared to the axillary approach (88% vs. 54%).

INFRACLAVICULAR APPROACH OF BRACHIAL PLEXUS BLOCK

The indications for infraclavicular block (ICB) of the brachial plexus are essentially the same as for axillary block, that is, surgery of the elbow, forearm, wrist, or hand. There have also been reports of successful use of ICB continuous infusions for individuals suffering from complex regional pain syndrome (CRPS) of the upper extremity.[96] For hand and wrist outpatient surgery, ICB compared to general anesthesia has been shown to provide time-efficient anesthesia, faster recovery, fewer adverse events, better analgesia, and greater patient acceptance.[97]

The major benefit of this approach, when compared to brachial plexus blocks above the clavicle, is the unlikely risk of encroaching upon the pleural space or lung parenchyma and causing a pneumothorax, while maintaining the high success rate of blocking the axillary and musculocutaneous nerves prior to their departure from the sheath of the brachial plexus.[98,99] The other major advantages of the ICB approach include a lower likelihood of tourniquet pain during surgery, and a more reliable blockade of the musculocutaneous and axillary nerves when compared to a single-injection axillary block. While the risk of pneumothorax should be insignificant with coracoid-based ICB, the vertical infraclavicular block technique, as studied in volunteers using MRI anatomic evaluation, is associated with a potential risk of pneumothorax, particularly in women or with needle advancement of more than 6 cm.[100] The negligible risk of clinically relevant hemidiaphragmatic paralysis from the paracoracoid approach is another advantage for selecting this block, as compared with supraclavicular techniques. Indeed, Sandhu et al. demonstrated that bilateral US-guided ICBs could be performed without interruption in ventilatory function.[101] However, Rettig et al.[102] did show a change in hemidiaphragmatic function when the more proximal vertical ICB was used in a group of 35 patients using an average volume of 38 ml of ropivacaine 0.75%. They noted that nine (26%) patients exhibited reduced hemidiaphragmatic function with an average of 25% reduction in both FVC and FEV1, which may be clinically relevant in patients with severe obstructive airway disease.

The ICB approach is ideally suited for continuous catheter insertion and maintenance, since the patient may move the head and arm without dislodging the catheter, which is well situated within the bulk of the pectoralis muscles.[103] The major theoretical disadvantage is the increased potential for pain during the block performance, since the pectoralis major and minor muscles must be traversed by the needle before reaching the cords of the brachial plexus. However, as regards discomfort, two recent studies suggest that when US is used, the discomfort of performing an ICB is actually less than that of axillary block.[104,105] Minville et al.[106] showed in a group of 104 patients undergoing ICB or midhumeral blocks, that the midhumeral block technique was associated with significantly more pain that an ICB, while having a similar overall success rate. The same study group also noted that ICB was faster to perform than the humeral block, but was associated with a slower block onset time.[107]

The more recently described coracoid approach[108] uses the coracoid process of the scapula as a major landmark for either peripheral nerve stimulation or US-guided techniques. The initial needle insertion point is typically located within 1 cm to the medial border of the coracoid process. In its final position, the needle tip should be situated at the level of the distal cords, ideally located within a central location (closest to the posterior cord, just posterior to the axillary artery) within the brachial plexus. Using the coracoid approach, studies have demonstrated a 75% to 85% blockade of the axillary nerve and an 80% to 100% blockade of the musculocutaneous nerve.[109,110] Additionally, since the paracoracoid approach is located more distally than the previously described vertical infraclavicular approach, the incidence of phrenic nerve block and resultant hemidiaphragmatic paralysis has been stated to be minimal.[111]

A double-stimulation technique has been described that relies upon first, stimulation of the musculocutaneous nerve, and subsequent stimulation of either the radial, median, or ulnar nerve using a modified coracoid approach. With this technique, successful blockade of four nerves occurred in 92% of patients at 30 min, with no observed complications.[112] The double-stimulation technique is easily taught to residents in training as well. The average time to complete the ICB by trainees was found to be 5.8 min compared with 3.9 min for staff anesthesiologists.[113] Using single-stimulation techniques, stimulation of the posterior cord was shown to have the highest success rate in a group of 369 patients undergoing PNS-guided blocks.[114] This finding was confirmed in a subsequent study of 70 patients undergoing coracoid technique for the ICB.[115]

In a study of 51 patients utilizing an US-guided parasagittal technique, a single injection of 30 ml of LA directly posterior to the axillary artery was shown to be superior in terms of success and complete sensory block as compared to a triple injection (10 ml each cranial, posterior, and inferior relative to the axillary artery) technique.[116] Furthermore, De Tran et al.[117] showed in a prospective, randomized, blinded study in 88 patients that an US-guided single-injection of 35 ml of LA directly posterior to the axillary artery was as effective as a double-injection technique (15 ml cranial and 20 ml dorsal relative to the axillary artery) in terms of ICB success (93.1–97.7%).

In our technique, the patient lies supine with the head in a neutral position or turned slightly toward the contralateral (nonblocked) side. The arm may be adducted, abducted, or extended out away from the body, but it is typically abducted at 90 degrees as for axillary block. This helps localize the axillary arterial pulse, a useful landmark

for completing this block. Using US, it has been noted that abduction of the arm brings the brachial plexus much closer to the skin and farther away from the pleura, but does not change the position of the axillary artery relative to the coracoid process or the pleura. Given the pressure to maintain transducer contact with the skin surface, using US may actually underestimate the actual depth of the plexus.[118] When using a handheld Doppler for vertical infraclavicular block, the needle was inserted at the point where the sound of the subclavian artery was noted to be maximally audible. Using this technique, the medial or posterior cord was found on one needle advancement in 89/100 consecutive patients.[119] Using the Doppler resulted in significantly more lateral needle insertion point compared with the classically described insertion point. Bigeleisen[120] found that a medial approach compared to a lateral approach, both with US guidance, resulted in reduced time to complete the ICB as well as providing a lower incidence of tourniquet pain and vascular puncture, while bringing the plexus closer to the skin (3.7 vs. 4.5 cm). Using the classically described paracoracoid PNS technique, the initial needle insertion point is 2 to 3 cm medial and 2 cm caudal to the midpoint of the coracoid process on the anterior chest wall. After the skin is infiltrated, the intended needle tract is anesthetized.[103] The parasagittal plane of needle insertion and advancement lie laterally to the rib cage and lung, and intersect the plexus at the level of the distal cords rather than at the level of the nerve trunks or divisions. The needle is passed directly posteriorly through the substance of the pectoralis major and minor muscles and is a potentially painful procedure. When the nerve stimulator is activated, there is direct motor stimulation of this large muscle mass at a depth of about 1 to 3 cm. Advancing an additional 2 to 4 cm, the brachial plexus cords are usually encountered by the stimulating needle. Often the musculocutaneous nerve is first encountered, since it exits the brachial plexus sheath at a site close to the coracoid process. Accepting this stimulation as an endpoint results in a higher failure rate than accepting an EMR of the hand, which indicates a more central location of the needle tip.[109,110] If no neural elements are stimulated on the initial pass of the needle, the needle should be redirected progressively more caudad along the same parasagittal plane until hand movement is noted. Since the needle is advanced lateral to the ribcage, pneumothorax remains an unlikely consequence of caudad advancement.[108] We use the same volume, concentration, and LA(s) as described for axillary block. When using a PNS-guided technique, a double-injection (EMR) technique of the brachial plexus cords increases success compared to single-injection techniques, particularly when the EMR targets the posterior cord. In contrast, a single stimulation of the posterior cord is superior to dual stimulation of the medial and lateral cords, indicating the importance of the central location of the posterior cord at the infraclavicular brachial plexus.

For the US-guided ICB technique the US transducer should be oriented perpendicular to the clavicle just medial to the coracoid process (Fig. 75-9). This orientation with the marker of the transducer oriented cephalad should provide a parasagittal cross-sectional view of the axillary artery and surrounding cords. Given the increased depth of the brachial plexus at the infraclavicular area, the frequency range of a broadband-width linear array transducer should be adjusted to "general" (frequency range of 6–10 MHz) or a low frequency (2–5 MHz) curved array transducer should be used to perform the block. The optimal short-axis US image should demonstrate the axillary artery and brachial plexus cords located immediately deep to the pectoralis minor muscle and its accompanying clavipectoral fascia (Fig. 75-10). With either the peripheral nerve stimulator technique, and especially with the US-guided technique, it is helpful to visualize the axillary artery in the center of clockface and the brachial plexus cords arranged around the axillary artery in a parasagittal topographic arrangement (Fig. 75-11). The brachial

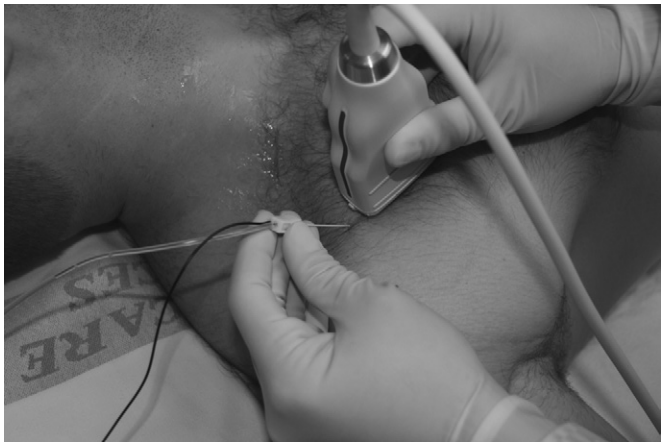

FIGURE 75-9 Illustration of the typical ultrasound transducer and needle placement for an ultrasound-guided infraclavicular block utilizing a short-axis-in-plane technique. The transducer is positioned just medial to the coracoid process and just caudal to the clavicle and the block needle is inserted superior to the transducer and advanced within the plane of the ultrasound beam.

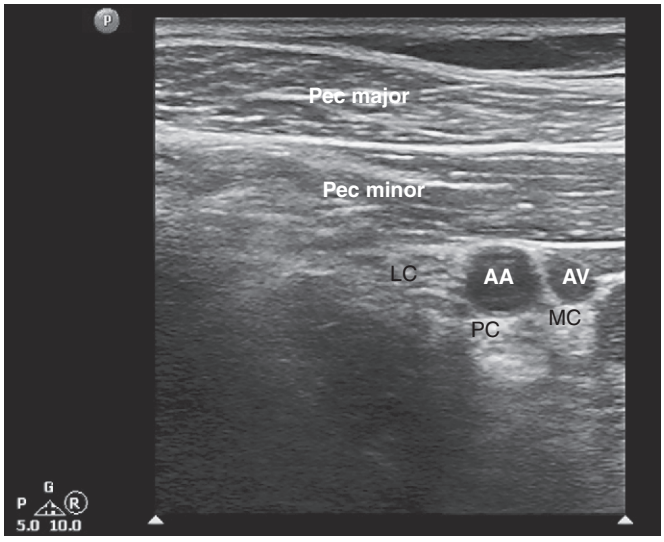

FIGURE 75-10 Ultrasound image of the typical hyperechoic polyfasciular appearance of the cords of the brachial plexus in the infraclavicular approach. The lateral, posterior, and medial cords are closely related to the axillary artery, positioned deep to the pectoralis major and pectoralis minor muscles.

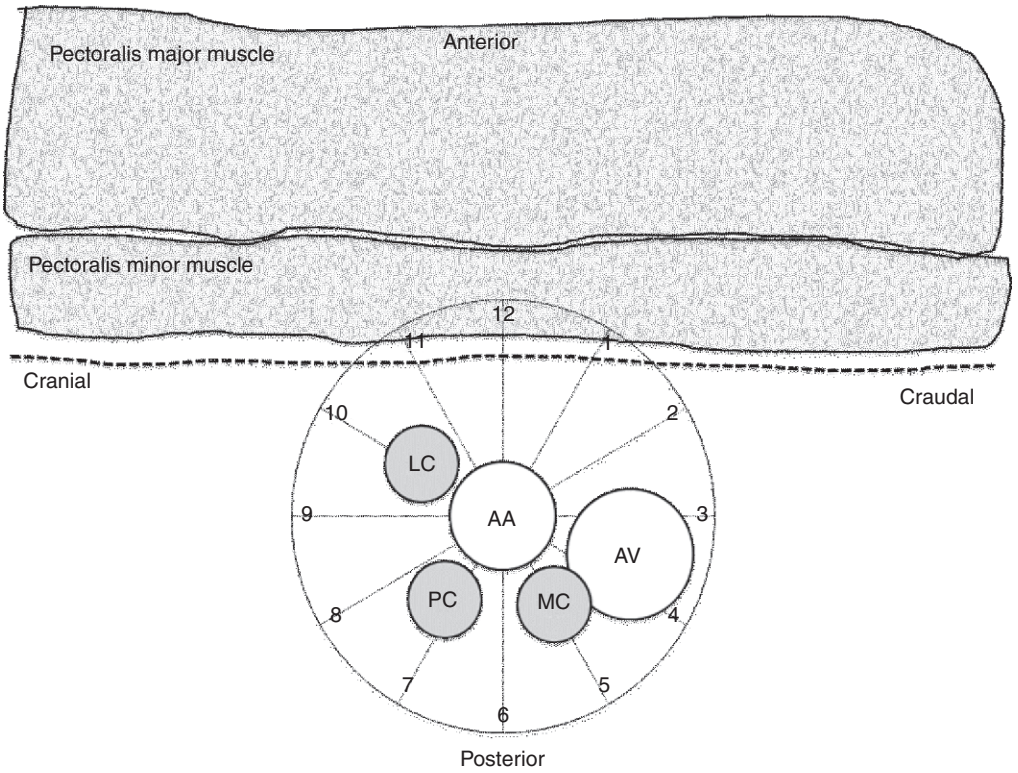

FIGURE 75-11 The topographic parasagittal anatomic arrangement of the cords of the brachial plexus. Note that the lateral cord is located most superficial and cephalad to the axillary artery while the medial cord is located deep and caudal to the axillary artery. The posterior cord is located just posterior to the axillary artery and centrally between the lateral and medial cords.

plexus cords should appear as hyperechoic polyfasicular (honeycomb appearance) structures arranged around the centrally located anechoic, pulsatile axillary artery. Most commonly, the lateral cord is located cephalad (9 to 11 o'clock position) to the axillary artery, the posterior cord is located immediatley deep to the lateral cord and axillary artery (6 to 8 o'clock position), and the medial cord is located caudal (3 to 5 o'clock) to the axillary artery. However, the exact position of the cords relative to the axillary artery is variable, but the posterior cord is always located in between the lateral and medial cords. The position of the axillary vein is also variable, but is typically located superficial and caudal to the axillary artery.

Needle insertion is typically 1 to 2 cm cephalad to the transducer, just below the clavicle and medial to the coracoid process. The needle is advanced in-plane in a parasagittal fashion and directed initially caudad to the axillary artery. It is important that the needle is deep to the clavipectoral fascia, below which is located the infraclavicular brachial plexus neurovascular bundle. At this point, 3 to 5 ml of LA is injected in order to create a space cephalad and posterior to the axillary artery. The needle tip is then advanced and placed in the immediate vicinity of where the posterior cord is typically located (which may be confirmed with a posterior cord EMR with a peripheral nerve stimulation if the sonoanatomy is less than optimal), and 20 to 30 ml of LA is injected incrementally. The optimal distribution of LA should be posterior (deep) to the axillary artery in either a circumferential (donut sign) or a "U-shaped" pattern (3 to 11 o'clock) around the axillary artery to ensure blockade of all three brachial plexus cords.

With US-guided techniques, a double-bubble sign has been described, wherein injection of the total volume of LA posterior to the artery, observed as a "bubble" of LA, results in an improved (100%) success rate of ICNB as compared with alternative US views of LA spread.[121] Spread of LA after radial nerve stimulation when US was used for confirmation was superior to a median nerve EMR (and LA spread) in terms of complete sensory block of three cords at 30 min.[122] Dingemans et al. showed, in a group of 72 patients recruited to undergo either US or US plus PNS-guided ICB, that US alone was more rapidly performed and yielded a higher success rate than that provided by the additional employment of the PNS. Indeed, block supplementation was more than three times higher when the PNS was added to the US (26% versus 8%).[123] For the lateral sagittal ICB technique, both US and PNS were equally effective in terms of block performance time, onset time of sensory block, and time for readiness for surgery.[124] In a study comparing PNS and US for lateral sagittal ICB, Gurkan et al. found that success rates were equivalent between the groups while vascular puncture was higher with the PNS use.[125] Taboada et al. also found that for coracoid ICNB, PNS use and US use were similar in terms of onset time, success rate, and duration of motor block; the main benefit of US use was in reduction in block performance time. These findings were complemented by almost identical findings of Brull et al.[127] US-guided placement and LA injection directly posterior to the axillary

artery appear to be associated with the highest success rate for ICB, especially compared to injection directed at either the lateral or medial cord.

Using US, it has been demonstrated that exceptionally small volumes of LA can be used to effect successful block. Sandhu et al. showed that a successful infraclavicular block in adults can be accomplished using volumes of 2% carbonated lidocaine with epinephrine as low as 14 ml.[128] In pediatrics, US use for ICB was shown to be superior to PNS use for blocks performed for children with radial club hands.[129]

INFRACLAVICULAR VERSUS AXILLARY BRACHIAL PLEXUS BLOCK

When the infraclavicular block is compared to axillary block for surgery of the arm and hand, approaches relying upon a single nerve–EMR failed to demonstrate a difference in success, latency, or duration of blockade.[109] Further, at least two nerves were blocked in 100% of the infraclavicular blocks versus in 85% of the axillary blocks. Musculocutaneous nerve block, as expected, was more successful following infraclavicular block, as compared to axillary block. In another study, however, the success rate of infraclavicular block was decidedly lower than it was for axillary block, with 57% of patients in the former group having anesthesia in the distributions of four nerves of the forearm and hand versus 87% in the latter group.[110] Latency of onset was shorter in the axillary group, while times to perform the block, and duration of action, did not differ significantly. The authors used a two-nerve injection technique for the infraclavicular block, and a four-nerve technique for the axillary block. In another study comparing vertical ICB and high axillary block, it was noted that both techniques provided sufficient surgical anesthesia, with no patient requiring either systemic supplementation or general anesthesia.[130] The vertical ICB technique was shown in a group of 60 patients to be superior to single-injection axillary block in terms of success (97% vs. 77%) with a shorter latency to onset when 0.5% ropivacaine was used.[131] The transarterial approach to brachial plexus block was recently shown to be equivalent to US-guided ICB in a group of 232 patients in terms of block performance time and adequacy for surgery, although significantly more patients in the US group had less pain at the block site.[132]

Infraclavicular block has also been compared with supraclavicular block. When the "corner pocket supraclavicular" technique was compared with a triple-point injection around the axillary artery for infraclavicular block, the ICB had a higher success rate of blocking four nerves (70% vs. 57%) at 30 min and a higher success rate during surgery as determined by lack of requirement for supplementation (93% vs. 67%).[133] ICB had a faster onset, better surgical anesthesia, and fewer adverse events when compared to supraclavicular block in a group of 120 patients undergoing blocks using ropivacaine and mepivacaine combinations.[134] Arcand et al. found that US-guided ICB was at least as rapidly executed as supraclavicular block with a similar degree of surgical anesthesia without supplementation.[135] Tran et al. randomly assigned 120 patients to receive one of three approaches to US-guided brachial plexus block. Axillary blocks required the greatest number of needle passes, a longer needling time, and a longer performance time, but otherwise there was no difference between the three US-guided approaches in terms of success rates, which were above 95% for all blocks.[136]

CONTINUOUS TECHNIQUES

Prolonging the duration of perioperative anesthesia and postoperative analgesia is the function of continuous catheter techniques. Originally designed in response to the need to provide antinociception for patients with chronic pain or with vascular insufficiency,[137–139] their use has been expanded to include routine catheter placement and for acute postoperative management in otherwise healthy outpatients.

Most reports of the use of continuous devices are simple observational analyses based upon the aggregate clinical experience of practitioners who employ these techniques.[140–142]

Studies have looked at serum concentrations of LAs to gauge the effect of alterations in delivery rates and LA concentrations on outcome and side effects. Other investigators have performed comparisons of LA infusions versus saline controls to gauge the efficacy of relieving postoperative pain following upper extremity surgery. Salonen et al.[143] prospectively evaluated 60 elective hand surgery patients receiving continuous catheter axillary blocks with ropivacaine. Postoperatively, three continuous infusion study groups were evaluated, including two distinct ropivacaine concentrations (0.1% and 0.2%) and a normal saline control. They found no apparent advantage to the two ropivacaine concentrations versus control as regards analgesia occurring after the initial 12 hr postoperatively. This demonstrates the need for additional studies on continuous catheter techniques for postoperative analgesia before advocating for their routine use.

When ICB continuous catheter techniques are used to prolong perioperative analgesia, Ilfeld et al. have shown that 0.2% ropivacaine delivered as a continuous infusion combined with patient-controlled boluses optimizes analgesia while minimizing oral analgesic use when compared with either a basal-only or a bolus-only dosing regimen.[144] Smaller volumes of relatively concentrated ropivacaine (0.4%; basal 4 ml plus bolus 2 ml) resulted in more insensate limbs than did use of 0.2% ropivacaine (basal 8 ml plus bolus 4 ml).[145]

Mariano et al. found that US use for catheter placement for continuous ICNB resulted in reduction in performance time, and higher success rates with fewer inadvertent vascular punctures as compared to PNS use.[146]

Whether or not to inject the first bolus dose of LA through the needle or through the continuous catheter has been studied. It appears that there is no difference in terms of success whether one undertakes to perform the injection through either, when US is used.[147] Although it is not always easy to visualize the catheter tip location when performing US-guided blocks, the use of agitated D_5W has been shown to be a valuable adjunct to enhance observation of the tip.[148] Using combined US and PNS techniques improves success and reduces secondary block failure during performance of ICB.[149] Stimulating catheters used for continuous ICB may be associated with improved

analgesic effect, versus nonstimulating catheters, according to a recent semiquantitative review.[150]

COMPLICATIONS

Axillary block is the technique of brachial plexus block most likely to be associated with intravascular injection. This is because it is the only site where the major, large vein lies within the sheath.[1] However, the axillary vein lies anterior and slightly inferior to the axillary artery (Fig. 75-2) and therefore is easily compressible beneath appropriately situated palpating fingers. Techniques advocating multiple injections or injections above and below the axillary artery enhance the likelihood of encountering the vein, and hence injecting into it. With the transarterial techniques, the possibility is real that the volume of LA might be injected directly intra-arterially, but due to the fractionation of injectate volumes that typically occurs with this approach, this should rarely occur. Stan et al.[23] reported that the total incidence of vascular complications following axillary block is 1.4%, including 0.2% incidence of intravascular injection, even with test dosing and aspiration. Brown et al.[151] suggested that the incidence of LA-induced seizures is 1/10,000 axillary blocks, which is less than that reported for supraclavicular or interscalene blocks, and which approximates the incidence during epidural block. Carles et al.[152] stated that the incidence of seizure was 1.2/1000 to 1.3/1000 following axillary block versus 7.6/1000 after interscalene and 7.9/1000 for supraclavicular block. The data were similar regardless of technique chosen (transarterial, peripheral nerve stimulator, humeral).

There is no evidence that the site of injection of LA (axillary vs. supraclavicular vs. interscalene) affects the actual blood level of LA,[153] although the peak blood level may occur more rapidly following injection with interscalene versus axillary block.[154] Hematoma is certainly a possibility with axillary block, but, fortunately, the area of injection (unlike for subclavian perivascular plexus block) is readily compressible. Ben-David and Stahl[155] reported on a case of radial nerve dysfunction associated with a large axillary hematoma following axillary block and the transarterial technique. Neurologic function was impaired for up to 6 months following this procedure. Hematoma formation needs to be considered in any patient with neurologic impairment following axillary or infraclavicular brachial blocks. Pseudoaneurysm formation may also complicate axillary block,[156,157] and may occur in the artery as well as in the axillary vien.[158]

The consequences of pseudoaneurysm formation include pressure-induced neural ischemia. In the case report of Groh et al.[156] the patient continued to experience severe median nerve dysfunction persisting 4 months postoperatively. A case of axillary artery dissection and subsequent thrombotic obliteration following axillary block without arterial puncture has been reported.[159] Vascular insufficiency is not an infrequent accompaniment of the transarterial technique, and results in severe blanching of the skin of the hand and wrist. We have seen several cases where the patient's hand takes on a "cadaveric" appearance. Additionally, the peripheral pulses (radial and ulnar arterial) are distant or absent. Stan et al.[23] noted that the incidence of transient arterial vasospasm may approach 1% in selected patient populations. We have observed this phenomenon in at least 50% of individuals receiving transarterial axillary blocks as described above.

Merrill et al.[160] reported on a case of arterial vasospasm lasting 15 min after axillary block with 20 ml of 1% lidocaine and 0.05% tetracaine with epinephrine 1:200,000. Fortunately, this phenomenon is reversible, in that we have not yet encountered a patient in whom this does not spontaneously reverse itself within about 15 min. This likely results from the intra-arterial injection of epinephrine-containing solutions, producing profound vasoconstriction of the axillary artery. The phenomenon reverses itself when the increase in blood flow from the sympathetic nervous system block produced by the axillary block results in effective dilution and washout of the locally injected epinephrine.

Pulmonary complications following axillary or infraclavicular block are virtually unheard of, yet must always be considered if the needle is directed away from the axilla and toward the chest wall, a decidedly unwise maneuver. Rodriguez et al.[111] found that respiratory function is not affected by axillary or infraclavicular block.

Neural injury following axillary block is gratefully a rare occurrence. Auroy's group performed a large, retrospective analysis of complications related to regional anesthesia in France.[161] In 11,024 axillary brachial blocks there were only two instances of neurologic injury noted, for an incidence of 1.9/10,000. All neurologic complications, occurred within 48 hr of surgery, and in 85% of cases the complications resolved within 3 months. They concluded that needle trauma and LA neurotoxicity were the etiologies of most neurologic complications. In that same study there was only one reported seizure, for an incidence of 0.9/10,000.[161]

The design of needles may have a bearing on nerve injury. It is clearly easier to enter a nerve fascicle with a sharply pointed needle,[87] but greater injury may be done when a blunt needle succeeds in penetrating the perineurium, even without injection.[162]

Paresthesia techniques and injecting after elicited paresthesias may contribute to perioperative neural injury. Selander et al.[163] found that unintentional paresthesias were elicited and injected upon in patients who ultimately experienced postoperative nerve injury. Yet, even without eliciting notable paresthesias, 19% of patients receiving axillary blocks had paresthesias persisting into the first postoperative day.[88] These were not associated with the type of LA, number of needle advances, anesthetic technique (paresthesia vs. transarterial), or duration of tourniquet inflation. However, there was a significant increase in the incidence of acute paresthesias in patients who had preoperative neurologic symptoms within an extremity. At 2 weeks, only 5% of patients continued to experience new postoperative paresthesias. Symptoms consisted solely of numbness and tingling in the fingers as well as forearm hyperesthesia. By 4 weeks, all patients except for one (0.4%) had resolution of their symptoms. Stan et al.[23] reported an incidence of 0.2% neurologic complications in almost 1000 patients undergoing axillary block using the transarterial approach. If a paresthesia was elicited, the LA was not injected, and the needle was redirected. In the 12% of patients who did have a periprocedural paresthesia there were no instances of postoperative neurologic complications, leading them to speculate that those individuals

who developed this complication experienced unintentional/unobserved mechanical trauma or intraneuronal injection during block supplementation.

Ischemia may be a mechanism contributing to damage that follows intrafascicular injection of LAs. Selander and Sjostrand[163] demonstrated that intrafascicular injections might lead to compressive nerve sheath pressures greater than 600 mmHg. This transient elevation in endoneural fluid pressure may exceed capillary perfusion pressure for up to 15 min, interfering with the nerve's endoneural microcirculation. Elevated pressures may also alter the permeability of the blood–nerve barrier within the endoneurium, possibly contributing to axonal degeneration, Schwann cell injury, and fibroblast proliferation.

In a large meta-analysis of neurologic injury occurring after regional anesthesia, Brull et al.[164] reviewed 10 years of studies, of which 32 met inclusion criteria. The incidence of neurlogic injury following axillary block was 1.48% versus 2.84% for ISB and 0.03% for supraclavicular block. ICB was not studied.

In any case of suspected neural injury following axillary or infraclavicular block the following steps ("minineurologic examination") should be undertaken immediately: the median nerve may be tested by using a pinprick over the palmar surface of the distal phalanx of the index finger; the ulnar nerve may be tested in similar fashion by pinprick testing of the palmar surface of the distal phalanx of the fifth finger; the radial nerve may be tested by asking the patient to extend the distal phalanx of the thumb; the musculocutaneous nerve function can be assessed by asking the patient to flex the forearm; and the axillary nerve may be assessed by abduction of the arm.[1] It is important to obtain electromyographic studies as quickly as possible following a suspected nerve injury, for the purposes of establishing a time frame of when the injury might have occurred. Electrodiagnostic studies should be obtained as expeditiously as possible to rule out the likelihood of preexisting lesions playing an integral part in the etiology of these processes.

Infectious complications may occur in the setting of continuous catheter use, although several large studies appear to imply that the incidence is higher when catheters are used for trauma, as opposed to when they are inserted and maintained for elective surgeries.[165]

Although US use appears to provide a margin of safety previously not encountered when PNS use alone was employed for ICB, there are nevertheless several case reports of pneumothorax occurring with both techniques.[166,167] Sanchez et al.[168] reported two cases of pneumothorax following US guided ICB performed at a training institution.

CONCLUSION

Techniques of brachial plexus block below the clavicle offer many unique advantages versus the supraclavicular approaches. They spare diaphragmatic function and are not associated with the higher risk of pneumothorax encountered above the clavicle, recurrent laryngeal nerve block, Horner's syndrome, or shoulder weakness. Some studies suggest that the incidence of neuropathy following their implementation is less than that of the supraclavicular blocks. Infraclavicular techniques are ideally suited for continuous catheter insertion and maintenance, since patient movement does not easily dislodge the devices. Future developments will focus on improving our understanding of how to maximize success rates and improve blockade of all four of the major nerves of the forearm and hand.

KEY POINTS

- There were no currently described techniques of brachial plexus block that rely upon blockade at the level of the divisions of the plexus until the advent of US guidance.
- It has been demonstrated that the capacity of the axillary perivascular sheath is 42 ml.
- Axillary and infraclavicular blocks of the brachial plexus are appropriate for surgeries of the upper extremity from the elbow to the fingers.
- Paresthesias occur in up to 40% of cases of axillary perivascular block, even when not intentionally sought.
- Axillary block is volume dependent up to 40 to 60 ml; LA drug mass (volume × concentration) is the main determinant of efficacy of the block.
- The axillary approach blocks the terminal nerves of the brachial plexus and the infraclavicular approach blocks the cords of the brachial plexus.
- For axillary brachial plexus peripheral nerve stimulation techniques, multiple EMRs are associated with a higher block success rate compared to single EMRs.
- For infraclavicular brachial plexus peripheral nerve stimulation techniques, stimulation of the posterior cord appears to be most important for block success.
- For US-guided techniques below the clavicle, there appears to be no significant increase in block success rates to date, but is associated with decreases in LA requirements, fewer needle passes, and decreased block associated pain.
- The infraclavicular technique is anatomically the most suitable of all brachial block techniques, including those performed above the clavicle, for the insertion and maintenance of continuous catheters.
- Of all the techniques of brachial block, axillary block is associated with the highest incidence of intravascular injection of LAs.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 76

Truncal Blocks: Intercostal, Paravertebral, Interpleural, Suprascapular, Ilioinguinal, and Iliohypogastric Nerve Blocks

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PARAVERTEBRAL BLOCK

Regional anesthetic techniques involving truncal neural blockade have enjoyed a resurgence in recent years, particularly with the introduction of ultrasound (US) guidance techniques. Epidural analgesia when compared to paravertebral blocks for patients undergoing thoracotomy, demonstrated no difference in opioid consumption or pain scores at 4 to 8, 24, and 48 hr, with fewer side effects including pulmonary complications, hypotension, urinary retention, and nausea and vomiting. Rates of failed blocks and complication rates were lower as well.[1]

ANATOMY

The paravertebral (PV) space is a wedge-shaped area adjacent to the vertebral column that contains the sympathetic chain, the dorsal and ventral (intercostal) roots of the spinal nerve, the white rami communicantes as well as fatty tissue and intercostal vessels (Fig. 76-1). The base of the wedge constitutes the medial border of the paravertebral space and is formed by the vertebral body and the intervertebral disc where there is communication with the epidural space via the intervertebral foramen. The posterior border of the PV space is the superior costotransverse ligament which extends laterally to become continuous with the aponeurosis of the internal intercostal muscle. This internal intercostal membrane runs between the ribs, whereas the superior costotransverse ligament runs from the inferior border of the transverse process above to the superior border of the rib tubercle below. As the wedge tapers off laterally, it is continuous with the intercostal space. Anterior and lateral to the PV space is the parietal pleura. Within the paravertebral space, the spinal nerves themselves do not have a fascial sheath and are easily susceptible to local anesthetic blockade. There is however the endothoracic fascia, which is the deep investing fascia of the thoracic cavity, within the PV space that can affect the spread of injected solutions.[2]

TECHNIQUES

Conventional Technique: Conventional techniques have described a loss-of-resistance approach to reach the PV space. A small-gauge Tuohy needle is inserted 2.5 cm lateral to the superior edge of the spinous process perpendicular to all planes and advanced until contact is made with the transverse process (TP). The needle is then withdrawn to the skin, redirected caudad or cephalad by 15 degrees and advanced deep to the superior costotransverse ligament at which point loss of resistance is achieved. To avoid pleural puncture, the needle is advanced 1 cm (and no further than 1.5 cm) past the point at which the TP was contacted. It is best to avoid medial angulation of the needle to minimize the risk of local anesthetic injection into a dural sleeve. It is also prudent to avoid lateral angulation given that the PV space is narrower laterally increasing the risk of pleural puncture (Fig. 76-3).

Ultrasound Guidance Technique: The addition of US guidance can be used to facilitate the thoracic PV block by aiding in determining needle insertion sites, depth to transverse process and pleura, and needle tip location. A linear, high-frequency probe can be used and in some instances, a curvilinear probe may offer a better approach to the paravertebral space. Three US-guided approaches have been described.

The first approach utilizes US primarily to identify the TP. Once the TP is contacted under US guidance, the conventional loss-of-resistance technique is utilized. To visualize the TP, the US probe is placed in a longitudinal parasagittal plane 2.5 cm from the midline. Generally, a 5- to 10-degree tilt laterally is needed to best visualize the TP, which appears as concave hyperechoic structure approximately 1 cm wide with anechoic space deep to it. This is commonly referred to as a "thumbprint sign." The parietal pleura can be visualized approximately 1 cm deep to the TP on either side as a sharp hyperechoic line (Fig. 76-2). The distance to the TP is variable depending on the level that is being blocked and the patient's body habitus. The TP is at its most superficial location at levels T3–T5, usually at a distance of 1.5 to 2.5 cm, and is located deeper at levels cephalad and caudad to this. US imaging has been shown to correlate well with the distance to the TP and the PV space,[3,4] and usually underestimates these distances by 0.3 to 0.7 mm due to skin compression by the scanning head. Initial contact with the TP should be made with a 22-gauge finder needle that can serve to infiltrate local anesthetic. Generous local anesthetic infiltration is recommended to minimize paraspinal muscle discomfort and can serve to echolocate the needle tip. Once the TP is contacted with the finder needle, the depth is noted and a Tuohy needle or blunt-bevel block needle is introduced. To minimize the risk of pleural puncture and development of pneumothorax, it is useful to have a needle with centimeter markings and a closed needle-syringe system relative to atmospheric pressure. Using an out-of-plane needle approach and similar to the conventional technique, the TP process is contacted and then redirected caudad 1 cm (and no more than 1.5 cm) past the TP. Loss of resistance to saline is confirmed and local anesthetic injection is performed by an assistant with intermittent aspiration while maintaining US visualization. It is important to note that loss of resistance can be very subtle and does not invariably occur. By using US, downward movement of the parietal pleura is seen as

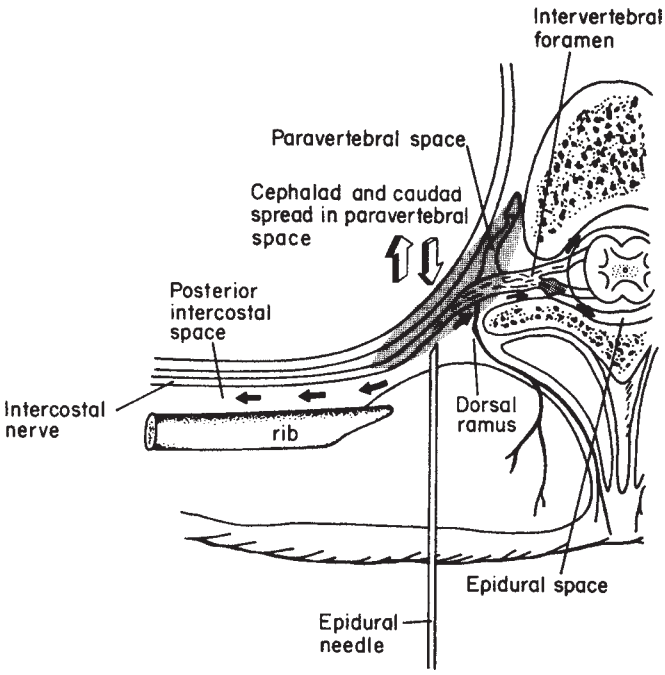

FIGURE 76-1 The paravertebral space is contiguous with surrounding spaces. *Arrows* depict spread of local anesthetic to the intercostal, epidural, and inferior and superior paravertebral spaces. *(From Chan VW, Ferrante FM: Continuous thoracic paravertebral block. In Ferrante FM, Vade Boncoeur TR, editors:* Postoperative pain management, *New York, 1993, Churchill Livingstone, p 408.)*

confirmation of correct local anesthetic placement. If a Tuohy needle was used, a catheter may be placed while maintaining lateral or cephalad needle tip orientation. One should expect slight resistance while passing the catheter. If no resistance is encountered, it is possible that the needle tip is in the intrapleural space.

