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William Bentley *Editors*

Urogenital Pain

A Clinicians Guide to Diagnosis and Interventional Treatments

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To my wife: Jenny, you are a beautiful person both inside and out. More people like you would make the world a better place to live. Thank you for always believing in me and bringing out the best of me. I love you.
To Sebastian and Milana: Your smiles brighten up the darkest days. You're the greatest children any parent could ask for. I love you both very much.

Michael Sabia, MD

To my parents: Thank you for all your love and support. You've always been there for me no matter what.
To my siblings: For always teaching and humbling me along the way.
To my pyaar: The love that we share grows stronger and stronger each day. You are truly a blessing in my life.

Jasjit Sehdev, MD

Thank you to the beautiful women in my life who are constantly pushing me and challenging me to greatness. Melissa, I cannot imagine my life or future without you.

Lacie, I never knew what love truly was until the day you were born. Taryn, I can't wait to meet you.

William Bentley, DO

Preface

Suffering from pain is undoubtedly one of the most unfortunate experiences any human can endure. Identifying areas where gaps in knowledge and treatment exist is one way we can help overcome this ill-fated circumstance (pain). The "work" put into this book is superseded by the extraordinary benefits the editors and authors are able to provide to those who gain understanding of urogenital pain and are able to offer treatment options in which they were previously unaware of. We are honored to offer such capability by incorporating an amalgamation of an amazing group of authors in this text.

Gaining in-depth perspective is better achieved by uniting a multidisciplinary task force as opposed to "an expert." This is the backbone of why such an amazing group of individuals were able to provide insight into a piece of medicine that currently has limited familiarity.

We are here to make the world a better place. Thanks to the exceptional list of authors in this text, this has come to fruition.

A special thank you to Springer and their publishing team for their expertise and guidance on how to execute this arduous task.

Camden, NJ, USA — Michael Sabia
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Chapter 1
Pelvic Floor Anatomy and Neurovasculature Related to Urogenital Pain

Ian James Brown, MD

Introduction

Pain has been defined in many iterations due to the complexity and intricacies associated within. A working definition has been described by Merskey et al. as follows:

- "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage*" [Merskey H, Bogduk N. *Classification of Chronic Pain*, 2nd ed, IASP Press, Seattle 1994.]
- Or more refined: "a somatic perception containing: (1) a bodily sensation with qualities like those reported during tissue-damaging stimulation, (2) an experienced threat associated with this sensation, and (3) a feeling of unpleasantness or other negative emotion based on this experienced threat" [Price DD. *Psychological Mechanisms of Pain and Analgesia In Progress in Pain Research and Management*, IASP Press, Seattle 1999. Vol 15.]

Components of Pain

Pain is a multifaceted gem; the perception of pain is a prevalent, poorly managed condition persistent throughout all stages of life, and intersects many of the other common thread domains. The perception of pain intersects the domains of stress (psychological component of pain perception), sexuality, sleep patterns, substance use, mobility, and end of life. Due to the entanglement of these comorbid domains, treating pain becomes increasingly complex. Pain can also be viewed classically through George Engel's BioPsychoSocial model as it encompasses all three aspects

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of the model simultaneously. Tracing the evolution and adaptation of the interwoven components in neuropathic pain we see that in 1977, Engel first introduced the concept of the BioPsychoSocial model for understanding pain [1]. In 1980, Richards et al. applied socio-environmental factors to pain analysis [2].

Pain is primarily categorized into nociceptive and neuropathic pain. Patients can simultaneously experience both types of pain, but the mechanisms and presentation of each are different. Nociceptive pain occurs in response to noxious stimuli and continues only in the maintained presence of noxious stimuli. Nociceptive pain alerts us to external stimuli, such as pinprick or excessive heat, and internal stimuli, such as myocardial ischemia in patients with coronary artery disease [3]. Nociceptive pain is the common pain typically imagined in any reference to pain; it allows us to react to and avoid damage to the body. Less common and less intuitive, neuropathic pain is defined as pain that occurs as a result of a primary lesion or a dysfunction in the nervous system [4]. Neuropathic pain substantially impairs patients' quality of life; it interferes with sleep and causes depressive and anxiety disorders [5].

Though seemingly straightforward to define, delineating between nociceptive pain and neuropathic pain can be difficult. The American Journal of Hospice and Palliative Medicine published a study to determine which words frequently describe these two categories of pain so that care providers can better decipher the cause and develop a treatment strategy. Though a subtle difference in adjectives, the following descriptors can be used clinically to delineate the presence of nociceptive, neuropathic pain, or a combination of the two:

- Nociceptive pain descriptors from the highest- to the lowest-frequency ranking were aching, throbbing, sharp, tender, dull, sore, hurting, and stabbing.
- Neuropathic pain descriptors ranked in their order of frequency include burning, shooting, numb, cold, itchy, stinging, tingling, and cool [6].

The characteristic word descriptors elucidated by the aforementioned study were reported by advanced cancer patients. However, neuropathic pain affects many other patient populations, thereby increasing the overall incidence and highlighting the need for treatment strategies.

A few of the commonly termed populations affected by neuropathic pain include cancer, spinal cord injury, sickle cell, amputation, diabetes, and elderly patients. Among the populations affected, we can first look at the biological aspect, following Engel's model. Expanding this list, the causes of a few of the chronic pain conditions that stem from neurological disturbances highlighted by the British Medical Journal are as follows: Diabetic sensorimotor polyneuropathy, spinal stenosis, brachial plexus traction injury, thoracic outlet syndrome, trigeminal neuralgia, alcoholism, thyroid disease, pernicious anemia, infections (e.g., HIV), polyneuropathies, polyradiculopathies, postherpetic neuralgia, and complex regional pain syndrome (formerly referred to as reflex sympathetic dystrophy and causalgia) [7].

Delving deeper into the biology behind the cause of pain, evidence shows that there are mechanisms common to inflammatory, dysfunctional, and neuropathic pain. Within the immune system, nociceptors respond directly to cytokines, chemokines, and other inflammatory mediators. Interleukin-1β (IL1β), tumor necrosis factor (TNF), bradykinin, and nerve growth factor elicit action potential discharge by increasing sodium and calcium currents at the nociceptor peripheral terminal. After neural damage, these same inflammatory mediators are produced by peripheral immune cells and microglia in the spinal cord and contribute to neuropathic pain by activating nociceptive neurons [3]. This explains how patients with chronic infections such as HIV, Herpes, and Lyme disease can develop neuropathic pain. Much in the same way immune mediators can activate spinal neuropathies, peripheral nerves can promote an increase in nociceptor production, transport and voltage-gated channels. Therefore, a lower stimulus is required to elicit response (thereby reducing effective pain threshold). Accordingly, a reduction in thermal and mechanical pain thresholds also occurs in some patients with peripheral nerve lesions, which might reflect nociceptor sensitization owing to increased membrane excitability without inflammation (irritable nociceptors) [8].

Tracing the route of pain from inflammation to peripheral sources, invariably the final path and source would be through the central nerves. Central nerves were targets from the two aforementioned mechanisms, but can also be the source of neuropathies. In neuropathic pain, ongoing activity originating from injured nerves is the trigger for central sensitization. Central sensitization resembles activity-dependent synaptic plasticity in the cortex with the involvement of various synaptic modulators and excitatory amino acids, alterations in ion channel kinetics and properties, increased density of ionotropic receptors, and activation of kinases pre- and postsynaptically. The increase in synaptic strength enables previously subthreshold inputs to activate nociceptive neurons, reducing their threshold, enhancing their responsiveness, and expanding their receptive fields [3].

Regardless of the site or source, neuroplasticity increases the number of pain receptors and subsequently increases signals (increased amplitude or temporal summation), which leads to an increased pain signal or response. In some cases, the inciting stress cannot be resolved and these lead to chronic neuropathic pain. Figure 1.1a (nociceptive) and 1.1d (neuropathic) in the addendum diagram show the site of initiating response, the signal, and the pathway of pain activation [9]. Normal responses to central nerve injury can be adaptive and protective. However, many are clearly maladaptive: abnormal stimulus thresholds and sensitivity, ectopic impulse generation, conduction slowing or block, reduced inhibition, inappropriate connectivity, abortive growth, neuronal loss, and glial scarring. Some of these changes occur early after the initial damage and participate in the induction phase of neuropathic pain, others develop later and help maintain the pain, and in some individuals there may occasionally be a slow resolution [3].

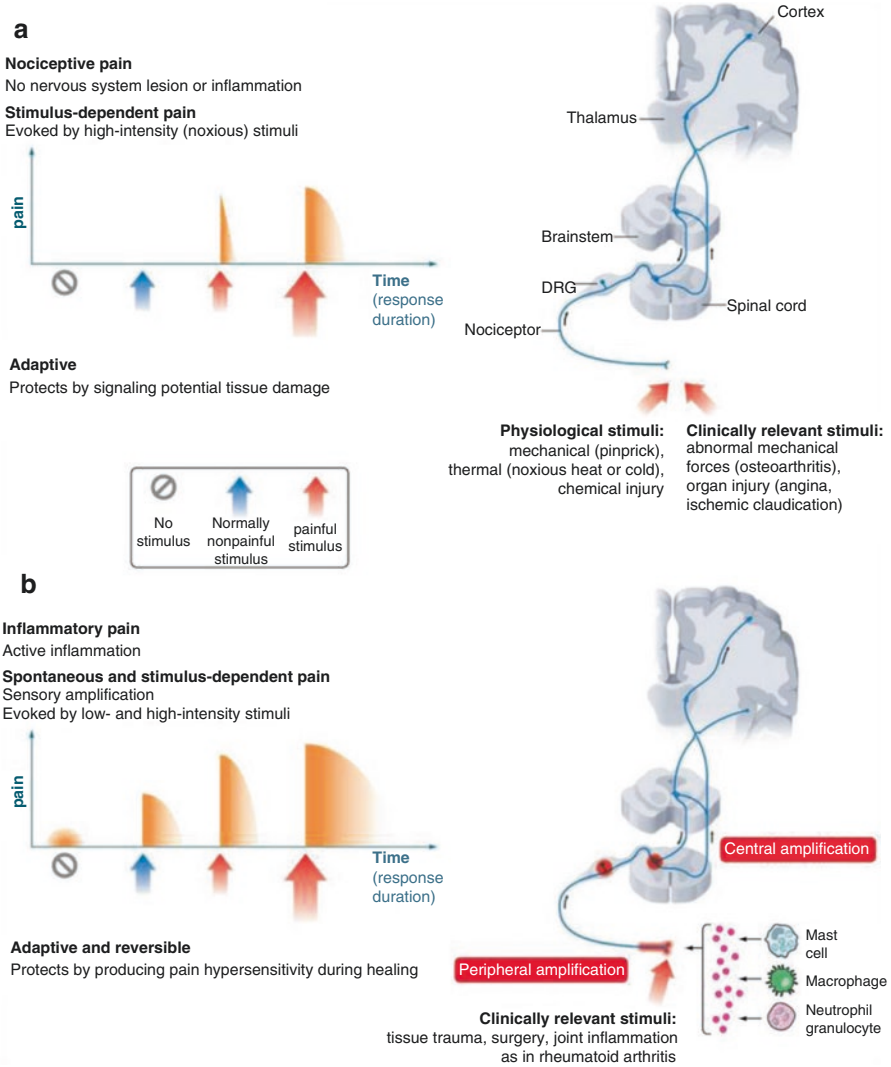


Fig. 1.1 (**a, b**) Nociceptive versus inflammatory pain signal stimuli and conduction pathways. (**c, d**) Dysfunctional versus neuropathic pain signal stimuli and conduction pathways

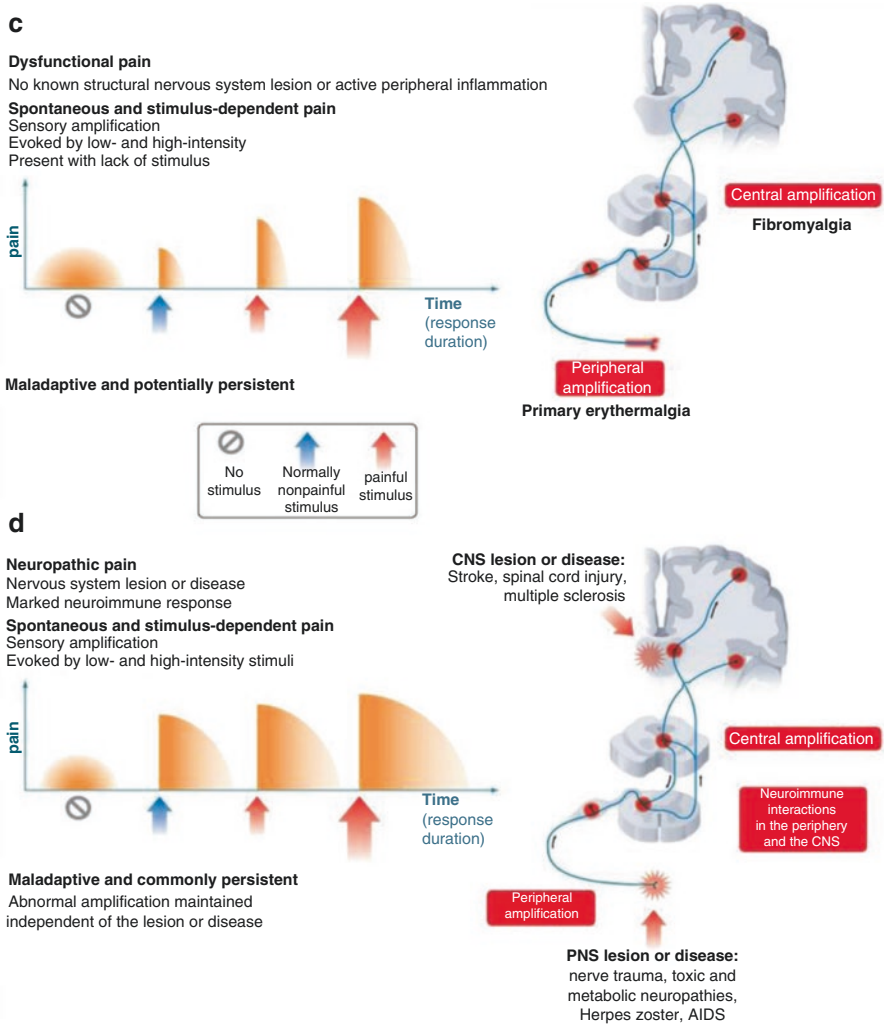


Fig. 1.1 (continued)

Nociceptive Versus Neuropathic Pain

Pain is often categorized as being either nociceptive or neuropathic. Other pain schemes define additional categories (psychogenic or muscle pain) [10, 11]. The primary distinction between nociceptive and neuropathic pain has implications for evaluation and treatment decisions.

Nociceptive Pain

A nociceptor is a nerve fiber preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged. Nociceptive pain is the perception of nociceptive input, usually due to tissue damage (e.g., postoperative pain). Nociceptive pain is further subdivided into somatic and visceral pain. Somatic pain arises from injury to body tissues. It is well localized but variable in description and experience. Visceral pain is pain arising from the viscera mediated by stretch receptors. It is poorly localized, deep, dull, and cramping (i.e., pain associated with appendicitis, cholecystitis, or pleurisy).

One classification system of pain further subdivides nociceptive pain as musculoskeletal pain, inflammatory pain (e.g., inflammatory arthropathies, postoperative pain, tissue injury, infection), or mechanical/compressive pain (e.g., low back pain, neck pain, visceral pain from expanding tumor masses) [12].

Neuropathic Pain

Neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system. It commonly persists without ongoing disease (e.g., diabetic neuropathy, trigeminal neuralgia, or thalamic pain syndrome). Neuropathic pain is further subdivided as follows:

- Sympathetically mediated pain (SMP) is pain arising from a peripheral nerve lesion and associated with autonomic changes (e.g., complex regional pain syndrome I and II, formerly known as reflex sympathetic dystrophy and causalgia) [13, 14].
- Peripheral neuropathic pain is due to damage to a peripheral nerve without autonomic change (e.g., postherpetic neuralgia, neuroma formation).
- Central pain arises from abnormal central nervous system (CNS) activity (e.g., phantom limb pain, pain from spinal cord injuries, and poststroke pain).
- Neuropathy is also described as mononeuropathy if one nerve is affected, mononeuropathy multiplex if several nerves in different areas of the body are involved, and polyneuropathy if symptoms are diffuse and bilateral.

Pathogenesis and Transmission of the Pain Signal

Pain sensation begins in the periphery of the nervous system. Pain stimuli are sensed by specialized nociceptors that are the nerve terminals of the primary afferent fibers. The pain signal is then transmitted to the dorsal horn of the spinal column and transmitted through the CNS where it is processed and interpreted in the somatosensory cerebral cortex (Fig. 1.2).

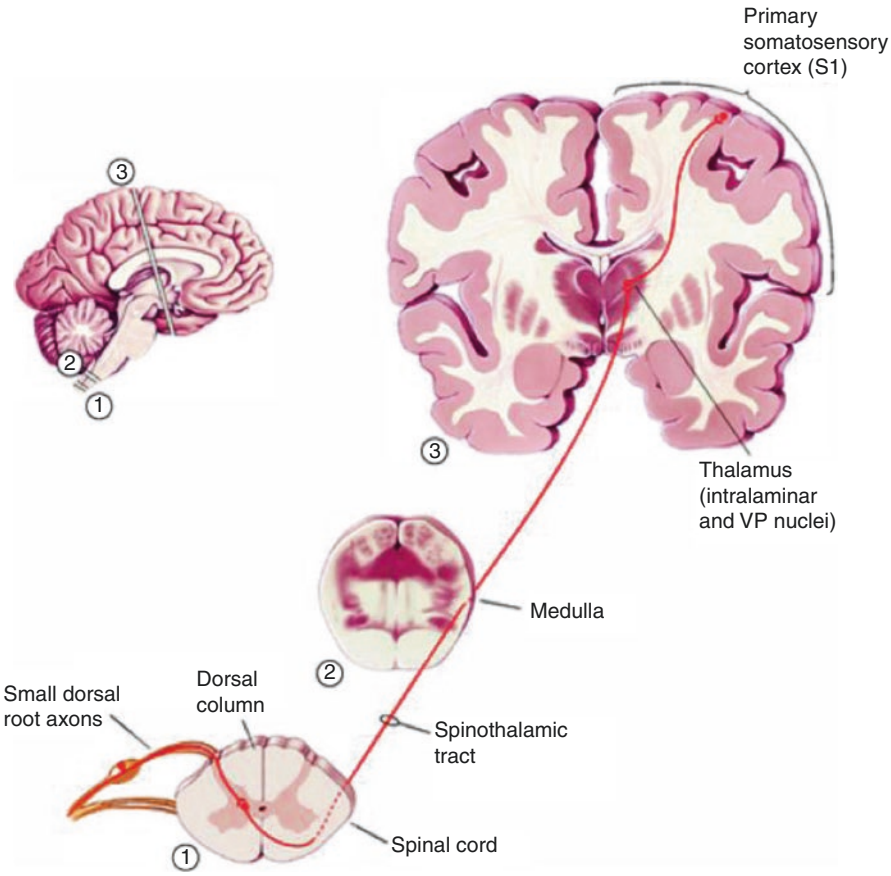


Fig. 1.2 This is the major route by which pain and temperature information ascend to the cerebral cortex (Reproduced with permission from: Bear MF, Connors BW, and Parasido, MA. *Neuroscience - Exploring the Brain*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2001. ©2001 Lippincott Williams & Wilkins)

Multiple ascending pathways may be involved in relaying nociceptive information to the brain, including spinocervical, spinobulbar, spinopontine, spinomesencephalic, spino-diencephalic (containing spinothalamic tracts), and spinotelencephalic pathways. The majority of the wide dynamic range and nociceptive-specific neurons project contralaterally within the spinal cord and ascend within the anterolateral quadrant, forming the spinothalamic tract, which synapses in the thalamus (Fig. 1.3). Neurons from the thalamus project to multiple brain areas in the primary and secondary somatosensory cortex, cingulate cortex, prefrontal cortex, insular cortex, amygdala, and the cerebellum.

Nerves involved (pain pathway/central perception center—spinothalamic) and the pain signal (biochemistry/receptors):

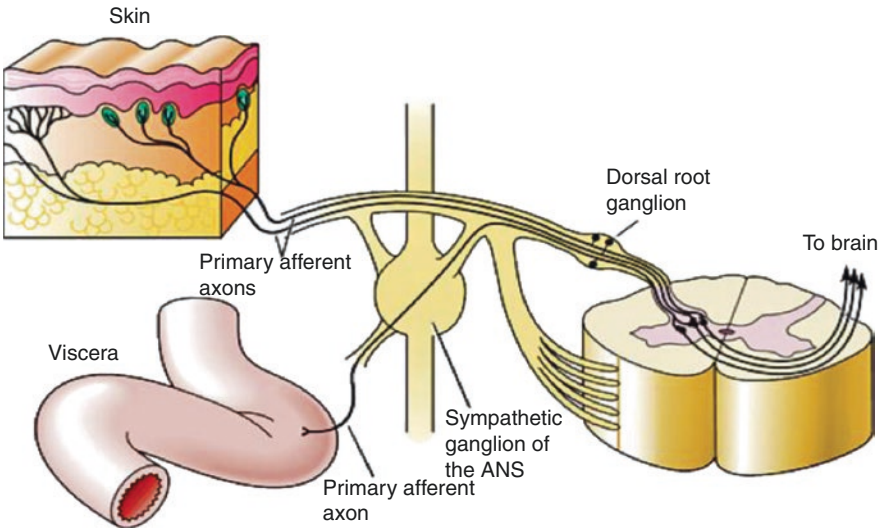
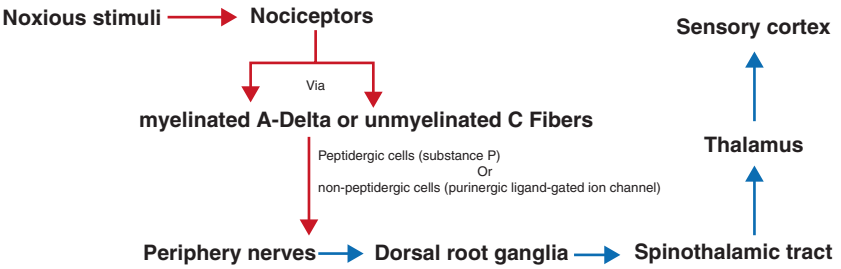


Fig. 1.3 Convergence of sensory nerves from the viscera and superficial areas onto the same neurons in spinal cord (Reproduced with permission from: Bear M, Conner B, Paradiso M. *Neuroscience, Exploring the Brain*, 2nd Ed. Baltimore: Lippincott Williams & Wilkins, 2000. ©2000 Lippincott Williams & Wilkins)



Once exposed to noxious stimuli, nociceptors initiate the pain signal via myelinated A-delta or unmyelinated C-fibers. The signal is transmitted via chemical transmission (either peptidergic cells (substance P) or non-peptidergic cells (purinergic ligand-gated ion channel)). The signal ascends from the viscera or periphery to the dorsal root ganglia of the spinal cord. Once received, the signal then ascends via the spinothalamic tract to the thalamus and is then transmitted to the sensory cortex for interpretation.

Four physiologic processes are associated with pain: transduction, transmission, modulation, and perception as follows:

- *Transduction* refers to the conversion of a noxious stimulus (thermal, mechanical, or chemical) into electrical activity in the peripheral terminals of nociceptor sensory fibers.
- *Transmission* refers to the passage of action potentials from the peripheral terminal along axons to the central terminal of nociceptors in the central nervous system. Conduction is the synaptic transfer of input from one neuron to another.
- *Modulation* refers to the alteration (e.g., augmentation or suppression) of sensory input.
- *Perception* refers to the "decoding"/interpretation of afferent input in the brain that gives rise to the individual's specific sensory experience.

Anatomy

Pelvis

The pelvis consists of the greater and lesser pelvis. Contained within, the pelvic girdle consists of the inferior-most portion of the abdominal cavity. The pelvis is part of the appendicular skeleton, providing structure for the lower limbs. The pelvis provides attachment for the muscles of the lower limbs and provides load bearing for the axial skeleton while sitting or standing. The pelvis is of critical importance to identifying landmarks of reference for many of the clinical procedures used to treat pain or anesthetize various nerve distributions. The pelvic girdle is formed by the right and left pelvic bones (consisting of the ilium, ischium, and pubis) and the sacrum medially and posteriorly. The landmarks of the ilium include the anterior superior iliac spine (ASIS) and the posterior superior iliac spine (PSIS). Each ischium contains an ischial tuberosity which is of clinical importance for procedures later discussed. The ischial tuberosities are the "sitting bones" which contact the sitting surface though protected by muscle, fascia, and connective tissue (Fig. 1.4).

Pelvic Floor

The pelvic floor is a conical structure consisting of the coccygeus and levator ani muscles and their accompanying the fascias (Figs. 1.5a, 1.6c and 1.7; Table 1.1.). The pelvic floor delineates the pelvic cavity and contents from the superficial

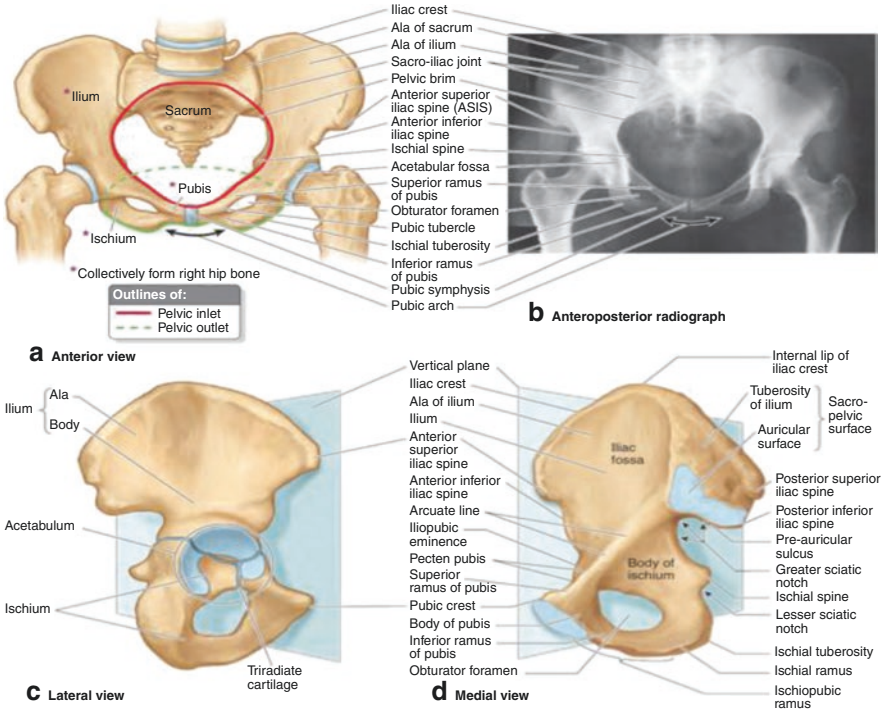


Fig. 1.4 Pelvic gridle. (**a**, **b**). Features of the pelvic gridle demonstrated anatomically (**a**) and radiographically (**b**). The pelvic gridle is formed by the two hip bones (of the inferior axial skeleton) anteriorly ad laterally and the sacrum (of the axial skeleton) posteriorily. (**c**). The hip bone is in the anatomical position when the anterior superior iliac spine (ASIS) and the anterior aspect of the pubis lie in the same vertical plane. The preadolescent hip bone is composed of three bones-ilium, ischium, and pubis – that meet in the cup – shaped acetabulum. Prior to their fusion, the bones are united by a triradiate cartilage along a Y-shaped line (*blue*). (**d**). An adult's right hip bone in the anatomical position shows the bones when fused. (**b** courtesy of Dr. E. L. Lansdown, Professor of Medical Imaging, University of Toronto, Toronto, ON, Canada.) (Moore – *Clinically Oriented Anatomy* 7th Edition pg. 329, 340)

perineum inferior to the pelvic floor structures. The lateral border is formed by the obturator internus muscle, innervated by the obturator nerves which are located medial to the obturator internus and are supplied by L5, S1, and S2. The obturator nerve is at risk for damage via compression during childbirth, causing painful stimuli to the medial thigh as well as cause spasms of the adductors. The postero-superior wall is contained by the piriformis which is innervated by S1 and S2. The inferior border consists of the coccygeus (ischiococcygeus) and Levator ani group (puborectalis, pubococcygeus, and iliococcygeus) all of which are primarily

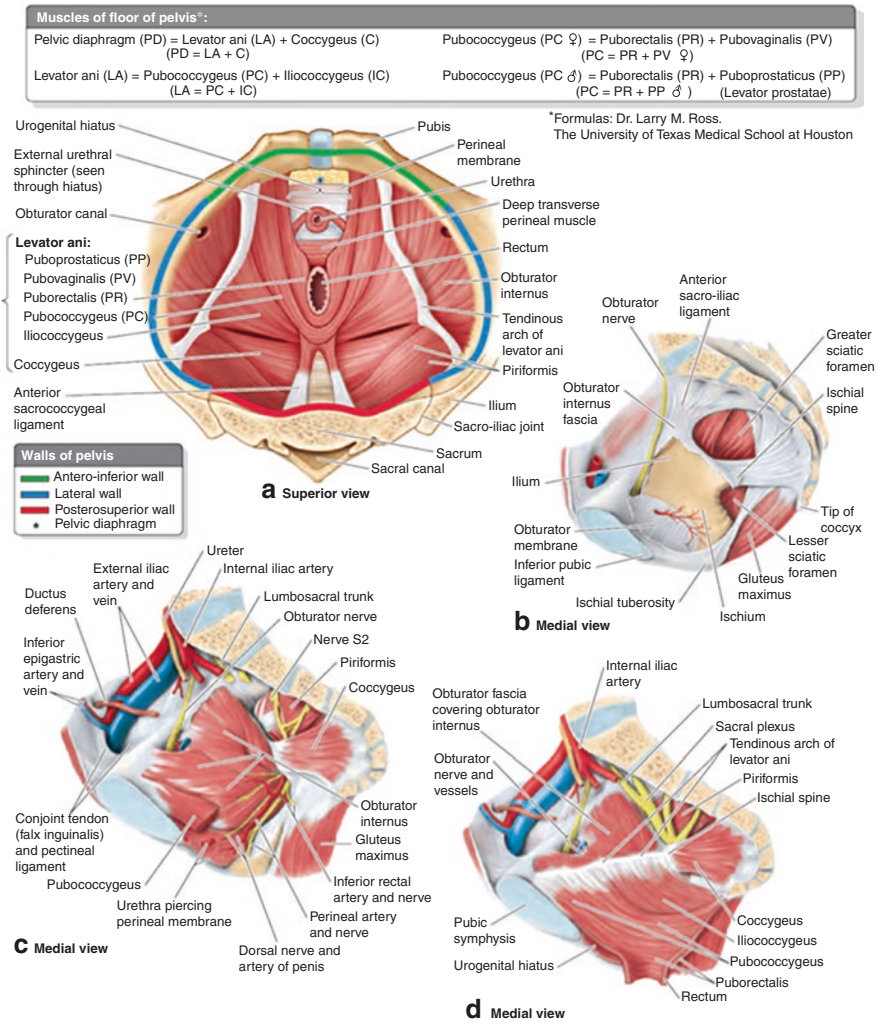


Fig. 1.5 Floor and walls of pelvis. (**a**). The floor of the pelvis is formed by the pelvic diaphragm, encircled by and suspended in part from the pubic symphysis and pubic bones anteriorly, the ilia laterally, and the sacrum and coccyx posteriorly. (**b**–**d**) show the staged reconstruction of the parietal structures of the right hemipelvis. (**b**) Posterolaterally, the coccyx and inferior part of the sacrum are attached to the ischial tuberosity by the sacrotuberous ligament and to the ischial spine by the sacrospinous ligament. The obturator membrane, composed of strong interlacing fibers, fills the obturator foramen. (**c**) The muscles of the lesser pelvis are added. The obturator internus pads the lateral walls of the pelvis, its fibers converging to escape posteriorly through the lesser sciatic foramen (see (**b**)). (**d**) The levator ani is added, suspended from a thickening in the obturator fascia (the tendinous arch), which extends from the pubic body to the ischial spine (Moore – *Clinically Oriented Anatomy* 7th Edition pg. 340)

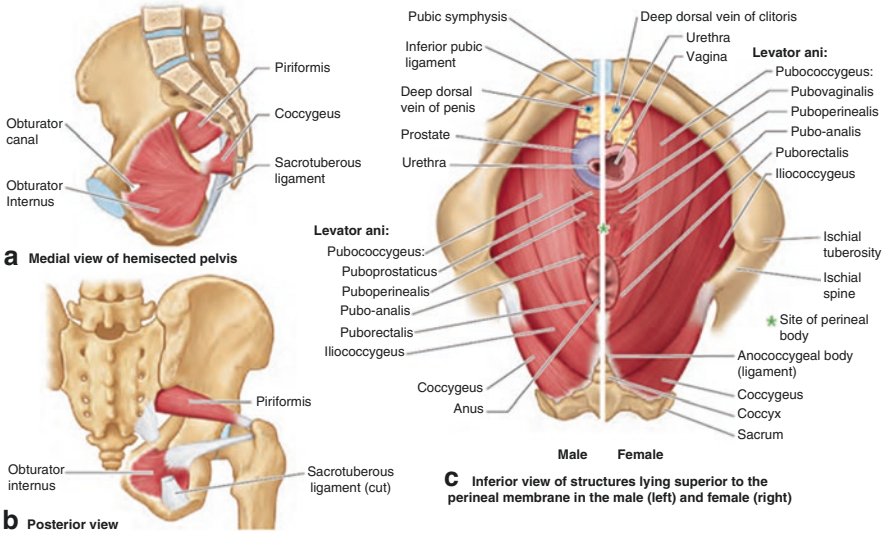


Fig. 1.6 Muscles of pelvic walls and floor. (**a**, **b**) The obturator internis and piriformis are muscles that act on the lower limb but are also components of the pelvic walls. (**c**) The muscles of the levator ani and the coccygeus comprise the pelvic diaphragm that forms the floor of the pelvic cavity. The fascia covering the inferior surface of the pelvic diaphragm forms the "roof" of the perineum (Moore – *Clinically Oriented Anatomy* 7th Edition pg. 341)

supplied by branches of S4 (and to a lesser degree by S5 in regard to the coccygeus).

Sacrum

The sacrum is a wedge-shaped bone formed by the fusion of the five sacral vertebrae. The sacrum provides strength and support to the posterior and superior portions of the pelvis. The sacrum contains the terminal portion of the spinal cord, the conus medullaris and the cauda equine, which are a collection of nerve roots resembling a horse tail. The anterior portion of the sacrum (the sacral promontory) provides a key landmark for obstetric procedures.

Nerve Plexuses of the Pelvis

Hypogastric Plexus

The hypogastric nerve plexus carry both sympathetic and parasympathetic signals via the splenic nerves receiving sympathetic fibers, via lumbar splanchnic nerves and parasympathetic fibers, and via pelvic splanchnic nerves. The hypogastric nerve plexus innervates the pelvic viscera (Fig. 1.8).

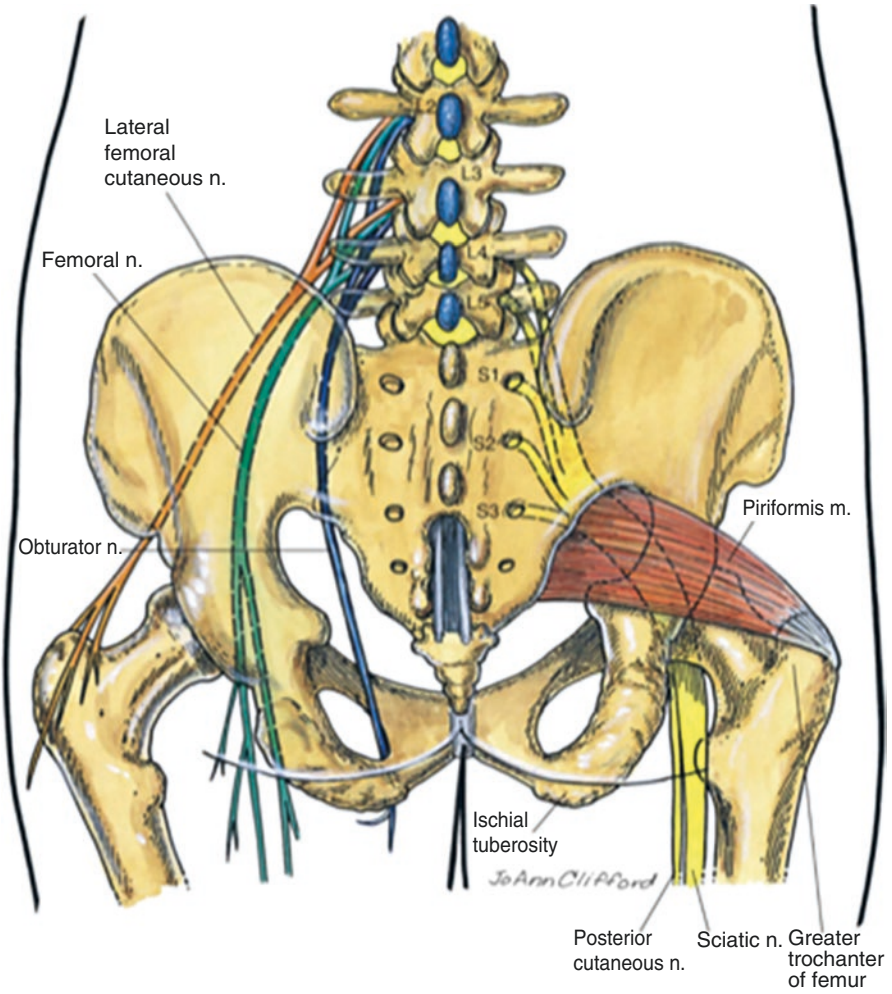


Fig. 1.7 Hypogastric plexus nerves exiting from the posterior view (Brown, DL. *Atlas of Regional Anesthesia*. Fourth Edition, Saunders Elsevier 2010. Figure 12-2)

The hypogastric nerves regulate fecal voiding or retention via parasympathetic or sympathetic signals (respectively).

Location and Innervation of Nerve Plexuses (Coccygeal Plexus, Sacral Plexus, and Ganglion Impar)

The sacral and coccygeal plexuses lay on top of the piriformis and coccygeus muscles, using them as a hammock for support. These plexuses contain the nerves which innervate the majority of the pelvis.

Table 1.1 Innervation and function of pelvic muscles

Muscle	Innervation	Action
Obturator internus	Nerve to obturator internus (L5, S1, S2)	Lateral rotation of the thigh; stabilizes the femur position in acetabulum
Piriformis	Anterior rami of S1 and S2	Lateral rotation and abduction of the thigh; stabilizes the femur position in acetabulum
Ischiococcygeus	Branches of S4 and S5 spinal nerves	Flexes the coccyx and forms a small part of the pelvic diaphragm that supports pelvic viscera
Levator ani (group): Puborectalis Pubococcygeus Iliococcygeus	Nerve to the levator ani (branches of S4), inferior rectal nerve, and coccygeal nerve plexus	Forms most of pelvic diaphragm to support pelvic viscera and resist intra-abdominal pressure

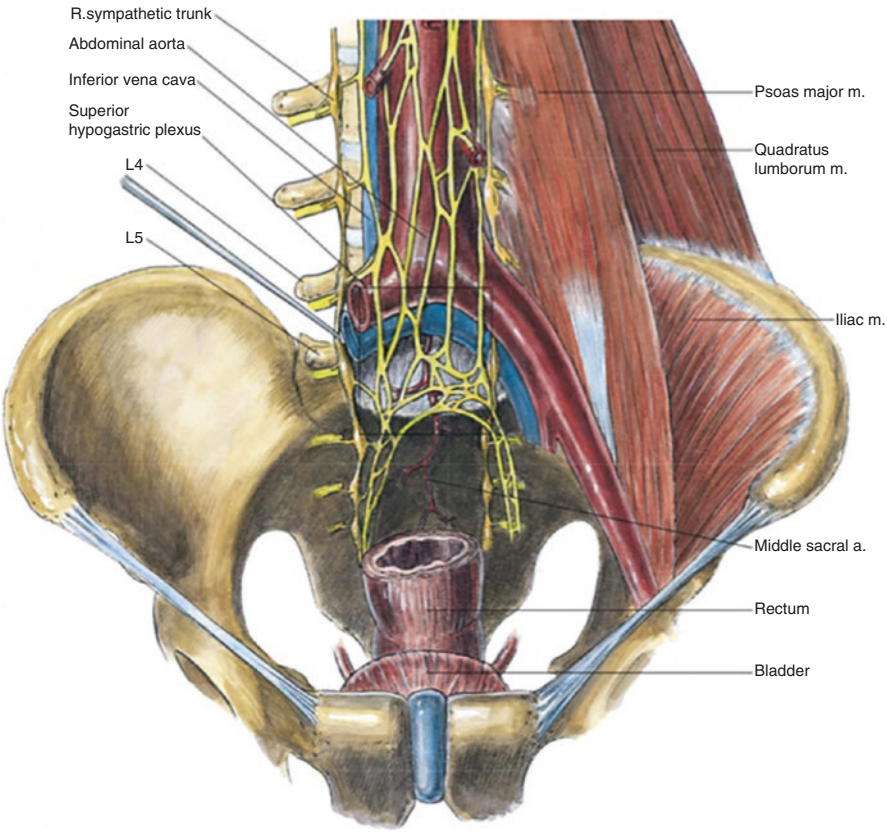


Fig. 1.8 Hypogastric nerve plexus anterior view (Brown, DL. *Atlas of Regional Anesthesia*. Fourth Edition, Saunders Elsevier 2010. Figure 48-1)

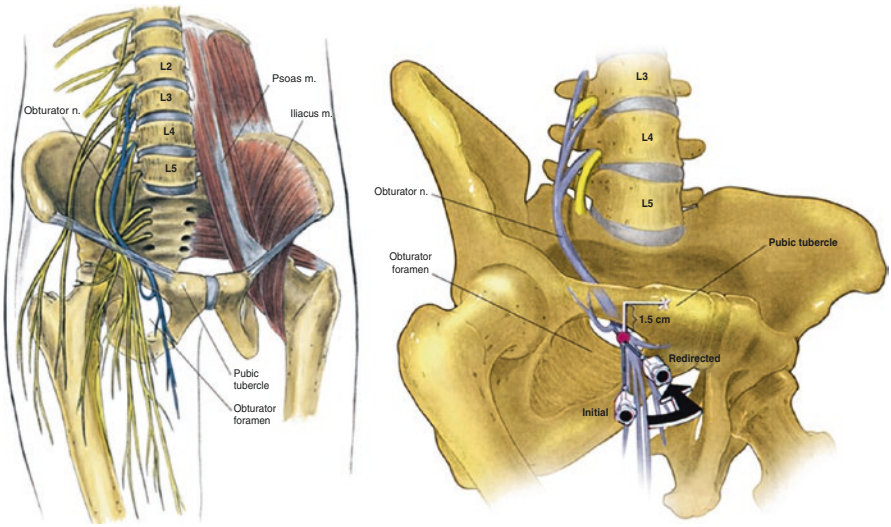


Fig. 1.9 Hypogastric nerve plexus pelvic outlet in anterior oblique view (Brown, DL. *Atlas of Regional Anesthesia*. Fourth Edition, Saunders Elsevier 2010. Figure 15-1(left) & 15-2 (right))

The Obturator Nerve

As mentioned, the obturator nerves are supplied by the anterior rami of L2–L4. The obturator nerve divides anteriorly and posteriorly. The branches of the obturator nerve then exit the pelvis to innervate the medial thigh muscles (Fig.1.9).

Sacral Plexus

The sacral plexus is of clinical importance because it contains the sciatic and pudendal nerves. Clinical interventions and their corresponding indications will be discussed in the chapters to follow. The sciatic nerve is the largest in the body and is supplied by the anterior rami of L4 through S3. The sciatic nerve passes through the greater sciatic foramen, typically inferior to the piriformis. The sciatic nerve innervates the foot, leg, and posterior thigh (Fig.1.10).

The pudendal nerve primarily supplies the perineum and external genitalia. The pudendal nerve exits the greater sciatic foramen between the coccygeus and piriformis, travels around the ischial spine and sacrospinous ligament, and then travels through the lesser sciatic foramen.

The superior gluteal nerve leaves the pelvis through the greater sciatic foramen, superior to the piriformis and the inferior gluteal nerve travels inferior to the piriformis.

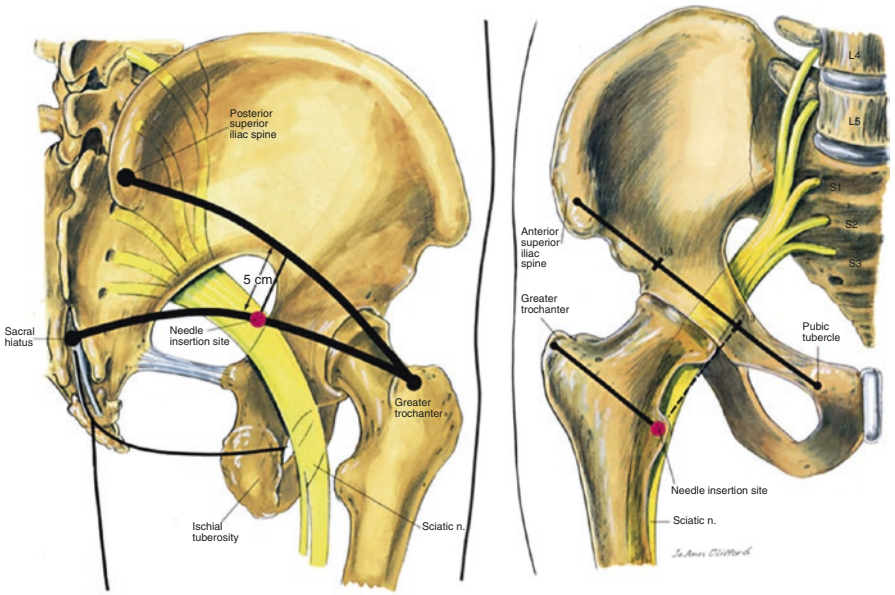


Fig. 1.10 Coccygeal plexus anterior and posterior views (Brown, DL. *Atlas of Regional Anesthesia*. Fourth Edition, Saunders Elsevier 2010. Figure 15-1(left) & 15-2 (right))

Coccygeal Plexus

The coccygeal plexus is supplied by the anterior rami of S4 and S5 to innervate the coccygeus and part of the levator ani.

Ganglion Impar

The ganglion impar (or coccygeal ganglion) is immediately anterior to the coccyx. The ganglion impar sends communicating branches to the sacral and coccygeal nerves (Figs. 1.11 and 1.12).

Terminal Branches of Nerves to the Pelvic Floor (Female Anatomy Demonstrated)

Autonomic nerves are demonstrated. The superior hypogastric plexus is a continuation of the aortic (intermesenteric) plexus. It divides into left and right hypogastric nerves as it enters the pelvis. The hypogastric and pelvic splanchnic nerves

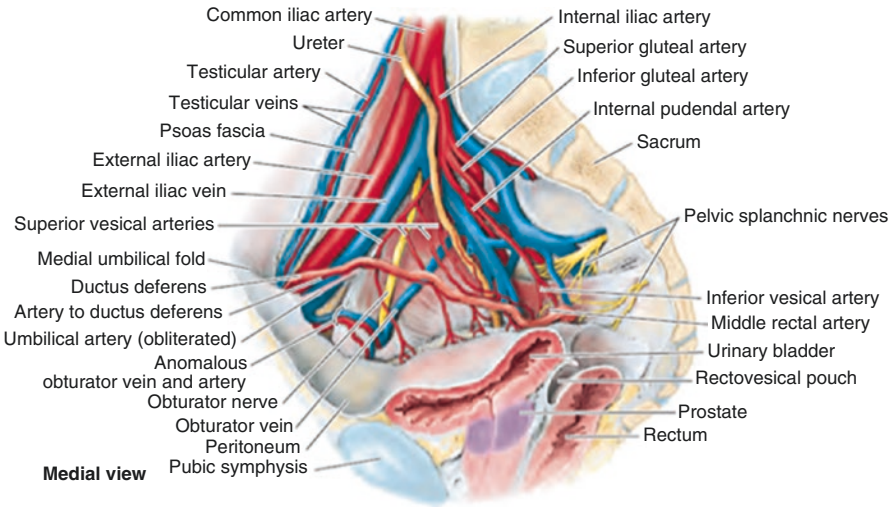


Fig. 1.11 Neurovascular relationships of pelvis. The neurovascular structures of the male pelvis are shown. Generally, the pelvic veins lie between the pelvic arteries (which lie medially or internally), and the somatic nerves (which lie laterally or externally) (Moore—*Clinically Oriented Anatomy* 7th Edition pg. 350)

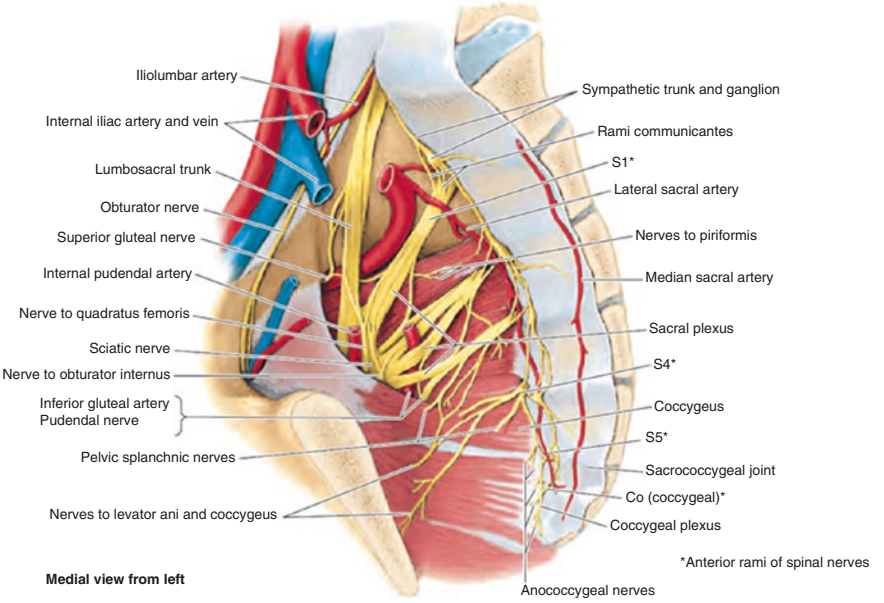


Fig. 1.12 Nerves and nerve plexuses of pelvis. Somatic nerves (sacral and coccygeal nerve plexuses) and the pelvic (sacral) part of the sympathetic trunk are shown. Although located in the pelvis, most of the nerves seen here are involved with the innervations of the lower limb rather than the pelvic structures

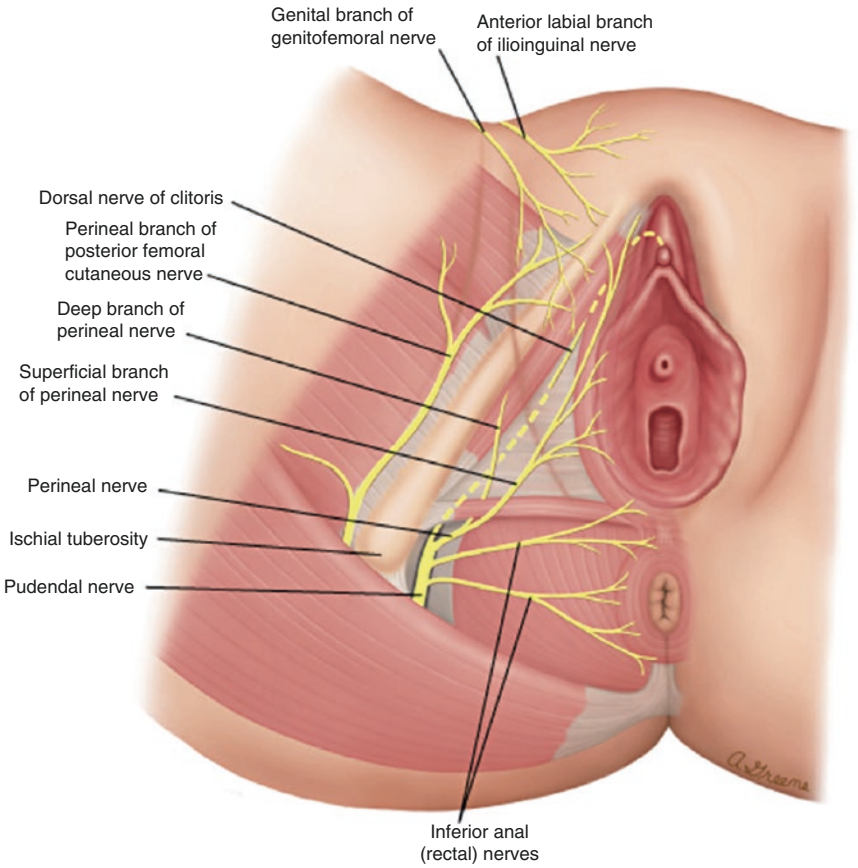


Fig. 1.13 Terminal pelvic nerve branches in lithotomy view (https://www.uptodate.com/contents/image?imageKey=OBGYN/74742&topicKey=OBGYN/14186&source=outline_link&search=urogenital&utdPopup=true)

merge to form the inferior hypogastric plexuses, which thus consist of both sympathetic and parasympathetic fibers. Autonomic (sympathetic) fibers also enter the pelvis via the sympathetic trunks and periarterial plexuses (Figs. 1.13, 1.14, 1.15 and 1.16). Cutaneous innervations are demarcated in specific distribution via associated nerve roots and carried via regional terminal nerves (Fig. 1.17).

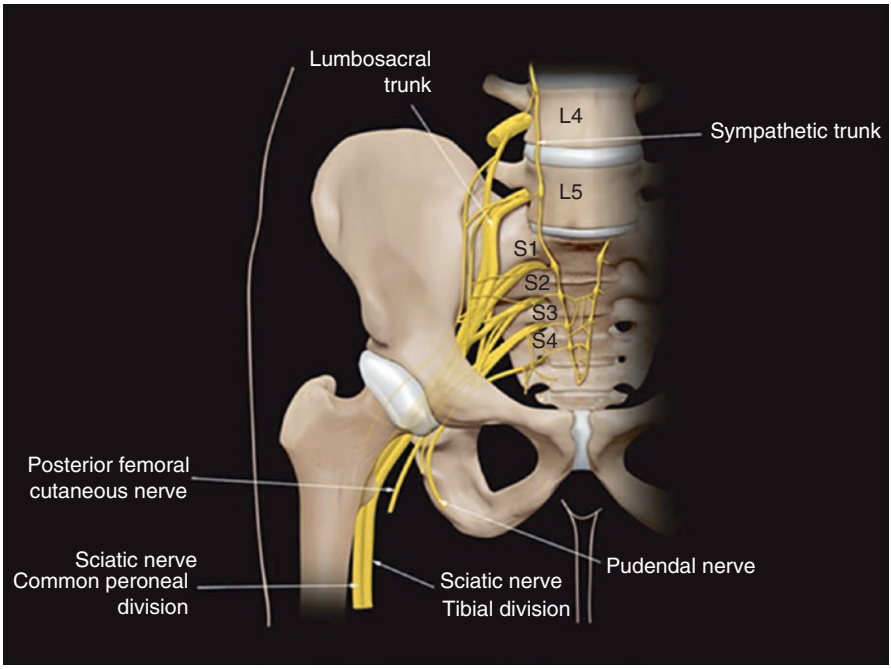


Fig. 1.14 Anatomical illustration showing the formation of the lumbosacral plexus by the union of the anterior primary rami of the *L4*, *L5*, *S1*, *S2*, *S3*, and *S4* spinal nerves (*Atlas of Functional Anatomy for Regional Anesthesiology and Pain Medicine* – pg 350 [15].)