The second approach is a slight variation of the first and utilizes an in-plane or out-of-plane approach to the PV space.[5] The probe is in the identical longitudinal parasagittal plane as described above and the PV space is approached directly without first contacting the TP process. If utilizing this approach, precise needle tip echolocation is important. If the needle tip is difficult to visualize, LA or saline can be injected incrementally to track needle tip advancement by hydrodissection. Again, a "pop" may be felt when the posterior costotransverse ligament is traversed with corresponding loss of resistance.

In the third approach, the TP is initially imaged with a similar longitudinal parasagittal view, and the probe is then rotated obliquely to allow for the best view of the posterior costotransverse ligament and the PV wedge. The needle is advanced carefully utilizing an in-plane needle approach[6,7] (Fig. 76-3).

Additionally, US-guided intercostal approaches to the PV space have been described, and will be discussed in the next section.

The presence of the endothoracic fascia within the PV space can affect spread of injected solutions, and therefore some authors have suggested nerve stimulation in addition to the loss of resistance technique. Nerve stimulation can allow for more accurate placement of local anesthetic within the PV space, that is, anterior to the endothoracic fascia.[8,9] Additionally, by injecting in this anterior location within the PV space, better craniocaudal spread in the paravertebral "gutter" may be achieved and the need for multiple level injections obviated. This technique has not been studied in conjunction with US use. Conversely, other experts have argued that needle readjustment within the PV space may lead to a higher incidence of intravascular injections and pneumothorax,[10] and that multiple-level PV injections allow for true graduated dosing of local anesthetic and result in a more reliable spread of injectate within the PV space.[11]

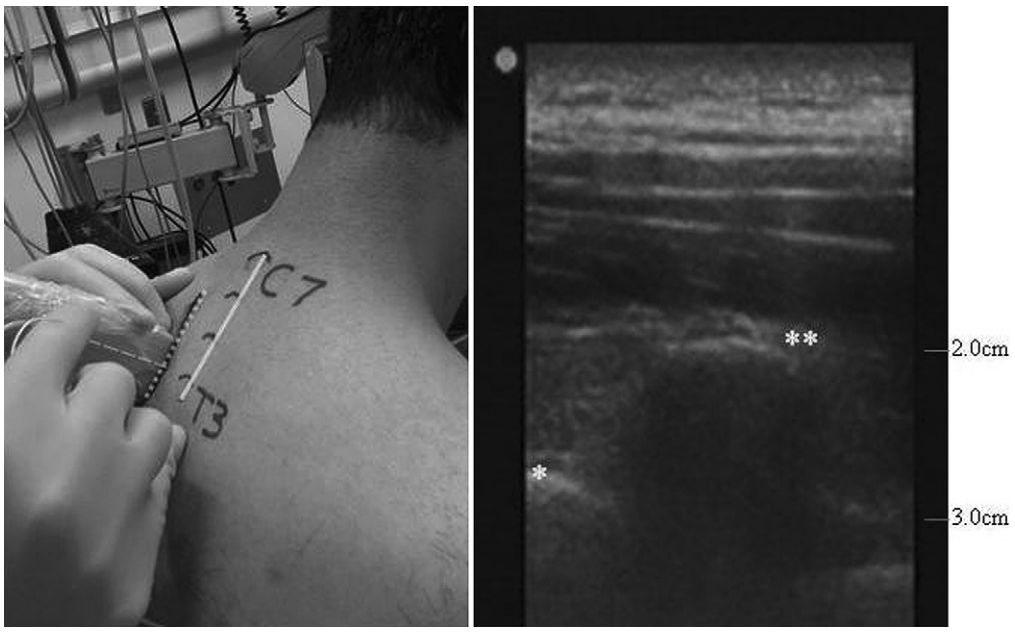

FIGURE 76-2 Paravertebral block. Solid line, midline of spinous process; dashed line represents 2.5 cm lateral of midline; *parietal pleura; **transverse process.

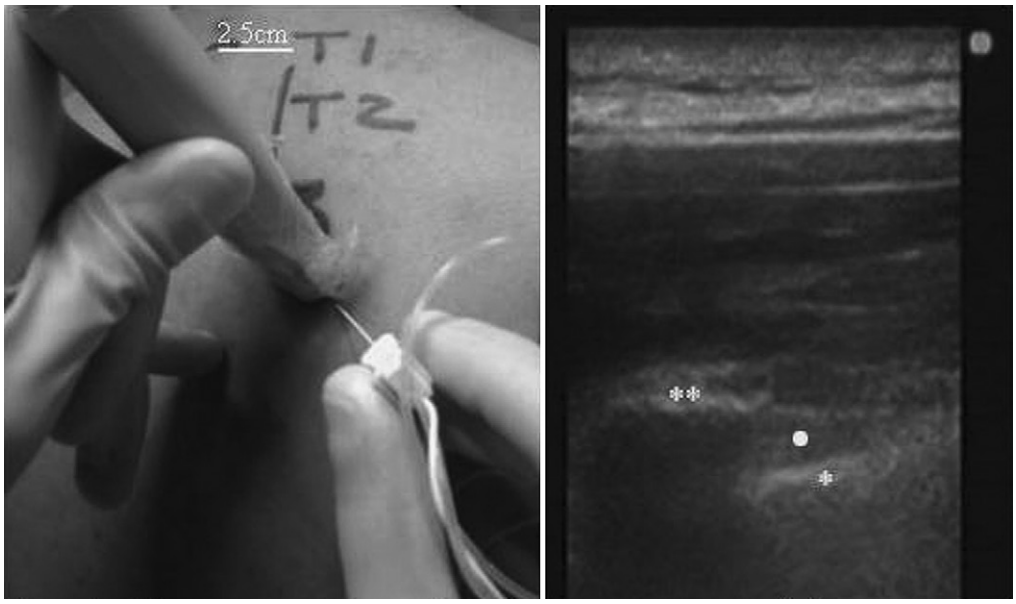

FIGURE 76-3 Paravertebral block. *parietal pleura; **transverse process; *dot*, paravertebral space.

DOSING

A single injection of 15 ml can be expected to provide analgesia over 3 to 4.6 dermatomes in the thoracic region.[11,12] Spread is initially at the level of injection and along the intercostal nerve, and progresses in the PV "gutter" to cover one dermatome above and two dermatomes below. Most studies have shown a preferential caudad spread of injectate.[11,12] Analgesia typically ranges from 6 to 12 hr for a single injection. If a catheter is placed, infusion of ropivacaine 0.2% to 0.5% at rates of 4 to 8 ml/hr may be used. Blood levels are similar to those seen with an epidural catheter.

COMPLICATIONS

Pneumothorax is estimated to occur in up to 0.5% of patients, yet most are not clinically significant and can be managed conservatively. Contrary to popular belief, violation of the parietal pleura does not result in aspiration of air unless the visceral pleura is also punctured or atmospheric air has entered the thoracic cavity. Instead, most patients will present with a sudden irritating cough or sharp pain in the chest. If the parietal pleura is violated, the block can be converted to an intrapleural block. It is important to remember that loss of resistance is not a consistent sign of entry into the PV space, and it is in these patients that US guidance should be of particular value. Also of note, patients with previous thoracotomy may have adhesions in the PV space, making PV catheter placement difficult.[8]

Life-threatening complications from PV blocks have occurred as a result of bolus dosing. A bolus dose can accidentally be injected into the intrathecal or epidural space, or into a blood vessel. Many authors have argued that it is bolus dosing with subsequent intrathecal or intravascular spread—and not pneumothorax—that is the greatest risk associated with this procedure.[13] Unilateral epidural spread is known to occur in 70% of patients; however, the majority of injectate remains confined to the PV and intercostal spaces.[14,15] Bilateral epidural spread can occur through the ipsilateral epidural space or the prevertebral space and is usually associated with bolus dosing or medial angulation of the needle. Vascular puncture has been reported to occur in up to 3.8% of patients.[14] Thus, graduated dosing either through a catheter or multiple injection points is recommended. Placement of PV blocks in the anticoagulated patient remains controversial and should probably be avoided, given that the space is in direct communication with the epidural space and not compressible.

CURRENT DEVELOPMENTS

A current focus in research involving PV blocks is centered around the hypothesis that regional analgesic techniques can reduce the risk of cancer recurrence in patients undergoing cancer surgery.[16] Proposed mechanisms include improved immune surveillance and natural killer cell function by reduction of the stress response to surgery.[17] Preoperative PV blocks can also decrease exposure to volatile anesthetics and morphine consumption, both of which have been shown to decrease both cellular and humoral immune function.[18,19] Morphine has also been shown to have proangiogenic properties and stimulates breast tumor growth by inducing tumor neovascularization.[18,19] Additional benefits of preoperative PV blocks include a decrease in the incidence of the development of chronic chest wall pain.[20]

INTERCOSTAL NERVE BLOCK

In patients with spinal anomalies, trauma, or previous spine surgery that have altered epidural or paravertebral anatomy, intercostal blocks can be used to provide chest wall analgesia.

ANATOMY

As nerves leave the PV space, they enter the intercostal space and lie between the innermost intercostal muscle and the pleura. Lateral to the paravertebral muscles, the prominent angles of the ribs are palpable as the primary landmark for intercostal nerve block. At the angle of the rib, the nerve lies between the innermost intercostal muscle and the inner intercostal muscle. Also, at this location, the thickness of the rib is 8 mm and the costal groove is known to be the widest.[21] Classically the intercostal nerves have been thought to lie caudad to the intercostal vein and artery, on the inferior portion of the rib. However, a cadaver study found that the intercostal nerve remained in a classic subcostal position only 17% of the time.[22] It was shown to be in a midcostal location most frequently (73%), and it was supracostal in some cadavers (10%). The intercostal nerves are the primary rami of thoracic nerves T1–T11. Most of the T1 nerve fibers combine with C8 to form the lower trunk of the brachial plexus. Fibers from T2 and T3 form the intercostobrachial nerve that supplies the upper chest wall along with cervical fibers from the brachial plexus. Intercostal nerves T4–T11 supply the thoracoabdominal wall from the nipple line to below the umbilicus. The T12 nerve is actually a subcostal nerve that contributes branches to the iliohypogastric and ilioinguinal nerves.[23]

TECHNIQUE

The ideal patient position is prone, with a pillow under the abdomen and both upper extremities hanging over the sides of the table, which maximizes retraction of the scapulae away from the upper ribs. This allows for bilateral blockade and posterior access to the angles of the ribs to enhance safety and success of the procedure. The lateral decubitus position is also quite satisfactory for unilateral blockade after rib fractures and lateral thoracotomy as well as for chest tube placement. The supine position may also be utilized for bilateral block at the level of the midaxillary line; however, the rib and intercostal space are narrower here.[24]

Classic techniques have described locating the angle of the rib (approximately 8 cm lateral to the midline) and using a 22-gauge, short-bevel needle to walk off 3 mm deep to the lower costal margin, and repeating this at the desired levels. More recently, US-guided approaches have been proposed.[25,26] US imaging is used to identify the space between the internal and innermost intercostal muscles 8 cm lateral to the spinous process, and D5W or saline can be injected to confirm needle tip position in the fascial plane and anterior pleural displacement. In a case report by Ben-Ari et al., the intercostal space was identified as described above, followed by placement of 19-gauge, wire-bound catheters.[25] The catheters were then advanced 7 cm to the PV space, achieving a spread of five dermatomes.

DOSING AND COMPLICATIONS

A single-shot intercostal block can be expected to provide analgesia for only 6 to 8 hours. Perineural catheter placement can provide for longer-lasting analgesia, and as described above the catheter can be advanced into the PV space. Total spinal anesthesia by injection into a dural sleeve is a rare but dangerous complication.[27] Local anesthesia toxicity as a result of bolus dosing may occur due to rapid uptake from the well vascularized intercostal space. Also, pneumothorax and liver subcapsular hematoma formation are potential complications. US guidance may aid in maintaining better needle tip control and minimizing the occurrence of these complications.

INTRAPLEURAL BLOCK

Intrapleural block may be used to provide unilateral chest wall analgesia during and after cholecystectomy, renal, breast, or thoracic surgery, as well for treatment of upper extremity ischemic and neuropathic pain, thoracic herpes zoster, pancreatitis, and thoracic cancer pain. When compared to intercostal blockade, intrapleural block produces analgesia that is less intense and of shorter duration.[28]

ANATOMY

The visceral layer of pleura surrounds the lung and reflects back on the chest wall and diaphragm to form the parietal pleura. The intrapleural space is a potential site for local anesthetic administration. Local anesthetics may block free nerve endings in the pleura and diffuse across the pleura to act on adjacent nerves. The intercostal nerves are present posteriorly and laterally, while the splanchnic nerves, sympathetic chain, phrenic and vagus nerves are medial to the pleura. The lowest roots of the brachial plexus pass superiorly, over the cupola of the lung.

TECHNIQUE

Intrapleural catheters are ideally placed in the lateral or semiprone position with the affected side uppermost. The ipsilateral arm should hang across the body or off the table to retract the scapula anteriorly. The endpoint for entry into the intrapleural space is detection of negative intrapleural pressure, which is present during spontaneous ventilation. Placement should be avoided during controlled ventilation to prevent catheter misplacement, lung injury, and pneumothorax.[29]

The site for catheter insertion is selected from the fifth through eighth intercostal spaces, and a skin wheal is raised immediately superior to the selected rib, approximately 8 to 10 cm lateral to the midline. A 17- or 18-gauge epidural needle is then inserted at the same site, with its bevel aimed in the direction of intended catheter insertion. The epidural needle is placed perpendicular to the skin, over the rib, and walked cephalad until contact with the superior edge of the rib is lost. Before slowly advancing the needle further, the needle stylet is removed, and a glass syringe containing approximately 2 ml of saline is attached. The entry into the pleural space is identified using passive loss-of-resistance technique. It is important to detect a plugged needle or a sticky syringe barrel, to prevent accidental placement of the needle through the visceral pleura into the lung parenchyma. When the needle tip is in the pleural space, the negative intrapleural pressure pulls down the syringe plunger and contained saline, and injection will be easy. The intrapleural catheter should be

threaded approximately 5 to 10 cm into the pleural space, taking care to reduce air entrained through the needle. An alternative technique utilizes a saline-filled syringe with its plunger removed. Entry into the pleural space is detected by a fall in the saline column, and the catheter may be introduced without having to remove the syringe.[30]

DOSING

The key to a successful analgesic response is proper patient positioning before local anesthetic injection. Injection with the operative side uppermost favors medial spread of solution and unilateral sympathetic block. Since the block sets up by mass action, delivery of the agent is influenced by gravity to thoracic spinal nerves emanating from the paravertebral area. Injection in the supine position favors blockade of the intercostal nerves with less sympathetic block. The block is then performed on the left side for pancreatic, gastric, or splenic pain and on the right side for hepatic or gallbladder pain. An initial test dose is used to detect accidental intravascular catheter placement. A therapeutic dose of 20 to 30 ml of 0.25% to 0.5% bupivacaine is delivered over 2 to 3 min, and patient position is subsequently maintained for 20 to 30 min during which time a chest tube should be clamped if present. Repeated bolus doses may be given every 6 hours, or as needed. A continuous infusion of 0.25% bupivacaine at 0.125 ml/kg/hr produced better analgesia after cholecystectomy, with lower blood levels, than intermittent bolus dosing.[31]

COMPLICATIONS

Complications from this procedure can be divided into two categories, those produced by traumatic injuries of either the needle or the catheter and those produced by systemic absorption of local anesthetic solution injected in the intrapleural space. Pneumothorax may occur in up to 2% of patients.[32] Pneumothorax or catheter malposition appear to be more likely with use of sharper needles, stiffer epidural catheters, and positive-pressure ventilation during needle and catheter placement. The following steps may minimize catheter-related risks: slow introduction of a soft, flexible tip catheter; use of a blunt epidural needle; and use of a heavy glass syringe barrel to better detect entry into the intrapleural space.[33] Systemic effects from drug absorption may occur, particularly with inflammation of pleural membranes. Local anesthetic toxicity was reported in 1.3% by Stromskag et al.[32] Peak local anesthetic levels occur after 20 to 30 min, and they exceed those seen after multiple intercostal blocks using equal doses. Pleural effusion has been reported infrequently, with a 0.4% incidence. Horner's syndrome occurs often after successful intrapleural block. Phrenic nerve palsy, bronchopleural fistula formation, empyema, and injury to the neurovascular bundle may also occur following this block. For these reasons, many physicians prefer to avoid bilateral blocks.

SUPRASCAPULAR NERVE BLOCK

Suprascapular nerve block (SSNB) is indicated for relief of acute and chronic pain in the shoulder, which may be due to bursitis, capsular tear, periarthritis, or arthritis.[34] Thirty-four patients with frozen shoulder received a series of three weekly suprascapular nerve blocks using 10 ml 0.5% bupivacaine or saline. A 64% reduction in the McGill Pain Questionnaire multidimensional pain descriptors score was observed in the treatment group, versus 13% in the placebo group, after 1 month.[35] In another randomized controlled trial, 83 patients with chronic shoulder pain due to arthritis received a single SSNB, for a total of 108 affected shoulders, using either 10 ml of 0.5% bupivacaine with 40 mg of methylprednisolone acetate or saline. Clinically significant improvements in all VAS pain scores, the shoulder pain disability index, the Short Form-36, and some range of movement scores were seen at weeks 1, 4, and 12 in the treatment group compared to placebo.[36] In conjunction with physical therapy, the SSNB increases the range of motion of the involved shoulder.

In a prospective, randomized, blind study, when SSNB was compared with interscalene nerve block for shoulder arthroscopy, it was found to be an appropriate alternative.[37] SSNB was used as a method of preemptive analgesia in patients who had various arthroscopic surgeries, and provided significant benefits days 1 to 3 after surgery.[38]

More recently, the SSNB has been used in conjunction with axillary nerve block to provide shoulder anesthesia and analgesia for shoulder surgery, including total shoulder arthroplasty.[39,40]

ANATOMY

The suprascapular nerve originates from the superior trunk of the brachial plexus (C4–C6), crosses the posterior triangle of the neck, and passes deep to the trapezius muscle. The nerve traverses the suprascapular notch and descends deep to the supraspinatus and the infraspinatus muscles,[41] supplying the two muscles and about 70% of the shoulder joint. Sensory innervation includes the posterior and posterosuperior regions of the shoulder joint and capsule, and the acromioclavicular joint (Fig. 76-4).

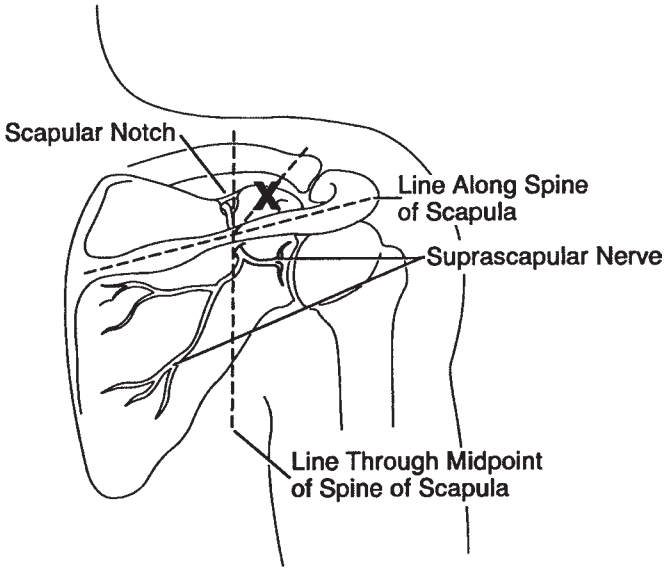

FIGURE 76-4 Anatomy and landmarks involved in suprascapular nerve block. *X* is the site of needle insertion. *(Adapted from Moore DC: Regional block: a handbook for use in the clinical practice of medicine and surgery, ed 4, Springfield, IL, 1979, Charles C Thomas, pp 300–303.)*

TECHNIQUE

The patient is positioned sitting, preferably with the arms folded across the abdomen. A line is drawn along the spine of the scapula from the tip of the acromion to the scapular border. The midpoint of this line is noted, and a vertical line, parallel to the vertebral spine, is drawn through it. The angle of the upper outer quadrant is bisected with a line; the site of insertion of the needle is 2.5 cm from the apex of the angle. A 3-inch (7.5 cm), 22-gauge needle is inserted perpendicular to the skin in all planes (Fig. 76-4). After contacting bone (i.e., the area surrounding the suprascapular notch) at approximately 5 to 6.5 cm, the needle is slightly withdrawn and redirected as needed until it slides into the notch. Up to 10 ml of local anesthetic is injected. No skin analgesia results from the block. Weakness of external shoulder rotation also confirms successful block.[42] Pneumothorax may occur in less than 1% of cases.

A modified lateral approach has been described as well, with 5 ml local anesthetic shown to be enough volume to fill the supraspinous fossa.[43]

Various guidance modalities, including fluoroscopy, fluoroscopy with nerve stimulation, CT guidance, and real-time US guidance have all been used. The US technique is less expensive, readily available, and devoid of radiation exposure for both personnel and patient.

ULTRASOUND GUIDANCE

The patient is positioned sitting. A high-frequency US probe is placed over the scapular spine in transverse orientation, and the suprascapular fossa with the supraspinatus muscle above it are scanned. Slight lateral movement will bring into view the suprascapular notch. The SSN is visualized as a hyperechoic structure beneath the transverse scapular ligament, in the suprascapular notch[44] (Fig. 76-5). High-frequency US has also been used to evaluate the suprascapular notch. The superior scapular ligament and the artery-vein complex, using color Doppler, were also visualized, in 96% and 86% of volunteers, respectively.[45]

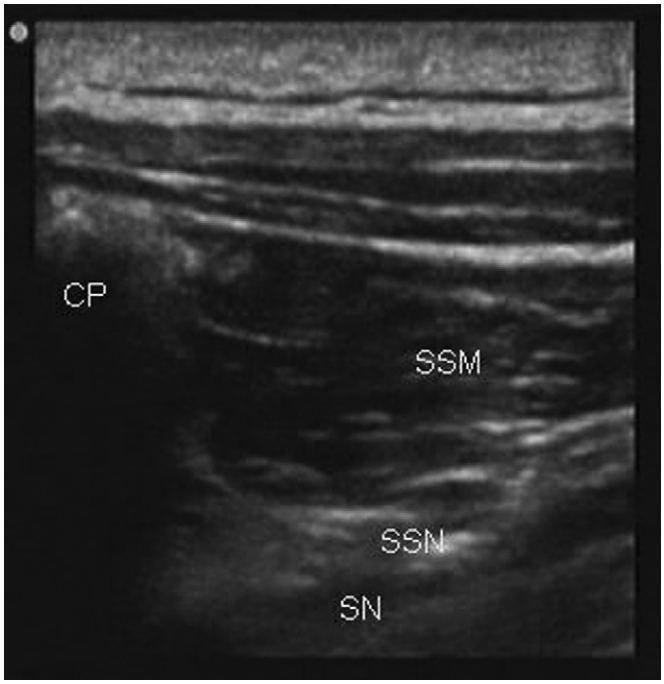

FIGURE 76-5 Ultrasonography of the suprascapular nerve. CP, coracoid process; SN, suprascapular notch; SSN, suprascapular nerve; SSM, supraspinatus muscle.

ILIOINGUINAL AND ILIOHYPOGASTRIC NERVE BLOCKS

Ilioinguinal and iliohypogastric nerve blocks may be used in the diagnosis and treatment of chronic suprapubic and inguinal pain after lower abdominal surgery or hernia repair. They may be combined with genitofemoral nerve block.[46] These blocks may be applied in the management of patients with neuralgias and nerve entrapment syndromes. Iliohypogastric and ilioinguinal nerve blocks are also important components of regional anesthesia of the inguinal region, typically performed for inguinal herniorrhaphy.[47-49] Bilateral ilioinguinal nerve block with 0.5% bupivacaine decreased analgesic requirements and pain scores for 24 hr after cesarean section performed under general anesthesia.[50]

A recent randomized, double-blind, placebo-controlled trial also showed that in patients post cesarean section, bilateral ilioinguinal iliohypogastric blocks using a multilevel technique were able to decrease the morphine consumption; however, there was no reduction in the opioid-related side effects.[51] These blocks do not provide visceral analgesia.

ANATOMY

The iliohypogastric (T12–L1) and ilioinguinal (L1) nerves emerge from the lateral border of the psoas major muscle, travel around the abdominal wall, and penetrate the transverse abdominal and the internal oblique muscles to innervate the hypogastric and inguinal areas. The anterior cutaneous branch of the iliohypogastric nerve passes through the internal oblique muscle just medial to the anterior superior iliac spine (ASIS), to lie next to the external oblique muscle. It then passes through the external oblique above the superficial inguinal ring, and supplies the suprapubic area. The ilioinguinal nerve remains between the deeper two muscle layers, it travels through the inguinal canal and supplies the upper medial thigh and superior inguinal region. An effective block of both nerves performed medial to the ASIS must be made at multiple depths, in various fascial planes. The genitofemoral (L1–L2) nerve passes through and along the anterior surface of the psoas major muscle, and it divides into genital and femoral branches above the inguinal ligament. Its genital branch travels with the spermatic cord and innervates the genitalia inferior to the area supplied by the ilioinguinal nerve.

TECHNIQUE

The patient is positioned supine, with a pillow under knees. The primary anatomic landmark is the ASIS, identified by palpation. The injection site is about 2 inches medial and 2 inches cephalad to the ASIS. A 25-gauge,

1.5-inch needle is inserted perpendicular to the skin, noting the double pop feeling when each layer of fascia is penetrated. Infiltration with about 10 ml of local anesthetic is performed at each depth and, subsequently, fanned in the area.[46] Supplemental infiltration of the incision and/or field block may be needed for surgery of the inguinal region. The genital branch of the genitofemoral nerve block can be blocked by infiltration of 5 to 10 ml of local anesthetic, using a 25-gauge, 1.5-inch needle inserted just lateral to the pubic tubercle and below the inguinal ligament. Infiltration around the spermatic cord at its exit from the inguinal canal is also an effective technique.[52]

Using anatomic landmarks in the setting of what is rather a field block can lead to variable results, not to mention the risk of visceral perforation in thin patients, especially in children.[53] US guidance allows a precise localization of nerves and surrounding sonoanatomy, visualization of injectate spread and increased safety with vizualization of peritoneum, bowels and vascular structures.

Ultrasound-guided approaches have been described both in children[54] and adults.[55] In a cadaver study Eichenberger et al had a simulated block success rate of 95%, when the nerves were targeted at 5 cm cranial and posterior to the ASIS.[56] US guidance also allowed for finding the optimal local anesthetic volume needed for this block, of only 0.075 ml/kg.[57]

The use of US-guided serial ilioinguinal nerve blocks has been recently reported for the treatment of chronic inguinal neuralgia in adolescents.[58]

Ultrasound Guidance: The patient is positioned supine, and a high-frequency US probe is placed superior and medial to the ASIS, on an imaginary line uniting the ASIS and the umbilicus. The nerves are usually visualized between the internal oblique and transversus muscles. An in-plane technique provides optimal access to the ilioinguinal and iliohypogastric nerves; hydrodissection may be useful to better delineate the narrow fascial plane. Small vessels, including the deep circumflex iliac artery, identified with color Doppler, may be present in the fascial plane. Deep to the transversus muscle the parietal peritoneum and bowel can be identified (Fig. 76-6).

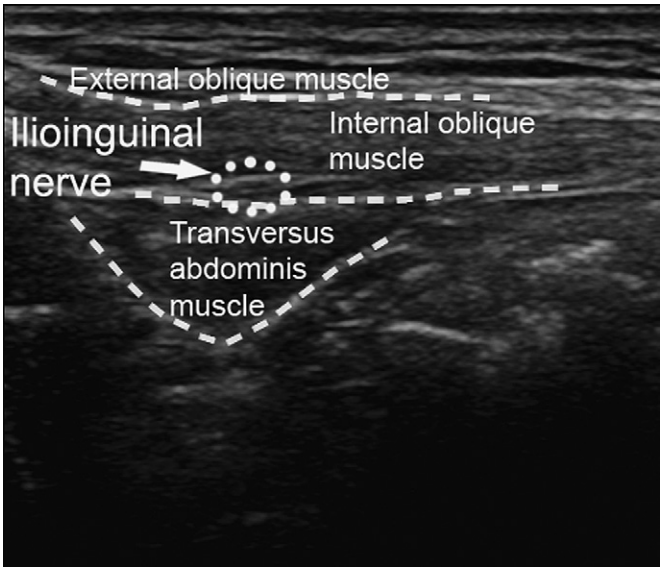

FIGURE 76-6 Ultrasonography of the ilioinguinal nerve.

COMPLICATIONS

A few complications can occur with these blocks, including ecchymosis, hematoma, visceral perforation, systemic toxicity, and infection. Accidental block of the lateral femoral cutaneous nerve and partial block of the femoral nerve may also occur.

TRANSVERSUS ABDOMINIS PLANE BLOCK

ANATOMY

The transversus abdominis plane (TAP) block, first described by McDonnell in 2007, uses anatomic landmarks to approach the plane through the triangle of Petit.[59] The triangle of Petit is bordered by latissimus dorsi posteriorly, the external oblique muscle anteriorly, and the ASIS as base of the triangle. The innervation of the anterior abdominal wall is provided by the anterior rami of the T7–T12 and L1 nerves, whose terminal branches are coursing in the fascial plane between the internal oblique and the transversus abdominis muscle, the transversus abdominis plane.

TECHNIQUE

Using anatomic landmarks, the TAP is accessed through the triangle of Petit. A "double-pop" technique is used to confirm the needle passage through the external oblique fascia, followed by the passage through the fascial plane between the internal oblique and the transversus abdominis muscles.

Ultrasound Guidance: The three muscle layers, the external oblique, internal oblique, and transversus abdominis, and needle insertion plane, between the internal oblique and transversus abdominis muscles, can be easily vizualized when the probe is placed above the ASIS.[60] An in-plane or out-of-plane technique can be used. Hydrodissection of the plane may facilitate accurate placement of the needle. Fifteen to 20 ml of local anesthetic are typically used on each side (Fig. 76-7).

Ultrasound-guided TAP blocks have been used to provide postoperative analgesia for lower abdominal surgeries, including inguinal hernia repair, cesarean section[61] and retropubic prostatectomy.[62] A subcostal approach has been described for laparoscopic cholecystectomy.[63] It has also been used to provide postoperative analgesia for other upper abdominal surgeries, including laparoscopic surgeries such as appendectomy and incisional hernia repair.[64]

Cadaver studies have confirmed T9–L1 spread,[65] and T9–T11 with the subcostal approach.[66] Radiologic studies have confirmed spread beyond the TAP to the paravertebral and intercostal space.[67] The TAP block is devoid of any hemodynamic effects, and provides no visceral analgesia.

Good pain control, with sparing of opioids consumption and increased patient satisfaction, have been demonstrated with abdominal and pelvic surgeries.

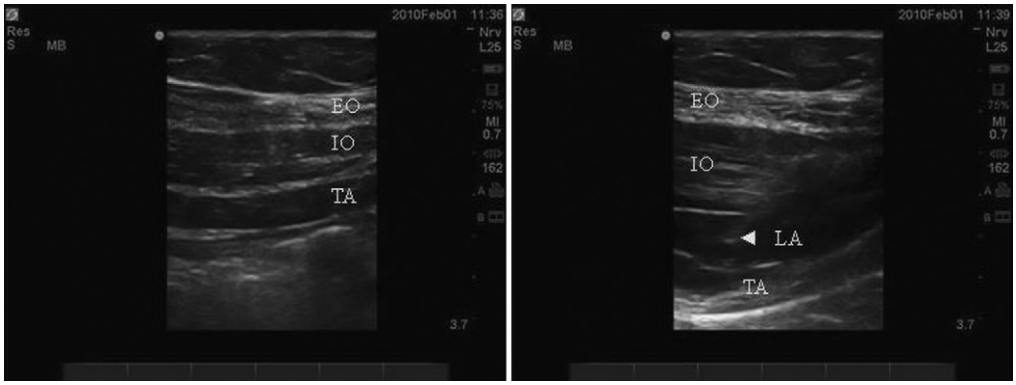

FIGURE 76-7 Ultrasonography of the transversus abdominis plane. EO, external oblique muscle; IO, internal oblique muscle; TA, transversus abdominis muscle; arrow, needle tip in transversus abdominis plane; LA, local anesthetic in transversus abdominis plane.

KEY POINTS

- When compared to epidural analgesia for thoracotomy, paravertebral blocks with catheters provide equipotent analgesia with a lower incidence of pulmonary complications, hypotension, urinary retention, nausea and vomiting, and failure rate.
- A single injection of 15 ml in a thoracic paravertebral space can be expected to provide analgesia over 3 to 4.6 dermatomes, with a preferential caudad spread of injectate.
- Ultrasound imaging usually underestimates the distance to the transverse process and paravertebral space by 0.3 to 0.7 mm because of skin compression by the scanning head.
- Total spinal anesthesia by injection into a dural sleeve is a rare but dangerous complication of both paravertebral and intercostal nerve blocks.
- Suprascapular nerve block has proven efficacy for significant pain relief and functional improvement in patients with shoulder arthritis or frozen shoulder.
- Ilioinguinal nerve block is effective in postinguinal hernia repair neuralgia.
- The US-guided TAP block is an attractive alternative for improved analgesia for various abdominal and pelvic surgeries.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 77

Blocks of the Lumbar Plexus and its Branches

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LUMBAR PLEXUS BLOCK

ANATOMIC CONSIDERATIONS

Unlike the brachial plexus, which is superficially located throughout most of its trajectory, the roots of the lumbar plexus are deeply located, coursing through the substance of the psoas major muscle in their journey from the lumbar paravertebral space to the lower extremity (Fig. 77-1).[1,2] The fasciae of the large psoas major muscle (anteriorly) and quadratus lumborum muscle (posteriorly) invest the lumbar plexus from its origin at the anterior primary rami of the L1, L2, L3, and L4 nerve roots. However, this relationship is inconsistent and somewhat unreliable. Successful lumbar plexus catheters have been found within the substance of the psoas major muscle in 74% of patients (59/80) and in the space between the psoas major and quadratus lumborum muscles in 22% of patients (18/80) when evaluated radiographically.[3] Occasionally, the lumbar plexus receives contributions from T12 or from L5. The proximal part of the lumbar plexus supplies the iliohypogastric and ilioinguinal nerves, which are in series with the thoracic nerves and innervate the lower trunk. The iliohypogastric nerve supplies the skin of the buttock and the muscles of the abdominal wall. The ilioinguinal nerve supplies the skin of the perineum and adjoining inner thigh. The genitofemoral nerve (from L1 and L2) supplies the genital area and adjacent thigh. The three major components of the lumbar plexus (femoral, lateral femoral cutaneous, obturator nerves) soon divide and take widely divergent courses down through the pelvis toward their ultimate destinations in the leg.[2] Of the three nerves, only the largest branch of the lumbar plexus, the femoral nerve, remains in close proximity to the psoas muscle as it descends toward the leg. The lateral femoral cutaneous nerve leaves the lateral border of the psoas major muscle at about its midpoint and enters the lateral thigh at a very superficial level. The obturator nerve leaves the medial border of the psoas major muscle and enters the medial thigh at a deeper level, within the adductor muscle compartment.

The femoral nerve derives from the dorsal portions of L2, L3, and L4, and descends from its origin to appear at the lateral margin of the psoas major at approximately the junction of the middle and lower thirds of that muscle. As the nerve continues on its descent toward the leg, it remains between the psoas major and the iliacus muscles so that, proximal to the inguinal ligament, the femoral nerve is surrounded laterally by the iliacus fascia, medially by the fascia of the psoas major, and anteriorly by the transversalis fascia. Distal to the inguinal ligament, the fused iliopsoas fascia continues to provide a posterior and lateral wall to this compartment.

At least in theory, the lumbar plexus may therefore be blocked using an anterior approach distal to the inguinal ligament (the inguinal paravascular technique) that attempts to block the three major nerves using a modification of the standard femoral nerve block technique (3-in-1 block). In practice, however, blockade of the three nerves using a single injection of local anesthetic (LA) in the inguinal area does not occur consistently. It has been reported that the lateral femoral cutaneous nerve is blocked only 96% of the time and the obturator nerve 0% to 47% of the time despite the use of a large volume of LA.[4–6] It is possible that when three nerves are successfully blocked with this approach, the local anesthetic actually spreads laterally along fascial planes rather than ascending to the roots of the lumbar plexus. A cadaver study of six specimens showed that no single sheath encompasses all three nerves in the inguinal region,[7] and a clinical study in patients undergoing muscle biopsy showed no evidence of obturator nerve block.[8] However, a recent magnetic resonance imaging (MRI) study in seven volunteers did demonstrate that the anterior branch of the obturator nerve is blocked using this technique, in addition to the femoral and lateral femoral cutaneous nerves, even though the spread of 30 ml of LA did not reach the lumbar plexus itself at the level of the psoas muscle.[9] The lumbar plexus can also be blocked with a posterior approach or psoas compartment block.

INDICATIONS

Lumbar plexus block is indicated for surgeries of the thigh or knee, including above-the-knee amputation,[10] as a diagnostic and therapeutic tool for chronic pain disorders, or to provide analgesia for painful conditions of the proximal leg, including herpes zoster.[11] It can also provide analgesia following a variety of surgical procedures of the thigh or knee, including femoral shaft surgery, total knee and hip replacements, and open-reduction and internal fixation of acetabular fractures.[12–17] It has been shown to reduce opioid requirements as part of a multimodal analgesic regimen following total hip or knee arthroplasty.[18–23] Blood loss following total hip arthroplasty is reduced using this block when compared with general anesthesia.[24] Because the associated sympathetic nerve block is unilateral and postganglionic, the degree of blood pressure fluctuations is more limited than that following neuraxial block in a given individual.

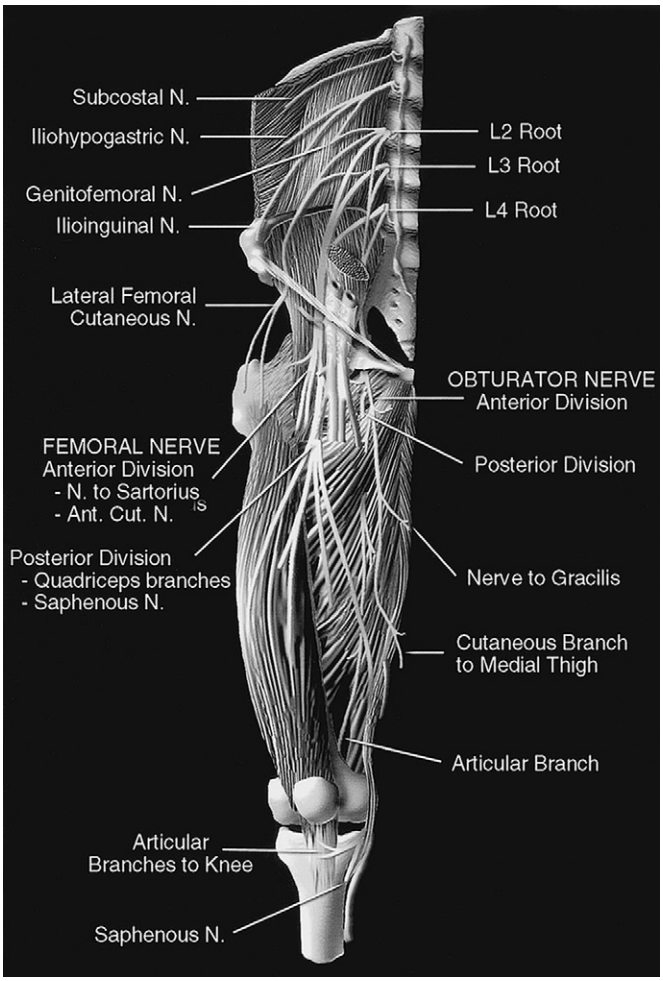

FIGURE 77-1 The lumbar plexus. Anterior view of the right leg. The three main roots (L2, L3, L4) are shown passing from their origins towards the psoas major muscle (transected in the figure), which they run through on their way toward the inguinal ligament. Demonstrated are the primary derivations of the plexus, the obturator, femoral, and lateral femoral cutaneous nerves, as well as the terminal branch of the femoral nerve, the saphenous nerve.

SURFACE LANDMARK–BASED TECHNIQUES

A posterior approach or psoas compartment block is typically performed with the patient in the lateral decubitus position with the intended surgical site uppermost. The upper thigh is flexed at the hip and the knee is flexed (i.e., Sim's position). A line is drawn between the iliac crests (intercristal line) and another one is drawn through the lumbar spinous processes. The posterior superior iliac spine (PSIS) is identified and marked. A line is drawn, parallel to that connecting the lumbar spinous processes from about L3 inferiorly, bisecting the PSIS. The site of needle insertion is where the parallel spinous line (or paraspinous line) bisects the intercristal line. An alternative technique, that of Chayen et al., moves the point of insertion about 3 cm distal to the intercristal line at the transverse process of L5 (Fig. 77-2).[25] Several investigators have found that this technique reliably produces blockade of the femoral, lateral femoral cutaneous, and obturator nerves in almost 100% of patients.[26,27] In either approach, a 4-inch, 22-gauge

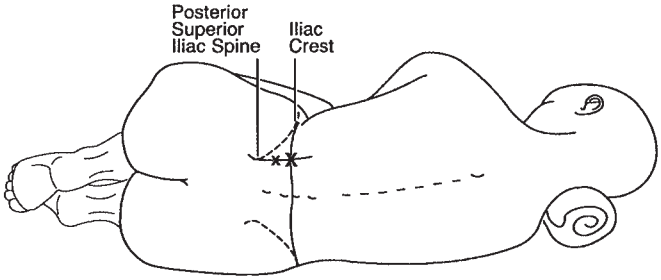

FIGURE 77-2 Psoas compartment block of Chayen and co-workers[25] and lumbar plexus block of Winnie and co-workers.[37]

insulated regional block needle is advanced perpendicular to all planes until the desired transverse process is encountered. The needle is then re-directed in a slightly cephalad direction and advanced slowly beyond the transverse process (not more than 2 cm after bony contact) until a quadriceps contraction is elicited, typically at a current of up to 0.5 mA.[28] The usual volume of local anesthetic is 30 ml, and agents commonly used are listed in Table 77-1.[3,29] Continuous catheter techniques can provide superior analgesia following major hip, thigh, or knee surgery. However, they are associated with an up to 2% risk of unintended epidural placement.[30] Other complications of posterior lumbar plexus block include systemic local anesthetic toxicity and retroperitoneal hematoma.[31,32]

The inguinal paravascular technique of lumbar plexus block (3-in-1 block) was originally described by Winnie, and his landmarks were later applied to nerve stimulator approaches.[33] With the patient in the supine position, the lateral edge of the femoral arterial pulse is palpated about 1 to 2 cm distal to the inguinal ligament. A 22-gauge, 2-inch insulated regional block needle is advanced using nerve stimulator guidance in a cephalad direction at about a 30° angle to the skin, with the needle entry point 1 cm lateral to the femoral artery. A quadriceps muscle response is sought at a current of up to 0.5 mA. Ultrasonic guidance has been used successfully to reduce the time to perform the block, improve complete sensory block, and reduce the amount of local anesthetic necessary for 3-in-1 block when compared with a nerve stimulator technique.[34,35] The desired volume of LA is then injected while maintaining firm digital pressure distal to the needle to encourage cephalad spread of the local anesthetic.[36–38] Increasing the volume of LA from 20 to 40 ml (mepivacaine 1%) modestly increases the chances of blockade of the three nerves.[39] Ropivacaine 0.25–0.5% and bupivacaine 0.25% provide similar degrees of analgesia following total knee replacement using a single-injection technique.[40,41] Other reported applications include hip fracture repair and knee arthroscopy.[42,43]

The major difference between 3-in-1 block and femoral nerve block is that a larger volume of LA is used, providing a greater degree of muscle relaxation and a longer duration of postoperative analgesia.[44] The benefit of a single-injection technique of lumbar plexus block versus separate blocks of the femoral, lateral femoral cutaneous, and obturator nerves is that it avoids multiple needle punctures.

TABLE 77–1 Local Anesthetics Commonly Used for Lumbar Plexus Block

Local Anesthetic Agent	Time to Onset (min)	Duration (hr)	Duration of POA* (hr)
Mepivacaine 1.5%	10–15	2.5–3	5–6
Mepivacaine 1.5% + Tetracaine 0.2%	10–15	3–4	8–12
Levobupivacaine 0.5%	20–30	4–5	12–16
Levobupivacaine 0.625%	10–15	5–7	16–24

** POA, postoperative analgesia.*
All local anesthetics include epinephrine 1:200,000 (5 mcg/ml).

ULTRASOUND-GUIDED TECHNIQUE

Ultrasound helps the anesthesiologist identify the relevant internal anatomic landmarks with precision to guide a safe and effective lumbar plexus block. The patient is positioned either in the sitting or lateral decubitus position with the side to be blocked uppermost. A low-frequency (4–5 MHz) curved array transducer ensures sufficient depth of imaging. An initial longitudinal paramedian scan allows precise identification of the intervertebral spaces. The probe is initially placed at the upper end of the sacrum (seen as a continuous hyperechoic line), just off the midline, in an oblique plane of imaging angulated toward the midline, and slowly maneuvered in a cephalad direction. The first "break" in this line represents the L5/S1 junction. The laminas of L5, L4, L3, and L2 are subsequently identified in a similar manner. The lower pole of the kidney can be found as caudally as L3/L4 on deep inspiration. It is prudent, therefore, to continue to scan higher and laterally until the kidney is identified (hypoechoic oval-shaped structure) to avoid accidental puncture (Fig. 77-3).[28]

The probe is then positioned at the interspinous level where the block is to be placed (Figs. 77-4 and 77-5) and rotated 90° from a longitudinal to a transverse orientation (Fig. 77-6). Important internal bony landmarks that need to be identified include the vertebral body, spinous

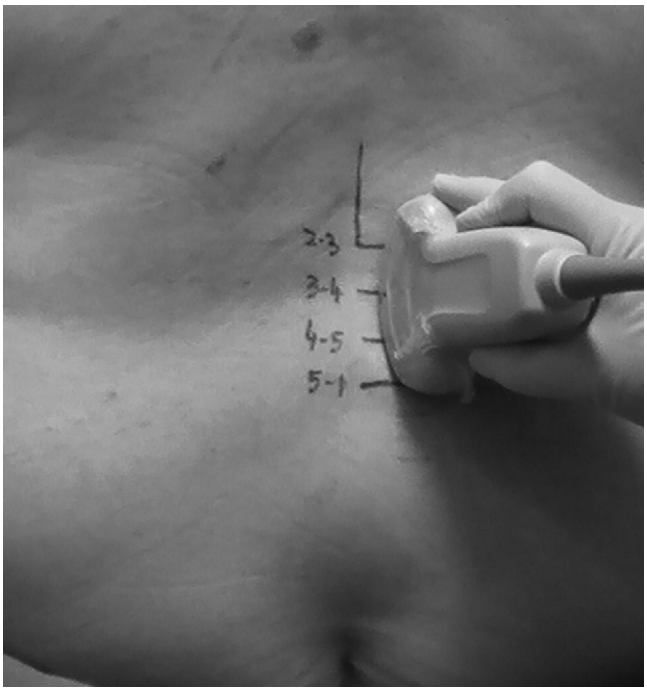

FIGURE 77-4 Lumbar spine. The probe is oriented in a longitudinal paravertebral plane, thus allowing the lumbar interspinous spaces to be identified.

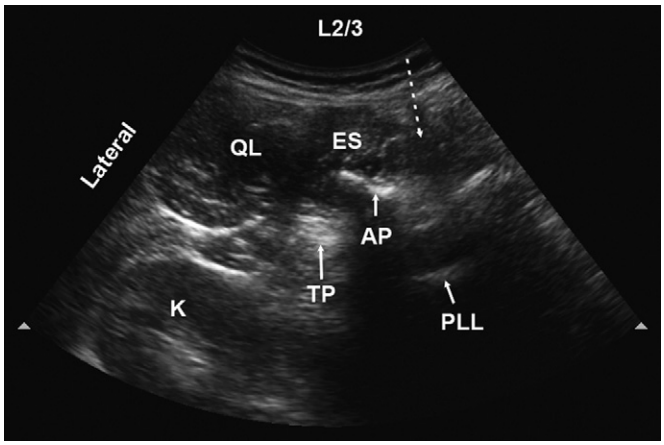

FIGURE 77-3 Transverse scan of L2/3 region. The psoas muscle is anterior (deep) to the transverse process. The bony shadow cast by the transverse process prevents the psoas muscle from being visualized. The kidney lies in close proximity. QL = quadratus lumborum; ES = erector spinae; AP = articular process; TP = transverse process; PLL = posterior longitudinal ligament; K = kidney; dotted arrow = midline.

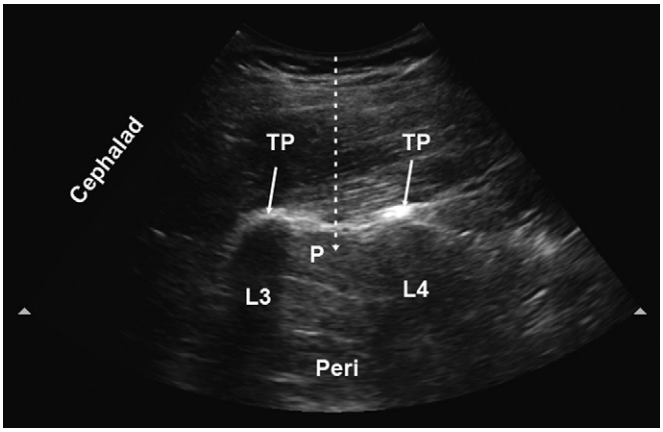

FIGURE 77-5 Longitudinal paravertebral scan at the L3/4 level. In this image the probe has been moved laterally to the tip of the transverse processes. The peritoneum lies anterior (deep) to the psoas muscle. P = psoas; TP = transverse process; dotted arrow = needle trajectory; Peri = peritoneum.

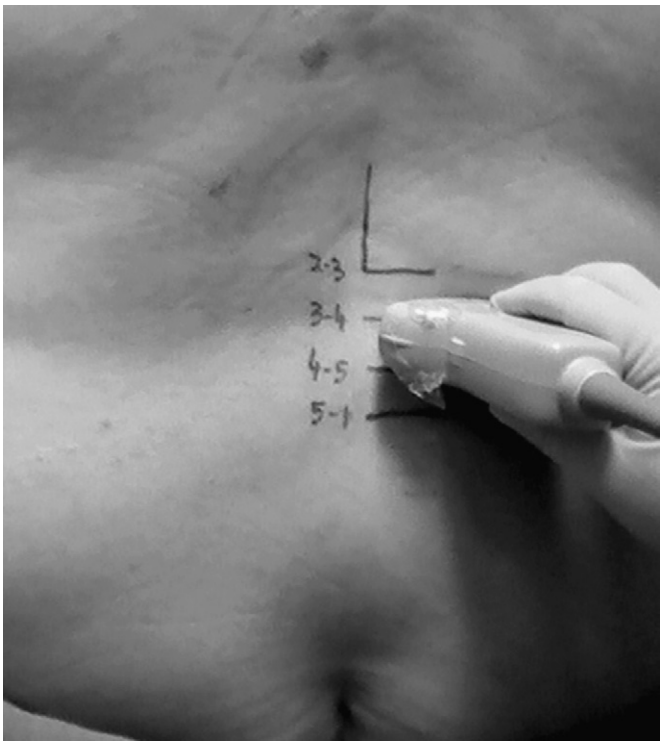

FIGURE 77-6 Lumbar plexus block. Scanning in a transverse paravertebral plane. The interspinous spaces have been identified and marked.

process, articular process, and transverse process. Important soft tissue structures to be identified include the erector spinae, quadratus lumborum, and psoas muscles (Fig. 77-7). Deep (anterior) to the psoas muscle, the intraperitoneal structures can be seen. The roots that form the lumbar plexus are rarely imaged in adults but are known to run through the posterior or middle third of the psoas muscle. It is this area that is targeted for LA injection. The distance from skin to the transverse process and from skin to the peritoneum should be measured for a precise estimation of the required needle insertion depth and the safety margin available for each individual patient.[45] A block needle can be inserted in-plane or out-of-plane with the ultrasound beam. Medial needle angulation is best avoided to prevent inadvertent subarachnoid injection. Imaging the entire needle shaft may not be possible due to the steep angulation required. Injecting 5% dextrose (D5W) in 0.5 to 1 ml increments can help locate the needle tip (the so-called hydrolocation technique). The needle should be advanced until its tip is positioned in the posterior third of the psoas muscle. A peripheral nerve stimulator can be used to confirm the position by observing quadriceps contraction. Color Doppler allows nearby vessels to be identified prior to LA injection. After negative aspiration, the desired LA volume may be administered in divided doses and fluid and tissue expansion can be observed within the psoas muscle. This technique can be modified for use in the prone position.[28,46] Pillows need to be placed under the abdomen to counteract the lumbar lordosis and widen the interspinous spaces. However, contraction of the quadriceps in response to nerve stimulation will be difficult to observe in this position. Alternatively, the lumbar plexus may be successfully blocked using the "trident" acoustic window (the shadows of the transverse processes in the longitudinal plane) as a landmark.[47] In a small case series using this approach, the lumbar plexus appeared hyperechoic, was sonographically distinct from the muscle fibers, and ran an oblique course through the psoas muscle. Similar to other nerves, the lumbar plexus roots may become sonographically more distinct after administration of LA.

In children the lumbar plexus itself can be more consistently visualized, likely due to a more superficial location, allowing higher frequency ultrasound probes with greater resolution to be used, and also the presence of larger soft tissue windows than in adults.[48]

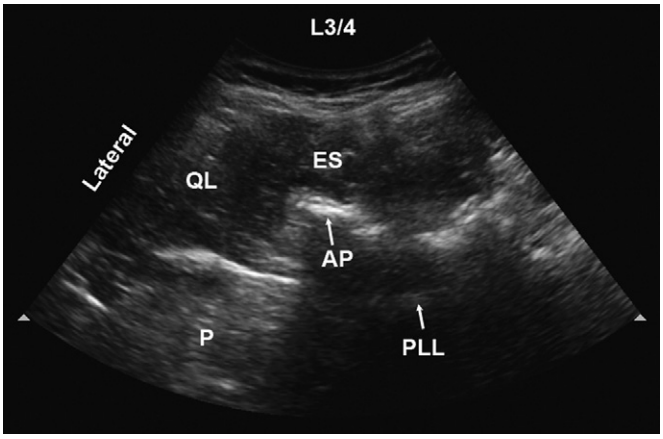

FIGURE 77-7 Transverse paravertebral scan at L3/4 interspace. The transverse process is not seen, as the ultrasound probe is positioned within the interspace. Moving in a cephalad–caudad direction will allow the transverse process to be visualized. P = psoas; QL = quadratus lumborum; ES = erector spinae; AP = articular process; PLL = posterior longitudinal ligament.

CONTINUOUS TECHNIQUES

If desired, continuous catheter techniques can be employed to prolong perioperative analgesia beyond the immediate perioperative period.[49–53] In early studies of 3-in-1 blocks, most intracaths were advanced 15 to 20 cm into the femoral sheath. However, it has been shown that complete 3-in-1 block is more likely following shorter catheter distances.[54,55] Several studies suggest lower pain scores and reduced opioid requirements as well as lower side effects in patients who received continuous 3-in-1 blocks following knee surgery, with comparable results to epidural analgesia.[56–61] Complications of continuous techniques are similar to those occurring after single-shot blocks and include femoral neuropathy and femoral nerve compression from a subfascial hematoma.[62,63] Systemic toxic reactions to local anesthetic may also occur from intravascular injection or from exceeding the recommended local dosing limits.[64] Arterial puncture and intravascular catheter placement, although rare, do occur, as does epidural block from advancing the catheter too far in a cephalad direction.[64]

FEMORAL NERVE BLOCK

ANATOMIC CONSIDERATIONS

The femoral nerve (L2–L4) courses from the lumbar plexus in the groove between the psoas major and iliacus muscles, where it enters the thigh by passing deep to the inguinal ligament. At the level of the groin crease, the femoral nerve lies anterior to the iliopsoas muscle and slightly lateral to the femoral artery (Figs. 77-8 and 77-9). At or above the inguinal ligament, the femoral nerve divides into anterior and posterior divisions; the anterior division innervates the skin over the anterior thigh and supplies the sartorius muscle, and the posterior division innervates the quadriceps femoris muscle, the knee joint, and its medial ligament, and also is the division from which the saphenous nerve is derived. Therefore posterior division block is essential for successful femoral nerve block for procedures of the anterior thigh and knee. The two divisions may lay one behind the other (Fig. 77-8) (as their names suggest, respectively), or side-by-side at the level of the groin crease (Fig. 77-9). Both divisions lie deep to the fascia iliaca. Stimulation of the anterior division results in muscle contraction of the medial thigh (sartorius twitch). The branches from the anterior division are primarily sensory and the branches from the posterior division are primarily motor. The technique of femoral nerve block is similar to the inguinal paravascular block of the lumbar plexus (Fig. 77-10).[65]

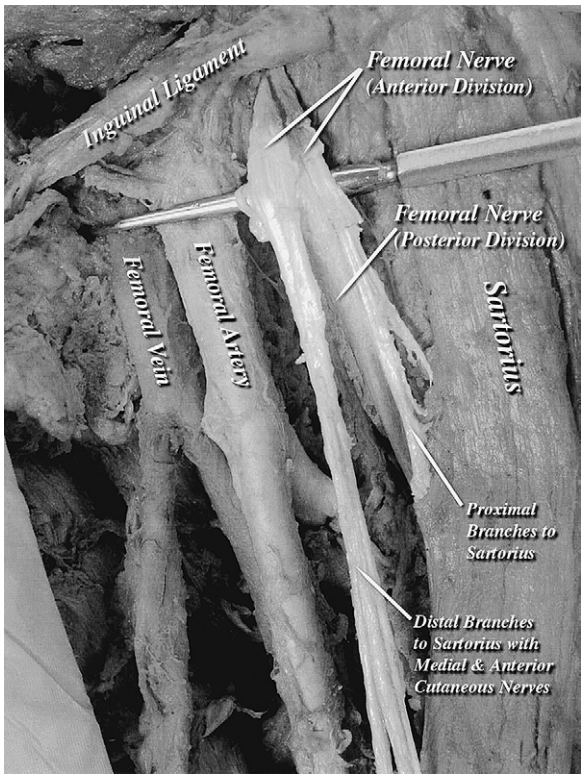

FIGURE 77-8 Cadaver dissection of the left femoral nerve, associated vascular structures, and the inguinal ligament. The posterior division of the femoral nerve is truly posterior to the anterior division and is seated somewhat medially.

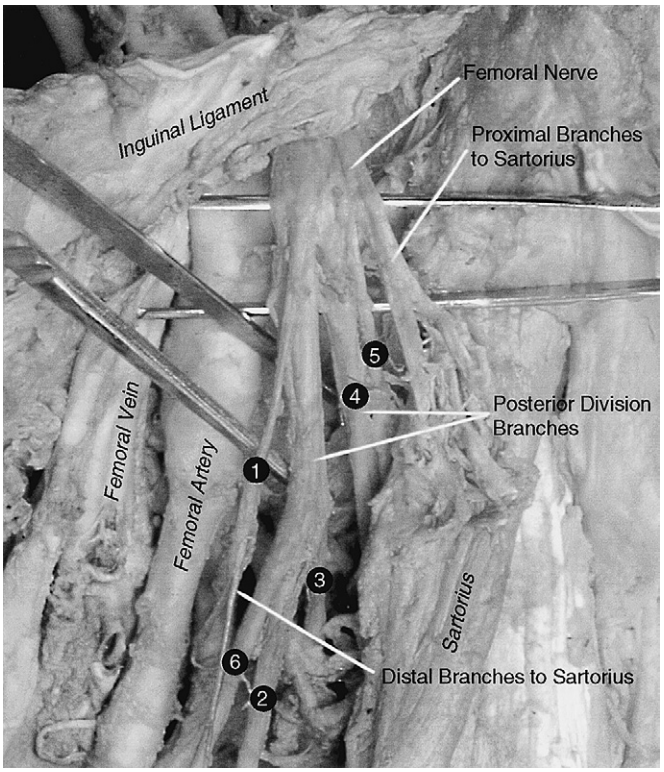

FIGURE 77-9 Cadaver dissection of a left femoral nerve, demonstrating a femoral nerve where the anterior and posterior divisions are seated side by side. *1*, Distal branches to the sartorius; *2*, saphenous nerve; *3*, nerve to the vastus lateralis; *4*, *5*, intermediate and medial femoral cutaneous nerves, respectively; *6*, nerve to the vastus medialis.

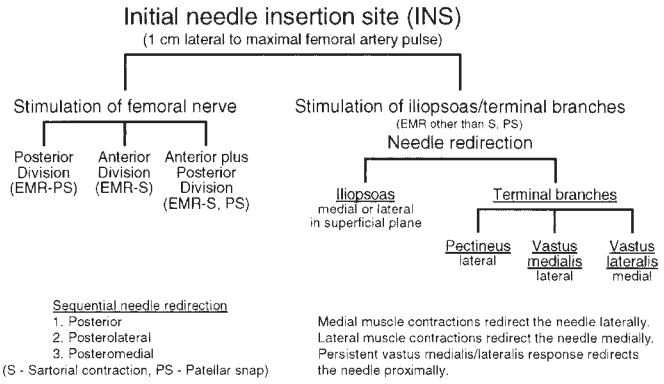

FIGURE 77-10 Algorithm for maximizing success using neurostimulation-assisted femoral nerve block (FNB).

INDICATIONS

Femoral nerve block can provide analgesia to a fractured shaft of the femur following total knee arthroplasty[66–68] and anterior cruciate ligament reconstruction,[69–71] or for skin graft donor sites of the anterior thigh. It may also suffice for analgesia following quadriceps tendon repair and in hemiplegic patients for the reduction of quadriceps spasticity.[72] It has been used in a patient-controlled analgesia (PCA) mode for analgesia following total hip or knee arthroplasty.[73,74] Compared with spinal block for saphenous vein stripping surgery, femoral and genitofemoral

nerve blocks provided superior analgesia and faster recovery times.[75] A large review of 1,200 cases seems to indicate that femoral nerve block is a valuable modality for reducing pain following complex knee surgeries.[76]

SURFACE LANDMARK–BASED TECHNIQUES:

The patient lies supine with the leg on the operative side extended. The needle entry site is marked using a felt-tipped marking pen, 1 cm lateral to the arterial pulsation at the level of the inguinal crease.[77,78] A 22-gauge, short-beveled, 2-inch insulated regional block needle is advanced from the injection site in a cephalad direction at a 60° angle to the skin surface. A peripheral nerve stimulator is used to elicit the "patellar snap" (quadriceps femoris muscle contraction) at a stimulating current of up to 0.5 mA. If a sartorius twitch is observed on the lower medial thigh, the stimulating needle should be advanced an additional 5 to 10 mm to stimulate the posterior division of the nerve (Fig. 77-8). Once a brisk patellar snap is observed, a volume of 20 to 25 ml of LA is incrementally injected. Bupivacaine or ropivacaine with epinephrine 1:200,000 are frequently used.[79–81] Alternatively, for shorter-duration block, 1% to 1.5% lidocaine or mepivacaine with epinephrine may be employed (see Table 77-1). Successful block is indicated by quadriceps muscle weakness, anterior thigh anesthesia, and saphenous nerve sensory analgesia.

ULTRASOUND-GUIDED TECHNIQUE

Ultrasound-guided femoral nerve block has been reported to improve onset time[35] and reduce the required LA volume.[82] The patient is positioned supine with the leg slightly abducted. A high frequency (10–15 MHz) linear array transducer is positioned over the inguinal crease (Fig. 77-11), and the femoral artery and vein are identified superficial to the ilio-psoas muscle. If more than one artery is observed, a location distal to the femoral artery bifurcation is implied, and the probe should be moved in a cephalad direction until the arteries converge.

The transducer is then moved laterally to locate the femoral nerve. The nerve is typically hyperechoic and located deep to the fascia iliaca (a continuous hyperechoic line) but superficial to the iliopsoas muscle (Fig. 77-12). It may appear oval, or more frequently, thin and flat. It has the typical honeycomb appearance of a peripheral nerve. The nerve may not necessarily be directly adjacent to the artery. Frequently, it is located some distance away from the vessels. The nerve can be distinguished from nearby lymph nodes by scanning in a proximal to distal direction. The nerve is a continuous structure, while lymph nodes are discrete.[45] A block needle is guided toward the lateral aspect of the nerve, where the posterior division of the nerve is often located. Either an in-plane (lateral to medial) or out-of-plane approach may be used. The needle tip must puncture the fascia iliaca. Dextrose 5% can be used to hydrodissect the area and enhance the image of the nerve. Nerve identity may be confirmed by obtaining a patellar twitch with peripheral nerve stimulation, if desired. However, no improvement in pre-operative efficacy has been found when nerve stimulation is used in conjunction with ultrasound compared with ultrasound alone for femoral nerve blockade.[83] After negative aspiration, the LA is injected in divided doses. A hypoechoic ring of LA should be observed below the fascia iliaca and anterolateral to the nerve. By scanning proximally and distally, the spread of LA can be noted. The above technique can be modified to allow for catheter placement. D5W may be used to expand the sheath compartment to facilitate catheter placement. An in-plane or out-of-plane approach may be used. Suggested methods to ease placement include keeping the needle tip slightly away from the target, turning the bevel to face in a cephalad direction, and caudal angulation of the needle hub.[84] No more than 3 to 4 cm of catheter need to be passed through the end of the needle.

Complications associated with femoral nerve block are similar to the inguinal paravascular block described previously and include vascular puncture with hematoma formation, intravascular injection, and femoral nerve palsy.

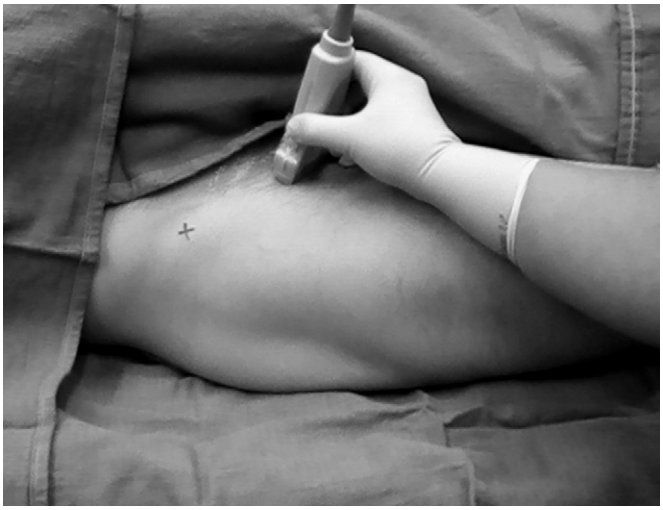

FIGURE 77-11 Femoral nerve block. The probe is placed transversely in the inguinal crease. X = anterior superior iliac spine.

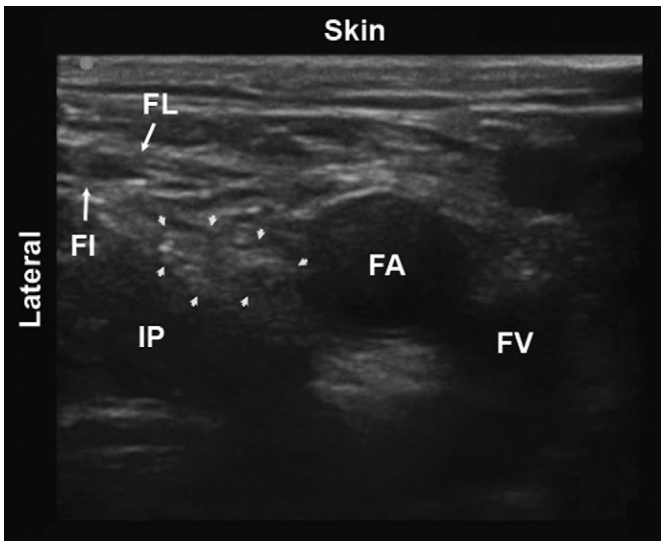

FIGURE 77-12 Ultrasound image of the inguinal region. *Arrowheads* = femoral nerve; FA = femoral artery; FV = femoral vein; IP = iliopsoas; FL = fascia lata; FI = fascia iliaca

Bacterial colonization of catheters is extremely common after 48 hours (57%) but catheter-related infection is very rare.[85] A history of previous ilio-inguinal surgery, including vascular grafting and resection of tumors or inguinal lymph nodes, is a relative contraindication to femoral nerve block.

LATERAL FEMORAL CUTANEOUS NERVE BLOCK

ANATOMIC CONSIDERATIONS

The lateral femoral cutaneous nerve (LFCN) is a purely sensory nerve that is derived from L2–L3 roots. After emerging from the lateral border of the psoas major muscle, the LFCN lies deep to the fascia lata, and medial and inferior to the anterior superior iliac spine (ASIS). The LFCN enters the thigh below the inguinal ligament, medial or lateral to the ASIS. There is a relatively consistent relationship between the LFCN and the tendinous origin of the sartorius muscle (Fig. 77-13), and LA infiltration anterior to the sartorius muscle, distal to the inguinal ligament, typically results in LFCN block. The LFCN divides into anterior and posterior branches about 7 to 10 cm below the ASIS. The anterior branch supplies the skin over the anterolateral aspect of the thigh as low as the knee, and the posterior branch supplies the skin over the lateral aspect of the thigh from just below the greater trochanter to about the mid-thigh. A peripheral nerve stimulator may be used to identify the posterior branch of the LFCN by eliciting a paresthesia over the lateral aspect of the thigh.

INDICATIONS

LFCN block can provide analgesia of a skin graft donor site on the lateral thigh, for performing muscle biopsies during work-up of malignant hyperthermia, or as a supplement to femoral and sciatic nerve blocks for lower extremity surgery where a thigh tourniquet will be required. LFCN block is an important aid in diagnosing the syndrome of meralgia paresthetica. Lack of significant pain relief in the presence of demonstrable analgesia in the lateral thigh area following the block may indicate a more proximal source of lateral thigh pain, including lumbar radiculopathy or intrapelvic pathology. Treatment of meralgia paresthetica may include repeated LFCN blocks using combinations of local anesthetics and corticosteroids. Following femoral neck surgery, LFCN block reduced opioid requirements postoperatively in a group of elderly patients.[86]

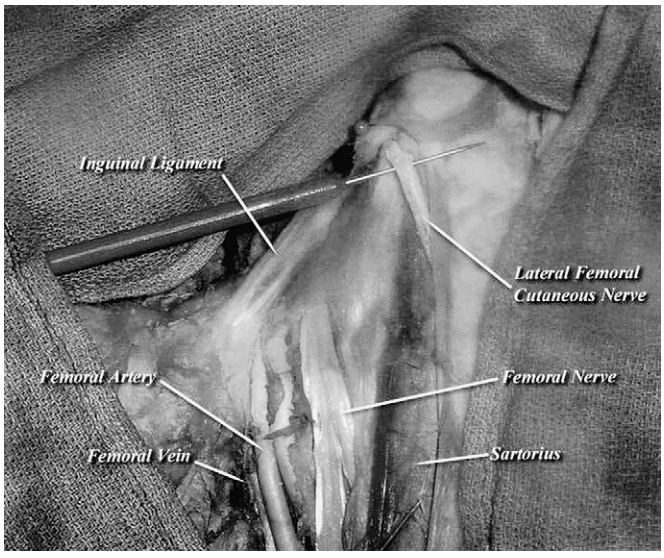

FIGURE 77-13 Cadaver dissection of the left thigh demonstrating the lateral femoral cutaneous nerve (LFCN) and its relationship to the sartorius muscle beneath the inguinal ligament.

SURFACE LANDMARK–BASED TECHNIQUES

The sensory stimulation technique is performed with the patient in the supine position. The ASIS is marked using a felt-tipped marking pen. A point 2 cm medial and inferior to the ASIS is identified and also marked.[87,88] A nerve stimulator is set to deliver a 2 to 3 mA current using a single-twitch cycle. The negative lead is moved from medial to lateral until a paresthesia is elicited corresponding to the innervation of the lateral thigh in the distribution of the posterior branch of the LFCN. This should represent an area variably described as an oblong spheroid shape on the lateral thigh from the greater trochanter inferiorly to the knee. The paresthesia should coincide with the nerve stimulation (i.e., the "beep" of the blockade monitor). An uninsulated 22-gauge, 2-inch regional block needle connected to the nerve stimulator is then introduced and the same paresthesia should be elicited at 0.5 to 0.6 mA at 1 Hz. A total volume of 5 to 8 ml of local anesthetic should be incrementally injected in divided doses. Success rates have been reported to be higher with this approach as compared to the classic technique (100% versus 40%).[87] For the blind infiltration technique (the so-called classic approach), the ASIS is again marked. A second point, 2 cm medial and 2 cm caudad to the ASIS is also marked. A 22-gauge, 2-inch short beveled needle is advanced through a local anesthetic skin wheal at this second point in a direction toward the ASIS (point one). As the needle traverses the fascia lata, a distinct "pop" will be felt. Fifteen to 20 ml of LA may be deposited in a fanwise manner, both above and below the fascia lata, specifically between the fascia lata and the sartorius (Fig. 77-14). Spillover of local anesthetic is always a possibility when performing LFCN block, being as high as 35% of cases, depending on the technique used.[87]

ULTRASOUND-GUIDED TECHNIQUE

With the patient in the supine position, a high-frequency linear array transducer is positioned transversely, just inferior and medial to the ASIS. By moving the probe in a caudad direction, the sartorius muscle is identified. This muscle has a triangular shape and runs obliquely and medially as it descends in the thigh. Superficial to the sartorius, the fascia lata and the fascia iliaca can be identified. The LFCN is located between these two fascial planes, running in a lateral direction anterior to the sartorius muscle (Fig. 77-15). Light pressure of the transducer prevents collapse of these fascial planes that house the nerve.

Identification of the nerve can be challenging due to its small size and lack of distinct accompanying vascular landmarks. It may appear as a discrete hyperechoic round,

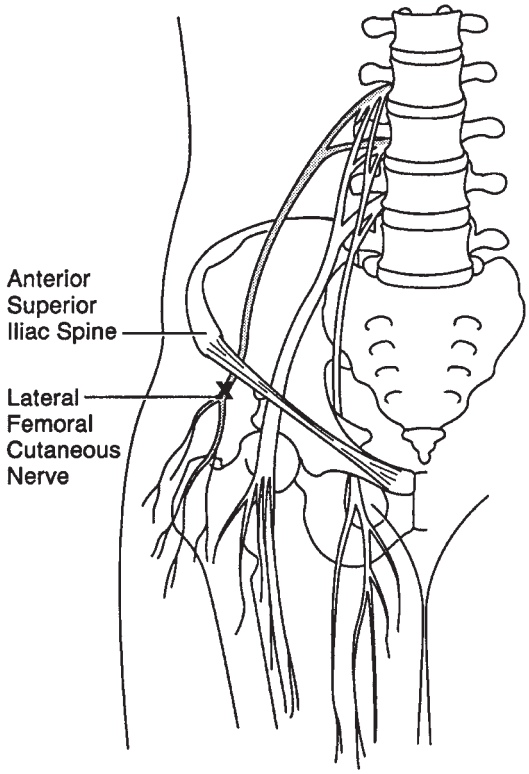

FIGURE 77-14 Lateral femoral cutaneous nerve block. The needle is inserted 2 cm medial and 2 cm inferior to the anterior superior iliac spine.

elliptical, or lip-shaped fibrillar structure. Moving the probe in a proximal-distal direction will help confirm the structure is a nerve. However, the LFCN will divide into multiple branches, making it harder to trace the more inferiorly the probe is moved.[89] Peripheral nerve stimulation may be used in conjunction with ultrasound to confirm nerve identification. Paresthesia in the distribution of the LFCN can then be sought prior to LA injection.[90]

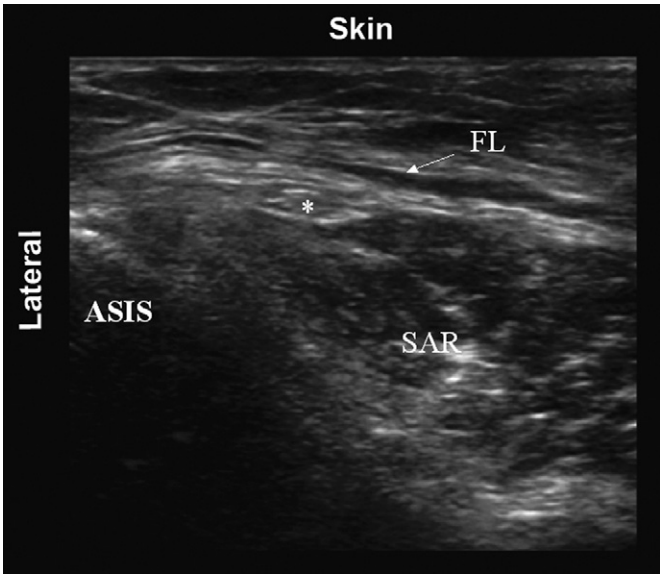

FIGURE 77-15 Ultrasound image of the lateral femoral cutaneous nerve of the thigh. *Asterisk* = LFCN; FL = fascia lata; SAR = sartorius; ASIS = anterior superior iliac spine.