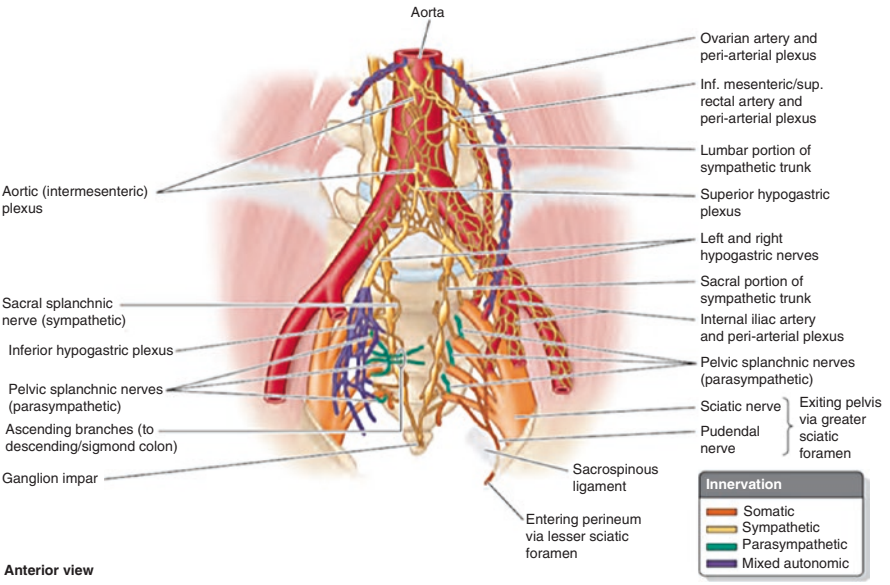


Fig. 1.15 Autonomic nerves of pelvis. The superior hypogastric plexus is a continuation of the aortic plexus that divides into left and right hypogastric nerves as it enters the pelvis. The hypogastric and pelvic splanchnic nerves merge to form the inferior hypogastric plexuses, which thus consist of both sympathetic and parasympathetic fibers. Autonomic (sympathetic) fibers also enter the pelvis via sympathetic trunks and peri-arterial plexuses (*Clinically Oriented Anatomy* 7th Edition pg. 360)

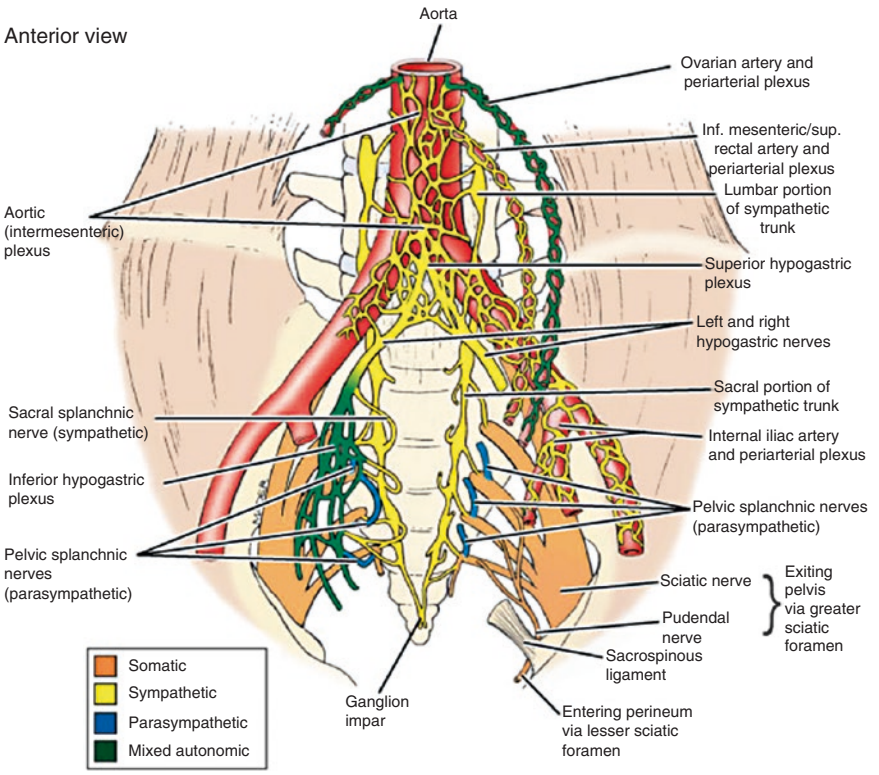


Fig. 1.16 Somatic versus autonomic nerve conduction signal delineation (Reproduced with permission from: Moore KL, Dalley AR. *Clinically Oriented Anatomy*, 5th ed, Lippincott Williams & Wilkins, Philadelphia 2006. © 2006 Lippincott Williams & Wilkins. www.lww.com. Graphic 56679 Version 10.0)

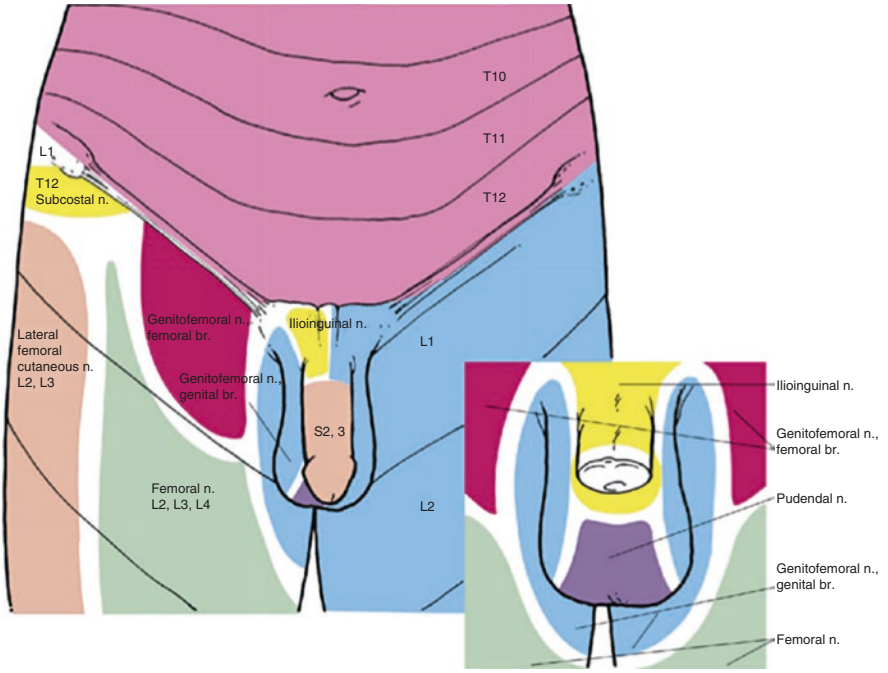


Fig. 1.17 Cutaneous innervation of pelvic nerves (Brown, DL. *Atlas of Regional Anesthesia*. Fourth Edition, Saunders Elsevier 2010. Figure 10-4 Pg. 240. http://www.elsevier.com/permissions)

Conclusion

This chapter provides a precursory understanding of the three-dimensional anatomy, the proximal and distal branches of pelvic nerves, and an understanding of their sensory and motor innervation. Correlated with clinical presentation of symptoms, and clinical regional anesthesia treatments, there is a basis for understanding pelvic pain and resolution. Later chapters will discuss using the clinical landmarks to administer regional pain treatment interventions.

References

1. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196:129–36.
2. Richards JS, Meredith RL, Nepomuceno C, Fine PR, Bennett G. Psychosocial aspects of chronic pain in spinal cord injury. Pain. 1980;8:355–66.
3. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009;32:1–32.
4. Backonja MM. Defining neuropathic pain. Anesth Analg. 2003;97:785–90.

5. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain. 2002;18:350–4.
6. Dorbatz MC. Word choices of advanced cancer patients: frequency of nociceptive and neuropathic pain. Am J Hosp Palliat Care. 2009;25:469.
7. Best Practice. Denver: British Medical Journal; 2016. http://us.bestpractice.bmj.com.ezproxy.rowan.edu/best-practice/monograph/694/basics/etiology.html. Accessed 1 Mar 2016.
8. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis. 1998;5:209–27. PubMed: 9848092.
9. Griffin RS, Woolf CJ. Pharmacology of analgesia (chapter 16). In: Golan DE, Tashjian AH, Armstrong E, Armstrong AW, editors. Principles of pharmacology: the pathophysiological basis of drug therapy. 2nd ed. Baltimore: Lippincott, Williams, and Wilkins; 2007. p. 263–82.
10. Portenoy RK. Mechanisms of clinical pain. Observations and speculations. Neurol Clin. 1989;7:205.
11. Institute for Clinical Systems Improvement. Assessment and management of chronic pain. November 2009. Available at: www.icsi.org. Accessed on 14 Apr 2010.
12. Institute for Clinical Systems Improvement. Health care guideline: assessment and management of chronic pain. Fourth edition November 2009. http://www.icsi.org/pain__chronic__assessment_and_management_of_14399/pain__chronic__assessment_and_management_of__guideline_.html. Accessed on 09 Dec 2010.
13. Bennett M. The LANSS pain scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001;92:147.
14. Stanton-Hicks M, Jänig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain. 1995;63:127.
15. Reina MA. Atlas of functional anatomy for regional anesthesia and pain medicine: human structure, ultrastructure and 3D reconstruction images. 2015. Cham: Springer International Publishing. p. 350.

Chapter 2
Ilioinguinal and Genitofemoral Neuralgia

Fatimah Habib

Introduction

Genitofemoral neuralgia is a syndrome of chronic pain in the distribution of the genitofemoral nerve (GFN), which can occur by entrapment or trauma to the nerve or its branches. The distribution of innervation by the GFN varies due to variations in its course in the inguinal region [29]. The typical manifestation of genitofemoral neuralgia is pain in the groin region and medial thigh, associated with paresthesias, decreased sensation, or burning pain [9]. GFN irritation can lead to labial pain in women and testicular pain in men, and can cause pain with ejaculation. The pain may or may not radiate to the hemi-scrotum, upper leg, or back [6]. The pain varies in intensity, can be exacerbated by hip extension, hip rotation (internal and external), stooping and walking, and is often relieved by hip flexion and recumbent position [6, 9, 17]. It was first described in 1942, and since then has been well documented in the literature [9, 23].

Anatomy

The ventral primary rami of L1 and L2 from the lumbar plexus fuse within the psoas muscle and give rise to the GFN. The GFN travels within the psoas muscle and pierces the anterior surface at its medial border at the level of L3/L4. After descending along the muscle, it passes the ureter and divides into the femoral branch and the genital branch proximal to the inguinal ligament [9]. The genital branch continues toward the deep inguinal ring and enters the inguinal canal. In males, within the inguinal canal, the relationship of the genital branch to the spermatic cord varies; it

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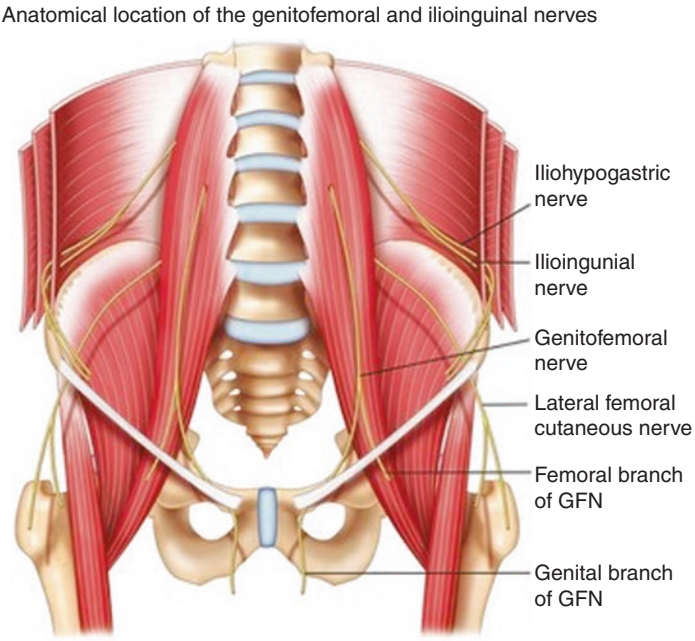

Fig. 2.1 Trajectory of the nerves in the pelvis, including the genitofemoral, ilioinguinal, and iliohypogastric nerves, often together known as the border nerves as they are responsible for providing sensation at the border of the lower abdomen and the pelvis (Image reproduced with permission from: Ultrasound for Regional Anesthesia, Toronto Western Hospital www.usra.ca)

can run outside of the cord dorsally, ventrally, or inferiorly, or it can incorporate into the cremaster muscle. It supplies motor innervation to the cremaster muscle and sensory innervation to the spermatic cord, scrotum, and the adjacent thigh region in males [9, 19, 28]. In females, it supplies sensory innervation to the labia majora, mons pubis, and the adjacent thigh by traveling through the deep inguinal ring, and incorporating with the round ligament of the uterus. The femoral branch travels on the psoas major muscle lateral to the genital branch, and courses posterior to the inguinal ligament after which it enters the proximal thigh by penetrating the fascia lata and entering the femoral sheath. In the sheath, it remains lateral to the femoral artery [28]. It provides cutaneous sensation to the anterior proximal thigh, just lateral to the area innervated by the ilioinguinal nerve—an area known as the femoral triangle [6, 9, 28]. There are no motor deficits with injury to the GFN alone, except for the loss of the cremasteric reflex which is clinically insignificant [6, 16] (see Fig. 2.1).

Etiology

Nerve injury can occur from multiple pathologic states. Symptoms of neuropathy can be caused by compression, stretching, contusion, crushing, partial or complete transection, electrical damage, neuroma formation, entrapment, or other trauma to

the nerve in question [6, 9]. The location of the GFN makes it especially vulnerable to compression, trauma from surgical instruments, and inadvertent transection during surgery. Understanding its anatomy makes it easy to understand why the most common etiology for genitofemoral neuralgia is iatrogenic following abdominal/pelvic surgery [9].

In general, there is a 2% incidence of nerve injury after pelvic surgery [16]. A review of the literature identifies reports of GFN injury following cesarean deliveries, abdominal lymph node biopsies, hernia repair surgeries, open herniorrhaphy, appendectomies, varicocele excision, trocar insertion in laparoscopies, and other surgeries in the inguinal region [1, 9]. The nerve can be injured by compression from retractors, entrapment, stretching, or even transection during dissection or movement of structures in the area [1, 16]. With newer operative approaches, the incidence of genitofemoral neuralgia has decreased. For example, fibrous tissue from open appendectomy scars was known to cause neuralgia of the femoral branch of the GFN via entrapment and compression. Incidence has decreased with the laparoscopic approach.

Other etiologies for injury to the GFN are trauma and idiopathic genitofemoral neuralgia. Pregnancy, retroperitoneal trauma, and trauma to the inguinal ligament are all instances of intrapelvic trauma that can give rise to genitofemoral neuralgia. Fortunately, the incidence of trauma to the GFN is rare; however, when it does occur, it can result in debilitating chronic pain. A case report from 1979 proposed tight-fitting jeans to be the etiology of genitofemoral neuralgia in one patient, and in 2001, a case report proposed bicycle riding as a potential cause of idiopathic genitofemoral neuralgia [9].

Diagnosis

The first step in diagnosis begins with a thorough history and physical exam, as well as good knowledge of the innervation and anatomy of the groin region. The history should include age, gender, medical comorbidities, social history, recent surgical history, and type and approach of surgery (open vs. laparoscopic), history of chronic pain syndromes, history of preoperative pain, and any postoperative complications. A complete pain assessment is also a critical part of the history. A focused physical exam is necessary to confirm or rule out other potential etiologies of pain. On exam, it is important to check sensory dermatomes, motor function, reflexes, and gait. Lumbar spine range of motion should be assessed with flexion, extension, and lateral rotation of the spine. To rule out any lumbar spine disease, physical maneuvers can be very useful. For example, facet disease can be assessed by having the patient remain in a seated position while they twist their torso, and then extend the spine, putting a load on the facet joints. Pain with this maneuver may indicate facet disease. A positive straight leg raise (patient in supine position and examiner passively raising the patient's leg without bending the knee) can indicate neural compression originating at the spine. A positive Patrick's test (also known as FABER for flexion, abduction, and external rotation of the hip) may indicate hip joint pain. Sacroiliac

(SI) joint disease can be tested using the Gaenslen test, which is done in the supine position, with one hip completely flexed (knee brought to the chest) and the other hip extended (leg allowed to fall over the side of the table). Both SI joints are flexed with this maneuver and pain can indicate SI joint disease, hip pathology, and L4 nerve root lesion or even stress on the femoral nerve. If other possible causes of pain are ruled out, neuropathic pain can be considered. Pain on palpation over the inguinal region or pubic tubercle can add some confirmation to the diagnosis of genitofemoral neuralgia, and tapping over an area of local tenderness (Tinel's sign) can reproduce neuropathic pain symptoms [6, 17].

Initial investigation into chronic groin pain should always try to identify and rule out non-neuropathic causes, such as a recurrent hernia or mesh infection. Using the history, physical, a clinical evaluation, and imaging studies such as ultrasound or magnetic resonance imaging (MRI), any potential non-neuropathic pain etiologies should be eliminated. Such causes need to be explored immediately because proper treatment is often required urgently to prevent further complications such as an increased risk of chronic pain development [6].

Pain from genitofemoral neuralgia often presents as groin pain below the inguinal ligament, radiating to the genital area and superior medial and anterior thigh. Pain in the inguinal region after a hernia repair that is most concentrated in the testicular region (orchialgia) is indicative of neuralgia of the genital branch of the GFN. Orchialgia can be idiopathic or non-idiopathic (infection, tumors, varicocele, spermatocele, or complication of surgery such as vasectomy or inguinal hernia repair). One case study from 2014 described a case of idiopathic chronic orchialgia that was confirmed by local nerve block to be attributed to the genital branch of the GFN [34]. Due to anatomic variability, it becomes difficult to pinpoint the source of the pain by symptoms alone and further diagnostic studies are often necessary.

Accurate diagnosis of genitofemoral neuralgia is difficult because of overlapping and varying areas of innervation of different nerves in the inguinal region [1]. The differential diagnosis for any chronic groin pain following a surgery in the abdominal or pelvic region should include genitofemoral neuralgia along with ilioinguinal neuralgia. One study on human cadavers found four different branching patterns of the genitofemoral and ilioinguinal nerves leading to four different patterns of cutaneous innervation. The cadavers were only 40.6 % of the time symmetric bilaterally; a patient can have different cutaneous innervation patterns on different sides of their groin [29]. Distinguishing among the different neuralgias can be done by different selective diagnostic blocks to determine the true etiology of the pain. Accurate diagnosis is necessary to prevent incorrect treatment (and potentially unnecessary surgical exploration) since different pelvic neuropathies have different treatment modalities [1, 9]. (See Fig. 2.2).

A diagnostic selective nerve block technique was identified in 2006 in an attempt to eliminate incorrect diagnoses when ilioinguinal and genitofemoral neuralgias were both being considered [9]. The ilioinguinal nerve block is a technically simpler procedure and therefore it is done first to rule out ilioinguinal neuropathy (approximately 2–3 cm inferior and medial to the anterior superior iliac spine (ASIS)) [28]. If the nerve block does not relieve the patient's symptoms, ilioingui-

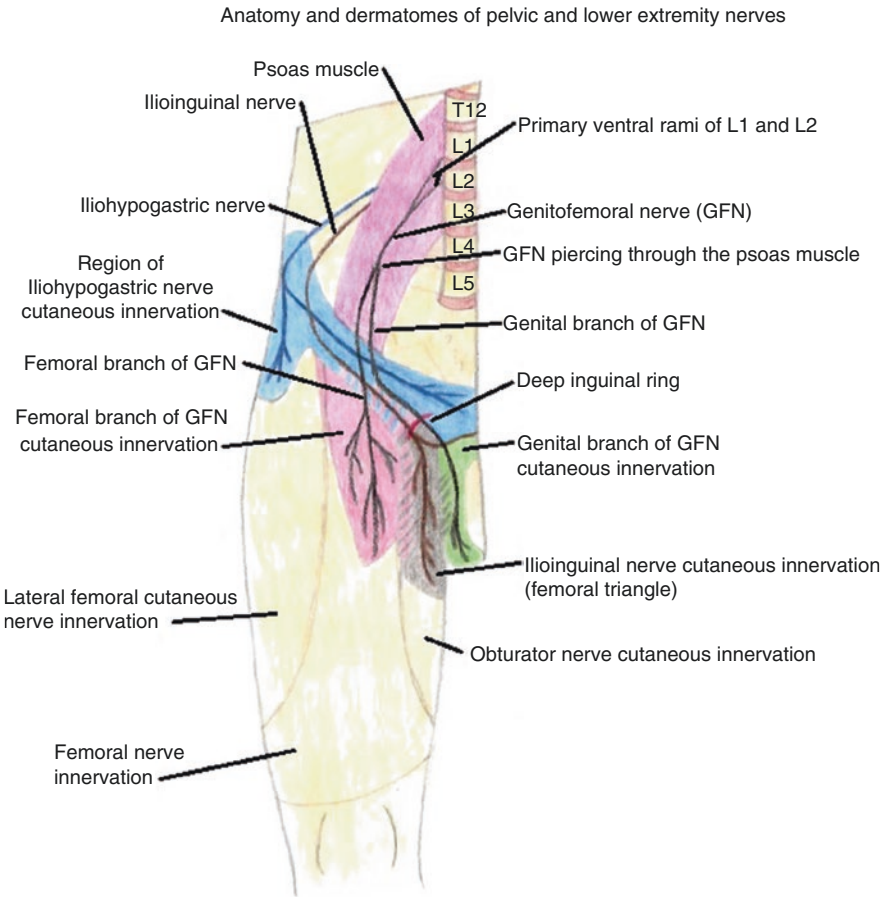

Fig. 2.2 The genitofemoral nerve arises from the fusion of the ventral primary rami of L1 and L2 and pierces the psoas muscle, then descends along its anterior surface and splits into the genital branch and the femoral branch proximal to the inguinal ligament. The genital branch supplies sensation to the spermatic cord, scrotum, and adjacent thigh in males and the labia majora, mons pubis, and adjacent thigh in females. It is shown passing through the deep inguinal ring. The femoral branch supplies sensation to the anterior proximal thigh just lateral to the femoral triangle. The ilioinguinal nerve arises from the anterior rami of L1 (and some contributing branches from T12) and originates at the lateral border of the psoas muscle. It travels down the anterior abdominal wall piercing through the transverse abdominus and the internal oblique muscles. It supplies sensation to the superior medial thigh, an area known as the femoral triangle, as well as the pubic symphysis

nal neuralgia can be ruled out. The next diagnostic tool should be a paravertebral L1/L2 nerve plexus block to determine whether the GFN is the culprit [9, 19]. This approach has been well documented; however, it may not always be successful. Other approaches (e.g., anteriorly at the level of the inguinal ligament, or superior lateral to the pubic tubercle) to diagnostically or therapeutically block the GFN have

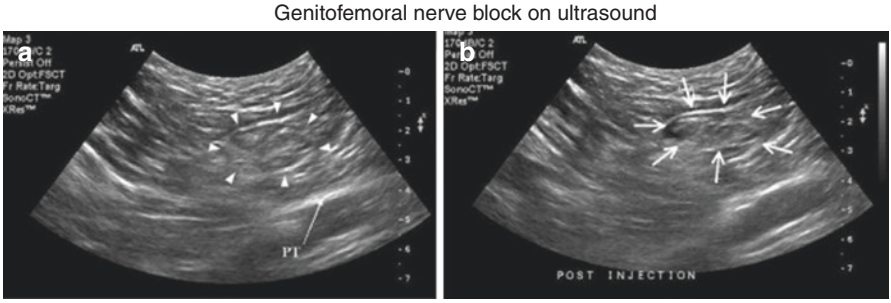

Fig. 2.3 Ultrasound picture showing pre- and postinjection into the spermatic cord. (**a**) Spermatic cord before injection. (**b**) Spermatic cord after injection. This technique (as described by Peng et al.) blocks the genital branch of the genitofemoral nerve. The ultrasound is held perpendicular to the inguinal ligament, about one finger breath lateral to the pubic tubercle (Reproduced with permission from Philip Peng Educational Series)

proved difficult since the GFN is retroperitoneal and not without risk. With a blind technique, structures such as the spermatic cord, vas deferens, testicular artery, and the peritoneum can be harmed [28]. In 2010, a computerized tomography (CT)-guided trans-psoas approach was described by Parris et al. The basis of the technique was to target a location of the nerve proximal to the injury, so impulses were blocked en route distally from the injured site, traveling proximally to the central nervous system. Their technique proved to be an effective option in a diagnostic evaluation of the GFN, and a potentially therapeutic option (via radiofrequency and phenol ablation, although long-term relief was not achieved) [9, 27]. An ultrasound-guided approach to block the genital branch of the GFN was described by Peng et al. in 2008, by identifying the spermatic cord on ultrasound one finger breadth lateral to the pubic tubercle, and injecting local anesthetic (without epinephrine to avoid the possibility of vasoconstriction of the testicular artery) both inside and outside of the spermatic cord [28]. In 2014, Terkawi et al. described identifying the spermatic cord on ultrasound by identifying the inferior epigastric vessels under the rectus sheath and moving caudally to localize where the inferior epigastric artery joins the external iliac artery. The spermatic cord can be found medial to their intersection point. Another approach described was to locate the femoral artery, follow it superiorly until it joins with the external iliac artery and at that level, medially shift to find the spermatic cord. In the case study, the diagnostic block proved confirmatory as the patient reported pain relief lasting 6 weeks [34] (see Fig. 2.3).

Treatment

Many algorithms have been suggested for the treatment of chronic groin pain, although none have been proven with randomized trials. There is currently no consensus for any one specific algorithm or even criteria for nonpharmacologic,

pharmacologic, or surgical treatment. In general, the management for genitofemoral neuralgia, such as all chronic pain syndromes, starts with noninvasive methods. Avoiding exacerbating factors is a key factor in management; however, maintaining a sedentary lifestyle if even walking causes pain is no longer recommended. Physical and psychological therapies include massage, physiotherapy, myofascial release, and acupuncture. Acupuncture is one of the oldest methods of achieving analgesia, dating back over 3000 years and originating in China. According to the World Health Organization, the use of acupuncture in postoperative pain has been confirmed in controlled studies and is well recognized. The effect of acupuncture to relieve acute postoperative pain after inguinal surgery has been studied and shown to be effective [33]. Early research demonstrates a place for acupuncture in chronic pain treatment as well, for example, to treat chronic low back pain, knee osteoarthritis, and prostatitis/chronic pelvic pain. One study focused on investigating at brain regions via neuroimaging that were known to have dysregulation in chronic pain. The study indicated that repeat acupuncture might work by restoring balance in important brain regions associated with chronic pain, specifically the periaqueductal gray, medial frontal cortex, and bilateral hippocampus. Balancing the connectivity in the important brain regions via acupuncture can potentially alter pain-related memory and attention [13]. Although massage therapy has not been specifically studied with regard to genitofemoral neuralgia, there have been studies evaluating the effectiveness of massage therapy on neuropathy-related pain such as pain from carpal tunnel syndrome and fibromyalgia. Preliminary-positive support for the treatment includes findings such as decreased pain as well as decreased depression and anxiety in the experimental group patients, including studies on chronic pain syndromes [35]. Other therapies such as myofascial release, heat, physical therapy, and topical analgesics have been attempted for chronic pain, with short-term varying success rates, and limited long-term pain relief [6].

Pharmacological treatment involves multiple medication options, which are recommended in a stepwise approach. Topical anesthetics such as lidocaine patches can be tried initially. Next in line for medical management includes tricyclic antidepressants (TCAs), which have been proven to be effective in treating neuropathic pain. If there is no improvement of symptoms, medications such as gabapentin (inhibiting glutamate release in the spinal cord dorsal horn) and pregabalin can be used, followed by opioids [1, 19]. Adjunctive medications such as non-steroidal anti-inflammatory drugs (NSAIDs), other anti-epileptics, selective serotonin reuptake inhibitors (SSRIs), selective serotonin/norepinephrine reuptake inhibitors (SNRIs), tramadol, and capsaicin cream can also be used as supplementation [1]. In many studies, NSAIDs were used as the first-line pharmacological therapy and gabapentin or oral steroids as second line [19]. However, the efficacy of any certain regimen has not been proven, and although recommendations have been made there is no solid consensus [17]. Capsaicin cream is a natural chemical derived from a plant that prevents substance P (chemo-mediator that helps transmission of pain to the central nervous system from the periphery) from re-accumulating in the peripheral sensory nerves, providing analgesia [16]. Nerve blocks are used initially for diagnosis, and may also be used for treatment; however, repetition is often necessary since nerve blocks only

provide temporary relief. Nerve blocks can be done using blind techniques, ultrasound guidance, and CT guidance. Imaging aids in targeting the correct region and therefore increasing the accuracy and effectiveness of the block.

The next step in the treatment of genitofemoral neuralgia should pharmacologic therapy fail to manage the symptoms is an ablative technique. If that should also fail, then surgery (neurectomy) is considered. Although there is no clear consensus on a recommended surgical time, a period of 6 months to 1 year of conservative management is suggested prior to proceeding with surgery. The definition of chronic pain consists of persistent symptoms for more than 3–6 months after the injury; therefore, at least 6 months is recommended. The logic for the recommended time frame is to allow for enough time for the major inflammatory process to decrease so that a neuropathic pain syndrome can be identified separate from inflammation post injury (or post trauma/post surgery), as well as attempted medical management [6, 17]. The ablative techniques are available at this time including radiofrequency ablation and cryoablation, and both are done with imaging, usually CT, fluoroscopy, or ultrasound guidance.

Radiofrequency ablation utilizes high temperatures targeted at a small area immediately in the vicinity of the target nerve to cause neurolysis and diminish the pain. It has been shown to provide long-term pain relief, without damaging the perineurium or epineurium, and therefore minimizing the risk of neuroma formation. The effect is not always long term, however, and repetition may be necessary [9]. Radiofrequency ablation has been utilized in the management of chronic pain since 1974 when continuous radiofrequency (CRF) ablation was used. Pulsed radiofrequency (PRF) was first used with clinical results in 1998 and was developed in an effort to minimize tissue damage that was a known complication with CRF. Other known complications of CRF included neuritis-like reactions, deafferentation pain, and possibly even motor deficits. CRF works by creating coagulation necrosis of the target tissue by a probe which heats to between 60 and 80 °C, causing tissue destruction [7]. Coagulative necrosis is a type of necrosis characterized by the maintenance of tissue architecture [31]. At temperatures of 60 °C and greater, coagulation necrosis occurs instantaneously, At 50–52 °C, necrosis occurs in approximately 4–6 min [15], and at 45 °C, in about 20–30 min [31]. CRF utilizes a high-frequency alternating current (between 200 and 1200 Hz) and creates well-circumscribed lesions. The degree of tissue destruction is dependent on the duration of radiofrequency, the size of the electrode tip, the temperature of the tissue, and also the distance of the tissue from the electrode tip. CRF differs from PRF in that PRF uses short high-voltage bursts of radiofrequency current, approximately 20 ms per burst, with a silent phase in between bursts to allow for heat to be decreased. The tissue temperature remains less than 42 °C. Theoretically, as well as based on a few histopathologic studies looking at dorsal root ganglia in rats, PRF causes only temporary endoneurial edema, and in general causes less tissue destruction than CRF while still allowing for pain relief. Due to the lower temperatures utilized by PRF, the mechanism of action involves a temperature-independent mechanism consisting of a rapidly changing electrical field, which alters the transmission of pain signals via a specific pathway [7]. Evidence to support such a theory is unfortunately inconclusive, so the mechanism of efficacy of PRF still remains unclear. It is known that PRF current

reversibly disrupts transmission of the pain impulse of C fibers (small unmyelinated pain fibers) selectively with larger pain fibers being preserved in their myelin sheaths [18]. The efficacy of PRF in treating chronic pain has been described in multiple different pain syndromes including inguinal pain and orchialgia. In one study, three patients with groin pain or orchialgia underwent PRF after diagnostic nerve blocks. Each patient had PRF to either the genitofemoral or the ilioinguinal nerve for 120 s at 42 °C, and had total resolution of symptoms at the 6-month follow-up [10]. In another study, one patient with chronic orchialgia attributed to the genital branch of the GFN underwent ultrasound-guided PRF ablation of the genital branch and was symptom-free during activity and at rest at the 7-month follow-up [34]. CT-guided radiofrequency and phenol ablation were demonstrated by Parris et al. in 2010 (with only short-term relief in pain).

Cryoablation utilizes rapid cycles of cooling to target the nerve myelin sheath and axon (Wallerian degeneration), blocking afferent impulses and decreasing the wind-up phenomenon in the central nervous system. Cold temperatures (as low as −40 °C) have been used in medicine since as early as the mid-nineteenth century, and in the twentieth century cryotherapy with liquid nitrogen was first used to treat liver tumors intraoperatively [31]. Only more recently has it been used for neurologic pain palliation purposes. The cold temperatures released from the probe cause ice formation intracellularly, which leads to direct cell death as well as extracellularly, which leads to indirect cell death via the formation of an osmotic gradient favoring cell dehydration and death. Cryotherapy also causes small-vessel thrombosis leading to cell death. Studies show potentially higher rates of analgesia and more immediate effects with cryoablation or RFA [9]. Again, there is preservation of the perineurium and epineurium, even more so than with thermal ablation techniques such as radiofrequency ablation. With both ablative approaches, axon regeneration does occur and therefore repetition may be necessary [9]. There is some research on ultrasound-guided cryoablation, the benefit of which is the avoidance of unnecessary radiation exposure, the ability to monitor ice formation in real time, and a potentially more effective nerve block [8, 31]. Ultrasound-guided cryoablation of the femoral branch of the GFN has been successfully used to treat chronic groin pain [8, 9]. Evidence suggests that there are overall better outcomes with neurectomy versus ablative techniques, but the ablative techniques can decrease the pain enough that surgery may be avoided altogether [6].

If all pharmacologic and ablative treatments fail to manage the symptoms, surgical treatment may be considered. Neurectomy has proven to be successful since the early 1940s. However, since then, the approach to neurectomy has changed and many different approaches have been suggested, including open, laparoscopic, or combined. More recently, a common approach to resection of the nerve is an extraperitoneal approach, which decreases the risks associated with the procedure, has less interruption of the primary surgery (e.g., does not interfere with the original hernia repair), and successfully resolves the chronic pain symptoms [9]. One study described ten patients with genitofemoral neuralgia from different causes (iatrogenic from different types of surgeries and trauma) with unsuccessful conservative therapy. Neurectomy was performed in all ten patients with successful relief of symptoms [25]. Ducic et al. described four patients with genitofemoral neuralgia who underwent genitofemoral

nerve neurectomy with 100% pain relief [12]. A triple neurectomy (neurectomy of the ilioinguinal, iliohypogastric, and genitofemoral nerves) has been suggested to treat postsurgical chronic groin pain, which may be beneficial if a single nerve cannot be identified as the sole culprit. The benefit is the resolution of symptoms of inguinodynia regardless of the culprit nerve. The risks include hypoesthesia of the areas in the groin region innervated by the three nerves, which can include the femoral triangle, the scrotum and penis in men, and the labia majora and mons pubis in women. There is no associated motor loss except for the loss of the cremasteric reflex which is generally insignificant [4, 6, 9]. If neuropathy occurred following hernia with mesh surgery, neurectomy with or without mesh removal is recommended (vs. mesh removal alone); however, as of yet there is no consensus on surgical approach or which nerve should be removed. During neurectomy, the entire length of the nerve or nerves should be removed so that all neural connections between the nerves involved have been excised [17]. The most common criteria for choosing surgery are the recurrence of pain after or failure of at least two consecutive nerve blocks. Based on research on patients with persistent postsurgical pain, patients suffering from central nervous system sensitization tend to be refractory to any form of treatment including surgery and thus are poor surgical candidates. For such patients, surgery should be avoided and nerve blocks and transcutaneous electrical nerve stimulation (TENS) may be more effective treatments [17, 22].

Ilioinguinal Neuralgia

Introduction

Ilioinguinal neuralgia is a chronic pain syndrome in the distribution of the ilioinguinal nerve, commonly due to nerve entrapment. The regions of innervation vary due to anatomic variability of sensory innervation in the groin region [26, 29]. The symptoms often include paresthesia or hypoesthesia in the area of the inguinal ligament, often radiating to the lower abdomen. Besides sensory impairment, pain can also exist. The pain can be localized to certain areas such as the inner thigh, medial groin, and scrotum in males or labia majora in females. The pain can be replicated with palpation at the region where the ilioinguinal nerve exits the inguinal canal, as well as pressure applied in the lower abdomen, medial to the anterior superior iliac spine. Symptoms increase with walking and hip extension, and are decreased with hip flexion [6].

Anatomy

The fusion of the anterior rami of L1 and contributing branches from T12 nerve roots gives rise to the ilioinguinal nerve. It originates at the lateral border of the psoas muscle and travels down the anterior abdominal wall, sub-peritoneal,

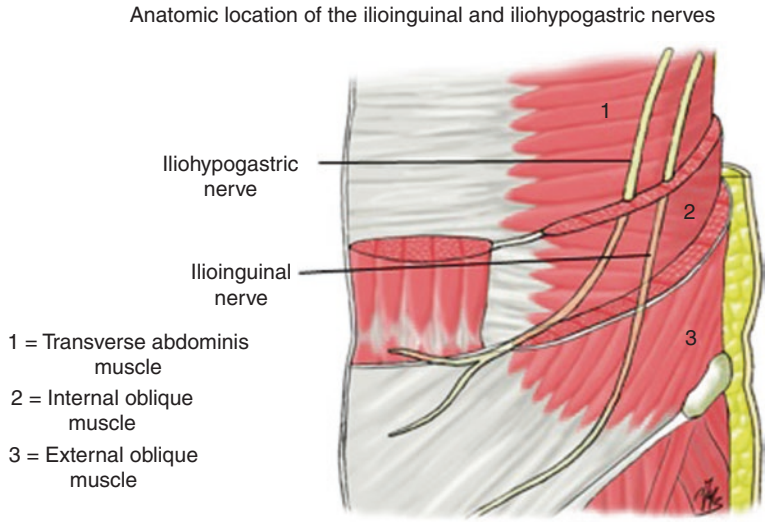

Fig. 2.4 The ilioinguinal and iliohypogastric nerves emerge from the lateral border of the psoas muscle after originating from the lumbar plexus (L1). The nerves run anterior to the quadratus lumborum and penetrate the transversus abdominus near the iliac crest (Image reproduced with permission from: Ultrasound for Regional Anesthesia, Toronto Western Hospital. www.usra.ca)

anterior to the quadratus lumborum, down to the iliac crest. It then penetrates the abdominal muscle layers, going through the transverse abdominus and the lower border of the internal oblique. The ilioinguinal nerve runs parallel to the iliohypogastric nerve until it pierces the internal oblique (the iliohypogastric gradually goes on to pierce the external oblique). It supplies the two muscle layers as well as supplying neural branches to the iliohypogastric nerve. The ilioinguinal nerve passes by the superficial inguinal ring and in front of the spermatic cord. It provides sensory innervation to the pubic symphysis and the femoral triangle (superior medial thigh). In males, it also provides sensory innervation to the root of the penis and anterior scrotum, and in females to the mons pubis and labia majora [6, 16, 19, 28]. It is important to note that there is considerable variability in the course of the two nerves, for example, the site where they enter the different layers of the abdominal muscles is quite variable. It is impossible to discuss the ilioinguinal nerve without referring to the iliohypogastric nerve and its relation to it. In some patients, one nerve can be entirely absent; in others, the ilioinguinal nerve may join with the iliohypogastric nerve. Generally, the size of one is inversely proportional to the other. The variability of these two nerves reflects the variability of all the border nerves and their innervation in the groin region [28]. To make things even more complicated, one study in 2001 on human cadavers showed that in 28 % of cases, the ilioinguinal nerve was exclusively responsible for cutaneous innervation of the genital branch of the genitofemoral nerve, and in 8 % of cases, there was shared innervation with the genital branch of the genitofemoral nerve [29] (see Fig. 2.4).

Etiology

Similar to genitofemoral neuralgia, ilioinguinal nerve injury leading to a chronic pain state often occurs from iatrogenic causes postoperatively. The surgeries that put the ilioinguinal nerve at risk are similar to those that can injury the GFN because of the close proximity of the nerves in the groin region. Injury can occur from a cesarean section, appendectomy, inguinal herniorrhaphy, iliac bone harvesting, abdominal hysterectomy, orchiectomy, and even small procedures such as femoral catheter placement [1, 19]. Pregnancy can also lead to ilioinguinal neuralgia from stretching/compression of the nerve. Early data indicate that 7 % of women with pfannenstiel incisions from cesarean sections (and possibly other transverse abdominal incisions) may develop chronic pain due to entrapment of the ilioinguinal or iliohypogastric nerves [16]. One cadaver study suggested that abdominal incisions below the anterior superior iliac spine and about 5 cm superior to the pubic symphysis had that highest likelihood of injuring the ilioinguinal or iliohypogastric nerves. If the transverse incision is too close to the pubic symphysis, the GFN and its femoral branch are at an increased risk of injury [16]. The laparoscopic approach to many surgeries has decreased the incidence of ilioinguinal neuralgia [19]. In hockey players, trauma leading to tearing of the lower external oblique aponeurosis has been known to cause damage to the ilioinguinal nerve [19].

Diagnosis

As with genitofemoral neuralgia, the first step in diagnosis for ilioinguinal neuralgia begins with a thorough history and physical exam, as well as good knowledge of the innervation and anatomy of the groin region. The history should include age, gender, medical comorbidities, social history, recent surgical history and type and approach of surgery (open vs. laparoscopic), history of chronic pain syndromes, history of preoperative pain and any postoperative complications, and lastly a complete pain assessment. A focused physical examination is necessary to confirm or rule out other potential etiologies of pain. On examination, it is important to check sensory dermatomes, motor function, reflexes, and gait. Physical maneuvers can be used to rule in or rule out other pathology such as that involving the lumbar spine, hip/pelvic joints, SI joints, and radiculopathy or other spinal canal or nerve root origins of pain (please see above *Diagnosis* under *Genitofemoral Neuralgia*, e.g., of useful diagnostic physical maneuvers).

Ilioinguinal neuralgia is often diagnosed by a triad of symptoms: burning pain radiating to the suprapubic area, thigh, or labia/scrotum, paresthesias and pain relief with a diagnostic block using local anesthetic [16]. If the pain is eliminated with the block, the source of pain can be appropriately attributed to ilioinguinal neuralgia. If the pain is not eliminated, the ilioinguinal nerve can be ruled out as the source of the pain and further testing is required to eliminate other possible causes of inguinal

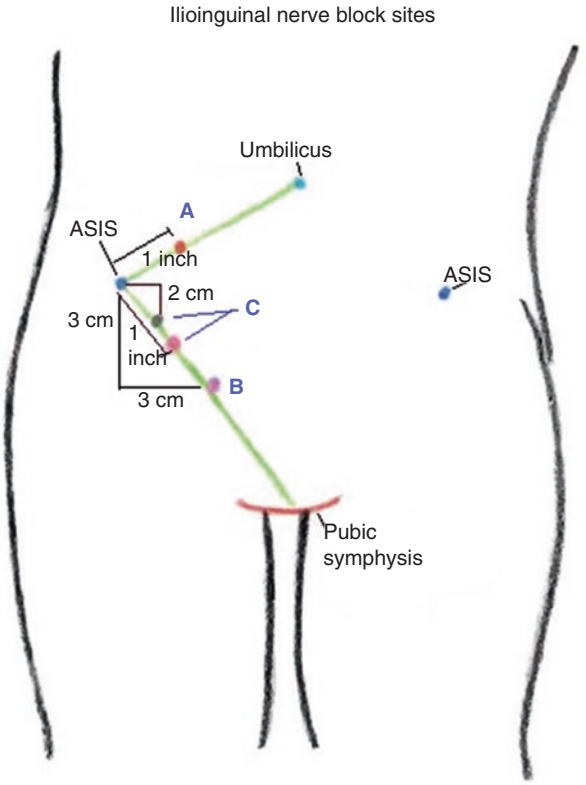

Fig. 2.5 Potential locations to perform an ilioinguinal/iliohypogastric nerve block. Different locations as described in the literature include: (**a**) a point on the line between the ASIS and the umbilicus, 1 inch medial to the ASIS, (**b**). A point on the line between the ASIS and the PS 3 cm medial and inferior to the ASIS, and (**c**). A split technique blocking the ilioinguinal nerve (2 cm medial and inferior to the ASIS on the line between the ASIS and the PS) and iliohypogastric nerve (1 inch inferior medial to the ASIS on the line between the ASIS and the PS) separately. *ASIS* anterior superior iliac spine, *PS* pubic symphysis

pain. The most common approaches to the ilioinguinal nerve block are usually a combination approach to block both ilioinguinal and iliohypogastric nerves [28]. Most approaches use the ASIS as a landmark. An early technique, suggested in 1985, describes drawing a line from the umbilicus to the ASIS, inserting the needle on that line at a point 1 in. medial to the ASIS and infiltrating the oblique muscles in a vertical and fanwise infiltration [28]. Another technique from 1999 describes the insertion point to be at a more inferior location, 3 cm medial and inferior to the ASIS on the line joining the ASIS to the pubic symphysis, with the needle directed cephalo-laterally [28]. A more recent approach splits the ilioinguinal and iliohypogastric blocks, and describes the insertion point for the ilioinguinal block at 2 cm medial and inferior to the ASIS, with the needle directed inferomedially toward the pubic symphysis [28] (Fig. 2.5).

Ultrasound has been a useful innovation for ilioinguinal nerve blocks, allowing a more exact location to insert the local anesthetic. Often, the nerves can be seen between the internal oblique and transversus abdominis fascial layers, and the presence of the local anesthetic after injection is confirmed by the splitting of the muscle

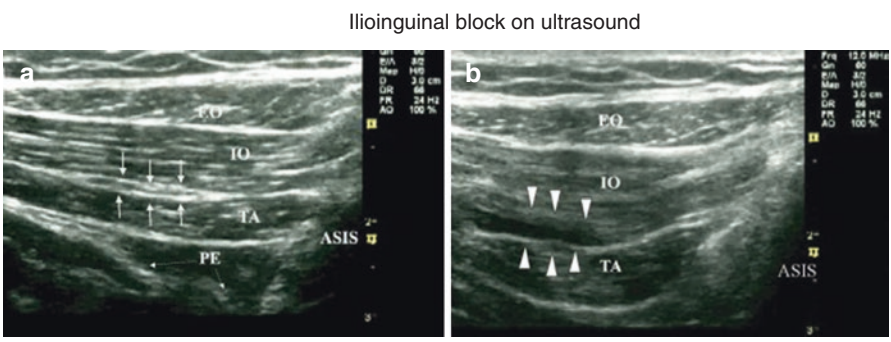

Fig. 2.6 Ultrasound pictures showing the fascia split before and after injection of a local anesthetic. (**a**) Ultrasound picture showing the three layers of abdominal muscle and the ilioinguinal and iliohypogastric nerves in the fascia split (*arrows*) between internal oblique and transversus abdominus muscles. (**b**) Presence of local anesthetic in the fascia split following injection. *EO* external oblique muscle, *IO* internal oblique muscle, *TA* transversus abdominus muscle, *PE* peritoneum, *ASIS* anterior superior iliac spine (Reproduced with permission from Philip Peng Educational Series)

layers. Steroid can be added to the local anesthetic in chronic pain patients as a therapeutic measure to increase the duration of the block (Fig. 2.6).

Treatment

The management for ilioinguinal neuralgia begins with noninvasive methods. A thorough history and physical exam should be conducted. Physical and psychological therapies include massage, myofascial release, and acupuncture. Acupuncture is one of the oldest methods of achieving analgesia; the World Health Organization acknowledges the efficacy of acupuncture as a treatment modality for many types of pain including postoperative pain and some chronic pain conditions. Limited studies are available to describe the efficacy of massage therapy for chronic or neuropathic pain conditions; however, early research offers positive support. Myofascial release is an alternative medicine treatment that is not well supported by evidence to be a sole treatment for pain. It involves reducing pain by muscle relaxation, tissue manipulation, muscle stretching, and increasing blood and lymphatic circulation. More studies are necessary to confirm its efficacy as an adjunct to conventional treatments.

Initial pharmacological treatment modalities include oral analgesics such as NSAIDs, TCAs, gabapentin, pregabalin, opioids, SSRIs, and SNRIs [19]. Nerve blocks can be used as a therapeutic modality, utilizing local anesthetic in combination with a steroid to provide a longer duration of relief. Physical therapy is a treatment modality that can be paired with either cryotherapy or TENS. One prospective randomized control trial in 2008 demonstrated successful control of postoperative

pain following inguinal herniorrhaphy with TENS [11]. Although the study tested acute postoperative pain and not chronic pain from neuralgia, it demonstrates the possible potential for control of chronic pain. Further research with TENS for chronic pain is required. One small study described the successful treatment of chronic ilioinguinal neuralgia using PRF, which differs from the CRF in that it is nondestructive to the tissue. The benefits include less pain at the time of the procedure and less risk of neuritis or neuroma formation. It also has a broader span of applicability for the treatment of chronic pain. Although the exact mechanism is not well understood, there is an interruption of the normal pain impulse transmission. The study demonstrated no pain in four out of five patients for up to 4–9 months post intervention [30]. In 2010, a case series described 15 patients with chronic inguinal pain who had failed conservative therapy and were treated successfully with spinal cord stimulation (SCS), with 75 % reduction in their pain score on the visual analog scale. The mechanism was to interrupt pain transmission to the spinal cord. When pharmacologic treatment, TENS, SCS, blocks, and ablative techniques are ineffective in the long term, surgery is considered. If the chronic pain began after a hernia repair with mesh, neurectomy and mesh excision may provide long-term pain relief [16]. If the etiology is iatrogenic (but not involving mesh), a neurectomy may provide definitive treatment. Neurectomy involves identifying and dissecting the nerve, proximal to the area of trauma, or if possible, the entire length of the nerve. One study found that 17/19 patients with ilioinguinal neuralgia were free of pain and symptoms after resection of the injured area of the nerve [32]. Many other studies support the efficacy of neurectomy for the treatment of ilioinguinal neuralgia [1, 2]. There is no consensus on any specific approach to neurectomy or whether a single neurectomy or triple neurectomy is superior. An international consensus conference in 2008 with experts in the field made recommendations for the prevention and treatment of chronic pain post inguinal hernia surgery. According to their recommendations, medical treatment should be attempted for at least a year after the start of pain (or after the original surgery), and if quality of life continues to be severely impaired, then a triple neurectomy should be considered [2].

Summary

The painful condition of genitofemoral neuralgia can be idiopathic, traumatic, and most commonly iatrogenic following groin or pelvic/abdominal surgery. The symptoms manifest as burning pain and decreased sensation or paresthesias in the anterior, medial thigh, and groin region. Ilioinguinal neuralgia is another painful condition that can be debilitating to the patient. It manifests as paresthesias and pain in the medial thigh region and can also occur postoperatively following lower abdominal/groin surgeries such as inguinal herniorrhaphy. Up to 10 % of patients can potentially develop severe pain following hernia surgery [6, 9].

The diagnosis is often challenging due to overlap of sensory innervation in the groin region. Accurate diagnosis is essential for appropriate management. Diagnosis

is obtained after a thorough history and physical exam, imaging studies, and diagnostic nerve blocks to rule out other possible causes of pain. Once the diagnosis is made, management begins with noninvasive treatment such as physical therapy, massage, and pharmacologic therapy. Nerve blocks can be diagnostic and therapeutic but may only provide temporary pain relief. Longer-lasting nonsurgical options include cryoablation, PRF, radiofrequency ablation, and SCS, all of which display promising evidence of efficacy. If pain is persistent despite aggressive minimally invasive means of treatment, surgical therapy may be considered. There are many different surgical approaches that have been recommended and tested but no consensus exists on the type of surgery or approach at this time. There is strong evidence for triple neurectomy as a definitive treatment option (up to 95 % pain relief), with the side effect of loss of inguinal sensation [6]. Further research may yield better diagnostic and treatment modalities for chronic groin pain.

References

1. Acar F, Ozdemir M, Bayrakli F, Cirak B, Coskun E, Burchiel K. Management of medically intractable genitofemoral and ilioinguinal neuralgia. Turk Neurosurg. 2013;23(6):753–7. doi:10.5137/1019-5149.JTN.7754-12.0.
2. Alfieri S, Amid PK, Campanelli G, Izard G, Kehlet K, Wijsmuller AR, Di Miceli D, Doglietto GB. International guidelines for prevention and management of postoperative chronic pain following inguinal hernia surgery. Hernia. 2011;15:239–49.
3. Alfieri S, Rotondi F, Di Giorgio A, Fumagalli U, Salzano A, Di Miceli D, Ridolfini MP, Sgagari A, Doglietto G. Influence of preservation versus division of ilioinguinal, iliohypogastric, and genital nerves during open mesh herniorrhaphy: prospective multicentric study of chronic pain. Ann Surg. 2006;243:538–53.
4. Amid PK. Causes, prevention and surgical treatment of postherniorrhaphy neuropathic inguinodynia: triple neurectomy with proximal end implantation. Hernia. 2004;8(4):343–9.
5. Amid PK, Chen DC. Surgical treatment of chronic groin and testicular pain after laparoscopic and open pre peritoneal inguinal hernia repair. J Am Coll Surg. 2011;213:531–6.
6. Bonwich JB. Persistent groin pain following hernia repair and post-herniorrhaphy neuralgia. UptoDate; 2013. https://www.uptodate.com. Accessed 14 Sept 2015
7. Byrd D, Mackey S. Pulsed radiofrequency for chronic pain. Curr Pain Headache Rep. 2008;12(1):37–41.
8. Campos NA, Chiles JH, Plunkett AR. Ultrasound-guided cryoablation of genitofemoral nerve for chronic inguinal pain. Pain Physician. 2009;12:997–1000.
9. Cesmebasi A, Yadav A, Gielecki J, Shane Tubbs R, Loukas M. Genitofemoral neuralgia: a review. Clin Anat. 2015;28:128–35.
10. Cohen SP, Foster A. Pulsed radiofrequency as a treatment for groin pain and orchialgia. Urology. 2003;61(3):645.
11. DeSantana JM, Santana-Filho VJ, Guerra DR, Sluka KA, Gurgel RQ, da Silva Jr WM. Hypoalgesic effect of the transcutaneous electrical nerve stimulation following inguinal herniorrhaphy: a randomized, controlled trial. J Pain. 2008;9(7):623–9. doi:10.1016/j.jpain.2008.01.337.
12. Ducic I, Dellon AL. Testicular pain after inguinal hernia repair: an approach to resection of the genital branch of genitofemoral nerve. J Am Coll Surg. 2004;198(2):181–4.
13. Egorova N, Gollub RL, Kong J. Repeated verum but not placebo acupuncture normalizes connectivity in brain regions dysregulated in chronic pain. Neuroimage Clin. 2015;9:430–5. doi:10.1016/j.nicl.2015.09.01.

14. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005;118:289–305.
15. Friedman M, Mikityansky I, Kam A, Libutti SK, Walther MM, Neeman Z, Locklin JK, Wood BJ. Radiofrequency ablation of cancer. Cardiovasc Intervent Radiol. 2008;27(5):427–34.
16. Gray JE. Nerve injury associated with pelvic surgery. Up to Date; 2013. https://www.uptodate.com. Accessed 14 Sept 2015
17. Hakeem A, Shanmugam V. Current trends in the diagnosis and management of post-herniorrhaphy chronic groin pain. World J Gastrointest Surg. 2011;3(6):73–81.
18. Hata J, DeSilva C, Leung D, Betesh N, Luo DZ, Dawodu S, Perret-Karimi D, Sinavsky K, Stokes OJ, English S. Pulsed radiofrequency current in the treatment of pain. Crit Rev Phys Rehabil Med. 2011;23:213–24.
19. Hollis MH, Lemay DE. Nerve entrapment syndromes of the lower extremities. Medscape; 2016. http://emedicine.medscape.com/article/2225774-overview. Accessed 10 Jan 2016.
20. Kastler A, Aubry S, Piccand V, Hadjidekov G, Tiberghien F, Kastler B. Radiofrequency neurolysis versus local nerve infiltration in 42 patients with refractory chronic inguinal neuralgia. Pain Physician. 2012;15:237–44.
21. Kehlet H. Chronic pain after groin hernia repair. Br J Surg. 2008;95:135–6.
22. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618–25.
23. Magee RK. Genitofemoral causalgia: (a new syndrome). Can Med Assoc J. 1942;46(4):326–32.
24. Martin DC. Pulsed radiofrequency application for inguinal herniorrhaphy pain. Pain Physician. 2006;9(2):153–15.
25. Murovic JA, Kim DH, Tiel RL, Kline DG. Surgical management of 10 genitofemoral neuralgias at the Louisiana State University Health Sciences Center. Neurosurg. 2005;56(2):298.
26. Ndiaye A, Diop M, Ndoye JM, Mane L, Nazarian S, Dia A. Emergence and distribution of the ilioinguinal nerve in the inguinal region: applications to the ilioinguinal anesthetic block (about 100 dissections). Surg Radiol Anat. 2010;32(1):55–62.
27. Parris D, Fischbein N, Mackey S, Carroll I. A novel CT-guided transpsoas approach to diagnostic GFN block and ablation. Pain Med. 2010;11:785–9.
28. Peng PWH, Tumber PS. Ultrasound-guided interventional procedures for patients with chronic pelvic pain - a description of techniques and review of literature. Pain Physician. 2008;11:214–24.
29. Rab M, Ebmer AJ, Dellon AL. Anatomic variability of the ilioinguinal and genitofemoral nerve: implications for the treatment of groin pain. Plast Reconstr Surg. 2001;108(6):1618–23.
30. Rozen D, Ahn J. Pulsed radiofrequency for the treatment of ilioinguinal neuralgia after inguinal herniorrhaphy. Mt Sinai J Med. 2006;73(4):716–8.
31. Saldanha DF, Khiantani VL, Carrillo TC, Yap FY, Bui JT, Knuttinen MG, Owens CA, Gaba RC. Current tumor ablation technologies: basic science and device review. Semin Intervent Radiol. 2010;27(3):247–54.
32. Starling JR, Harms BA. Diagnosis and treatment of genitofemoral and ilioinguinal neuralgia. World J Surg. 1989;13(5):586–91.
33. Taghavi R, Tabasi KT, Mogharabian N, Asadpour A, Golchian A, Mohamadi S, Kabiri AA. The effect of acupuncture on relieving pain after inguinal surgeries. Korean J Pain. 2013;26(1):46–50.
34. Terkawi AS, Romdhane K. Ultrasound-guided pulsed radiofrequency ablation of the genital branch of the genitofemoral nerve for treatment of intractable orchialgia. Saudi J Anaesth. 2014;8(2):294–89.
35. Tsao JCI. Effectiveness of massage therapy for chronic, non-malignant pain: a review. Evid Based Complement Alternat Med. 2007;4(2):165–79.

Chapter 3
Myofascial Pelvic Pain

Henry C. Chou, Robert Kelly, and David Huaguang Qu

Chronic Pelvic Pain

Chronic pelvic pain can be a difficult condition to diagnose and manage. It encompasses a diverse group of medical conditions including vulvodynia, prostatitis, cystitis, endometriosis, and dyspareunia among others. Chronic pelvic pain can originate from gynecological, psychological, myofascial, urological, or gastrointestinal causes [1]. It is defined by The American College of Obstetricians and Gynecologists as pain of six or more months in duration that is located in the abdomen, groin, or low back. The prevalence of chronic pelvic pain is approximately up to 15 % in women and 2–10 % in men [2, 3]. In addition, chronic pelvic pain accounts for 40 % of gynecological laparoscopic procedures [4].

Myofascial pelvic pain, or myofascial pain syndrome (MPS) of the pelvis, refers to the pain originating from the pelvic floor musculatures and the associated connecting fascia and connective tissues. This pain syndrome often arises from preexisting urological, gynecological, or colorectal medical conditions or it can exist alone with no concomitant pathologies. Musculoskeletal/myofascial causes of pelvic pain is often overlooked because it is hard to diagnose. There is lack of highly sensitive and specific noninvasive diagnostic modalities, and the etiology of the pelvic floor muscle pain is not fully understood with several different existing theories. Also, the physical exam of pelvic floor muscle requires entry into the vaginal vault or rectum, which can be uncomfortable for patients. Furthermore, many providers are simply not adequately trained in this technique resulting in low numbers

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of proper digital palpation of the pelvic floor muscle during gynecological, urological, and colorectal examinations [5]. In this chapter, the overview of MPS, anatomy of the pelvic floor, the epidemiology/etiology, diagnosis, and treatment of myofascial pelvic pain will be discussed.

Myofascial Pain Syndrome

MPS is defined as the musculoskeletal pain characterized by sensory, motor, and autonomic dysfunction due to myofascial trigger points (MTrPs) in the muscle, fascia, or tendinous insertions. A trigger point (TrP) is a tiny discrete area or nodule approximately 5–10 mm in diameter that is hyperirritable/tender in a taut band of skeletal muscle. Reproducible pain upon palpation is required for the clinical diagnosis of MPS [6].

Two types of TrPs exist [6] as follows:

1. Active TrP: It is a spot or spots in the skeletal muscle that is spontaneously painful and tender without physical stimulation. It causes the clinical pain complaint. Palpation, compression, stretching, or mobilization of the active TrP in the muscle worsens the pain, and it causes local motor and often autonomic symptoms of the affected muscle. The active TrP can also produce a referred pain to a remote area in a defined pattern resulting in the activation of TrPs in the remote site.
2. Latent TrP: It has all the features of the active TrP when it becomes "activated," but it is clinically quiet without spontaneous pain. Similar to active TrP, a latent TrP always have a taut band and it restrict the mobility of the affected skeletal muscle. Latent TrP only becomes painful when stimulated and start behaving like an active TrP. Individuals with latent TrP are asymptomatic in terms of pain complaint.

In contrast with the TrPs are the tender points, which are used for the diagnosis of fibromyalgia. TrPs produce a specific referred pain pattern to a distant site while tender points only produce a local response in their immediate surroundings. Many features of MPS and fibromyalgia overlap but they are two separate entities.

Myofascial pain is very common; however, in terms of the MPS diagnosis, the exact prevalence has not been obtained. The more broad diagnosis of chronic musculoskeletal pain is estimated to affect between 10 and 20 % of the population. One study reported about 85 % of patients seeking care at pain clinic to have MPS, but there has not been a study looking at the myofascial pain of the pelvic floor muscles specifically [7]. Overall, MPS is equally distributed between men and women, but for pelvic/urogenital myofascial pain, it is more common in women than in men. Difference in the incidence of MPS among races has not been reported in literature. However, the likelihood of developing active TrP increases with age and with a sedentary lifestyle [7].

There are several theories that have been proposed to correctly identify the etiology/pathophysiology of the MPS. A modern understanding of myofascial pain can

be derived from the work of Dr. Janet Travell and Dr. David Simons. Their book, Myofascial Pain and Dysfunction: The Trigger Point Manual, is instrumental in defining the diagnosis and treatment of MPS. Simons postulated the integrated TrP hypothesis, which is one of the most accepted theories for myofascial pain, and it served as the groundwork for researchers after him.

Integrated TrP Hypothesis

Before discussing the integrated TrP hypothesis, the basic mechanism of muscle contraction and relaxation is reviewed: an action potential travels down a nerve axon causing acetylcholine (ACh) release into the neuromuscular junction [6]. ACh travels across the junction and binds to ACh receptors initiating an end-plate potential, which propagates along the sarcoplasmic reticulum down the T-tubule and triggers a downstream release of calcium. Calcium binds with troponin allowing actin–myosin crossbridge formation and subsequent muscle contraction. In order for the muscle to relax, adenosine triphosphate (ATP) is required for the release of actin–myosin crossbridge and the detachment of calcium from the troponin. In addition, ATP is required to actively pump calcium back into the sarcoplasmic reticulum. As hypothesized by Dr. David Simons, there is an abnormally excessive release of ACh resulting in increase of end-plate potential and subsequently causing overall increased muscle contraction/tension, which manifest as the taut band found in a MTrP. The taut band causes a state of energy crisis via reduced blood flow resulting in local hypoxia, increased metabolic demand, and ultimately overall decreased level of ATP. During this state of metabolic imbalance/energy crisis, noxious substances are released such as substance P, bradykinin, calcitonin gene-related peptide (CGRP), prostaglandins, and inflammatory cytokines. These noxious chemicals may account for the sensitization of the peripheral nociceptors and contribute to the pain associated with the active TrP [8–10].

Cinderella Hypothesis

Around the same time the integrated TrP hypothesis came out, Hagg et al. postulated the Cinderella hypothesis. Many of the tenets overlap with integrated TrP hypothesis. The Cinderella hypothesis theorized the state of sustained, low level, and repetitive muscle contractions results in hypoxia, ischemia, and reduced ATP production and is responsible for reduced pH, increased acidity, calcium accumulation, and ultimately sarcomere contraction. Constant muscle contraction leads to the release of several sensitizing substances causing peripheral sensitization similar to the integrated TrP hypothesis [10].

Expansion of the Integrated TrP Hypothesis

Many researchers including Gerwin and his colleagues further expand on Simons' integrated TrP hypothesis. The inciting event is that the muscles are being stressed beyond normally tolerated level causing muscle injury and capillary constriction. Muscle injury triggers the release of noxious chemicals that activate the nociceptors causing pain, which then further cause the sympathetic activation leading to more capillary constriction and decreased blood perfusion. The pH becomes acidic, inhibiting acetylcholinesterase (AChE) causing more ACh reaching the motor end plate. One of the noxious chemicals released from the injured muscle includes CGRP, and CGRP causes further inhibition of AChE and facilitate more ACh release and upregulate the ACh receptors at the motor end plate. The end result is the altered activity at the motor end plate triggering more end-plate potential, muscle contraction, and increased muscle activity forming the taut band of the TrP [11].

Central Sensitization

The theories discussed above involve the sensitization of the peripheral nociceptors. Researchers now have shown that there is modification of the central nervous system and this further complicates the muscle pain associated with MTrP. With the nociceptors activation/peripheral sensitization, the signal also travels via the afferent fiber to the dorsal root ganglion and triggers the release of substance P and CGRP from the dorsal root ganglion to the peripheral tissues. The release of these chemicals into the periphery causes further noxious chemical release leading to more local hyperalgesia and exacerbates local tissue tenderness. Overtime, the continuous and repetitive activation of these primary afferent activities results in the modulation of the dorsal root ganglion and dorsal horn neurons, a process known as central sensitization. The overall effect of central sensitization is increased pain and making the active TrP even more painful and tender [8–10].

Etiology of Myofascial Pelvic Pain

As explained earlier, MTrP is the underlying cause of MPS. In the pelvis, there is an extensive network of muscles, fascia, and connective tissue where TrPs can be found. These active and/or latent TrPs of the pelvic muscles, or any muscle in the body, can develop due to mechanical, physical, organ system, and psychological stressors. Examples of mechanical stressors include improper posture, leg length discrepancy, overuse of muscles, prolonged mobility/immobility, and

dysfunctional gait among others. Events such as pelvic surgeries, colonoscopy, vagina ultrasound, pelvic/rectal exam, and childbirth are examples of physical stressor that can produce localized trauma and ultimately the development of TrPs. Emotional or psychological stressors such as prior history of sexual abuse, depression, lack of sleep, or general stress/anxiety in life can often cause dysfunction to the pelvic muscles resulting in TrPs and myofascial pain in the area. Lastly, pathologies in the pelvic region such as prostatitis, endometriosis, chronic cystitis, colitis, or hemorrhoids can cause TrPs to the pelvic floor muscles via a viscerosomatic reflex [2, 6, 12].

In addition, researchers have also looked into the role of nutritional deficiencies of water-soluble vitamins, folic acid, vitamin C, calcium, iron, and potassium in the development of MTrPs. Vitamin C in particular is an important cofactor for norepinephrine and serotonin production, and these chemicals are involved with the modulation of pain transmission. Vitamin C is also involved in collagen synthesis, which is important for muscle, ligament, bone, and joint health [13, 14].

Myofascial pelvic pain or pelvic MPS can be explained by three general tenets with the understanding of the pathophysiology of the MTrP discussed earlier: (1) viscerosomatic reflex, (2) somatovisceral reflex, and (3) central sensitization.

1. Viscerosomatic reflex: a visceral organ pathology (i.e., chronic cholecystitis) transmits afferent neural impulse to the dorsal horn of the spinal cord where the signal triggers a reflexive efferent sympathetic and motor activation result in changes of the somatic tissues of the muscle, skin, and surrounding blood vessels [2, 15].
2. Somatovisceral reflex: muscles, ligaments, and fascia in the pelvis lie closely to the pelvic visceral organs. These connective tissues are important in providing support and sphincter control. However, local hypertonicity or tension of these pelvic floor muscles from repeated stress can cause direct compression of the visceral organ. Or in similar fashion to the viscerosomatic reflex, somatic pain from local hypertonicity and TrP produces an afferent signal to the dorsal horn of the spinal cord and triggers an efferent reflexive pain pattern perceived by the peripheral visceral organs [2, 15].
3. Central sensitization (Please see section above "Central Sensitization").

Anatomy of the Pelvic Floor

Pelvic floor muscles function to support the pelvic organs, assist with urinary and bowel continence, stabilize the connecting joints, and act as venous and lymphatic pump for the pelvis. In addition, just like other muscles, pelvic floor muscles are susceptible to MTrP. Here outlines the anatomy of *the* pelvic floor muscles and their functions.

Levator Ani Muscles

The paired levator ani muscles come together and form the pelvic diaphragm. Levator ani consists of two separate muscles: pubococcygeus and iliococcygeus. Pubococcygeus lies more anterior or lower in the pelvis. The paired anterior fibers of the pubococcygeus that meet at the perineal body are called levator prostate for the male and pubovaginalis for the female. The posterior fibers of the pubococcygeus are called puborectalis, and the paired fibers together form a sling around the rectum. The posterior part of the levator ani, the iliococcygeus, attaches the levator ani above the spine of ischium. Iliococcygeus attaches to the anococcygeal body and the coccyx [4, 5, 16].

Levator ani is innervated by the pudendal nerve (S3, S4) and the sacral S3, S4, and S5 nerve roots. The functions of levator ani are to elevate the pelvic floor and help resist intra-abdominal pressure increase. In male, the levator prostate applies upward pressure on the prostate, and in female the pubovaginalis serves as the sphincter for vagina and constricts. Posteriorly, the puborectalis helps constrict the anus [6, 16–18].

Sphincter Ani Muscles

Sphincter ani has two parts: internus and externus, and together they are four rings of muscle. Sphincter ani internus muscle fibers, the innermost ring, are autonomically innervated and they function as involuntary control of the anal wall. The other three rings, which are deep, superficial, and subcutaneous, are formed by the sphincter ani externus. Innervation of the sphincter ani externus includes the sacral nerve S4, and the inferior rectal branch of the pudendal nerve. Together with the puborectalis of the levator ani, sphincter ani externus allows for the voluntary control of the anal sphincter [6, 16–18].

Coccygeus Muscle

The coccygeus, locates in the posterior perineum, lies superiorly to the iliococcygeus of the levator ani muscle. Laterally, it inserts into the ischial spine and sacrospinous ligament. Medially, it inserts into the margins of the coccyx. Coccygeus muscle is innervated by the pudendal nerve and the S4 and S5 nerve roots. The function of this muscle is to pull coccyx forward, resist intra-abdominal pressure increase, and to stabilize the sacroiliac joint [6, 16–18].

Obturator Internus Muscle

Obturator internus originates from inside the pelvis and exits the pelvic cavity via the lesser sciatic foramen and attaches to the greater trochanter of the femur. The portion inside the pelvis covers greater part of the obturator foramen, and it originates from the ischiopubic ramus. It is innervated by the nerve to the obturator internus (L5, S1, S2). The muscle functions to laterally rotate the femur with hip in extension, and abduct the femur with hip flexion [6, 16–18].

Bulbospongiosus and Ischiocavernosus Muscles

The bulbospongiosus is one of the superficial muscles of the perineum. In males, it covers the bulb of the pens, and in females it covers the vestibular bulb. In both sexes, it is innervated by the branch of the pudendal nerve. Functionally for males, it contributes to erection, orgasm, and ejaculation. In females, it contributes to clitoral erection, orgasm, and closes the vagina. This muscle also serves to empty the urethra, after the bladder has expelled its contents [6, 16–18].

Ischiocavernosus is located in the anterior of the perineum and courses laterally to the bulbospongiosus. In males, it terminates in the body of the penis. In females, it forms the lateral side of the triangle formed by bulbospongiosus, and transversus perinei. The ischiocavernosus is also innervated by branches of the pudendal nerve. It functions to flex the anus, erect the penis for males, and tense the vagina during orgasm [6, 16–18].

Anatomic to Clinical Correlation

Levator ani muscles:

- Most widely recognized source of referral pain in the perineal region [6, 16–18].
- Pain in the rectum, sacrum, perirectal area, vagina, penis, or low back.
- Makes sitting uncomfortable.
- Anterior portion: affecting levator prostate, responsible for pain in the penis, fullness, and pressure in the prostate, pain to the vagina, pain referred to the urethra and the bladder.
- Inferior portion: referred pain to the perineum and the penis.
- Middle portion: referred pain to the later wall, perineum, and anal sphincter.
- Posterior portion: sensation of fullness in rectum, pain with bowel movement.

Sphincter ani muscles:

- Pain in the anus, anal sphincter, and painful bowel movement.

Coccygeus muscles:

- Pain referred to coccyx, buttocks, hips, or low back.
- Common source of low back pain in pregnant women, or those women with low back pain seen for infertility.

Obturator internus muscle:

- Pain referred to the hip, and occasionally down the back of the thigh.
- Sensation of fullness in the rectum.
- Vulvar and urethral pain in women.

Bulbospongiosus and ischiocavernosus:

- For women, bulbospongiosus TrPs cause dyspareunia and pain in the perineum. For men, they may cause scrotal pain, discomfort sitting, painful erections, and potentially impotence.
- Ischiocavernosus causes referred pain to the perineum as well, but less likely to interfere with sexual intercourse.

Other sources of myofascial referred pain to the pelvis:

- Although not extensively reviewed in this chapter, MTrPs outside the pelvic cavity can also cause referred pain into the pelvic area.
- According to Travell and Simons', the adductor magnus is the most likely to refer pain into the pelvis.
- Quadratus lumborum muscle: inguinal, lower abdominal, and low back pain.
- Iliopsoas muscle: low back and inguinal pain.
- Rectus abdominis muscle: prostate, penis, and lower abdominal pain.
- Abdominal oblique muscle: testicular, inguinal pain.
- Pyramidalis muscle: bladder, urethra, pubic bone, and buttock pain.
- Gluteus muscles: testicular, coccyx, sacrum, buttock, and pelvic girdle pain.

Diagnosis

What makes myofascial pain in the pelvis more difficult compared to other muscles such as the shoulder girdle is that the pelvic floor muscles and fascia lie closely with organs, and it may be hard for the patient and clinician to distinguish the pain from muscles or organs. TrPs in the pelvic muscles often go undetected and the discomfort/pain they produce often leads to misdiagnosis because they often are thought to be stemming from the pelvic organs. One of the main reasons for misdiagnosis is that patients usually seek out their primary-care physicians, gastroenterologist, obstetrician, gynecologist, or urologist. These physicians often have limited training

in musculoskeletal disorder or MTrPs. As a result, the patients with chronic pelvic pain usually end up with a diagnosis according to each practitioner's specialty guideline and scope of practice, and the myofascial pain source may be overlooked. However, the detection of pelvic organ pathology should remain a priority and disease processes need to be excluded first. When this workup is inconclusive, a myofascial source of pain must be considered. This is precisely the reason proper diagnosis with a good history and physical exam is important to avoid unnecessary studies.

History

Patients usually present with chronic vague regional pain. Characteristic of the pain including location, quality, intensity, duration, aggravating factors, alleviating factors, associated factors, and evolution of the pain over time should be investigated. Patients with MPS usually present with deep tense muscle pain, well discriminated, varying in intensity, sudden or gradual in onset, with usual increment with movement. With TrPs, the complaint is usually stiffness, fatigue, and muscle weakness [2, 5, 16].

The patient's age, hobbies, sports, stress, occupation, job satisfaction, lifestyle, sleep pattern, family history of musculoskeletal pain, past surgical history especially involving the abdomen and pelvis, and sexual history including prior abuse should be investigated. These histories may reveal precipitating factors such as repetitive movements, prolonged abnormal posture, or psychosocial stressors. It is common that patients may initially complain with urinary symptoms such as urinary urgency, urinary frequency, pain with urination, pain with defecation, low back pain, and finally sexual dysfunctions [5, 16].

Physical Examination

The focus of the physical exam should be first on gait, biomechanical discrepancy, sitting and standing postural imbalance, pelvic symmetry/asymmetry, active and passive range of motion of low back and proximal lower extremities, and acquired or congenital disorders such as scoliosis and leg length discrepancies. In addition, examination of surgical scars and their immediate surrounding is important if scars are present [5, 16].

Palpation of the pelvic floor muscle is perhaps the most important aspect of the physical exam for patients with chronic pelvic pain to assess for MTrPs. Pelvic floor muscles can be palpated externally and internally. It is usually recommended to begin the examination externally due to anxiety and apprehension to the more invasive intravaginal or intrarectal internal palpation. Starting externally also helps patient prepare for the internal exam. If the patients already

have exquisite tenderness during the external palpation of the pelvic floor muscles, or if patients experience severe anxiety, the internal palpation can be avoided initially [5, 6, 16].

Before palpation, observe the contraction and relaxation of the pelvic floor muscles. With MTrPs, these muscles may have absent or uncoordinated relaxation, and the actual muscle contraction itself may be painful or difficult.

During palpation, it is important that the examiner identify whether the tender points produce a referred pain pattern or local tenderness. Palpation externally involves "around-the-clock" techniques: With the landmark of 12 o'clock – pubic symphysis, clitoris, and urethra; 3 and 9 o'clock – ischial tuberosity; and 6 o'clock – coccyx, palpation with one digit of a gloved hand should begin at the 12 o'clock position. The 1 and 11 o'clock positions just lateral to pubic symphysis are where the left and right bulbocavernosus muscles are located. Under the 3 and 9 o'clock positions of ischial tuberosity lies the superficial transverse perineal muscles. The 4 and 8 o'clock positions are associated with anterior levator ani muscles, and lastly the 5 and 7 o'clock positions are associated with posterior levator ani muscles. Examination should focus on locating the "taut band," referred pain or patient's presenting symptoms. In addition, hyperirritability, immobility, tenderness, edema, tension, and muscle contracture can be palpated [5, 6, 16].

The internal palpation for women requires entry into the vaginal canal, and it can be uncomfortable for the patient. The examination may be better done at subsequent visits after the patient gains comfort and trust with the examiner. The key of the internal exam is keeping the patient relaxed and calm. It is best to proceed slowly and with lubrication. The landmark used to identify the specific pelvic floor muscles is the depth of the finger for the examination (index or middle finger). Using the hymen as starting point, the first knuckle of the finger corresponds to the superficial layer consisting of bulbocavernosus, ischiocavernosus, superficial transverse perineal, and external anal sphincter muscles. The middle knuckle is associated with the second layer including urethra muscles and deep perineal muscles. The deepest layer is approximately the length of the finger which consist of levator ani, coccygeus, and obturator internus muscles. Around-the-clock approach is used for the internal palpation as well, and the examiner feels for tender or TrPs. The "jump sign" can be a typical finding as well [5, 6, 16].

Treatments

First, the focus of the treatment should target the underlying cause of pelvic pain stemming from psychosocial stressors/posttraumatic stress and pelvic organs whether it is endometriosis, chronic prostatitis, or others. However, treating myofascial pelvic pain at the same time as other pelvic organs or psychosocial stressors can be beneficial and provide relief sooner. Aside from organic causes, it is important to

diagnose and treat the underlying biomechanical pathologies such as abnormal posture, incorrect muscle activities, and anatomical defects. Otherwise, the treatment of MTrP will not yield good long-term results.

Most commonly prescribed treatments for myofascial pelvic pain are designed to address pain, range of motion of the targeting muscle, fascia, and joints. Comparing nonsurgical treatment for other pain conditions, the mainstay of the myofascial pelvic pain is relatively the same and includes a combination of (1) lifestyle modification, (2) modalities/complementary medicine, (3) oral medication, and (4) interventional therapy. Modalities, medications, and interventional therapy will be discussed here.

Physical Therapy Modalities

Most of the physical therapy modalities involve the transfer of heat/energy into myofascial tissue resulting in the relaxation of the tissues. Heating pads, ultrasound, iontophoresis, phonophoresis, electrical stimulation, and laser therapy all have been used for the treatment of myofascial pain. Ultrasound appears to be beneficial for short-term pain relief based on the current literature [2, 5, 6, 9].

Manual therapies include myofascial release, deep-pressure massage, osteopathic manipulation, chiropractic treatments, cool spray and stretch, augmented stretching, post-isometric relaxation, biofeedback with stretching and relaxation, deep digital pressure for ischemic compression, and acupressure [2, 5, 6, 9].

The myofascial release technique consists of applying a gentle and gradually increasing pressure until myofascial tissue resistance is met with the palpating fingers. The pressure is maintained until the clinician notices a reduction in tension with the palpating finger. Then, the clinician increases the pressure on the fingers until the next resistive tension is met and maintains this pressure on the finger until that tension is released [5, 6].

Other Modalities

Acupuncture, which achieves analgesic effect through increasing endogenous endorphin levels, and herbal remedies such as lavender, rosemary, passionflower, and lemon balm all have been found helpful in treating myofascial pain [19, 20].

Medications

There is some evidence that supports the short-term use of benzodiazepines in combination with ibuprofen and amitriptyline. There is also evidence to suggest topical agent such as menthol, diclofenac patches, and methyl salicylate may be beneficial.

Other adjunctive pain medications that may provide relief are muscle relaxers: cyclobenzaprine and tizanidine; antidepressants: nortriptyline, duloxetine, and venlafaxine; anticonvulsants: gabapentin and pregabalin. There is insufficient evidence to support the use of opioid analgesics for myofascial pain [20].

Interventional Therapy

TrP injection and dry needling are the main interventional treatment of MTrP. Dry needling is minimally invasive, inexpensive, and easy to learn and has low risk. Dry needling for TrP release has become increasingly popular, as a port of physical therapy treatment. Sometimes, dry needling is combined with electrical stimulation via the inserted needle to treat MTrP. TrP injection involves infiltration of the MTrP with anesthetic, most commonly lidocaine. Lidocaine helps with reducing the intensity and duration of postinjection soreness. Studies have shown lidocaine is faster, more effective, and causes less discomfort than dry needling alone. However, there are insufficient data to suggest whether TrP injection with anesthetics is superior to dry needling alone. The best response to dry needling or TrP injection is when there is a local twitch response after the needle is inserted [6, 20].

Corticosteroid is sometimes used in combination with local anesthetic for TrP injection; the theory is to reduce inflammation, but repeated use of steroid can cause muscle necrosis. In addition, there is no evidence that shows corticosteroid combined with local anesthetics for TrP injection improves clinical outcome compared to local anesthetics alone. When there is a refractory TrP resulting in severe muscle spasm/contracture, botulinum toxin can be considered in TrP injection [6, 9, 20].

Complications of TrP injection or dry needling include pneumothorax, infection, and abscess. Relative contraindications for TrP injection include bleeding disorders, anticoagulation, local infection, and acute muscle trauma. TrP injections and/or dry needling may provide faster muscle tension release compared to oral medication or physical therapy [6, 9, 20].

Conclusion

Overall, the management of myofascial pelvic pain should involve, but not be limited to, the following steps [21]:

- Modifying activities or avoiding activities that worsen the pain, such as sit-ups, wearing tight fitting clothes, and Kegel exercises.
- Proper posture and evaluating ergonomics at work and in the car.
- Diagnosing and managing anatomical abnormalities or scarring from previous surgeries.
- Diagnosing and treating underlying pathologies or disease process such as prostatitis, chronic urethritis/cystitis, endometriosis, or psychiatric illness.

- Treatment of the extra-abdominal and extra-pelvic TrPs.
- Treatment of the abdominal and/or pelvic TrPs using a combination of manual techniques such as myofascial release, postisometric relaxation, and physical therapy modalities such as ultrasound, heat, as well as TrP injections and/or dry needling.
- Home exercise program with stretching, relaxation technique of the pelvic floor muscles.

References

1. Reiter RC, Gambone JC. Demographic and historic variables in women with idiopathic chronic pelvic pain. Obstet Gynecol. 1990;75:428–32.
2. Mathis SD, Kuppermann M, Liberman RF, et al. Chronic pelvic pain: prevalence health related quality of life, and economic correlates. Obstet Gynecol. 1996;87(3):321–7.
3. Krieger JN, Riley DE, Cheah PY, et al. Epidemiology of prostatitis: new evidence for a worldwide problem. World J Urol. 2003;21:70–4.
4. Carter JE. A systemic history for the patient with chronic pelvic pain. JSLS. 1999;3:245–52.
5. Pastore EA, Katzman WB. Recognizing myofascial pelvic pain in the female patients with chronic pelvic pain. J Obstet Gynecol Neonatal Nurs. 2012;41(5):680–91.
6. Somons DG, Travell JG. Travell & Simon's myofascial pain and dysfunction: the trigger point manual volume 1 &2. 2nd ed. Baltimore: Williams & Wilkins; 1999.
7. Skootsky SA, Jaiger B, Oye RK. Prevalence of myofascial pain in general internal medicine practice. West J Med. 1989;151:157–60.
8. Gerwin RD. Classification, epidemiology, and natural history of myofascial pain syndrome. Curr Pain Headache Rep. 2001;5:412–20.
9. Shah JP, Thaker N, Heimur J, et al. Myofascial trigger points then and now: a historic and scientific perspective. PM R. 2015;7:746–61.
10. Bron C, Dommerholt JD. Etiology of myofascial trigger points. Curr Pain Headache Rep. 2012;16(5):439–44.
11. Gerwin RD, Dommerholt JD, Sha JP. An expansion of Simon's integrated hypothesis of trigger point formation. Curr Pain Headache Rep. 2004;8:468–79.
12. Spitznagle TM, Robinson CM. Myofascial pelvic pain. Obstet Gynecol Clin North Am. 2014;41:409–32.
13. Dickerson JW. Vitamin requirements in different clinical conditions. Bibl Nutr Dieta. 1985;35:44–52. Review.
14. Schneider HA, Anderson CE, Coursin DB. Nutritional support of medical practice. 2nd ed. Philadelphia: Harper and Row; 1983.
15. Giambernardino MA, Bigontina P, De Mortegiani C, Vecchiet L. Effects of extracorporeal shock-wave lithotripsy on referred hyperalgesia from renal/urethral calculosis. Pain. 1994;56:77–83.
16. Fitzgerald MP, Kotarinos R. Rehabilitation of the short pelvic floor. I: background and patient evaluation. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14:269–75.
17. Anderson RU, Wise D, Sawyer T, Chan CA. Integration of myofascial trigger point release and paradoxical relaxation training treatment of chronic pelvic pain in men. J Urol. 2005;174(1):155–60.
18. Anderson RU, Wise D, Sawyer T, Chan C. Sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: improvement after trigger point release and paradoxical relaxation training. J Urol. 2006;176(4):1534–9.
19. Chen RC, Nickel JC. Acupuncture for chronic prostatitis/chronic pelvic pain syndrome. Curr Urol Rep. 2004;5(4):305–8.

20. Annaswamy TM, De Luigi AK, O'Neill BK, et al. Emerging concepts in the treatment of myofascial pain: a review of medications, modalities, and needle-based interventions. PM R. 2001;3(10):940–61.
21. Fitzgerald MP, Kotarinos R. Rehabilitation of the short pelvic floor. II: treatment of the patient with the short pelvic floor. M.P. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14:269–75.

Chapter 4
Sacroiliac Joint Complex Pain

Hieu Hoang

Introduction

The sacroiliac joint (SIJ) complex pain is included in the broad differential diagnosis of urogenital pain, pelvic pain, and low back pain (LBP). It can arise from any of the structures of the SIJ region. In other words, SIJC pain implies a collection of various pains instead of a single separate entity. Even though it has been extensively studied, the unique structure and function and complex innervation of the SIJ grant its diagnosis to be challenging. As a result, the long-term success rates of its treatment are neither uniform nor universal.

Structure, Function, Age Changes, and Innervation

The SIJ is the largest axial joint in the body (see Fig. 4.1). There is great variability in size, shape, and surface contour in adult SIJC [1, 2]. In general, the joint is an auricular-shaped, diarthrodial joint. The iliac and sacral articular surfaces are covered with hyaline and fibrocartilage, respectively, and their corrugations serve as locking mechanism [3, 4]. It is thought that the sacral cartilage is designed for transmitting forces, whereas the iliac cartilage is designed to absorb them [5]. The joint is further interlocked by an intricate network of thick ligaments including the interosseous ligament, posterior ligament, anterior ligament, sacrospinous, and sacrotuberous ligaments [6] (see Fig. 4.1). There is a fibrous ventral capsule containing synovial fluid [7], whereas the dorsal capsule is rudimentary or absent [1]. An array of muscles including the gluteus maximus, gluteus medius, biceps femoris, piriformis, latissimus dorsi, and the erector spinae helps stabilize the joint [8].

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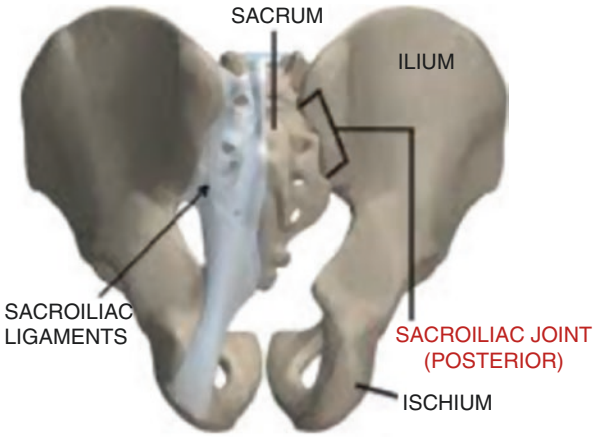

Fig. 4.1 Posterior view of the sacroiliac joint and its associated ligaments

Although the structure of the SIJ is well defined, its exact role has been contentious from being considered of minimal functional significance (due to its limited movement) to being of important primary movements (that can be assessed clinically like any other large joints in the body). Both extreme views prove to be problematic [9]. According to one study, the SIJ ranges of movements are limited to translational and rotational motions along six degrees of freedom [6]. In a more recent in vivo analysis, even smaller degrees of movements in all planes (mean rotation of 2.5°, mean translation of 0.7 mm) exist among symptomatic and nonsymptomatic joints [10]. In essence, SIJ is a stress-relieving joint with limited motion. The joint complex helps buffer the torsional stress to prevent the sacrum and pelvic ring to fracture and transmit the longitudinal stress between the vertebral column and the lower limbs during movements [9].

Developmentally, the SIJ begins to appear during the second month of fetal development and a synovial membrane manifests by 37 weeks [3]. During the first 10 years of life, the joint grows in size but its surfaces remain flat [3]. During the second decade, the joint surfaces start to become irregular with a depression along the articular surface of the sacrum and a reciprocal ridge along the ilium. Degenerative changes in the SIJ start in puberty and continue throughout life. They accelerate during the third and fourth decades of life and are manifested by increasing surface irregularities, osteophyte formation, eroded cartilage, and accumulation of fibrous plaques. The iliac surfaces tend to age faster than the sacral side. By the sixth decade, sinuous corrugations are well established, the capsule becomes collagenous and the joint mobility becomes further restricted [3]. By the eighth decade, fibrous ankylosis and the thinning of the articular cartilage with less than 1 mm on the sacrum and 0.5 mm on the ilium are inevitable [3].

Despite increasing literature on the innervation of the SIJ, the subject continues to draw great debate. It is still undecided to which extent the anterior and posterior joints are innervated and by which neural segments. Studies were conducted in the late nineteenth and early twentieth centuries to assert that the joint was innervated

anteriorly by branches of the lumbosacral trunk, the superior gluteal, and obturator nerves, and posteriorly by branches of the S1 and S2 dorsal rami [11, 12]. Yet modern studies provide conflicting conclusions. A German study reported a posterior innervation exclusively from the S1 and S2 dorsal rami but denied an anterior innervation from the sacral plexus or the obturator nerve [13]. However, a Japanese study reported a posterior innervation from the L5 and sacral dorsal rami and an anterior innervation from the L5 and S2 ventral rami [14]. Overall, the posterior joint is well understood and more clinically relevant for interventional pain specialists; its innervation appears to arise mainly from the dorsal rami of S1–3, with contributions from L5 (or L4 in case of sacralization of L5) and S4 in many individuals [15, 16]. Both intra-articular (IA) and extra-articular (EA) structures can be sources of pain. An electrophysiological study in cats identified nociceptive receptors in both the joint capsule and the adjacent muscles, with most residing within the capsule [17]. Immunohistochemical studies in human cadavers have demonstrated calcitonin-gene-related peptide and substance P immunoreactive nociceptors in both capsular and interosseous ligaments [18]. Clinical studies in asymptomatic volunteers and pain patients prove that pain can be reproduced with both capsular distension and ligamentous provocation [19–23].

Epidemiology

The SIJ was first described as a potential pain source in 1905 [24]. However, it was not precisely defined until 1994, when Fortin et al. demonstrated the pain syndrome in asymptomatic volunteers by distending the SIJ with a contrast medium and diagnosed by analgesic responses to image-guided IA local anesthetic injections [25, 26]. The lack of standardization in methodology and patient population led to a wide range of prevalence rates. Furthermore, the data on the prevalence of SIJC pain have been derived mostly from patients with nonspecific LBP.

In seven prevalence studies using concordant pain relief with lidocaine and bupivacaine as the diagnostic criterion, the prevalence rates for SIJ pain varied between 10 and 45 % with the false-positive rates ranging between 0 and 43 % [27–33]. In an early study in patients with LBP below L5–S1 ($n=43$), Schwartzer et al. found the prevalence rate of 30 % (CI: 16–44 %) based solely on the analgesic response ($\geq$75 %) to a single lidocaine block, 21 % based on pain relief and a ventral capsular tear on computed tomography, 16 % based on a combination of analgesic response, concordant pain provocation, and imaging findings [27]. In another study in patients with unilateral LBP ($n=54$) who failed epidural steroid and facet injections, Maigne et al. reported an 18.5 % prevalence rate using an analgesic response to two different local anesthetics [29]. Manchikanti et al. reported a low prevalence rate of 10 % in 20 pts who underwent double confirmatory blocks [30]. Laslett et al. reported a 26 % prevalence rate in 48 patients with buttock pain [31]. In a retrospective review of 158 patients with LBP and/or leg pain, Irwin et al. calculated a similar prevalence rate of 26.6 % [29]. Both van de Wurff et al. and Liliang et al. reported high prevalence rates

of 45 and 40 %, respectively [32, 33]. All these studies relied solely on IA injections as the diagnostic criterion; as a result, they likely exclude patients with EA pathology. In summary, SIJ complex (SIJC) pain seems to have a bimodal distribution, with higher rates in younger athletes and the elderly, and it appears fairly common in patients with chronic axial LBP below L5 [34, 35].

Etiology

The causes of SIJC pain are numerous. Essentially, the pain is a result of a combination of axial loading and abrupt rotation [36]. Immunohistological studies have indicated nociceptors throughout the joint capsules, ligaments, and subchondral bone, implying that these structures can be potential sources of pain [37, 38]. Furthermore, clinical studies have demonstrated pain provocation in asymptomatic volunteers using both capsular distension and ligamentous probing [25, 39]. Because both IA and periarticular SIJ injections have resulted in significant pain relief, the etiologies of SIJC pain can be divided into IA and EA sources (Table 4.1). Among IA causes, arthritis and spondyloarthropathies (Table 4.2) are the two most common ones, though the latter may also be associated with EA pathology [40]. For EA causes, myofascial and ligamentous injury manifest most frequently [41]. Distinguishing IA and EA pain generators is clinically relevant. Dreyfuss et al. found that multisite lateral branch blocks provided more pain relief for ligamentous probing than for capsular distension [42]. In contrast to IA pathology, EA sources likely occur in younger individuals with more prominent and unilateral tenderness, following a specific inciting event.

Table 4.1 Causes of intra-articular and extra-articular SU complex pain

Intra-articular	Extra-articular
Arthritis	Ligamentous injury
Spondyloarthropathy	Myofascial pain
Trauma	Trauma/fractures
Infection	Enthesopathy
Cystic disease	Pregnancy
	Cystic disease

Table 4.2 SIJ involvement in adult spondyloarthropathies

Ankylosing spondylitis	Reactive arthritis	Psoriatic arthritis	Enteropathic arthritis
Almost 100 %, symmetric/alternating	20–30 %, mostly asymmetric	20–30 %, mostly asymmetric	15–25 %, mostly asymmetric
M:F = 3:1, <35 years of age	M:F = 5:1, young to middle-aged	M:F = 1:1, young to middle-aged	M:F = 1:1, young to middle-aged
20–30 % PJ	90 % PJ	Almost 100 % PJ	15–30 % PJ

SIJC pain tends to occur following a triggering event. Up to 50 % of patients with injection- confirmed SIJC pain can identify a specific trigger. The most frequent inciting events in descending order for trauma-induced SIJC pain are motor vehicle accidents, falls onto the buttock, pregnancy, athletic injuries, prolonged lifting and bending, and torsional strain [27, 43–46]. Other recognized rare-precipitating events include pyogenic infection and malignancy [47, 48].

A variety of risk factors can predispose patients to SIJC pain. These include true and apparent leg length discrepancy [49], gait and biomechanical abnormalities [50], prolonged vigorous exercise [51], scoliosis [52], pregnancy [53], and spine surgery [54]. True and functional leg length discrepancies can increase stress and abnormal force vectors on the ipsilateral lower extremity [55]. Patients with chronic LBP were significantly (75 %) more likely to have a leg length discrepancy of >5 mm than a matched asymptomatic cohort (44 %) [56]. Pregnancy can predispose women to SIJC pain via weight gain, exaggerated lordotic posture, hormone-induced ligamentous laxity, and the pelvic trauma of parturition [57, 58]. Spine surgery may be a trigger of SIJC pain, especially fusion to the sacrum. Ivanov et al. found the greatest increase in SIJ stress after L4–S1 fusion [59]. Ha et al. reported a nearly twofold increase in SIJ degeneration in the fusion cohort compared with the control group (75 % vs. 38.2 %), with the highest incidence in patients with fusions to the sacrum [60]. These findings are consistent with prevalence studies reporting 32–61 % of post-fusion patients experience SIJC pain [61, 62].

History and Physical Exam

Given its heterogeneous presentation from patient to patient, the SIJ-mediated pain cannot be reliably diagnosed by history and physical examination alone. Several investigators have attempted to map pain-referral patterns associated with the SIJ. By injecting contrast and lidocaine in asymptomatic volunteers, Fortin et al. generated a composite map on the patient's buttocks, inferior from the posterior inferior iliac spine [25]. This mapping was later confirmed in a clinical study that found that those with buttock pain radiating into the posterolateral thigh reported pain with SIJ provocation and had negative facet blocks and discography [26]. Two studies found that if the most painful area is located within 10 cm of the posterior superior iliac spine, it is most likely caused by SIJ-based pain [26, 63]. In another study using >80 % pain relief following single SIJ blocks in 50 patients, the distribution patterns are: 94 % buttock pain, 72 % lumbar pain, 50 % pain extending into the lower extremity, 28 % pain below the knee, and 14 % pain radiating to the groin [64]. SIJ pain is more likely to be located laterally [34, 65]. A cross-sectional prevalence study found that pain referral to the groin was the only pain distribution that could reliably distinguish SIJ pain from other sources of LBP [27]. Yet another study suggested that pain arising

Fig. 4.2 Flexion, abduction, and external rotation (FABER) test of the right sacroiliac joint

from sitting, unilateral pain, and absence of lumbar pain were the most reliable symptoms to separate SIJ pain from facetogenic and discogenic pain [66].

Like the history, physical examination maneuvers cannot reliably diagnose SIJC pain [67]. One study of 50 patients who had three or more provocation maneuvers reported 60 % positive-predictive value for response to a single SIJ injection; as a result, it concluded that provocative tests should not be considered sole diagnostic criteria [68]. However, several investigators have found that the presence of three or more positive provocative tests appears to have reasonable sensitivity and specificity in identifying patients who will positively respond to diagnostic injections (Fig. 4.2). In a double-blind, placebo-controlled study, FABER (flexion, abduction, and external rotation), posterior shear, and resisted abduction tests had a sensitivity ranging between 77 and 87 %, and all with 100 % specificity [68] (see Fig. 4.2). In a blinded validity study performed in 48 patients, a battery of three out of six provocation tests had 94 % sensitivity and 78 % specificity in predicting a positive response to a single diagnostic SIJ injection [31]. Another study using double blocks as the diagnostic standards in 60 patients reported similar finding, the presence of three out of five positive provocation tests had 85 % sensitivity and 79 % specificity [32]. In a recent systematic review, the authors concluded that three positive provocation tests had significant diagnostic odds ratio of 17.16 using two positive blocks [69]. Lastly, research has found provocation tests to be more reliable than motion measurement tests [70, 71].

In summary, a thorough history and physical examination may reveal important clues to etiologies to guide diagnostic workup and treatment plan. A combination of symptoms and signs can be utilized to select right candidates for SIJ blocks. For example, the SIJC pain is likely relieved from diagnostic injections when pain is located predominantly below L5, exacerbated by rising from a sitting position, most tender over the joint and associated with at least three or more provocative signs.

Table 4.3 Imaging modalities

MRI	Modality of choice: 85 % sensitivity for active sacroiliitis. Cannot detect noninflammatory causes. STIR and contrast-enhanced preferred
CAT	58 % sensitivity and 69 % specificity. Cannot detect inflammation
Bone scans	Low sensitivity, >90 % specificity
X-rays	Very low sensitivity, high specificity
Ultrasound	Can detect posterior ligamentous pathology. Can be useful during pregnancy

Diagnostic Imaging

A number of diagnostic imaging studies including CT, MRI, and radionuclide bone scanning have attempted to correlate radiological findings with the results of diagnostic blocks with varying success. CT is considered to be the gold standard for identifying bony pathology. In a retrospective study performed in 112 patients using diagnostic blocks as the reference standard, the investigators found that CT was associated with 58 % sensitivity and 69 % specificity [72, 73]. MRI can be useful in detecting early spondyloarthropathic SIJ pathologies with greater than 90 % sensitivity but is not effective in identifying noninflammatory etiologies [74].

Radionuclide bone scanning has been reported to have low sensitivity. In a clinical trial performed in 50 patients who underwent radionuclide imaging and diagnostic SIJ injections, the sensitivity and specificity were reported to be 13 and 100 %, respectively. In another similar study, nuclide imaging was found to have 46 % sensitivity and 90 % specificity (see Table 4.3).

Diagnostic Injection

SIJ injections are generally considered the most reliable means to diagnose SIJC pain. They have been used as the reference standard in most clinical studies investigating the predictive value of history and physical examination, referring pain patterns and imaging modalities. In almost all cases, these injections have been IA which may underestimate the true prevalence of SIJC. The false-positive rate of uncontrolled SIJ blocks is estimated to be 20 %, making controlled blocks with two different local anesthetic drugs or placebo-controlled blocks the best way to identify a painful SIJ and to predict treatment response to radiofrequency denervation. However, this methodology may be prone to a higher false-negative rate and may be less cost-effective.

Treatment

Conservative Treatment

Conservative management can serve as a first-line option with fewer risks to address the underlying pathology. True and functional leg length discrepancy can be treated with shoe lifts and physical therapy. Strength and flexibility training can help correct

the maladaptive biomechanical imbalance [75]. Most studies on physical therapy focused on core strengthening and were conducted in peri- and postpartum women who routinely suffer from SIJ dysfunction [76].

A study evaluating three different physical modalities in pregnant women diagnosed with SIJC pain based on provocation maneuvers found that nonelastic SI belts, home exercise, and a structured clinical exercise are equally effective at 38 weeks gestation and 12 months postpartum [77]. A physical rehabilitation and exercise program should be individualized based on clinical findings, physical capacity, and anticipated compliance [56].

Manipulation such as osteopathic and chiropractic adjustments has been reported to be of value, although prospective controlled studies are lacking [78, 79]. Uncontrolled or inadequately controlled trials using different techniques and methodology have shown significant clinical benefits of pain originating from SIJ [53, 80–82]. SIJ bony asymmetries have been shown to resolve with manipulation [53, 83]. However, an early study showed no significant correlation between joint motion and response to diagnostic blocks [67], and a later study found no change in SIJ bony positioning after manipulation [79]. There are anecdotal reports of improved tone and pain involving SIJ-related soft tissues (quadriceps, abdominal musculature, and hamstrings after manipulation [83–86]). A well-designed study failed to demonstrate an association between spinal manipulation success and the presence of SIJ provocation maneuvers [78].

Pharmacotherapy should be considered as part of a multimodal treatment paradigm. In patients with acute nonneuropathic pain, oral or topical anti-inflammatory and muscle relaxants may be effective, though the treatment effect is relatively small. For patients with spondyloarthropathies, cytokine inhibitors and methotrexate may limit disease progression, improve pain relief, and increase function.

Interventional Treatment

Prolotherapy (Aka Proliferative Therapy)

It is hypothesized that the injection of nonpharmacological and nonactive irritant solutions such as dextrose and platelet-rich plasma into the joint, tendons, or ligaments will initiate an inflammatory process that may lead to enhanced blood flow and accelerated tissue repair. As a result, the injection may strengthen connective tissue and relieve musculoskeletal pain. In one randomized study comparing four biweekly IA prolotherapy with dextrose of 25 % to the IA steroid for injection-confirmed SIJ pain, both groups experienced significant but similar improvement at 2 weeks, but at 15 months post treatment, positive outcome sustained in 58.7 % of patients in the prolotherapy group versus 10.2 % in the steroid group [87]. An observational study evaluating three injections of hypertonic dextrose into the SIJ ligaments reported success rates of 76, 76, and 32 % at 3-, 12-, and 24-month follow-up visits, respectively. Despite these results, placebo-controlled studies are needed to establish the efficacy of prolotherapy for SIJC pain.

EA Steroid Injections

Two randomized controlled trials evaluated single periarticular injections with 3 mL of steroid and local anesthetic or 3 mL of saline and local anesthetic. The first study done in patients with seronegative spondyloarthropathy demonstrated that the steroid cohort experienced better pain relief than the control group at 2-month follow-up [40]. The second study done in patients with nonspondyloarthropathic SIJC pain showed similar result at 1-month follow-up [41]. In a nonrandomized study comparing IA and EA injections in patients with pain in the SIJ region and three positive provocative tests, pain improvement was observed in 100 % of EA group and 36 % of IA group [88]. In a retrospective study comparing IA blocks and combination of IA and EA blocks (to include the lateral branches and posterior ligaments), 50 % or greater pain relief was seen in 42.5 versus 27.5 % at 3 weeks and 31.2 versus 12.5 % at 3 months for the combination group and IA group, respectively [80]. Further studies with larger sample size with long-term follow-ups are needed to identify the subgroups that most benefit from EA injections.

IA Steroid Injections (Fig. 4.3)

A prospective study in children with juvenile spondyloarthropathy who failed to respond to nonsteroidal anti-inflammatory drugs (NSAIDS) found CT-guided IA steroids to be effective with a mean duration of benefit of 12 months [90]. Another investigation evaluated the effect of IA steroid injections in patients with inflammatory spondyloarthropathy and MRI evidence of sacroiliitis and that in patients without radiologic-confirmed SIJ inflammation. Significant but similar improvements in pain scores and function were reported in both groups between 1 and 3 months [91]. In a randomized trial, ten patients with spondyloarthropathy and sacroiliitis received either IA steroids or saline [92]. Five of six steroid-injected joints had >70 % improvement compared to zero out of seven saline-injected joints at 1-month follow-up. Six of seven saline-injected joints were then injected with steroids, resulting in an overall 87.5 % with positive outcome at 1 month. The positive outcome declined to 62 and 58 % at 3 and 6 months, respectively. Overall, the evidence supporting IA steroid injections is more robust for spondyloarthropathy than for nonspondyloarthropathy.

Other IA Injections

Investigators have looked into phenol and hyaluronic acid solutions in an attempt to prolong the intrinsic short-term relief with corticosteroid injections. One report of IA phenol in patients who had short-term relief with IA steroid injections, nine out of ten patients experienced a median 20.5-week pain relief [93]. Given the high rates of ventral capsular tears and uncontrolled spread of injectate into the epidural space or sacral foramina [27, 94], IA phenol is considered high risk and therefore

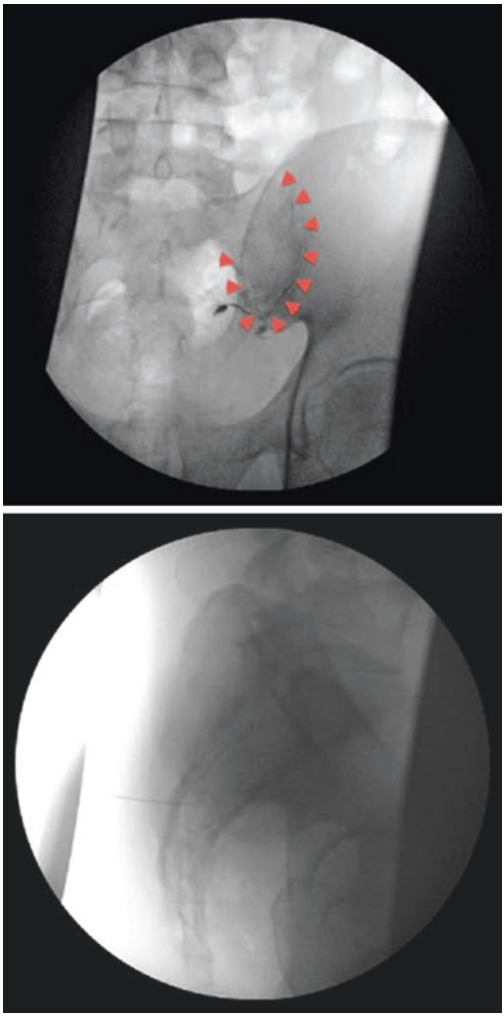

Fig. 4.3 Anteroposterior and lateral fluoroscopic images demonstrating a right-sided sacroiliac joint block with an appropriate spread of contrast in the joint (*arrowheads*)

rarely done clinically. In a case series, four patients who underwent a series of three IA hyaluronic acid injections experienced 12–16 months of significant pain relief [95]. However, this treatment effect size is considered modest at best and may benefit a subgroup of patients with degenerative SIJ osteoarthritis.