The block needle is inserted in-plane to the probe and directed toward the nerve using a shallow angle. Like most other peripheral nerve blocks, needle advancement and LA spread may be guided in real time. A cadaveric study demonstrated greater accuracy of needle placement when the LFCN was identified using ultrasound guidance compared with the landmark technique.[91] This may reflect the highly variable course of the LFCN within the inguinal region. Alternatively, hydrodissection with D5W between the fascia lata and fascia iliaca may enhance the visibility of the LFCN.[45] In a study of 10 healthy volunteers, the best view of the nerve from the ASIS was on average 14.1 mm medial, 50.8 mm inferior, and at a depth of 6.1 mm when the US position was verified using a hand-held transdermal nerve stimulator.[91] As mentioned earlier, inadvertent blockade of the femoral and obturator nerves can occur with landmark techniques when blocking the LFCN. Ultrasound guidance may allow more accurate placement of the LA and the use of smaller volumes, thus decreasing the likelihood of blocking these two other nerves. A case series of 10 patients had successful blockade of solely the LFCN after 1 to 2 ml of LA was injected perineurally under ultrasound guidance.[92]

OBTURATOR NERVE BLOCK

ANATOMIC CONSIDERATIONS

The obturator nerve is derived from L2–L4, although the contribution from L2 is frequently small or even nonexistent.[88] The nerve emerges at the upper level of the medial border of the psoas major muscle at the approximate level of the sacroiliac joint and passes behind the iliac vessels from which it is separated by the fascia iliaca (Fig. 77-1). It continues its downward course with the iliac vessels and obturator artery and vein along the obturator groove and passes through the obturator foramen into the thigh. At the level of the obturator foramen or canal, the nerve divides into two terminal branches (anterior and posterior) that supply the medial thigh. The anterior branch supplies an articular branch to the hip joint and the anterior adductor muscles (pectineus, adductor longus, adductor brevis), and makes a small cutaneous contribution to the medial and inferior thigh. The posterior branch innervates the deep adductor muscles (adductor brevis and magnus, obturator externus) and frequently sends a contribution to the knee joint. This small contribution may be important for determining analgesia following knee surgeries. Up to 30% of individuals may have a small accessory obturator nerve derived from the ventral rami of L3 and L4. This accessory branch may give off rami to the pectineus and hip joint.[93]

INDICATIONS

Obturator nerve block is indicated in the diagnosis and management of painful conditions of the hip and for the relief of adductor spasm of the hip. Radiofrequency lesioning of sensory branches of the nerve has been successfully used to treat hip joint pain in 14 patients.[94] The block is also a valuable adjunct to femoral and lateral femoral cutaneous

nerve blocks for surgeries of the knee, or for analgesia for surgical tourniquets placed on the thigh. In a group of 60 patients, obturator block provided superior analgesia when combined with femoral and sciatic nerve blocks for total knee replacement, versus those cases unaccompanied by obturator block.[95] The nerve may also be blocked as an adjunct for transurethral surgeries for bladder tumors, since subarachnoid block or general anesthesia without the aid of muscle relaxants does not routinely prevent adductor muscle contractions that could contribute to bladder perforation, bleeding, or incomplete resection.[96–99]

SURFACE LANDMARK–BASED TECHNIQUE

The patient is placed in the supine position with the leg to be blocked slightly abducted. The pubic tubercle is palpated and a local anesthetic skin wheal is raised 1 to 2 cm below and 1 to 2 cm lateral to it. A short-beveled, 22-gauge, 3.5-inch needle is advanced through the skin wheal in a slightly mesiad direction until the ramus of the pubis is contacted. Once the horizontal ramus is identified, typically at a depth of about 1.5 to 4 cm, the needle is withdrawn and re-advanced in a cephalad direction to attempt to enter the obturator canal. This should occur at a depth about 2 to 3 cm deeper than that at which the ramus was contacted. Once the canal has been contacted, the needle must again be withdrawn and redirected slightly laterally and inferiorly until it enters the obturator canal (Fig. 77-16). Once within the canal, the needle is advanced 2 to 3 cm, and after ascertaining via negative aspiration that the obturator vessels have not been punctured, 10 to 15 ml of local anesthetic are incrementally injected. It is essential to identify the bony wall of the obturator canal to verify that the needle has not entered contiguous structures such as the rectum or vagina, which lie medially and superiorly.[88] As an alternative technique, a peripheral nerve stimulator may be used to find the nerve. In this approach, the 22-gauge insulated regional block needle is advanced until adduction of the thigh is noted at stimulating currents of less than 0.5 mA. Successful block is heralded by the onset of weakness of thigh adduction.[88,100,101] A modification of the above-mentioned techniques is the use of the upper end of the adductor longus muscle as a landmark for needle insertion.[102] The needle is directed laterally and in a cephalad direction using nerve stimulator guidance, and has been reported to result in a higher success rate than the traditional block (80% versus 60%).

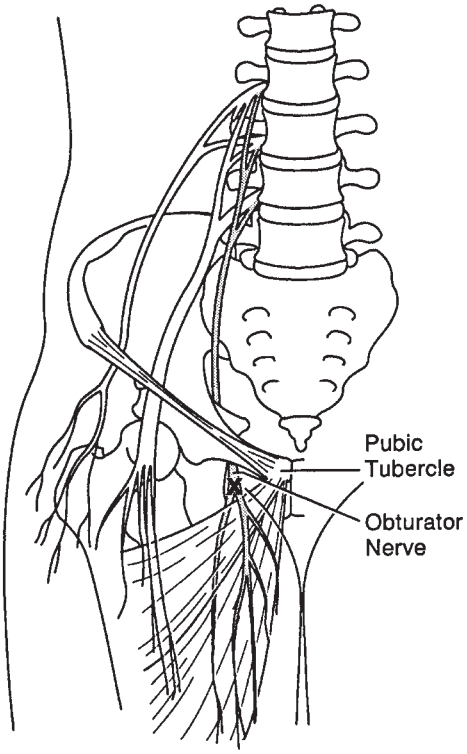

FIGURE 77-16 Obturator nerve block. The site of needle insertion is 1 to 2 cm inferior and 1 to 2 cm lateral to the pubic tubercle. The needle is redirected in a lateral and superior direction after the horizontal ramus of the pubic bone is contacted.

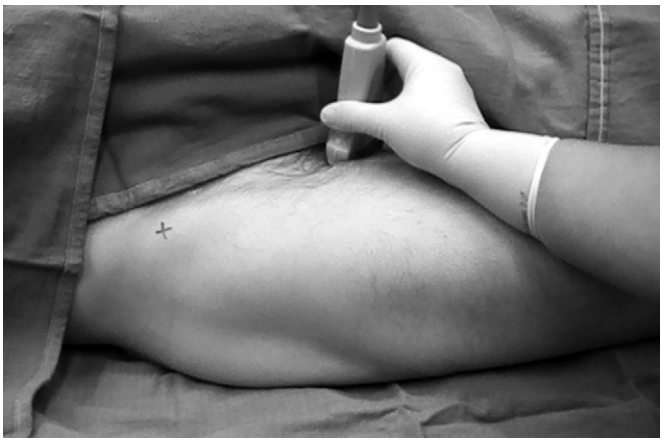

FIGURE 77-17 Obturator nerve block. The probe is placed transversely on the medial aspect of the inguinal crease/upper thigh. X = anterior superior iliac spine.

ULTRASOUND-GUIDED TECHNIQUE

With the patient in a position similar to that for a landmark-based technique, a high-frequency linear-array transducer is placed in the inguinal crease and the femoral vessels are identified (Fig. 77-17).[103] Medial to the vessels lies the pectineus muscle. More medially the three adductor muscles can be observed—adductor longus (the most superficial), adductor brevis, and adductor magnus (the deepest). At this location the nerve has most likely divided into its anterior and posterior branches (Fig. 77-18). These branches are small in size (2–3 mm in diameter) and are found within the fascial planes investing adductor brevis. (The anterior division lies between adductor longus and adductor brevis; the posterior branch between adductor brevis and adductor magnus.) Tilting the probe 30° to 60° cranially may help visualize the nerves or fascial planes,[104,105] The nerves usually appear as fascicular structures, flat or lip-shaped with discrete hypoechoic internal areas.[103–105] In a study with 20 volunteers, divisions were observed more often (anterior 85%, posterior 87.5%) than the common obturator nerve (25%).[103] The common and posterior nerves lie deeper than the anterior branch. The block needle is advanced, aiming to target both branches. An out-of-plane[45] or in-plane[106] (lateral to postero-medial direction) approach may be used.

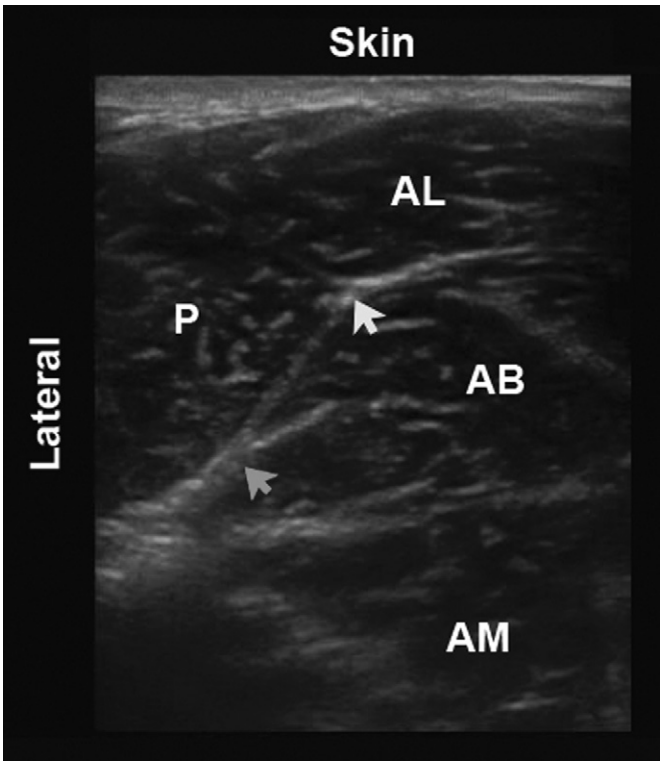

FIGURE 77-18 Ultrasound scan of the obturator nerve. The obturator nerve has divided into its anterior and posterior divisions. These branches lie within the fascial planes investing adductor brevis. *White arrowhead* = anterior division of obturator nerve; *gray arrowhead* = posterior division of obturator nerve; P = pectineus; AL = adductor longus; AB = adductor brevis; AM = adductor magnus.

A peripheral nerve stimulator confirms adductor motor response.[45] The LA should be deposited around each branch. Injection of LA around only one branch may lead to an incomplete block.[107,108] It is imperative to see interfascial spread, not muscle swelling. Hydrodissection between the fascial planes with D5W may enhance nerve visualization. Studies have shown that this block can be successfully performed using ultrasound but without nerve recognition by depositing LA between the fascial planes with[104] or without the aid of a nerve stimulator.[106] Potential side effects and complications of obturator block include intravascular injection, nerve injury with resultant neurapraxia or neurotmesis, and the aforementioned injection into contiguous, unintentional sites such as the rectum or vagina. Obturator arterial injury has also been reported in a patient undergoing resection of a bladder tumor.[109]

SAPHENOUS NERVE BLOCK

ANATOMIC CONSIDERATIONS

The saphenous nerve is the only cutaneous branch of the posterior division of the femoral nerve. It arises in the femoral triangle, descends lateral to the femoral artery, and then enters the adductor canal of Hunter, where it crosses over the artery to lie in an anteromedial position.[110] The saphenous nerve supplies an extensive cutaneous area over the medial side of the knee, leg, ankle, and foot. The nerve exits the lower part of the canal by emerging between the sartorius and gracilis muscles. At this level this small nerve becomes superficial (subcutaneous), and it soon divides into two branches: the infrapatellar branch innervates a small cutaneous area distal to the knee, and the sartorial branch runs down the medial aspect of the leg, innervating this area all the way to the ankle and sometimes the medial aspect of the foot.

INDICATIONS

Saphenous nerve block is required in conjunction with sciatic nerve block to provide complete anesthesia or analgesia to the ankle and as a component of ankle block for foot surgery. Chronic pain applications include blocks for saphenous neuralgia or saphenous nerve entrapment at the adductor canal.[111]

SURFACE LANDMARK–BASED TECHNIQUES

There are several approaches to blockade of the saphenous nerve. The saphenous nerve can be blocked above the knee, at the level of the knee, below the knee, and just above the medial malleolus. Blockade above the knee includes the perifemoral, subsartorial, and transsartorial approaches,[112–115] while blockade at the level of the knee includes the paracondylar saphenous field block (PSFB)[116,117] and the nerve stimulator technique,[118] where the nerve is blocked at the level of the medial femoral condyle. The saphenous nerve has also been blocked by subcutaneous infiltration below the knee distal to the medial condyle of the tibia (below-the-knee field block [BKFB])[119,120] and the paravenous approach.[121] Finally, the saphenous nerve can be blocked just above the medial malleolus of the foot.[119,120]

PERIFEMORAL APPROACH

The site of needle insertion is 5 to 6 cm distal to the inguinal crease, 0.5 cm lateral to the femoral artery.[122] At 2 to 4 cm depth, the nerve to the vastus medialis muscle is stimulated, resulting in the contraction of the medial aspect of the thigh. The vastus medialis muscle contracts secondary to stimulation of the nerve to the vastus medialis muscle, which runs alongside the saphenous nerve. The nerve to the vastus medialis muscle is used as a landmark to locate the saphenous nerve since the saphenous nerve is purely a sensory nerve.[112] Other investigators insert their needle on the line of the inguinal fold.[114] The higher needle insertion may block the other muscular branches of the femoral nerve, resulting in thigh muscle weakness.

TRANSSARTORIAL APPROACH

The sartorius muscle is identified; this is facilitated in the supine patient who elevates the extended leg. The site of needle insertion is 3 to 4 cm superior and 6 to 8 cm posterior to the superomedial border of the patella.[122] The insulated needle is inserted at an angle of 45° caudally and directed slightly posteriorly. Paresthesia may be elicited with a nerve stimulator at 3 to 5 cm depth.

In the original description of the transsartorial technique, a 17-gauge Touhy needle was inserted at one finger width proximal to the patella at an angle of 45° and advanced in a

caudad direction, through the belly of the sartorius muscle, until a loss of resistance was felt at a depth of 1.5 to 3 cm.[115] This implies that the needle tip is at the adductor hiatus and the local anesthetic is injected. We have noted that paresthesia to the medial leg and foot with the nerve stimulator is a very reliable indicator of saphenous nerve stimulation and consequent blockade.[122]

BELOW THE KNEE FIELD BLOCK

A linear subcutaneous injection of local anesthetic is made immediately below the insertion of the sartorius tendon at the tibial tubercle.[119,120] The infiltration is made in an anterior and posterior direction up to the anteromedial aspect of the gastrocnemius muscle.

Another approach in this area is the paravenous approach,[121] wherein the saphenous vein is identified in the medial head of the gastrocnemius muscle at the level of the tibial tubercle. Subcutaneous infiltration is made lateral and medial to the saphenous vein. In this technique the patient's leg hangs down and a tourniquet is used to make the saphenous vein prominent. A success rate of 100% has been reported with this technique.

BLOCKADE AT THE MEDIAL MALLEOLUS

Local anesthetic is injected subcutaneously above the medial malleolus of the foot.[119,123] The injection extended anteriorly and posteriorly above the medial malleolus. Other authors have recommended a subcutaneous infiltration around the great saphenous vein, immediately above the medial malleolus.[124]

A 10 ml volume of local anesthetic is injected with each of the above approaches. The reported success rates of the different approaches were 80% with the perifemoral approach, 90% with the transsartorial approach, 40% with the paracondylar approach, and 40% to 65% with the below-the-knee field block.

The most commonly used landmark approaches are the perifemoral approach, below-the-knee field block, and blockade of the nerve above the medial malleolus. The ultrasound-guided technique at the distal adductor canal (see below), especially with the saphenous branch of the descending genicular artery (SBDGA) as a landmark, has gained popularity.

ULTRASOUND-GUIDED TECHNIQUE

A well recognized limitation for saphenous nerve blockade is its small size (2–3 mm diameter) and the fact that it is exclusively sensory. For this reason, it has been suggested that blockade distally within the adductor canal before this nerve becomes subcutaneous provides consistent internal anatomic landmarks for the identification of this small nerve when using ultrasound. At the level of the adductor canal the saphenous nerve lies in close proximity to the femoral artery, immediately deep to the sartorius muscle. The patient is supine with the leg abducted and slightly externally rotated. A high frequency linear array transducer is placed on the medial aspect of the distal thigh perpendicular to the long axis of the leg (Fig. 77-19). Sartorius, vastus medialis, and the femoral artery are identified. In this area, the nerve is located antero-medial to the artery, deep to the sartorius muscle and medial to the vastus medialis (Fig. 77-20). It appears as a small, hyperechoic structure with a honeycomb internal appearance. The structure is confirmed to be neural by tracing its course as far as the adductor hiatus. Successful blockade can occur within the adductor canal (approximately 10–13 cm proximal to the knee crease) using the femoral artery as the landmark.[125,126] Using an in-plane needle approach in this area, 100% success has been reported in a series of 20 patients.[125] If the nerve cannot be visualized, placement of the LA immediately around the femoral artery and deep to the sartorius muscle may suffice. A potential downside of blocking the saphenous nerve at the adductor canal is concurrent blockade of some of the most distal branches of the motor nerve to the vastus medialis, which also accompanies the femoral artery in this region.[127] However, this will not result in complete quadriceps

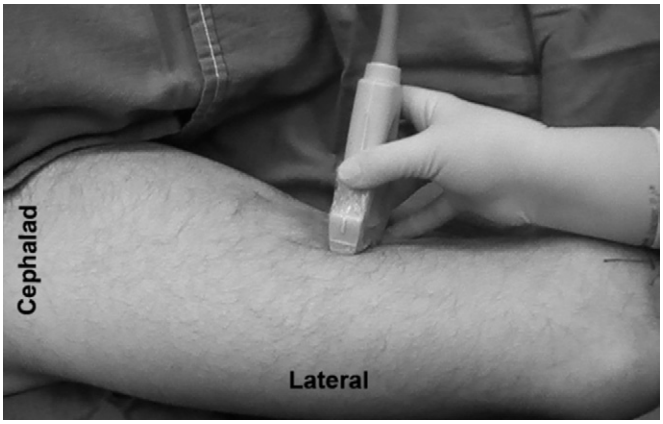

FIGURE 77-19 Saphenous nerve block. The probe is placed transversely over the medial aspect of the distal thigh. The leg is externally rotated.

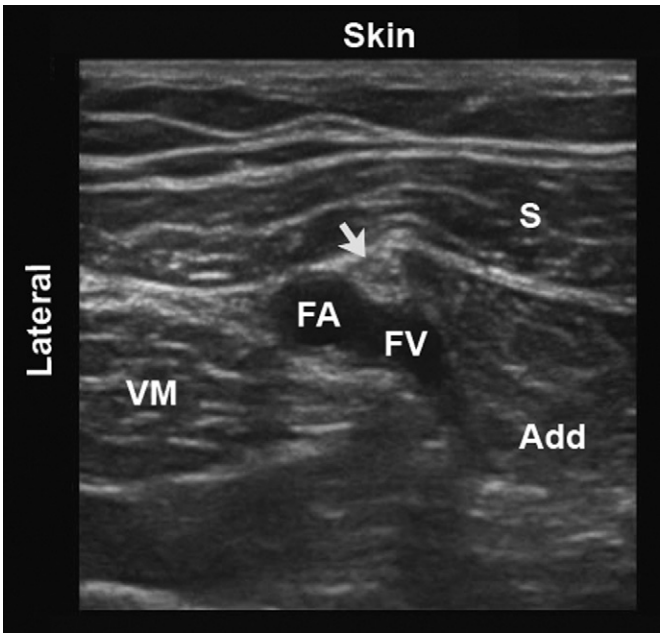

FIGURE 77-20 Ultrasound scan of the saphenous nerve. *Arrow* = saphenous nerve; VM = vastus medialis; S = sartorius; Add = adductor muscles; FA = femoral artery; FV = femoral vein.

weakness, only partial weakness of the vastus medialis. A suggested alternative approach is to block the nerve more distally after it leaves the adductor canal by piercing the fascial plane between the sartorius and gracilis muscles, using the saphenous branch of the descending genicular artery (SBDGA) as a landmark.[128,129] Cadaveric studies show that where this nerve divides, it is at its closest approximation to the SBDGA.[128] Color Doppler flow will help identify the artery. If the nerve cannot be seen, LA may be deposited under the sartorius, close to this artery. However, clinical experience is still limited. Blockade of the infrapatellar branch of the saphenous nerve has been reported.[130] Below the knee, the nerve is difficult to visualize. Its anatomic relationship to the saphenous vein in the proximal leg provides a substitute landmark (the nerve is adjacent to the vein). Application of a tourniquet allows the vein to become distended and more visible. Light probe pressure is required. A perivenous injection of LA may then be administered.[45] This same method can also be applied at the level of the ankle.

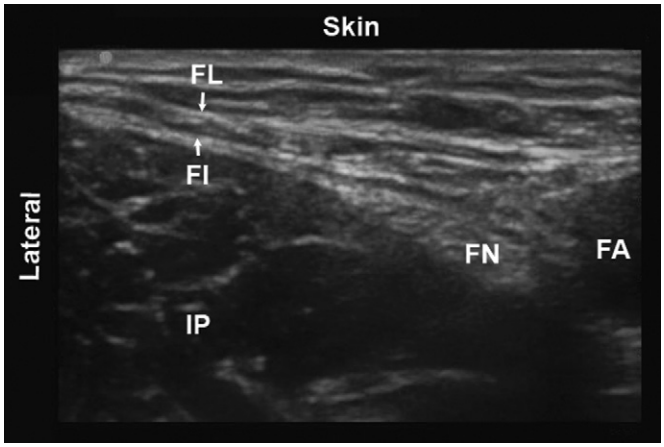

FIGURE 77-21 Ultrasound image for fascia iliaca block. FI = fascia iliaca; FL = fascia lata; FN= femoral nerve; FA = femoral artery; IP = iliopsoas.

FASCIA ILIACA BLOCK

ANATOMIC CONSIDERATIONS

The femoral nerve, LFCN, and obturator nerve run a considerable part of their course close to the inner aspect of the fascia iliaca. The fascia iliaca is attached medially to the vertebral column and upper part of the sacrum. It covers the psoas muscle and iliacus muscle and is attached to the inner lip of the iliac crest and pelvic brim. At the groin the fascia iliaca is continuous with the posterior margin of the inguinal ligament. Laterally it attaches to the ASIS. Medially it blends with the pectineal fascia. The fascia iliaca reflection thus forms a triangular potential space, the "fascia iliaca compartment." Distally, at the level of the femoral triangle, the fascia iliaca becomes narrow. It is covered by the fascia lata and forms the roof of an adipose-filled space known as the lacuna musculorum, which lies adjacent to the femoral vessels. It is postulated that injection of a sufficient volume of local anesthetic solution into the lacuna musculorum favors cephalad migration toward the iliacus muscle, facilitating spread of LA within the entire fascia iliaca compartment and resulting in blockade of all three component nerves (femoral, obturator, LFCN) that lie within it.[131]

INDICATIONS

Indications for fascia iliaca block are similar to those of inguinal paravascular lumbar plexus block. The technique has been successfully used in the prehospital treatment of femoral fractures.[132] It can provide analgesia following total knee replacement surgery and a variety of other proximal surgeries of the lower extremity.[133–137]

SURFACE LANDMARK–BASED TECHNIQUE

With the patient in the supine position, a line is identified from the anterior superior iliac spine to the pubic tubercle. The needle entry site is 1 cm distal to the point where the middle and lateral thirds of the inguinal line meet. A 22-gauge short-beveled regional block needle is inserted at the marked site and advanced in a cephalad direction at a 75° angle to the skin. Alternatively, a 20-gauge Tuohy-type needle may be substituted. The "loss of resistance" (tissue "pop") will be appreciated as the needle tip traverses the fascia lata.[135,136] The needle continues to be advanced, however, until a second loss of resistance is experienced. This second loss of resistance corresponds to the needle entering and passing through the fascia iliaca. The 75° angle of the needle to the skin is then reduced to about 30° and the needle is advanced an additional 1 cm in a cephalad direction. After negative aspiration tests, a volume of local anesthetic (25 to 30 ml) is incrementally injected in divided doses.

ULTRASOUND-GUIDED TECHNIQUE

Ultrasound scanning of the inguinal area has revealed the existence of multiple fascial planes.[138] It has been postulated that blind penetration of this area may result in the deposition of LA into the wrong fascial space and a subsequent failed block. The addition of ultrasound to the traditional landmark technique could ensure placement of the LA within the correct plane. A high-frequency linear-array transducer is placed transversely over the area of the inguinal ligament. Two fascial planes (fascia lata and the deeper fascia iliaca) will be observed. They appear as two distinct continuous hyperechoic lines (Fig. 77-21). Slight tilting of the probe in a cephalad or caudad direction may improve the view of these two planes. A block needle is inserted in-plane to the probe. The needle tip should lie just below and deeper to the fascia iliaca. After negative aspiration, the desired LA is then injected in divided doses. LA should be noted to spread both in a medial and lateral direction under the fascia iliaca. A study of 80 patients comparing the traditional landmark technique with ultrasound-guided fascia iliaca block demonstrated an increase in sensory loss in the medial, anterior, and lateral aspects of the thigh within the ultrasound group. This group also showed an increase in femoral and obturator motor blockade.[138]

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Access the reference list online at http://www.expertconsult.com

CHAPTER 78

Sciatic Nerve Block and Ankle Block

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INTRODUCTION

The sciatic nerve provides sensory innervation to the back of the thigh and the entire leg below the knee except for its medial aspect, which is innervated by the saphenous nerve. It also provides motor innervation to the hamstrings and all the muscles below the knee. Sciatic nerve block in conjunction with lumbar plexus block, femoral nerve block, or saphenous nerve block can be used to provide anesthesia and analgesia for surgical procedures of the lower extremity and the hip. Lower extremity peripheral nerve blocks provide cost-effective anesthesia and postoperative analgesia with a favorable postoperative recovery profile.[1,2] Peripheral nerve blocks have the following distinct advantages over general or central neuraxial anesthesia: (1) no autonomic blockade, with no risk of hemodynamic instability and urinary retention; (2) unilateral block; (3) no risk of spinal hematoma in the anticoagulated patient; (4) prolonged postoperative analgesia provided either by injecting a long-acting local anesthetic or by a continuous infusion of local anesthetic via an indwelling catheter and infusion pump; (5) decreased need for postoperative nursing due to minimal side effects such as uncontrolled pain, emesis, sedation, and respiratory depression; (6) early ambulation and discharge. Single-shot and continuous sciatic or popliteal block for patients undergoing reconstructive foot and ankle surgery have been recognized as safe and effective techniques for perioperative analgesia with high patient satisfaction.[2–5]

Despite the potential advantages, lower extremity nerve blocks have not been used to their full potential in clinical practice. The primary reason for this clinical trend has been a general perception among clinical anesthesiologists that sciatic nerve block is technically demanding with a variable success rate.[6–8] This perception may have stemmed from unfamiliarity with the technique, because most residency training programs were found in the past to be deficient in the teaching of peripheral nerve blocks: specifically, the lower extremity nerve blocks.[9–11] The latency of block onset in the sciatic area also has been a deterrent in the climate of operating room utilization, unless these blocks are performed in a designated block area. There has been an explosion in the description of new techniques of sciatic nerve blockade over the last decade, even more so with the advent of the use of ultrasound guidance over the past 5 years. These techniques block the sciatic nerve at varying anatomic sites along the course of nerve from the pelvis to the popliteal fossa.[6–8,12–20] A significant amount of research has been done to define strategies to reduce latency and improve the success of a complete block of the two neural components of sciatic nerve, the tibial and peroneal nerves.[18,21,22]

The advantage of ultrasound guidance for nerve localization in lower extremity blocks has been documented in the recent 2009 Cochrane review.[23] Ultrasound guidance may improve quality, decrease time to perform and latency of onset, reduce complication rates, such as the incidence of vascular puncture and subsequent hematoma and pain during the procedure, with increased patient satisfaction.[23–25] Increased success rates, shorter onset, and longer duration of the nerve blockade were also confirmed in a recent meta-analysis of 13 randomized controlled trials.[26]

Perlas et al.[27] and Sinha et al.[28] have documented the unreliability of neurostimulation in relation to needle and nerve interaction.[27,28] Often the motor response is not elicited even on direct contact with the nerve. Many leading institutions across the world thus have adopted ultrasound guidance as a standard of care. This chapter will describe the traditional neurostimulation technique and a corresponding ultrasound-guided technique of sciatic blockade at various locations along the course of the sciatic nerve (Fig. 78-1).

REGIONAL ANATOMY PERTINENT TO SCIATIC NERVE BLOCK

The sciatic nerve, formed by the ventral rami of L4, L5 and S1, S2, S3 nerve roots, is the largest nerve in the body, measuring 0.8 to 1.5 cm in width. The roots exit the pelvis as they unite to form the sciatic nerve through the greater sciatic foramen and travel on the anterior surface of the piriformis muscle accompanied by the superior gluteal artery, the largest and shortest branch of the internal iliac artery. Throughout their course the two divisions of the sciatic nerve, tibial nerve (medial position), and peroneal nerve (lateral position) are distinctly separate, but appear combined into one large trunk by a connective tissue sheath. Proximally, the nerve lies over the posterior surface of the ischium. In this location the sciatic nerve is accompanied by the posterior cutaneous nerve of the thigh and further down, the inferior gluteal artery. Distal to the piriformis muscle the nerve travels posterior to the superior gemellus, tendon of obturator internus, the inferior gemellus, quadratus femoris, and adductor magnus muscles. In the gluteal area it is covered by the gluteus maximus muscle posteriorly. In the infragluteal location, the sciatic nerve lies in close proximity to the lesser trochanter, over the adductor magnus muscle and is crossed obliquely in a mediolateral direction by the long head of the biceps femoris muscle. The sciatic nerve continues distally in the thigh under the biceps femoris muscle. At the cephalad portion of popliteal fossa or distal third of the thigh, the sciatic nerve divides into its two terminal branches, the posterior tibial and common peroneal nerves. In the popliteal area the nerve picks up more connective tissue, resulting in increased connective tissue to neuronal tissue ratio, which may explain the increased latency of onset seen with the popliteal sciatic blocks compared with more proximal locations.[29]

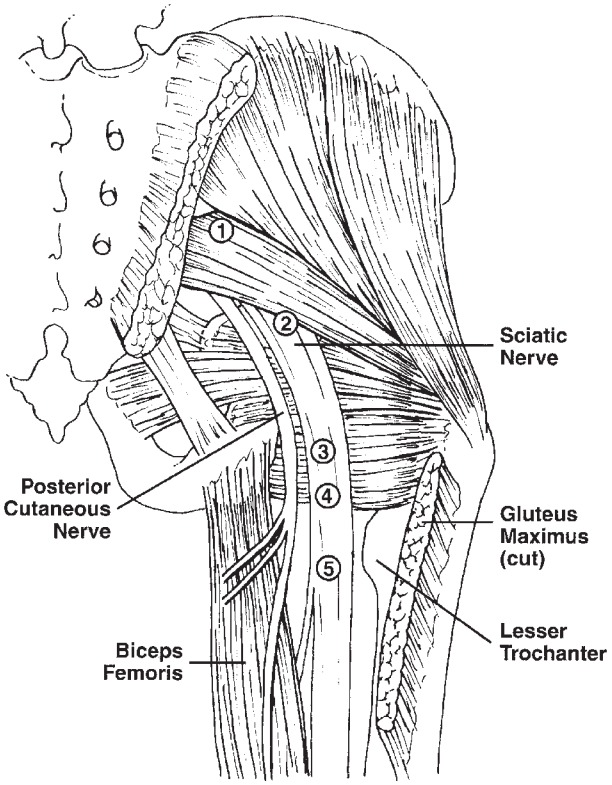

FIGURE 78-1 Sites for the various posterior approaches to sciatic nerve block. (1) Parasacral approach of Mansour—at the point where the nerve exits from the greater sciatic foramen. (2) Labat approach—at the lower border of the piriformis fossa. (3) Raj's approach—midway between the greater trochanter and ischial tuberosity. (4) Subgluteal approach (di Benedetto et al.)—over the adductor magnus, 4 cm caudal to the midpoint of a line joining the greater trochanter and the ischial tuberosity. (5) Infragluteal parabiceps (Sukhani et al.)—between the lesser trochanter and the lateral border of the biceps femoris as the nerve overlies the adductor magnus.

INDICATIONS

The sciatic nerve block can be used for lower extremity surgery, including hip, tibia and fibula, knee, ankle, and foot surgery, and also for above and below knee amputation. There is evidence to support its use in chronic pain syndromes of the lower extremity, including complex regional pain syndromes, or to pre-empt phantom limb pain.

TECHNIQUES OF SCIATIC NERVE BLOCK

To be widely accepted in clinical anesthesia practice, a nerve block technique must be simple, use easily identifiable landmarks, produce minimal patient discomfort, provide reliable onset of surgical anesthesia, and have minimal adverse outcomes. This block did not initially achieve wider acceptance among clinicians because of limitations in identifying bony landmarks (in overweight patients), substantial patient discomfort (needle passage through dense muscles), unpredictable success, and increased latency of onset.

Different approaches to sciatic nerve block have been described, using peripheral nerve stimulation (PNS), ultrasound (US), or a combination of the two (dual technique) for nerve localization. Whereas the traditional approaches rely on anatomic landmarks, which might be difficult to appreciate in every patient, the ultrasound allows visualization of these landmarks as well as the surrounding sonoanatomy and the nerve in its entire path, nerve to needle interaction, and spread of the local anesthetic injectate. There have been techniques described using injection in the subgluteal plane without actually contacting the nerve.[30]

PARASACRAL APPROACH (MANSOUR)

Mansour described the parasacral approach to sciatic nerve block in 1993.[14] The local anesthetic is deposited in the fascial plane enclosing the L4–S3 nerve roots of sacral plexus, as they unite to form the main trunk of the sciatic nerve under the piriformis muscle. Using a single-injection technique the success rate in the distribution of the sciatic nerve was 97%. This was also associated with blockade of the obturator nerve in 93% of subjects.[31] This is particularly important if a surgical block is intended for total knee joint replacement.

Surface Anatomy and Technique

The patient is placed in the lateral (Sim's) position with the operative side up. The posterior superior iliac spine (PSIS) and ischial tuberosity are marked and united by a line. The point of needle entry is approximately 6 cm from the PSIS along this line (Fig. 78-2). A 100-mm, 22-gauge insulated block needle is inserted and advanced maintaining a parasagittal orientation, until motor responses are elicited in the foot/ankle at a current of less than 0.5 mA. The nerve roots of the sacral plexus are usually contacted at 5 to 8 cm depth. Twenty to 30 ml of local anesthetic is injected after ensuring that the twitches disappear with currents at 0.2 mA and there is no resistance to injection. (See Table 78-1 for appropriate evoked motor response EMR.) It is important to remember that the superior gluteal artery, which curves

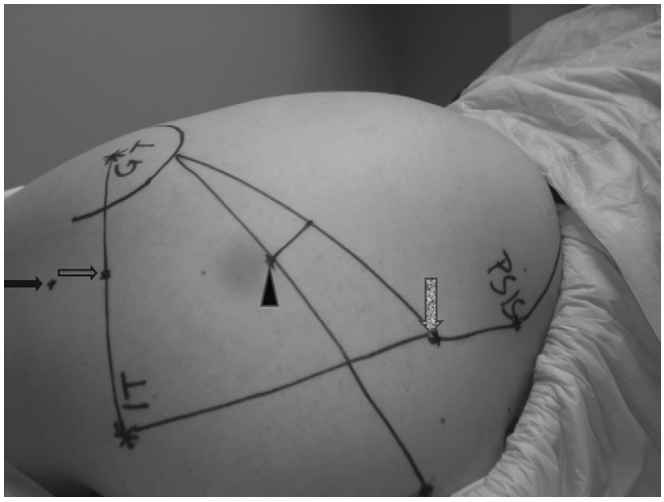

FIGURE 78-2 Surface landmarks for posterior sciatic nerve blocks; patient is in Sim's position. GT = greater trochanter, IT = ischial tuberosity, PSIS = posterior superior iliac spine; Needle entry point: *Stippled arrow* = parasacral block; *Arrowhead* = Labat's block; *Unfilled arrow* = Raj block; *Solid arrow* = subgluteal di Benedetto's block.

TABLE 78–1 Major Muscles Supplied by Branches of the Sciatic Nerve and Their Action with Regard to Movement of the Foot and Toes

Muscle Supplied	Action
I. Tibial nerve	
A. Wide part of sciatic nerve	
1. Gastrocnemius	Plantar flexion
2. Soleus	Plantar flexion
B. After division of sciatic nerve	
1. Tibialis posterior	Inversion; assist in plantar flexion
2. Flexor digitorum longus	Plantar flexion (toes)
3. Flexor hallucis longus	Plantar flexion (toes)
4. Soleus	Plantar flexion (toes)
II. Deep peroneal (anterior tibial) nerve	
1. Tibialis anterior	Inversion; dorsiflexion
2. Extensor hallucis longus	Dorsiflexion
3. Extensor digitorum	Dorsiflexion longus
4. Peroneus tertius	Dorsiflexion
5. Extensor digitorum	Extension (toes) brevis
III. Superficial peroneal nerve	
1. Peroneus longus	Eversion; assist in plantar flexion
2. Peroneus brevis	Eversion; assist in plantar flexion

The sural nerve has no muscular branch.
Data compiled and reproduced from Calilet R: Foot and ankle pain, *Philadelphia, 1983, FA Davis, pp 1–46; Mayo Clinic and Mayo Foundation:* Clinical examinations in neurology, *Philadelphia, 1981, WB Saunders, pp 168–188.*

around the upper lip of the greater sciatic notch, should not be injured, as it is a short branch of the internal iliac artery and will retract back into the pelvis if severed. The authors use the paradigm that if bone is contacted, the next step is to move the needle inferomedially.

Ultrasound-Guided Technique

This approach has been described by Ben-Ari et al.[32] A curved low-frequency (C2-5 MHz) probe is positioned across the gluteal region and slid caudad while watching the linear hyperechoic shadow of the back of the ischium (Fig. 78-3). The sciatic notch looks like a discontinuity in this line, with the piriformis muscle covering the notch. Hip adduction and abduction help identify the piriformis. The sciatic nerve is seen in short axis deeper to the piriformis (Fig. 78-4). Rotation of the probe by 45° will bring about the long axis view of the sciatic nerve as it exits the greater sciatic notch (Fig. 78-5). Color Doppler interrogation reveals the superior gluteal vessels in this area.

Advantages and Limitations

This is a block of the sacral plexus rather than of the peripheral nerve. It has been claimed to be technically easy and quick to perform, providing a high success rate, up to 94% in one study of 400 blocks,[33] and with less discomfort to the patient. The posterior cutaneous nerve of the thigh and

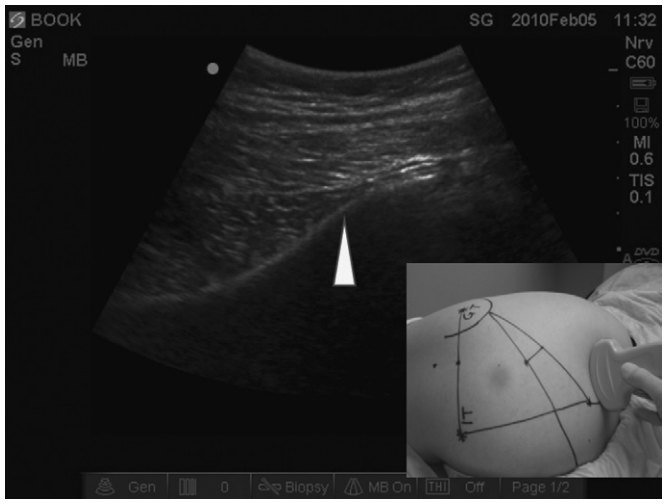

FIGURE 78-3 US probe positioned across the upper gluteal region, shown in the inset. Arrowhead points to the horizontal hyperechoic shadow cast by the ischium.

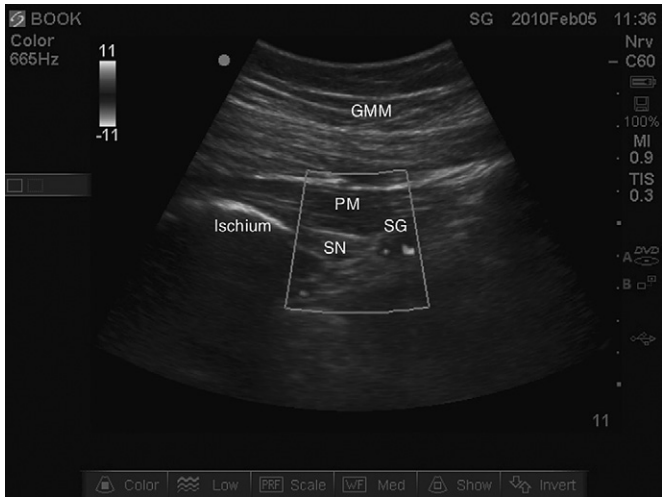

FIGURE 78-4 Ultrasonography of parasacral sciatic nerve. SN = sciatic nerve, GMM = gluteus maximus muscle; PM = piriformis muscle. Color Doppler reveals the superior gluteal vessels (SG).

the obturator nerve are blocked as well. Almost always, the parasacral approach also blocks the pudendal nerve with resultant anesthesia of the perineum. Despite the close proximity of somatic and sympathetic nerve supply of the bladder to the injection site and resultant blockade of these nerves, voiding difficulties requiring bladder catheterizations are occasionally seen but are uncommon.[31]

Known complications of the traditional approach, such as hematoma, rectal perforation, and transient sciatic neuralgia were not seen with the ultrasound guidance.[32]

CLASSIC POSTERIOR APPROACH (LABAT TECHNIQUE)

The sciatic nerve is blocked at the level of the greater sciatic notch distal to the piriformis muscle (Fig. 78-1).[6,12]

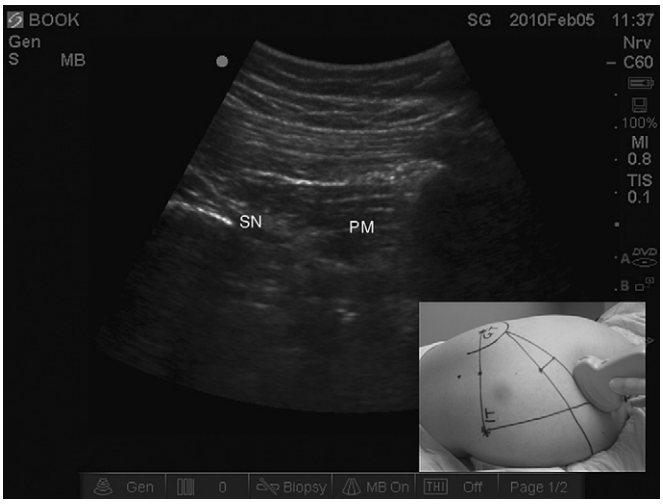

FIGURE 78-5 Ultrasonography of the parasacral sciatic nerve in long axis. SN = sciatic nerve; PM = piriformis muscle.

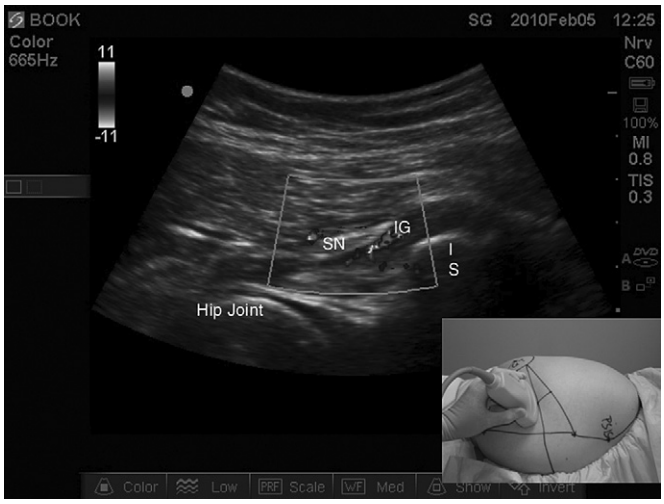

FIGURE 78-6 Ultrasonography of the classic Labat sciatic nerve. SN = sciatic nerve, HJ = hip joint; IS = ischium. Color Doppler reveals the inferior gluteal vessels (IG). Inset shows the probe position.

Surface Anatomy and Technique

The patient is placed in the lateral Sim's position with the thigh and knee flexed 90° and the dependent lower extremity extended. A line is drawn between the tip of greater trochanter (GT) and the PSIS, line 1. A second line is drawn connecting the GT and sacral hiatus, line 2. A perpendicular line, line 3, is drawn from the midpoint of line 1 to bisect line 2. The point of intersection between lines 2 and 3 is the needle entry site (Fig. 78-2). A 100- to 150-mm 22-gauge insulated block needle is inserted perpendicular to the skin and advanced and redirected as needed until an appropriate EMR is obtained at less than 0.5 mA (Table 78-1). The depth of the nerve from the skin usually ranges from 7 to 15 cm. Twenty to 30 ml of local anesthetic is injected after negative aspiration and absence of paresthesia.

Ultrasound-Guided Technique

The technique could be considered an extension of the parasacral block. After finding the piriformis muscle, the probe is moved further inferiorly. The ischium ends in a spiny protrusion, which is the ischial spine. With color Doppler one often will see the pudendal nerve and internal pudendal vessels close to the ischial spine. Lateral to the spine and superficial to the flat surface of the ischium, the sciatic nerve is seen in short axis with the superior gemellus muscle underneath it. The easier approach is to position the probe horizontally at the level of the greater trochanter, which is a dome-shaped hyperechoic rim with anechoic shadowing underneath. More medially one will see the ischial tuberosity as another dome-shaped structure. Between these two shadows will be the sciatic nerve with gluteus maximus superficial and the gemellus deep to it. Moving the probe proximal to distal will bring the ischial spine into view. Inferior gluteal vessels will be seen close to the ischial tuberosity. Deep to the gemellus, one often sees the capsule of the hip joint and the head of the femur just outside the acetabular rim (Fig. 78-6).

Advantages and Limitations

This approach also blocks the posterior cutaneous nerve of the thigh and the pudendal nerve. It can produce significant discomfort and pain as the needle passes through the gluteal muscle mass. From the ultrasonographic image, one can see the hip joint at risk.

SUPINE LITHOTOMY APPROACH (RAJ TECHNIQUE)

The sciatic nerve is blocked at a more distal level, between the ischial tuberosity and the greater trochanter (Fig. 78-1).[7]

Surface Anatomy and Technique

The patient is in supine position with the extremity to be blocked supported by an assistant, in maximal hip flexion and 90° knee flexion. Maximal flexion at the hip thins out the gluteus maximus (GM) muscle and decreases redundant tissue on the buttock. If there is no help, alternatively, the foot can be tucked under the contralateral thigh with some rotation at the knee level. This may reduce the amount of stretch of the GM. The needle entry point is the midpoint of a line between the tip of the greater trochanter (GT) and ischial tuberosity (IT). A 100-mm insulated 22-gauge block needle is inserted perpendicular to the skin, advanced and redirected as needed until an appropriate EMR is elicited at less than 0.5 mA (Table 78-1).

Ultrasound-Guided Technique

The block can be done supine or in Sim's position. A C2-5 MHz ultrasound probe positioned across the buttock will reveal the GT and IT and the sciatic nerve in between (Fig. 78-7).

Advantages and Limitations

The sciatic nerve in this location is more superficial and less patient discomfort is expected. The supine position can be useful in obese patients and patients with painful

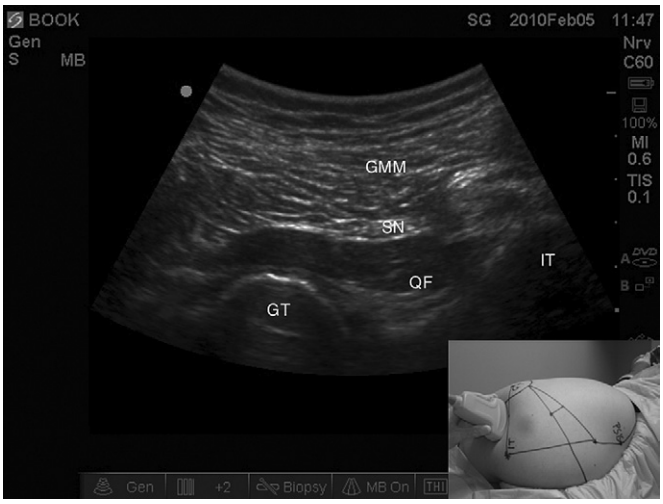

FIGURE 78-7 Ultrasonography of Raj's sciatic nerve. GT = greater trochanter; IT = ischial tuberosity; SN = sciatic nerve; QF = quadratus femoris muscle; GMM = lower end of gluteus maximus muscle. Inset shows the probe position.

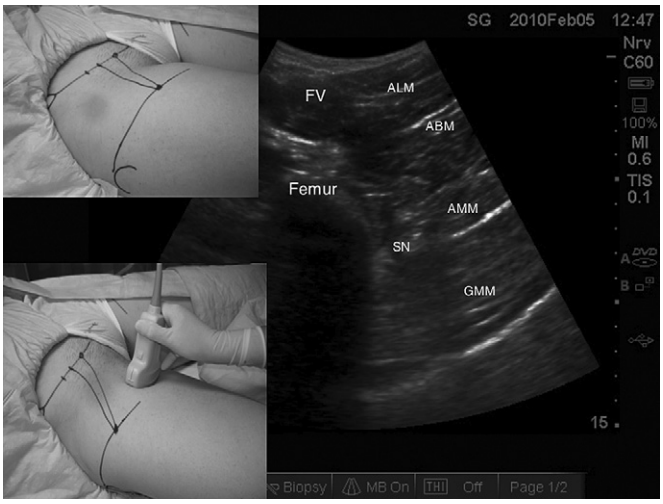

FIGURE 78-8 Ultrasonography of the anterior sciatic nerve. SN = sciatic nerve; ALM = adductor longus muscle; AB = Adductor brevis muscle; AMM = adductor magnus muscle; GMM = gluteus maximus muscle; FV = femoral vessels. Top inset shows surface landmarks for the anterior sciatic block. GT = greater trochanter; ASIS = anterior superior iliac spine. Bottom inset shows the probe position in short axis, with the thigh abducted and externally rotated.

traumatic injuries to the extremity. The posterior cutaneous nerve of the thigh may not be blocked with this more distal approach.

ANTERIOR APPROACH

The anterior approach to sciatic block was first described by Beck in 1962[8] and subsequently modified by Chelly and Delauney in 1999.[15] The sciatic nerve lies posterior to the muscles of the anterior compartment of the thigh, in the proximity of the lesser trochanter. The posterior cutaneous nerve of the thigh will be missed with this approach.

Surface Anatomy and Technique

The patient is placed supine with the lower extremities in neutral position. A line is constructed between the anterior superior iliac spine and the pubic tubercle, marking the reflection of the inguinal ligament. The second line is constructed parallel to the first line, at the level of the greater trochanter. In Beck's approach, a perpendicular line is drawn at the junction of the lateral two-thirds and medial one-third of the first line to contact the second line. The needle entry site for Beck's approach is the junction of the perpendicular and the second line. In Chelly's modification the inguinal ligament line is bisected and a perpendicular line is extended down from the bisected point by 8 cm. Chelly's modification does not require palpation of the greater trochanter (Fig. 78-8). The block is performed with a 150-mm, 22-gauge insulated block needle as the nerve lies deep under the anterior thigh muscles. Often one encounters the branches of the femoral nerve as the needle is advanced posteriorly, with potential for injury. A nerve stimulator is used during the advancement to avoid injury to the femoral nerve. The sciatic nerve may not be encountered until a depth of 12 to 15 cm. Local anesthetic is injected when an appropriate EMR is obtained at less than 0.5 mA (Table 78-1).

Advantages and Limitations

The anterior approach is unique in that it can be performed with the patient supine, and the time required for a combination of blocks is reduced because only one area of skin preparation is required. Pain with bone contact, insertion via major muscles, and difficult landmarks in obese patients may pose some limitations. Vloka et al.[34] reported that the sciatic nerve at this site lies posterior to the lesser trochanter and is not accessible to the needle using the direct anterior approach. Two strategies to overcome this limitation include the insertion of the needle at a more distal level (4 cm distal to the lesser trochanter) and internal rotation of the foot (femur) so the sciatic nerve moves medial to the lesser trochanter.[34,35]

Ultrasound-Guided Technique

In a volunteer study, Chan et al. positioned the patient supine, with the thigh externally rotated at approximately 45°, the hip and knee flexed, and scanned the proximal thigh approximately 8 cm distal to the inguinal crease.[36] A C2-5 MHz probe is positioned at the inguinal crease and gradually moved inferiorly until the lesser trochanter is seen as a widening of the femoral circumference. One would see the femoral vessels and nerves more superficially and laterally. At the level where the adductor muscles meet the femur, the sciatic nerve is seen as a hyperechoic round or oval structure, posterior to the adductor magnus (Fig. 78-8). The needle is inserted from the medial side of the thigh through the adductor muscles. Occasionally branches of the obturator nerve may be encountered. An ultrasound-guided anterior approach has also been described by Fondi et al., in a plane close to the lesser trochanter.[37] The critical point in their study was the close proximity of the femoral vessels in over 50% of cases.

Tsui has recently described a longitudinal approach.[38] The sciatic nerve appears in longitudinal view as a cable-like structure medial to the femur and deep to the adductor magnus muscle. Confirmatory longitudinal spread of the local anesthetic can easily be observed as well.

LATERAL APPROACH

The original block described by Ichiyanagi in 1959[13] was modified by Guardini et al. in 1985 and claimed to be technically easier.[16] The sciatic nerve is blocked in the subgluteal space, dorsal to the plane of the quadratus femoris muscle, between the femur and ischial tuberosity (Fig. 78-1). The other structures in the subgluteal space are the posterior cutaneous nerve of the thigh, the inferior gluteal nerve and vessels, and the ascending branch of the circumflex femoral artery.

Surface Anatomy and Technique

The block is performed with the patient supine and the hip in neutral position. The needle insertion site is 3 cm distal to the point of maximum lateral prominence of the greater trochanter. The ischial tuberosity can be palpated with the nondominant hand. The needle is inserted perpendicular to the major axis of the limb and advanced toward the femur. Once it contacts the femur it is withdrawn slightly, redirected 20° under the femur, and advanced toward the ischial tuberosity. The sciatic nerve is contacted at a depth of 8 to 12 cm. Local anesthetic solution is injected after appropriate EMR is obtained (Table 78-1).

Advantages and Limitations

This approach has not received wide acceptance. It can produce significant patient discomfort because the needle has to travel deep. It can stimulate other motor nerves and multiple attempts may be needed.

POSTERIOR SUBGLUTEUS APPROACH (di BENEDETTO)

This approach blocks the nerve at a location more distal than that of the classic posterior approach described by Labat.[17] In this location the nerve overlies the adductor magnus muscle, is posterior to the lesser trochanter, and is approximately 3 cm above the lower border of the gluteus maximus muscle (Fig. 78-1).

Surface Anatomy and Technique

The patient is placed in the lateral (Sim's) position with the operated side up. A line is drawn from the greater trochanter to the ischial tuberosity and a second line is drawn from the midpoint of this line, extending caudally for 4 cm (Fig. 78-2). The needle insertion site is the distal point of the second line. A stimulating 100-mm, 22-gauge insulated block needle is inserted perpendicular to the skin and advanced to elicit an appropriate EMR at less than 0.5 mA (Table 78-1).

Midgluteal and subgluteal approaches have also been described by Franco, who identified the sciatic nerve at 10 cm lateral to the midline in patients of both sexes, regardless of weight.[39,40] In the midgluteal approach, the patient is placed in lateral decubitus with the operating site up and the entry point of the needle is 10 cm from midline, from the midpoint of the intergluteal sulcus. In the subgluteal approach, the entry point of the needle is in the subgluteal fold at 10 cm from midline. The authors reported a 100% success rate in locating the sciatic nerve.

Ultrasound-Guided Technique

A C2-5 MHz curved probe positioned horizontally to view the greater trochanter, ischial tuberosity, and the sciatic nerve in between, is gradually moved caudad on the posterior thigh. The shadows of the hip joint will disappear and the nerve will move into an intermuscular cleft just medial to the femur. In this location it is covered by the lower end of the gluteus maximus, which is thin (Fig. 78-9). Ultrasonographic evaluations of Franco's block have not been yet published. The advantage of the US is that one can do the procedure where the nerve is seen best and not depend on surface landmarks.

Advantages and Limitations

The posterior subgluteus approach is easy and reliable, with less patient discomfort because the needle traverses less muscle tissue (the average depth from the skin is 4.5 cm with the subgluteus approach, and 6.7 cm for the classic posterior approach). It may not block the posterior cutaneous nerve of the thigh.

INFRAGLUTEAL PARABICEPS APPROACH

The sciatic nerve is blocked at a site more distal to the classic Labat approach.[18] Distal to the gluteus maximus, the sciatic nerve lies over the adductor magnus and is crossed obliquely in a mediolateral direction by the long head of the biceps femoris muscle. The sciatic nerve therefore lies further lateral and subsequently deep to the long head of the biceps femoris. For a short distance of 3 to 4 cm, where the nerve is lateral to the long head of the biceps femoris, there is little to no overlying musculature

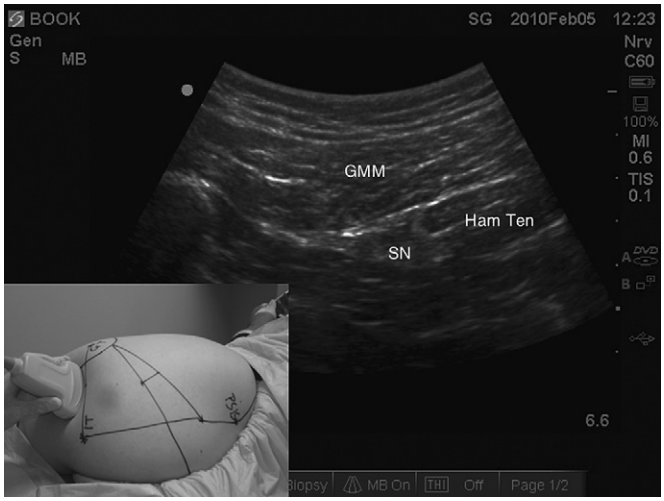

FIGURE 78-9 Ultrasonography of di Benedetto's subgluteal sciatic nerve. SN = sciatic nerve; GMM = lower end of gluteus maximus; Ham Ten = Hamstring tendons. Inset shows the probe position.

and the nerve is covered only by skin and subcutaneous tissue.

Surface Anatomy and Technique

The surface landmarks for this approach are the lateral border of the biceps femoris and the gluteal crease. The lateral border of the biceps femoris muscle is identified by asking the patient to flex the knee while resistance is applied to the calf muscles. The site of needle insertion is along the lateral border of the biceps femoris 1 cm caudal to the gluteal crease. A 100-mm, 22-gauge insulated block needle is inserted at an angle of 70° to 80° to the skin with a cephalad and anterior orientation within the parasagittal plane. The femur lies lateral to the nerve and the biceps femoris is medial to the nerve. The needle is moved only in one plane from the lateral to medial, and redirected to elicit the appropriate EMR (Table 78-1). The type of EMR is known to affect the latency of onset and success of complete sciatic nerve block. An EMR of inversion is associated with complete block in 100% cases, with the shortest latency to sensory and motor block of both components of the sciatic nerve.[18,21]

Advantages and Limitations

The infragluteal approach is easy, reliable, and produces less patient discomfort because the needle traverses minimal muscle tissue. The posterior cutaneous nerve of the thigh is not blocked.

Ultrasound-Guided Technique

In a volunteer and cadaver study, Bruhn et al. evaluated the tendon of the long head of the biceps femoris muscle as a soft landmark for a US-guided infragluteal approach, and found a constant relationship with the sciatic nerve.[41] Patient discomfort was greatly reduced as no peripheral nerve stimulation was used.

In our institution we almost exclusively use the ultrasound-guided, nerve stimulator–assisted infragluteal parabiceps approach. The patient is positioned prone and the biceps tendon is identified by asking the patient to flex the knee. A high frequency ultrasound probe is placed at the level of the gluteal crease or slightly below, and the sciatic nerve is identified at the lateral border of the biceps femoris, posterior to the muscle (Fig. 78-10). An appropriate EMR at less than 0.5 mA may be used if needed.

MID-THIGH APPROACH

The ultrasound has allowed description of relevant anatomy in the absence of anatomic landmarks.

ULTRASOUND-GUIDED TECHNIQUE

Barrington et al. have evaluated the mid-thigh approach under ultrasound guidance in a clinical and anatomic study.[42] Biceps femoris, vastus lateralis, adductor magnus muscles, the lateral intermuscular septum between biceps femoris and vastus lateralis, and linea aspera were among the landmarks on the mid-thigh sonograms. In 37.5% of the patients, peripheral nerve stimulation was needed to confirm that the structure seen is indeed the sciatic nerve (Fig. 78-11).

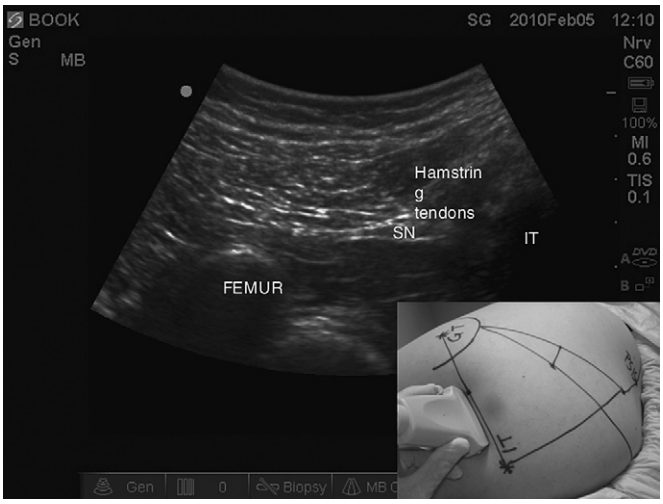

FIGURE 78-10 Ultrasonography of the infragluteal parabiceps sciatic nerve. SN = sciatic nerve; BFM = biceps femoris muscle. Inset shows probe position.

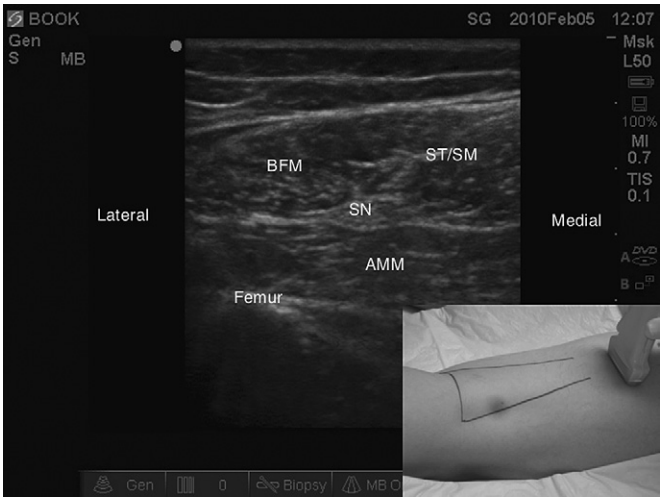

FIGURE 78-11 Ultrasonography of the sciatic nerve at mid thigh. SN = sciatic nerve; BFM = biceps femoris muscle; SM/ST = semimembranosus/semitendinosus muscles; AMM = adductor magnus muscle. Inset shows probe position.

SCIATIC NERVE BLOCK AT THE POPLITEAL FOSSA

Surface Anatomy and Technique

The popliteal fossa is a diamond-shaped area bound by the semitendinosus and semimembranosus muscles medially, the biceps femoris muscle laterally, and by the two heads of the gastrocnemius muscle inferiorly (Fig. 78-12).[21] The popliteal vessels, with the artery located deeper and anterior to the vein, are medial to the sciatic nerve. Occasionally, the tibial and common peroneal nerves are two separate nerves as soon as they descend from the sacrosciatic foramen. If the sciatic nerve is one nerve, the division occurs at or above the apex of the popliteal fossa, between 4 and 13 cm above the popliteal crease.[21] The tibial nerve immediately gives off the sural nerve and, at the level just above the sole of the foot, gives off the medial calcaneal

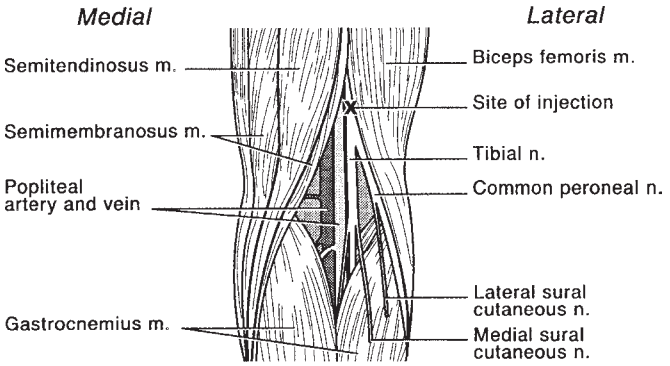

FIGURE 78-12 Anatomy of the popliteal fossa and technique of sciatic nerve blockade (see text for the technique of nerve blockade). *(Reproduced with permission from Benzon HT, Kim C, Benzon HP, et al: Correlation between evoked motor response of the sciatic nerve and sensory blockade.* Anesthesiology *87:547–552, 1997.)*

nerve. The tibial nerve then continues as the posterior tibial nerve that terminates into the medial plantar and lateral plantar nerves. The common peroneal nerve gives off a sural communicating branch and, once it is below the head of the fibula, divides into the deep peroneal and superficial peroneal nerves. Except for the sural nerve, the major branches of the sciatic nerve have motor function. The sensory innervation of the foot is supplied by branches of the tibial nerve, the common peroneal nerve, and the saphenous nerve. The posterior tibial nerve supplies the sole of the foot, the deep peroneal nerve supplies the web between the great toe and the second toe, the superficial peroneal nerve supplies the dorsum of the foot, and the sural nerve supplies the lateral aspect of the heel and foot and the fifth toe. It is important to remember that the saphenous nerve, the terminal branch of the femoral nerve, supplies the medial aspect of the foot.[43,44]

The use of a nerve stimulator is recommended in the performance of sciatic block at the popliteal fossa. (See Table 78-1 for appropriate EMR.) Eliciting foot inversion is the best EMR since it signifies stimulation of both branches of the sciatic nerve.[21] Elicitation of foot dorsiflexion signifies stimulation of the deep peroneal nerve, while plantar flexion signifies stimulation of the tibial nerve.[21] The needle would have to be redirected medially or laterally to elicit the other response to block both branches of the sciatic nerve.

Indications

Popliteal sciatic block is indicated for anesthesia/analgesia for foot and ankle surgery or for diagnostic/therapeutic blockade for pain management. The block is especially useful when ankle blocks are contraindicated because of the presence of swelling or infection in the ankle, and can be accomplished with a single needle insertion. A posterior, lateral, and medial approach have been described.

Posterior Approach

The patient is positioned prone with a pillow or rolled blanket under the ankle. A 22-Ga insulated block needle is inserted 5 to 7 cm above the popliteal crease and 1 cm lateral to a line that bisects the superior part of the fossa. The needle is advanced at a 45° angle to the skin and inserted to a depth of 2 to 5 cm until the desired EMR of inversion or combined inversion and plantar flexion is elicited with the stimulating current of less than 0.5 mA.[21,45,46] A volume of 30 ml of local anesthetic is adequate to block the sciatic nerve. Patchy sensory blockade of the foot may result, probably secondary to the considerable size of the sciatic nerve, the thickness of its epineurium, increased fibrofatty perineural tissue, as well as the variable level at which the sciatic nerve divides into the tibial and common peroneal nerves.[21,47] The mean distance above the popliteal crease at which the sciatic nerve divides into its major branches is 6.5 ± 2.7 cm, with a range of 1 to 11 cm.[48] A nerve stimulator is required to identify the nerve being stimulated for a double-injection technique. More rapid onset and increased efficacy of the block have been noted with the double-injection technique, where two 15 ml injections are made after the tibial and peroneal nerves are stimulated.[49,50]

A modified posterior approach has been recently described by Nader et al.[51] In their prospective randomized study, the sciatic nerve was blocked using either a modified intertendinous approach (12–14 cm above the popliteal crease, where the apex muscles of the popliteal fossa overlap) or the traditional posterior approach. A complete block was achieved in 85% of cases of the former, versus 70.9% of the latter. Block latency was also reduced when the accepted EMR was inversion.

Lateral Approach

This approach was first described by Collum and Courtney.[52] The patient is supine and the upper edge of the patella and the groove between the tendon of the biceps femoris and the iliotibial tract are palpated. Identification of the groove is made easier by flexion followed by extension of the patient's knee. The site of needle insertion is at the intersection of a line drawn from the upper edge of the patella and the intermuscular groove. The insulated needle is inserted 20° to 30° posteriorly to the horizontal plane and directed slightly caudad.[53] The common peroneal nerve, located laterally, is stimulated first followed by the tibial nerve. After obtaining an appropriate EMR at less than 0.5 mA (Table 78-1), 10 to 15 ml of local anesthetic is injected for each nerve.

Other authors insert their needle at a higher level. Vloka et al. inserted their needle 7 cm cephalad to the lateral femoral epicondyle, in the groove between the biceps femoris and the vastus lateralis muscles.[54] At 7 cm above the femoral condyle, the sciatic nerve runs in a sheath, which allows the cephalad spread of injected solutions. The needle is advanced until the shaft of the femur is contacted, then withdrawn, redirected posteriorly at a 30° angle to the horizontal plane, and advanced until dorsiflexion of the foot is elicited. After injection of local anesthetic, the needle is directed medially and slightly posterior to identify the tibial nerve. One has to remember the risk of passing through a partially anesthetized nerve.

The posterior and lateral approaches are equally effective. More attempts were necessary in the lateral approach, and stimulation of the common peroneal nerve was more frequent in the lateral approach.[55] One advantage of the lateral approach is that the patient is supine. Slight discomfort with this approach may be expected as the needle passes through the muscles.

Ultrasound-Guided Technique

The patient is positioned prone. Depending on the size of the patient, a curved 2-5 MHz or a high frequency linear probe is positioned at the popliteal crease horizontally. Release of pressure on the probe reveals the popliteal vein as it fills up, with the tibial nerve located posterolateral to the vein. The tibial nerve is traced proximally in the thigh and the nerve looks broader as the peroneal nerve joins the tibial nerve. At this location, caudad angling of the probe will reveal the two components as two distinct bundles and the common peroneal is often more hypoechoic (Fig. 78-13). With plantar flexion and dorsiflexion of the foot, one may see the two components sliding up and down, the "seesaw" sign.[56] The popliteal vessels can be identified with color Doppler. The needle may be inserted where the sciatic is a single bundle to surround the entire nerve with local anesthetic. Continuous perineural catheters can be inserted in this location.

McCartney et al. have described in a case report a lateral ultrasound-guided approach that was followed by the insertion of a continuous catheter for postoperative analgesia.[57] Perlas et al. in a randomized prospective study on 74 patients who received a popliteal block demonstrated that the success rate is higher in the US-guidance group versus the PNS group, 89.2% versus 60.6%, respectively.[58] Studies are underway to improve block performance by decreasing latency time, with above versus below bifurcation delivery of the local anesthetic.

Continuous Sciatic Nerve Block

While single-injection techniques of peripheral nerve blocks provide a limited duration of postoperative analgesia, continuous techniques are optimal for extended duration of analgesia.[59,60] With continuous sciatic blocks, the opioid analgesic requirements are reduced, patient satisfaction is increased, and earlier discharge is feasible.[61] Issues such as complexity of the technique with respect to the placement and maintenance of the catheter, potential for nerve injury, and potential risk of systemic toxicity with continuous infusions of potent long-acting local anesthetic had initially limited the applicability and acceptance of continuous catheters in ambulatory settings.[62–64] More recent studies in large series of ambulatory patients have confirmed that patients are comfortable managing and removing perineural catheters at home, with fewer than expected interventions from an anesthesiologist needed.[65] Feasibility studies in children have confirmed the same.[66]

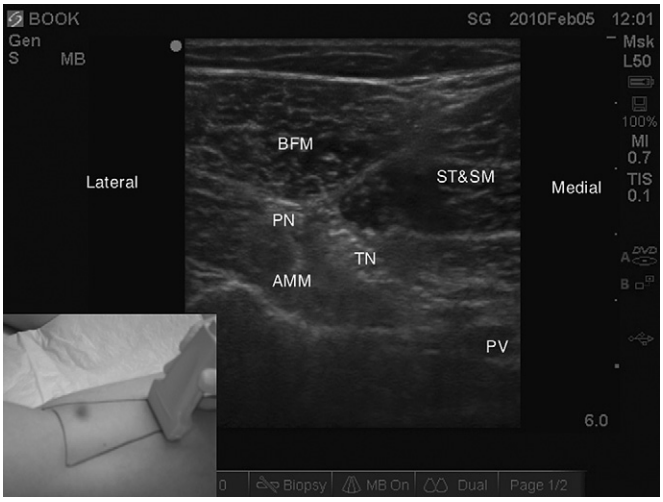

FIGURE 78-13 Ultrasonography of the sciatic nerve in the popliteal fossa. TN = tibial nerve; PN = peroneal nerve; AMM = adductor magnus muscle; ST/SM = semitendinosus/semimembranosus muscle; BF = biceps femoris muscle; PV = popliteal vessels. Inset shows probe position.

CHOICE OF LOCAL ANESTHETICS

A single injection of 20 to 30 ml of a long-acting local anesthetic such as bupivacaine provides 12 to 24 hours (19 ± 6 hours) of postoperative analgesia.[18] This long duration favors the use of a single-injection technique for postoperative analgesia for the vast majority of orthopedic surgical procedures below the knee. The use of a continuous catheter technique is indicated primarily when postoperative analgesia greater than 24 hours is desired.