Radiofrequency Ablation (RFA) (Fig. 4.4)

There are several forms of radiofrequency ablation (RFA) including thermal RFA, cooled RFA, bipolar RFA, and pulsed RFA. Overall controlled and uncontrolled studies have reported positive results with radiofrequency lesioning of the lateral

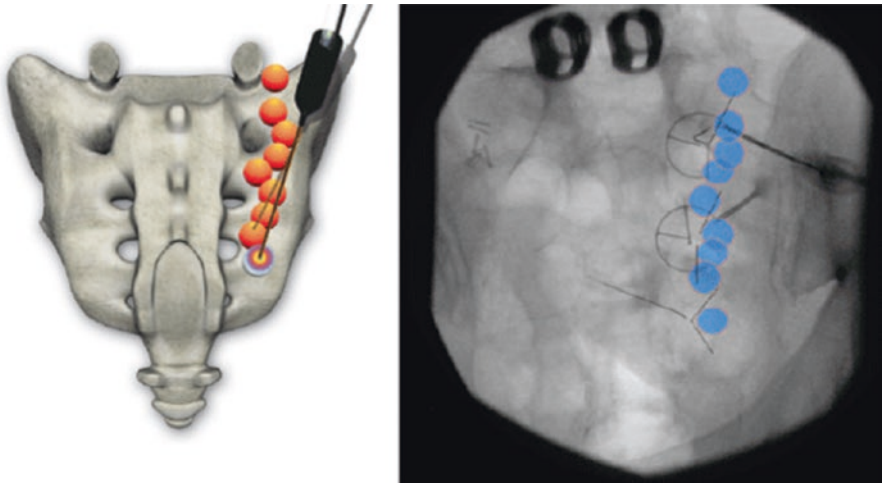

Fig. 4.4 Schematic diagram and fluoroscopic image depicting targeted lesions for right-sided radiofrequency ablation of the L5 dorsal branch and S1–3 lateral branches

branch nerves innervating the SIJ. In theory, either lateral branch or EA blocks can serve as a better prognostic tool than IA blocks for lateral branch RFA response. Yet, this reasoning has to be confirmed clinically. Like other interventional treatments, a successful outcome requires proper patient selection, accurate diagnosis, and correct technique.

Multiple uncontrolled studies utilizing different methodologies have demonstrated positive outcomes using thermal RF lesioning [96–98]. In a retrospective study performed in 77 patients with injection-confirmed SIJ pain, the investigators noted a trend but patients who underwent cooled RF had greater pain relief [44]. By contrast, a recent retrospective study performed in 88 patients showed no significant benefit of cooled over thermal RFA [99]. The major limitation to thermal RF is the small lesion size of about 4 mm in horizontal diameter.

Given the wide variability in lateral nerve number and location, multiple lesions need to be created around each foramen to capture all or most of the nociceptive input transmitted from the SIJ. One technique to overcome this limitation, that is, to enhance lesion size by approximately 50 %, is to inject local anesthetic before lesioning.

Cooled RFA has been adapted from use in tumor and cardiac arrhythmia ablation [100–103] in order to amplify the lesion size. The technique features an internally cooled, large bore electrode which gradually heats the surrounding tissues to neuroablative temperatures while preventing the immediately adjacent tissue from being charred, allowing for greater lesion expansion. With the substantially increased ablation diameter (twofold increase over thermal RF), depth (>3-cm distal to the active tip), and area (eightfold increase), strategically placed cooled electrodes around the sacral foramina would likely allow complete and successful neurotomy. Both controlled and uncontrolled studies reported the benefit of cooled

RFA in SIJ pain. In a randomized placebo-controlled study in 51 patients who received either cooled or sham RF of L5–S3 after two positive L5 dorsal ramus and S1–3 lateral branch blocks, the investigators found statistically significant improvements (47 % vs. 12 %) in pain, physical function, disability, and quality of life at 3-month follow-up. At 6- and 9-month follow-ups, 59 and 38 % and 59 % of active treatment group maintained a positive outcome, respectively [104].

An earlier randomized, placebo-controlled trial in 28 patients who had a positive IA injection reported 64 and 57 % of patients after the L4–S3 (S4) denervation to have greater than 50 % pain relief along with functional improvement and medication reduction at their 3- and 6-month follow-ups, respectively [105]. The drawbacks of cooled RFA include the greater cost, longer lesioning time, increased bleeding risk, procedure-related pain, and higher incidence of cutaneous paresthesias.

In bipolar RFA, two electrodes are placed in close proximity to create current flows between them, which create a continuous lesion. Conceptually, the technique can maximize lesion size by the use of an enclosed electrical circuit, so that the placement of electrodes around the foramen can completely sever all nociceptive input from the SIJ. In a retrospective study in 33 patients, bipolar electrodes were placed sequentially within 1 cm of each other along the posteroinferior margin of the joint to create strip lesions. The authors found a 36.4 % success rate (greater than 50 % decrease in visual analog scale pain scores) at 6-month follow-up visit. In an observation study in nine patients with positive SIJ and lateral branch nerve blocks, the investigators sequentially leapfrogged 20-gauge electrodes around the S1–3 foramina to create bipolar strip lesions [106]. They reported 89 % success rate, with two-thirds sustaining meaningful relief at 1-year post treatment.

Pulsed RFA is nonneuroablative technique in which an electrical field is created to interrupt the transmission of A-delta and C-fibers and possibly by enhancing descending modulatory pathways [107, 108]. Therefore, the primary indication for pulsed RFA is neuropathic pain, with minimal violation of the nerve architecture. There is scant evidence for the use of pulsed RFA in SIJC pain. In only one uncontrolled prospective observational study in 22 patients who had a positive SIJ injection, 73 % reported at least 50 % pain relief and improved quality of life with a 20-week median duration of benefit [109].

A combination of ligamentous and neural RFA was attempted to capture multiple sources of SIJ pain. In an only observational study in 38 patients who responded positively to intra-ligamentous injections, the authors used CT guidance to lesion the L5 dorsal ramus and create three lesions in the posterior interosseous ligaments [110]. They reported 65 % of patients with substantial pain relief lasting at least 3 months.

Cryoanalgesia

Cryoanalgesia forms ice crystal around the tip of the electrode, which damages the vasa nervorum, resulting in severe endoneurial edema and disruption of neural transmission. In comparison to thermal RFA, cryoanalgesia creates a larger

lesion size and leaves the myelin sheath and endoneurium intact. Due to the large probe and needle size, the risk of bleeding and nerve injury is likely higher. At the present time, there are no controlled studies investigating this modality for SIJC pain.

Neuromodulation

Neuromodulation is well established for neuropathic pain. However, evidence for spinal cord and peripheral nerve stimulation in SIJC pain is sparse, only anecdotal. Two case reports showed benefit using either S1 stimulation [111] or S3 stimulation [112]. Currently, there are no studies on peripheral nerve field stimulation.

Surgical Intervention

Surgical intervention for SIJC pain has been offered to patients who fail conservative management and nerve blocks; however, its utility has been a source of contention in recent years. A most recent systematic review included a total of 430 patients undergoing either open surgery or minimally invasive surgery (MIS) for SIJ fusion (115). The pathologies are widely mixed including SIJ degeneration/arthrosis, SIJ dysfunction, postpartum instability, posttraumatic, idiopathic, pathological fractures, and rheumatoid arthritis. The rates of excellent satisfaction, determined by pain reduction, function, and quality of life, exhibit a wide interval of 18–100 % (mean 54 %) for open surgeries and 56–100 % (mean 84 %) for MIS. The authors concluded that evidence for the efficacy of SIJ fusion is lacking and surgical intervention appears to be beneficial in a subset of patients.

Conclusion

SIJC has been emerged as a significant pain generator for many patients experiencing low back, pelvic, and urogenital pain. In fact, it affects up to 30 % of patients with chronic axial lumbar pain. History and physical examination are not diagnostic. Provocative tests may serve as a prognostic tool. The reference standard for diagnosis remains low-volume image-guided local anesthetic blocks. Conservative and alternative therapies may benefit patients with biomechanical or soft-tissue pathologies, but there are no high-quality studies evaluating these modalities in patients with injection-confirmed SIJ pain. Both IA and EA steroid injections may provide short-term relief in a certain subsets of patients. For these patients, RFA of

the lower lumbar dorsal rami and S1–3 [4] lateral branches can extend pain relief up to 12 months.

References

1. Bernard TN, Cassidy JD. The sacroiliac syndrome: pathophysiology, diagnosis and management. In: Frymoyer JW, editor. The adult spine: principles and practice. New York: Raven; 1991. p. 2107–30.
2. Vleeming A, van Wingerden JP, Snijders CJ, et al. Load application to the sacrotuberous ligament: influence on sacroiliac joint mechanics. Clin Biomech. 1989;4:204–9.
3. Bowen V, Cassidy JD. Macroscopic and microscopic anatomy of the sacroiliac joint from embryonic life until the eighth decade. Spine. 1981;6:620–8.
4. Bellamy N, Park W, Rooney PJ. What do we know about the sacroiliac joint? Semin Arthritis Rheum. 1983;12:282–313.
5. McLauchlan GJ, Gardner DL. Sacral and iliac articular cartilage thickness and cellularity: relationship to subchondral bone end-plate thickness and cancellous bone density. Rheumatology. 2002;41:375–80.
6. Harrison DE, Harrison DD, Troyanovich SJ. The sacroiliac joint: a review of anatomy and biomechanics with clinical implications. J Manipulative Physiol Ther. 1997;20(9):607–17.
7. Williams PL, editor. Gray's anatomy. 38th ed. Edinburgh: Churchill Livingstone; 1995.
8. Forst SL, Wheeler MT, Fortin JD, Vilensky JA. The sacroiliac joint: anatomy, physiology and clinical significance. Pain Physician. 2006;9(1):61–7.
9. Bogduk N. Clinical and radiological anatomy of the lumbar spine. 5th ed. Edinburgh: Churchill Livingstone; 2012.
10. Sturesson B, Selvik G, Udén A. Movements of the sacroiliac joints. A roentgen stereophotogrammetric analysis. Spine. 1989;14(2):162–5.
11. Pitkin HC, Pheasant HC. Sacrarthogenetic telalgia I. a study of referred pain. J Bone Joint Surg. 1936;18:111–33.
12. Solonen KA. The sacroiliac joint in the light of anatomical, roentgenological and clinical studies. Acta Orthop Scand Suppl. 1957;27:1–127.
13. Grob KR, Neuhuber WL, Kissling RO. Innervation of the human sacroiliac joint. Z Rheumatol. 1995;54:117–22.
14. Ikeda R. Innervation of the sacroiliac joint: macroscopical and histological studies. Nippon Ika Daigaku Zasshe. 1991;58:587–96.
15. Cohen SP. Sacroiliac joint pain: a comprehensive review of anatomy, diagnosis, and treatment. Anesth Analg. 2005;101(5):1440–53.
16. McGrath MC, Zhang M. Lateral branches of dorsal sacral nerve plexus and the long posterior sacroiliac ligament. Surg Radiol Anat. 2005;27(4):327–30.
17. Zondervan KT, Yudkin PL, Vessey MP, et al. The community prevalence of chronic pelvic pain in women and associated illness behaviour. Br J Gen Pract. 2001;51:541–7.
18. Blasco A, Berzosa M, Iranzo V, et al. Update in cancer pain. Cancer Chemother Rev. 2009;4:95–109.
19. Stovall TG, Ling FW, Crawford DA. Hysterectomy for chronic pelvic pain of presumed uterine etiology. Obstet Gynecol. 1990;75:676–9.
20. Stout AL, Steege JF, Dodson WC, et al. Relationship of laparoscopic findings to self-report of pelvic pain. Am J Obstet Gynecol. 1991;164:73–9.
21. Soysal ME, Soysal S, Gurses E, et al. Laparoscopic presacral neurolysis for endometriosis-related pelvic pain. Hum Reprod. 2003;18:588–92.
22. Peters AA, Trimbos-Kemper GC, Admiraal C, et al. A randomized clinical trial on the benefit of adhesiolysis in patients with intraperitoneal adhesions and chronic pelvic pain. Br J Obstet Gynaecol. 1992;99:59–62.

23. Williams R, Hartmann K, Sandler R, et al. Prevalence and characteristics of irritable bowel syndrome among women with chronic pelvic pain. Obstet Gynecol. 2004;104: 452–8.
24. Goldthwaite GE, Osgood RB. A consideration of the pelvic articulations from an anatomical, pathological, and clinical standpoint. Boston Med Surg J. 1905;152:593–601.
25. Fortin JD, Dwyer AP, West S, Pier J. Sacroiliac joint: pain referral maps upon applying a new injection/arthrography technique. Part I: asymptomatic volunteers. Spine. 1994;19:1475–82.
26. Fortin JD, Aprill CN, Ponthieux B, Pier J, Derby Jr R. Sacroiliac joint: pain referral maps upon applying a new injection/arthrography technique. Part II: Clinical evaluation. Spine. 1994;19:1483–9.
27. Schwarzer AC, Aprill CN, Bogduk N. The sacroiliac joint in chronic low back pain. Spine. 1995;20(1):31–7.
28. Maigne JY, Aivaliklis A, Pfefer F. Results of sacroiliac joint double block and value of sacroiliac pain provocation tests in 54 patients with low back pain. Spine. 1996;21(16): 1889–92.
29. Irwin RW, Watson T, Minick RP, Ambrosius WT. Age, body mass index, and gender differences in sacroiliac joint pathology. Am J Phys Med Rehabil. 2007;86(1):37–44.
30. Manchikanti L, Singh V, Pampati V, et al. Evaluation of the relative contributions of various structures in chronic low back pain. Pain Physician. 2001;4(4):308–16.
31. Laslett M, Aprill CN, McDonald B, Young SB. Diagnosis of sacroiliac joint pain: validity of individual provocation tests and composites of tests. Man Ther. 2005;10(3):207–18.
32. van der Wurff P, Buijs EJ, Groen GJ. A multitest regimen of pain provocation tests as an aid to reduce unnecessary minimally invasive sacroiliac joint procedures. Arch Phys Med Rehabil. 2006;87(1):10–4.
33. Liliang PC, Lu K, Liang CL, Tsai YD, Wang KW, Chen HJ. Sacroiliac joint pain after lumbar and lumbosacral fusion: findings using dual sacroiliac joint blocks. Pain Med. 2011;91(4):1283–5.
34. Depalma MJ, Ketchum JM, Trussell BS, Saullo TR, Slipman CW. Does the location of low back pain predict its source? PMR. 2011;3(1):33–9.
35. Laplante BL, Ketchum JM, Saullo TR, DePalma MJ. Multivariable analysis of the relationship between pain referral patterns and the source of chronic low back pain. Pain Physician. 2012;15(2):171–8.
36. Dreyfuss P, Cole AJ, Pauza K. Sacroiliac joint injection techniques. Phys Med Rehabil Clin North Am. 1995;6:785–813.
37. Szadek KM, Hoogland PV, Zuurmond WW, de Lange JJ, Perez RS. Nociceptive nerve fibers in the sacroiliac joint in humans. Reg Anesth Pain Med. 2008;33(1):36–43.
38. Szadek KM, Hoogland PV, Zuurmond WW, De Lange JJ, Perez RS. Possible nociceptive structures in the sacroiliac joint cartilage: an immunohistochemical study. Clin Anat. 2010; 23(2):192–8.
39. Dreyfuss P, Snyder BD, Park K, Willard F, Carreiro J, Bogduk N. The ability of single site, single depth sacral lateral branch blocks to anesthetize the sacroiliac joint complex. Pain Med. 2008;9(7):844–50.
40. Luukkainen R, Nissilä M, Asikainen E, et al. Periarticular corticosteroid treatment of the sacroiliac joint in patients with seronegative spondyloarthropathy. Clin Exp Rheumatol. 1999;17(1):88–90.
41. Luukkainen RK, Wennerstrand PV, Kautiainen HH, Sanila MT, Asikainen EL. Efficacy of periarticular corticosteroid treatment of the sacroiliac joint in non-spondylarthropathic patient's with chronic low back pain in the region of the sacroiliac joint. Clin Exp Rheumatol. 2002;20(1):52–4.
42. Dreyfuss P, Henning T, Malladi N, Goldstein B, Bogduk N. The ability of multi-site, multi-depth sacral lateral branch blocks to anesthetize the sacroiliac joint complex. Pain Med. 2009;10(4):679–88.
43. Chou LH, Slipman CW, Bhagia SM, et al. Inciting events initiating injection-proven sacroiliac joint syndrome. Pain Med. 2004;5(1):26–32.

44. Cohen SP, Strassels SA, Kurihara C, et al. Outcome predictors for sacroiliac joint (lateral branch) radiofrequency denervation. Reg Anesth Pain Med. 2009;34(3):206–14.
45. Baquie P, Brukner P. Injuries presenting to an Australian sports medicine center: a 12-month study. Clin J Sport Med. 1997;7:28–31.
46. LeBlanc KE. Sacroiliac sprain: an overlooked cause of back pain. Am Fam Physician. 1992;46:1459–63.
47. Dunn EJ, Bryan DM, Nugent JT, Robinson RA. Pyogenic infections of the sacro-iliac joint. Clin Orthop. 1976;118:113–7.
48. Humphrey SM, Inman RD. Metastatic adenocarcinoma mimicking unilateral sacroiliitis. J Rheumatol. 1995;22:970–2.
49. Schuit D, McPoil TG, Mulesa P. Incidence of sacroiliac joint malalignment in leg length discrepancies. J Am Podiatr Med Assoc. 1989;79:380–3.
50. Herzog W, Conway PJ. Gait analysis of sacroiliac joint patients. J Manipulative Physiol Ther. 1994;17:124–7.
51. Marymont JV, Lynch MA, Henning CE. Exercise-related stress reaction of the sacroiliac joint: an unusual cause of low back pain in athletes. Am J Sports Med. 1986;14:320–3.
52. Schoenberger M, Hellmich K. Sacroiliac dislocation and scoliosis. Hippokrates. 1964;35: 476–9.
53. Daly JM, Frame PS, Rapoza PA. Sacroiliac subluxation: a common treatable cause of low-back pain in pregnancy. Fam Pract Res J. 1991;11:149–59.
54. Onsel C, Collier BD, Meting K, et al. Increased sacroiliac joint uptake after lumbar fusion and/or laminectomy. Clin Nucl Med. 1992;17:283–7.
55. Timgren J, Soinila S. Reversible pelvic asymmetry: an overlooked syndrome manifesting as scoliosis, apparent leg-length difference, and neurologic symptoms. J Manipulative Physiol Ther. 2006;29(7):561–5.
56. Friberg O. Clinical symptoms and biomechanics of lumbar spine and hip joint in leg length inequality. Spine. 1983;8(6):643–51.
57. Ostgaard HC, Andersson GB, Karlsson K. Prevalence of back pain in pregnancy. Spine. 1991;16(5):549–52.
58. Gutke A, Ostgaard HC, Oberg B. Pelvic girdle pain and lumbar pain in pregnancy: a cohort study of the consequences in terms of health and functioning. Spine. 2006;31(5):149–55.
59. Ivanov AA, Kiapour A, Ebraheim NA, Goel V. Lumbar fusion leads to increases in angular motion and stress across sacroiliac joint: a finite element study. Spine. 2009;34(5):162–9.
60. Ha KY, Lee JS, Kim KW. Degeneration of sacroiliac joint after instrumented lumbar or lumbosacral fusion: a prospective cohort study over five-year follow-up. Spine. 2008;33(11):1192–8.
61. Maigne JY, Planchon CA. Sacroiliac joint pain after lumbar fusion. A study with anesthetic blocks. Eur Spine J. 2005;14(7):654–8.
62. Katz V, Schofferman J, Reynolds J. The sacroiliac joint: a potential cause of pain after lumbar fusion to the sacrum. J Spinal Disord Tech. 2003;16(1):96–9.
63. Murakami E, Aizawa T, Noguchi K, Kanno H, Okuno H, Uozumi H. Diagram specific to sacroiliac joint pain site indicated by one-finger test. J Orthop Sci. 2008;13(6):492–7.
64. Slipman CW, Jackson HB, Lipetz JS, Chan KT, Lenrow D, Vresilovic EJ. Sacroiliac joint pain referral zones. Arch Phys Med Rehabil. 2000;81(3):334–8.
65. Laslett M. Evidence-based diagnosis and treatment of the painful sacroiliac joint. J Man Manip Ther. 2008;16(3):142–52.
66. Young S, Aprill C, Laslett M. Correlation of clinical examination characteristics with three sources of chronic low back pain. Spine J. 2003;3(6):460–5.
67. Dreyfuss P, Michaelsen M, Pauza K, McLarty J, Bogduk N. The value of medical history and physical examination in diagnosing sacroiliac joint pain. Spine. 1996;21(22):2594–602.
68. Slipman CW, Sterenfeld EB, Chou LH, Herzog R, Vresilovic E. The predictive value of provocative sacroiliac joint stress maneuvers in the diagnosis of sacroiliac joint syndrome. Arch Phys Med Rehabil. 1998;79(3):288–92.

69. Broadhurst NA, Bond MJ. Pain provocation tests for the assessment of sacroiliac joint dysfunction. J Spinal Disord. 1998;11(4):341–5.
70. Szadek KM, van der Wurff P, van Tulder MW, Zuurmond WW, Perez RS. Diagnostic validity of criteria for sacroiliac joint pain: a systematic review. J Pain. 2009;10(4):354–68.
71. Laslett M, Williams M. The reliability of selected pain provocation tests for sacroiliac joint pathology. Spine. 1994;19(11):1243–9.
72. Van der Wurff P, Hagmeijer RH, Meyne W. Clinical tests of the sacroiliac joint. A systematic methodological review. Part 1: reliability. Man Ther. 2000;5(1):30–6.
73. Elgafy H, Semaan HB, Ebraheim NA, Coombs RJ. Computed tomography findings in patients with sacroiliac pain. Clin Orthop Relat Res. 2001;382:112–8.
74. Puhakka KB, Jurik AG, Schiøttz-Christensen B, et al. MRI abnormalities of sacroiliac joints in early spondylarthropathy: a 1-year follow-up study. Scand J Rheumatol. 2004;33(5):332–8.
75. Prather H, Hunt D. Conservative management of low back pain, part I. Sacroiliac joint pain. Dis Mon. 2004;50(12):670–83.
76. Mens JM, Snijders CJ, Stam HJ. Diagonal trunk muscle exercises in peripartum pelvic pain: a randomized clinical trial. Phys Ther. 2000;80(12):1164–73.
77. Nilsson-Wikmar L, Holm K, Oijerstedt R, Harms-Ringdahl K. Effect of three different physical therapy treatments on pain and activity in pregnant women with pelvic girdle pain: a randomized clinical trial with 3, 6, and 12 months follow-up postpartum. Spine. 2005; 30(8):850–6.
78. Flynn T, Fritz J, Whitman J, et al. A clinical prediction rule for classifying patients with low back pain who demonstrate short-term improvement with spinal manipulation. Spine. 2002;27(24):2835–43.
79. Tullberg T, Blomberg S, Branth B, Johnsson R. Manipulation does not alter the position of the sacroiliac joint. A roentgen stereophotogrammetric analysis. Spine. 1998;23(10):1124–8; discussion 1129.
80. Delitto A, Cibulka MT, Erhard RE, Bowling RW, Tenhula JA. Evidence for use of an extension-mobilization category in acute low back syndrome: a prescriptive validation pilot study. Phys Ther. 1993;73(4):216–22; discussion 223.
81. Dontigny RL. Dysfunction of the sacroiliac joint and its treatment*. J Orthop Sports Phys Ther. 1979;1(1):23–35.
82. Wreje U, Nordgren B, Aberg H. Treatment of pelvic joint dysfunction in primary care – a controlled study. Scand J Prim Health Care. 1992;10(4):310–5.
83. Cibulka MT, Delitto A, Koldehoff RM. Changes in innominate tilt after manipulation of the sacroiliac joint in patients with low back pain. An experimental study. Phys Ther. 1988;68(9):1359–63.
84. Suter E, McMorland G, Herzog W, Bray R. Decrease in quadriceps inhibition after sacroiliac joint manipulation in patients with anterior knee pain. J Manipulative Physiol Ther. 1999;22(3):149–53.
85. Marshall P, Murphy B. The effect of sacroiliac joint manipulation on feedforward activation times of the deep abdominal musculature. J Manipulative Physiol Ther. 2006;29(3): 196–202.
86. Cibulka MT, Rose SJ, Delitto A, Sinacore DR. Hamstring muscle strain treated by mobilizing the sacroiliac joint. Phys Ther. 1986;66(8):1220–3.
87. Kim WM, Lee HG, Jeong CW, Kim CM, Yoon MH. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. J Altern Complement Med. 2010;16(12):1285–90.
88. Murakami E, Tanaka Y, Aizawa T, Ishizuka M, Kokubun S. Effect of periarticular and intraarticular lidocaine injections for sacroiliac joint pain: prospective comparative study. J Orthop Sci. 2007;12(3):274–80.
89. Borowsky CD, Fagen G. Sources of sacroiliac region pain: insights gained from a study comparing standard intra-articular injection with a technique combining intra- and peri-articular injection. Arch Phys Med Rehabil. 2008;89(11):2048–56.

90. Fischer T, Biedermann T, Hermann KG, et al. [Sacroiliitis in children with spondyloarthropathy: therapeutic effect of CT-Guided intra-articular corticosteroid injection]. Rofo. 2003; 175(6):814–21.
91. Hanly JG, Mitchell M, MacMillan L, Mosher D, Sutton E. Efficacy of sacroiliac corticosteroid injections in patients with inflammatory spondyloarthropathy: results of a 6 month controlled study. J. Rheumatol. 2000;27(3):719–22
92. Maugars Y, Mathis C, Berthelot JM, Charlier C, Prost A. Assessment of the efficacy of sacroiliac corticosteroid injections in spondyloarthropathies: a double-blind study. Br J Rheumatol. 1996;35(8):767–70.
93. Ward S, Jenson M, Royal MA, Movva V, Bhakta B, Gunyea I. Fluoroscopy-guided sacroiliac joint injections with phenol ablation for persistent sacroiliitis: a case series. Pain Pract. 2002;2(4):332–5.
94. Rosenberg JM, Quint TJ, de Rosayro AM. Computerized tomographic localization of clinically-guided sacroiliac joint injections. Clin J Pain. 2000;16(1):18–21.
95. Srejic U, Calvillo O, Kabakibou K. Viscosupplementation: a new concept in the treatment of sacroiliac joint syndrome: a preliminary report of four cases. Reg Anesth Pain Med. 1999; 24(1):84–8.
96. Aydin SM, Gharibo CG, Mehnert M, Stitik TP. The role of radiofrequency ablation for sacroiliac joint pain: a meta-analysis. PM R. 2010;2(9):842–51.
97. Yin W, Willard F, Carreiro J, Dreyfuss P. Sensory stimulation-guided sacroiliac joint radiofrequency neurotomy: technique based on neuroanatomy of the dorsal sacral plexus. Spine. 2003;28(20):2419–25.
98. Buijs E, Kamphuis E, Groen G. Radiofrequency treatment of sacroiliac joint-related pain aimed at the first three sacral dorsal rami: a minimal approach. Pain Clinic. 2004; 16(2):139–46.
99. Cheng J, Pope JE, Dalton JE, Cheng O, Bensitel A. Comparative outcomes of cooled versus traditional radiofrequency ablation of the lateral branches for sacroiliac joint pain. Clin J Pain. 2013;29:132–7.
100. Solbiati L, Goldberg SN, Ierace T, et al. Hepatic metastases: percutaneous radio-frequency ablation with cooled-tip electrodes. Radiology. 1997;205(2):367–73.
101. Goldberg SN, Gazelle GS, Solbiati L, Rittman WJ, Mueller PR. Radiofrequency tissue ablation: increased lesion diameter with a perfusion electrode. Acad Radiol. 1996;3(8): 636–44.
102. Delacretaz E, Stevenson WG, Winters GL, et al. Ablation of ventricular tachycardia with a saline-cooled radiofrequency catheter: anatomic and histologic characteristics of the lesions in Humans. J Cardiovasc Electrophysiol. 1999;10(6):860–5.
103. Patel N, Gross A, Brown L, Gekht G. A randomized, placebo-controlled study to assess the efficacy of lateral branch neurotomy for chronic sacroiliac joint pain. Pain Med. 2012; 13(3):383–98.
104. Cohen SP, Hurley RW, Buckenmaier 3rd CC, Kurihara C, Morlando B, Dragovich A. Randomized placebo-controlled study evaluating lateral branch radiofrequency denervation for sacroiliac joint pain. Anesthesiology. 2008;109(2):279–88.
105. Burnham RS, Yasui Y. An alternate method of radiofrequency neurotomy of the sacroiliac joint: a pilot study of the effect on pain, function, and satisfaction. Reg Anesth Pain Med. 2007;32(1):12–9.
106. Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications-a review. Acta Neurochir (Wien). 2011;153(4):763–71. yes.
107. Hagiwara S, Iwasaka H, Takeshima N, Noguchi T. Mechanisms of analgesic action of pulsed radiofrequency on adjuvant-induced pain in the rat: roles of descending adrenergic and serotonergic systems. Eur J Pain. 2009;13(3):249–52.
108. Vallejo R, Benyamin RM, Kramer J, Stanton G, Joseph NJ. Pulsed radiofrequency denervation for the treatment of sacroiliac joint syndrome. Pain Med. 2006;7(5):429–34.

109. Gevargez A, Groenemeyer D, Schirp S, Braun M. CT-guided percutaneous radiofrequency denervation of the sacroiliac joint. Eur Radiol. 2002;12(6):1360–5.
110. Kim YH, Moon DE. Sacral nerve stimulation for the treatment of sacroiliac joint dysfunction: a case report. Neuromodulation. 2010;13(4):306–10.
111. Calvillo O, Esses SI, Ponder C, D'Agostino C, Tanhui E. Neuroaugmentation in the management of sacroiliac joint pain: report of two cases. Spine. 1998;23(9):1069–72.
112. Zaidi HA, Montoure AJ, Dickman CA. J Neurosurg Spine. 2015;23(1):59–66. doi:10.3171/2014.10.SPINE14516. Epub 2015 Apr 3.

Chapter 5
Piriformis Syndrome and Pudendal Neuralgia

Taral Patel and Michael Sabia

Piriformis Anatomy

In order to understand any disease process, it is essential to know the underlying anatomy and physiology. The piriformis muscle lies in the gluteal region deep to the gluteus maximus muscle. It originates from the anterior surface of the 2nd–4th sacral segments and sacrotuberous ligament and inserts into the greater trochanter. It is innervated by the ventral rami of the S1 and S2 spinal nerves. Its function is to externally rotate the femur at the hip joint, abduct the flexed thigh, and stabilize the hip joint. Repetitive hip and lower extremity motions along with trauma to the sacral or gluteal area are usually the culprit for piriformis syndrome. In 78–84 % of the population, the sciatic nerve passes anterior to the piriformis muscle, while in 12–21 %, it passes posterior to the muscle (Fig. 5.1) [1].

Diagnosis

When it comes to diagnosing piriformis syndrome, there are many physical findings that can promote the diagnosis. The common symptoms of piriformis syndrome include pain in the buttock with or without radiation in the distribution of the ipsilateral sciatic nerve (down the posterior aspect of the leg). More often than not patients will complain of pain that worsens with sitting or standing from a sitting

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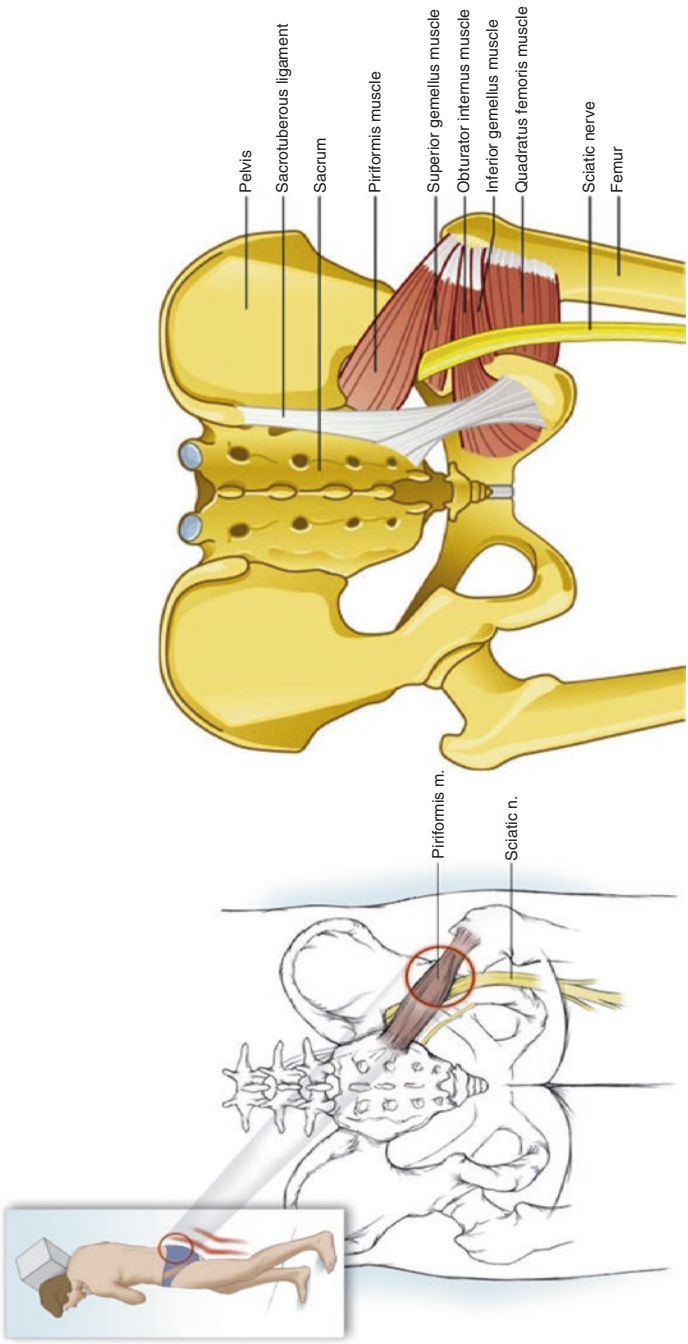

Fig. 5.1 Piriformis muscle in relation to surrounding muscles and sciatic nerve (Source: *Atlas of Common Pain Syndromes*, Chapter 84, 266–268 [1])

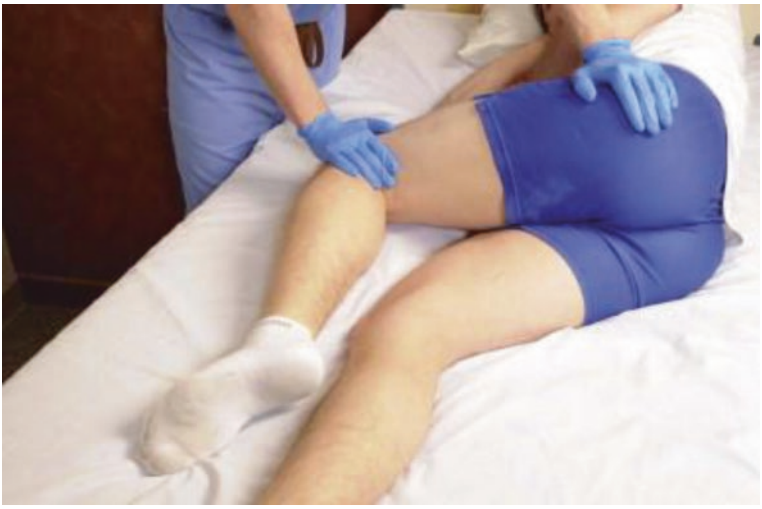

Fig. 5.2 Piriformis syndrome provocation test (Source: *Atlas of Interventional Pain Management*, Chapter 130, 711–724 [2])

position along with increased pain when lifting or flexing forward at the waist. Advanced piriformis syndrome may cause weakness in the ipsilateral gluteal and lower extremity muscles. It is often difficult to distinguish piriformis syndrome from lumbar radiculopathy. Generally speaking, patients with lumbar radiculopathy have back pain with associated motor, sensory, and reflex changes, whereas those with piriformis syndrome lack reflex changes. Plain films are an initial imaging modality that is often performed to rule out any bony abnormalities. Magnetic resonance imaging (MRI) is often next in line to detect a herniated disc or spinal stenosis. Physical examination still remains of utmost importance. There are a handful of provocative maneuvers that can point toward a diagnosis of piriformis syndrome. These include the following:

1. *Pace sign* – pain and weakness with seated abduction of hip against resistance.
2. *Lasèague's sign (straight leg test)* – pain with unresisted flexion, adduction, and internal rotation of flexed him in the distribution of the sciatic nerve.
3. *Freiberg's sign* – pain with forced internal rotation of extended hip.
4. *Tinel sign* – Similar to that used in the diagnosis of carpal tunnel, it can also be elicited over the sciatic nerve. Tapping just underneath the gluteal fold will cause paresthesias in the distribution of the sciatic nerve.
5. *Piriformis syndrome provocation test* – Patient is placed in modified Sims' position with the affected leg facing the ceiling. The hip of the affected leg is flexed 50°, the ipsilateral hip is stabilized, and the affected leg is pushed toward the floor. Reproduction of pain carries high sensitivity for the diagnosis of piriformis syndrome (Figs. 5.2 and 5.3)

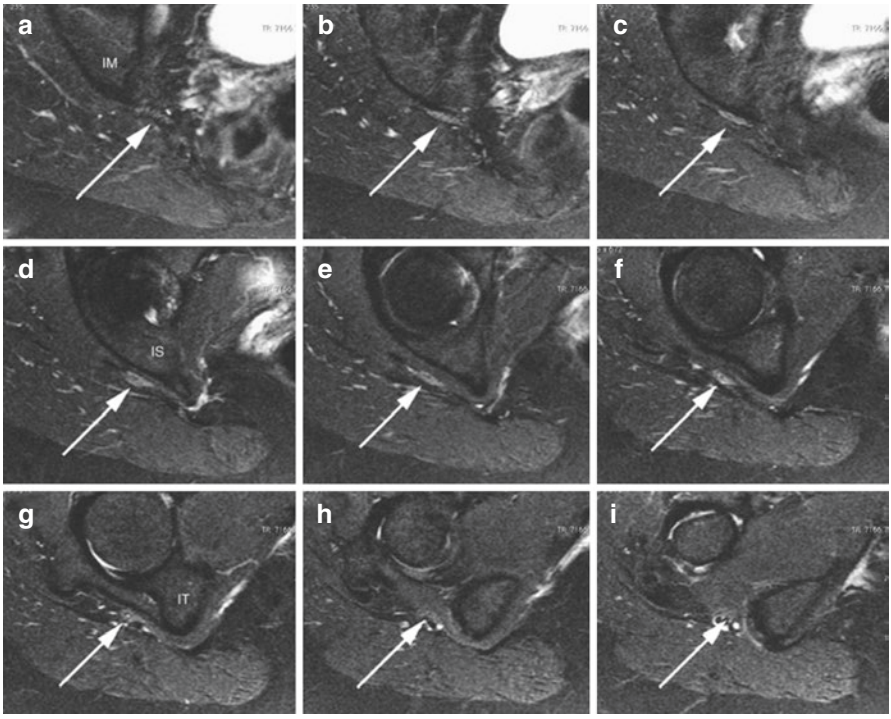

Fig. 5.3 (**a**) The sciatic nerve is bowed over the medial surface of the piriformis muscle. (**b**) Nerve image intensity increases as the nerve passes between the piriformis tendon and the ischial margin. (**c–f**) The image intensity increase persists as the nerve descends through the ischial tunnel. (**g–i**) Nerve image intensity progressively normalizes, with the nerve becoming isointense with surrounding muscle as it descends into the upper thigh. *Arrows* indicate the sciatic nerve. *IM* ischial margin, *IS* ischial spine, *IT* ischial tuberosity (Source: Filler [8]. *Atlas of Interventional Pain Management*, Chapter 130, 711–724 [2])

Treatment

The treatment options for piriformis syndrome are extensive, ranging from conservative medical management to interventional injection techniques. Initial treatment usually begins with a combination of nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors and physical therapy. Sleeping with a pillow between the legs may also help to alleviate the pain as well.

The above exercises (Fig 5.4) have been shown to be effective in strengthening the piriformis muscle and relieving the pain of piriformis syndrome and are explained as follows:

1. *Gluteal stretch* – Patient lies on their back with both knees bent and rests the ankle of the injured side over the opposite knee. Thigh is held on the uninjured side, pulled toward the chest for 15–30 s and repeated three times.

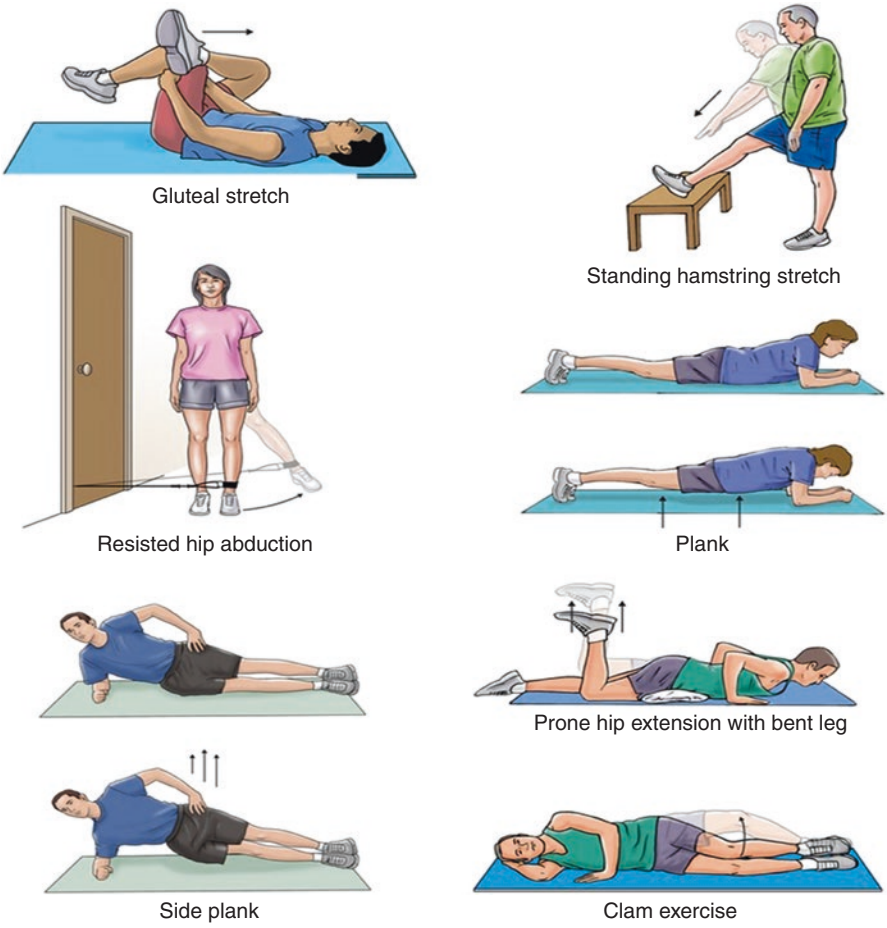

Fig. 5.4 Piriformis syndrome rehabilitation exercises (©2014 McKesson Corporation and/or one of its subsidiaries. All rights reserved)

2. *Standing Hamstring stretch* – Place the heel of the injured side on a stool about 15 inches high and keep leg straight. Lean forward until stretch is felt in the hamstring area. Hold for 15–30 s and repeat three times.
3. *Resisted hip abduction* – Stand near a door with the injured side away from the door. Tie an elastic band around the ankle on the injured side and attach the other end to the door. Pull the injured leg away from the door keeping the leg straight. Perform two sets of 15 repetitions.
4. *Plank* – Lie on stomach resting on the forearms. Keeping the legs straight, lift hips off the floor until they are in line with the shoulders. Support with forearms and toes. Hold for 15 s and repeat. Work up to 60 s.

5. *Side plank* – Lie on slide with legs, hips, and shoulders in a straight line. Lift hips off the floor and support weight on forearm with elbow under the shoulder. Hold this for 15 s and work up to 1 min.
6. *Prone hip extension* – Lie on stomach with a pillow under the hips. Bend the knee on the injured side. Tighten the abdominal muscles. Lift the bent leg off the floor about 6 inches and hold for 5 s. Perform two sets of 15 repetitions.
7. Clam *exercise* – Lie on the uninjured side with hips and knees bent and feet together. Raise the top leg toward the ceiling keeping heels touching. Hold for 2 s and lower slowly. Do two sets of 15 repetitions.

Injection

If conservative management with the above fails, the next step is piriformis injections that can be performed with or without image guidance. This section will go over some of the different interventional techniques that exist for the treatment of piriformis syndrome.

Both anterior and posterior approach exist injections without the use of image guidance. In order to perform the posterior approach, the patient is placed in the modified Sims' position with the affected side facing up. First locate the posterior superior iliac spine (PSIS) and greater trochanter and draw a line connecting these two points. A 22G needle is then inserted about 4 cm below the midpoint of this line in a perpendicular fashion. Advance the needle slowly with the assistance of a nerve stimulator. Eventually, dorsiflexion or plantar flexion of the ankle and foot will occur. To increase the chances of successful treatment, stimulation of the above response must occur between 0.2 and 0.5 mA. Here, the local anesthetic + steroid combination is injected [1, 2].

Anterior Approach

Patient is placed in the supine position. Here, the inguinal region and femoral crease is exposed. Palpate the femoral artery in the femoral crease and draw a perpendicular line in the caudad direction to a point roughly 5 cm away from the palpated pulse. Here, the needle is inserted in a perpendicular fashion. Initially, a quadriceps twitch will be elicited. Upon advancing the needle, further a calf and hamstring twitch will also occur. Another variation to the anterior approach also exists. Draw an imaginary line between the anterior superior iliac spine (ASIS) and pubic tubercle and split that line into thirds. Then, draw another line from the greater trochanter to the lesser trochanter. Next draw a perpendicular line from the distal third of the first line to the second line. This intersection point is where the needle will be inserted (Fig. 5.5) [1, 2].

Ultrasound-guided piriformis injections have also been well described in the literature. This technique is more difficult to visually appreciate than with fluoros-

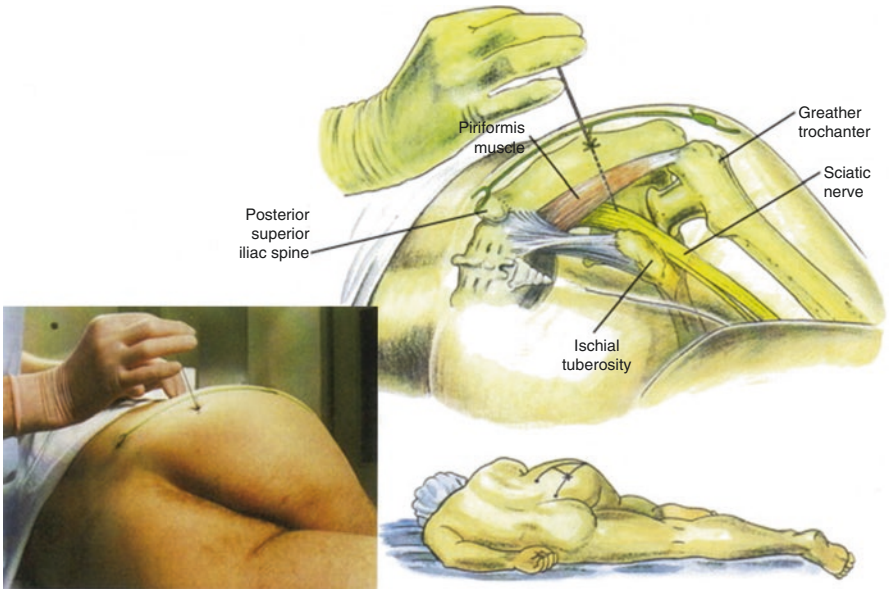

Fig. 5.5 Posterior approach to piriformis injection

copy; however, an endpoint can be obtained with an adequate image on ultrasound. In this technique, the patient is placed prone on the examination table and the ultrasound placed on the opposite side of the operator. A curved low-frequency ultrasound probe is recommended for this injection. If the ultrasound being used has Doppler capabilities, it may be useful to identify the inferior gluteal artery medial to the sciatic nerve and anterior to the piriformis. Place the ultrasound transducer in a transverse position over the sacroiliac (SI) joint. Move caudal with the transducer until the ilium is no longer visualized, that is where the greater sciatic notch is located. Using a 20–22 g 10- to 12-cm needle, advance the needle through skin and fat. At this point, the gluteus maximus is seen. Piriformis is a muscle that resides deep in the gluteus maximus. Deep and medial to the piriformis, the sciatic nerve can be seen. Another option is to place the ultrasound transducer over an imaginary line between the greater trochanter and ischial tuberosity and move the probe superior. Here, the piriformis muscle should also be seen just inferior to the gluteus maximus. To confirm that the appropriate structures are being seen the patient is asked to flex the knee to 90° and rotate the hip internally and externally. With these motions, the piriformis can be seen sliding over the ischium (Figs. 5.6 and 5.7) [3].

Lastly, fluoroscopic technique is often and more commonly used for piriformis injections. Patient is placed prone on the fluoroscopy table. The inferior margin of the SI joint is imaged and the point of entry for the needle in this technique is 1–2 cm caudal and lateral to this point. An insulated needle is advanced with the nerve stimulator turned on until a motor response in the sciatic nerve distribution is achieved (plantar flexion and inversion at the ankle). Motor response should be achieved at 0.2–0.5 mA. 40 mg of methylprednisolone or triamcinolone with 5 ml of saline is

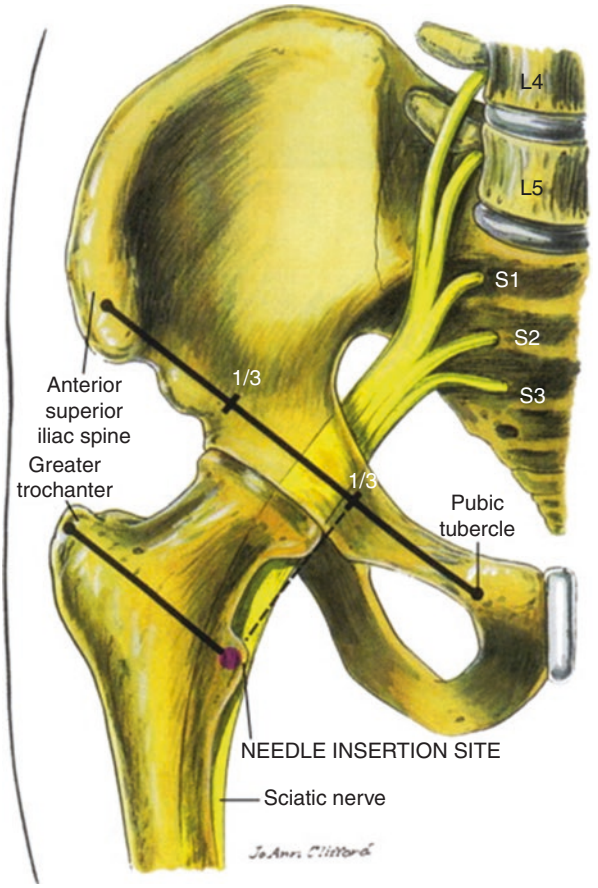

Fig. 5.6 Anterior approach to piriformis injection

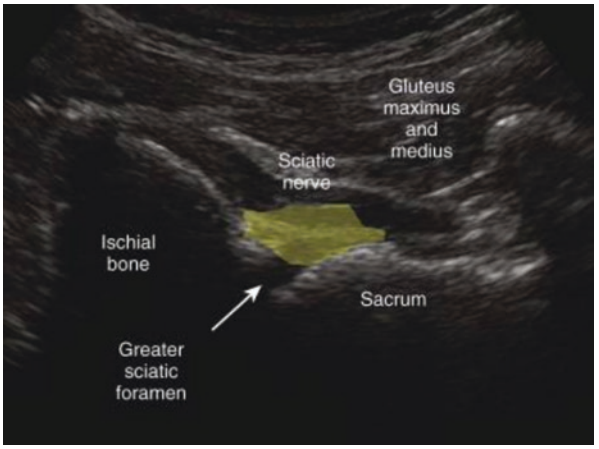

Fig. 5.7 Ultrasound-guided image of piriformis injection

injected. Then the needle is pulled back 1 cm into the piriformis muscle itself and 1–2 cm of contrast is injected to achieve an outline of the piriformis muscle. About 5 ml of 0.25 or 0.5 % bupivacaine with 40 mg of steroid is injected (Fig. 5.8).

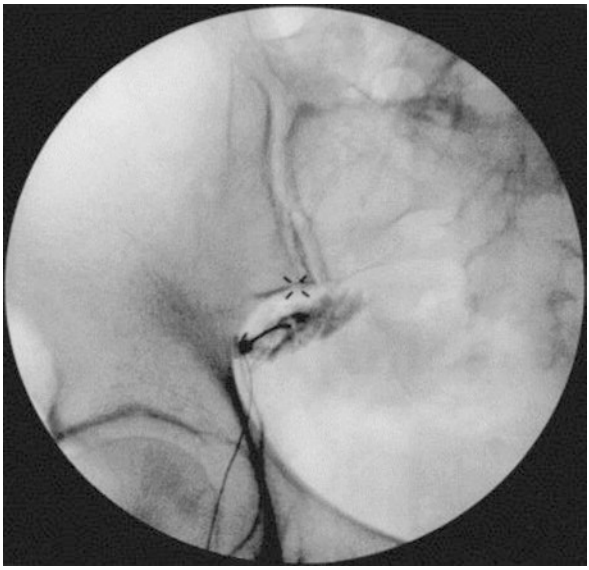

Fig. 5.8 Fluoroscopic image of a piriformis injection. Contrast is seen enveloping the piriformis muscle

Patients who may not be experiencing any sciatic syndromes may still have symptoms associated with piriformis inflammation and irritation. In this instance, it may be beneficial to perform an injection into the belly of the piriformis similar to a trigger point injection, usually a combination of local anesthetic and steroid. This can usually be done without any imaging. The insertion points of the needle are at points one-third and two-thirds along a line connecting the PSIS and greater trochanter. Two more injections are done 1–3 cm below these two points. The end point of the needle advancement can be determined when a fascial click is felt, usually about 4–5 cm deep. If sciatic symptoms are elicited, the needle should be withdrawn until the symptoms disappear. A successful injection is usually when the patient has pain on abduction of the lower limb [4].

Another method is to identify the greater trochanter and ischial tuberosity on the involved side. Draw an imaginary line between these two points. The midpoint of this line is where the sciatic nerve usually lies. Using a 25G 3.5-inch needle, advance the needle perpendicular to the skin until a paresthesia in the sciatic distribution is achieved then the needle withdrawn 1 mm (Fig. 5.9).

Caudal steroid injections and local anesthetic injections have also been anecdotally shown to be effective likely due to diffusion of the medication along the nerve roots to the sciatic nerve and blocking the innervation of the piriformis muscle.