Historically, the sciatic nerve block has been considered to have the longest latency to onset of surgical anesthesia. The delay in the onset of block can be minimized by observing the appropriate technique (see the section on the methods of nerve localization) and by using higher concentrations of local anesthetic.[31,67,68] A quick onset of block with prolonged postoperative analgesia is an important goal in peripheral nerve blocks. Although intermediate-acting local anesthetics such as mepivacaine and lidocaine have a faster onset time to surgical anesthesia compared with bupivacaine, the duration of the postoperative analgesia is limited to 4 to 6 hours. Ropivacaine 0.75% for sciatic block was found to have an onset time similar to 2% mepivacaine and a duration of postoperative analgesia between 0.5% bupivacaine and 2% mepivacaine (ropivacaine 670 ± 227 minutes, bupivacaine 880 ± 312 minutes, and mepivacaine 251 ± 47 minutes).[69]

For a continuous infusion technique for lower extremity nerve blocks, a dilute solution of a long-acting local anesthetic such as bupivacaine 0.1% to 0.25% or ropivacaine 0.2% is adequate.[4,5,60] The administration of these concentrations at 8 to 10 ml/hour for 48 to 72 hours does not result in toxic blood levels of local anesthetics. A continuous infusion with lower basal rate and added patient-controlled boluses was found to optimize infusion benefits.[70]

METHODS OF NERVE LOCALIZATION

Three methods of peripheral nerve localization have been used in clinical practice: (1) elicitation of paresthesia; (2) neurostimulation technique with a low-intensity electrical current (PNS); (3) ultrasound guidance. A combination of PNS and ultrasound guidance, known as dual technique, has a recognized place as well. The paresthesia approach has been largely replaced by the other two methods, provided equipment is available. Because of the two distinct components within the epineural sheath, a single-injection technique may result in incomplete block of the sciatic nerve. The use of the nerve stimulator allows for a precise identification of the two components of the sciatic nerve.[18,21] Two strategies have been proposed to improve

the latency of onset, and the success of a complete block of the sciatic nerve. The proximity of the stimulating needle tip to both components of the sciatic nerve is ensured prior to local anesthetic injection. The EMR to neurostimulation determines the sciatic nerve component being stimulated.[21] There are four possible foot movements in response to sciatic nerve stimulation: (1) plantar flexion; (2) dorsiflexion; (3) inversion; and (4) eversion. Elicitation of EMR of inversion implies that the nerve needle is stimulating both the tibial and deep peroneal nerve.[21]

Using the endpoint of EMR at less than 0.4 mA, Vloka et al. reported 100% success in achieving complete block of the sciatic nerve at the popliteal fossa, regardless of the type of EMR obtained.[22] By applying the two strategies outlined above, that is, aiming for EMR inversion at less than 0.4 mA, one can achieve 100% success (versus 33%–95%) with a latency of less than 10 minutes (versus 30 minutes) for sciatic nerve block.[18]

With ultrasound guidance, visualization of the nerve in longitudinal axis may help with catheter insertion. Recent imaging studies using ultrasound or CT looked at the location of the nerve block needle, and catheter after placement using a PNS and obtaining an appropriate EMR. In one study on popliteal fossa sciatic nerve blocks, the intraneural injection was found to be a common occurrence, reported in 76% of cases. Nerve swelling with fascicular separation was observed in 88% of cases. This was associated with faster onset of the block. No neurologic complications were reported at 1 week after the block.[71]

The unintentional intraneural placement of catheters was also thought to be a more common occurrence. When intraneural catheter placement was found, a relatively small dose of 3 to 5 ml local anesthetic was enough to produce early surgical anesthesia.[72] Kapur's study in canines[73] as well as Bigeliesen's study[74] have suggested that intraneural injections do not always lead to neurologic deficit, mostly when the injection pressures were less than 12 psi. The current US machines have inadequate resolution to identify a subperineural or intrafascicular injection.

COMPLICATIONS OF SCIATIC NERVE BLOCK

The sciatic nerve does not lie in the close vicinity of other nerves, sympathetic chain, or central neuraxis. Therefore there are no complications related to the spread of local anesthetics to these adjacent structures, unless one injects intrafascicularly within the perineurium. The exception, however, is the parasacral approach of Mansour,[14] where the local anesthetic is deposited on the sacral plexus within the pelvis, in close vicinity of pelvic vasculature and viscera. The complications of sciatic nerve block, common to peripheral nerve blockade, can be categorized into systemic toxicity, infectious, and neurologic complications.

Relatively larger doses of local anesthetics need to be administered for surgical anesthesia, and it is almost always combined with other blocks, therefore a finite risk of systemic toxicity exists. Several studies have examined the blood levels of local anesthetics following combined blocks of lower extremity utilizing higher than recommended doses of local anesthetics.[75,76] Mepivacaine, lidocaine, and bupivacaine in doses exceeding 150% of the recommended doses did not produce systemic toxicity or excessive plasma levels. The addition of epinephrine to the local anesthetics in the combined blocks also minimizes the blood levels of the local anesthetics by slowing absorption.[77]

Neurologic injury secondary to sciatic nerve block is infrequent. In a recent report on major complications of regional anesthesia in France, peripheral neuropathy following sciatic nerve block occurred in 2.4 per 10,000 cases.[78] In comparison, the frequency of peripheral neuropathy following popliteal block was much higher at 31.5 per 10,000 cases. The use of nerve stimulation for peripheral nerve blocks in the series did not prevent occurrences of neurologic injury. A more recent prospective study on 400 patients who received a continuous popliteal catheter for postoperative analgesia after foot surgery showed an 89% patient satisfaction rate. The authors documented an incidence of severe neuropathy of 0.5%, and a 0.25% incidence of infectious complications.[79]

Nerve injury after PNB is reported to be about 0.4%, and is considered to be a multifactorial event.

A few strategies could be considered to minimize the risk of neurologic injury following peripheral nerve blocks:

- Moderate sedation should be used, so that the patient is able to report paresthesia if it occurs.
- If neurostimulation is used to localize the nerve, EMR elicited at currents of less than 0.5 mA ensures that the needle is close enough to the nerve to obtain a successful block. The EMR at currents lower than 0.2 mA, however, may suggest that the needle is too close to nerve with a risk of nerve damage from intraneural injection of local anesthetic.[67]

Although this concept of loss of EMR with lower current strength providing a margin of safety is commonly quoted, a recent study by Chan et al. has revealed that one may not get an EMR even when the needle is inside a compound nerve.[80] Monitoring injection pressures may be useful as subperineural injections always require a higher pressure for injection. Lastly, visualizing the dispersion of local anesthetic during injection under ultrasound guidance is important.

Epinephrine in the local anesthetic solution might impact nerve blood flow and has been implicated in neurologic injury following peripheral nerve blocks.[63] This rather theoretical risk is increased in patients with compromised blood flow from diabetes and atherosclerotic disease. Weaker concentrations (1:300,000 to 1:400,000) of epinephrine are therefore suggested in high-risk patients.

ANKLE BLOCK

Ankle block is a common and successful means of providing surgical anesthesia and postoperative analgesia for midfoot and forefoot surgery. Ankle block is not suitable for ankle surgery. Ankle block involves anesthetizing five nerves: the posterior tibial, superficial peroneal, deep peroneal, saphenous, and sural. All are branches of the sciatic nerve except for the saphenous, which is the terminal branch of the femoral nerve. Familiarity with the anatomy and innervation of the foot allows more precise location of the five

nerves involved in performing an ankle block and a higher success of complete block.

Techniques of nerve localization include paresthesia, peripheral nerve stimulation, and ultrasound. Ultrasound guidance of posterior tibial nerve (PTN) block[81] and sural nerve block[82] has been shown to improve the quality and success of a complete block. With US one can visualize the circumferential spread of local anesthetic and the nerve to needle interaction. The posterior tibial artery and vein, and the lesser saphenous vein, can be visualized with the aid of color Doppler.

The nerve supply to the foot and ankle is provided by the four terminal branches of the sciatic nerve and the saphenous nerve (terminal branch of the femoral nerve). Except for the posterior tibial nerve, the other nerves are all sensory nerves. The cutaneous innervation of these five branches supplying the foot is as follows (Fig. 78-14)[83]:

1. Posterior tibial nerve—plantar surface of the foot and toes by its three divisions: medial plantar nerve, lateral plantar nerve, and medial calcaneal nerve.
2. Deep peroneal nerve—the dorsal surface of the foot between the great and second toe.
3. Sural nerve—the lateral surface of the foot (dorsolateral cutaneous nerve) and the heel (lateral calcaneal nerve). A medial branch unites with the intermediate cutaneous nerve of the superficial peroneal nerve innervating the web spaces of the third and fourth toes.
4. Superficial peroneal nerve—the dorsal surface of the foot and toes, except the web space between the first and second toes and the lateral aspect of the foot, including the fifth toe and lateral half of the fourth toe.
5. Saphenous nerve—the skin over the medial malleolus, medial surface of the foot up to the medial arch, and to the medial side of the great toe.

Dermatomal nerve supply of the foot is highly variable. Thus, complete ankle block involves anesthesia of all five nerves, with the PTN being the major component as it innervates all five toes.

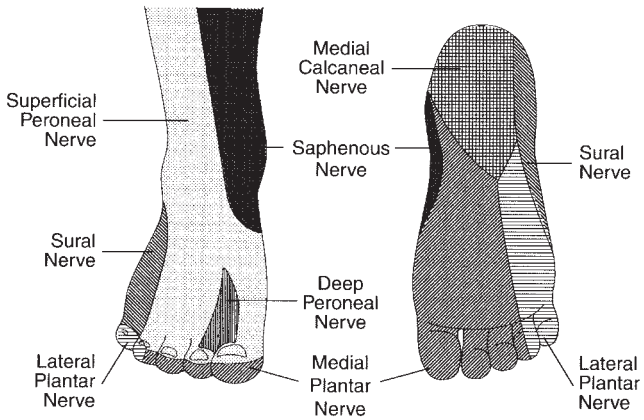

FIGURE 78-14 Cutaneous innervation of the foot. The medial plantar nerve, lateral plantar nerve, and medial calcaneal nerve are branches of the posterior tibial nerve.

POSTERIOR TIBIAL NERVE

Anatomy[83]: The PTN is one of the two terminal divisions of the sciatic nerve and consists of muscular, cutaneous, and articular branches. In the upper two-thirds of the leg the nerve is located deep in the posterior compartment, while in the lower one-third of the leg it assumes a superficial location along the medial border of the Achilles tendon. The PTN lies lateral and posterior to the posterior tibial artery and vein. In the talocalcaneal canal the PTN divides into its terminal branches: the medial plantar (MPN) and lateral plantar (LPN) nerves. This division occurs within 2 cm of the tip of medial malleolus in 93% of cases, and more proximal in 7% of cases. Blocking the PTN at a distal site in these patients may result in partial block of the nerve.

The MPN supplies the muscular branches to the abductor hallucis, flexor digitorum brevis, flexor hallucis brevis, and lumbricals. Neurostimulation of the MPN produces flexion of all toes, except the great toe, and abduction of the great toe. The LPN supplies muscular branches to the abductor digiti minimi, adductor hallucis, quadratus plantae, short flexors, and opponens of the fifth and fourth toes (sometimes the third toe), lumbricals, and interossei. Neurostimulation of the LPN produces adduction of the great toe, abduction of the fifth toe, and contraction of the musculotendinous arch of the foot. The PTN also gives off a medial calcaneal branch, with variable origin, supplying the medial side of the heel.

The PTN can be blocked by several approaches.

DISTAL APPROACH (TRADITIONAL SITE)

The PTN can be blocked at the level of the medial malleolus within 2 to 3 cm of its tip, within the tibiocalcaneal canal. The nerve in this location lies under the flexor reticulum, posterior to the tibial artery and vein. The limitations of the distal approach are:

- The diffusion barrier imposed by the flexor reticulum.
- A partial and incomplete block because the calcaneal branch may have taken off at a higher level (40%) and the two terminal divisions of the nerve may have separated (7%–13% of cases).
- In patients with an altered and/or distorted ankle anatomy (inflammation, edema, poor vascular anatomy) the block may be technically difficult.

Technique[84,85]: The patient is positioned prone or supine with the foot elevated. The needle entry site is 2 to 3 cm proximal to the tip of the medial malleolus and 1 cm from the medial border of the Achilles tendon. A 22-gauge insulated needle is directed toward the posterior aspect of the tibia, posterior to the tibial artery pulsation (if palpable), seeking to obtain toes flexion at less than 0.5 mA. Five to 7 ml of local anesthetic is injected incrementally after negative aspiration of blood. This volume is thought to usually be all that is required to block each nerve.[86]

PROXIMAL APPROACH

The PTN is blocked before it has given off its medial calcaneal branch and before its division.

This approach is practiced extensively at the authors' institution and is associated with a high success of complete block.[87] The needle entry site is 7 to 8 cm proximal to the superior border of the medial malleolus and approximately 1 cm anterior to the medial border of the Achilles tendon, in the groove between the flexor digitorum and flexor hallucis longus. A 50-mm, 22-gauge insulated needle is directed anterior and slightly caudad 60° to the sagittal plane until the appropriate EMR is obtained at less than 0.5 mA (see Table 78-1). Seven to 10 ml of local anesthetic is injected incrementally after negative aspiration of blood.

MIDTARSAL APPROACH[88]

The PTN can be blocked distal to the flexor reticulum where it is relatively superficial. The needle is inserted on either side of the posterior tibial artery and advanced toward the calcaneus. After bone contact is made, the needle is slightly withdrawn and 5 to 7 ml of local anesthetic is injected. This a more distal PTN block for mid- or forefoot surgery and the calcaneal branch may be missed.

SUBCALCANEAL APPROACH[89]

The PTN is in close and consistent relation to the bony ridge of the calcaneus. The needle is inserted posteroinferiorly to the bony ridge until bone is contacted. The needle is slightly withdrawn and 5 to 7 ml of local anesthetic is injected. The calcaneal branch may be missed. Contact with periosteum is often painful.

ULTRASOUND-GUIDED TECHNIQUE

Ultrasound guidance may avoid the limitations of the landmark-based technique,[90] and has been shown to improve the success rate of the PTN block, in comparison with the landmark-based technique.[81]

The patient is positioned supine with the foot elevated, or prone, and using a high-frequency transducer, the area proximal to the medial malleolus is scanned to visualize the PTN, located posteromedial to the posterior tibial artery (Fig. 78-15). Using a proximal, ultrasound-guided, nerve stimulator–assisted approach, Doty et al. obtained a 100% success rate within 6 minutes in all PTN sensory distributions.[91]

If prolonged postoperative analgesia is desired, an ultrasound-guided perineural catheter may be inserted in this location. It is important to remember that blockade in this area will not cover the area of tourniquet.

DEEP PERONEAL NERVE (DPN) BLOCK

Anatomy[83]: The DPN is located approximately 2.5 to 5 cm above the ankle, between the extensor digitorum longus (EDL) and extensor hallucis longus (EHL) tendons, mostly lateral to the anterior tibial artery. At the level of the malleoli, the nerve becomes more medial. In 98% of cases the DPN divides into lateral and medial terminal branches 1 cm above the ankle joint.

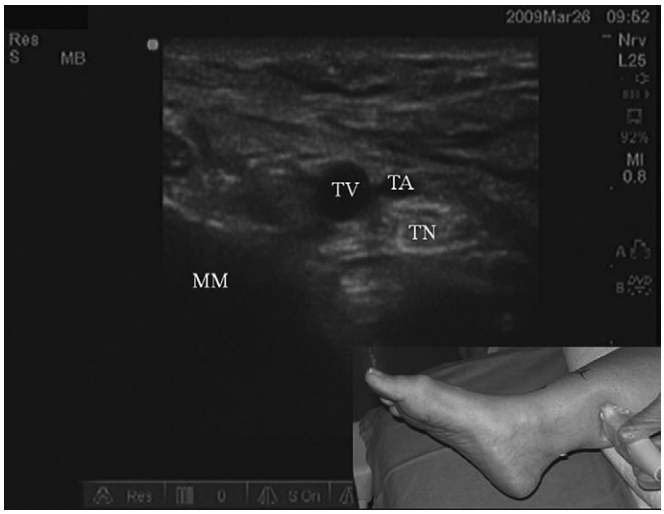

FIGURE 78-15 Ultrasonography of the posterior tibial nerve above the medial malleoli. TN = tibial nerve; TA = posterior tibial artery; TV = tibial vein; MM = medial malleoli.

The lateral branch supplies the extensor digitorum brevis. The medial branch supplies dorsal cutaneous branches to the great toe and the second toe.

Technique: The most consistent location of the DPN is 2.5 cm above the level of the ankle joint at the upper border of EHL laterally and EDL medially. Dorsiflexion of the great toe (EHL) and small toes (EDL) allows identification of these two tendons.[92] The needle is advanced perpendicular to the ankle joint until bone is contacted, withdrawn slightly, and 5 ml of local anesthetic is injected. If a nerve stimulator is used, the appropriate EMR is extension of the lateral four toes.

Ultrasound-guided technique: A high-frequency ultrasound probe is placed on the ankle proximal to the malleoli line to identify the pulsating posterior tibial artery between EDL and EHL tendons. The DPN is usually visualized lateral to the artery (Fig. 78-16).[92] If the nerve is not visualized, perivascular spread of the local anesthetic may suffice.

SUPERFICIAL PERONEAL NERVE (SPN) BLOCK

Anatomy[83]: The SPN is a sensory branch of the common peroneal nerve. After coursing in the anterolateral compartment of the leg, the nerve pierces the deep fascia 10 to 15 cm from the tip of lateral malleolus. Afterward the SPN lies subcutaneously and divides into branches that supply the dorsum of the foot and toes.

Technique: The SPN can be blocked by subcutaneous infiltration of 5 to 7 ml of local anesthetic between the lateral border of the tibia and the superior aspect of the lateral malleolus.

SURAL NERVE BLOCK

Anatomy[83]: The sural nerve is formed by the union of the medial sural nerve (branch of the tibial nerve) and the lateral sural nerve (branch of the common peroneal nerve). It courses along the lateral border of the Achilles tendon,

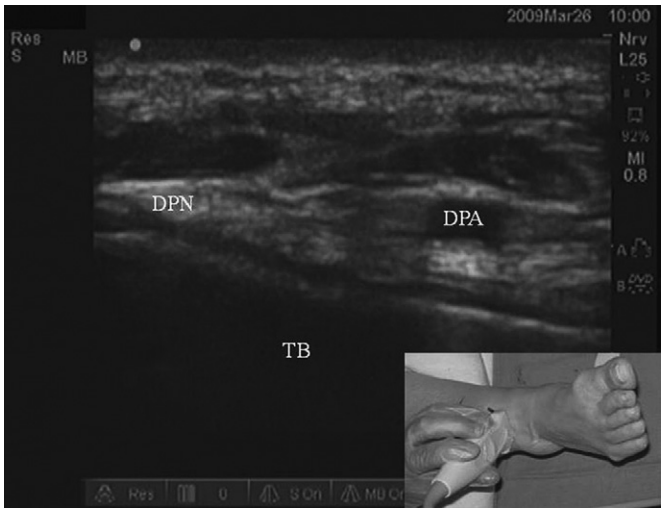

FIGURE 78-16 Ultrasonography of the deep peroneal nerve at the ankle. DPN = deep peroneal nerve; DPA = dorsalis pedis artery.

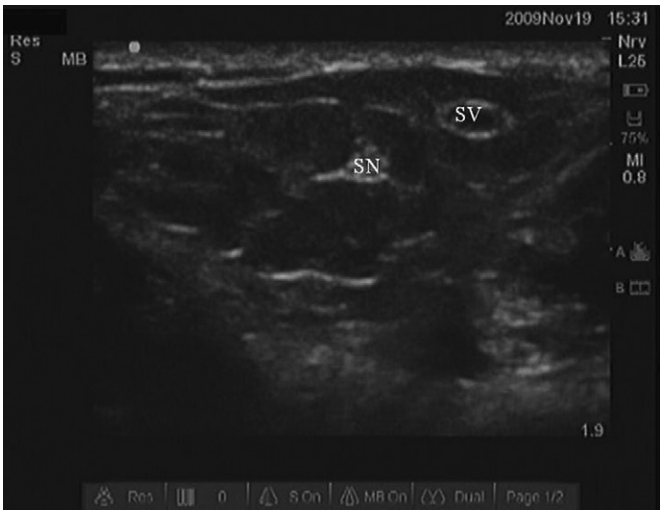

FIGURE 78-17 Ultrasonography of the sural nerve at the ankle. SN = sural nerve; LSV = lesser saphenous vein.

posteromedial to the lesser saphenous vein, and then around the posterior border of the lateral malleolus. At the level of the base of the fifth metatarsal, the nerve divides into its two terminal branches. The nerve supplies sensory innervation to the lateral border of the foot, the fourth and fifth toes, and the web spaces of the third and fourth toes. It also gives off two lateral calcaneal branches above the tip of the lateral malleolus.

Technique: The patient is positioned supine and the foot is internally rotated. Up to 5 ml of local anesthetic is infiltrated subcutaneously anterolateral to the lateral border of the Achilles tendon at the level of lateral malleolus. The nerve may also be blocked 7 to 10 cm above the superior border of the lateral malleolus, at the lateral border of Achilles tendon, posteromedially to the lesser saphenous vein. For surgery on the midfoot or third and fourth toes, a full sural nerve block may not be needed if the lateral aspect of the foot is not involved. The medial branch of the sural nerve can be blocked with 3 to 5 ml of local anesthetic superficially infiltrated at the anterior border of the lateral malleolus.

Ultrasound-guided technique: The patient is positioned prone with a tourniquet on the proximal calf to distend the lesser saphenous vein. A high-frequency ultrasound probe is placed above the lateral malleolus and the vein is visualized. Using an in- or out-of-plane approach, the block needle is directed as needed with the goal of circumferential spread of local anesthetic around the vein (Fig. 78-17).[82]

SAPHENOUS NERVE BLOCK

Anatomy:[83] The saphenous nerve is the terminal branch of the femoral nerve. After travelling in the subsartorial canal along with the femoral artery and nerve to vastus medialis, the nerve becomes superficial at the medial border of the knee joint as it pierces the fascia between the gracilis and sartorius muscles. It runs distally behind the medial border of the tibia, posterior to the greater saphenous vein. It divides into two branches, one ending at the ankle and the second one passing in front of the medial malleolus, close to the greater saphenous vein. It provides cutaneous innervation to the medial site of the foot up to the medial side of the big toe.

Technique: The saphenous nerve is blocked by subcutaneous infiltration of 3 to 5 ml of local anesthetic along the upper border of the medial malleolus near the greater saphenous vein.

LOCAL ANESTHETIC CHOICE AND DOSE FOR ANKLE BLOCK

The PTN is a fairly large nerve and is the major component nerve involved in performing an ankle block for surgical procedures of the midfoot, forefoot, and hind foot. If an appropriate EMR at less than 0.5 mA is obtained, 5 to 7 ml of local anesthetic may suffice, otherwise a higher volume of local anesthetic may be preferable to ensure adequate diffusion.

Duration of surgery and, most important, duration of postoperative analgesia are important considerations in the selection of the local anesthetic agent for ankle block. The use of epinephrine as an adjuvant is an absolute contraindication in an ankle block, as it can have a major impact on the blood supply in the foot.

SUMMARY

Lower extremity nerve blocks are increasingly popular for surgical anesthesia and postoperative analgesia. They provide distinct advantages over general and neuraxial anesthesia in inpatient and outpatient settings. Use of continuous catheter techniques allows extended, superior postoperative analgesia with minimal side effects. Neurostimulation and ultrasound guidance have allowed precise nerve identification with minimal risk of nerve injury and limited discomfort to the patient.

KEY POINTS

- The sciatic nerve is the largest nerve in the body and innervates the entire leg below the knee and the foot, except for its medial aspect, which is innervated by the

saphenous nerve. Its two divisions, the tibial nerve and the peroneal nerve, while separate entities, are covered by a continuous connective tissue sheath.

- The sciatic nerve can be blocked at different levels along its entire length as it exits the pelvis at the greater sciatic foramen to its termination in the popliteal fossa. The posterior subgluteus and the infragluteal parabiceps approaches are associated with less patient discomfort since the sciatic nerve is blocked at shallower depths.
- The use of nerve stimulation facilitates easy identification of the sciatic nerve. The EMR should be obtained at stimulation intensities of less than 0.5 mA. The appropriate EMR is inversion because it signifies stimulation of both divisions of the sciatic nerve, and the latency of onset is shortened.
- Sciatic nerve block in the popliteal fossa can be performed through the posterior or lateral approach, both equally effective.
- The two-stimulation technique takes advantage of the anatomic relationship of the tibial and common peroneal nerves in the popliteal fossa. The needle is redirected to elicit appropriate EMR for each nerve as it is stimulated. Ultrasound guidance of a two-injections technique may shorten the latency of onset.
- Ankle block is an effective means of providing anesthesia for midfoot and forefoot surgery.
- Ultrasound guidance has been shown to decrease the latency of onset, improve performance of nerve blocks, and increase patient satisfaction.
- Stimulating continuous peripheral catheters shorten onset times, allow reduction of the local anesthetic volume needed for surgical anesthesia, and provide superior postoperative analgesia with increased patient satisfaction.

REFERENCES

Access the reference list online at http://www.expertconsult.com

CHAPTER 79

Peripheral Sympathetic Blocks

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Jonnesco[1] first described the cervicothoracic block in 1920, followed by Lawen[1] for the differential diagnosis of abdominal pain. Kappis[1] used sympathetic blocks for the treatment of severe pain in visceral pain syndromes, including the blockade of the stellate ganglion. In the early 1930s, investigators established the technique and indications for the blockade of the sympathetic trunk of the stellate ganglion. Brunn and Mandl[2,3] first described lumbar sympathetic blocks in 1924. They became popular in the 1950s for the management of causalgia and reflex sympathetic dystrophies.[2]

The number of indications for sympathetic blockade has since grown (Tables 79-1 and 79-2). Sympathetic blocks can be used for diagnostic, prognostic, and therapeutic purposes. Diagnostic blocks are done to determine if the pain is sympathetically mediated or not. Prognostically, the blocks are done to determine if neurolysis or surgical sympathectomy could be beneficial.[5] Finally, therapeutic blocks (usually in a series with local anesthetics) are done to treat conditions such as complex regional pain syndromes (CRPSs),[4,5] phantom limb pain,[1] postherpetic neuralgia,[7,8] and ischemic[9] and cancer pain.[10] The role of therapeutic blocks are best utilized as part of a comprehensive functional restoration program.[5] Multiple indications for sympathetic blocks are listed but there are only a few randomized, placebo-controlled outcome studies to demonstrate their effectiveness.[11] After completion of the block, monitoring is required to confirm that the sympathetic axis was indeed blocked. If pain improves after the block, the optimum number of blocks performed is still in question.

STELLATE GANGLION BLOCK

ANATOMY

The cervical sympathetic trunk contains three interconnected ganglia: the superior, middle, and inferior cervical ganglia. In 80% of people the lowest cervical ganglion is fused with the first thoracic ganglion to form the cervicothoracic (stellate) ganglion.[10,12] If not connected, the first thoracic ganglion is labeled as the stellate ganglion. The ganglion is oval shaped and measures 2.5 cm long, 1 cm wide, and 0.5 cm thick.[10]

The cervical ganglia receive preganglionic fibers from the lateral gray column of the spinal cord; the myelinated preganglionic cell axons originate from the anterolateral horn of the spinal cord. The nerve fibers emerge from the upper thoracic spinal cord through the ventral spinal root, joining the spinal nerves at the start of the ventral rami. They leave the spinal nerve through the white rami communicantes, which enter the corresponding thoracic ganglia, through which they ascend into the neck. The preganglionic fibers for the head and neck emerge from the upper five thoracic spinal nerves (mainly the upper three), ascending in the sympathetic trunk to synapse in the cervical ganglia. The preganglionic fibers supplying the upper limb originate from the upper thoracic segment, probably T2–T6; ascend via the sympathetic trunk to synapse in the cervicothoracic ganglion, where postganglionic fibers pass to the brachial plexus.

The white ramus to the cervicothoracic ganglion contains most of the preganglionic fibers for the head and neck; these ascend the trunk to the superior cervical ganglion from which postganglionic branches supply vasoconstrictor and sudomotor nerves to the face and neck, secretory fibers to the salivary glands, dilator pupillae, and nonstriated muscle in the eyelid and orbitalis. Blockade of this ramus leads to ptosis, miosis, enophthalmos, and loss of sweating of the face and neck (Horner's syndrome). The cervicothoracic ganglion sends gray ramus communicantes to the seventh and eighth cervical and first thoracic nerves and gives off a cardiac branch, branches to nearby vessels, and sometimes a branch to the vagus nerve.

To achieve successful sympathetic denervation of the head and neck, one should block the stellate ganglion because all preganglionic nerves either synapse or pass through the ganglion on their way to the more cephalad ganglia. Blood vessels of the upper limb beyond the first part of the axillary artery receive their sympathetic supply via branches of the adjacent brachial plexus. The first and second (and occasionally the third) intercostal nerves may be interconnected by postganglionic fibers from their gray rami; these fibers provide another pathway by which postganglionic nerves pass from the upper thoracic ganglia to the brachial plexus. These anomalous pathways have been termed Kuntz's nerves and are implicated in cases of inadequate relief of sympathetic mediated pain despite evidences of cervical ganglia block.

The cervical sympathetic chain lies anterior to the prevertebral fascia. It is enclosed within the lateral aspect of the alar fascia (the thin layer of fascia immediately anterior to the prevertebral fascia that separates the cervical sympathetic chain from the retropharyngeal space). It is medial to the carotid sheath. The carotid sheath is connected to the alar fascia by a variable mesothelium-like fascia. The fascial plane enclosing the cervical sympathetic chain may be in direct communication with several spaces including the space in front of the scalenus anterior muscle, the brachial plexus, spinal nerve roots, the prevertebral portion of the vertebral artery, and between the endothoracic fascia and the thoracic wall muscle at the T1–T2 level. These communications may explain some of the side effects of stellate ganglion block. In the upper thorax the thoracic sympathetic chain lies lateral to the longus colli muscle and posterior to the endothoracic fascia, which is the inferior continuation of the prevertebral fascia.

TABLE 79–1 Potential Indications for Stellate Ganglion Blockade

Complex regional pain syndrome, types I and II
Vascular insufficiency–Raynaud's syndrome, vasospasm, vascular disease
Accidental intra-atrial injection of drug
Postherpetic neuralgia and acute herpes zoster
Phantom pain
Frostbite
Complex regional pain syndrome, breast and postmastectomy pain
Quinine poisoning
Hyperhidrosis of upper extremity
Cardiac arrhythmias
Angina
Vascular headaches
Neuropathic pain syndromes including central pain
Cancer pain
Facial pain—atypical and trigeminal neuralgia
Hot flashes

TABLE 79–2 Potential Indications for Lumbar Sympathetic Blockade

Complex regional pain syndrome, types I and II
Phantom pain
Arterial insufficiency of lower extremity
Raynaud's syndrome
Acute herpes zoster
Hyperhidrosis
Frostbite
Lower extremity crush injury

The cervicothoracic ganglion lies on or just lateral to the longus colli muscle between the base of the seventh cervical transverse process and the neck of the first rib (which are posterior to the ganglion), the vertebral vessels are anterior, and the nerve roots that contribute to the inferior portion of the brachial plexus are posterior to the ganglion. The vertebral artery, which originates from the subclavian artery, passes anterior to the ganglion at C7 and enters the vertebral foramen, posterior to the anterior tubercle of C6 in 90% of cases. In the other 10% of cases, the artery may enter at C5 or higher. Recent studies have demonstrated that there is a variable thickness to the longus colli muscle which may affect block outcome and complications.[13] This may account for variable blockade and failed neurolysis in the presence of successful blockade.

INDICATIONS

Most of the indications for stellate ganglion block are based on case reports or case series.[1,10] Table 79-1 lists some of the indications based on these case reports or case series with the exception of CRPS and Raynaud's disease, which have outcome studies (see Studies section at the end of this chapter).

TECHNIQUES

There are multiple approaches to the stellate or cervical ganglion block with variable success rates (16%–100%).[14] Image guidance appears to have improved success but practicality and approach continues to be debated along with imaging modality. CT guidance has a high success rate,[15] but is cumbersome to use and exposes all to high doses of radiation. Ultrasound technology makes possible visualization of soft tissues along with the stellate or cervical ganglion.[16] Further studies have revealed other landmarks as potential targets for cervical sympathetic blocks including the longus capitis muscle.[17]

Surface Landmark (Non–Image Guided) Technique: The blind technique relies on the use of landmarks described in the anatomy section. After monitors are applied and IV access is obtained, the patient is positioned supine with the neck slightly extended. A small shoulder roll may be placed but is not necessary. The mouth can be slightly opened to relax the neck muscles. The cricoid cartilage is palpated to find the C6 level and, more specifically, the transverse process. The skin crease just caudal to the thyroid may be helpful as it is found to cross the C6 transverse process in 71% of cases. The Chassaignac's tubercle at C6 is identified with palpation. In most individuals, the tubercle is located approximately 3 cm cephalad to the sternoclavicular joint at the medial border of the sternocleidomastoid muscle. The trachea and carotid pulse is palpated gently by placing the index and middle fingers between the sternocleidomastoid muscle and the trachea. The carotid is retracted slightly laterally while local anesthetic is placed intradermally with a 27-gauge needle. This is followed by the placement of either 22-gauge Quincke or pencil-point needle perpendicularly in an anterior to posterior fashion until the needle contacts bone and then withdrawn 2 mm. After negative aspiration, 0.5 to 1 ml of local anesthetic is injected slowly while the patient is awake and responsive to detect aberrant spread of the local anesthetic to surrounding structures. If negative, 5 to 8 ml of 0.25% bupivacaine is injected incrementally with frequent aspiration. The patient is then monitored for a minimum of 30 min to assess response to the blockade.

Fluoroscopic Technique: The procedure is essentially as described as above for patient preparation and positioning. Once the patient is in proper position, the fluoroscope is brought in and a posteroanterior image is taken. The vertebrae are counted and both the C6 and C7 levels are noted along with the trachea. Either level can be utilized so long as the operator has thorough knowledge of the anatomy described in the previous section. The C7 level is preferred because of its closer proximity to the stellate ganglion, but the vertebral artery is uncovered at this level unlike at the C6 level where the vertebral artery travels posterior to Chassaignac's tubercle. If the C7 level is the final location of the needle tip, then it is important to keep the needle more medial on the transverse process to avoid the vertebral artery (Fig. 79-1).

After local anesthetic infiltration, a 25- or 22-gauge 1.5- or 2-inch needle is advanced coaxially to the anterior transverse process of the chosen level. Once contact is made, the needle is withdrawn 2 mm so that it is not in contact with periosteum. A lateral image maybe taken to

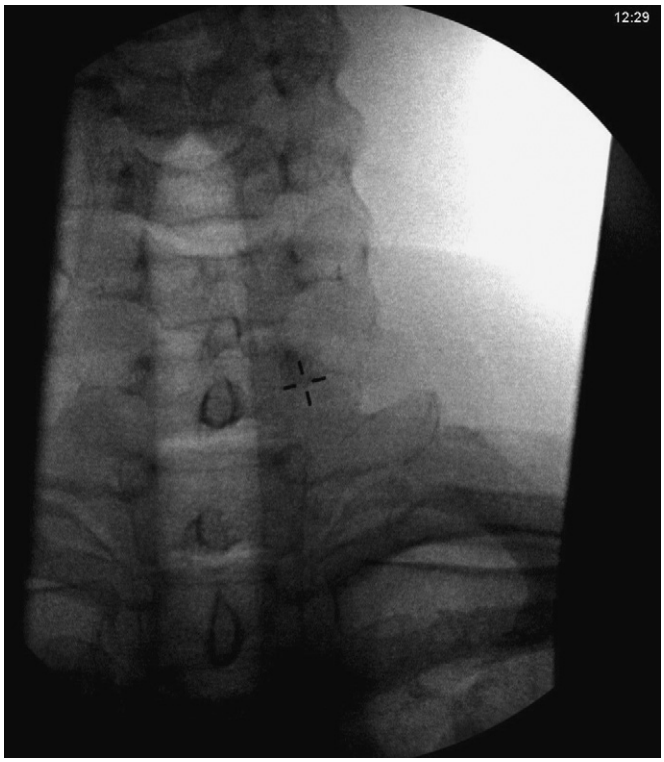

FIGURE 79-1 Target for stellate ganglion block at C7 level. Note the more medial target to avoid the vertebral artery.

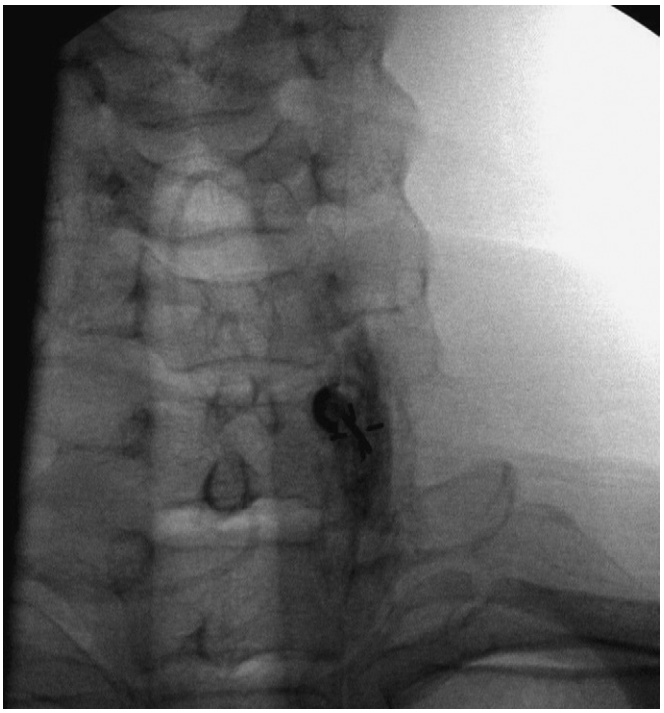

FIGURE 79-2 Correct placement and contrast pattern for stellate ganglion block.

confirm that the needle is anterior to the vertebral body, but is not always necessary. A pre-contrast flushed extension set is connected to the needle and, after negative aspiration for blood, under live, real-time fluoroscopy, or digital subtraction angiography, 1 to 5 ml of contrast is injected. The optimal spread of contrast should cover the C6–T2 levels to ensure blockade of the stellate ganglion (Fig. 79-2). A test dose is then injected with 0.5 to 1 ml of 1% lidocaine through the extension tubing (to minimize needle movement) assuring that the local anesthetic passes through the tubing. The patient is continuously assessed for possible intravascular or neuraxial spread. After a negative test dose, approximately 5 to 10 ml of local anesthetic is injected incrementally. The greater the volume injected, the greater the likelihood of spread to the recurrent laryngeal nerve, phrenic nerve, or brachial plexus. It is important to intremittently aspirate during the injection.