Side Effects and Complications

The most common side effect of any piriformis injection is ecchymosis and hematoma. These can be avoided by putting pressure on the injection site after the block is complete. Nerve injury is also possible as the techniques mentioned above can

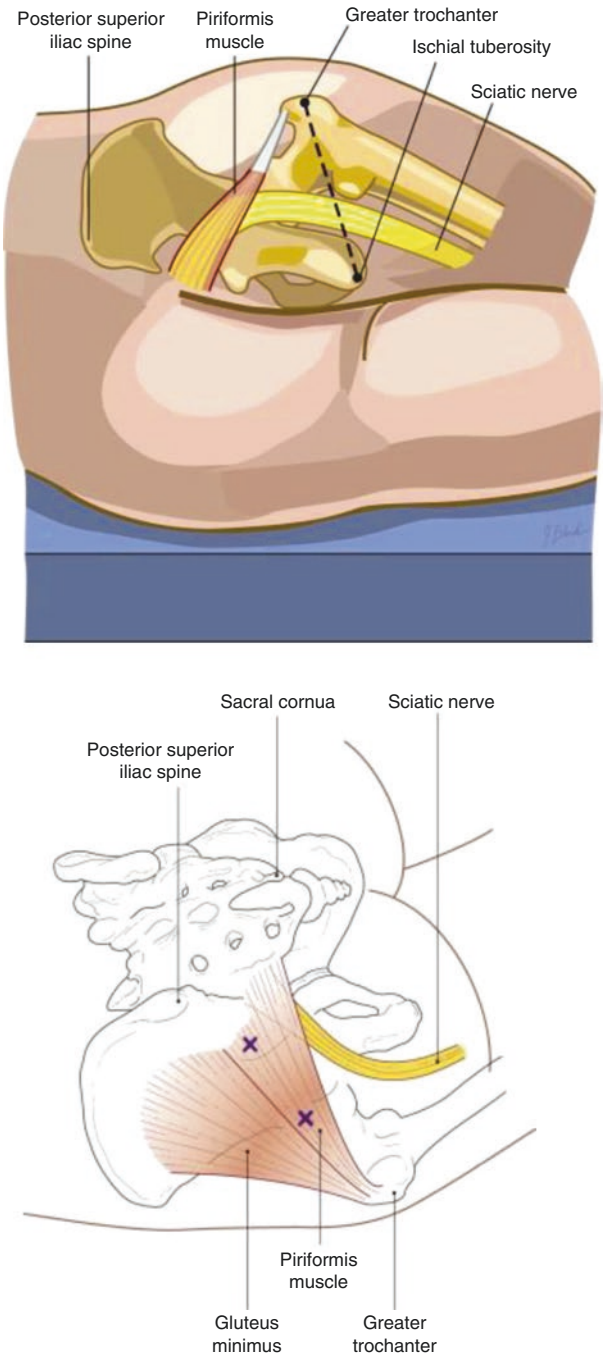

Fig. 5.9 Landmarks for direct piriformis muscle injection (Source: *Atlas of Interventional Pain Management*, Chapter 130, 711–724 [2])

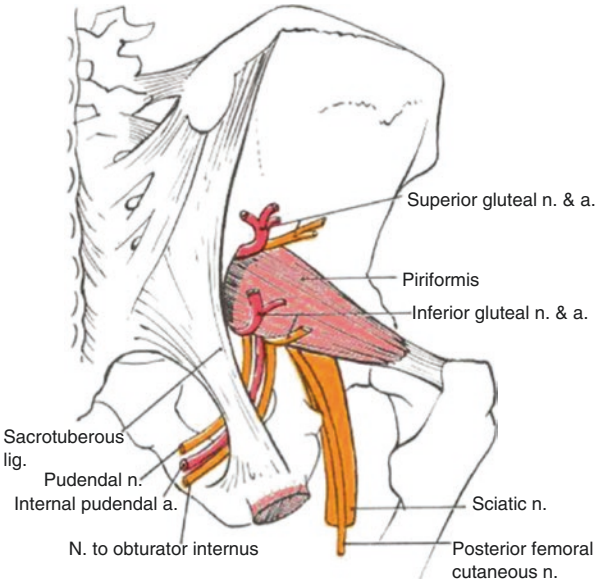

Fig. 5.10 Anatomy of the pudendal nerve [7]

often cause paresthesias in the sciatic nerve distribution. Advancing the needle slowly and avoiding intraneural injection can prevent this complication.

Pudendal Neuralgia

Pudendal nerve entrapment can lead to a condition known as pudendal neuralgia (also known as cyclist's syndrome, pudendal canal syndrome, or Alcock's syndrome). The pudendal nerve is the main nerve of the perineum and carries sensation from the external genitalia of both males and females and also the skin around the anus. It is also responsible for the motor function of the male and female external urethral sphincter. Its anatomical location proves to be significant when discussing piriformis syndrome and its various treatment modalities. The pudendal nerve originates from the sacral rami of S2–S4. It passes between the piriformis and coccygeus muscles after it exits the greater sciatic foramen. It then reenters the pelvis via the lesser sciatic foramen. Here, it traverses the pudendal canal with the internal pudendal artery and vein to become the inferior anal nerve, perineal nerve, and dorsal nerve of the penis and clitoris. Pain with this syndrome involves the urethra, perineum, clitoris, mons pubis, vulva, lower one-third of the vagina, and labia. In men, it also includes the penis and scrotum. Pain is worse with sitting and typically worsens throughout the day. Generally, it is a neuropathic-type pain commonly described as burning and numbness but can also include straining/burning with urination, dyspareunia, and persistent genital arousal disorder (Fig. 5.10).

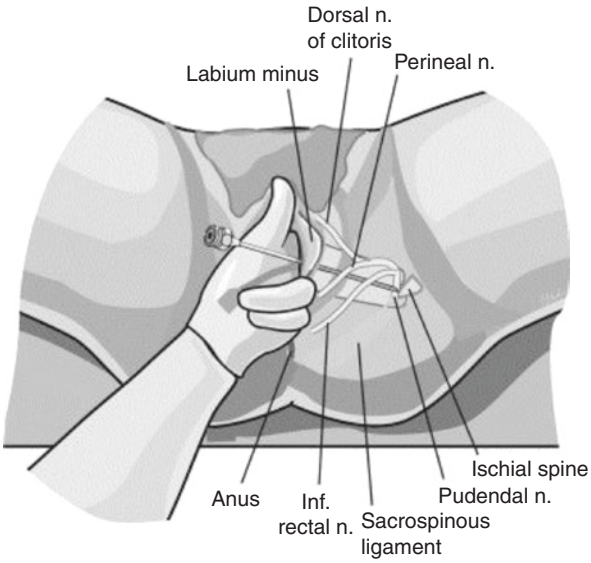

Fig. 5.11 Tranvaginal approach to pudendal nerve injection

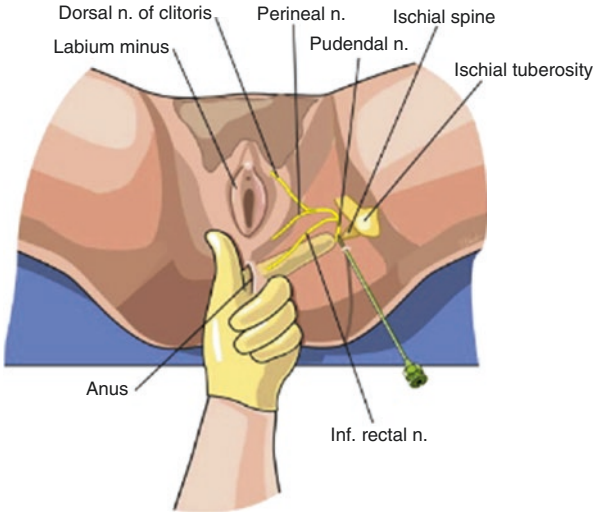

Fig. 5.12 Transperineal approach to pudendal nerve block

Diagnosis

Diagnosis is made largely based on the patient's history and symptoms. Another common inciting event is prolonged time in the lithotomy position, either under general anesthesia or in pregnant patients. It may also result from pelvic sling

operations where the pudendal nerve can become entrapped in a malpositioned stitch. There is no accurate test to make the diagnosis; however, pudendal nerve motor latency test, electromyography (EMG), and diagnostic nerve blocks can be utilized.

Treatment

Like any other disease process, treatment usually begins with conservative management. This consists of NSAIDs, antiepileptic or TCA meds, and possibly opioids. Another common treatment option to avoid entrapment while sleeping is to place a doughnut-shaped pillow between the legs.

Transvaginal Approach

Patient in lithotomy position, index and middle fingers on nondominant hand are placed into vagina until ischial spine is palpated. Needle guide is then inserted between the fingers and placed against mucosa anterior to ischial spine. A 20G 6-inch needle is placed through guide through sacrospinous ligament just beyond ischial spine. Loss of resistance is felt. 10 cc of 1 % lidocaine is injected. Needle is withdrawn and additional 3–4 cc is injected to block inferior rectal nerve (Fig. 5.11) [5].

Transperineal Approach

Patient in lithotomy position. Ischial tuberosity palpated and area one inch lateral and posterior to this is prepared. Index finger on nondominant hand is inserted into rectum to identify ischial spine. A 6-inch needle is then placed in previously prepared area and directed toward ischial spine. Finger in the rectum helps guide needle just beyond ischial spine. After negative aspiration for heme, inject 10 ml of 1 % lidocaine and withdraw to cover inferior rectal nerve (Fig. 5.12) [6].

These pudendal nerve blocks are commonly employed in obstetrics during vaginal delivery. Somatic pain during the second stage of labor, which involves time from maximal cervical dilation to delivery of the baby, occurs in the S2–S4 segment. Pain impulses travel down these nerve roots via the pudendal nerve. Pudendal nerve blocks can provide quick and effective pain relief during this stage of labor. Pudendal artery and vein are in close proximity to the nerve so intravascular injection is possible. Rectal perforation is also theoretically possible however it is a much lower risk.

Other Treatment Modalities

Besides the treatments mentioned earlier, other less common and less well-known treatment techniques exist. Rolfing can be employed to help treat the pain associated with the syndromes above, paying close attention to the gluteal and lumbosacral areas. This deep tissue massage technique aims to restructure and reset structural misalignments within muscle, connective tissue, and fascia. Contraindications to rolfing include connective tissue disorders in the affected area, individuals with cancer where massage may disrupt the protective connective tissue and advance malignant cells, and those with deep vein thrombosis where a clot can become dislodged. Myofascial release can also be employed. With this technique, the aim is to release, or soften, the fascia that envelops muscles. By doing this, blood and lymphatic flow is improved and tissue becomes more mobilized. Acupuncture can also be used and the theory behind this is that local tissue trauma causes the release of endorphins that provides pain relief. Additionally, in accordance with the gate theory, acupuncture stimulates peripheral nerves and turns off specific nerve fibers in the central nervous system (CNS) that prevents the transmission of pain. Topical agents such as lidocaine patches, diclofenac gel (Voltaren®), and compound creams can also be used for temporary relief.

References

1. Waldman SD. Piriformis syndrome. Atlas of common pain syndromes. Philadelphia: Elsevier Saunders, Inc; 2012. p. 266–8.
2. Waldman SD. Piriformis block. Atlas of interventional pain management. Philadelphia: Elsevier Saunders, Inc; 2015. p. 711–24.
3. Brown D. Sciatic block. Atlas of regional anesthesia. Philadelphia: Elsevier Saunders, Inc; 2010. p. 101–10.
4. Abram SE, O'Connor TC. Muscle injection. Atlas of pain injection techniques. Philadelphia: Elsevier Saunders, Inc; 2014. p. 101–10.
5. Waldman SD. Pudendal nerve block: transvaginal approach. Atlas of interventional pain management. Philadelphia: Elsevier Saunders, Inc; 2015. p. 638–40.
6. Waldman SD. Pudendal nerve block: transanal approach. Atlas of interventional pain management. Philadelphia: Elsevier Saunders, Inc; 2015. p. 641–7.
7. Dartmouth Medical School [Internet]. New Hampshire: O'Rahilly, 2009. Basic human anatomy; Figure 14.2. Available from http://www.dartmouth.edu/figures/chapter_14/14-2.HTM.
8. Filler AG. Piriformis and related entrapment syndromes: diagnosis and management. Neurosurg Clin N Am. 2008;19(4):609–22.

Chapter 6
Lumbar and Sacral Radiculitis

Natalie Trautman and Michael Sabia

Introduction

Lumbar and sacral radiculopathy is a major cause of low back and lower extremity pain, numbness, and weakness but can also cause pain of the urogenital areas. There are various pathologies that can lead to urogenital pain emanating from the back, such as disc herniation, spinal stenosis, spondylolisthesis, mechanical compression, coccygodynia, orchialgia, and nerve entrapment. Once diagnosed, there are multiple treatment modalities available, ranging from conservative to interventional. Interventional techniques include epidural steroid injections (ESIs), medial branch blocks, and radiofrequency ablation. Surgical management is considered occasionally in patients with severe, difficult to treat symptoms.

Anatomy

Vertebral Column

The back is composed of two major divisions, namely the anterior portion and the posterior portion. The anterior part is made up of 33 vertebral bodies connected to intervertebral discs and supported anteriorly by the anterior longitudinal ligament

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and posteriorly by the posterior longitudinal ligament. The posterior portion of the back mainly consists of the bony pedicles, transverse processes, laminae, and spinous processes [1]. The primary function of the vertebral column is to protect the spinal cord [2].

Joints

The intervertebral joints describe the articulation of each vertebra with the vertebra above and below it. The facet, or zygapophysial, joints are composed of the inferior articular process of one vertebra and the superior articular process of the neighboring vertebra. The lumbar facet joints constitute the posterior border of the neural foramen [2].

Innervation

The spine is innervated by 31 pairs of spinal nerves, named after their respective vertebrae. Beginning with the eighth spinal nerve, they exit below their specific vertebrae and each is composed of a dorsal and ventral root. The facet joints derive their innervation from the medial branch of the posterior dorsal rami of each spinal nerve. There are unique aspects of the lumbar spine which contribute to more frequent compression and therefore radiculopathy. For example, the L5 nerve is the largest of the spinal nerves in relation to its foramen and hence is more prone to compression [2]. In addition, lumbar nerve roots course laterally 1–2 cm prior to leaving through the vertebral foramina, thus increasing the chances of compression. This is in contrast to cervical and upper thoracic nerve roots, which exit the foramina at virtually the same level at which they entered [1].

Spinal Cord

The spinal canal houses the spinal cord, its meninges, fat, lymphatics, and a venous plexus. The spinal cord is covered by the pia mater, the first of the three meninges. The next layer is the arachnoid mater and the space between the two is known as the subarachnoid space and contains cerebrospinal fluid (CSF). The subdural space is a potential space that exists between the arachnoid mater and the dura mater. Outside of the dura mater is the epidural space, the target of many interventional pain injections [1]. The spinal cord begins at the foramen magnum and continues until L1–L2 in adults and L2–L3 in children [1, 2]. It ends in the conus medullaris and attaches to the periosteum of the coccyx via the filum terminale, which is a continuation of the pia mater [1, 3].

Lumbar and Sacral Radiculopathies and Urogenital Pain

Disc Herniation

The intervertebral discs in the vertebral column are composed of an outer annulus fibrosus layer and an inner gelatinous nucleus pulposus. Over time as aging occurs, the annulus fibrosus and posterior longitudinal ligament can weaken and allow the inner nucleus pulposus to herniate into the spinal canal. This herniation occurs most commonly in the posterolateral direction due to the thin structure of the annulus posteriorly. During herniation, the contents of the intervertebral disc can compress spinal nerve roots, thus causing pain of that particular dermatome [1].

Patients with disc herniation often complain of lower back pain extending to the hips and buttocks with occasional radiation down the leg of the involved side, numbness, weakness, tingling, paresthesias, and muscle spasms. Rarely, if disc contents compress the cauda equina, a medical emergency termed "cauda equina syndrome" can occur, with leg weakness and bowel and bladder incontinence [4]. Patients commonly report exacerbation of pain with back flexion, lifting, sitting for long periods of time, and maneuvers that inadvertently cause increases in intraabdominal pressure, such as coughing, and alleviation of pain with laying down [1]. A positive straight leg raise performed in a supine patient, combined with radicular symptoms, weakness, and decreased reflexes, can indicate nerve root compression or dysfunction [5].

Atypical presentations of disc herniation have also been described in the literature, such as Wouda et al's case reports. The case reports described two patients who both presented initially with longstanding scrotal pain which later began to radiate to the back. These patients underwent extensive surgical and urologic work-ups without definitive diagnosis. Eventually imaging of the lumbar spine was obtained and showed disc herniation and both patients' scrotal pain resolved completely following lumbar discectomy [6]. The scrotum derives its innervation from L1–L2 and S2–S3 and it is reasonable that compression of these nerve roots by disc herniation, or other causes, can lead to scrotal pain, either alone or in combination with more typical radicular symptoms. It has been found that groin pain due to lumbar disc herniations occurs more frequently with herniations at the L4–L5 level rather than the L5–S1 level and is more common when the herniation is posterocentral, rather than anterior or lateral [7]. Peng et al. also described a male patient with back pain, numbness, and paresthesias of the lower extremity, and unilateral testicular pain in whom imaging showed an L4–L5 spondylolisthesis. He underwent lumbar decompression with subsequent resolution of his sciatic and scrotal symptoms. This report theorizes that the testicular pain experienced with lumbar spine pathology is referred via the genital branch of genitofemoral and ilioinguinal nerves [8]. Holland, Feldman, and Gilbert concluded in their review of chronic orchialgia that the most common cause of this severe, persistent testicular pain is referred pain due to lumbar radiculitis [9].

For diagnosis of disc herniation, magnetic resonance imaging (MRI) is the best imaging modality to evaluate the lumbar spine anatomy. In patients with contraindications to MRI, computed tomography (CT) or myelography can be used. For further

evaluation, electromyography (EMG) and nerve conduction velocity testing can provide valuable information about the individual nerve roots and can be used to differentiate between plexopathies, radiculopathies, and entrapment neuropathies [4]. Treatment of radicular pain due to disc herniation depends on its chronicity. Acute short-term symptoms typically resolve in under 2 months with conservative management, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, activity modification, and physical therapy. Pain lasting greater than 3 months can be termed chronic and treatment focuses on a multidisciplinary approach, incorporating more physical therapy and antidepressants [1]. ESIs, which will be discussed in more detail later, can be used as an adjuvant in both cases.

Spinal Stenosis

Spinal stenosis is another form of lumbar pathology that may manifest as urogenital pain. It can be classified as either congenital or acquired, in which the congenital form is a developmental disorder and the acquired form is a degenerative process over time [10]. Acquired spinal stenosis usually presents with increasing age and is caused by gradual narrowing of the spinal canal. This process begins with age-related deterioration of the nucleus pulposus and progressive formation of osteophytes between the vertebral bodies. The surrounding ligaments and facet joints, over time, can grow and calcify and further constrict the spinal canal [1].

The symptoms of spinal stenosis can be similar to disc herniation and include back pain radiating to buttocks and lower extremities, weakness, and numbness in the dermatomal distribution of the lumbar nerve roots where compression is occurring. These symptoms, often described as pseudoclaudication or neurogenic claudication, tend to worsen with ambulation or standing and improve with rest, specifically with sitting and lumbar spine flexion. Physical exam can show decrease in sensation and motor strength of the legs, and loss of reflexes.

Diagnosis requires a combination of thorough patient history and physical examination in conjunction with imaging, such as MRI and CT scans [4]. Midsagittal views on imaging can show the lumbar canal diameter and are used to further classify spinal stenosis. A lumbar spinal canal diameter of 10–13 mm is consistent with relative stenosis, and a diameter of less than 10 mm constitutes absolute stenosis [10, 11]. Treatment of spinal stenosis is multimodal and similar to disc herniation, incorporating NSAIDs, muscle relaxants, physical therapy, and antidepressants. Interventions such as ESIs, particular caudal blocks, can be beneficial [4].

Facet Joint Disease

The facet joints of the lumbar spine, also known as the zygapophysial joints, serve as additional stabilizers, aid with back extension, and restrict over-rotation of the spine (Fig. 6.1). As intervertebral discs degenerate over time, the facet joints help to uniformly distribute the weight of the spinal column. These joints can also undergo

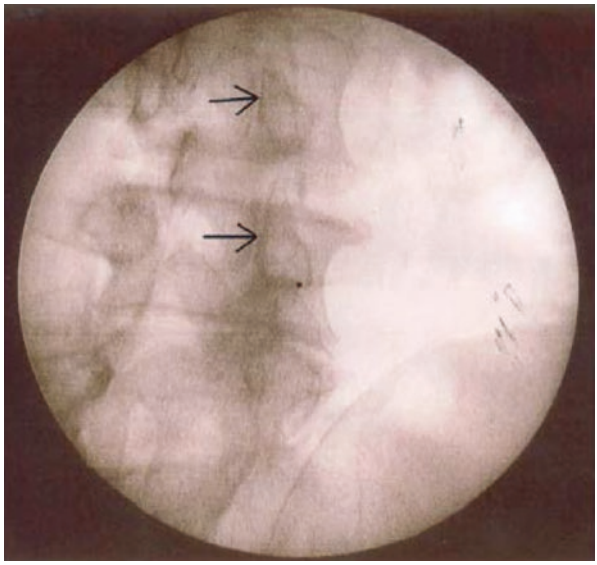

Fig. 6.1 The *arrows* depict the left L3–L4 and L4–L5 facet joints (From Cosgrove et al. [12])

arthritic changes and deterioration with increased strain during the aging process [2]. The symptoms of facet joint disease are achy low back pain that radiates to the gluteal area, flank, hip, and thigh [13]. The etiology of this nonspecific dull pain of the buttocks and flanks can be unclear upon presentation.

Physical exam maneuvers, such as bending, extension, and rotation of the back, aggravate the pain and aid in diagnosis. The patient usually exhibits tenderness to palpation surrounding the paraspinal region [5]. The mainstay of diagnosis lies in the diagnostic medial branch block, in which local anesthetic, alone or in combination with steroid, is injected around the medial branch portion of the spinal nerves which innervate the facet joints. A positive response occurs when the patient experiences significant but temporary pain relief and suggests that facet disease is the cause of the patient's pain. In patients with successful medial branch blocks, longer-term radiofrequency ablation of the medial branch nerves can be considered and will be discussed later in this chapter [2].

Mechanical Compression

Occasionally, tumors or masses can arise in various areas of the spine and cause radicular-like symptoms that involve the urogenital dermatomes. These can include benign tumors such as bone cysts or hemangiomas, as well as primary malignancies like osteosarcomas [14]. In addition, a variety of cancers preferentially metastasize to the spine, such as prostate, breast, lung, and multiple myeloma. These bony metastases can cause bone pain or have the potential to cause neural and vascular compression, thus resulting in radiculopathy. The location of the pain, that is, pelvis, low back, sacral, depends on where the tumor is situated and what structures

surround it [1]. The exact sacral innervation was determined during past radiofrequency ablation procedures of sacral nerve roots. The S2 dermatome reflects the innervation of the groin, buttocks, genitals, and posterior thigh, while the S3 dermatome covers the genitals, rectum, and perianal region. S4 and S5 dermatomes include the vagina and anus [15].

Cysts are another form of physical occurrence that can affect the pelvis and sacral nerves to cause urogenital symptoms. Sacral cysts, also known as Tarlov cysts, have been described as occurring in 4.6–9 % of the adult population [16] and are irregular protrusions of the meninges that occur in close proximity to the sacral nerve roots. These perineural cysts contain cerebrospinal fluid and at times have a connection with the general subarachnoid space, although that does not always occur. Past surgical examination of these cysts has shown that the walls contain sacral nerve roots that have lengthened and elongated over time as the cysts increased in size. Patients with sacral cysts often describe atypical and persistent pain, tingling, and dysesthesias in the region of the buttocks, perineum, rectum, and vagina [15] and even bowel and bladder dysfunction, sacral pain, and impotence [16].

In imaging Tarlov cysts, MRI is utilized first line to show the specific location of the cyst and its relationship to surrounding structures, as well as to quantify the amount of CSF contained. CT myelography can be used afterwards to better evaluate its features. Treatment of sacral cysts include conservative forms, such as NSAIDs, physical therapy, caudal ESIs [17], lumbar CSF drainage or cyst drainage, and surgical options, such as cyst excision, although surgery is typically reserved for patients who show no response to medical management [16].

There have been reports in the literature of schwannomas occurring in sacral nerve roots and causing pelvic pain and lumbosacral radicular symptoms. Schwannomas are nerve sheath tumors that can occur throughout the body and can cause compression of the nerve roots leading to pain and other symptoms. Possover and Kostov discussed three women who presented with long-standing pelvic pain unresponsive to various medications. Physical exam revealed S2–S4 radiculopathy and imaging, both transvaginal ultrasound and MRI, showed a sacral mass. Each of these patients underwent laparoscopy for tumor resection and recovered with complete resolution of vulvar and coccyx pain postoperatively. The reasoning for the varied symptoms experienced by the patients, from urogenital discomfort to lumbosacral radiculopathy, stems from the combined involvement of the S2–S4 nerve roots and compression of them by the schwannoma [18].

Coccygodynia

Coccygodynia is a disease process described as pain in the area of the coccyx that usually presents when a person is sitting. It can be idiopathic in patients with normal coccygeal mobility or it can arise with atypical mobility of the coccyx, such as after trauma, fractures, or childbirth. It occurs more commonly in women than in men and presents with sacrococcygeal pain that is usually exacerbated by sitting on the

buttocks. Physical exam can show tenderness to palpation of the coccyx or on rectal examination.

Dynamic X-ray imaging can commonly display hypermobility or subluxation of the coccyx. Treatment includes conservative management with NSAIDs, heat, physical therapy, massage, and local anesthetic/steroid injection at the ganglion impar, or can be more aggressive with coccygectomy for severe intractable pain [19].

Other Radiculopathies

Diabetic radiculopathy is a phenomenon that has been described, occasionally with features clinically indistinguishable from lumbar disc herniation. It can produce symptoms of lumbar and/or sacral radiculopathy, including pelvic and urogenital discomfort. Naftulin et al. discussed several case reports in which diabetic patients presented with lower extremity pain, pelvic and groin pain, weakness, decreased sensation, and decreased reflexes. They underwent thorough work-ups with EMGs that showed denervation and were treated conservatively with NSAIDs, adjuvant medications, physical therapy, bed rest, and tighter glucose control. These patients have the potential for spontaneous improvement of some, if not all, of their symptomatology [20].

Another unique pathology is herpes zoster-related radiculopathy. Helfgott et al. described the case report of a patient with buttock and lower extremity pain upon presentation, with physical exam showing motor weakness, decreased reflexes, and positive straight leg raise. After several days, the patient had new cutaneous lesions of the knee, thigh, and gluteal region diagnostic of herpes zoster, which later progressed to bladder dysfunction. EMG and nerve conduction studies showed denervation in the left-sided L3–L5 nerve roots, and the patient improved progressively over the next several months. In this form of radiculopathy, diagnosis can be difficult as the radicular symptoms can often predate the skin findings [21].

Treatment

Lumbar Epidural Steroid Injections

ESIs performed under fluoroscopy are a nonsurgical intervention used to treat symptoms of radiculopathy caused by inflammation in the area of disc herniation or similar pathology in the lumbar spine [1]. The theory behind the mechanism of action of these injections states that during disc herniation, the nucleus pulposus releases multiple inflammatory factors into the spine, such as phospholipase A-2, prostaglandins, leukotrienes, IL-6, IL-8, and TNF-α. The epidural steroids serve to moderate this inflammatory process and thus reduce the pain and other radicular symptoms that patients can feel. The various corticosteroids currently in use consist of triamcinolone,

methylprednisone, betamethasone, and dexamethasone. Additionally, the mixture includes a local anesthetic such as bupivacaine and a contrast agent [2]. The local anesthetic alleviates the patient's pain initially after injection and the steroid takes action several days later [1].

There are numerous indications for lumbar ESIs (LESIs), including disc herniation, spinal stenosis, and nerve root compression and/or inflammation. Contraindications include sepsis, local infection at the site to be injected, coagulopathy including increased international normalized ratio (INR) or thrombocytopenia, elevated intracranial pressure, and allergy to any of the injected substances [2].

The epidural space, the target of these injections, extends from foramen magnum down to the sacrococcygeal membrane. When starting at the skin, the planes traversed by the epidural needle include the subcutaneous tissue and fat, supraspinous ligament, interspinous ligament, the ligamentum flavum, and then finally the epidural space. The ligamentum flavum is very dense and lends a feeling of increased resistance on the needle as one is performing an epidural. Once the ligamentum is passed, there is an immediate and characteristic "loss of resistance" which signifies entry into the epidural space [22].

There are several approaches to performing a LESI: interlaminar, transforaminal, and caudal. The interlaminar approach is usually attempted with the patient in the prone position and a pillow or blanket under the abdomen to aid in opening the interlaminar space. The fluoroscope is used initially to determine the target, after which the back is prepped and draped in sterile fashion. Lidocaine or similar local anesthetic is infiltrated to numb the skin, and then, the epidural Tuohy needle is inserted. Typically, the loss of resistance technique is utilized in combination with fluoroscopy to identify the epidural space and contrast is injected. Following epidurography, the steroid/local anesthetic mixture is administered. After this procedure, the patient is then routinely monitored in a recovery area to ensure that no neurologic deficits or pain has developed [2].

The transforaminal approach to LESIs (TFLESI) focuses on application of the steroid medication anteriorly close to the nerve root, and thus, the source of the patient's pain and other symptoms [2]. This injection is performed through the intervertebral foramen of the spine, as opposed to interlaminar injections, which are performed between the laminae [23]. The theory behind this technique is based on the belief that interlaminar LESIs can be too dispersed and that concentrating the medication close to the affected nerve can increase pain relief [24]. TFLESIs are accomplished exclusively under fluoroscopic guidance with similar equipment and preparation as for an interlaminar epidural.

Another variation of ESI to treat radicular pain is the caudal injection (Fig. 6.2). Caudal epidural injections are performed under fluoroscopy, using the sacral hiatus as an initial landmark. Once the steroid mixture is injected, it moves upward within the epidural space to approximately the L4 level [2]. Caudals typically require a greater volume of injectate than LESIs and TFLESIs, varying from 10 to 64 mL [24].

The volume of medication to be injected has been evaluated, although no standard of care currently exists. Rabinovitch found in his systematic review that the greater the volume injected, the greater degree of radicular pain relief that patients

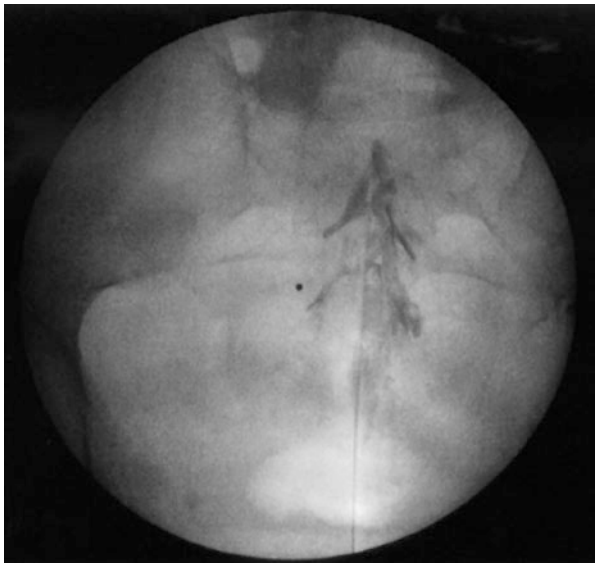

Fig. 6.2 Fluoroscopic image of a caudal epidural steroid injection (From Cosgrove et al. [12])

experienced [25]. Lee, however, performed a retrospective review of patients receiving various ESIs and found no significant difference in pain relief between small and large volumes of injectate in transforaminal injections. In addition, there are potential consequences associated with injecting larger volumes into the epidural space, including spinal cord compression, and these must be kept in mind when performing these procedures [26].

Another controversial variable in ESIs is the plica mediana dorsalis. This is a reported connective tissue band within the dorsal midline of the epidural space. Various studies have been performed that have verified its existence using epidurography, epiduroscopy, and injection of resin into cadavers, although others believe that it may only exist as an artifact. Some believe that the plica mediana dorsalis has the potential to interfere with LESIs by blocking medication spread in the epidural space or causing unilateral spread. It has even been mentioned that this debatable anatomical variant can affect correct positioning of epidural catheters [27].

During these interventions, there is always the risk of complications, as with any procedure. Infection can occur but is rare. Allergic reactions to any of the medications injected can occur but are also uncommon. The incidence of dural puncture, in which the needle passes through the epidural space and pierces the dura, is approximately 5 %, which is greatly reduced during the caudal approach. Occasionally, patients will experience an increase in back and leg pain following the procedure, and this risk can be lessened by injecting slowly during the procedure. Headache occurs in about 1 % of LESIs and can be due to CSF leak during dural puncture (postdural puncture headache) or to the entrapment of air in the subarachnoid space. These headaches usually resolve on their own but have been described in the literature as lasting for greater than 1 year in 0.1 % of patients [24].

Patients receiving transforaminal injections are particularly at an increased risk of spinal cord injury as compared to interlaminar LESIs. There have been reported cases of paraplegia at various levels following TFLESIs and although rare, this complication can be devastating. At the lumbar level, the implicated mechanism is either injection of particulate steroids into a radicular artery or from radicular artery spasm caused by needle disruption. Several forms of steroids used in these injections, such as methylprednisolone, triamcinolone, and betamethasone, are particulate and can amass. If this occurs upon injection into an artery, there is a risk of embolization and thrombosis, leading to spinal cord ischemia and possibly paraplegia [28]. Another complication associated with TFLESIs include the risk of intrathecal injection from inadvertent dural puncture, leading to hypotension, prolonged anesthesia, and even arachnoiditis [2].

In an effort to decrease the incidence of these events, the FDA's Safe Use Initiative recently reviewed the current recommendations for interlaminar and transforaminal ESIs and released a consensus of clinical safeguards to be followed for these procedures that aim to reduce the risk of neurologic complications. They recommend proper use of fluoroscopy views (lateral, oblique, AP) to gauge needle position and depth prior to injection and the necessity for contrast injection under real-time fluoroscopy or digital subtraction imaging, if available, during transforaminal injection. The SUI also advocate use of extension tubing for TFLESIs to prevent dislodgment of the needle when syringes are connected, nonparticulate steroids such as dexamethasone as a first-line agent in lumbar transforaminal injections and to abstain from heavy sedation during these injections for patients to retain the ability to communicate any negative effects or sensations during the procedure [28].

Lumbar Medial Branch Blocks and Radiofrequency Ablation

Medial branch blocks are a diagnostic tool used when the suspected etiology of radicular pain are the facet joints. In this technique, local anesthetic is injected into the area of the facet joint to block the medial branches of the spinal nerve roots that innervate that joint (Fig. 6.3). A positive response in which a patient experiences significant pain relief (at least 50 % reduction) following the block can signify that the patient is a candidate for radiofrequency ablation [2].

Radiofrequency ablation is an option for long-lasting pain relief for patients who responded well to the diagnostic medial branch blocks. It involves the application of electric current at an elevated temperature to the medial branches in an effort to create lesions. These lesions selectively disrupt the Aδ and C pain fibers and not the motor or sensory portions of the nerves [2]. This thermal, or continuous, radiofrequency technique works by providing a high-frequency alternating current through an electrode which causes ion movement. This increases the temperature of the tissues that are being treated and thus lesioning of the nerve takes place, also known as coagulation. The critical temperature required for cell death is approximately

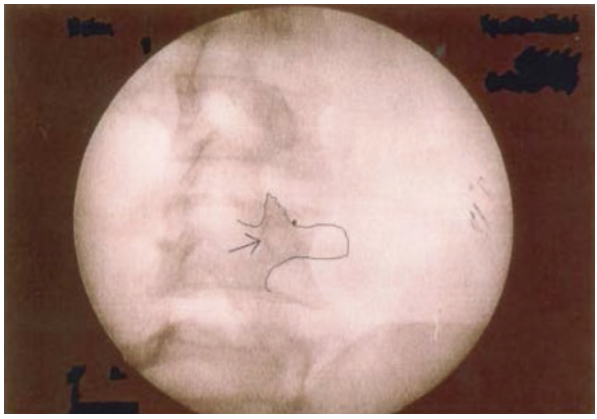

Fig. 6.3 The "Scotty dog" is outlined in this image. The *arrow* shows left L4 pedicle and the *dot* depicts the target for a medial branch block, the eye of the Scotty dog

45–50 °C, but for this procedure, a temperature of 80 °C is maintained for 60–90 s. During this time, coagulation occurs and the lesion expands.

Pulsed radiofrequency is another option for pain control in patients with facet pain. It differs from thermal radiofrequency in that the alternating current is provided in bursts at temperatures at or below 42 °C, as opposed to the continuous high-heat thermal technique. Based on current studies, however, it appears that continuous radiofrequency provides superior results for pain control in terms of both amount of pain relief and duration [24].

Following the ablation procedure, it can take up to 3 weeks for the patient to experience the full effects. Possible complications include brief numbness or increase in pain, also known as postprocedure neuritis, following the radiofrequency lesioning that is self-limited [2]. This tends to resolve on its own within 3 months, but it is now customary to inject a steroid preparation after the conclusion of the radiofrequency lesioning to reduce the incidence of neuritis [29].

Surgery

Occasionally, there are patients for whom conservative techniques do not provide adequate pain control for their radiculopathy symptoms. These patients have usually completed oral analgesics, physical therapy, and minimally invasive injections as described earlier. Patients with herniated discs can undergo a surgery termed discectomy or hemilaminectomy, in which the disc material is removed operatively, with or without the removal of a portion of the lamina. Spinal stenosis can be treated with a laminectomy, a surgery during which multiple levels of lamina are removed in order to create more space and relieve pressure in the spinal canal. Fusion can also be performed to increase stability in the lumbar spine.

In addition to the array of complications that can occur with any surgery, it is unclear whether these surgical techniques can truly provide long-lasting pain relief.

Ultimately this varies from patient to patient. Prior to undertaking surgery as a form of treatment, it is key to perform a thorough history and physical examination, and to exhaust the conservative approaches of treatment [15].

Conclusion

Urogenital pain is a complex disease process with a multitude of etiologies, including various lumbosacral disorders. Although lumbar and sacral pathologies are varied and can range from the common disc herniation to the more obscure Tarlov cysts, the effects oftentimes are similar, with patients experiencing pain and paresthesias of the urogenital region. Treatment is multidisciplinary, often combining physical therapy techniques with interventional procedures. Epidural steroid injections serve to reduce inflammation and thus radicular symptoms, while medial branch blocks and radiofrequency ablation improve the pain of facet joint disease. Lumbosacral pathologies thus require a thorough evaluation and a combination of treatments to best alleviate a patient's pain.

References

1. Butterworth JF, Mackey DC, Wasnick JD. Morgan and Mikhail's clinical anesthesiology. 5th ed. New York: The McGraw-Hill Companies Inc; 2013. p. 943–1076.
2. Gupta A, editor. Interventional pain medicine. New York: Oxford University Press; 2012. p. 5–174.
3. Erdmann A. Concise anatomy for anaesthesia. London: Greenwich Medical Media; 2001. p. 44.
4. Waldman SD. Atlas of common pain syndromes. Philadelphia: Saunders; 2012. p. 238–47.
5. Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical anesthesia. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 1511–3.
6. Wouda EJ, Leenstra S, Vanneste JA. Scrotal pain as the presenting symptom of lumbar disc herniation: a report of 2 cases. Spine. 2005;30(2):E47–9.
7. Yukawa Y, Kato F, Kajino G, Nakamura S, Nitta H. Groin pain associated with lower lumbar disc herniation. Spine. 1997;22(15):1736–9.
8. Peng B, Li D, Pang X. Degenerative lumbar spondylolisthesis with testicular pain. Pain Med. 2014;15(1):169–70.
9. Holland JM, Feldman JL, Gilbert HC. Phantom orchialgia. J Urol. 1994;152(6 Pt 2):2291–3.
10. Arbit E, Pannullo S. Lumbar stenosis: a clinical review. Clin Orthop Relat Res. 2001;384:137–43.
11. Genevay S, Atlas SJ. Lumbar spinal stenosis. Best Pract Res Clin Rheumatol. 2010;24(2): 253–65.
12. Cosgrove MA, Towns DK, Fanciullo GJ, Kaye AD. Interventional pain management. In: Vadivelu N et al., editors. Essentials of pain management. New York: Springer; 2010. p. 271–5.
13. Brummett CM, Cohen SP. Facet syndrome: facet joint injections, medial branch blocks, and radiofrequency denervation'. In: Benzon HT, Raja SN, Liu SS, Fishman SM, Cohen SP, Hurley RW, Narouze S, Malik KM, Candido KD, editors. Essentials of pain medicine. Philadelphia: Saunders; 2011. p. 322–9.

14. Yamamoto T, Fujita I, Kurosaka M, Mizuno K. Sacral radiculopathy secondary to multicentric osteosarcoma. Spine. 2001;26(15):1729–32.
15. Melzack R, Wall PD, editors. Handbook of pain management. Philadelphia: Elsevier; 2003. p. 295–1027.
16. Acosta Jr FL, Quinones-Hinojosa A, Schmidt MH, Weinstein PR. Diagnosis and management of sacral Tarlov cysts: case report and review of the literature. Neurosurg Focus. 2003;15(2): 1–7.
17. Freidenstein J, Aldrete JA, Ness T. Minimally invasive interventional therapy for Tarlov cysts causing symptoms of interstitial cystitis. Pain Physician. 2012;15(2):141–6.
18. Possover M, Kostov P. Laparoscopic management of sacral nerve root schwannoma with intractable vulvococcygodynia: report of three cases and review of literature. J Minim Invasive Gynecol. 2013;20(3):394–7.
19. Fogel GR, Cunningham PY, Esses SI. Coccygodynia: evaluation and management. J Am Acad Orthop Surg. 2004;12(1):49–54.
20. Naftulin S, Fast A, Thomas M. Diabetic lumbar radiculopathy: sciatica without disc herniation. Spine. 1993;18(16):2419–22.
21. Helfgott SM, Picard DA, Cook JS. Herpes zoster radiculopathy. Spine. 1993;18(16):2523–4.
22. Waldman SD. Atlas of interventional pain management. Philadelphia: Saunders; 2015. p. 500–13.
23. Goodman BS, Posecion LW, Mallempati S, Bayazitoglu M. Complications and pitfalls of lumbar interlaminar and transforaminal epidural injections. Curr Rev Musculoskelet Med. 2008;1(3–4):212–22.
24. Fishman S, Ballantyne J, Rathmell J. Bonica's management of pain. Philadelphia: Lippincott Williams and Wilkins; 2010.
25. Rabinovitch DL, Peliowski A, Furlan AD. Influence of lumbar epidural injection volume on pain relief for radicular leg pain and/or low back pain. Spine J. 2009;9(6):509–17.
26. Lee JH, Moon J, Lee SH. Comparison of effectiveness according to different approaches of epidural steroid injection in lumbosacral herniated disk and spinal stenosis. J Back Musculoskelet Rehabil. 2008;22(2):83–9.
27. Stevens DS, Balkany AD. Appearance of plica mediana dorsalis during epidurography. Pain Physician. 2006;9(3):268–70.
28. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, Riew KD, Rosenquist RW, Aprill C, Rost NS, Buvanendran A, Kreiner DS, Bogduk N, Fourney DR, Fraifeld E, Horn S, Stone J, Vorenkamp K, Lawler G, Summers J, Kloth D, O'Brien Jr D, Tutton S. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. Anesthesiology. 2015;122(5):974–84. doi:10.1097/ALN.0000000000000614.
29. Pope JE. Complications of radiofrequency rhizotomy for facet syndrome. In: Ranson MT, editor. Reducing risks and complications of interventional pain procedures. Philadelphia: Saunders; 2012. p. 126–31.

Chapter 7
Scrotal Pain

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Abbreviations

CRP	C-reactive protein
NSAID	Non-steroidal anti-inflammatory drug
US	Ultrasound

Introduction

Scrotal pain, whether it is acute or chronic, often provides a diagnostic challenge for the urologist. Each case must be carefully approached in a systematic fashion starting with a full patient history and physical examination. During the history, it is important to characterize the pain and differentiate between chronic and acute pain to help the clinician follow the correct diagnostic path.

Physical Examination

The physical examination of the scrotum may often be limited by pain, swelling, and skin changes [1]. It is important to carefully examine the skin of the scrotum, as there are both hair follicles and apocrine glands making it a frequent location for infection and sebaceous cysts. The testicles should be gently palpated between the fingertips using both hands. Under normal circumstances, the testicles should

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be firm and rubbery in consistency with a smooth surface. The epididymis is palpable as a ridge posterior to each testicle. In order to examine for a hernia, the clinician should place his or her index finger at the external inguinal ring by gently invaginating the scrotum. A hernia will be felt as a bulge when the patient is asked to bear down or valsalva. The valsalva maneuver will also make a varicocele more obvious on physical examination. Transillumination of the scrotum may be helpful in determining the difference between a solid mass or cystic mass [2].

Anatomy and Embryology

In order to have a proper understanding of scrotal pain, one must first have a fundamental understanding of the anatomy and embryology of the scrotum and its contents. Understanding the origin of the testicle is very important as it helps to explain its vascular supply and innervation. For example, the close location of the developing kidneys and testes helps to explain why stones of the urinary tract can often present as testicular pain.

The developing testes are held loosely in place near the developing kidney by two ligamentous structures (the dorsal ligament or cranial suspensory ligament and the ventral ligament). Between 10 and 15 weeks gestation, the testes remains close to the inguinal region by enlargement of the gubernaculum and regression of the cranial suspensory ligament in the setting of enlargement of the abdominal cavity [3].

The layers covering the testicle starting from the outside include the skin, dartos fascia, external spermatic fascia, cremasteric fascia, cremasteric muscle, internal spermatic fascia, tunica vaginalis (parietal and then visceral), and lastly the tunica albuginea. The normal adult testis measures 4–5 cm in length, 3 cm in width, and 2.5 cm in depth with a volume of approximately 30 ml [4]. The right testicle usually lies anterior to the left [2].

The blood supply to the testicle is robust – there are three separate sources. The testicular artery (or gonadal artery) is the main blood supply to the testicle and arises directly from the aorta inferior to the superior mesenteric artery. Additional blood supply to the testicle comes from the cremasteric artery (branch of inferior epigastric) and the artery of the vas deferens (branch of the vesical arteries) [5].

The venous drainage of the testicle forms a pampiniform plexus that surrounds the testicular artery within the spermatic cord. Within the inguinal canal, these veins join to form larger veins and ultimately the gonadal vein in the abdomen. The gonadal vein on the right drains directly into the vena cava, while on the left it drains into the left renal vein [4].

The innervation of the testes arises from the aortic and renal plexus and travels along the course of the gonadal vessels [4]. Again this provides an explanation for referred pain patterns in obstructive ureteral stones. Nerves also arise from the pelvic plexus and travel next to the vas deferens. The relative anatomy of the nerves to

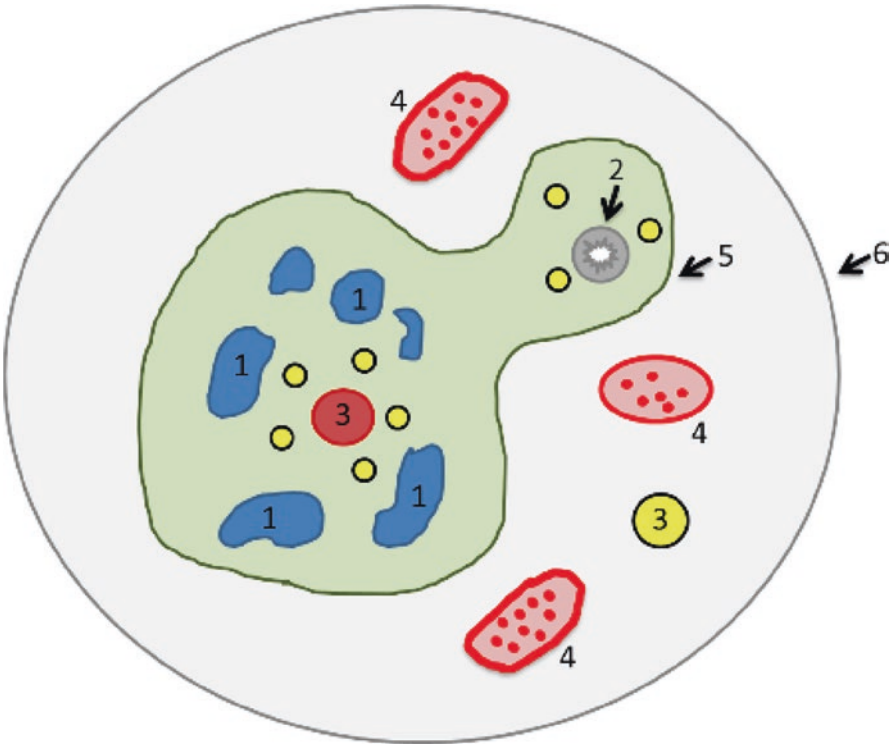

Fig. 7.1 Cross section of the spermatic cord. Neural innervation (*in yellow*) includes plexus around the vas deferens and testicular artery, and the genitofemoral nerve located between the internal and external spermatic fascia. *1* Pampiniform plexus, *2* Vas deferens, *3* Testicular artery, *4* Cremasteric muscle, *5* Internal spermatic fascia, *6* External spermatic fascia

recognizable structures is illustrated in Fig. 7.1. There may be cross-communication in these plexuses, explaining while testicular pain may be bilateral when there is only one diseased testis. The parietal and visceral tunica vaginalis and scrotal tissue are supplied by the genital branch of the genitofemoral nerve. However, its innervations stop at the tunica albuginea as the seminiferous tubules have no innervation [6].

Acute Scrotal Pain

Acute scrotal pain is potentially a medical emergency requiring necessitating a prompt evaluation to prevent potential testicular loss. The most common causes of acute scrotal pain include testicular torsion, torsion of the appendix testis, acute epididymitis, and testicular trauma. They will be discussed below.

Testicular Torsion

Testicular torsion is defined as ischemia of the testicle secondary to rotation of the testicle along its longitudinal axis. There is a short window of approximately 4–8 h from the start of torsion symptoms until surgical intervention is required to save the affected testicle [7].

The prevalence of testicular torsion in men aged 1–25 years in the United States has been estimated from a nationwide inpatient sample to be 4.5 cases per 100,000 male patients per year [7]. The age distribution of testicular torsion has is bimodal, with an increased frequency in the first year of life and in early adolescence. In a cohort analysis of 2443 patients ages 1 to less than 18, testicular loss was seen in 42 % of the boys undergoing surgery for testicular torsion. Age less than 10 is associated with increased rate of loss [8].

Extravaginal torsion, defined as twisting of the entire cord and processus vaginalis, is more common in the neonatal period. Intravaginal torsion, defined as twisting of the cord within the tunica vaginalis, is seen in early adolescence. It has a higher incidence and is seen with the bell-clapper deformity, a condition in which the testicle has more mobility within the tunica vaginalis [9, 10]. The majority of testicular torsion occurs in a medial direction and clinicians can attempt de-torsion by turning the testicle in the same way they turn the pages of a book. However, several studies have shown torsion in the lateral direction in up to 29–33 % of cases [11, 12].

Testicular torsion often has a classic presentation of sudden onset severe unilateral scrotal pain. Pain that persists after the administration of opioid analgesia makes the suspicion for torsion higher. The patient may report previous bouts of intermittent pain likely secondary to episodes of torsion and spontaneous detorsion. The presences of reflexive nausea and emesis can also be seen in up to 57–69 % of patients. On physical examination, the affected testicle is usually high riding and extremely tender. Venous distention and transudate often cause the affected testicle to be large in size compared to the contralateral testicle. Loss of the cremasteric reflex is also an important finding that increases suspicion for torsion [11].

Patients who have a history and physical exam strongly concerning for testicular torsion should be referred immediately for surgical exploration. Surgical exploration should not be delayed to obtain imaging as each minute of extending ischemia can decrease testicular survival rates [9]. The testicle can usually be saved 90 % of the time if de-torsion is performed within 6 h. After 12 h 50 % of testicles are viable. After 24 h less than 10 % are viable [13]. Doppler ultrasound is the most commonly used to evaluate the acute scrotum and has been found to be highly sensitive (88.9 %) and specific (98.8 %) for testicular torsion with a 1 % false-negative rate [14].

During testicular exploration, the testicle should be detorsed as quickly as possible and bilateral orchiopexy should be performed with permanent suture. The contralateral testicle is pexied regardless of the viability of the affected testicle [15] because the bell-clapper deformity is bilateral in up to 80 % of patients [16].

The urgency of diagnosis and treatment and a relatively high rate of adverse outcomes make testicular torsion a common area of litigation. The urologist usually

suffers the bulk of the litigation burden. The most common liability seen in litigation is a missed diagnosis. The urologist does not need to practice defensive medicine. However, he or she should strongly consider exploring the scrotum when the diagnosis is in question. Furthermore, based on previous litigation data, a prophylactic contralateral orchiopexy should always be performed when torsion is found [17].

Torsion of Appendix Testis

The testicular appendage is a remnant of the Mullerian duct, whereas epididymal appendages are from the mesonephric or Wolffian duct [18]. In a retrospective study of 138 patients with acute scrotal symptoms, 67 % of patients had torsion of an appendix testis [19]. Torsion of an appendage occurs more frequently in the prepubertal age group likely because increased hormonal stimulation enlarges the appendages, making them more susceptible to twisting. The presentation of a patient with torsion of an appendix testis usually has a sudden onset of pain similar to testicular torsion [18]. However, the occurrence of nausea and vomiting is usually less frequent [19].

Early after the onset of torsion on physical exam, the inflamed and ischemic appendage can be seen through the skin and is known as the "blue-dot sign." However, as local inflammation occurs the surrounding tissues become edematous and the diagnosis is not always clear. The use of a scrotal ultrasound after the inflammation has occurred often observes increased blood flow to the adjacent epididymis and testis and possibly a reactive hydrocele. These findings often cause many clinicians to come to the incorrect diagnosis of acute epididymitis or epididymo-orchitis. Fortunately, torsion of the appendix testis is self-limited and surgical intervention is not necessary. As the appendage infarcts the pain dissipates. Nonsteroidal anti-inflammatory medications (NSAIDS) are the mainstay of treatment in addition to comfort measures such as limited activity and warm compresses. A patient can present with torsion of an appendage more than once; there are potentially five anatomic sites where appendages may exist and more than one appendage may occur in a given site [18].

Epididymitis and Epididymo-Orchitis

Epididymitis is extremely common and usually secondary to retrograde ascent of an infectious pathogen. It has been reported to account for 0.3–0.69 % of outpatient visits [20, 21]. In men between the ages of 14 and 35, the most common infectious organisms are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. In patients younger than 14 or older than 35, epididymitis is usually caused by common urinary tract pathogens [21]. In about 30–40 % of patients, the etiology of the epididymitis cannot be found [20].

The presentation of epididymitis is usually gradual onset of pain. If caused by urinary tract pathogens, lower urinary tract symptoms, such as frequency urgency, hematuria, and dysuria, may be present. Having such lower urinary tract symptoms would be rare in testicular torsion. Nausea and vomiting is not common and can help differentiate between epididymitis and testicular torsion [21]. Acute-phase proteins, such as C-reactive protein (CRP), have also been used to help differentiate between epididymitis and testicular torsion. A significant elevation in CRP had a 96.2 sensitivity and 94.25 specificity in a study of 104 patients with an acute scrotum [22]. On ultrasound examination, one usually finds an enlarged epididymitis with increased Doppler flow. In one study on children, color Doppler ultrasound was shown to have a 70 % sensitivity and 88 % specificity for epididymitis [23]. However, in cases where there are any doubts about the diagnosis operative exploration should be performed.

Acute Orchitis

Isolated inflammation of the testicle is relatively uncommon; however, it can be seen with viruses such as mumps and coxsackie or bacteria, such as *Mycobacterium tuberculosis*, *Treponema pallidum* and *Brucella* spp [28]. Viral orchitis is usually associated with an abrupt onset of unilateral pain. Mumps orchitis is a common cause of viral and occurs in 20–30 % of males with a mumps infection [21]. With a mumps infection, the orchitis usually develops 4–7 days after the development of parotitis [20, 21].

Scrotal Trauma

Scrotal trauma can occur commonly during sports, motor vehicle accidents, assaults, and straddle injuries. Testicular rupture requires urgent surgical exploration. Additionally, if a scrotal hematoma is large enough exploration should be strongly considered [24]. Avulsion injuries of the scrotum can usually be closed even with large tissue loss. All penetrating injuries that violate the dartos fascia should be explored [25]. In cases of children with scrotal trauma, sexual abuse should be considered.