Other Fluoroscopic Approaches: Patient preparation is essentially the same with the patient placed in the supine position with established IV access. The head is then turned to the side opposite to be blocked. The fluoroscope is brought in to demarcate the C5–C6 disc on AP view. The C-arm is then rotated ipsilateral oblique until the foramina are clearly demarcated. The target of the injection is the junction of the uncinate process and the vertebral body of C7. A 25-gauge needle is then passed coaxially with the fluoroscope beam until it reaches the target. As with all image-guided procedures, it is important to keep the needle coaxial and, in this case, avoid the needle going posterior into the foramina (direct entry into the thecal sac). Once contact with bone occurs, the stylet is removed and contrast is injected as described above in the previous section. Three to 5 ml of local anesthetic is all that is needed to block the stellate ganglion with this technique. The advantage of the technique is that the needle is placed obliquely to allow for placement at C7 while avoiding the vertebral artery (which is anterior to the stellate ganglion) and the pleural dome in non-emphysematous patients (based on cadaver studies). There are no prospective studies on the above technique that consider outcome or complications.[18]

They outlined the following advantages:

- Eliminates pushing away vasculature and pressing on the potentially painful Chaissagnac's tubercle
- Minimizes the chance of intravascular injection
- Minimizes esophageal perforation
- Minimizes the chance of recurrent laryngeal nerve paralysis
- Reduces the volume of local anesthetic
- Easy to teach trainees

Ultrasound Approach: Kapral et al.[19] first described the use of ultrasound guidance for blockade of the stellate ganglion to decrease the incidence of retropharyngeal hematoma and increase the safety and efficacy of the block. Ultrasound allows direct visualization of the thyroid gland, vertebral artery, esophagus, pleura, nerve roots, longus colli muscle, and the correct fascial planes for nerve blockade along with real time, direct visualization of local anesthetic spread.[16,20]

Positioning for the procedure is the same as the other anterior techniques. A linear-array, 3- to 12-MHz frequency probe is placed transversely at the level of C6, just lateral to the trachea. Fluoroscopy may be utilized initially to identify

the C6 level. In a case report by Narouze et al.,[20] the initial needle placement was done under fluoroscopy. After placement of an ultrasound, they noted that the needle was advancing towards thyroid tissue. They also noticed an esophageal outpouching consistent with a Zenker's diverticulum with the ultrasound. With ultrasound guidance, corrections were made and the needle was advanced using in-plane technique and the needle tip placed anterior to the longus colli muscle. One milliliter of contrast demonstrated appropriate spread without vascular uptake. Under real-time ultrasound imaging, 5 ml of 0.25% bupivicaine were injected in divided doses demonstrating excellent caudal and cephalad spread. Appropriate sympathetic blockade was monitored and achieved based on the presence of Horner's syndrome and increased extremity temperature without recurrent laryngeal nerve blockade.

There is one validation study using the ultrasound approach which revealed that at the C6 level, the cervical sympathetic trunk lays entirely subfascially, and, subfascial injection via the lateral approach ensures reliable spread of solution to the stellate ganglion.[16] There are no randomized, prospective, outcome studies on using the ultrasound approach.

Posterior Approach: This approach is normally utilized when there is a failure of achieving sympathetic blockade of the upper extremity or when the block is done as a precursor to percutaneous or surgical sympathectomy. Some advocate that this approach should be utilized for all upper extremity sympathectomies.[21]

The patient is in the prone position, and image guidance is an absolute necessity (usually fluoroscopy, but CT can be utilized). The fluoroscope is utilized to obtain AP images of the T2 and T3 vertebrae. The C-arm is then rotated obliquely until the transverse process is just over the vertebral body followed by cephalocaudal rotation until the first rib is squared off. The target is then the midpoint of the T2 and/or the T3 vertebra. A less oblique angle can also be used if there is concern for pneumothorax, but may make it more difficult to pass the needle adjacent to the vertebral body. Strict coaxial technique must be used to minimize complications and the final needle position is determined. After the needle is in the correct position, 0.5 to 3 ml of contrast is injected under real-time imaging or digital subtraction angiography to observe for vascular uptake or extraneous spread. Five milliliters of local anesthetic is then injected in divided doses and the patient is monitored for sympathetic blockade.

Volumes of Injectate: Variable injection volumes have been suggested from 5 to 20 ml.[22] Feigl et al.[22] studied 42 cadavers to determine optimum volume of injectate for blockade. They used the blind paratracheal approach at C6 and found that 5 ml of injectate almost always demonstrated spread over the C6–T2 levels without spread ventrally or laterally, whereas 10 and 20 ml of injectate almost always spread to other spaces which can cause recurrent laryngeal nerve and/or phrenic nerve blockade. Hardy and Wells[23] demonstrated that with 10 ml of local anesthetic injection, there is a 10% incidence of recurrent laryngeal nerve block; this increases to 80% with the injection of 20 ml. However, larger volumes may be needed to obtain complete blockade of T1 and T2 ganglia if injection is done at C6 compared to C7.[24]

LUMBAR SYMPATHETIC BLOCKS

ANATOMY

The lumbar sympathetic chain consists of four to five paired ganglia that lie along the anterolateral surface of the lumbar vertebral bodies with the psoas muscle and fascia separating the sympathetic nerves from the somatic nerves. The lumbar sympathetic chain contains pre- and post-ganglionic fibers to the pelvis and lower extremities. Cadaver studies have identified that the sympathetic ganglia were most frequently located at the inferior third of the L2 vertebra, L2–L3 disc space, and at the superior third of the L3 vertebra.[25] Also, all of the sympathetic fibers from the lower extremity pass through the L2 and L3 ganglion. Therefore, the best site for placement of the tip of the needle is the anterolateral surface of the lower third of the second vertebral body or at the upper third of the third vertebral body.[25] The segmental artery and vein pass along the midportion of the lumbar vertebral body in a tunnel under the dense fascia. Solutions injected at the mid-vertebral level may pass posteriorly in this tunnel to the epidural space. Crossover of the sympathetic fibers to the other side has been described.

INDICATIONS

The indications for lumbar sympathetic blocks are similar to stellate ganglion blocks. Any pain syndrome that includes a sympathetically mediated or atypical pattern maybe considered for diagnostic sympathetic block. Most of the indications are based on case reports; there are a few controlled trials on CRPS (Table 79-2).

TECHNIQUES

Sympathetic block was first done blindly by starting 5 to 8 cm lateral to the spinous processes of L2–L4 and using contact with the transverse process as a gauge of depth and then walking anteriorly off of the vertebral body.[2,26] Though this technique is described in many pain textbooks and is the original approach described in the 1920s, it is rarely used since image guidance allows for better placement and hopefully fewer complications. The materials needed are similar to stellate ganglion blocks with the exception of needle length, which is usually 5 to 7 inches.

Fluoroscopic Approach (Paradiscal): The original fluoroscopic approaches described the placement of the needle at the anterolateral surface of L2, L3, and L4. Datta and Pai[27] described the paradiscal approach is probably the most common technique utilized. The approach is based on their anatomic studies that demonstrated the most likely position of the sympathetic ganglia are near the intervertebral discs and the likelihood of injuring the spinal nerves was minimized along with avoiding the lumbar arteries which are more commonly located at the middle third of the vertebral body. They also advocated the use of at least two needles and that the needles should be extraforaminal.[27]

The patient is positioned prone. The fluoroscope is brought in to identify the L2, L3, and L4 levels. The fluoroscope is angulated cephalocaudad to square off the L2–L3 disc space, and the fluoroscope is rotated ipsilateral oblique

20 to 30 degrees so that the transverse process of L3 is visualized over the vertebral body. The target is at the anterosuperior portion of L3 or anteroinferior portion of L2 (hence the term "paradiscal"). After local anesthetic infiltration, a 22-gauge by 5-to-7 inch needle is advanced coaxially with the beam of the fluoroscope until it make contact with the vertebral body.

The fluoroscope is then rotated to AP view to confirm that the needle is contacting the vertebral body and not the transverse process or entering the intervertebral disc. The fluoroscope is then rotated to the lateral view and the needle tip is walked anteriorly to the anterior one-third of the vertebral body, or, if needed, to the anterior portion of the vertebral body. Once proper location is identified, 1 to 5 ml of contrast is injected under real time fluoroscopy to confirm correct placement. Common errors in needle location include placement of needle within the psoas muscle or incorrect fascial plane of the needle. If the needle is advanced too anteriorly, the aorta may be pierced; if too posteriorly, the block may be unsuccessful. Once the needle is in an appropriate place, 5 to 20 ml of local anesthetic is injected incrementally (Figs. 79-3 and 79-4).

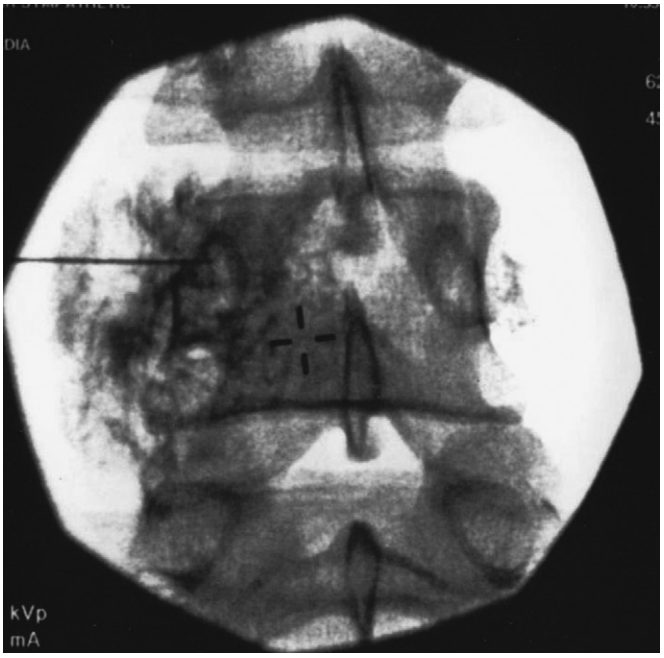

FIGURE 79-4 Correct anteroposterior position of needle for lumbar sympathetic block.

TRANSDISCAL APPROACH

The benefits of this technique[28] include decreased incidence of genitofemoral neuritis, decreased incidence of injuring lumbar arteries,[27]closer proximity to the ganglia,[25] decreased scarring of the paravertebral muscles (for repeated neurolysis), and decreased spread of contrast to the psoas muscle (relative to the blind approach). Potential risks are similar to performing sympathetic blocks as described as well as those described for discography. The technique is similar to performing a discography using either a single or double needle technique, except that the final needle position is anterior to the disc rather than in the middle of the disc. The injectate volume is similar to that described above.

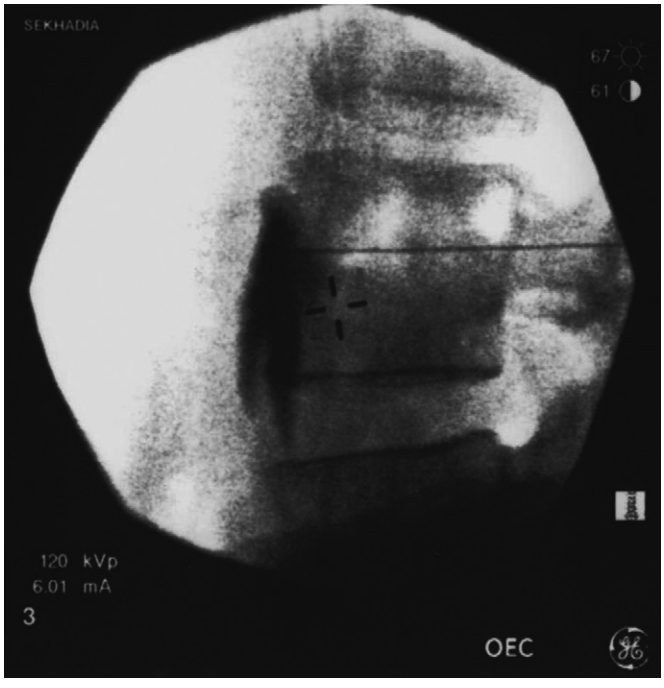

FIGURE 79-3 Lateral image of correct placement and contrast pattern for lumbar sympathetic block.

NEUROLYSIS

Percutaneous neurolysis has been performed successfully for both the stellate ganglion and the lumbar sympathetics. The two options for neurolysis are radiofrequency (RF) (pulsed and thermal) versus chemical (phenol and alcohol). Radiofrequency techniques allow for more controlled lesions, while chemical lesions may allow for larger lesions, and are dependent on the volume of agent injected. Both techniques have been utilized when the effect of local anesthetic is confirmed but relief is unsustained. There are no randomized, placebo-controlled, prospective trials with neurolytic blocks for nonmalignant pain.

CHEMICAL NEUROLYSIS

At the stellate[29] or lumbar levels,[30] 2 to 3 ml of phenol (3%–6%) or alcohol (50%–100%) is injected to minimize spread to adjacent structures. Phenol is usually the agent of choice because of a decrease in incidence of neuritis post procedure. The usual concentration of phenol is 6%, but one study demonstrated that 10% to 12% solution produced longer neurological destruction in cat sciatic nerves.[2] Neurolysis at the stellate level can be done similar to the anterior approach at C6 or C7, or can be done via the posterior approach at T2 or T3 for upper extremity problems. A test dose of local anesthetic should be injected prior to a chemical neurolysis to ensure a negative motor and sensory block prior to the injection of the neurolytic agent.

For larger lesions at this level, multiple needles should be placed with the same amount of volume injected at each needle and appropriate contrast studies prior to injection of the neurolytic agent.[1,29] The lumbar level is much more forgiving as far as higher volumes and complications. Most authors advocate placing multiple needles, although one needle can be placed and up to 15 ml of agent is injected through a single needle with the same efficacy and safety profile as smaller volumes through multiple needles.[1]

RADIOFREQUENCY LESIONING

Radiofrequency lesioning is a more controlled method of neurolysis as the only areas lesioned are at the tip of the needle. Options include a nondestructive pulsed lesion or a more conventional, destructive thermal lesion. The RF needle can be electrically stimulated prior to lesioning, this helps to avoid lesioning of unwanted surrounding structures such as the recurrent laryngeal nerve or genitofemoral nerve.

For RF lesion of the stellate ganglion at the C7 level, then stimulation can be done while the patient says "EE" to see if there is any stimulation of the recurrent laryngeal nerve as well as phrenic nerve. A 22-gauge cannula with 50-mm length and 5-mm active tip, is utilized and performed similarly to the anterior approach as described above, with fluoroscopic guidance. Stimulation is performed at 2 Hz and up to 2.5 V (typical for motor stimulation) prior to injection of local anesthetic and lesioning. The posterior approach at T2 and/or T3 will most likely avoid these two nerves.[10,31]

At the lumbar level, the needles can be placed at the inferior third of L2, superior or middle third of L3, or middle third of L4. Multiple needles should be placed to obtain the best neurolysis. Sluijter[6] described a technique that relies on placing the needle at the midpoint of each vertebral body with the knowledge that contact can be made with the respective anterior ramus at each level. He notes that at the L4–L5 disc the sympathetic chain is in a more superficial position. He also recommends lesioning at L5. The initial needle placement is in the concavity of each vertebral body where the sympathetic chain courses. The needle is advanced, under lateral view, to just anterior to the vertebral body. An anteroposterior view is used to confirm that the needle tip is at the level of the facet column.

For pulsed lesions, the needle tip is slightly withdrawn because the target should be in front of the needle, as opposed to parallel to the needle for thermal lesions. Sensory stimulation is performed (50 Hz) to determine the lowest threshold of stimulation and motor stimulation is also carried out before doing the doing a thermal lesion (2–5 Hz up to 3 V). Pulsed lesions are carried out at 42° C, pulsed mode, 2 × 20 ms/sec, 40 to 45 V for 120 sec. Thermal lesions require local anesthetic prior to lesioning (2 ml of 2% lidocaine or equivalent), and the tip temperature is brought to 80° C for 60 to 90 sec.[1,6,10]

COMPLICATIONS

Stellate ganglion blockade and neurolysis[10]:

- Bleeding/hematoma
- Pneumothorax, hemothorax
- Vertebral artery injury or inadvertent injection
- Inadvertent injection into neuraxis
- Esophageal trauma
- Tracheal trauma
- Phrenic nerve injury
- Brachial plexus injury
- Recurrent laryngeal nerve injury
- Neuritis—any nerve or plexus listed above
- Postsympathectomy syndrome

Lumbar sympathetic blockade and neurolysis:

- Bleeding
- Infection
- Intravascular injection[32]
- Intralymphatic injection[33]
- Subarachnoid injection
- Discitis (transdiscal approach)
- Back pain
- Spinal nerve injury
- Genitofemoral nerve injury (L4 and L5 levels and too posterior and lateral placement)[34]
- Lumbar plexus injury
- Neuritis
- Horner's syndrome and brachial paresis[35]

MONITORING ADEQUACY OF SYMPATHETIC BLOCKADE

Successful stellate ganglion block denervates the upper cervical segments to produce Horner's syndrome, which includes ptosis, miosis, and anhidrosis. Other signs include unilateral nasal stuffiness (Guttman's sign) and warmth of the face. The presence of Horner's syndrome signifies cephalic sympathetic blockade and does not imply sympathetic denervation of the arm.[36] If the block is used to treat the shoulder or upper limb, additional signs are needed to determine sympathetic blockade in the area. Complete block is reliably detected when a test of adrenergic fiber activity (thermography, plethysmography, laser Doppler flowmetry) is combined with a test of sympathetic cholinergic (sudomotor) fiber activity (sweat test, sympathogalvanic response).

Increase in skin temperature is the most commonly used clinical sign of sympathetic blockade. Different investigators considered different increases in skin temperature as signifying effective sympathetic blockade. After a stellate ganglion block, skin temperature increases of 1.5° C,[37] 3.8° C,[38] and 7.5° C[15] have been considered as signifying successful sympathetic blockade. A mean increase of 3° C was noted after a lumbar paravertebral sympathetic block.[39] Hogan et al. recommended that the ipsilateral temperature increase should exceed that of the contralateral side to indicate successful sympathetic blockade.[36] Stevens et al. found that a temperature increase that was 2° C higher than the contralateral extremity signified complete sympathetic blockade in most patients but it was not sufficient to guarantee a complete sympathetic block.[40] The magnitude of temperature increases after complete sympathetic blockade depends on the baseline values; greater increases are noted in patients with lower preblock temperatures.[41] With vasodilatation, the skin temperature will approximate core body temperature. Since the upper limit of skin temperature in the fingers and toes is 35° to 36° C,[42] patients other

than those with organic peripheral vascular disease can approach 35 to 36° C.[41] Patients whose baseline skin temperatures are low because of vasoconstriction (those with late-stage CRPS) will have large increases after complete sympathetic blockade. A patient who has vasodilatation of the involved extremity (a person with early-stage CRPS), cannot be expected to have a large temperature increase.

Laser Doppler flowmetry is a sensitive method to evaluate skin blood flow and to detect the presence of sympathetic blockade. Some investigators consider a 50% or greater increase in the skin blood flow to signify successful sympathetic block.[43] Blood flow can be determined accurately by using plethysmographic methods such as venous-occlusion plethysmography. After successful sympathetic block of the extremity, there is a marked increase of the upward slope because of a significant increase in the pulse wave. Investigators found a better correlation of the blood flow measured by volume plethysmography with skin surface temperature gradients than blood flow measurements by laser Doppler flowmetry.[43]

Abolition of sweating and of the sympathogalvanic response (SGR) are among the standard tests of complete sympathetic blockade.[36–46] The older starch iodine test is messy and cumbersome, while the newer sweat tests, the cobalt blue and the ninhydrin sweat tests, are easier to perform. The sweat tests are performed in the following manner. The patient's fingers or toes are wiped dry and the cobalt blue– or ninhydrin–impregnated filter paper is taped on them. A transparent tape is used so the change in color of the cobalt blue paper secondary to sweating can be seen. Sweating is signified by a change in color of the cobalt blue filter paper from blue to pink and the appearance of purple dots in the ninhydrin filter paper. Unfortunately, the cobalt blue and ninhydrin sweat tests are not available commercially.

The SGR can be recorded using a regular ECG machine. The right and left arm leads of the ECG are placed on the dorsum and palm of the hand (or dorsum and sole of the foot) while the other leads are placed on the contralateral extremity, and the lead selector switch turned to lead I. The stimulus can be a deep breath, pinprick, or loud noise. The response consists of an upward or downward deflection of the ECG tracing; either monophasic or biphasic. Partial sympathetic block reduces the response while complete block abolishes it, that is, the tracing is a straight line. The SGR has several shortcomings including marked variations in the responses of patients to the different stimuli and difficulty in obtaining a satisfactory recording under clinical conditions. There is also a rapid habituation to the stimuli used, that is, the patient has no SGR in the absence of a sympathetic block after several SGR recordings with the same stimulus.

The two sweat tests are more reliable than the SGR in predicting complete sympathetic blockade.[46] The sensitivities of the sweat tests and the SGR were found to be 90%. The specificity of the SGR was 56% compared to 100% for the sweat tests; their accuracy was 74% and 95%, respectively.[46] Since these tests are rarely used clinically, temperature increases to 35° or 36° C can be considered as signifying complete sympathetic blockade.

Relief of pain does not imply complete sympathetic blockade since patients with chronic pain may exhibit complete pain relief after partial sympathetic blockade. Partial pain relief, on the other hand, signifies one of two things: the patient's pain may be due to causes other than sympathetic-mediated pain (e.g., combined somatic sensory- and sympathetic-mediated pain or combined sympathetic-mediated and central pain) or the sympathetic blockade may be partial. A sign of complete sympathetic blockade is therefore necessary in these instances. It is also valuable after surgical or chemical sympathectomy to demonstrate complete sympathetic interruption and to correlate recurrence of pain with sympathetic recovery.[47]

STUDIES

Day[48] reviewed the literature for both stellate ganglion and lumbar sympathetic blocks. For the stellate ganglion block, he found 11 reviewable articles of which 4 were case reports, 5 were case series, 1 retrospective review,[49] and 1 double-blind, placebo-controlled study.[50] Based on sample sizes and quality of studies (using the Guyatt grading recommendations) he concluded that there was at best 1B, but mostly 1C evidence for stellate ganglion blocks (strong evidence with low quality or very low quality evidence). The single double-blind, placebo-controlled study only contained four patients and thus only received a 1C grade.[50] For lumbar sympathetic blocks, he found 11 articles that were reviewable with 9 case series/case reports, 1 prospective randomized,[30] and 1 prospective, randomized, controlled trial.[9] The prospective studies compared either phenol versus RF neurolysis[30] or chemical neurolysis versus bupivacaine.[9] The best grade given for these articles was 1B (strong recommendation with moderate quality evidence).

Gabrhelik et al.[51] prospectively compared two techniques for percutaneous sympathectomy via RF lesioning at T2 and T3 versus phenol/RF at T2 for the treatment of refractory Raynaud's phenomenon. They randomly assigned 50 patients to either of these two groups after confirmed diagnosis of advanced Raynaud's (no prior blockade). Patients were observed over 3 months for changes in cold perception, visual analog scale (VAS) pain score, and quality of life, while blood circulation in the upper extremity was evaluated with infrared thermography. There were statistically significant decreases in VAS, improvements in quality of life, as well as an increase in peripheral temperature in the upper extremities with both techniques. The authors concluded that both techniques are efficacious for the treatment of resistant forms of Raynaud's phenomenon. Criticisms with the study include the absence of placebo control or blinding.

Lipov et al.[52] recently published a pilot study on the effects of stellate ganglion block for hot flashes and night awakenings in survivors of breast cancer. They prospectively studied 13 breast cancer survivors (in remission) with severe hot flashes and night awakenings on a weekly basis for 12 weeks following a single stellate ganglion block with 7 ml of 0.5% bupivicaine. They noted a decrease in hot flash score from a mean of 79.4 to 49.9 (standard deviation [SD] 37.4 and 39.9, respectively) as well as a decrease in number of night awakenings from 19.5 to 7.3 (SD 14.8 and 7.3, respectively) over the first 2 weeks after the procedure. All patients continued to show a decrease in

both over weeks 3 to 12 with a final mean score of 8.1 for hot flashes and 1.4 for night awakenings.

Meier et al.[53] performed a double-blind, placebo-controlled crossover trial using lumbar sympathetic blocks (LSB) in children with CRPS. They studied a total of 23 patients between the ages of 10 to 18 and placed catheters at the anteromedial border of the L2 or L3 vertebral bodies with fluoroscopic guidance along with epidural catheters (for pain control at the completion of the study). Randomly chosen patients were injected with lidocaine through LSB catheters and IV saline, or, conversely, saline through the LSB catheter and IV lidocaine. A blinded researcher tested the patients to see if there was sympathetic blockade by increased ipsilateral skin temperature and reduction of evoked pain. Outcome measures included spontaneous and evoked mechanical pain intensity and thermal QST thresholds. Also assessed were global four-point verbal pain scales, color analog scale (CAS) for spontaneous pain, brush allodynia, and allodynia to pinprick and pinprick temporal summation. The authors found that there was a reduction in mean pain intensity of allodynia to brush and to pinprick temporal summation with lumbar sympathetic blockade with lidocaine compared to IV lidocaine. They also found that sympathetic blockade with lidocaine produced significant statistical and clinical reduction in allodynia to brush and temporal summation compared to pretreatment values. Sympathetic blockade produced clinically relevant improvement in verbal pain scores in 9 patients and no change in 14 patients, while the IV lidocaine produced reduction of pain in 3 patients and worsened pain in 5 patients. The authors concluded that there is some direct evidence that a component of CRPS is sympathetically mediated. The study limitations are that very small doses of lidocaine were used for the sympathetic blockade which produced benefits in some, but not all patients. Failure to achieve pain relief can also be accounted by the injection of local anesthetic through indwelling catheters which may have migrated. The authors also acknowledge that complete sympathetic nerve blockade was not measured with objective signs such as sweat testing.

KEY POINTS

- The stellate ganglion is located just anterior or lateral to the longus colli muscle between the base of the seventh cervical transverse process and the neck of the first rib.
- The appearance of Horner's syndrome does not signify sympathetic blockade of the upper extremity.
- The evidence for the efficacy of stellate ganglion blocks is based mostly on case reports.
- The risks of potential complications with stellate ganglion blocks are rare, but real, and may be decreased by the use of image guidance.
- Lumbar sympathetic blocks are best performed at the inferior third of L2, L2–L3 intervertebral disc level, or superior third of L3.
- There is evidence that lumbar sympathetic blocks are efficacious for decreasing allodynia to brush and temporal summation to pinprick in complex regional pain syndromes in the pediatric patient.
- Neurolysis of the sympathetic ganglia can be performed with chemical or RF ablation. Proper needle placement, sensory, and motor testing should be done before RF procedures.
- Abolition of sweating and SGR are the standard tests of complete sympathetic blockade.

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Access the reference list online at http://www.expertconsult.com

CHAPTER 80

Anticoagulants and Neuraxial and Peripheral Nerve Blocks

Honorio T. Benzon, MD

In 1997, the American Society of Regional Anesthesia and Pain Medicine (ASRAPM) convened a panel of experts to discuss the increased number of reports of epidural hematoma secondary to the then newly introduced low-molecular-weight heparin (LMWH) enoxaparin. The panel published their guidelines in a supplemental issue of the ASRAPM journal, *Regional Anesthesia and Pain Medicine*, in 1998.[1] The guidelines, which set standards for patient safety, were widely adhered to by the various medical specialties. The same panel revised their guidelines in 2003 to include the newer antiplatelet drugs.[2] The third edition of the guidelines was published in 2010 partly to make recommendations on the issue of anticoagulants and plexus and peripheral nerve blockade.[3] Neuraxial blockade in pregnant patients who are on anticoagulants was also discussed. This chapter covers the problem of deep vein thrombosis and neuraxial, plexus, and peripheral nerve injections in the presence of anticoagulants.

PERIOPERATIVE DEEP VENOUS THROMBOSIS

Approximately 50% of deep venous thromboses (DVTs) after total joint surgery begin intraoperatively, with the highest incidence occurring during the surgery and the first postoperative day.[4] Almost 75% of DVTs develop within the first 48 hr after surgery. Other investigators identified the fourth postoperative day as the peak occurrence of DVT and another smaller peak incidence on day 13. The risk of DVT is minimal after postoperative day 17.[4]

The predisposing factors to the development of DVTs during surgery include stasis, intimal injury, and hypercoagulability.[5] Some of the risk factors for the development of DVTs are previous history of DVT or pulmonary embolism, major surgery, age over 60, obesity, malignancy, increased duration of surgery, prolonged immobilization, presence of varicose veins, and the use of estrogen.[5] The problem is pronounced in total joint operations where intraoperative factors predispose to the development of DVTs. During total hip replacement (THR), the lower extremity is placed into positions of flexion, rotation, and adduction—manipulations that may damage the femoral vein and produce severe venous stasis.[6] In fact, intraoperative venograms performed during total hip arthroplasty revealed significant occlusion and twisting of the femoral vein causing stagnation of the limb blood flow.[7] In total knee replacement (TKR), the knee is flexed causing compression of the blood vessels. A tourniquet is used compressing the underlying venous structures and causing intimal vessel injury. The increased coagulability of the blood is aggravated by decreases in antithrombin III and tissue plasminogen activator (t-PA).

The incidences of DVT in patients without prophylaxis are 54% to 57% for total hip arthroplasty and 40% to 84% for TKR.[5,8] Most of the DVTs after TKR are located in the calf veins (24–60% of DVTs) compared to the more proximal veins (3–20% of DVTs).[7] In contrast, a higher incidence of DVTs after THR develop in the more proximal veins. There is a greater tendency of proximal veins to embolize to the lung; hence, the reason for the higher incidence of pulmonary embolism in THR surgery. Although calf vein thromboses do not embolize to the lung as much, 24% of these thromboses propagate to the more proximal veins.[9] Fatal pulmonary embolism occurs in 0.34% to 6% for THR and 0.2% to 0.7% for TKR.[5]

Ascending venous contrast venography is considered the most reliable diagnostic test for DVT, its sensitivity approaching 100%.[10] It is invasive, requires a radiology suite, and is more expensive than other tests. B-mode compression ultrasonography with and without Doppler is the first-line modality for confirming diagnosis in symptomatic patients. It is portable and the most accurate noninvasive study of DVTs. Failure of the vein to compress is indirect evidence that a thrombus is present.[10]

PERIOPERATIVE PROPHYLAXIS OF DEEP VENOUS THROMBOSIS IN TOTAL JOINT SURGERY

The prevention of DVT after total joint surgery includes intraoperative, mechanical, and pharmacologic measures. The use of epidural hypotensive anesthesia is associated with improved visualization of the operative field, less intraoperative blood loss, and shorter duration of surgery.[5] All of these factors lead to a lower incidence of DVT formation. Mechanical devices decrease stasis by augmenting venous flow in the lower legs,[9] and appear to have a fibrinolytic effect through a reduction in plasminogen activator inhibitor.[5] Various types of mechanical devices include calf-length sleeve, thigh-length stockings, and foot pump devices. In patients who underwent TKR the use of intermittent pulsatile compression of the plantar venous plexus and aspirin was found to be superior to aspirin alone in preventing DVTs (27–59%).[11] A combination of mechanical and pharmacologic measures is probably the most efficacious way of preventing DVT.

The pharmacologic management of DVTs includes the use of aspirin, warfarin, LMWH, thrombin inhibitors, and the newer drugs including rivaroxaban. For aspirin, most regimens use doses of 325 to 650 mg twice a day. The risks of aspirin use are gastritis and gastric erosions or ulcers. Early reports showed the efficacy of aspirin in DVT prophylaxis in total joint surgery but later investigations showed it not to be very effective. The incidence of DVT

when aspirin alone is used in TKR ranges from 41% to 78%.[9]

Heparin, LMWH, and warfarin are used perioperatively to prevent DVTs after surgery. For warfarin, the usual dosing regimen is 5 mg given the night of surgery, followed by adjustment of the dose to maintain an international normalized ratio (INR) of 2.0 to 2.5. Higher INRs may result in hemarthromas. The incidence of DVT with warfarin is 25% to 59%.[9] The therapy is maintained for 1 month after surgery. Because of warfarin's delayed effect and the early development of postoperative thrombus (most postoperative DVTs occur intraoperatively or in the first 2 days), some surgeons add an LMWH as a "bridge therapy" while the effect of warfarin is commencing.

Heparin is not widely used for postoperative prophylaxis after total joint surgery probably because of the better bioavailability and predictability of LMWH. LMWH is an effective prophylaxis against DVT after total joint surgery,[12–14] and appears to be more effective than warfarin. The incidence of DVT in patients who had total hip surgery is 5% with enoxaparin and 12% with warfarin.[12,13] Dalteparin is also associated with lower incidence of DVTs after total hip arthroplasty when compared to warfarin (13% versus 24%).[14] Compared to mechanical prophylaxis, LMWH is more effective in reducing the incidence of DVTs (27% versus 65%).[15] The LMWH therapy is continued for 1 to 2 weeks after the surgery. Fondaparinux, a specific Xa inhibitor, is given for 5 to 9 days after surgery at a daily dose of 2.5 mg. The drug reduces the incidence of venous thromboembolism by 57%, comparable to enoxaparin.[16]

Ximelagatran, an oral thrombin inhibitor, was noted to be superior to warfarin for the prevention of deep venous thromboembolism after TKR surgery.[17] However, its use resulted in severe liver toxicity and this led to the Food and Drug Administration (FDA) recommending against its approval. The recombinant hirudin derivative desirudin (Revasc®) has been investigated as a thromboprophylaxis after THR.[18] Dabigatran etexilate, a new oral direct thrombin inhibitor, has been approved for clinical use in Europe. Studies showed dabigatran (150 or 220 mg daily) to be less effective than enoxaparin (30 mg BID) when used for thromboprophylaxis after total joint surgery.[19,20]

A working group of the American Academy of Orthopaedic Surgeons, with the assistance of the Center for Clinical Evidence Synthesis at Tufts-New England Medical Center, has proposed a guideline for the prevention of pulmonary embolism in patients undergoing total hip and knee arthroplasty.[21] The medication recommendations of the group for patients at standard risk of both pulmonary embolism and bleeding, and for patients at elevated risk for pulmonary embolism and standard risk of major bleeding, include the following (in alphabetical order): aspirin; LWMH, pentassacharides, and warfarin (INR goal of ≤2.0). For patients at standard risk of pulmonary embolism and elevated risk of bleeding, and for patients at elevated risk of both pulmonary embolism and major bleeding, the group recommended the following medications: aspirin and warfarin (INR goal of ≤2.0).[21] The advantages and disadvantages of these agents have been discussed by orthopedic surgeons.[22]

PHARMACOLOGIC PROPHYLAXIS OF VENOUS THROMBOEMBOLISM IN OTHER SURGERIES

The American College of Chest Physicians published their guidelines for antithrombotic and thrombolytic therapy wherein they gave recommendations on the prevention of venous thromboembolism in patients undergoing general or vascular surgery, gynecologic, and urologic surgery.[23] General surgeons now prescribe subcutaneous heparin 3 times a day based on the recent ACCP guidelines,[23] reports showed an increased risk of bleeding in patients receiving TID subcutaneous heparin.[24] Other guidelines have been published for plastic surgery and for the cancer surgical patient.[25,26]

ANTICOAGULANTS FOR ACUTE MYOCARDIAL INFARCTION, ATRIAL FIBRILLATION, AND STROKE PROPHYLAXIS

In 2007, the American College of Cardiology and American Heart Association updated their guidelines on the management of patients with ST-elevation myocardial infarction (STEMI).[27] With regards to anticoagulants, the task force recommended the addition of clopidogrel to aspirin in patients with STEMI regardless of whether they undergo reperfusion or fibrinolytic therapy. This ACA/AHA guideline was also considered appropriate by the European guidelines.[28,29] The discontinuation of COX-2 inhibitors and NSAIDs were advised by the ACA/AHA, European, and Canadian guidelines.[27–30] The ACA/AHA guidelines recommended that clopidogrel should be discontinued for at least 5 days and preferably 7 days unless the urgency for revascularization outweighs the risks of excess bleeding. For STEMI patients who do not undergo reperfusion therapy, the ACA/AHA guidelines stated that it is reasonable to give IV or subcutaneous unfractionated heparin (UFH) or subcutaneous LMWH for at least 48 hr.[27] For patients who undergo invasive management, anticoagulant therapy with unfractionated heparin or LMWH is recommended.[27,31] After stent placement, it has been recommended that aspirin be continued for 1 month after a bare-metal stent, 3 months after a sirolimus-eluting stent, and 6 months after a paclitaxel-eluting stent.[27,31] For clopidogrel, it has been recommended that the drug be continued for at least 1 month and ideally up to a year, and for at least 1 year after both sirolimus- and paclitaxel-eluting stent.[31]

For patients with atrial fibrillation, several trials have shown the efficacy of warfarin in reducing stroke in these patients.[32,33] Problems with warfarin include its narrow therapeutic range (INR 2–3), unpredictable and patient-specific dose response, delayed onset and offset of action, need for anticoagulation monitoring, slow reversibility, and many drug–drug and drug–food interactions. The use of aspirin in these patients is controversial. Emerging drugs include dabigatran and rivaroxaban.

Antiplatelet therapy is highly effective in reducing the risk of recurrent ischemic stroke or TIA and is recommended over oral anticoagulant for noncardioembolic stroke.[33] Clinical trials showed the superiority of clopidogrel and the combination of aspirin plus dipirydamole over aspirin monotherapy.[34]

RELEVANT PHARMACOLOGY OF ANTICOAGULANTS AND IMPLICATIONS FOR NEURAXIAL BLOCKADE

Aspirin irreversibly binds to the platelet COX enzyme inhibiting the formation of thromboxane A_2 that causes platelet aggregation, resulting in the formation of an adequate but fragile clot. Most regimens use doses of 325 to 650 mg twice a day. Lower doses of aspirin are more effective in preventing clot formation, as the platelet COX enzyme is blocked, decreasing the formation of thromboxane A_2, which causes platelet aggregation. Higher doses of aspirin inhibit the COX enzyme in the platelets and in the vascular endothelium; this inhibition also results in decreased levels of PGI_2, which inhibits platelet aggregation. The ultimate effect of higher dosages is therefore a reflection of the antagonistic effects of reduced levels of thromboxane A_2 and PGI_2. Clinically, the mean bleeding times and the incidence of prolonged bleeding times of patients who were on daily low-dose aspirin (1–2 tablets of 325-mg aspirin), medium-dose aspirin (3–10 tablets), and high-dose aspirin (>10 tablets) were noted to be the same.[35] Nonsteroidal anti-inflammatory drugs (NSAIDs) also bind to the platelet COX enzyme but the binding is reversible; their effect on platelet function usually normalizes within 3 days.[36]

The large intra- and inter-patient variability in the results of the bleeding time led to the more common usage of the platelet function analyzer (PFA). The PFA is a test of in vitro platelet function, as well as a good screening test for von Willebrand disease, monitoring the effect of DDAVP administration, and is prolonged after antiplatelet therapy.[37] The test measures the ability of platelets to occlude a microscopic aperture in a membrane coated with collagen and epinephrine (C-EPI or PFA-I) or collagen and adenosine diphosphate (C-ADP or PFA II) under controlled high shear rates. The time required to obtain a complete platelet plug is the closure time in seconds. The normal closure times are 60 to 160 s for C-EPI and 50 to 124 s for C-ADP. Aspirin and NSAIDs prolong the closure time of C-EPI, while clopidogrel, von Willebrand disease, low platelet count, low hematocrit, and renal failure prolong the closure time for C-ADP.