Fournier Gangrene

Given the large amount of hair follicles and apocrine glands on the scrotum infections of the scrotal wall are not uncommon. Fournier gangrene or necrotizing fasciitis involving the genital area is rare but has high lethal potential. Diabetes,

alcoholism, urethral stricture disease, and immunosuppression place individuals at higher risk. Local trauma, urine extravasation, paraphimosis, perianal infections, and surgery in the region can be inciting factors. Early symptoms are similar to cellulitis; however, Fournier's gangrene progresses rapidly and causes swelling, crepitus, discoloration, and necrosis of the skin and soft tissue. Prompt diagnosis, emergent antibiotics and surgical debridement is essential [26].

Other Causes

Other notable causes of acute scrotal pain include inguinal hernias, acute idiopathic scrotal edema, testicular cancer, varicocele, hydrocele, Henoch–Schonlein purpura, and referred pain.

Chronic Scrotal Pain

A patient is defined as having chronic orchialgia or testicular pain syndrome if they have intermittent or constant testicular pain for 3 months or longer and if it significantly interferes with their daily activities [27, 28]. As will often have pain involving the epididymis, vas deferens, and adjacent paratesticular structures chronic scrotal content pain is typically the nomenclature used [27].

Chronic scrotal pain is common and it has been estimated that 2.5 % of all urology visits are attributable to chronic scrotal pain. Scrotal pain is a difficult problem for both the patient and physician as there is no standard protocol for treatment or evaluation. A proposed treatment algorithm is shown in Fig. 7.2. While chronic scrotal content pain can occur at any age, it is more common in the mid to late 30s [27].

Chronic scrotal content pain can be debilitating and often leads to limitation in work, social, and sexual interactions. Not surprisingly, these patients are commonly depressed [27]. Similar to patients with chronic pelvic pain, men with chronic scrotal pain report less sexual interactions, diminished arousal, lower orgasmic function, and have an increased frequency of pain during and after sexual activity [29].

Somatic nerves from the genital branch of the genitofemoral nerve and the ilioinguinal nerve, as well as autonomic branches from the parasympathetic ganglia of T10–L1, provide innervation to the scrotum [27, 30]. Anatomically, impulses through nociceptors are carried to dorsal horn nuclei via intraspinal nerve roots and travels through the medial and lateral spinothalamic tracts to the brain [27].

The transition from acute pain to chronic pain is not completely understood. Normally, pain stimuli diminish as healing occurs, and ultimately, the pain sensation resolves. However, when painful stimuli are intense and persistent, peripheral and central modulation can occur where a new lower threshold is created. Additionally, there can be an increased frequency response, decreased latency response, latency amplification, and ultimately spontaneous nerve firing resulting in

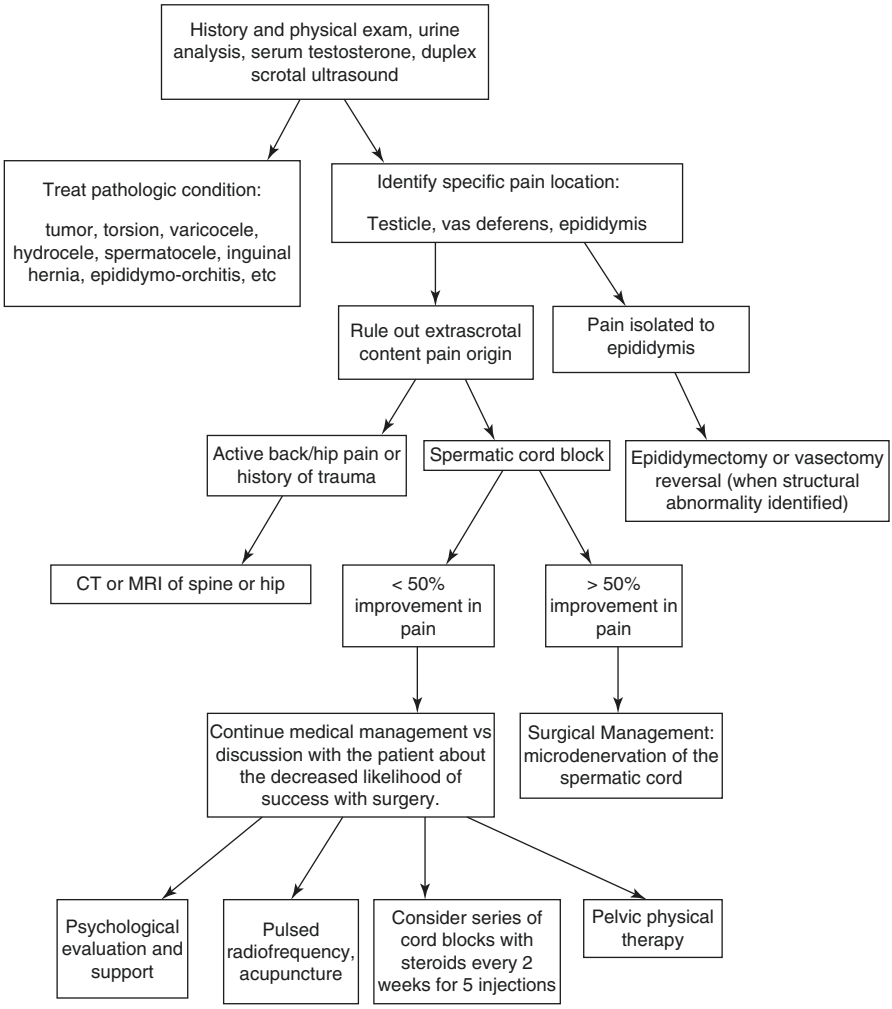

Fig. 7.2 A proposed system for evaluation of scrotal pain (Reprinted with permission from Levine and Hoeh [27])

allodynia, hyperalgesia, and hyperpathia [31]. It has also been shown that in patients with chronic scrotal pain there is a higher number of scrotal nerve fibers with evidence of Wallerian degeneration compared to normal [30].

The etiology of chronic scrotal content pain cannot be determined in up to 50 % of patients. Direct sources of pain include varicocele, spermatocele, tumor, infection, rarely hydrocele, trauma, pelvic floor dysfunction, and iatrogenic injury following vasectomy or inguinal hernia repair. Referred pain as mentioned previously can also cause chronic pain to the scrotum. One must look for ureteral stone disease, inguinal hernias, pelvic floor pathology, intervertebral disk pathology, and (rarely) retroperitoneal tumors [27].

Postvasectomy Pain Syndrome

The incidence of postvasectomy pain syndrome has been reported to be anywhere between 0.9 % and 54 %. However, fewer than 10 % of patients tend to seek treatment and evaluation. Studies in animals and humans have demonstrated that the pressure inside the proximal vas deferens and epididymal tubules increase in subjects with chronic pain. The disruption of electrical signals that travel adjacent to the vas deferens may also could also be a possible etiology of pain [27]. Sperm granulomas at the vasectomy site may also play a role. However, in a study of 505 men, 10 years after vasectomy, orchialgia was less common in men without sperm granulomas. This study suggested that an open-end vasectomy could cause less pain at the cost of a higher rate of recanalization [28]. All men seeking vasectomy should be counseled on the possibility of developing chronic pain [27].

Chronic Epididymitis

Chronic epididymitis has been defined as "symptoms of discomfort and/or pain of least 3 months in duration in the scrotum, testicle, or epididymis, located to one or both epididymis on clinical examination." The etiology of chronic epididymitis is not well understood and often no cause can be identified. Chronic epididymitis is thought to be associated with inflammatory, infectious, or obstructive factors. In a small analysis of 50 men with chronic epididymitis compared to controls, they were observed to have more sexual partners, a higher incidence of past sexually transmitted disease, and more self-reported musculoskeletal, neurologic, infectious, or inflammatory medical problems [32]. This finding supports the belief in a postinfective chronic epididymitis where inflammation and discomfort persists after an acute bacterial epididymitis. Some known etiologies of entities of chronic epididymitis include granulomatous epididymitis (e.g., tuberculosis or Bacillus Calmette-Guerin), drug-induced epididymitis (e.g., Amiodarone), generalized inflammatory illnesses (e.g., Behcet's disease), and obstruction distal to the epididymitis (e.g., vasectomy) [33].

Treatment of Chronic Scrotal Content Pain

Given the lack of evidenced based guidelines the treatment of chronic scrotal content pain can be troublesome [27]. When a varicocele, spermatocele, tumor, or hydrocele exist, surgery should be the first line therapy. In many studies, over 75 % of the patients reported pain relief after removal of the intrascrotal lesion [27, 34]. In patients with postvasectomy pain, syndrome vasectomy reversal has effective at alleviating of pain. Small studies have shown 50–69 % complete pain relief with partial improvement in pain up to 100 % [35, 36].

When there is no intrascrotal lesion to be removed, conservative management should be first line therapy. Simple treatments, such as scrotal support, NSAIDs, and antibiotics, when infection is present are usually attempted first. Quinolone antibiotics are preferred for treatment due to their higher penetration into the epididymis and testis [27]. However, it has been reported that in the majority of men with chronic scrotal pain, bacteria of clinical relevance cannot be isolated. Widespread use of antibiotics to all patients with chronic scrotal pain should be avoided to prevent resistance [37].

Other medications that can be used for chronic pain include antidepressants (e.g., amitriptyline, nortriptyline), gabapentin, and pregabalin. A trial of an alpha adrenergic antagonist could also be tried to relieve a functional obstruction or spasm [28]. However, when first-line measures fail, a multidisciplinary approach is recommended. It is especially useful to refer patients to a pelvic floor physical therapist when pelvic floor dysfunction is suspected. Similarly, a psychologist should be considered when a patient has signs/symptoms of depression [27]. A study utilizing a psychologist, anesthesiologist, physical therapist, and occupational therapist showed greater than 50 % symptomatic improvement in the majority of men treated with gabapentin or nortriptyline. One exception is men with postvasectomy pain syndrome: 7.5 % saw symptomatic improvement with either medication [38].

A spermatic cord block can also be used to try to break a pain cycle or help make the decision of whether surgical treatment might be helpful. A spermatic cord block can be done with or without steroids. The procedure is performed while the patient is in the supine position and the needle is inserted directly downward 1 cm inferior and 1 cm medial to the pubic tubercle. Immobilizing the palpable cord with the thumb and index finger of one's nondominant hand can be very helpful (Fig. 7.3). Spermatic cord block can also be done under US guidance by isolating the cord, locating structures with ultrasound, and injecting in the area of the neural plexuses as illustrated in Fig. 7.1. Content of injection includes botulinum toxin [39], and lidocaine with epinephrine and bupivacaine combination (Fig. 7.4) [40]. It has been shown that a temporary reduction in pain from a spermatic cord block is an independent predictor of success from microdenervation of the spermatic cord [41]. Pulsed radiofrequency ablation of the genitofemoral nerve is another recently studied method that may provide benefit in patients who temporarily respond to spermatic cord block [42, 43].

Microdenervation of the spermatic cord has been shown to be a safe and effective option for the treatment of idiopathic chronic scrotal pain after conservative efforts have failed. It has the advantage of sparing the testicle. Microdenervation of the spermatic cord results in complete relief in pain in as high as 71–100 % of patients. During the procedure, all structures are divided with the exception of for the identified arteries, lymphatics, and stripped vas deferens if patient has not had a prior vasectomy. If patient had a previous vasectomy, the vas deferens is divided again (Fig. 7.5) [27]. A last resort epididymectomy or orchiectomy may be considered. However, the success rate of this procedure is variable. If an orchiectomy is performed an inguinal approach has shown better success than a transscrotal approach [28].

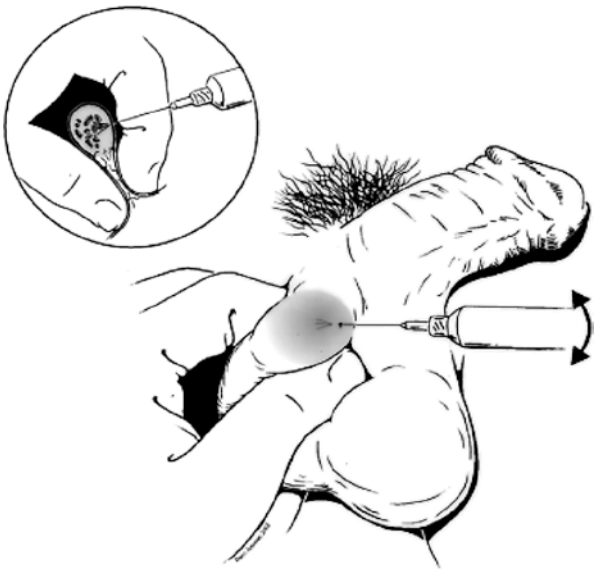

Fig. 7.3 Technique for spermatic cord block. The spermatic cord is isolated by palpation and local anesthetic is injected into the region (Reprinted with Permission from Issa et al. [43])

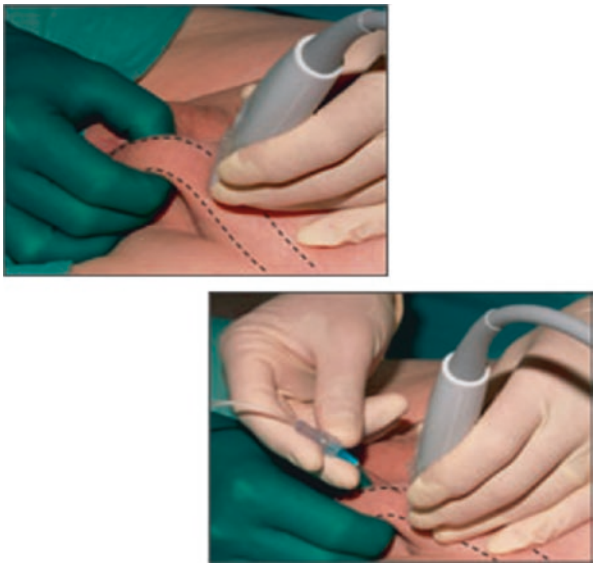

Fig. 7.4 Images showing the technique of the US-guided spermatic cord block. (**a**) The spermatic cord is grabbed with two fingers and gently lifted by the assistant. With one hand, the surgeon holds the US transducer transversely just distally of the superficial inguinal ring representing the morphological structures of the spermatic cord. (**b**) With his other hand, he injects the local anesthetic, avoiding vascular structures (Reprinted with permission from Birkhauser et al. [44])

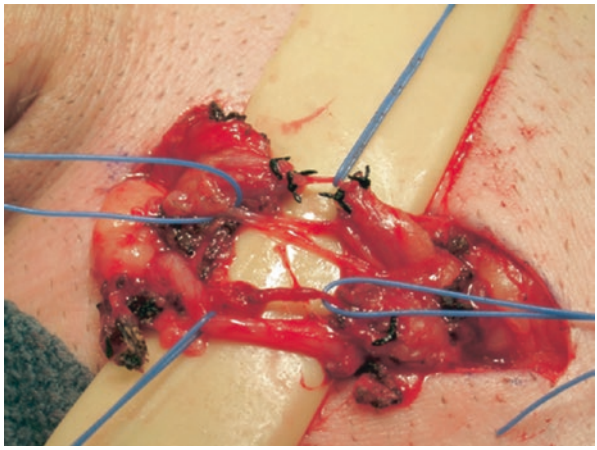

Fig. 7.5 Completed dissection of cremasteric artery, lymphatics, internal spermatic artery, vas deferens (*top to bottom*) as seen in a microdenervation surgery (Reprinted with permission from Levine and Hoeh [27])

Conclusion

Scrotal pain is a common symptom patients present with to an urologist's office. It can be challenging to diagnose and treat. Work-up starts with differentiating acute and chronic testicular pain. An accurate history and physical along with imaging is essential for accurate diagnosis and treatment of both acute and chronic scrotal pain. Acute pain should be ruled out for life-threatening or organ-threatening pathologies such as Fournier's gangrene or testicular torsion. After such pathologies are ruled out, there is currently no standard treatment protocol for orchialgia. Basic principles for acute and chronic pain include look for etiologies correctable by medical or surgical treatment. In instances where no specific diagnosis or etiology of scrotal pain is discernible, a multidisciplinary treatment plan including NSAIDS, spermatic cord block, microdenervation, and pelvic physical therapy are used to alleviate symptoms. It is important to recognize treatment modalities should begin with conservative approaches and progress to interventional approaches as needed.

References

1. Gordhan CG, Sadeghi-Nejad H. Scrotal pain: evaluation and management. Korean J Urol. 2015;56(1):3–11.
2. Gerber G, Brendler C. Evaluation of the urologic patient: history, physical examination, and urinalysis. In: Wein A, Kavoussi L, Novick A, Partin A, Peters C, editors. Campbell-Walsh urology, vol. 1. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 73–98.
3. Park J. Normal development of the genitourinary tract. In: Wein A, Kavoussi L, Novick A, Partin A, Peters C, editors. Campbell-Walsh urology, vol. 4. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 2975–3001.
4. Chung B, Sommer G, Brooks J. Anatomy of the lower urinary tract and male genitalia. In: Wein A, Kavoussi L, Novick A, Partin A, Peters C, editors. Campbell-Walsh urology, vol. 1. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 33–70.

5. Moore KKA. Testicles: undescended, retractile, and ascended. In: Palmer JS, editor. Current clinical urology: pediatric Urology. New York: Humana Press; 2011. p. 203–15.
6. Steger KWW. Anatomy of the male reproductive system. In: Chapple C, Steers W, editors. Practical urology: essential principles and practice. London: Springer; 2011. p. 57–68.
7. Mansbach JM, Forbes P, Peters C. Testicular torsion and risk factors for orchiectomy. Arch Pediatr Adolesc Med. 2005;159(12):1167–71.
8. Zhao LC, Lautz TB, Meeks JJ, Maizels M. Pediatric testicular torsion epidemiology using a national database: incidence, risk of orchiectomy and possible measures toward improving the quality of care. J Urol. 2011;186(5):2009–13.
9. Sharp VJ, Kieran K, Arlen AM. Testicular torsion: diagnosis, evaluation, and management. Am Fam Physician. 2013;88(12):835–40.
10. Karaguzel E, Kadihasanoglu M, Kutlu O. Mechanisms of testicular torsion and potential protective agents. Nat Rev Urol. 2014;11(7):391–9.
11. Ta A, D'Arcy FT, Hoag N, D'Arcy JP, Lawrentschuk N. Testicular torsion and the acute scrotum: current emergency management. Eur J Emerg Med. 2015;23(3):160–5.
12. Sessions AE, Rabinowitz R, Hulbert WC, Goldstein MM, Mevorach RA. Testicular torsion: direction, degree, duration and disinformation. J Urol. 2003;169(2):663–5.
13. Ringdahl E, Teague L. Testicular torsion. Am Fam Physician. 2006;74(10):1739–43.
14. Baker LA, Sigman D, Mathews RI, Benson J, Docimo SG. An analysis of clinical outcomes using color doppler testicular ultrasound for testicular torsion. Pediatrics. 2000;105(3 Pt 1):604.
15. Bolln C, Driver CP, Youngson GG. Operative management of testicular torsion: current practice within the UK and Ireland. J Pediatr Urol. 2006;2(3):190–3.
16. Favorito LA, Cavalcante AG, Costa WS. Anatomic aspects of epididymis and tunica vaginalis in patients with testicular torsion. Int Braz J Urol. 2004;30(5):420–4.
17. Matteson JR, Stock JA, Hanna MK, Arnold TV, Nagler HM. Medicolegal aspects of testicular torsion. Urology. 2001;57(4):783–6; discussion 6–7.
18. Gatti JM, Patrick Murphy J. Current management of the acute scrotum. Semin Pediatr Surg. 2007;16(1):58–63.
19. Boettcher M, Bergholz R, Krebs TF, Wenke K, Aronson DC. Clinical predictors of testicular torsion in children. Urology. 2012;79(3):670–4.
20. Ludwig M. Diagnosis and therapy of acute prostatitis, epididymitis and orchitis. Andrologia. 2008;40(2):76–80.
21. Trojian TH, Lishnak TS, Heiman D. Epididymitis and orchitis: an overview. Am Fam Physician. 2009;79(7):583–7.
22. Doehn C, Fornara P, Kausch I, Büttner H, Friedrich HJ, Jocham D. Value of acute-phase proteins in the differential diagnosis of acute scrotum. Eur Urol. 2001;39(2):215–21.
23. Stehr M, Boehm R. Critical validation of colour Doppler ultrasound in diagnostics of acute scrotum in children. Eur J Pediatr Surg. 2003;13(6):386–92.
24. Wright S, Hoffmann B. Emergency ultrasound of acute scrotal pain. Eur J Emerg Med. 2015;22(1):2–9.
25. Chang AJ, Brandes SB. Advances in diagnosis and management of genital injuries. Urol Clin North Am. 2013;40(3):427–38.
26. Schaeffer A, Schaeffer E. Infections of the urinary tract. In: Wein A, Kavoussi L, Novick A, Partin A, Peters C, editors. Campbell-Walsh urology, vol. 1. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 257–326.
27. Levine LA, Hoeh MP. Evaluation and management of chronic scrotal content pain. Curr Urol Rep. 2015;16(6):36.
28. Granitsiotis P, Kirk D. Chronic testicular pain: an overview. Eur Urol. 2004;45(4):430–6.
29. Aubin S, Berger RE, Heiman JR, Ciol MA. The association between sexual function, pain, and psychological adaptation of men diagnosed with chronic pelvic pain syndrome type III. J Sex Med. 2008;5(3):657–67.
30. Parekattil SJ, Gudeloglu A, Brahmbhatt JV, Priola KB, Vieweg J, Allan RW. Trifecta nerve complex: potential anatomical basis for microsurgical denervation of the spermatic cord for chronic orchialgia. J Urol. 2013;190(1):265–70.

31. Voscopoulos C, Lema M. When does acute pain become chronic? Br J Anaesth. 2010;105 Suppl 1:i69–85.
32. Nickel JC. Chronic epididymitis: a practical approach to understanding and managing a difficult urologic enigma. Rev Urol. 2003;5(4):209–15.
33. Nickel JC, Siemens DR, Nickel KR, Downey J. The patient with chronic epididymitis: characterization of an enigmatic syndrome. J Urol. 2002;167(4):1701–4.
34. Gray CL, Powell CR, Amling CL. Outcomes for surgical management of orchialgia in patients with identifiable intrascrotal lesions. Eur Urol. 2001;39(4):455–9.
35. Myers SA, Mershon CE, Fuchs EF. Vasectomy reversal for treatment of the post-vasectomy pain syndrome. J Urol. 1997;157(2):518–20.
36. Horovitz D, Tjong V, Domes T, Lo K, Grober ED, Jarvi K. Vasectomy reversal provides long-term pain relief for men with the post-vasectomy pain syndrome. J Urol. 2012;187(2):613–7.
37. Strebel RT, Schmidt C, Beatrice J, Sulser T. Chronic scrotal pain syndrome (CSPS): the widespread use of antibiotics is not justified. Andrology. 2013;1(1):155–9.
38. Sinclair AM, Miller B, Lee LK. Chronic orchialgia: consider gabapentin or nortriptyline before considering surgery. Int J Urol. 2007;14(7):622–5.
39. Khambati A, Lau S, Gordo A, Jarvi KA. OnabotulinumtoxinA (botox) nerve blocks provide durable pain relief for men with chronic scrotal pain: a pilot open-label trial. J Sex Med. 2014;11(12):3072–7.
40. Issa MM, Hsiao K, Bassel Y, Bouet R, Young M, Petros J. Spermatic cord anesthesia block for scrotal procedure in outpatient clinic setting. J Urol. 2005;172:2358–61.
41. Benson JS, Abern MR, Larsen S, Levine LA. Does a positive response to spermatic cord block predict response to microdenervation of the spermatic cord for chronic scrotal content pain? J Sex Med. 2013;10(3):876–82.
42. Terkawi AS, Romdhane K. Ultrasound-guided pulsed radiofrequency ablation of the genital branch of the genitofemoral nerve for treatment of intractable orchialgia. Saudi J Anaesth. 2014;8(2):294–8.
43. Misra S, Ward S, Coker C. Pulsed radiofrequency for chronic testicular pain – a preliminary report. Pain Med. 2009;10:673.
44. Birkhauser FD, Wipfli M, Eichenberger U, Luyet C, Grief R, Thalmann G. Vasectomy reversal with ultrasonography-guided spermatic cord block. BJU Int. 2011;110:1796–800.

Chapter 8
Chronic Pelvic Pain of Urogynecologic Origin

Karolynn Echols, Tamara Toidze, and Gunda Simpkins

Introduction

Interstitial cystitis is a poorly understood condition that can have a devastating effect on quality of life. There are 3.3–7.9 million women 18 years or older in the United States that may have interstitial cystitis and bladder pain syndrome. That is about 3–6 % of all adult women in the United States [1].

It is a condition that results in recurring discomfort or pain in the bladder and the surrounding pelvic area and is often associated with urinary urgency and frequency. Because the symptoms and severity of interstitial cystitis (IC) vary, it is believed that it is symptomatic of several diseases. Recently, we adopted the use of the term bladder pain syndrome (BPS) to describe cases with painful urinary symptoms that may not fit the definition of IC. The term IC is used alone when describing cases that meet all the IC criteria established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The term IC/BPS is used in cases of urinary pain that do not meet all the IC criteria (associated with previous infection or history of urinary stones) [2].

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Causes

Postoperative Mesh/Reconstructive Surgery Sequelae

One cannot discuss pelvic pain in urogynecology without addressing pain caused or exacerbated by the utilization of transvaginal mesh (TVM). Mesh procedures for pelvic organ prolapse (POP), especially the utilization of transvaginal mesh, has almost doubled since 2005 [3]. With the FDA notification in 2008, the FDA update in 2011, and the subsequent development of the 522-industry-sponsored, FDA-required trials, transvaginal mesh could significantly affect the current routine practice for POP [4–6]. Although this is not a debate in the use of transvaginal mesh, our discussion of chronic pelvic pain (CPP) in urogynecology would not be complete if we did not address the pain related sequelae (dyspareunia, vaginal scarring with shrinkage, neuromuscular problems) that can subsequently develop.

Dyspareunia or painful intercourse after placement of transvaginal mesh generally develops with the exacerbation of the preoperative presence of neuromuscular problems, that is, vulvovaginal atrophy, myofascial pain, vaginismus, peripheral neuropathy (ies), and/or consequent vaginal scarring with shrinkage and pain. Caution should be taken in utilizing TVM in patients with the former comorbidities; however, there are options for these patients should this occur. Documentation of any related morbidity encountered before insertion of TVM should be comprehensive.

Vaginal scarring most commonly occurs after placement of TVM with fixation arms (see Fig. 8.1). There have been reports of up to 50% mesh shrinkage seen in women [7]. The focal site of most pain is located where the fixation arms insert into the body

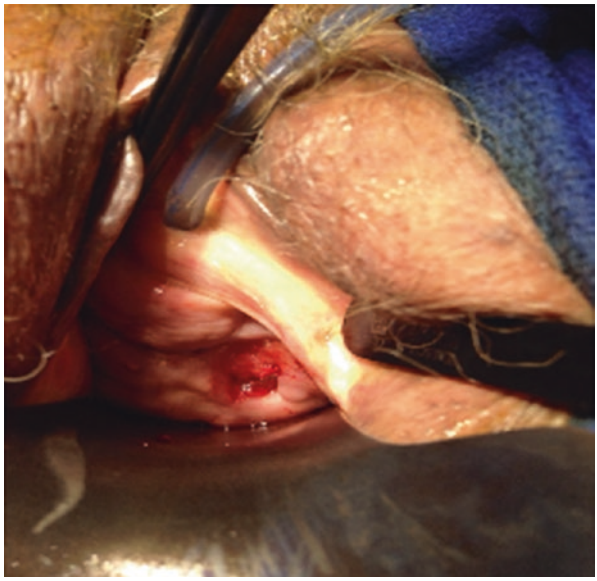

Fig. 8.1 Vaginal Scarring and mesh exposure (Photograph credit: Karolynn Echols, MD)

of the mesh, however pain can occur anywhere along the contracted portion(s) [8]. This results in painful intercourse and chronic pelvic pain especially with movement.

Chronic mesh pain syndrome (CMPS) is another related sequela where pain following TVM persists greater than 90 days postoperatively [9]. This pelvic pain results from upregulation of related pain pathways in the peripheral and central nervous system and does not correlate with physical examination findings. Besides preoperative risk factors mentioned briefly above, surgical technique and type and size of mesh utilized play a large role. Medical and surgical treatments usually fail to alleviate symptoms, thus a multidisciplinary approach to this challenging complication must be developed.

Other (Vulvodynia, Endometriosis, Myofascial Pain)

Vulvodynia, endometriosis, myofascial pain or high tone pelvic floor spasm must be considered when managing CPP of urogynecologic origin as they can be present in IC/BPS. These pain syndromes are beyond the scope of this chapter but will be briefly mentioned here.

Vulvodynia

Vulvodynia is defined as vulvar discomfort in the absence of clinically identifiable or laboratory findings. Its incidence is 17 % and prevalence is 7 %. Latina women have the highest risk [10]. Women describe it as vulvar irritation, soreness, tearing sensation, burning, redness or stinging, infrequently accompanied by an itching sensation and almost always accompanied by painful intercourse. Vulvodynia is classified as either localized or generalized; provoked (elicited by touch, friction, pressure, etc.), unprovoked (spontaneous discomfort/pain) or mixed; and based on the site of the pain [11] (see Table 8.1). There is no one single cause for vulvodynia although genetic, immunologic or embryologic factors, inflammation, infection, neuropathic changes or increased urinary oxalates have been suggested.

After a thorough history and physical examination and absence of laboratory findings reveal vulvodynia, management should be multidisciplinary. This includes treatment of vulvar and vaginal atrophy and hygiene counseling regarding irritants, chemicals, and potential allergens. Management of any associated pelvic floor dysfunction, neuropathies, and psychological factors must be addressed. Patient education, counseling, and support are crucial as vulvodynia is frequently not completely curable.

Endometriosis

Endometriosis affects up to 10 % of women of reproductive age. Women will present with CPP, painful intercourse and infertility [12]. Endometriosis is defined as the presence of endometrial tissue external to the uterine cavity. This tissue could be

Table 8.1 Classification of vulvodynia (vulvar vestibulitis syndrome, vulvar dysthesia, vulvar adenitis)

Generalized (*widespread or migratory*)
Provoked (*sexual*, *nonsexual or both*)
Unprovoked
Mixed
Localized
Vestibulodynia
Provoked (*sexual*, *nonsexual or both*)
Unprovoked
Mixed
Clitorodynia
Provoked (*sexual*, *nonsexual or both*)
Unprovoked
Mixed

located in the muscle of the uterus (adenomyosis), in the pelvis (peritoneum or ovaries), or distal sites (i.e., bowel, abdominal skin). The mechanisms and theories behind this disease are beyond the scope of this chapter; however, in women of reproductive age who present with cyclical CPP where pain is localized to the bladder or urethra or who have a surgical history that includes a diagnostic laparoscopy for pain, endometriosis should be in the differential diagnosis.

Definition

IC/BPS is a chronic and debilitating condition that is comprised of pelvic pain and urinary symptoms, occurs disproportionately in women, and has a poorly understood etiology [13]. A consistent definition of IC/BPS remains elusive and is a major factor in the paucity of research on the subject to date. In fact, although IC/BPS was first recognized in the nineteenth century, acceptance of the first formal definition devised by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) occurred 100 years later [14]. This and other definitions formulated for use in research, however, often do not prove useful in clinical practice, as many who are diagnosed with IC/BPS clinically [15]. An evolution of the definition of IC/BPS is shown in [16, 17].

Epidemiology

As previously mentioned, the lack of a consistent definition of IC/BPS necessarily affects the quality of research on the subject. Use of varying definitions renders making comparisons difficult, if not impossible, and prevalence of the condition is

challenging to estimate accurately when using either these multiple, inconsistent definitions or one overly restrictive one.

Estimates of prevalence have mostly been carried out using medical records and mailed questionnaires in various specific settings, geographic locations, or with specific subsets of the population. The resulting prevalence range from these studies is 0.45–12.6 % [26–30]. The first population-based symptom prevalence estimate among United States adult females was reported by Berry et al. in 2011, using the 2006 United States Census and a random sampling of households telephoned to question about bladder symptoms or a diagnosis of IC/BPS [1]. Those identified with symptoms were screened a second time with an in-depth 60-min interview. In a previous study, recognizing the shortcomings of established definitions of BPS/IC in epidemiologic research, the authors developed and validated two definitions with expert input, and found that, as was the case in other studies, neither demonstrated both high sensitivity and high specificity, though they were comparable or superior to established definitions (RICE definitions in Table 8.2) [23]. Both of these previously developed and validated definitions were used in the current study. Use of the high sensitivity or most inclusive definition yielded a prevalence estimate of 6.53 %; use of the high specificity definition yielded a prevalence estimate of 2.70 %. Further, while most women in the study saw at least one physician for their symptoms (87.1 %), less than half had a diagnosis for their symptoms (45.8 %) and only one-tenth (9.7 %) were diagnosed with IC/BPS, suggesting that the condition is underdiagnosed and undertreated [1]. Suskind et al. used a modified version of the definitions for use in studying the prevalence in men [31]. The result was a prevalence estimate of 2.9–4.2 % for IC/BPS, suggesting that the prevalence rate in men is closer to that in women, contrary to what has historically been reported and lending support to the under diagnosis of the condition in men, just as has been suggested for women.

Presentation

Pain or pressure/discomfort, especially suprapubic pain, related to bladder filling is the key symptom in IC/BPS. This sensation can be described by patients as being experienced throughout the pelvis, in the urethra, vulva, vagina, rectum, lower abdomen, and even the back. Other specific aspects of the pain experienced in IC/BPS include pain that worsens with certain foods or drinks, worsens with bladder filling, and/or improves with urination [32].

Typically, IC/BPS patients may also present with marked urinary urgency and frequency. Qualitatively different from the urgency in overactive bladder (OAB), IC/BPS patients tend to void to prevent or relieve pain, rather than to avoid incontinence [16, 24]. About 18–36 % of women with IC/BPS present with a history of a recent culture-positive urinary tract infection (UTI), with subsequent cultures, however, being negative [32]. Many may initially complain of one symptom, such as

Table 8.2 Epidemiological definitions of IC/BPS

Year	Organization	Definition
1987	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	(Diagnostic criteria):
		Category A: At least one of the following findings on cystoscopy:
		Diffuse glomerulations (at least 10 per quadrant) in at least three quadrants of the bladder (Fig. 8.2)
		A classic Hunner ulcer
		Category B: At least one of the following symptoms:
		Pain associated with the bladder
		Urinary urgency
		Exclusion criteria:
		Age <18 years
		Relative exclusion criteria:
		Urinary frequency while awake <8 times per day
		Nocturia fewer than two times per night
		Maximal bladder capacity >350 mL while patient is awake
		The absence of an intense urge to void with bladder filled to 150 mL of water with medium filling rate (30–100 mL/min) during cystometry
		Involuntary bladder contractions on cystometry using medium filling rate
		Duration of symptoms <9 months
		Symptoms relieved by antimicrobial agents (antibiotics, urinary antiseptics), anticholinergics, or antispasmodics
		Bladder or ureteral calculi
		Urethral diverticulum
		History of cyclophosphamide or chemical cystitis or tuberculosis or radiation cystitis
		Benign or malignant bladder tumors [18]
2002	International Continence Society (ICS)	Painful bladder syndrome (PBS): Complaint of suprapubic pain with bladder filling accompanied by other symptoms, such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology [19].
2008	European Society for the Study of IC (ESSIC)	Bladder pain syndrome (BPS): Chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as persistent urge to void or urinary frequency for more than 6 months [20].
2009	Society for Urodynamics and Female Urology (SUFU)	BPS/IC: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes [21].

Table 8.2 (continued)

2010	European Association of Urology (EAU)	BPS should be diagnosed on the basis of symptoms of pain associated with the urinary bladder accompanied by at least one other symptom, such as daytime and/or nighttime urinary frequency [22].
2011	RICE (RAND Interstitial Cystitis Epidemiology) (NIDDK/RAND Corporation)	High sensitivity definition criteria:
		1. Pain, pressure, or discomfort in the pelvic area AND
		2. Daytime urinary frequency 10+ or urgency due to pain, pressure, or discomfort, not fear of wetting
		High specificity definition criteria:
		1. Pain, pressure, or discomfort in the pelvic area AND
		2. Daytime urinary frequency 10+ or urgency due to pain, pressure, or discomfort, not fear of wetting AND
		3. No treatment with hormone injection therapy for endometriosis [23].
2011, 2015	American Urological Association (AUA)	IC/BPS: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes [24, 25].

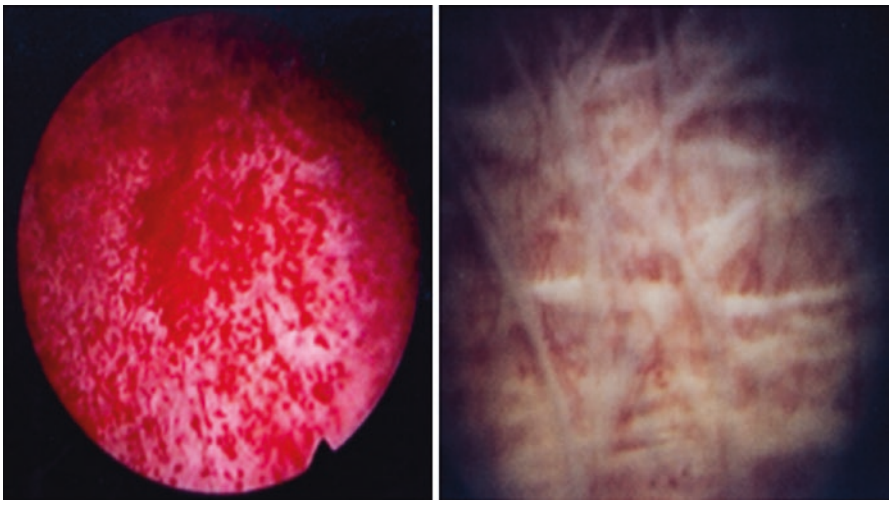

Fig. 8.2 Glomerulations (*right*) and trabeculations/linear scarring (*left*) seen on cystoscopy (Photograph credit: Ricardo Caraballo, MD)

dysuria, frequency, or pain, with progression to multiple symptoms [33, 34]. It is not uncommon for IC/BPS patients to experience symptom flares, during which their symptoms suddenly intensify for several hours, days, or weeks.

Frequently, these patients have a history of prior pelvic surgery, especially hysterectomy, and levator ani pain, suggesting that trauma or other local factors may contribute to symptoms [35]. In considering this association, it is important to bear in mind that it is possible that these pelvic procedures were performed as a result of a misdiagnosis and were not a contributing factor to patients' symptoms, themselves.

Finally, IC/BPS patients commonly present with other unexplained medical conditions. These conditions may include fibromyalgia (FM), irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), allergies, asthma, sicca syndrome, chronic pelvic pain (CPP), endometriosis, back disorders, Sjogren's syndrome, chronic headaches/migraines, temporomandibular disorder, vulvodynia, depression, and anxiety [36–43].

Diagnosis

In light of the complicated history and symptomatology of patients presenting with IC/BPS, diagnosis of the condition is very challenging. Its wide array of symptoms, physical examination findings, and medical test results frequently lead to misdiagnosis, underdiagnosis, and delayed diagnosis [44]. According to the Bladder Pain Syndrome Committee of the International Consultation on Incontinence from 2009, the diagnosis should be made based on exclusion of confounding diseases and confirmation of the specific combination of symptoms of BPS [45].

The group further describes the effort that has been put forth to attempt to identify objective diagnostic criteria including cystoscopy, bladder distention with notation of bladder capacity and/or the presence of glomerulations and Hunner's lesions, bladder wall biopsies evaluated for inflammation, ulcers, fibrosis, mast cells, etc., and urodynamics with registration of bladder capacity, compliance, and bladder stability. Ultimately, however, the results of those efforts have been frustrating and the group concluded that it is more effective to establish a broad clinical diagnosis, mainly on the basis of symptoms, physical examination, and exclusion of other diseases and then stratifying patients by urodynamic, cystoscopic, histological, and other tests on the basis of the significance of the findings for the treatment and prognosis of disease [46]. With respect to specific testing, the committee further suggests that urodynamics be considered an optional procedure, primarily for patients with a complicated history that suggests the possibility of other diagnoses that may account for the symptoms. The committee designates this guideline as a Level of Evidence 4, Grade of Recommendation C.

The AUA Guideline Amendment from 2015 concludes that insufficient evidence exists for guiding diagnosis of IC/BPS in clinical practice and designates its recommendations as Clinical Principle or Expert Opinion [25]. These recommendations

include basic assessment consisting of history, frequency charting, postvoid residual, physical exam, urinalysis/culture, cytology (if smoking history), symptom questionnaire, and pain evaluation. After ruling out other conditions, further testing such as urine cytology, imaging, cystoscopy, urodynamics, laparoscopy, and specialist referral may also be considered.

Etiology

The etiology of IC/BPS remains unknown, though it is thought to be multifactorial. In fact, especially in the absence of a specific marker that confirms its presence, it is not known if IC/BPS symptoms constitute a single disorder or if they are perhaps symptoms of a more generalized systemic chronic pain disorder affecting the bladder, but also other visceral organs. As described earlier, associations have been shown to exist between IC and many other medical conditions. Warren et al. in 2011 reviewed the cross-sectional studies making associations between IC/BPS and non-bladder syndromes (NBS) and concluded that while additional cross-sectional studies would be helpful to generating more hypotheses about the pathogenesis of IC/BPS, prospective studies will most likely be necessary to test the hypotheses formulated and to discover the temporal relationship of these conditions to the pathophysiology of IC/BPS [47]. Existing theories include: environmental factors, a defective bladder urothelial layer, alteration in afferent sensation, and inflammation.

A group of researchers in Sweden used a large twin database to evaluate genetic and environmental influences on IC/BPS, among other conditions [48, 49]. Genetic influences were found only to be modest in IC/BPS, whereas environmental factors had a pronounced influence. Another proposed model of pathogenesis of IC/BPS is a defective bladder urothelial barrier, due to a deficiency in the glycosaminoglycan (GAG) mucin layer coating that leads to increased epithelial permeability [50]. This increased permeability leads to bladder injury resulting in symptoms of urgency and pain. Specifically, it is hypothesized that the increased permeability allows irritants to pass through the bladder urothelium, activating mast cells, essential for the development of allergic hypersensitivity reactions. A harmful cycle is initiated when bladder injury results in urothelial dysfunction, solute leak, activation of C fibers, and mast cell degranulation, causing further damage [51] (see Fig. 8.3). While data mostly support potassium as the urinary metabolite initiating the cascade of events leading to bladder symptoms when the epithelium is disrupted, it has been proposed that there must be a balance of all urinary cations and anions to prevent damage to the bladder mucus layer. Too little of the protective factors or too many of the toxic cations could increase the risk for bladder disease [52]. Increasing our understanding of this required balance may help to develop treatments to target either end of the uneven distribution of substances in order to reduce this risk.

Inflammation is recognized to play a key role in the development of the symptoms of frequency, urgency, and pelvic pain experienced in IC/BPS. Study findings supporting the role of inflammation have noted significantly higher C-reactive

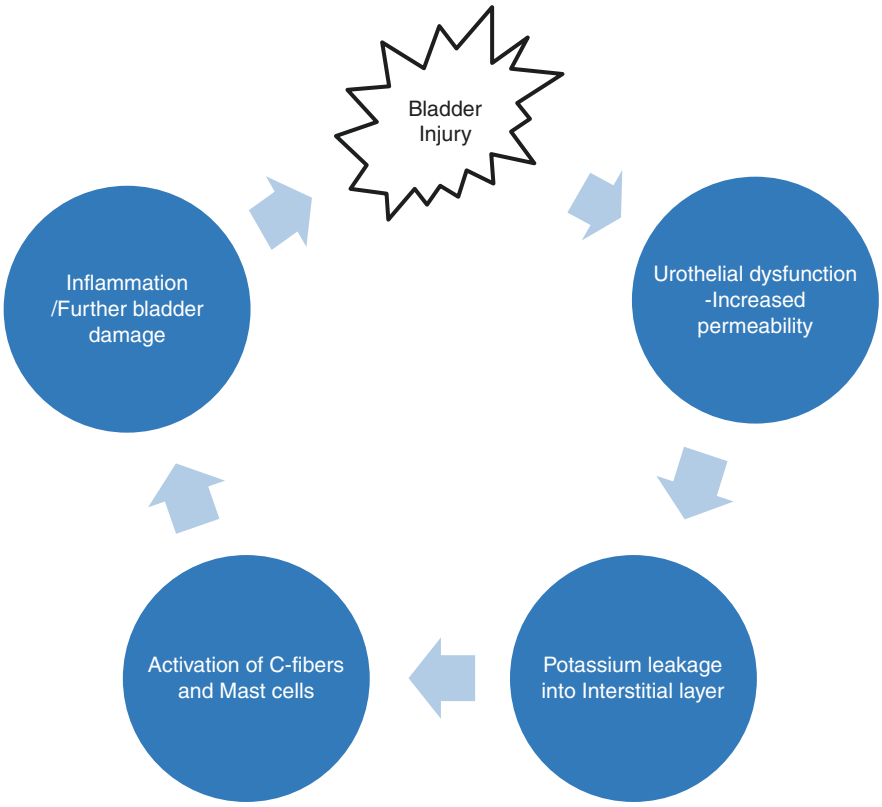

Fig. 8.3 Underlying processes in interstitial cystitis (Adapted from: Evans [51])

protein (CRP) levels in patients with IC/BPS [53]. Other findings suggest a possible exaggerated C-fiber excitation, associated with inflammation in the bladder [54, 55]. It is postulated that this hyperactivity of the C-fiber afferents may lead to pain with normal distention of the bladder [56]. Further, studies have supported chronic inflammation as an underlying cause by observing increased nerve growth factor (NGF) production and, on histological analysis of the bladders of patients with IC/BPS, marked edema, vasodilation, proliferation of nerve fibers and infiltration of mast cells, as well as significantly greater numbers of nerve fibers expressing substance P, a major neurotransmitter of C-fiber afferents [50, 57, 58].

An association between urinary calculi (UC) and IC/BPS has been supported in a study using a population-based dataset in Taiwan [59]. The authors found that IC/BPS was significantly associated with UC, regardless of stone location, after adjusting for CPP, IBS, FM, CFS, depression, panic disorder, migraine, sicca syndrome, allergy, endometriosis, and asthma. It was theorized that the stone could cause irritation initiating an inflammatory cascade leading to chronic inflammation and recurrent bladder epithelium injury [60].

Although much effort has been exerted in the investigation of the pathogenesis of IC/BPS, ultimately, as Yoshimura et al. 2014 point out, no one pathological process has been identified in every IC/BPS patient. The authors conclude, then, that it is likely that IC/BPS could have multiple etiologies resulting in similar clinical manifestations and that afferent hyperexcitability could therefore be a key pathophysiological basis of IC/BPS that could be targeted with the development of multiple treatment modalities [55].

Management of Interstitial Cystitis and Bladder Pain Syndrome

Interstitial cystitis and bladder pain syndrome (IC/BPS) is only one subgroup of a broader bladder disease complex, which includes bladder, urethral, and/or pelvic pain, lower urinary tract symptoms, and sterile urine cultures, with many identifiable causes. Our definition of IC/BPS is an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes [21].

Since there is no clear etiology of IC/BPS, the therapy is based on an understanding of the pathophysiology of the disease. There are many therapeutic methods of treatment of IC/BPS and none of them have been proven to be effective. The Interstitial Cystitis Database Study analyzed 581 women with IC/BPS who underwent 183 different types of therapy over several years including follow up. No single therapy was successful in the majority of patients [61]. The treatments offered were divided into first-line through sixth-line therapy. The initial treatment type and level depended on severity, location and progression of symptoms, comorbidities (e.g., fibromyalgia, irritable bowel syndrome, depression, anxiety), and patient preference.

Life-Style Modifications

First-line treatment should be offered to all patients. If the patient has mild symptoms, first-line therapy can be effective, though additional therapy may be required for adequate symptom control. First-line treatment includes education of normal bladder function, information about chronic nature of IC/BPS, a typical course involving symptoms and exacerbations and remission. Also, self-care and behavioral modifications should be discussed with the patient. These include application of local heat or cold over the bladder and perineum; avoidance of certain foods known to be common irritants for IC/BPS patients (e.g., coffee, tea, soda, chocolate, alcohol, artificial sweeteners, tomato-based products, spicy foods, MSG, citrus products); use of over the counter products (e.g., nutraceuticals such as L-arginine,

calcium glycerophosphate (Prelief), phenazopyridine (Pyridium)); pelvic floor relaxation; trigger point and hypersensitive area treatments; and bladder training with urge suppression [24, 62–64]. Also, patients should be encouraged to implement stress management techniques to help alleviate or prevent flare-ups, especially in the case of comorbidities such as irritable bowel syndrome, endometriosis, recurrent vaginitis/vestibulitis, depression, or anxiety [65].

Second-line therapy includes: appropriate physical therapy; pain management, including medications, stress management, and manual therapy; and oral medications and bladder instillations. During the initial evaluation of the patient, some patients may experience pelvic floor muscle tenderness, along with other soft-tissue abnormalities. This presentation of pelvic floor muscle tenderness can be interpreted as a primary pain or as a secondary event elicited by the bladder pain of IC/BPS. In these cases, it is suggested that manual physical therapy, targeted on pelvic floor muscle relaxation, can be beneficial for symptom relief [35, 66, 67].

Pharmacotherapy

Similar principles should guide pharmacotherapy of pain in IC/BPS as in any other chronic pain management. The goal of pharmacotherapy is to find medication or a combination of medications to provide significant pain relief with minimal side effects. Medications for pain management include urinary analgesics, NSAIDs, opioids, and a variety of nonopioid medications used for chronic pain management, which are also used for the treatment of depression, epilepsy, allergies, arrhythmias, etc. Patients may require opioid medications, which present risks of tolerance and dependence. Thus, there are several principles of pain management of IC/BPS that need to be followed. Whenever using opioid medication, it is important to re-evaluate at least every 3 months to determine whether the benefit outweighs the risk of continuing this therapy. Prescribers should utilize prescription-monitoring programs at least quarterly, as all opioid prescriptions should be coming from a single source. The patient must be appropriately counseled regarding side effects of medications, as well as rights and responsibilities of the patient and treating physician. The lowest effective dose of medication should always be used while maximizing nonopioid medications and alternative therapies. Patients who require long-term opioid therapy may benefit from long-acting opioids, using small doses of short acting opioids for breakthrough pain. In order to minimize dependence, combinations of physical therapy, stress management and counseling should be used. Also, patients need express understanding of reasonable goals, e.g., that 100 % pain relief often cannot be achieved and is unreasonable. The goal of pain management is to minimize discomfort and maximize patient's ability to function in daily life [61].

Amitriptyline is the most widely used medication for initial pharmacologic treatment of IC/BPS. The dosing regimen is typically started at 10 mg at bedtime, and the dose is titrated up weekly (25 mg, 50 mg, 75 mg or to the maximum tolerated dose). Adverse effects include anticholinergic effects (dry mouth, constipation, urinary reten-

tion), sedation, weight gain, orthostatic hypotension, and cardiac arrhythmias [67]. The medication is most likely effective in higher doses; however, many patients cannot tolerate these doses. Conflicting data exist about the efficacy of amitriptyline in the treatment of IC/BPS. One multicenter randomized trial showed that low dose amitriptyline in combination with education and behavioral modification program did not significantly improve symptoms in the treatment of patients with IC/BPS [24], though it can be beneficial in patients who can achieve a daily dose of 50 mg or greater [68].

Pentosan polysulfate sodium can provide symptom reduction in IC/BPS patients. Symptomatic relief usually appears 3–6 months after initiation of therapy. The accepted regimen of pentosan polysulfate sodium is 100 mg three times daily. Side effects can include abdominal bloating and discomfort, which could be relieved by opening up the capsule and sprinkling its contents on food. Adverse events include hair loss and mild elevation of liver enzymes, although they are typically mild and reversible [1].

Use of antihistamines for IC/BPS is based on the hypothesis of hypersensitivity as a pathophysiologic mechanism, although there are no quality data to support the treatment. It is used in patients with IC/BPS and allergic disorders. Hydroxyzine is the most commonly used antihistamine in treatment of IC/BPS. The typical dose of hydroxyzine is 25 or 50 mg. It can be used at bedtime in patients with insomnia, coursed by nocturia.

A pilot trial that compared safety and efficacy rates for oral pentosan polysulfate sodium versus its use combined with hydroxyzine suggested that neither provided benefit to the majority of patients with IC [69]. Medication management of IC/BPS can include bladder instillations. A "cocktail" preparation, including heparin or pentosan polysulfate, sodium bicarbonate, local steroid, and/or lidocaine preparation, which can be administered in office settings, as a weekly preparation, can be used as a treatment providing relief ranging from 6 weeks to 12 months.

Other Interventional Therapies

The third-, fourth-, and fifth-line therapies are more invasive and are reserved for patients who have failed other treatment approaches. Third-line therapy includes cystoscopy procedure, accompanied with low-pressure bladder hydrodistension, and is performed under deep sedation or general anesthesia. The symptom relief after bladder hydrodistension is possibly related to the disruption of sensory nerves within the bladder wall. Bladder hydrodistension can provide significant relief to some patients, but it can decline over the course of time. Some studies have reported symptoms improvement of 70%, while other studies showed 56% improvement, but the duration was short lived [70, 71].

The technique of bladder hydrodistension typically uses low distension pressure (60–80 cm H_2O) for a short duration of less than 10 min. The use of higher pressure is associated with bladder rupture or bladder necrosis. Prior to distension, the bladder is surveyed for the presence bladder masses, stones, and for Hunner lesions (see Fig. 8.4).

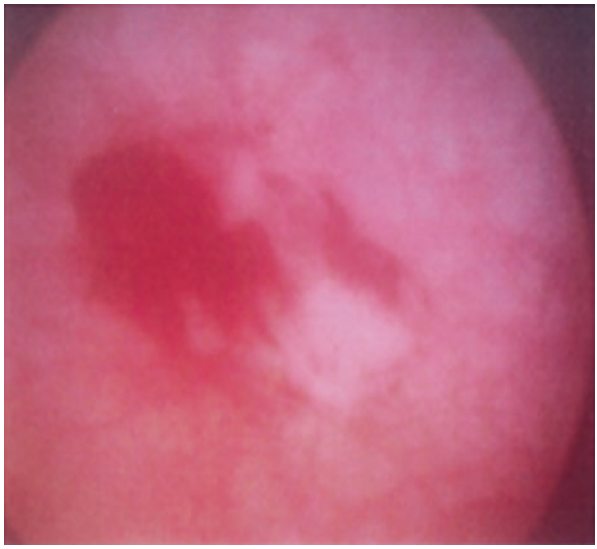

Fig. 8.4 Hunner's lesion (Photograph credit: Ricardo Caraballo, MD)

Hunner lesions can be treated via fulguration (laser, cautery) and/or injection of corticosteroid. The response of these treatment modalities varies and at a certain point patients will have interval treatment [72–74].

The fourth-line therapy for IC/BPS is sacral neuromodulation and intradetrusor botulinum toxin A injection. Sacral neuromodulation is a minimally invasive surgical procedure, and it has its own associated risks. The implantable device consists of an implantable lead placed along the S3 nerve root, which is attached to an implanted pulse generator. It is not currently FDA approved for the treatment of IC/BPS, but it is used for the treatment of urinary urgency and frequency; thus, it can be used in patients who meet the urgency/frequency indication. The recent available data suggest that a sacral neuromodulation device significantly improves symptoms of urgency and frequency, nocturia, and pain in IC/BPS patients both short term and long term [75–79]. However, given the small number of patients studied, the invasiveness of the procedure, and insufficient data on patients with IC/BPS, the sacral neuromodulation is reserved for IC/BPS patients who present with symptoms of urinary urgency/frequency that are refractory to other less invasive treatment methods. The patient should be carefully selected and the decision should be made individually for each patient.