There have been several studies that looked into the incidence of intraspinal hematoma in patients who were on aspirin or NSAIDs.[35,38–41] Some of these studies looked at large number of patients and found no incidence of intraspinal hematoma.[40,41] Although there have been case reports of intraspinal hematoma in patients on aspirin and NSAIDs, there were complicating factors in these case reports, including concomitant heparin administration, epidural venous angioma, and technical difficulty in performing the procedure.[42] Technical difficulties in performing the injection have been identified as a major risk factor in the development of intraspinal hematoma after neuraxial injections.

The COX-2 inhibitors have analgesic effects, several studies showed their perioperative analgesic property in different surgical settings.[43–45] They have less gastrointestinal toxicity and compared to aspirin or NSAIDS, the effects of the COX-2 inhibitors on platelet aggregation and bleeding times were not different from a placebo.[46,47] These effects make these drugs ideal for perioperative use when neuraxial injections are planned.

The thienopyridine drugs ticlopidine and clopidogrel have no direct effect on arachidonic acid metabolism. They inhibit platelet aggregation by inhibiting ADP receptor-mediated platelet activation.[42,48] These drugs also modulate vascular smooth muscle reducing vascular contraction.[49] Clopidogrel is 40 to 100 times more potent than ticlopidine.[50] The doses employed are 75 mg daily for clopidogrel and 250 mg twice a day for ticlopidine. Ticlopidine is rarely used because it causes hypercholesterolemia, neutropenia, and thrombocytopenic purpura. There is also a possible delayed antithrombotic effect of ticlopidine and may not offer protection in the cardiac patient for the first 2 weeks of ticlopidine therapy. Clopidogrel is preferred because it has a better safety profile and appears to have a better effect than aspirin in patients with peripheral vascular disease and is increasingly used in these patients.[51] The maximal inhibition of ADP-induced platelet aggregation with clopidogrel occurs 3 to 5 days after initiation of a standard dose (75 mg), but within 4 to 6 hr after the administration of a large loading dose (300–600 mg).[52] The large loading dose is given to patients before they undergo percutaneous coronary intervention. There has been a case report of spinal hematoma in a patient on ticlopidine.[53] While there has been no case of intraspinal hematoma in a patient on clopidogrel alone, there has been a case of quadriplegia in a patient on clopidogrel, diclofenac, and possible aspirin.[42]

ASRA RECOMMENDATIONS FOR ANTIPLATELET THERAPY AND NEURAXIAL BLOCK

The ASRA concluded that neuraxial blocks may be performed in patients on aspirin or NSAIDs.[54] This recommendation is supported by numerous studies that showed the safety of neuraxial injections in patients who were on these medications. Neuraxial blocks in patients on COX-2 inhibitors are safe, although the concomitant use of COX-2 inhibitors and warfarin may increase the risk of bleeding. For clopidogrel, it is recommended that the drug be discontinued for 7 days before a neuraxial injection. In contrast, a delay of 10 to 14 days is recommended with ticlopidine. This is because the half-life of ticlopidine increases from 12 hr after a single dose to 4 to 5 days after a steady state is reached.

Aspirin and NSAIDs alone do not significantly increase the risk of spinal hematoma. The combination of these drugs, however, increases the risk of spontaneous hemorrhagic complications, bleeding at puncture sites, and spinal hematoma.[2] Spinal hematomas have been reported in patients on LMWH and antiplatelet medications and in patients on combined clopidogrel and aspirin therapy.[2,42] The society cautioned the performance of intraspinal injections in patients who are on combined antiplatelet medications.

The above recommendations apply to patients having neuraxial injections for surgery and for pain clinic interventions. In the pain clinic the interventional physician has to decide whether it is prudent to continue the aspirin or NSAIDs before a neuraxial injection. If the indication for

the aspirin is not strong, such as routine daily aspirin in an elderly but healthy patient, then the physician may choose to stop the medication especially in cervical and thoracic injections. This is because in these patients it is difficult to differentiate between new or old symptoms (numbness and weakness) or between real and imagined pathology. Greater caution is advised in cervical and thoracic injections since the epidural space is narrower in these levels, the presence of the spinal cord in the area, and the fact that the studies on neuraxial injections in the presence of antiplatelet therapy were done mostly in patients who had lumbar injections.

For patients on clopidogrel and aspirin, it is recommended that the clopidogrel be stopped for 7 days and the patient placed on aspirin therapy. The aspirin is then continued up to the time of injection, after which the patient is switched back on clopidogrel after the block. If the indication for the anticoagulation is very strong then LMWH can be given during the 7 days that the clopidogrel is stopped. These changes are made in conjunction with the managing physician. In the surgical setting, these drugs are usually stopped by the surgeons before the surgery.

There have been case reports of the epidural catheter being removed or neuraxial injections done in patients before clopidogrel is stopped for 7 days. There is a case report of a safe removal of an epidural catheter in a patient 24 hr after discontinuation of the clopidogrel; rotational thrombelastometry demonstrated normal coagulation, the platelet aggregation test evoked by ADP showed "marked improvement," while the platelet aggregation test evoked by arachidonic acid "barely improved."[55] There is a case report of a caudal steroid injection 5 days after discontinuation of the clopidogrel, with the patient continuing to take his aspirin.[56] No test of platelet function was performed in the patient. Rather, the authors based their decision on a published recommendation that 5 days of discontinuation of clopidogrel is adequate before surgery is performed,[57] a recommendation based on a study in healthy volunteers.[58] There is another report of spinal anesthesia 5 days after the patient's clopidogrel was stopped. In this patient, there was minimal inhibition (8%) of his platelet activity in the P2Y12 assay.[59]

WARFARIN: PHARMACOLOGY AND ASRA RECOMMENDATIONS

Warfarin is an oral anticoagulant that interferes with the synthesis of the vitamin K–dependent clotting factors II, VII, IX, and X.[60,61] It also inhibits the anticoagulant protein C. Both factor VII and protein C have short half-lives (6–7 hr) and increase in the INR is the result of the competing effects of reduced factor VII and protein C and the washout of existing clotting factors. The unpredictability of the INR values during the initial stage of warfarin therapy was shown by a study in which 2 of 24 patients had INRs greater than 2.0 at 36 hr after warfarin intake.[62] A more recent study showed poor correlation between the INR and factor on the first day of warfarin therapy.[63]

Prophylactic anticoagulation (INRs of 2.0–2.5) is reached 48 to 72 hr after the initial dose. The anticoagulant effect of warfarin is primarily dependent on the levels of factor II that has a half-life of 50 hr. Maximal anticoagulation is reached in 4 to 5 days when factor II is sufficiently reduced. The risks of warfarin usage are bleeding and the rare occurrence of skin necrosis. Its drawbacks include the necessity of monitoring its effect with serial INR monitoring, its interaction with a host of other drugs, and the fact that it has to be stopped a few days before surgery.[60,61,64]

The ASRA recommended an INR of 1.4 for safe placement of the epidural catheter. At INR values of 1.5 to 2.0, the concentrations of factor II were found to be 74% to 82% of baseline while factor VII levels were 27% to 54% of baseline values.[62] Levels of 20% of normal are considered adequate for normal hemostasis at the time of major surgery.[65] A study that looked into the importance of the individual clotting factors on the generation of prothrombinase activity in the plasma of anticoagulated patients demonstrated that the concentration below which the factors VII, IX, and X start to have a measurable effect were 5%, 20%, and 30%, respectively.[66]

The same INR value was recommended for removal of the epidural catheter. It should be noted that the same laboratory values apply to placement and removal of the epidural catheter[67] because intraspinal hematomas have occurred after removal of the catheter.[68] The safety of removing the epidural catheters at these values was shown by Horlocker et al.[69] and Wu and Perkins.[70] A dilemma occurs when the INR is greater than 1.4 the day after warfarin therapy. A recent study showed that the activities of factor VII at 12 to 14 hr after warfarin intake were normal (60–160% activity) with INRs up to 1.9.[63] In this scenario and in the absence of other risk factors, it has been recommended that the epidural catheter be removed. If risk factors such as low platelets, advanced age, kidney failure, or intake of other anticoagulants are present then the factor VII activity should be determined.[63]

Warfarin is metabolized primarily by the CYP2C9 enzyme of the cytochrome P450 system.[61] Mutations in the gene coding for the hepatic microsomal enzyme affect the elimination clearance of warfarin by impairing the patient's ability to metabolize S-warfarin. Other genetic factors affecting the warfarin dose-response relationship include polymorphisms of the vitamin K oxide reductase (VKOR) enzyme, the target of warfarin's inhibitory effect on the vitamin K cycle. Mutations in the gene encoding for isoforms of the protein can lead to enzymes with varied sensitivities to warfarin. The American College of Chest Physicians advises against pharmacokinetic-based initial dosing of warfarin at this time.[61]

HEPARIN AND LMWH: PHARMACOLOGY AND ASRA RECOMMENDATIONS

Heparins are glycosaminoglycans that consist of chains of alternating residues of D-glucosamine and uronic acid, either glucuronic acid or iduronic acid. Unfractionated heparin is a heterogeneous mixture of polysaccharide chains ranging in molecular weight from 3000 to 30,000. A unique pentasaccharide sequence, randomly distributed along the heparin chains, binds to antithrombin (AT).[71] The binding of the heparin pentasaccharide to AT causes

a conformational change in AT that accelerates its ability to inactivate thrombin, factor Xa, and factor IXa. In addition, UFH releases tissue factor pathway inhibitor from endothelium, enhancing its activity against factor Xa.[72] The anticoagulant effect of heparin is not linear but increases disproportionately with increasing dosages. The anticoagulant effect of subcutaneous heparin takes 1 to 2 hr but the effect of intravenous heparin is immediate. The aPTT is used to monitor the effect of heparin; therapeutic anticoagulation is achieved with a prolongation of the aPTT to greater than 1.5 times the baseline value or a heparin level of 0.2 to 0.4 U/ml.[73] The aPTT is usually not prolonged by the subcutaneous administration of low doses of heparin and is not monitored.

UFH is either administered as an intravenous injection or as subcutaneous injection for DVT prophylaxis. The risk factors in the development of intraspinal hematoma in patients who are given systemic heparin were identified by Ruff and Dougherty as follows[74]: (1) an interval of less than 1 hr between the lumbar puncture and heparin administration; (2) concomitant use of other anticoagulants such as aspirin; and (3) traumatic needle placements.

For patients who are scheduled for vascular procedures and given intravenous UFH during the surgery, it was noted that it was safe to perform preoperative neuraxial blocks if some precautions are observed.[75] The cancellation of the proposed surgery has been recommended in cases of bloody or traumatic taps but there appears to be no data to support this recommendation. In summary, the ASRA guidelines on the performance of neuraxial procedures in patients who are anticoagulated with heparin are as follows[2,3,76]: (1) the neuraxial technique should be avoided in patients with other coagulopathies; (2) although the occurrence of bloody or difficult needle placement increases the risk of hematoma, discussion with the surgeon of the risk/benefit ratio should determine cancellation or noncancellation of the case; (3) the heparin administration should be delayed for 1 hr after needle placement; (4) indwelling neuraxial catheters should be removed 2 to 4 hr after the last heparin dose, and the patient's coagulation status is evaluated and reheparinization occurs 1 hr after catheter removal; and (5) minimal concentrations of local anesthetics should be used for early detection of signs of spinal hematoma and the patient is monitored postoperatively for signs of hematoma.

In general surgery and urology, patients who undergo major procedures, the subcutaneous UFH is given perioperatively for DVT prophylaxis. Heparin, 5000 U, when given subcutaneously every 12 hr, causes barely detectable changes in the aPTT; the very few patients that have prolongations of their aPTT do not exceed 1.5 times the normal levels. Liu and Mulroy noted the relative safety of performing neuraxial procedures and continuing the epidural catheters in these patients.[76] However, there are reports of spinal hematoma in this setting.[3] Further, the reports of paralysis from spinal hematoma in the ASA Closed Claims database[77] warrant vigilance and further examination of the risk factors in this setting. This is especially important in that surgeons are now giving perioperative subcutaneous heparin three times daily based on the recent ACCP guidelines,[23] a practice associated with increased bleeding.[24] Surveys in the late 1990s, when subcutaneous heparin was given twice daily, showed that the anesthesiologists were not concerned with the heparin dosing.[78–80] The paucity of reports of spinal hematoma may be attributed to the clinicians not following the ACCP guidelines.[81]

There appears to be a continuing debate as to whether neuraxial procedures should be performed in patients who undergo cardiopulmonary bypass. In these patients the following precautions have been recommended: (1) neuraxial procedures should be avoided in patients with a known coagulopathy, (2) surgery should be delayed 24 hr in the patient with a traumatic tap, (3) the time from the neuraxial procedure to the systemic heparinization should exceed 1 hr, (4) heparinization and reversal should be monitored and controlled tightly, and (5) the epidural catheter should be removed when normal coagulation is restored and the patient should be monitored closely for signs of spinal hematoma after the catheter is removed.[82]

Heparin is not the ideal anticoagulant: it is a mixture of molecules of which only a fraction has anticoagulant activity. It binds to platelet factor IV, which is released from activated platelets, to a number of plasma proteins, and to high-molecular-weight multimers of von Willebrand factor that are released from platelets and endothelial cells.[83] The heparin–antithrombin complex is also not very effective in neutralizing clot-bound thrombin. These factors result in an unpredictable anticoagulant effect of heparin necessitating careful laboratory monitoring when it is used in therapeutic dosages. Finally, heparin causes immunologic thrombocytopenia after 5 days of therapy.[84] These drawbacks of heparin led to increased use of LMWHs.

LOW-MOLECULAR-WEIGHT HEPARIN

Low-molecular-weight heparins are the fractionated forms of heparin with a mean molecular weight of 5000.[85] Similar to unfractionated heparin, LMWH activates antithrombin, accelerating antithrombin's interaction with thrombin and factor Xa. LMWH, like unfractionated heparin, also releases tissue factor pathway from the endothelium. The LMWHs have a longer half-life and dose-independent clearance compared to heparin, resulting in a more predictable anticoagulant response. The reduced binding with plasma proteins and endothelium results in the LMWHs' better bioavailability and predictability than unfractionated heparin. Although unfractionated heparin has equivalent activity against thrombin and factor Xa, LMWH has a greater activity against factor Xa. The plasma half-life of the LMWHs ranges from 2 to 4 hr after an intravenous injection and 3 to 6 hr after a subcutaneous injection. It should be noted that anti-Xa activity is still present 12 hr after injection of LMWH. In fact, it has been noted that the anticoagulant effect of LMWH was still present at the time of removal of the epidural catheter.[86] The recovery of anti-factor Xa activity after a subcutaneous injection of LMWH approaches 100% compared to approximately 30% for UFH.[87] Laboratory monitoring is not necessary except in patients with renal insufficiency or those with body weight less than 50 kg or more than 80 kg.[85]

The reaction time (r-time) from the thrombelastogram, a test that is easily available, was found to correlate with the serum anti-Xa concentration.[88]

Clinical studies showed the efficacy and safety of LMWHs in the prevention and treatment of venous thrombosis. They have been used a prophylaxis against thromboembolism in surgical settings such as general surgery,[89] total hip and knee replacements,[12–14,90–94] surgery for hip fractures,[95] and multiple trauma.[96] Also, LMWHs have been used in unstable angina,[97–99] acute myocardial infarction,[100] and ischemic stroke.[101]

The most commonly used LMWHs in the United States include enoxaparin (Lovenox) and dalteparin (Fragmin). Enoxaparin is either given once daily or every 12 hr (a dosing that is assocaited with increased risk of spinal hematoma), while dalteparin is given once a day. There are very few studies that directly compared two or more LMWHs. A review of the literature showed the drugs to have comparable efficacy in the treatment and prevention of venous thromboembolism. Enoxaparin and dalteparin have similar efficacy in the prevention of venous thrombosis after general surgery and after total hip replacement. The two drugs also have comparable efficacy in the prevention of death or myocardial infarction among patients with unstable angina. For all remaining indications, the literature supports the use of enoxaparin.[102] The economic implications of once-daily dosing for dateparin resulted in some hospitals using dalteparin. The incidence of spinal hematoma is probably similar among the LMWHs.[103]

There have been reports of spinal hematomas in patients on LMWH, in the absence of neuraxial injections[104,105] and in patients who had neuraxial blocks and the ASRA guidelines followed.[3,106,107] The occurrence of spontaneous spinal hematomas shows that bleeding can occur anywhere in patients on LMWH. In the patients who had neuraxial injections, they had renal insufficiency and this may have resulted in a prolonged anti-Xa of the enoxaparin.[3,106,107] The other contributing factors in the reported cases include the presence of other mild anticoagulants (NSAIDs, ketorolac), inadequate interval between the LMWH injection and placement/removal of the epidural catheter, and spinal stenosis.[3,108]

The recommendations of the ASRA for patients receiving LMWH and neuraxial anesthesia are as follows[2,3,109]:

- Monitoring of the anti-Xa level is not recommended.
- The administration of antiplatelet or oral anticoagulant medications with LMWHs may increase the risk of spinal hematoma.
- The presence of blood during needle placement and catheter placement does not necessitate postponement of surgery. However, the initiation of LMWH therapy should be delayed for 24 hr postoperatively.
- The first dose of LMWH prophylaxis after twice-daily enoxaparin should be given no earlier than 24 hr postoperatively and only in the presence of adequate hemostasis. It may be given 6 to 8 hr after a once-daily dosing of enoxaparin.
- In patients who are on LMWH, needle/catheter placement should occur at least 12 hr after the last prophylactic dose of enoxaparin or 24 hr after dalteparin (120 U/kg every 12 hr or 200 U/kg every 12 hr), or after higher doses of enoxaparin (1 mg/kg every 12 hr; 1.5 mg/kg daily).
- There should be a 12-hr interval between the last prophylactic dose of enoxaparin and removal of the epidural catheter. For higher doses of enoxaparin, a 24-hr delay is recommended.
- The LMWH may be administered 2 hr after the epidural catheter is removed.

FONDAPARINUX

Fondaparinux is a synthetic anticoagulant that is a selective Xa inhibitor.[110] Because it is synthesized chemically, it exhibits batch-to-batch consistency. The drug is rapidly absorbed, reaching a maximum concentration within 1.7 hr of dosing and has a half-life of 21 hr.[110] It has 100% bioavailability. A dose of 2.5 mg is given subcutaneously 6 hr after surgery, and subsequently once a day. Studies showed the incidence of DVT following major hip and knee surgery to be comparable to enoxaparin,[16] or lower with fondaparinux compared to enoxaparin.[111] It was also found to be as effective as unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.[112]

A recent study showed no complications in patients who had neuraxial injections or deep peripheral nerve blocks.[113] In this study, the catheters were removed 36 hr after the last dose of fondaparinux and dosing was delayed for 12 hr after the catheter was removed. In a review article, Rosencher et al.[114] recommended that catheter removal should be delayed at least 36 hr (equivalent to two half-lives) and that the subsequent injection should be at least 7 hr after removal of the catheter. Although the 36-hr interval implies residual anticoagulant effect, Rosencher et al. thought that it is a compromise between patient safety and the ocurrence of spinal hematoma. The risk of spinal hematoma in patients on fondaparinux is not known at this time, so ASRA recommended that neuraxial injections should involve single-needle pass, atraumatic needle placements, and avoidance of intraspinal catheters.[2,3]

THROMBIN INHIBITORS

Hirudo medicinalis, the medicinal leech, produces hirudin, a direct thrombin inhibitor. Hirudin acts independently of antithrombin and other plasma proteins. The commercially available thrombin inhibitors include the recombinant hirudin derivatives desirudin (Revasc®), lepirudin (Refludan®), and bivalirudin (Angiomax®), and the synthetic L-arginine derivative argatroban (Acova®). These drugs can neutralize free and clot-bound thrombin and are used in the treatment of thrombosis in patients with heparin-induced thrombocytopenia and in the prevention of thromboembolic complications after total hip replacement.[115–117] Their anticoagulant effect is present for 1 to 3 hr and is monitored by the aPTT. There is no pharmacologic reversal to the effect of these drugs. There has been no case report of spinal hematoma in patients who had thrombin inhibitors and had neuraxial anesthesia. This is most probably related to anesthesiologists waiting at least 3 to 4 hr after the thrombin inhibitor was given or to their hesitancy to perform neuraxial injections in

patients who are on these drugs. The lack of adequate studies led ASRA not to make any recommendation in their most recent guidelines with regard to these drugs.

NEWER ANTICOAGULANTS

Dabigatran etexilate is an oral direct thrombin inhibitor. Bioavailability is only 5%, peak plasma levels occur at 2 hr, and its half-life is 8 hr after a single dose, although it can be up to 17 hr after multiple doses. The drug has been approved for clinical use in Europe. Studies showed dabigatran (150 or 220 mg daily) to be either similar in efficacy (enoxaparin 40 mg daily) or less effective than enoxaparin (30 mg BID) when used for thromboprophylaxis after total joint surgery.[118–121] It is possible that it may find its use as an adjunct treatment for atrial fibrillation in this country.

Rivaroxaban is an oral factor Xa inhibitor that has been approved for use in Europe and Canada and is awaiting approval by the FDA. It has an 80% bioavalability; its peak effect occurs after 1 to 4 hr and its duration of effect is 12 hr. It has a half-life of 9 to 13 hr. The drug offers several salutary characteristics including efficacy and simplicity of once-daily oral dosing. Clinical studies comparing the rivaroxaban, at doses of 5 to 40 mg, with enoxaparin showed similar or superior efficacy.[19,20,122–125] There were no reports of spinal hematoma in these studies. Apparently, a 24-hr interval (2× half-life) was observed between the rivaroxiban dose and epidural catheter placement or removal; subsequent dosing of the drug was 6 hr after removal of the catheter (personal communication with the company).

Prasugrel is an oral anticoagulant prodrug. Its mechanism of action is similar to clopidogrel, that is, noncompetitive antagonist of P2Y12, inhibiting the ability of platelet ADP to induce aggregation for the life of the platelet.[126] Prasugrel has a quicker onset of action, the effect of 60 mg is 1 to 1.5 hr compared to 6 hr with 300 mg clopidogrel. It is 10 times more potent and is less prone to drug–drug interactions and patient nonresponsiveness.[126,127] The drug causes 90% platelet inhibition and a 7-day interval between discontinuation of the drug and neuraxial injection is recommended. The drug appears to be a promising treatment option for patients with acute coronary syndromes who undergo percutaneous coronary interventions.[126,127] Other novel antiplatelet drugs in development include ticagrelor and cangrelor, which are being studied in patients with acute coronary syndromes.[128]

HERBAL THERAPIES

Garlic inhibits platelet aggregation and its effect on hemostasis appears to last 7 days. Ginkgo inhibits platelet-activating factor and its effect lasts 36 hr, while the effect of ginseng lasts 24 hr.[2,3] The effects of dietary supplements on platelet function and coagulation are not well described and outcomes are difficult to predict.[129] In spite of their effect on platelet function, herbal drugs by themselves appear to present no added significant risk in the development of spinal hematoma in patients having epidural or spinal anesthesia. At this time, there appears to be no specific concerns as to the timing of neuraxial block in relationship to the dosing of herbal therapy, postoperative monitoring, or the timing of neuraxial catheter removal.[2,3]

ANTICOAGULATION AND NEURAXIAL INJECTIONS DURING PREGNANCY

Pregnancy and puerperium are accompanied by increased risk of thrombosis. Thromboprophylaxis is recommended in women with AT deficiency, homozygosity for the factor V Leiden mutation, homozygosity for the prothrombin gene G20210A mutation, or homozygosity for both mutations.[130] The ACCP guidelines did not recommend anticoagulation in pregnant women without thrombophilia or in women with thrombophilia but without a history of thromboembolism or poor pregnancy outcome.

The following recommendations have been made with regards to anticoagulation during pregnancy: (1) oral anticoagulants should be switched to LMWH or unfractionated heparin no later than 36 weeks, (2) LMWH should be discontinued and switched to heparin at least 36 hr before induction of labor or cesarean section delivery, (3) IV heparin should be discontinued 4 to 6 hr before the anticipated delivery.[131] A review article and recent ASRA guidelines recommended that the guidelines for surgical patients apply to pregnant patients.[3,132]

ANTICOAGULATION AND PERIPHERAL NERVE BLOCKS

Spontaneous hematomas have been reported in patients who took anticoagulants. Abdominal wall hematomas, intracranial hemorrhage, psoas hematoma, intrahepatic hemorrhage, and spinal hematomas have occurred after LMWH.[104,105,133–136] In fact, major hemorrhagic complications occur in 1.9% to 6.5% of patients on enoxaparin.[137] The increased bleeding that occurs after vascular or cardiac procedures, and regional nerve blocks, in these patients may result in an expanding hematoma that may result in ischemia of the nerve.

There has been no prospective study on peripheral nerve blocks in the presence of anticoagulants. However, there have been several case reports of hematomas when peripheral blocks are performed in patients who are on these drugs. The hematomas occurred in patients with abnormal and normal coagulation status, and in patients who were given MLWH, ticlopidine and clopidogrel, warfarin, heparin, or a combination of these drugs.[138–144] In most cases, recovery of neurologic deficits occurred within a year.

The diagnosis of bleeding after peripheral nerve block in patients on anticoagulants include pain (flank or paravertebral pain or groin pain in psoas bleeding), tenderness in the area, fall in hemoglobin/hematocrit, fall in blood pressure, and sensory and motor deficits. Although definitive diagnosis is made by computed tomography, ultrasound can be a diagnostic aid and its increasing use will make this modality a useful tool in diagnosing and following peripheral hematomas. Treatments of peripheral hematomas usually include surgical consult, blood transfusion as necessary, and watchful waiting versus surgical drainage.

The most recent ASRA guidelines[3] recommended that the same guidelines on neuraxial injections should apply to deep plexus or peripheral nerve blocks. Some clinicians may find this to be too restrictive and apply the guidelines

only to deep plexus and noncompressible blocks (e.g., lumbar plexus block, deep cervical plexus blocks) or to blocks near vascular areas such as celiac plexus blocks or superior hypogastric plexus blocks. If peripheral nerve blocks are performed in the presence of anticoagulants, then the anesthesiologists should discuss the risks and benefits of the block to the patient and the surgeon, and follow the patient very closely after the block.

COMPARISON OF ASRA, BELGIAN, GERMAN, AND NORDIC GUIDELINES

There are similarities and differences between the new ASRA guidelines[3] and the Belgian and German guidelines.[145–147] The guidelines of the three organizations are similar with regards to antiplatelet medications, unfractionated heparin, and thrombolytic agents. Regarding LMWH, the ASRA guidelines are more conservative partly due to the differences in the dosing of the drug. For fondaparinux, the German guidelines allow an indwelling epidural catheter while the ASRA and the Belgian guidelines recommend against it. The Belgian and German guidelines allow neuraxial injections in patients on direct thrombin inhibitors while the ASRA guidelines do not. Finally, some of the newer anticoagulants have been approved for use in Europe and are awaiting approval in the United States; hence, ASRA guidelines on these drugs are forthcoming. The Nordic guidelines appear to be more restrictive in terms of aspirin and NSAIDs but allow 5 days of discontinuation for clopidogrel.[147] It also made recommendations as to when neuraxial injections can be done after thrombolytic drugs.

SUMMARY

The observance of the ASRA guidelines has resulted in a decreased number of spinal hematomas, improved vigilance, and better patient care of patients on anticoagulants in whom nerve blocks are performed or entertained. Consensus guidelines are recommendations and specific decisions on nerve blocks in patients on anticoagulants should be individualized.[148,149] Optimal monitoring, adequate follow-up, and timely treatment should be observed in patients on anticoagulants who had neuraxial or peripheral nerve blocks.

KEY POINTS

- Some 50% of DVTs after total joint surgery begin intraoperatively; the highest incidence occurs during surgery and the first postoperative day. Almost 75% of DVTs develop within the first 48 hr after surgery.
- Case reports of intraspinal hematoma after aspirin and NSAIDs had complicating factors such as concomitant administration of other anticoagulant, epidural vascular abnormalities, and technical difficulties. The intake of different antiplatelet medications has been identified as a major risk factor in the development of spinal hematoma after neuraxial injections.
- ASRA recommended that clopidogrel be stopped for 7 days before a neuraxial injection. If a neuraxial injection has to be performed at 5 days after discontinuation of clopidogrel, then a PFA II or a P2Y12 assay must be performed. Platelet inhibition of less than 10% in the P2Y12 assay signifies safe neuraxial injection.
- An INR value of 1.4 or less is considered by ASRA as a safe value for placement or removal of an epidural catheter. There is very little correlation between the INR and factor VII during the early phase of warfarin therapy. At 12 to 14 hr after warfarin, it is probably safe to remove the epidural catheter in the presence of an elevated INR of up to 1.9 since the activity of factor VII were noted to correlate with adequate hemostasis.
- Subcutaneous TID heparin is associated with increased bleeding. ASRA recommended against neuraxial injections in patients on subcutaneous TID heparin because of reports of increased bleeding and the absence of prospective studies in this setting.
- The studies on neuraxial injections and fondaparinux followed guidelines (single needle pass, atraumatic placement, no indwelling catheters) that are hard to duplicate in the clinical setting.
- ASRA recommended that the same guidelines on neuraxial injections be followed for peripheral nerve blocks. This is especially important in deep plexus and noncompressible blocks (e.g., lumbar plexus block, deep cervical plexus blocks) or blocks near vascular areas such as celiac plexus blocks or superior hypogastric plexus blocks.

REFERENCES

Access the reference list online at http://www.expertconsult.com

TABLE 80–1 Summary of Guidelines on Anticoagulants and Neuraxial Blocks

I. Antiplatelet Medications

1. Aspirin, NSAIDs, COX-2 inhibitors
   May continue
   Pain clinic patients: aspirin preferably stopped 2–3 days in thoracic and cervical epidurals.
2. Thienopyridine derivatives
   (a) Clopidogrel (Plavix): discontinue for 7 days.
      May perform neuraxial block after 5 days if P2Y12 assay shows less than 10% platelet inhibition.
   (b) Ticlopidine (Ticlid): discontinue for 14 days.
      Prasugrel: discontinue for 7-10 days.
      Do not perform a neuraxial block in patients on more than one antiplatelet drug.
3. Glycoprotein IIb/IIIa inhibitors: time to normal platelet aggregation
   (a) Abciximab (ReoPro) = 24 to 48 hr
   (b) Eptifibatide (Integrilin) = 4 to 8 hr
   (c) Tirofiban (Aggrastat) = 4 to 8 hr

Antiplatelet medications (ASA, Plavix) are usually given after glycoprotein IIb/IIIa inhibitors. The above guidelines on aspirin and Plavix should be adhered to.

II. Warfarin

Check INR (coagulant response time).
INR <1.5 before neuraxial block or epidural catheter removal.

III. Heparin

1. Subcutaneous heparin (5000 units SC q 12 hr)
   Subcutaneous heparin BID is not a contraindication against a neuraxial block.
   Neuraxial injection may not be performed in a patient on subcutaneous heparin TID.
   Neuraxial block should preferably be performed before SC heparin is given.
   Risk of decreased platelet count with SC heparin therapy >5 days.
2. Intravenous heparin
   Neuraxial block: 2 to 4 hr after the last intravenous heparin dose
   Wait ≥1 hr after neuraxial block before giving intravenous heparin.

IV. LMWH

No concomitant antiplatelet medication, heparin, or dextran

1. LMWH preoperative
   (a) Wait 12 hr before a neuraxial block:
      Enoxaparin (Lovenox) 0.5 mg/kg BID (prophylactic dose)
   (b) Wait 24 hr before a neuraxial block:
      Enoxaparin (Lovenox), 1 mg/kg BID (therapeutic dose)
      Enoxaparin (Lovenox), 1.5 mg/kg QD
      Dalteparin (Fragmin), 120 units/kg BID
      Dalteparin (Fragmin), 200 units/kg QD
      Tinzaparin (Innohep), 175 units/kg QD
2. LMWH postoperative
   Twice-daily dosing: LMWH should not be started until after 24 hr after surgery.
   Once-daily dosing: LMWH may be given 6 to 8 hr.
   LMWH should not be given until ≥2 hr after epidural catheter removal.
3. Patients with epidural catheter who are given LMWH
   The catheter should be removed at the earliest opportunity.
   Enoxaparin (0.5 mg/kg): remove the epidural catheter ≥12 hr after last dose.
   Enoxaparin (1 to 1.5 mg/kg), dalteparin, tinzaparin: remove the epidural catheter ≥24 hr after last dose.
   Restart the LMWH ≥2 hr after the catheter removal.
   Summary recommendations for LMWH (preoperative and postoperative): Wait 24 hr except for patients on low-dose enoxaparin (0.5 mg/kg), in which case a 12-hr interval is adequate.
   Wait 2 hr after the catheter is removed before starting LMWH.

Continued

TABLE 80–1 Summary of Guidelines on Anticoagulants and Neuraxial Blocks—cont'd

V. Specific Xa Inhibitor: Fondaparinux (Arixtra)
Short onset, long duration (plasma half-life: 21 hr)
ASRA: no definite recommendation
If neuraxial procedure has to be performed, recommend single-needle atraumatic placement, avoid indwelling catheter.
Rivaroxaban: a new oral factor Xa inhibitor, half-life of 9–13 hr. Approximately a 24-hr interval, or 2× the drug's half-life, between the drug and epidural placement was observed in studies.
VI. Fibrinolytic/Thrombolytic Drugs
No data on safety interval for performance of neuraxial procedure
Follow fibrinogen levels
ASRA: no definite recommendation
VII. Thrombin Inhibitors
Anticoagulant effect lasts 3 hr
Monitored by aPTT
ASRA: no recommendation at this time because of paucity of data
Dabigatran: a new oral direct thrombin inhibitor, half-life of 8-17 hours (recommended interval between drug discontinuation and neuraxial injections is 2-3 half-lives).
VIII. Herbal Therapy
Mechanism of anticoagulant effect and time to normal hemostasis:
Garlic: inhibits platelet aggregation, increased fibrinolysis; 7 days
Ginkgo: inhibits platelet-activating factor; 36 hr
Ginseng: increased PT and PTT; 24 hr
ASRA: neuraxial block not contraindicated for single herbal medication use
The guidelines are the same for the placement and removal of epidural catheters.

aPTT, activated partial thromboplastin time; ASRA, American Society of Regional Anesthesia; COX, cyclooxygenase; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneous.

Sources: Heit JA, Horlocker TT, editors: Neuraxial anesthesia and anti coagulation. Reg Anesth Pain Med *23:S129–S193, 1998; Horlocker TT, Wedel DJ, Benzon HT, et al: Regional anesthesia in the anticoagulated patient: Defining the risks (the second ASRA consensus conference on neuraxial anesthesia and anticoagulation).* Reg Anesth Pain Med *28:171–197, 2003; and Horlocker TT, Wedel DJ, Rowlingson JC, et al: Regional anesthesia in the patient receiving antithrombotic therapy or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition).* Reg Anesth Pain Med *35:64–101, 2010.*

TABLE 80–2 Comparison of Society Guidelines

Drug	ASRA Guidelines	Belgian Guidelines	German Guidelines	Nordic Guidelines
Antiplatelets	ASA, NSAIDs: Not contraindicated	Same as ASRA	Same as ASRA	ASA: Continue if used for coronary event or stroke, discontinue for 3 days if used for arterial thrombotic events, 1 week if >1 g/day
	Discontinue ticlopidine for 14 days and clopidogrel 7 days	Same as ASRA	Thienopyridine contraindicated	NSAIDs: Discontinue 12 to 48 hours, depending on drug, 2 weeks for piroxicam and tenoxicam
				Clopidogrel: Discontinue at least 5 days
Heparin	Subcutaneous: No contraindication with BID dosing, contraindicated with TID dosing	Not discussed	Neuraxial injection 4 hr after heparin, subsequent dose after catheter placement/removal	Subcutaneous: No recommendation
	IV: Heparin 1 hr after neuraxial injection, remove catheter 2–4 hr after heparin	IV: Heparin 1 hr after neuraxial injection, remove catheter when aPTT normal	IV: Neuraxial injection 4 hr after heparin, heparin 1 hr after neuraxial injection	IV: Same as German guidelines
LMWH	BID dosing: LMWH 24 hr after surgery, remove catheter 2 hr before LMWH	Neuraxial injection 10–12 hr after LMWH, 24 hr after therapeutic dose; next dose at 4 hr	Same as Belgian guidelines	Same as Belgian and German guidelines; next dose at 6 hr
	Once-daily dosing: Same as European			
Warfarin	INR ≤ 1.5	INR ≤ 1.4	INR ≤ 1.4	INR ≤ 1.4
Fondaparinux	Single injection, atraumatic placement, no indwelling catheter	Needle placement 36 hr after last dose, no indwelling catheter	Needle placement 36–42 hr after last dose, subsequent dose 6–12 after catheter removal	Same as German guidelines, subsequent dose 6 hr
Thrombin inhibitors	Suggest avoidance because of insufficient information	Needle placement 8–10 hr after last dose, subsequent dose 2–4 hr after injection	Same as Belgian	First dose at least 6 hr after neuraxial injection or catheter removal
Thrombolytics	Contraindicated	Contraindicated	Contraindicated	Streptokinase, Reteplase 24 hr
				Alteplase 6 hr before neuraxial injection

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