Intradetrusor botulinum toxin A (BoNT-A) is one of the treatment options in patients when other therapies fail. It is not currently approved by the FDA for the treatment of IC/BPS and the decision to use that treatment option is made based on patient preferences and extensive counseling about the possible adverse effects. BoNT-A is a potent neurotoxin derived from anaerobic bacterium *Clostridium botulinum*. The mechanism of action is likely associated with the ability of BoNT-A to modulate sensory neurotransmission and reduce inflammation. This impairs the release of neuropeptides, such as substance P, calcitonin-related peptide, and glutamate, which are

involved in pain transmission from either dorsal root ganglion neurons, sensory afferent nerves, and/or urothelial cells [80, 81]. Administration of BoNT-A leads to a decrease of input for these neuropeptides, thus assisting in analgesia.

The acceptable dose of BTX-A is 100 U. Initially, 200 U of BoNT-A was used, but adverse effects occurred in most patients, including acute or chronic urinary retention and severe dysuria, and the dose was decreased to 100 U. The dose of 100 U can be used alone and in combination with bladder hydrodistension. Intravesical injections of BoNT-A in combination with bladder hydrodistension seem to produce a better clinical response than hydrodistention alone [82].

In the absence of placebo-controlled studies, the true effect of BoNT-A is not possible to determine. However, overall studies suggest that there is a group of patients experiencing symptom relief for several months after treatment with a return to baseline symptoms over the course of time. Observational studies showed that repeat injections help to maintain symptom control [83–85]. Common adverse effects of BoNT-A injections are dysuria, abdominal straining to void, large postvoid residuals, and the risk of intermittent self-catheterization for 1–3 months after treatment. Hence, it is important to counsel patients in great detail about these complications. BoNT-A is contraindicated in patients with peripheral motor neuropathy (ALS), neuromuscular junction disorders (e.g., myasthenia gravis, Lambert Eaton syndrome), and patients who are taking medications interfering with neuromuscular transmission (e.g., aminoglycosides, curare-like compounds such as succinylcholine, pancuronium).

Cyclosporine A has been suggested as a fifth-line therapy. Success rates are much higher among the patients with Hunner's lesions compared to those without [86]. Cyclosporine use has a high chance of adverse effects, including increased serum creatinine level, hypertension, alopecia, cutaneous lymphoma, mouth ulcers, and acute gout. The long-term results of cyclosporine A treatment of IC/BPS are reported by two observational studies, though the number of patients is relatively small [87, 88]. Given that fact, as well as potential adverse effects, there is some uncertainty in the balance of benefits and risks of its use.

Radical Treatments

Surgery can be considered as a sixth-line therapy in patients with significant symptoms affecting quality of life, where all other therapies for IC/BPS have failed, and when all other etiologies are ruled out. The currently accepted surgical therapy is urinary diversion with or without cystectomy, involving excision of ureters from the bladder creating a continent pouch, which requires self-catheterization, or creating an incontinent conduit from the ileal loop. Where standard therapies and other interventions have failed, urinary diversion can improve quality of life for select patients who have Hunner's lesions and whose main complaint is frequency. Patients should be carefully counseled that relief of symptoms is not guaranteed and pain can still persist, even after surgery, especially in the cases of nonnuclear

IC/BPS [89]. High morbidity from these procedures (pyocystis, hemorrhage, severe pain, intractable pain) shows that surgery should be considered only on a case-by-case basis.

Integrative Medicine

Since there is no "cure" for IC/BPS, a multidisciplinary individualized approach to management is crucial. Frequently women resort to alternative therapies in addition to or in replacement of conventional therapies. Integrative Medicine (IM) is the scope of medical practice that considers the patient as a whole: mind, body, and soul, community and way of life. It utilizes all appropriate evidence-based resources and therapeutic options: conventional and complementary alternative medicine (CAM). IM begins with influencing the body's natural ability to heal itself. Therefore, when practicing IM, it is necessary to identify the multidimensional aspects of what makes a person healthy.

As certain illnesses, such as diabetes or fibromyalgia, and previous surgeries, such as prior bladder or neurologic surgery can cause or aggravate symptoms, it is important to elicit a thorough medical and surgical history. One must not forget to address all allergies and sensitivities as well as medications, vitamins, herbs, and supplements. Of note, there are drugs such as metformin and proton pump inhibitors (PPIs) that can decrease absorption of certain vitamins and minerals that contribute to bladder health. It is essential to discuss diet and lifestyle history and any presence of stressors as certain modifications can alleviate IC/BPS symptoms. A thorough physical exam will eliminate the presence of pelvic organ prolapse, masses, and vulvar dystrophies which can contribute to the discomfort and pain.

Dietary and Lifestyle Changes

Dietary and lifestyle modifications are first-line treatment for IC/BPS. Acidity of the urine will wear down the GAG layer leading to a Hunner's ulcer making the bladder more susceptible to acidic foods. The most consistent way to prevent further damage to the GAG layer is by removing acidic foods from the diet and replacing them with alkaline foods (see Table 8.3), which will make the urine more alkaline (pH = 7.0). Drinking two tablespoons of Apple Cider Vinegar (becomes alkaline after digestion through an oxidative process) in 8 oz of water or taking potassium or sodium citrate or bicarbonate can immediately alkalinize the urine and decrease pain. The potassium version of the above should be recommended in those patients with hypertension [90].

Removal of trigger foods through the elimination diet can be performed by one of two ways. Either eliminate all of the proposed aggravating foods and then add them back one by one every week or 2 or eliminate one at a time for at least 1–2 weeks to evaluate symptom relief.

Table 8.3 IC/BPS foods table

Products bothersome for IC/BPS patients/high acidity (pro-inflammatory)	Products least bothersome for IC/BPS patients/alkaline (anti-inflammatory)
Coffee	Water
Tea	Milk
Alcohol (hard liquor < beer < wine)	Watermelon
Carbonated beverages	Bananas
Fruit juice sweetened with white sugar	Pears
Citrus fruit and juices	Blueberries
Pineapple fruit and juices	Carrots
Cranberries	Cucumber
Strawberries	Peas
Tomato and tomato base products	Brussel sprouts
Spicy food	Cauliflower
Mustard	Mushrooms
Vinegar	Squash
Soy sauce	Zucchini
Meat (pork < beef)	Potatoes (white, sweet)
Nuts	Eggs
Chocolate	Turkey
Artificial sweeteners (aspartame, Sweet N Low, NutraSweet, Equal, Splenda)	Chicken
Cheese (processed)	Fish
Smoked fish	White bread
Bread (sourdough, rye)	Pasta
	Rice
	Oats
	Popcorn

Nutraceuticals

In the presence of a PPI, there is a possibility of magnesium deficiency due to decreased stomach absorption. In 2011, the FDA issued a Drug Safety Communication on low magnesium levels potentially being associated with long-term use of proton pump inhibitor drugs (PPIs) [91]. There is evidence of IC symptomatic relief in women who were supplemented with magnesium (and calcium) as it is alkalizing [92]. Reassurance of normal kidney function is essential as magnesium clearance is dependent on good kidney function. Magnesium glycinate or chelated magnesium in doses of 400–600 mg daily are less harsh on the GI tract and may help those who have IBS, constipation in addition to their IC/BPS.

L-arginine is an essential amino acid that is an immunomodulator that has antimicrobial and smooth muscle relaxant properties through an increase in nitric oxide synthetase (NOS) and nitric oxide (NO). Although its use in IC/BPS is controversial, there may be some benefit in certain patients. The suggested dose is 1500 mg daily [93].

The aloe plant otherwise known as the "medicine plant" is a natural anti-microbial, analgesic and anti-inflammatory. A small double-blind, placebo-controlled crossover trial showed significant symptomatic relief of bladder pain in the majority of patients after 3 months [94].

Quercetin is a bioflavonoid found in red wine and tea, dark berries (blackberries, blueberries, bilberries), apples and citrus fruits, onions, parsley, sage and olive oil. It is a strong antioxidant and has been shown to be beneficial in patients with IC/BPS [95]. The dose used was 500 mg twice daily for 4 weeks. Side effects are infrequent and may include headaches, stomachaches and loss of protein function. At high doses (over 1 g), it has been nephrotoxic; therefore, it should be avoided in women who are pregnant or breastfeeding or have an underlying kidney disease.

Mindfulness-Based Therapy

Guided imagery is a mindfulness-based therapy that uses music, words, or images to attain a beneficial response. A randomized-controlled pilot study was conducted on 30 women with pelvic pain and IC. The study showed a trend toward improvement of IC symptoms with twice a day guided imagery therapy after 8 weeks [63].

Stress reduction is essential to achieve in patients with CPP. Stress can cause detrimental effects to the patient's health by stimulating the pro-inflammatory cascade. Effective stress management and treatment has positive and lasting effects on mental stability and function and ultimately pain management [96].

There is limited evidence looking at yoga and IC. Close to 90% of participants who took an 8-week hatha yoga class reported a reduction in their IC symptoms and stress levels [97]. There are several studies supporting yoga therapy in the reduction of stress and anxiety, which is extremely important for coping and functioning with this chronic and sometimes debilitating illness. In a study of 24 emotionally distressed women who underwent 3 months of 90-min Iyengar yoga classes twice weekly significant improvements were seen on measurements of stress and psychological outcomes [98].

Reflexology

- Carter and Weber report utilizing reflexology to relieve lower urinary tract symptoms [99].

Traditional Chinese Medicine (TCM)

- In TCM, it is thought that IC/BPS occurs when the kidney qi is weak.

Acupuncture/Acupressure

- Acupuncture works by neuromodulation, which establishes the balance between Yin and Yang
- Rapkin and Kames studied 14 patients and found that 6–8 weeks of acupuncture applied to the bladder meridians reduced IC pain [100].

Herbal Treatment

Gotu kola (Centella asiatica) and horsetail (Equisetum aryense) have the most consistent evidence supporting bladder health. Gotu kola stimulates the GAG layer and horsetail is an astringent. Pumpkin seed extract (cucubita pepo) has also been shown to be beneficial [101]. There is also Chinese herbal tea developed by Dr. Ching Yao Shi used to treat IC in the US. She combined kidney tonic herbs with gardenia and rhubarb, which is reported to provide significant relief in approximately 60 % of patients after 4 weeks and an additional 20 % after 3 months [102].

Conclusion

Pelvic pain in urogynecology specifically IC/BPS can be a challenging and debilitating condition that takes a multifaceted approach to successfully improve symptoms and subsequently quality of life. A comprehensive history, physical and other evaluation modalities along with an individualized management plan are imperative. Coping skills and mental health are important aspects of IC/BPS that must not be ignored and in frequent cases may take psychological expertise. Conservative management should be attempted primarily with diet and lifestyle changes adjunctive to pharmacotherapy, manual therapy and complementary alternative modalities before utilizing more invasive measures. Radical surgery should only be considered after exhausting all other options.

References

1. Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, Nyberg L, Clemens JQ. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol. 2011;186(2):540–4.
2. http://www.niddk.nih.gov.
3. Jonsson Funk M, Edenfield AL, Pate V, Visco AG, Weidner AC, WU JM. Trends in use of surgical mesh for pelvic organ prolapse. Am J Obstet Gynecol. 2013;208(1):79.e1–7.
4. FDA Public Health Notification: serious complications associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse. Issued: 20 Oct 2008 at http://

www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/ucm061976.htm.
5. FDA Safety Communication: update on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse. Issued on 13 July 2011 at http://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm262435.htm.
6. https://clinicaltrials.gov.
7. Gauruder-Burmester A, Koutouzidou P, Rohne J, Gronewold M, Tunn R. Follow-up after polypropylene mesh repair of anterior and posterior compartments in patients with recurrent prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18:1059–64.
8. Feiner B, Maher C. Vaginal mesh contraction: definition, clinical presentation, and management. Obstet Gynecol. 2010;115(2 Pt 1):325–30.
9. Lin LL, Haessler AL, Ho MH, Betson LH, Alinsod RM, Bhatia NN. Dyspareunia and chronic pelvic pain after polypropylene mesh augmentation for transvaginal repair of anterior vaginal wall prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(6):675–8.
10. Reed BD, Harlow SD, Sen A, et al. Prevalence and demographic characteristics of vulvodynia in a population-based sample. Am J Obstet Gynecol. 2012;206:170.e1–9.
11. Vulvodynia. ACOG Committee Opinion No. 345. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2006;108:1049–52. (9. Edwards L. Vulvodynia. Clin Obstet Gynecol. 58(1):143–52).
12. Bulun SE. Endometriosis mechanisms of disease. N Engl J Med. 2009;360(3):268–79.
13. Hanno P, Lin A, Nordling J, et al. Bladder pain syndrome committee of the international consultation on incontinence. Neurourol Urodyn. 2010;29:191–8.
14. Wein AJ, Hanno PM, Gillenwater JY. Interstitial cystitis: an introduction to the problem. In: Hanno PM, Stasking DR, Krane RJ, editors. Interstitial cystitis. London: Springer; 1990.
15. Hanno PM, Landis JR, Matthews-Cook Y, et al. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health interstitial cystitis database study. J Urol. 1999;161(2):553–7.
16. Castro-Diaz D, Cardozo L, Chapple CR, et al. Urgency and pain in patients with overactive bladder and bladder pain syndrome. What are the differences? Int J Clin Pract. 2014;68(3):356–62.
17. Bologna RA, Whitmore KE. Hypersensitivity disorders of the lower urinary tract. In: Walters MD, editor. Urogynecology and reconstructive pelvic surgery. 4th ed. Philadelphia: Elsevier; 2015.
18. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases workshop on interstitial cystitis, National Institutes of Health, Bethesda, MD, August 28–29, 1987. J Urol. 1988;140:203–6.
19. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function. Report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167–78.
20. Van der Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008;3:60–8.
21. Hanno P, Dmochowski R. Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. Neurourol Urodyn. 2009;28:274–86.
22. Fall M, Baranowski AP, Elneil S, et al. EAU guidelines on chronic pelvic pain. Eur Urol. 2010;57:35–48.
23. Berry SH, Bogart LM, Pham C, et al. Development, validation and testing of an epidemiological case definition of interstitial cystitis/painful bladder syndrome. J Urol. 2010;183:1848–52.
24. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. American Urological Association Education and Research, Inc. J Urol. 2011;185(6):2162–70.

25. Hanno PM, Erickson D, Moldwin R, Faraday MM. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol. 2015;193(5):1545–53.
26. Leppilahti M, Tammela TL, Huhtala H, et al. Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. J Urol. 2002;168:139–43.
27. Clemens JQ, Meenan PR, O'Keeffe Rosetti MC, et al. Prevalence of interstitial cystitis symptoms in a managed care population. J Urol. 2005;174:576–80.
28. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. J Urol. 2005;174:2231–4.
29. Rosenberg MT, Page S, Hazzard MA. Prevalence of interstitial cystitis in a primary care setting. Urology. 2007;69:48–52.
30. Lifford KL, Curhan GC. Prevalence of painful bladder syndrome in older women. Urology. 2009;73:494–8.
31. Suskind AM, et al. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology Male Study. J Urol. 2013;189:141–5.
32. Warren JW, Brown J, Tracy JK, et al. Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. Urology. 2008;71:444–8.
33. Warren JW, Diggs C, Brown V, et al. Dysuria at onset of interstitial cystitis/painful bladder syndrome in women. Urology. 2006;68:477–81.
34. Driscoll A, Teichman JM. How do patients with interstitial cystitis present? J Urol. 2001;166:2118–20.
35. Peters KM, Carrico DJ, Kalinowski SE, et al. Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. Urology. 2007;70(1):16–8.
36. Alagiri M, Chottiner S, Ratner V, et al. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology. 1997;49(5A suppl):52–7.
37. Clauw DJ, Schmidt M, Radulovic D, et al. The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res. 1997;31:125–31.
38. Wu EQ, Birnbaum H, Mareva M, et al. Interstitial cystitis: cost, treatment and co-morbidities in an employed population. Pharmacoeconomics. 2006;24:55–65.
39. Clemens JQ, Meenan RT, O'Keeffe-Rosetti MC, et al. Case–control study of medical comorbidities in women with interstitial cystitis. J Urol. 2008;179:2222–5.
40. Warren JW, Howard FM, Cross RK, et al. Antecedent non bladder syndromes in case–control study of interstitial cystitis/painful bladder syndrome. Urology. 2009;73:52–7.
41. Nickel JC, Tripp DA, Pontari M, et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. J Urol. 2010;184:1358–63.
42. Nickel JC, Tripp DA, Pontari M, et al. Psychosocial phenotyping in women with interstitial cystitis/painful bladder syndrome: a case control study. J Urol. 2010;183:167–72.
43. Rodriguez MA, Afari N, Buchwald DS, et al. National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Urological Chronic Pelvic Pain: evidence for overlap between urological and non urological unexplained clinical conditions. J Urol. 2009;182:2123–31.
44. Johnson JE, Johnson KE. Ambiguous chronic illness in women: community health nursing concern. J Community Health Nurs. 2006;23:159–67.
45. Hanno P, Lin A, Nordling J, Nyberg L, et al. Bladder pain syndrome international consultation on incontinence. Neurourol Urodyn. 2009;29:191–8.
46. Nordling J, Anjum FH, Bade JJ, et al. Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol. 2004;45:662–9.
47. Warren JW, Van de Merwe JP, Nickel JC. Interstitial cystitis/bladder pain syndrome and non bladder syndromes: facts and hypotheses. J Urol. 2011;78:727–32.
48. Altman D, Lundholm C, Milsom I, et al. The genetic and environmental contribution to the occurrence of bladder pain syndrome: an empirical approach in a nationwide population sample. Eur Urol. 2011;59:280–5.

49. Wennberg AL, Molander U, Fall M, Edlund C, Peeker R, Milsom I. A longitudinal population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. Eur Urol. 2009;55:783–91.
50. Parsons CL. The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis, and gynaecological chronic pelvic pain. BJU Int. 2010;107:370–5.
51. Evans RJ. Treatment approaches for interstitial cystitis: multimodality therapy. Rev Urol. 2002;4 Suppl 1:S16–20.
52. Parsons CL, Shaw T, Berecz Z, Su Y, Zupkas P, Argade S. Role of urinary cations in the aetiology of bladder symptoms and interstitial cystitis. BJU Int. 2013;114:286–93.
53. Chung S-D, Liu H-T, Lin H, Kuo H-C. Elevation of serum C-reactive protein in patients with OAB and IC/BPS implies chronic inflammation in the urinary bladder. Neurourol Urodyn. 2011;30:417–20.
54. Cruz F, Dinis P. Resiniferatoxin and botulinum toxin type A for treatment of lower urinary tract symptoms. Neurourol Urodyn. 2007;26:920–7.
55. Yoshimura N, Seki S, Chancellor MB, de Groat WC, Ueda T. Targeting afferent hyperexcitability for therapy of the painful bladder syndrome. Urology. 2002;59(5 Suppl 1):61–7.
56. Yoshimura N, Oguchi T, Yokoyama H, et al. Bladder afferent hyperexcitability in bladder pain syndrome/interstitial cystitis. Int J Urol. 2014;21 Suppl 1:18–25.
57. Jacobs BL, Smaldone MC, Tyagi V, et al. Increased nerve growth factor in neurogenic overactive bladder and interstitial cystitis patients. Can J Urol. 2010;17(1):4989–94.
58. Sukiennik A, Carr DB, Bonney I, Marchand JE, Wurm H, Sant GR. The effect of short-term epidural local anesthetic blockade on urinary levels of substance P in interstitial cystitis. Anesth Analg. 2004;98:846–50.
59. Keller J, Chen Y-K, Lin H-C. Association of bladder pain syndrome/interstitial cystitis with urinary calculus: a nationwide population-based study. Int Urogynecol J. 2013;24:565–71.
60. Sant GR, Kempuraj D, Marchand JE, Theoharides TC. The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. Urology. 2007;69:34–40.
61. Rovner E, Propert KJ, Brensinger C, Wein AJ, Foy M, Kirkemo A, Landis JR, Kusek JW, Nyberg LM. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Database Study Group. Urology. 2000;56(6):940–5.
62. Foster Jr HE, Hanno PM, Nickel JC, Payne CK, Mayer RD, Burks DA, Yang CC, Chai TC, Kreder KJ, Peters KM, Lukacz ES, FitzGerald MP, Cen L, Landis JR, Propert KJ, Yang W, Kusek JW, Nyberg LM. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. J Urol. 2010;183(5):1853–8.
63. Carrico DJ, Peters KM, Diokno AC. Guided imagery for women with interstitial cystitis: results of a prospective, randomized controlled pilot study. J Altern Complement Med. 2008; 14(1):53–60.
64. Shorter B, Lesser M, Moldwin RM, Kushner L. Effect of comestibles on symptoms of interstitial cystitis. J Urol. 2007;178(1):145–52.
65. Rothrock NE, Lutgendorf SK, Kreder KJ, Ratliff T, Zimmerman B. Stress and symptoms in patients with interstitial cystitis: a life stress model. Urology. 2001;57(3):422–7.
66. Bassaly R, Tidwell N, Bertolino S, Hoyte L, Downes K, Hart S. Myofascial pain and pelvic floor dysfunction in patients with interstitial cystitis. Int Urogynecol J. 2011;22(4):413–8.
67. FitzGerald MP, Payne CK, Lukacz ES, Yang CC, Peters KM, Chai TC, Nickel JC, Hanno PM, Kreder KJ, Burks DA, Mayer R, Kotarinos R, Fortman C, Allen TM, Fraser L, Mason-Cover M, Furey C, Odabachian L, Sanfield A, Chu J, Huestis K, Tata GE, Dugan N, Sheth H, Bewyer K, Anaeme A, Newton K, Featherstone W, Halle-Podell R, Cen L, Landis JR, Propert KJ, Foster Jr HE, Kusek JW, Nyberg LM. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. J Urol. 2012;187(6):2113.
68. Van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol. 2004;172(2):533–6.

69. Sant GR, Propert KJ, Hanno PM, Burks D, Culkin D, Diokno AC, Hardy C, Landis JR, Mayer R, Madigan R, Messing EM, Peters K, Theoharides TC, Warren J, Wein AJ, Steers W, Kusek JW, Nyberg LM. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol. 2003;170(3):810–5.
70. Yamada T, Murayama T, Andoh M. Adjuvant hydrodistension under epidural anesthesia for interstitial cystitis. Int J Urol. 2003;10(9):463–8.
71. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology. 2005;66(3):494–9.
72. Chennamsetty A, Khourdaji I, Goike J, Killinger KA, Girdler B, Peters KM. Electrosurgical management of Hunner ulcers in a referral center's interstitial cystitis population. Urology. 2015;85(1):74–8.
73. Cox M, Klutke JJ, Klutke CG. Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. Can J Urol. 2009;16(2):4536–40.
74. Payne RA, O'Connor RC, Kressin M, Guralnick ML. Endoscopic ablation of Hunner's lesions in interstitial cystitis patients. Can Urol Assoc J. 2009;3(6):473–7.
75. Peters KM, Feber KM, Bennett RC. A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. BJU Int. 2007;100(4):835–9.
76. Peters KM, Konstandt D. Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. BJU Int. 2004;93(6):777–9.
77. Zabihi N, Mourtzinos A, Maher MG, Raz S, Rodríguez LV. Short-term results of bilateral S2-S4 sacral neuromodulation for the treatment of refractory interstitial cystitis, painful bladder syndrome, and chronic pelvic pain. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(4):553–7.
78. Powell CR, Kreder KJ. Long-term outcomes of urgency-frequency syndrome due to painful bladder syndrome treated with sacral neuromodulation and analysis of failures. J Urol. 2010;183(1):173–6.
79. Peters KM, Jayabalan N, Bui D, Killinger K, Chancellor M, Tyagi P. Effect of sacral neuromodulation on outcome measures and urine chemokines in interstitial cystitis/painful bladder syndrome patients. Low Urin Tract Symptoms. 2015;7(2):77–83.
80. Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. J Urol. 2006;175(3 Pt 1):1138–42.
81. Manning J, Dwyer P, Rosamilia A, Colyvas K, Murray C, Fitzgerald E. A multicentre, prospective, randomised, double-blind study to measure the treatment effectiveness of abobotulinum A (AboBTXA) among women with refractory interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2014;25(5):593–9.
82. Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int. 2009;104(5):657–61.
83. Pinto R, Lopes T, Frias B, Silva A, Silva JA, Silva CM, Cruz C, Cruz F, Dinis P. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. Eur Urol. 2010;58(3):360–5.
84. Pinto R, Lopes T, Silva J, Silva C, Dinis P, Cruz F. Persistent therapeutic effect of repeated injections of onabotulinum toxin a in refractory bladder pain syndrome/interstitial cystitis. J Urol. 2013;189(2):548–53. PMID: 23253961.
85. Chung SD, Kuo YC, Kuo HC. Intravesical onabotulinumtoxin A injections for refractory painful bladder syndrome. Pain Physician. 2012;15(3):197–202.
86. Forrest JB, Payne CK, Erickson DR. Cyclosporine A for refractory interstitial cystitis/bladder pain syndrome: experience of 3 tertiary centers. J Urol. 2012;188(4):1186–91.
87. Forsell T, Ruutu M, Isoniemi H, Ahonen J, Alfthan O. Cyclosporine in severe interstitial cystitis. J Urol. 1996;155(5):1591–3.
88. Sairanen J, Forsell T, Ruutu M. Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol. 2004;171(6 Pt 1):2138–41.
89. Rössberger J, Fall M, Jonsson O, Peeker R. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: subtyping is imperative. Urology. 2007;70(4):638–42.

90. Head KA. Natural approaches to prevention and treatment of infections of the lower urinary tract. Altern Med Rev. 2008;13(3):227–44.
91. http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm. Accessed Jan 2016.
92. Webster DC, Brennan T. Use and effectiveness of physical self-care strategies for interstitial cystitis. Nurs Pract. 1994;19(10):55–60.
93. Korting GE, Smith SD, Wheeler MA, Weiss RM, Foster Jr HE. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol. 1999;161(2):558–65.
94. Czarapata BJ. Super-strength, freeze-dried Aloe vera capsules in interstitial cystitis, painful bladder syndrome, chronic pelvic pain, and nonbacterial prostatitis: a double-blind, placebo-controlled crossover trial using Desert Harvest Aloe vera at the Urology Wellness Center, Rockville, Maryland. Proceedings of the NIDDK Scientific Symposium, San Diego, California. National Institutes of Health, Rockville, Maryland. 1995. Accessed Jan 2016.
95. Katske F, Shoskes DA, Sender M, Poliakin R, Gagliano K, Rajfer J. Treatment of interstitial cystitis with a quercetin supplement. Tech Urol. 2001;7(1):44–6.
96. Mendelowitz F, Moldwin R. Complementary therapies in the management of interstitial cystitis. In: Sant G, editor. Interstitial cystitis. Philadelphia: Lippincott-Raven; 1997. p. 235–9.
97. Ripoll E, Mahowald D. Interstitial cystitis and yoga: can it help? Interstitial Cystitis Network. http://www.ic-network.com. Published 2002. Accessed 15 Jan 2016.
98. Michalsen A, Grossman P, Acil A, Langhorst J, Lüdtke R, Esch T, Stefano GB, Dobos GJ. Rapid stress reduction and anxiolysis among distressed women as a consequence of a three-month intensive yoga program. Med Sci Monit. 2005;11(12):CR555–61.
99. Carter M, Weber T. Body reflexology: healing at your fingertips. Englewood Cliffs: Prentice-Hall; 1994.
100. Rapkin AJ, Kames LD. The pain management approach to chronic pelvic pain. J Reprod Med. 1987;32:323–7.
101. Dharmananda S. Treatment of interstitial cystitis with Chinese medicine. Institute for Traditional Medicine. http://www.itmonline.org. Published 2003. Accessed 24 Jan 2016.
102. Whitmore KE. Complementary and alternative therapies as treatment alternatives for interstitial cystitis. Rev Urol. 2002;4 Suppl 1:S28–35.

Chapter 9
Rehabilitation of the Pelvis and Pelvic Floor

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Introduction

Pelvic pain can be divided into acute and chronic components. Acute pelvic pain typically has a specific cause that is often alleviated after treatment or diminished over time with natural healing. Chronic pelvic pain (CPP), on the other hand, is defined as consistent or recurring pain below the umbilicus greater than 6 months duration that causes functional and/or psychological impairment prompting intervention [1]. CPP is estimated to affect about 15 % of the female population and to have a significant financial burden totaling over 881.5 billion dollars in health year costs annually and contributing to decreased work productivity and work revenue [2].

Given our scientific limitations, a readily identifiable and treatable cause often remains elusive. Commonly implicated causes in women include endometriosis, pelvic floor prolapse, and pelvic congestion syndrome; however, it is estimated that even in women who underwent a diagnostic laparoscopy, up to 40 % still lacked a definitive diagnosis [3]. There may be correlations between CPP in women with

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history of sexual trauma/abuse, multiple sexual partners, and spontaneous abortion [4]. In the pediatric literature, these factors do not appear to affect the incidence of chronic pelvic pain [5]. Those with CPP have been found to have an increased incidence of depression, anxiety, irritable bowel syndrome, and constipation [6]. CPP in men commonly manifests in the form of interstitial cystitis, chronic prostatitis, or musculoskeletal disturbances.

History Taking and Physical Examination

The International Pelvic Pain Society has distributed an extensive Pelvic Pain Assessment Form to better organize and guide patient encounters [7]. Pain with urination, frequency, or hesitancy may shed light on possible urologic causes. Additionally, a provider should attempt to differentiate between visceral, somatic, and neuropathic pain, although this may be difficult because of common nerve pathways. Nonetheless, visceral pain is typically poorly localized, dull, crampy and may be associated with autonomic responses. Somatic pain is usually well localized to muscle, bone, or joint and is often described as sharp, constant, and exacerbated with movement. Patient's sexual history and any high-risk behavior should be documented thoroughly along with any recent surgeries or pregnancies as adhesions can often be a culprit for pain in patients with the appropriate history. The timing of the pain in relation to menses and intercourse can better elucidate gynecologic etiologies. Neuropathic pain, due to neuronal injury, is often described as sharp, burning, or electrical in nature. History taking should also include prior psychiatric history and any functional impairments.

Gait and body positioning should be assessed as it can give a clue into possible musculoskeletal etiologies or ramifications of CPP. Additionally, psoas tightness should be tested with resisted knee and hip flexion. Pelvic ring stability is assessed, particularly in patients with recent surgery, trauma, or childbirth. Inspection of the abdominal and pelvic region should look to identify any prior scarring, ecchymosis, or rashes. Abdominal examination and palpation should be performed with attempted localization of pain and to rule out abdominal wall defects, potential distention or bowel obstruction and potential visceral causes of the pain. A thorough pelvic examination should be performed beginning with inspection for possible discharge, erythema, or urinary leakage. Bimanual vaginal examination and Pap smear should be performed along with a rectal examination. During the vaginal examination, the pelvic floor muscles should be evaluated for possible muscle tightness or spasm. Coccygodynia can be assessed during the rectal examination. Even the most astute practitioner may not be able to elucidate a clear cause of CPP through history taking and physical examination, so imaging studies may be necessary to aid in diagnosis. Magnetic resonance imaging (MRI) has been shown to help identify a cause of CPP in the symptomatic patient with no specific clinical findings in 39 % of cases [8].

Table 9.1 Common causes of chronic pelvic pain

Gastroenterologic	Urologic	Gynecologic	Musculoskeletal	Other
Constipation	Interstitial cystitis	Adenomyosis	Myofascial pain	Chronic pain
Hemorrhoids Anal fissures Chronic proctalgia	Chronic pelvic pain syndrome Chronic UTI	Endometriosis Menstrual cramps Ectopic pregnancy	Nerve entrapments Levator syndrome Pelvic girdle pain	Infection Psychiatric disorders
Neoplasm	Neoplasm	Neoplasm	Psoas tightness	Sickle cell
Irritable bowel syndrome Inflammatory bowel disease	Suburethral diverticulitis Detrusor dysfunction	Miscarriage Vulvodynia Pelvic inflammatory disease	Sacroiliac joint dysfunction Coccygodynia Pelvic floor prolapse	Physical/sexual abuse
Proctalgia fugax Appendicitis	Urethral syndrome Ureteral calculi	Pelvic congestion syndrome	Degenerative joint disease	

Causes of CPP

CPP is a broad entity with the potential of hundreds of causes, which can often be multifactorial. In those patients with multiple medical conditions, studies have shown the pain to be more severe than in those with only one etiology [9]. The common etiologic causes of CPP can be grossly divided into organ systems with the most common ones being gastroenterologic, urologic, gynecologic, and musculoskeletal (Table 9.1).

There are several infectious causes of pelvic pain. These include urinary tract infections (UTIs), sexual transmitted diseases (STDs), and vaginal infections. UTIs are relatively more common in women than men. The most common symptoms include dysuria, frequency, urgency, suprapubic pain, and/or cloudy or foul-smelling urine. When UTI is suspected, a urine sample is obtained for urinalysis and urine culture. Then, the patient is started on early, aggressive antibiotic therapy. While *Escherichia coli* is the most common bacterial cause of UTI, various Gram-negative and Gram-positive pathogens may be implicated. As a result, the ultimate choice of streamlining antibiotic choice is dependent on the susceptibilities of the isolated organism.

STDs are another commonly encountered cause of pelvic pain. *Trichomonas vaginalis* is the second most common STD in the United States, behind human papilloma virus. Typically presenting as itching and burning, there is pain with intercourse. Examination will often show an inflamed cervix with a green frothy discharge caused by the trichomonas protozoa. Treatment is typically with metronidazole. While not an STD, bacterial vaginosis is an imbalance of the normal vaginal

flora. Often characterized by a fishy odor and thin grayish discharge, the implicated organism is *Gardnerella vaginalis*. Treatment is usually with metronidazole or clindamycin. Another commonly encountered condition is vulvovaginal candidiasis, caused by the fungus *Candida albicans*; there is often a white, curd-like discharge with pseudohyphae seen on KOH preparation slide mounts. Treatment is with either oral fluconazole or azole creams.

Urinalysis and urine cultures are routinely ordered as part of the work-up of pelvic pain. If there is vaginal discharge, it should be cultured as well as prepared for possible wet mount. Antibiotic options are often specific to the implicated organism; however, acutely broad spectrum coverage is advocated. Blood work to assess for elevated white blood cell count may also be warranted. If the patients were to develop systemic symptoms, such as fever, chills, or rigors, it would be reasonable to obtain blood cultures to rule out bacteremia. Often managed by primary care providers, referral to infectious disease may be warranted in refractory cases or in patients with a complex medical background.

Gastroenterologic causes can be wide ranging from common causes such as constipation, hemorrhoids, and anal fissures to more involved diagnoses. Chronic proctalgia is an often under diagnosed condition defined by the presence of chronic or recurrent anorectal pain greater than 20 min after other anorectal causes have been ruled out. Patients may describe a burning type of pain that is worse with defecation and relieved when supine. Proctalgia fugax is a sudden night-time cramping pain in the anus or lower rectum that occurs and remits spontaneously. The episodes can last seconds to minutes and there is complete cessation of symptoms in between episodes. In those with gastroenterologic causes of CPP the incidence of proctalgia fugax ranges from 8 to 18 %, while chronic proctalgia is between 2 and 5 % [10, 11]. Irritable bowel syndrome (IBS) is thought to be a multifactorial diagnosis of exclusion in which there is abdominal pain or discomfort for at least 3 days a month coupled with changes in stool frequency or consistency. IBS can lead to visceral hypersensitivity with distention and changes in gastrointestinal (GI) motility as well as disruption of the hypothalamic pituitary axis [12]. It has been shown that those with IBS have a strong association with CPP, estimated to be between 65 and 79 % [13]. Other conditions such as Crohn's disease, appendicitis, diverticulitis, and GI infectious etiologies must be ruled out.

In men, CPP often involves the urological system. CPP syndrome or chronic prostatitis is CPP with voiding dysfunction after etiologies, such as urinary tract infection, structural abnormality, and malignancy, have been ruled out. As there may be inflammatory or noninflammatory subtypes, the presence of leukocytes may or may not be present.

Interstitial cystitis (IC) is usually classified by suprapubic pain with urinary symptoms such as frequency, hesitancy, and/or nocturia. The pain from IC may often present as low back or buttock pain. Other comorbidities, such as anxiety, depression, vulvodynia, and fibromyalgia, have been associated with IC so they must be investigated in order to apply an effective treatment regimen [14].

Urethral syndrome is burning during urination and incomplete emptying, particularly noted after sexual intercourse. This noninfectious cause of CPP is thought to be attributed to fibrotic and stenotic changes of the urethra.

Gynecologic causes are the leading cause of CPP in women. Endometriosis has been shown to be present in up to 70 % of women with CPP and 60 % of women with dysmenorrhea [15]. The presence of endometrial tissue outside of the uterine cavity can be proximal or distal and its effect can be drastic depending on the level of invasion. Patients typically present with pain correlated to their menstrual cycle and it may be associated with deep dyspareunia and infertility.

Pelvic congestion is another gynecologic cause of CPP and is the female equivalent of a scrotal varicocele in men. The dilated venous plexus contributes to a dull, aching pain that is often worse with prolonged standing, prior to menstruation and postcoital. Imaging is often utilized with the presence of dilated vessels being the hallmark of diagnosis. Syndromes of the anterior compartment, such as vulvodynia, vaginitis, and vulvar vestibulitis, are thought to be due to contact irritation, muscle stretching, hormonal changes, or a combination of the three [6]. These patients complain of intermittent burning, itching, redness, or stinging pain and may be preceded by trauma.

Musculoskeletal causes of CPP can be due to a variety of causes, with pelvic floor prolapse being a relatively common cause. Noted in up to 50 % of multiparous women, this multifactorial cause of the pain has been attributed to a combination of aging, trauma, decreased estrogen, and change in the nature of the tissue in regards to vascularity and collagen content. There may also be associated organ prolapse into the anterior compartment from a cystocele, rectocele, or uterine prolapse.

Pelvic girdle pain is a presentation of CPP as buttock or sacral pain that is typically associated with pregnancy. It is due to stretching of the pelvic ligaments which contribute to pelvic instability resulting in pain that typically worsens with weight-bearing activities.

Levator syndrome presents as a dull, aching pain caused by the spasm of the pelvic floor muscles, particularly the piriformis and puborectalis. It may be associated with incomplete evacuation and there will be tenderness to palpation of the muscles on physical examination.

Coccydynia is pain at or around the coccyx and has been seen to occur with local trauma, particularly in cyclists and in patients with prolonged sitting. The pain is thought to be due to increased tone of the pelvic floor as well as a local inflammatory response; however, up to 30 % of cases are ultimately identified as idiopathic [16].

Other causes of CPP can include infectious etiologies such as sexually transmitted infections: HIV, herpes, syphilis, chlamydia, and gonorrhea. In women, abnormal vaginal discharge and cervical motion tenderness may be elicited on vaginal examination. As chronic infections can lead to infertility and further complications, appropriate treatment requires partner involvement in order to prevent reinfection.

Chronic pain syndromes can also contribute to pelvic pain. In this situation, there is hypersensitivity of the neuronal network and alteration of the autonomic nervous system leading to central sensitization. This results in normally non-noxious stimuli evoking or maintaining a pain response [17].

Conservative Treatment

A multimodal approach to the treatment of CPP is needed because of its complex nature. The pelvic floor muscles consist of the coccygeus muscle and the levator ani, a three muscle complex consisting of the iliococcygeus, pubococcygeus, and the puborectalis. These muscles provide a hammock support system for the pelvic organs while also playing a role in maintaining urinary and fecal continence. Strengthening of the pelvic floor muscles by providing increased muscle endurance can improve incontinence and improve pelvic pain through reduction of muscle spasm. Physical therapy for the pelvic floor muscles includes numerous elements including external and internal mobilization techniques, Kegel exercises, biofeedback, and electrical stimulation.

External techniques can utilize connective tissue manipulation, myofascial release, trigger point therapy or joint mobilization. With these techniques, stretching exercises are taught in order to maintain the proper resting tone of the pelvic, abdominal, hip, thighs, hamstrings, and lower back muscles. Additionally, core strengthening is performed to increase pelvic stability. Connective tissue manipulation, or "skin rolling," aims to decrease tight skin and fascia of the abdomen and inner thighs which are thought to cause referred pain as well as have an association with trigger point activity. The therapist palpates the affected tissue between the thumb and fourth fingers to mobilize the thickened, restricted tissue to increase blood flow and restore mobility. While skin rolling anecdotally leads to improved pain, large randomized placebo-controlled trials are lacking. Myofascial release aims to restore symmetry to the pelvic anatomy by stretching fascial planes. In addition to its use for the back, hip, and hamstring muscles, the pelvic floor muscles can be directly targeted by using the ischial tuberosities as grips in order to obtain a full stretching of those muscles. Joint mobilization consists of passively moving a joint that is restricted and cannot be adequately stretched by the patient alone. After manipulation, the patient has greater mobility which can be maintained with stretching exercises. This is often done in sacroiliac joint dysfunction [18]. Therapists that specialize in pelvic therapy often undergo numerous courses and require certification particularly if they perform some of the more invasive maneuvers and manipulations.

Treatment of the pelvic floor internally involves the insertion of a finger or instrument into the vagina or rectum. The muscles and connective tissues are directly massaged to release trigger points. Applying pressure until the trigger point relaxes may be done along with trigger point injection therapy.

Kegel exercises involve contracting and relaxing the pelvic floor muscles in order to increase muscle tone and maintain an appropriate balance of the pelvic musculature. The key to Kegel exercises is to identify the proper muscles in which to contract and relax. An often cited approach is stopping the flow of urine which will identify that you have targeted the proper muscles. The correct approach is then to perform these exercises on a regular basis on an empty bladder; starting and stopping your urine flow may actually do harm. Patients are often told to hold the contraction for

2–3 s with 5 sets of 10 repetitions every day. While performing any of these exercises, it is important to keep your abdominal muscles, buttocks, and thighs relaxed.

Biofeedback therapy utilizes an immediate feedback system with physiologic neuromuscular activity assessment and amplification. The goal of biofeedback being the immediate reinforcement of a specific behavior or movement in order to establish a learned routine. Its use for bladder control and anal sphincter control can improve incontinence while the ability to emphasize muscle relaxation of the pelvic floor muscles can be utilized in pelvic pain patients [19]. When the activity of a physiologic process via cutaneous or intravaginal/intrarectal sensors is noted, an auditory or visual response is generated. The signals of muscle contractions, relaxation, and muscle activity are generated in real time and allow for the patient to immediately see when the appropriate muscles are contracted. The frequencies of sessions are individualized and may be once a week or even monthly. Improvement may be seen rapidly within the first few sessions but have shown significant improvement after 3–6 months [18].

Measuring the electrical activity of a muscle through electromyography (EMG) may be preferred over the manometric pressure readings in biofeedback as electromyography will show the electrical potentials of a depolarized muscle as well as monitoring of motor units bioelectrical activity. This in turn provides a good indicator of physiologic muscle activity with more lightweight and activity tolerating electrodes than compared to pressure probes [19].

Often the utilization of electrical stimulation is performed in conjunction with biofeedback in order to assist with the appropriate isolation and identification of the pelvic floor muscles. By applying a small electrical current to the pelvic floor muscles you can increase muscle strength, decrease muscle spasm and increase endurance via recruitment of fast twitch pelvic muscle fibers [20].

Topical agents have been trialed for the treatment of pelvic pain. Acyclovir ointment applied to painful areas has shown improvement in painful symptoms. Corticosteroids are often utilized, although when combined with lidocaine, amitriptyline, or ketoprofen, the topical compounded treatment showed increased efficacy. Topical amitriptyline–ketamine used for the treatment of pelvic and perineal pain has been shown to have pain relief in 85 % of patients with a low incidence of adverse effects [21]. The use of 5-fluorouracil has fallen out of favor because of a higher incidence of adverse effects [19].

Vaginal diazepam has anecdotally been used for the treatment of chronic pelvic pain. It was thought to have the effect of decreasing skeletal muscle spasm via decreased neuronal depolarization without the adverse effects commonly seen with oral diazepam. As women with vulvar pain syndromes were found to have hypertonicity of the pelvic floor musculature, vaginal diazepam seemed to offer an additional treatment option [44]. Currently, it is being used off-label for pelvic floor dysfunction and urogenital pain. While a few small studies have shown some improved outcomes, large randomized, placebo-controlled trials are lacking [45–47].

In terms of oral analgesic medications, acetaminophen and nonsteriodal anti-inflammatory drugs (NSAIDs) are often considered initially. Tramadol and opioids may be utilized as well [22]. Antidepressants, particularly tricyclic antidepressants

(TCA) have a long history of efficacy in treating pain syndromes while SSRIs and SNRIs have shown more conflicting results [1]. Anticonvulsants, such as gabapentin and pregabalin, have also shown promising results when used in the treatment of chronic pain [22].

Particularly, in the case of interstitial cystitis (IC), treatment options expand farther than conservative dietary and lifestyle modifications. Pentosan polysulfate orally is an option approved by the FDA for treatment of IC. Amitriptyline was shown to have good effects however was limited by its side effects [23]. Cyclosporine and prednisone are immunosuppressants that may be used as second-line agents in order to reduce inflammation.

Intravesical treatments of IC were reviewed which showed mixed results. Dimethyl sulfoxide (DMSO) despite its muscle relaxation, anti-inflammatory, and analgesic effects showed no improvement in pain. Similarly, resiniferatoxin, which causes bladder desensitization, showed no outcome differences. Bacillus Calmette-Guerin's (BCG) immune altering effects were shown to decrease pain but had no difference in quality of life. Intravesical pentosan polysulfate's ability to decrease toxin translocation across the bladder wall had limited evidence. [24].

Studies aimed at reducing bladder spasm with the anticholinergic oxybutynin did not measure pain [24]. The use of internal bladder wall components, such as hyaluronic acid and chondroitin, has shown promising results, but remains with the need for further studies [25]. Studies on botulinum toxin A's analgesia in IC have been inconclusive at this time [26].

Bladder hydrodistention procedures may be utilized for diagnosis and for treatment as a third-line agent of IC [27]. In this outpatient surgical procedure, the bladder is expanded with fluid at low pressures and left distended for 5–10 min. After the fluid is drained, the bladder wall is revisualized with cystoscopy to check for areas of irritation.

In addition to pharmacotherapy, psychotherapy has been incorporated into a multimodal approach for the treatment of chronic pain in the form of cognitive-behavioral therapy, counseling, biofeedback and group therapy. When incorporating a multidisciplinary approach to treatment, Complementary alternative medical (CAM) options, such as acupuncture/acupressure, myofascial release, massage therapy, stretching, and reiki, are combined with both pharmacological and interventional options.

Interventional Therapies

Following failure of conservative therapies and with unremitting pain, patient and provider may elect to undergo neurolytic or neuroablative therapies. The focus of these interventions aim to target a particular nerve or neural plexus, particularly the superior and inferior hypogastric plexuses as well as the ganglion impar, with the hope of reducing pain (Fig. 9.1). This nonsurgical approach may utilize chemical denervation, cryoablation, or thermoablation.

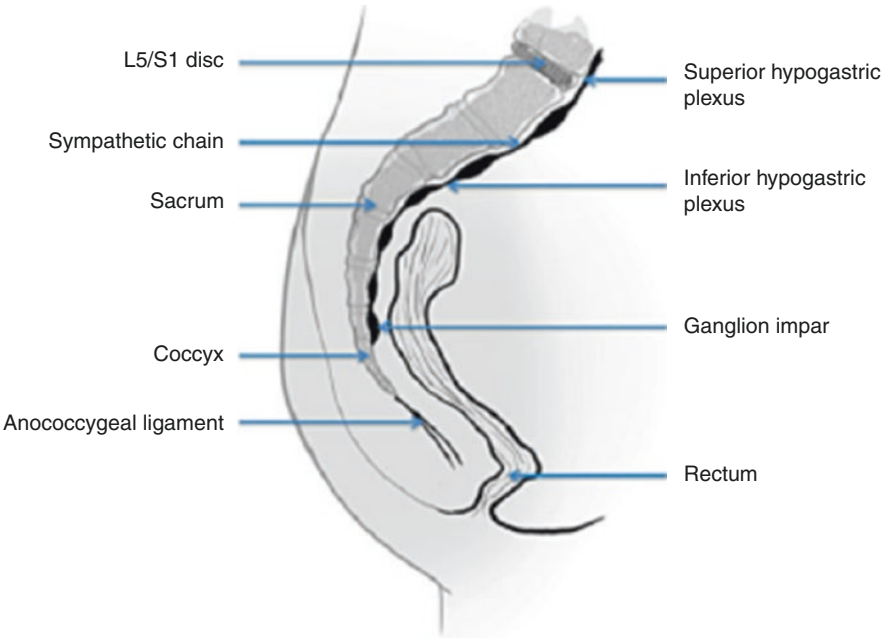

Fig. 9.1 The superior hypogastric plexus, inferior hypogastric plexus, and ganglion impar can be targeted in the treatment of CPP. The SPH is targeted at the level of the L5–S1 disc space. The IHP is targeted at the level of the S2 foramen. The ganglion impar is located at the sacrococcygeal junction [42]

Located from L3 to S1 in the anterior retroperitoneum, the bilateral superior hypogastric plexuses are one of the three large sympathetic plexuses. They carry pelvic viscera afferent fibers thus lending themselves available for potential neurolysis. Diagnostic blocks with local anesthetic can be performed to assess the potential long-term analgesic effect of such a block. If the patient experiences relief with the anesthetic, the physician can disrupt the neural networks, with phenol, glycerin, or alcohol. This is usually preferred over neurolytic agents, such as benzocaine, lidocaine, or ropivacaine, as the latter agents act on the axon not the cell bodies that would allow for axonal regeneration and thus only temporary pain relief [28].

This technique has been used for pain relief in patients with pelvic cancer pain, penile pain, distal inflammatory bowel disease, chronic pelvic pain amongst others. Typically, the patient is positioned prone with arms off of the table. A pillow may be placed under the abdomen to reduce lumbar lordosis. After palpation of the L4–L5 interspace, fluoroscopic confirmation is performed. Now, however, fluoroscopic, computed tomography (CT), or ultrasound guidance is utilized with good pain relief and the avoidance of adverse events [29–31]. Anatomical difficulties with the classic approach, particularly the iliac crest and L5 transverse process, as well as the potential for damage to bowel, bladder, and the common iliac artery, have led to a plethora of different approaches with various image guidance systems. The traditional approach

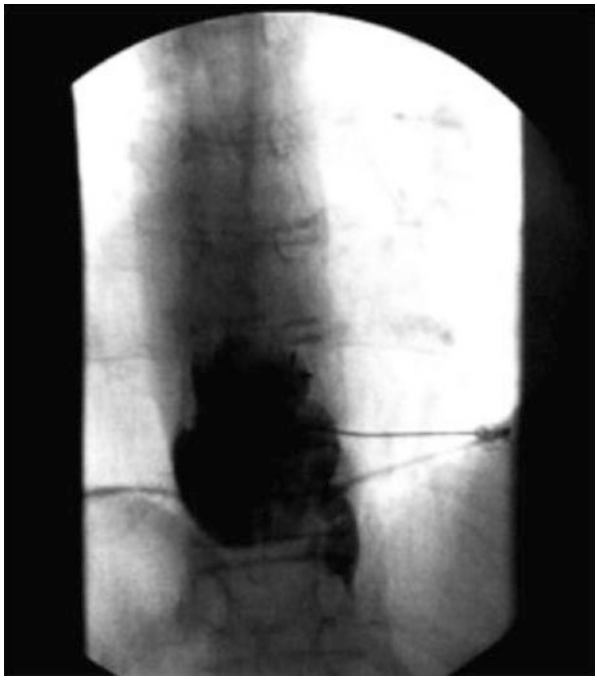

Fig. 9.2 Superior hypogastric plexus block showing advancement of the needle tip into the retroperitoneal space. Contrast spread is noted within the retroperitoneal space anterior to the vertebral body ensuring proper needle location [42]

has the tip of the needle oriented anterolateral to the bottom of L5 vertebral body and advanced until the body of L5 is seen. At which point the fascial plane of the psoas muscle is penetrated and felt as a loss of resistance, leading to entrance to the retroperitoneal space. The same is done on the contralateral side. Confirmatory needle location prior to neurolysis is performed with radiographic contrast to ensure avoidance of the vertebral column as well as the nearby common iliac vessels and ensure entrance into the retroperitoneal space (Figs. 9.2 and 9.3). In one study, the superior hypogastric plexus block has obtained a positive response in 79 % of the patients retained pain relief of 69 % at the 6-month mark and a decrease in opioid consumption of 67 % [32].

Not as frequently utilized as the superior hypogastric plexus blocks for interventional blockage are the bilateral inferior hypogastric plexuses. Located ventral to the rectum bilaterally at the level of the S2–S4 spinal segments, this presacral plexus also carries pelvic viscera afferent fibers. Good results have been seen with inferior hypogastric plexus blockade particularly with a trans-sacral approach resulting in similar pain relief as a superior hypogastric plexus block but with a safer and easier approach [33]. While there is a need for larger randomized controlled trials, this potential intervention remains promising.

The ganglion impar, or ganglion of Walther, is the most inferior sympathetic ganglion that results from the convergence of the bilateral sympathetic pelvic trunks anterior to the coccyx. It has been implicated in CPP and is well described as being a focus for nerve block injection for the treatment of coccygodynia with good pain

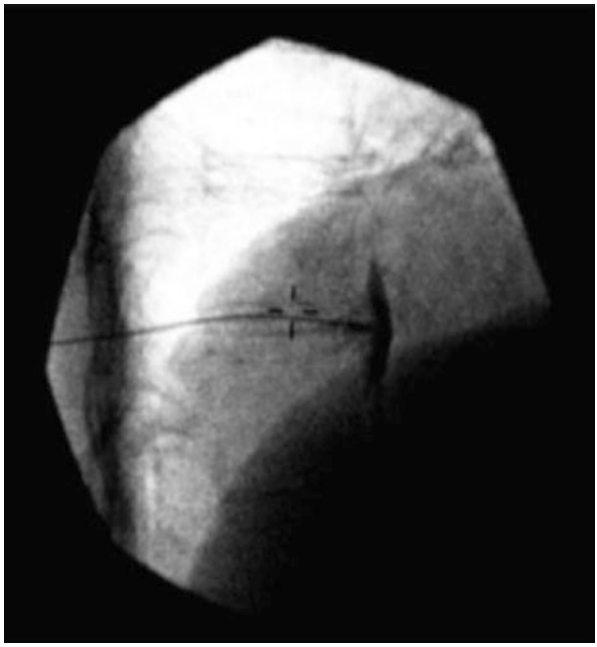

Fig. 9.3 Superior hypogastric plexus block showing advancement of the needle tip into the retroperitoneal space through the disc with contrast noted to spread within the retroperitoneal space [42]

relief [34]. Patients often complain of a burning pain and/or urinary and rectal urgency when the ganglion impar is involved. The patient is positioned in a prone or lateral recumbent position and the tip of the coccyx is palpated. Typically, under fluoroscopic guidance, a bent needle is inserted through the anococcygeal membrane and directed toward to the location of the ganglion impar just below the sacrococcygeal junction. The best positioning of the needle is seen when angled toward the ventral surface of the sacrococcygeal joint after introducing at a slight cranial orientation. Ultrasound guidance and varying approaches, including transdiscal and trans-sacrococcygeal approaches, have also been described [35, 36]. Regardless of the approach, proper needle location confirmation is done with contrast prior to delivery of the neurolytic agent (Fig. 9.4). Recently, the use of a dual superior hypogastric plexus block and ganglion impar block has been shown to safe and effective while decreasing the amount of opiate consumption, although larger trials remain needed [37].

Sacral nerve stimulation has been applied for the treatment of CPP with seemingly good results. The use of neuromodulation for the treatment of various pelvic dysfunction etiologies extends across many years and has shown good results after failed conservative treatment of IC. There was a significant decrease in pain levels and urinary measures along with minimal side effects after percutaneous sacral nerve stimulation [38]. Expanded beyond use in IC, sacral nerve stimulation for unrelenting CPP of varying causes was shown to have pain relieving effects lasting up to 3 years after placement of the stimulator [39, 40]. In appropriately trialed patients, sacral nerve stimulation can be a valuable treatment asset. Neuromodulation

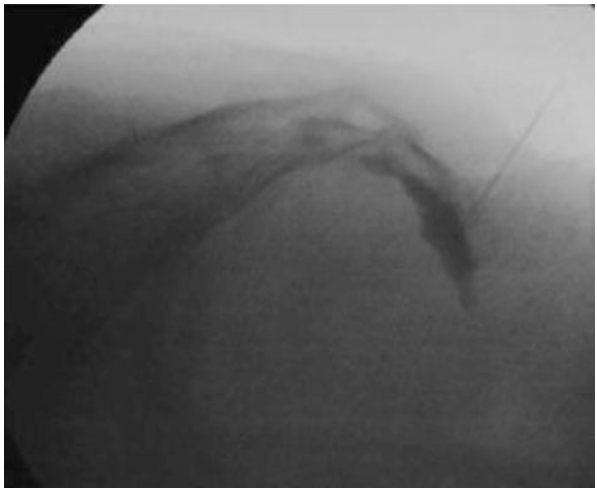

Fig. 9.4 The ganglion impar block. After insertion at the level of the sacrococcygeal junction, needle position was confirmed with contrast and demonstrates the "comma" sign of contrast flow along the ventral sacrum [43]

at the level of the spinal cord may yield good results as dorsal column pathway stimulation can provide pain relief through the alteration of visceral pain perception and processing.

Additionally, the use of chronic pudendal nerve stimulation can provide pain relief for refractory pelvic pain. As an alternative to sacral nerve stimulation, this treatment option showed that in patients with CPP who had previously had sacral stimulation, 93.2 % experienced pain relief after undergoing pudendal nerve stimulation [41].

Conclusion

CPP is a complex and often times multifaceted disorder with the potential involvement of many organs including the urogenital, gynecological, musculoskeletal, and gastroenterologic systems. A thorough history and physical examination coupled with a focused evaluation plan is necessary as CPP treatment often requires an interdisciplinary approach. The Pelvic Pain Assessment Form, as put forth by the International Pelvic Pain Society, can be utilized to give structure and uniformity to the evaluation of CPP [6]. Often times a clear cut pain generator is not found, but the background obtained can help to guide a treatment plan. Conservative treatments can include an amalgamation of medical management with oral agents along with psychotherapy and complementary alternative medicine options. Failure of conservative treatment may require the additional use of interventional procedures including superior hypogastric plexus block, inferior hypogastric block, or ganglion impar block. CPP is a vast and complex disease process that requires a multidisciplinary approach in regards to examination and treatment options in order to maximize pain relief.

References

1. Green IC, Cohen SL, Finkenzeller D, et al. Interventional therapies for controlling pelvic pain: what is the evidence? Curr Pain Headache Rep. 2010;14:22–32.
2. Mathis SD, Kuppermann M, Liberman RF, et al. Chronic pelvic pain: prevalence health related quality of life, and economic correlates. Obstet Gynecol. 1996;87(3):321–7.
3. Garry R. Diagnosis of endometriosis and pelvic pain. Fertil Steril. 2006;86:1307–9.
4. Reiter RC, Gambone JC. Demographic and historic variables in women with idiopathic chronic pelvic pain. Obstet Gynecol. 1990;75:428–32.
5. Berger MY. Chronic abdominal pain in children. BMJ. 2007;334:997–1002.
6. Stein SL. Chronic pelvic pain. Gastroenterol Clin N Am. 2013;42:785–800.
7. International Pelvic Pain Society – Pelvic pain assessment form. http://www.pelvicpain.org/docs/resources/forms/History-and-Physical-Form-English.aspx.
8. Dwarkasing RS, Schouten WR, Geeraedts TE, et al. Chronic anal and perianal pain resolved with MRI. AJR Am J Roentgenol. 2012;200(5):1034–41.
9. Zondervan KT, Yudkin PL, Vessey MP, et al. Chronic pelvic pain in the community: symptoms, investigations, and diagnoses. Am J Obstet Gynecol. 2001;164:1149.
10. Rao SS, Paulson J, Mata M, et al. Clinical trial: effects of botulinum toxin on levator ani syndrome – a double-blind, placebo controlled study. Aliment Pharmacol Ther. 2009;29:985–91.
11. Mazza L, Formento E, Fonda G. Anorectal and perineal pain: new pathophysiological hypothesis. Tech Coloproctol. 2004;8:77–83.
12. Shin JH, Howard FM. Management of chronic pelvic pain. Curr Pain Headache Rep. 2011; 15:377–85.
13. Hogston P. Irritable bowel syndrome as a cause of chronic pain in women attending a gynaecology clinic. Br Med J. 1987;294(6577):934–5.
14. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. Obstet Gynecol. 2002;100:337–41.
15. Farquhar C. Endometriosis. Endometriosis Br Med J. 2007;334:249–53.
16. Patijn J, Janssen M, Hayek S, et al. Coccygodynia. Pain Pract. 2010;10(6):554–9.
17. Janicki TI. Chronic pelvic pain as a form of complex regional pain syndrome. Clin Obstet Gynecol. 2003;46(4):797–803.
18. Potts JM. Therapeutic options for chronic prostatitis/chronic pelvic pain syndrome. Curr Urol Rep. 2005;6(4):313–7.
19. Howard FM, Perry CP, Carter JE, et al. Pelvic pain diagnosis and management. Philadelphia: Lippincott Williams & Wilkins; 2000. ISBN 0-7817-1724-8.
20. Newman DK. Pelvic floor muscle rehabilitation using biofeedback. Urol Nurs. 2014; 34(4):193–202.
21. Poterucha TJ, Murphy SL, Rho RH, et al. Topical amitriptyline-ketamine for treatment of rectal, genital, and perineal pain and discomfort. Pain Physician. 2012;15(6):485–8.
22. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hosp Pyschiatry. 2009;31:206–19.
23. Van Ophoven A, Hertle L. Long-term results of amitriptyline treatment of interstitial cystitis. J Urol. 2005;174:1837–40.
24. Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/interstitial cystitis. Cochrane Database Syst Rev. 2007;4:CD006113.
25. Cervigni M, Natale F, Natasa L, et al. A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. Int Urogynecol J. 2008;19:943–7.
26. Toft BR, Nordling J. Recent developments of intravesical therapy of painful bladder syndrome/interstitial cystitis: a review. Curr Opin Urol. 2006;16:268–72.
27. American Urological Association Guideline. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. 2014. https://www.auanet.org/education/guidelines/ic-bladder-pain-syndrome.cfm.

28. Plancarte R, Amescua C, Patt RB, et al. Superior hypogastric plexus block for pelvic cancer pain. Anesthesiology. 1990;73:236–9.
29. de Leon-Casasola OA, Kent E, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain. 1993;54(2):145–51.
30. Ghoneim AA, Mansour SM. Comparative study between computed tomography guided superior hypogastric plexus block and the classic posterior approach: a prospective randomized study. Saudi J Anaesth. 2014;8(3):378–83.
31. Mishra S, Bhatnagar S, Rana SP, et al. Efficacy of the anterior ultrasound-guided superior hypogastric plexus neurolysis in pelvic cancer pain in advanced gynecological cancer patients. Pain Med. 2013;14(6):837–42.
32. Plancarte R, de Leon-Casacola OA, El-Helaly M, et al. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Reg Anesth. 1997;22:562–8.
33. Schutz DM. Inferior hypogastric plexus blockade: a transsacral approach. Pain Physician. 2007;10(6):757–63.
34. Foye P, Buttaci C, Stitik T. Successful injection for coccyx pain. Am J Phys Med Rehabil. 2006;85(9):783–4.
35. Johnston PJ, Michalek P. Blockade of the ganglion impar (walther), using ultrasound and a loss of resistance technique. Prague Med Rep. 2012;113(1):53–7.
36. Wemm Jr K, Saberski L. Modified approach to block the ganglion impar (ganglion of Walther). Reg Anesth. 1995;20(6):544–5.
37. Ahmed DG, Mohamad MF, Mohamad SA. Superior hypogastric plexus combined with ganglion impar neurolytic blocks for pelvic and/or perineal cancer pain relief. Pain Physician. 2015;18:E49–56.
38. Whitemore KE, Payne CK, Diokno AC, et al. Sacral neuromodulation in patient with interstitial cystitis: a multicenter clinical trial. Int Urogynecol J. 2003;14:305–9.
39. Seigel S, Paszkiewicz E, Kirkpatrick C, et al. Sacral nerve stimulation in patient with chronic intractable pelvic pain. J Urol. 2001;166:1742–5.
40. Everaert K, Devulder J, De Muynk M, et al. The pain cycle: implications for the diagnosis and treatment of pelvic pain syndromes. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12:9–14.
41. Peters KM, Killineger KA, Boguslawski BM, et al. Chronic pudendal neuromodulation: expanding available treatment options for refractory urologic symptoms. Neurourol Urodyn. 2010;29(7):1267–71.
42. Bolash R, Vrooman B. Chapter sympathetic blocks for chronic abdominal pain. In: Kapural L, editor. Chronic abdominal pain: an evidence based, comprehensive guide to clinical management. New York: Springer; 2015. p. 143–52.
43. Scott-Warren JT, Hill V, Rajasekaran A. Ganglion impar blockade: a review. Curr Pain Headache Rep. 2013;17:306.
44. Reissing ED, Brown C, Lord MJ, et al. Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. J Psychosom Obstet Gynecol. 2005;26(2):107–13.
45. Carrico DJ, Peters KM. Vaginal diazepam use with urogenital pain/pelvic floor dysfunction. Urol Nurs. 2011;31(5):279–84.
46. Crisp CC, Vacarro CM, Estanol MV, et al. Intra-vaginal diazepam for high-tone pelvic floor dysfunction: a randomized placebo-controlled trial. Int Urogynecol J. 2013;24(11):1915–23.
47. Rogalski MJ, Kellog-Spadt S, Hoffman AR, et al. Retrospective chart review of vaginal diazepam suppository use in high-tone pelvic floor dysfunction. Int Urogynecol J. 2010;2 1(7):895–9.

Chapter 10
Cancer Pain in the Urogenital Region

Samuel Hardy, Mark Angelo, Krista Haas, Huda Sayed, and Vincent J. Vanston

Introduction

According to the International Association of Pain, pain is defined as an "unpleasant, multidimensional, sensory, and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (iasp-pain.org). This definition is no less accurate when it is applied to patients suffering from cancer-related pain.

The effective treatment of pain in patients with cancer remains a pressing concern. Studies reveal the prevalence of pain in up to 25 % of those first diagnosed with cancer, 33 % of those undergoing treatment, and 75 % of those in the terminal phase of their disease [1–4]. Despite these compelling figures, inadequate treatment of cancer pain persists. In a large prospective study, Fisch et al. followed more than 3000 patients with breast, colorectal, or prostate cancer [5]. Of the 2000 patients who reported pain, 670 (34 %) were not receiving adequate pain medication. Twenty-three percent of patients with severe pain and 27 % of those with moderate pain received no analgesics at all. The barriers to adequate cancer pain management are plenty. Inadequate education, legislative barriers, political obstacles, and patient and family attitudes have been implicated in contributing to ineffective care.

When managing those with cancer pain, the entire experience of the patient must be explored. In 1978, Cicely Saunders introduced the concept of "total pain" [6].

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That is, pain includes all aspects of a person. It has physical, psychological, spiritual, and interpersonal dimensions. To be truly effective, a comprehensive assessment must take into account all of these dimensions.

Expert consensus and guidelines, such as those put forth by the Agency for Healthcare Policy and Research and the National Comprehensive Cancer Network, describe those elements of care essential for effective cancer pain management in any region of the body [7, 8]. They are given as follows:

Ask About Pain at Each Visit and Believe the Patient

Patients will sometimes assume that pain is a low priority for the physician or that they will be judged for complaining about pain. It is essential that healthcare providers assure the patient that their experience of pain is an important part of each visit. Healthcare providers must avoid common errors in assessment. For example, one must recall that patients with chronic pain will not exhibit the autonomic changes seen in acute pain. Cultural and racial biases can further impede effective evaluation.

Perform a Comprehensive Pain Assessment and Measure Pain Intensity

A comprehensive pain assessment begins with a detailed history. A pain history should include its precipitating factors, quality, radiation, and severity. Moreover, the temporal patterns of the pain can help the provider characterize the pain as acute, subacute, chronic, episodic, intermittent, breakthrough, or incidental in nature.

The AHCPR guidelines stress that "the patient's self-report" should be the primary source of assessment. Toward that end, measurement tools have been developed by which healthcare providers and patients can communicate. In some institutions, pain has been measured as a fifth vital sign along with pulse, respiratory rate, blood pressure, and temperature.

Common assessment tools include the Visual Analog scale, 0–10 numeric scales and simple descriptive scales (Fig. 10.1). These scales do require an element of abstract thinking. One must, therefore, confirm that the patient understands and is comfortable with the tool employed. For children or for those with language barriers, the Wong-Baker faces can be an invaluable tool (Fig. 10.2). For those with dementia or other significant cognitive impairment, the PAINAD scale (Fig. 10.3) can allow for consistent assessment. Finally, for more comprehensive assessments, the memorial pain assessment tool (Fig. 10.4) or the Wisconsin Brief Pain Inventory are examples of detailed scales which measure not only pain intensity, but also its impact on other functional dimensions of the person.

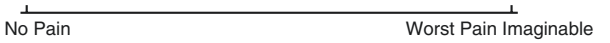

Fig. 10.1 Visual analog scale

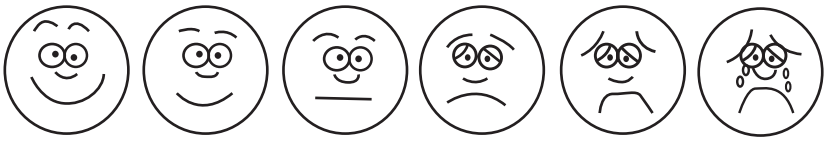

Fig. 10.2 Wong-baker scale

Pain Assessment in Advanced Dementia Scale (PAINAD)

Instructions: Observe the patient for five minutes before scoring his or her behaviors. Score the behaviors according to the following chart. Definitions of each item are provided on the following page. The patient can be observed under different conditions (e.g., at rest, during a pleasant activity, during caregiving, after the administration of pain medication).

Behavior	0	1	2	Score
Breathing Independent of vocalization	• Normal	• Occasional labored breathing • Short period of hyperventilation	• Noisy labored breathing • Long period of hyperventilation • Cheyne-Stokes respirations	
Negative vocalization	• None	• Occasional moan or groan • Low-level speech with a negative or disapproving quality	• Repeated troubled calling out • Loud moaning or groaning • Crying	
Facial expression	• Smiling or inexpressive	• Sad • Frightened • Frown	• Facial grimacing	
Body language	• Relaxed	• Tense • Distressed pacing • Fidgeting	• Rigid • Fists clenched • Knees pulled up • Pulling or pushing away • Striking out	
Consolability	• No need to console	• Distracted or reassured by voice or touch	• Unable to console, distract, or reassure	
			TOTAL SCORE	

(Warden et al., 2003)

Scoring:

The total score ranges from 0–10 points. A possible interpretation of the scores is: 1–3 = mild pain; 4–6 = moderate pain; 7–10 = severe pain. These ranges are based on a standard 0–10 scale of pain, but have not been substantiated in the literature for this tool.

Source:

Warden V. Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. *J Am Med Dir Assoc.* 2003;4(1):9–15.

Fig. 10.3 PAINAD scale

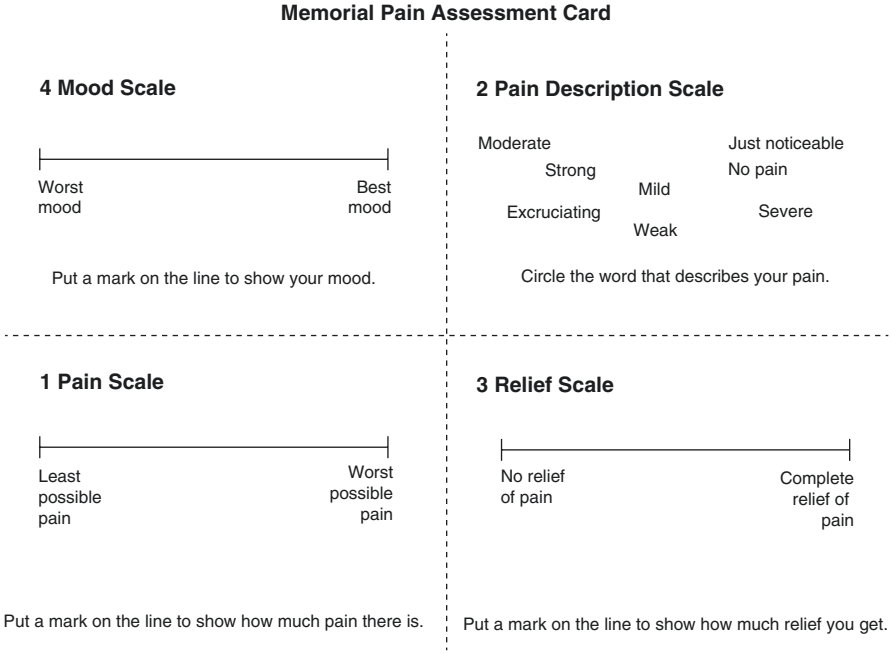

Fig. 10.4 Memory pain assessment card

In keeping with the concept of "total pain," one must explore the psychosocial and spiritual impact of the patient's pain. How has the person coped with significant stressors in his past? Are anxiety or depression contributing to the pain? Has this individual relied on alcohol or other substances to cope? Has there been a history of opioid misuse or abuse? What kind of social support surrounds the patient? Finally, what is the meaning of pain for that individual? The answers to these questions can often provide insight into how to craft an effective management plan.

Perform a Complete Physical and Neurological Examination

If one has taken a truly comprehensive pain history, the physical and neurological examination should serve to confirm or further narrow the differential diagnosis for the patient's pain. Additional testing should serve the purpose of both clarifying the diagnosis and assisting with the development of a management plan. Clearly, one must avoid burdensome studies or procedures that will not ultimately serve to lessen the patient's pain.

Develop a Comprehensive Pain Management Plan

After a comprehensive history, physical examination, and appropriate studies, one can develop a comprehensive approach to the patient's pain. Ideally, this should address not only the physical, but also the psychological and spiritual concerns of the patient.

As part of the plan, regular follow-up is essential. The healthcare provider and patient should approach the plan as partners, both empowered to work toward relief.

Cancer Pain Syndromes of the Genitourinary Region

Patients with known or suspected prostate cancer may require transrectal prostate biopsy. In a prospective study, 16 % of patients undergoing transrectal prostatic biopsy without anesthesia reported at least moderate ≥5 intensity pain, and 19 % reported that they would not agree to undergo the procedure again without anesthesia [9]. Clinician experience as well as patient factors and preferences determine anesthetic technique for this. Published studies support infiltrative and noninfiltrative techniques. Significant pain reduction is reported with pudendal nerve block [10], periprostatic lidocaine infiltration [11], periprostatic tramadol [12], intrarectal 2 % lidocaine cream [13], and intrarectal ice applied 5 min prior to the procedure [14].

For women with intraepithelial neoplasia, cervical cryosurgery is associated with pain and cramping. Paracervical block with 1 % lidocaine and 1:100,000 epinephrine significantly reduces these symptoms [15]. Intramucosal block is an effective alternative [16]. Pretreatment with NSAIDs is not shown to reduce pain and cramping during cervical cryosurgery [17].

Perineal pain is commonly associated with cancers originating in the distal genitourinary system. A syndrome similar to tension myalgia of the pelvic floor can occur when tumor invades the musculature of the deep pelvis, causing an aching or heavy sensation that worsens with upright posture [18]. In patients who have undergone pelvic tumor resection, the onset of severe perineal pain may indicate recurrence of disease [19, 20].

In burning perineum syndrome, pelvic radiation therapy results in persistent perineal pain. The pain is typically described as burning in quality and it can radiate to the vagina or scrotum. The latency period of burning perineum syndrome is 6–18 months. Recurrent tumor should be excluded [21, 22].

When cancer metastasizes to the sacrum, it can produce severe pain that radiates to the buttocks, perineum, or posterior thighs, is worse with sitting or lying down, and improves when standing or walking [23, 24]. Tumor invasion of the muscles that rotate the hip can produce a malignant “pyriformis syndrome” with buttock (or posterior thigh) pain that worsens with internal rotation.

Pharmacologic Management of Cancer-Related Pain

Most cancer pain practitioners take a multifaceted, multidisciplinary approach to the comprehensive pain management of the patient with cancer. This type of pain management involves the use of pharmacologic treatments as well as nonpharmacologic treatments and interventions.

Cancer pain can be categorized as neuropathic or nociceptive. Nociceptive pain is further subdivided into somatic and visceral pain. It is important to understand the etiology of the pain as this will help the practitioner to select appropriate therapies.

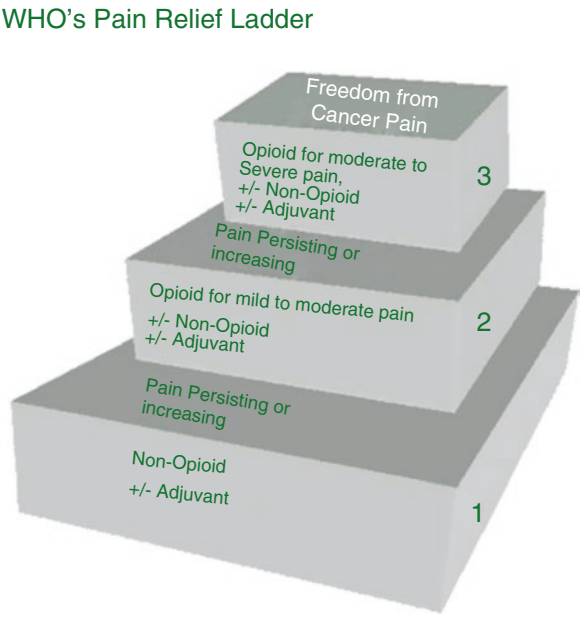

Fig. 10.5 World Health Organization (WHO) analgesic ladder (reprinted from WHO.org)

World Health Organization (WHO) Analgesic Ladder

The World Health Organization provides a framework for analgesic administration in the setting of cancer-related pain. This framework is represented in Figs. 10.5 and 10.6.

Step 1: Mild Pain in the Urogenital Region in the Cancer Patient

Nonopioid analgesia represents the first step in the treatment of cancer-related pain. Pharmacologic treatment options in this category include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Table 10.1 provides a list of NSAIDs commonly used in practice.

Acetaminophen (paracetamol) is a well-tolerated, antipyretic, and analgesic drug that is recommended in many circumstances as a first step in the pharmacologic management of mild cancer pain. The mechanism of action of acetaminophen is only partially understood. It is thought that acetaminophen is a weak inhibitor of prostaglandin synthesis and most likely works in the central nervous system (CNS) via the activation of serotonergic pathways [25]. Acetaminophen can cause severe liver toxicity and failure, especially in the setting of existing liver disease. Typically,

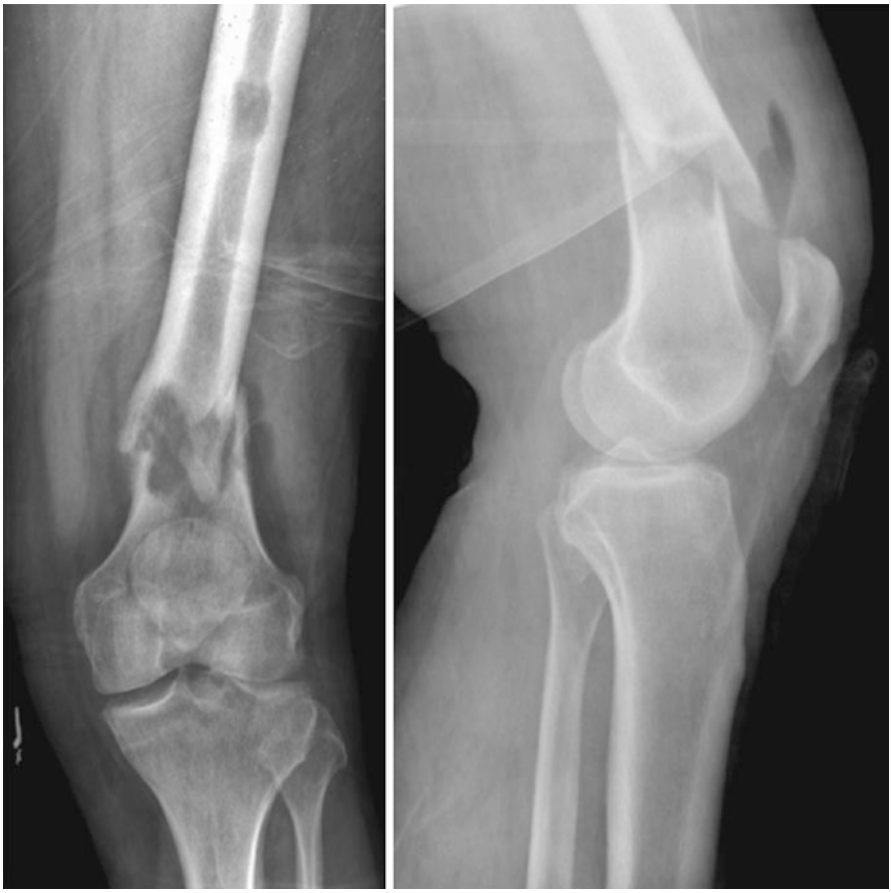

Fig. 10.6 Pathologic supracondylar fracture of the left femur. (Source: Rommens and Hessmann [54])

the maximum dose of acetaminophen for adults is 4000 mg per day or 2000 mg per day in the setting of liver disease. In the setting of advanced liver disease or liver failure, an alternative therapeutic is recommended. Practitioners should recognize that acetaminophen is contained in many over-the-counter combination cold remedies

Nonsteroidal anti-inflammatory drugs represent a well-tolerated, heterogeneous group of compounds that produce analgesia through the inhibition of prostaglandin and other inflammatory mediator synthesis. NSAIDs include aspirin and other pharmaceuticals that inhibit the cyclooxygenase (COX). This enzyme is necessary for the conversion of arachidonic acid to prostaglandins, and leukotrienes that activate

Table 10.1 NSAIDs and cyclooxygenase selectivity and typical oral adult starting dose [26]

Nonselective COX inhibitors	Partially selective COX-2 inhibitors	COX-2 inhibitors
Diclofenac sodium (50 mg twice daily)	Etodolac (200 mg every 6 h)	Celecoxib (200 mg daily)
Diclofenac potassium (50 mg twice daily)	Meloxicam (7.5 mg daily)	–
Fenoprofen (600 mg three times per day)	Nabumetone (500 mg twice daily)	–
Ibuprofen (400 mg three times per day)	–	–
Ketoprofen (50 mg four times per day)	–	–
Naproxen (500 mg twice per day)	–	–
Naproxen sodium (550 mg twice per day)	–	–
Oxaprozin (1200 mg daily)	–	–
Sulindac (150 mg twice per day)	–	–
Piroxicam (20 mg daily)	–	–

the nociceptive pathway. NSAIDs are also known to cause platelet inhibition. Aspirin-induced platelet inhibition is irreversible, while platelet inhibition by other NSAIDs is reversible.

NSAIDs are classified as either COX-2 selective, partially selective, or nonselective. Nonselective inhibitors are more inclined to cause gastrointestinal distress, bleeding, and ulcer formation, though any NSAID should be avoided in patients with a bleeding diathesis. Selective COX-2 inhibitors are associated with less risk of gastrointestinal bleeding but still are not for use in patients with a bleeding diathesis. Caution also needs to be taken with the NSAID class and renal or cardiac dysfunction as these drugs are known to decrease glomerular filtration rate and cause fluid retention and hypertension.

NSAIDs should be used with caution in patients with cancer. While these medications are considered a mainstay of analgesic therapy in the benign setting, the clinician must weigh the risks and benefits of the drug in patients with cancer. Patients with a bleeding diathesis should not receive NSAIDs due to risk of severe or even fatal bleeding. Patients who are on chemotherapy or who have severe bone marrow replacement are known to have thrombocytopenia which should be considered a contraindication for NSAID therapy.

Tramadol is also considered in this step. Tramadol is a racemic cyclohexyl analgesic that acts centrally acting analgesic that has agonist activity at the mu receptor similar to an opioid as well as norepinephrine/serotonin reuptake inhibition giving it nonopioid analgesic properties. Similar to tramadol is tapentadol which has stronger mu receptor agonist activity. Tapentadol functions more like a strong opioid in this sense and may be considered in the third step of the WHO analgesic ladder. Both tramadol and tapentadol should be used with caution in patients with a seizure

disorder or who are concurrently treated with selective serotonin reuptake inhibitors or tricyclic antidepressants [27].

Step 3: Severe Pain in the Urogenital Region in the Patient with Cancer

For patients who cannot achieve satisfactory analgesia with step two of the WHO analgesic ladder, the next step is to begin a strong opioid in addition to adjunctive, nonopioid, analgesics. Opioids in this class include medications such as morphine, oxycodone, hydromorphone, fentanyl, and methadone.

Opioids and Pain Management in the Patient with Cancer

Opioids are considered the mainstay of treatment of cancer-related pain. Opioids are a class of drugs that are structurally similar to endogenous peptides known as endorphins, dynorphins, and enkephalins in that they act by binding to the opioid receptor on the presynaptic neuron in the CNS. Activation of the opioid receptor stabilizes the presynaptic membrane leading to a decrease in the exocytosis of substance P and glutamate in the pain pathway. Decreased exocytosis of substance P and glutamate leads to lesser activation of the postsynaptic neuron.

There are several types of opioid receptors in the CNS, including the mu, kappa, delta, and sigma receptors. Of note, only the mu opioid receptor (MOR), kappa opioid receptor (KOR), and delta opioid receptor (DOR) are of clinical importance when considering analgesia based on current knowledge and there are numerous subtypes of these receptors as well. The opioid receptor type and subtype predominance provides a fingerprint which determines susceptibility to particular opioids based on receptor affinity.

Opioids that are in use currently all exert at least some agonistic activity at the MOR with varying activity at other opioid receptors. Activity at the MOR is responsible for much of the analgesic properties as well as the side-effects of opioids.

Side effects of opioid receptor activity can commonly include euphoria or dysphoria, constipation, urinary retention, sedation, and nausea. Opioids are known to diminish airway reflexes and must be used in caution in patients with hypercarbic respiratory failure or sleep disordered breathing. Opioids also may cause histamine release and result in pruritus or a decrease in peripheral vascular resistance. These compounds are also well known for their abuse and diversion potential and should be used in caution in patients who would be considered high risk. There are numerous other side effects of opioids that limit their use in many clinical settings [28].

Morphine is often considered a prototype drug for the opioid class. It can be used orally as an immediate-release or sustained-release preparation. It is available in liquid or tablet form. In addition to oral use, morphine can be administered intravenously, subcutaneously, intramuscularly, intrathecally, or rectally. Typically, the drug is absorbed rapidly through the gastrointestinal tract and peak blood levels

occur in 30 min. Bioavailability of the drug is limited by approximately two-third first pass metabolism in the liver, leaving approximately one-third of the orally administered drug available for serum concentrations.

In the liver, morphine is metabolized to morphine-3-glucuronide (M3G), which is pharmacologically inactive, as well as morphine-6-glucuronide (M6G), an active metabolite. These metabolites are excreted in the urine. Patients with renal failure may exhibit potential neurotoxic side effects of the morphine glucuronides including myoclonus and even seizures [29].

If a patient with cancer has ongoing pain in the urogenital system and the underlying pathology is unlikely to improve quickly, it may be advisable to utilize a regimen with a sustained-release opioid. Typically, a sustained-release opioid is given on a continual basis and an immediate release preparation is administered as needed to assist with breakthrough pain that is not fully alleviated by the sustained-release medication. Opioid side effects, such as constipation and nausea, must be addressed in this type of regimen. Often, nausea will abate over time, but constipation is a side effect that does not improve with ongoing opioid administration.

Treatment of Neuropathic Urogenital Pain in the Patient with Cancer

Neuropathic pain results from damage or impingement upon the somatosensory neural pathway. It is often treated differently than nociceptive pain as noted earlier. Neuropathic pain in the patient with cancer can occur as a result of the following:

- tumor burden resulting in direct compressive forces
- loss of structural integrity of the spine resulting in nerve compromise
- nerve damage as a result of cancer treatments such as chemotherapy or radiation

The primary treatment of neuropathic pain in the patient with cancer should involve the removal of the offending agent where feasible. If tumor compression can be alleviated by radiation, surgery, or radiosurgical options, that should be considered the preferred method of treatment. No drug treatments are US FDA approved for the treatment of cancer-associated neuropathic pain, chemotherapy-induced peripheral neuropathy (CIPN), or radiation neuritis. Treatment recommendations are evidence-based as well as based on clinical experience. Current guidelines are derived from an expert panel and published by the *American Society of Clinical Oncology (ASCO)* in 2014 [30]. Patients should be informed that there are no approved treatments for neuropathy and there is little evidence for the efficacy of specific therapies.

The ASCO guidelines assert that duloxetine may be offered as first-line treatment for the alleviation of neuropathic pain in the patient with cancer. Duloxetine, a serotonin and norepinephrine reuptake inhibitor is known to augment one's innate

ability to modulate the pain signal through the descending pathway. Pain practitioners and oncologists often prescribe gabapentin and pregabalin for the treatment of neuropathic pain. The current ASCO guidelines state that there is not enough supporting evidence to recommend for or against these medications for neuropathic pain. The ASCO guidelines also make no recommendation on acetyl-L-carnitine or tricyclic antidepressants, which are also often prescribed as therapy for neuropathic pain. The guidelines further assert that there are no established agents for the prevention of CIPN based on scarce and inconsistent data.

Some opioids have been used in the treatment of neuropathic pain though it should be noted that these are not the preferred agents. Oxycodone is thought to be more effective for neuropathic pain based on the activity at the KOR. Also, methadone is used in some refractory cases. In addition to working as a classic opioid, methadone is known to work on the modulation of the pain signal as well.

Other Pharmacologic Management of Urogenital Pain in the Patient with Cancer

Steroids are often employed in the treatment of cancer-related pain. Oral or intravenous steroids are often used for refractory urogenital pain related to cancer especially in the setting of associated inflammation. Steroids are a hallmark of therapy in patients with spinal cord injuries as well as intestinal obstruction related to malignancy. Steroids are also used for the treatment of bone pain related to metastasis and to alleviate neuropathic pain in the setting of tumor compression. Steroids are accompanied by many long-term side effects including bone loss and osteoporosis, glaucoma, central obesity, hyperglycemia, and elevated blood pressure.

Antispasmodics are often used in the treatment of muscle spasm that may be associated with bone, nerve, or muscle involvement. This can be especially important in the setting of spinal cord damage that may lead to chronic muscle spasticity and chronic pain. Baclofen is commonly recommended in the setting of painful muscle spasm in the patient with cancer. Other pharmacologic agents include cyclobenzaprine, tizanidine, and benzodiazepines such as diazepam. Problematic side effects, such as sedation, are often dose limiting in the setting of muscle spasm associated with cancer pain.

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that is often used as an anesthetic agent. Lower doses of ketamine can be used for the treatment of refractory cancer-related pain in the urogenital region. Dosing of ketamine is limited by side effects such as sedation, and delirium, and these patients must be monitored on specialty-trained units [31].

Clonidine is described in the literature for use as an epidural agent for intractable cancer pain. Some practitioners have tried this medication especially in the setting of central pain syndrome. There is no good evidence for the oral or topical use of clonidine in cancer pain. This drug is limited by side effects such as hypotension and bradycardia.

Role of Radiation Therapy in Management of Cancer-Related Pain

Up to 80 % of patients with solid tumors develop painful bone metastases to the pelvis, spine, or extremities during the course of their illness [32]. Patients with bony metastases now have a much longer survival time as antitumor strategies continue to improve. The palliative treatment for bone metastases are intended to relieve pain, preserve functions, and maintain skeletal integrity. Thus, patients with one or two areas of severe bone pain, which is either inadequately controlled with opioids or which requires unacceptably high doses of opioids, should be referred to radiation oncology for consultation.

In 1982, the Radiation Therapy Oncology Group (RTOG) for the first time reported that short-course RT schedules were as effective as longer-treatment programs in achieving pain relief from bone metastases [33]. Radiotherapy (such as external beam radiotherapy, EBRT) and radiopharmaceutical agents provide successful palliation of painful bone metastasis with very few side effects. EBRT can provide significant palliation of painful bone metastases in 50–80 % of patients, with up to one-third of patients achieving complete pain relief at the treated site [34]. When bone pain is limited to a single or a limited number of sites, local field external beam radiation therapy (RT) to the painful sites can provide pain relief in approximately 60–85 % of cases, with complete pain response reported in 15– 58 % [33]. If symptomatic lesions are widespread, radiopharmaceuticals or hemibody radiation may provide useful palliative alternatives. Although treatment can be effective for patients with mild, moderate, or severe pain, early intervention may be useful in maintaining quality of life and minimizing side effects of analgesic medications [35]. The onset of pain relief may be as soon as 48 h after the initiation of therapy, although some patients will not experience maximal relief for up to 2 weeks after therapy is complete. Patients should be educated that a transient worsening of pain may occur and it typically occurs in the first few days after RT, and generally lasts 1–2 days. This transient worsening of pain occurs in approximately 30–40 % of patients [36]. Treatment with dexamethasone may reduce the frequency of a pain flare [37].

Guidelines from the American Society for Radiation Oncology (ASTRO) recommend treatment with a single fraction of radiation using a dose of 8 Gy to provide palliation for relief of pain from bone metastases [33]. Most randomized trials have shown no significant difference between the short-course or long-course schemes in terms of pain control and adverse effects. A single-dose treatment is more convenient and cost effective compared with fractionated schedules. Retreatment was necessary in approximately 20 % of patients treated with a single fraction compared with 8 % in those initially managed with a fractionated regimen [33]. There was no evidence that the use of a single-fraction regimen was associated with an increase in acute or late toxicity. Reirradiation may be a useful option for patients with painful bone metastases if the initial treatment fails to adequately relieve bone pain or there is a subsequent relapse after an initial response.

Systemic radioisotopes, such as strontium-89 and samarium-153, deliver high-dose radiation to bone lesions without significantly affecting normal bone and can provide palliative benefit to patients with widespread, painful bone metastases, which are refractory to opioid analgesia. The effect is best documented in prostate cancer, where bone lesions are predominantly osteosclerotic. The average onset of pain relief is somewhat slower, taking 2–4 weeks. Radioisotope therapy is as effective as external radiotherapy in the alleviation of pain [32]. However, these agents have the potential to cause significant bone marrow suppression and should be used cautiously in patients with low baseline blood counts or patients receiving concomitant chemotherapy.

Hemibody irradiation refers to treating a large portion of the body with external beam irradiation and can provide rapid pain relief when multiple sites of symptomatic bone metastases are present [32, 33]. It relieves pain as effectively as local external radiotherapy. In patients with advanced disease, more than half stay free from pain for the remainder of their lives. Half of those who respond obtain pain relief within 48 h, and 80 % experience relief within a week [38]. The side effects include nausea, vomiting, diarrhea, fever, transient increase in bone pain, hematologic toxicity, and, rarely, pneumonitis. An interval of at least 4 weeks is recommended before administering the other half-body treatment or continuing chemotherapy to avoid severe hematologic toxicity. The use of hemibody irradiation has largely been replaced by the administration of radioisotopes, which offer a similar degree of pain relief and may be associated with less toxicity. Hemibody irradiation may be an option when access to radiopharmaceuticals is limited.

Interventional Pain Management in Urogenital Cancer Pain

Cancer patients with tumor extension into the pelvis may experience severe somatic and neuropathic pain unresponsive to both oral and parenteral opioids. Additionally, side effects of opioids including excess sedation and severe opioid-induced constipation may interfere with needed escalation to analgesic effect [39]. Intractable malignant pain resistant to conventional opioids lead the World Health Organization (WHO) to integrate interventional pain management as its fourth analgesic step [40].

Clinical practice guidelines provide the framework for identifying patients for whom to consider interventional pain management. Prerequisites prior to interventional pain procedures include an optimal trial of analgesics in accordance with the WHO analgesic ladder. The patient should be evaluated by an interventional pain provider who will complete history and physical examination including any pertinent imaging or laboratory studies. At this consultation, any neurologic deficits, medical comorbidities, drug allergies, and contraindications to intervention should be reviewed and discussed. This consultation should include a site inspection to ensure the procedural site is clear of infection or local tumor invasion. Any preop-

erative laboratory or imaging studies should be ordered and reviewed. As in any surgical procedure, written informed consent should be obtained [40].

Patient refusal, local, or systemic infection, coagulopathies, and allergies to the medications to be administered are contraindications to any interventional pain procedure. Patients who are uncooperative or with a history of substance abuse or drug seeking behavior should be determined a candidate on a case-by-case basis [40].

Regional and Peripheral Nerve Blocks

Peripheral nerve blocks or plexus blocks are used when the source of pain is located in the vicinity of one or more peripheral nerves. Peripheral nerve blocks are rarely stand-alone therapy but are often used in conjunction with opioids, radiotherapy, and chemotherapy. Patients with significant peripheral edema and absence of peripheral pulses are poor candidates for peripheral nerve blocks as it makes finding landmarks technically difficult. Tumor invasion and compression may also distort the neuroanatomical landmarks [41].

Hypogastric Blocks

Hypogastric plexus blocks are performed for the treatment of sympathetically mediated pain arising from the pelvic viscera. The pain may come from the bladder, uterus or ovaries, prostate or testicles, or other parts of the pelvis. The hypogastric plexus is a bundle of nerves situated on the vertebral bodies anterior to the bifurcation of the abdominal aorta. From the plexus, sympathetic fibers diverge into the pelvis as two main trunks comprising the right and left hypogastric nerves. The right and left hypogastric nerves continue as the inferior hypogastric plexus. These hypogastric nerves send sympathetic fibers to the ovarian and ureteric plexus. The superior hypogastric plexus receives contributions from the two lower lumbar splanchnic nerves (L1–L2), which are branches of the chain ganglia. They also contain parasympathetic fibers which arise from pelvic splanchnic nerve (S2–S4) and ascend from inferior hypogastric plexus [42].

Multiple techniques can be performed to block the hypogastric plexus including the single-needle transdiscal technique, the single-needle anterior approach, the single-needle medial paraspinal technique, and the classic two-needle technique.

The advantage of the anterior approach is the ease of exposure and the ability to be performed quickly. This approach has less periprocedural pain as compared to the posterior approach. Additionally, it eliminates the need for prone positioning which is often very painful in patients with intra-abdominal or intrapelvic tumor burden making this a better approach for the cancer population. The supine position is also preferred to patients with ostomies as lying prone can increase discomfort and lead to spilling of the gastric content from pressure on the ostomy bag. The anterior approach uses a single needle and bypasses the periosteum and nerve roots

that pass through the paraspinal musculature also decreasing periprocedure pain. The risk of accidental neurologic injury is reduced due to placement of the needle in the presacral space as opposed to the posterior approach where drug may spread to the epidural, subdural, or subarachnoid space [43].

The two-needle approach is preferred for patients in which presacral tumor or adenopathy prohibits contralateral spread of solutions injected through a single needle. This block requires the patient to lie in the prone position throughout the procedure so that the transverse process of L5 and the sacral ala is accessible. Patients with cancer may not tolerate the prone position due to increased pain or due to ostomy or other drains prohibiting adequate positioning [43, 44].

Risks of the hypogastric plexus block include bleeding and intravascular injection due to the proximity of the hypogastric nerves to the iliac vessels. Damage to the pelvic viscera including the ureters due to the anatomical location of the hypogastric plexus is also a potential complication. As with any surgical procedure, infection can be caused by introduction of bacteria during the injection. This risk is increased in immunocompromised patients especially patients undergoing chemotherapy [45].

Pudendal Blocks

Pudendal blocks are used for the treatment of pain originating in the perineum, penis, scrotum, vulva, or vagina. The pudendal nerve is comprised of fibers from S2, S3, and S4 nerves. The pudendal nerve is the main nerve of the perineum. It carries sensation from the external genitalia of both sexes and the skin around the anus and perineum, as well as motor function to various pelvic muscles, including the male or female external urethral sphincter and the external anal sphincter. The nerve passes inferiorly between piriformis and coccygeal muscles. The pudendal nerve exits the pelvis via the greater sciatic foramen. The nerve then passes the medial portion of the ischial spine to re-enter the pelvis via the greater sciatic foramen. The nerve then divides into three terminal branches: the inferior rectal nerve which innervates the anal sphincter and perianal region, the perineal nerve which innervates the posterior two thirds of the scrotum or labia majora and the muscles of the urogenital triangle, and the dorsal nerve of the penis or clitoris. Pudendal blocks can be performed via the transvaginal or transperineal approach. In women with tumor or radiation-induced fibrosis of the cervix or vagina, the transperineal approach is preferred.

Risk factors for pudendal blocks include intravascular injection due to proximity to the pudendal artery. Patients who are immunocompromised or had previous radiation to the perineum are at an increased risk of infection or fistula formation due to the proximity to the rectum [43].

Ganglion of Walther (Impar) Blocks

A ganglion impar block is procedure used to sympathetic pain of the pelvis, genitals, perineum, and anus. This block is used primarily in the treatment of malignant pain.

The ganglion of Walther lies in front of the sacrococcygeal junction. The ganglion receives impulses from the lumbar and sacral portion of the sympathetic and parasympathetic nervous systems. Additionally, it provides sympathetic innervation to portions of the pelvic viscera and genitalia. This block is performed in the prone position making it difficult to perform in patients with significant abdominal pain or ostomies [43].

Risk of the ganglion impar blocks includes perforation of the rectum and tracking of fecal contaminants through the needle track. In patients who are immunocompromised or previously received radiation to the perineum, infection and fistula formation may lead to life-threatening complications [41].

Neuraxial blocks

Neuraxial blocks provide analgesia by targeting the opioid receptors in the spinal cord. Drug delivery is administered via the epidural or intrathecal route with an external syringe pump or with implantable device. The benefit of neuraxial blocks includes excellent analgesia without systemic effects. Although this method avoids systemic effects, this method should only be performed in patients in which simpler methods have failed to achieve adequate analgesia [41].

Patients with cancer may not be suitable candidates for neuraxial blocks due to multiple contraindications. Patients with coagulopathies and who are immunocompromised may be at an increased risk of life threatening complications.

Considerations for Interventional Pain Management

As in all surgical or interventional procedures, selecting an experienced and competent surgeon is imperative. Surgeons should be proficient in identifying anatomical landmarks and comfortable with using the latest imaging guidance to prevent devastating complications. Cancer patients with immunosuppression from chemotherapy should consult with their oncologist prior to undergoing any interventional procedure. Laboratory studies to evaluate for neutropenia and thrombocytopenia must be performed to protect from infection or severe bleeding. Patient selection should be a multidisciplinary approach including the patient's oncologist, palliative care specialist, and interventional pain specialist. The goal of any interventional procedure should be to restore function and increase quality of life.

Conclusion

Cancer pain, in the urogenital region and elsewhere, requires thorough evaluation and often benefits from a multimodal, multidisciplinary approach. Pharmacologic management of cancer pain is rooted in the concept of the WHO analgesic ladder,

utilizing nonopioid and opioid medications. Radiation therapy for patients with painful bone metastases is highly effective, well tolerated, and can often be delivered in a single-dose fraction. Nerve blocks play an important role in managing the pain of many patients with cancer and should be considered, especially for those whose cancer pain is refractory to other modalities.

References

1. Ripamonti CI, Santini D, Maranzo E, et al. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol. 2012;23:139–54.
2. Cohen MZ, Easley MK, Ellis C, et al. Cancer pain management and the JCAHO's pain standards: an institutional challenge. J Pain Symptom Manage. 2003;25:519–27.
3. Svendsen KB, Anersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. Eur J Pain. 2005;9:195–206.
4. Goudas LC, Bloch R, Gialeli-Goudas M, et al. The epidemiology of cancer pain. Cancer Invest. 2005;23:182–90.
5. Fisch MJ, LKee JW, Weiss M, et al. Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. J Clin Oncol. 2012;30:1980–8.
6. Saunders CM. The management of terminal malignant disease. 1st ed. London: Edward Arnold; 1978.
7. Clinical practice guideline for the management of cancer pain – AHCPR archives. Clinical guideline number 9 AHCPR publication no. 94–0592: March 1994.
8. NCCN Guidelines Version 1.2014 Adult Cancer Pain.
9. Irani J, Fournier F, Bon D, et al. Patient tolerance of transrectal ultrasound-guided biopsy of the prostate. Br J Urol. 1997;79:608–10.
10. Bhomi KK, Lim HH, Consigliere DT, et al. Control of pain during transrectal ultrasound-guided prostate biopsy: a prospective study comparing two methods. Urol Int. 2007;79:332–5.
11. Gurbuz C, Canat L, Bayram G, et al. Visual pain score during transrectal ultrasound-guided prostate biopsy using no anaesthesia or three different types of local anaesthetic application. Scand J Urol Nephrol. 2010;44:212–6.
12. Seçkiner I, Haluk S, Erturhan S, Yagci F. A prospective, randomized control study comparing lidocaine and tramadol in periprostatic nerve blockage for transrectal ultrasound-guided prostate biopsy. Urology. 2011;78:257–60.
13. Skriapas K, Konstandinidis C, Samarinas M, et al. Pain level and anal discomfort during transrectal ultrasound for guided prostate biopsy. Does intrarectal administration of local anesthetic before periprostatic anesthesia makes any difference? Minerva Urol Nefrol. 2009;61:137–42.
14. Caliskan B, Mutlu N. Intrarectal ice application prior to transrectal prostate biopsy: a prospective randomized trial assessing pain and collateral effects. Int Braz J Urol. 2015;41:101–9.
15. Harper DM. Paracervical block diminishes cramping associated with cryosurgery. J Fam Pract. 1997;44(1):71–5.
16. Harper DM, Cobb JL. Cervical mucosal block effectively reduces the pain and cramping from cryosurgery. J Fam Pract. 1998;l47(4):285–9.
17. Harper DM. Pain and cramping associated with cryosurgery. J Fam Pract. 1994;39(6):551–7.
18. Sinaki M, Merritt JL, Stillwell GK. Tension myalgia of the pelvic floor. Mayo Clin Proc. 1977;52:717–22.
19. Boas RA, Schug SA, Acland RH. Perineal pain after rectal amputation: a 5-year follow-up. Pain. 1993;52:67.
20. Rigor BM. Pelvic cancer pain. J Surg Oncol. 2000;75:280–300.

21. Minsky BD, Cohen AM. Minimizing the toxicity of pelvic radiation therapy in rectal cancer. Oncology. 1988;2:28–9.
22. Mannaerts GH, Rutten HJ, Martijn H, et al. Effects on functional outcome after IORT-containing multimodality treatment for locally advanced primary and locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 2002;54:1082–8.
23. Nader R, Rhines LD, Mendel E. Metastatic sacral tumors. Neurosurg Clin N Am. 2004;15:453–7.
24. Payer M. Neurological manifestation of sacral tumors. Neurosurg Focus. 2003;15:E1.
25. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther. 2005;12(1):46–55.
26. Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for osteoarthritis: an update of the 2006 comparative effectiveness review. Comparative effectiveness review No. 38. (Prepared by the Oregon Evidence-based Practice Center under Contract No. HHSA 290 2007 10057 I) AHRQ publication no. 11(12)-EHC076-EF. Rockville: Agency for Healthcare Research and Quality. October 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
27. Raffa RB, Buschman H, Christoph T, Eichenbaum G, Englberger W, Flores CM, et al. Mechanistic and functional differentiation of tapentadol and tramadol. Expert Opin Pharmacother. 2012;13(10):1437–49.
28. Pathan H, Williams J. Basic opioid pharmacology: an update. Br J Pain. 2012;6(1):11–6.
29. Quigley C, Joel S, Patel N, Baksh A, Sleven M. Plasma concentrations of morphine, morphine-6-glucuronide, and morphine-3-glucuronide and their relationship with analgesia and side effects in patients with cancer related pain. Palliat Med. 2003;17(2):185–90.
30. Hershman DL, Lacchetti C, Dworkin RH, Smith EML, Bleeker J, Cavaletti G, et al. Prevention and Management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology guideline. J Clin Oncol. 2014;32:1–30. doi:10.1200/JCO.2013.54.0914.
31. http://www.iasp-pain.org/Taxonomy#Pain. Accessed 3 Jan 2016.
32. Hardy J, Quinn S, Fazekas B, et al. Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. J Clin Oncol. 2012;30:3611–7.
33. Nielson OS. Palliative radiotherapy of bone metastases: there is now evidence for the use of single fractions. Radiother Oncol. 1999;52:95.
34. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. Cancer. 1982;50:893–9.
35. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol. 2007;25:1423–36.
36. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2009;75:193.
37. Hird A, Chow E, Zhang L, et al. Determining the incidence of pain flare following palliative radiotherapy for symptomatic bone metastases: results from three Canadian cancer centers. Int J Radiat Oncol Biol Phys. 2009;75(1):193–7.
38. Chow E, Meyer RM, Ding K, et al. Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind randomized placebo-controlled, phase 3 trial. Lancet Oncol. 2015;16:1463.
39. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol. 2005;6:392–400.
40. Mishra S, Bhatnagar S, Gupta D, Thulkar S. Anterior ultrasound-guided superior hypogastric plexus neurolysis in pelvic cancer pain. Anaesth Intensive Care. 2008;36(5):732–5.
41. Bhatnagar S, Gupta M. Evidence-based clinical practice guidelines for interventional pain management in cancer pain. Indian J Palliat Care. 2016;21(2):137–47.
42. Chambers WA. Nerve blocks in palliative care. Cr J Anesth. 2008;101(1):95–100.
43. Ahmed D, Mohamed M, Abd-Elbaky Mohamed S. Superior hypogastric plexus combined with ganglion impar neurolytic blocks for pelvic and/or perineal cancer pain relief. Pain Physician. 2014;18:E49–56.

44. Waldman SD. Atlas of interventional pain management. 4th ed. Philadelphia: Saunders Elsevier; 2014.
45. Kitoh T, Tanaka S, Ono K, Ohfusa Y, Ina H, Otagiri T. Combined neurolytic block of celiac, inferior mesenteric, and superior hypogastric plexuses for incapacitating abdominal and/or pelvic cancer pain. J Anesth. 2005;328–32.

Further Reading

1. Wilsey C, Ashford N, Dolin S. Presacral neurolytic block for relief of pain from pelvic cancer: description and use of a CT-guided lateral approach. Palliat Med. 2002;16(5):441–4.
2. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore: Johns Hopkins University Press; 2014.
3. Auret K, Schug SA. Pain management for the cancer patient – current practice and future developments. Best Pract Res Clin Anaesthesiol. 2013;27:545–61.
4. Dy SM, Asch SM, Naeim A, Sanati H, Walling A, Lorenz KA. Evidence-based standards for cancer pain management. J Clin Oncol. 2008;26(23):3879–85.
5. Jeffrey B. Halter, Joseph G. Ouslander, Mary E. Tinetti, Stephanie Studenski, Kevin P. High, Sanjay Asthana. Hazzard's geriatirc medicine and gerontology, 6e.
6. Nersesyan H, Slavin KV. Current approach to cancer pain management: availability and implications of different treatment options. Ther Clin Risk Manag. 2007;3(3):381–400.
7. Portenoy RK. Treatment of cancer pain. Lancet. 2011;377(9784):2236–47.
8. Zhu YJ. Palliative radiotherapy for painful bone metastasis: short-course or long-course? Ann Palliat Med. 2012;1(1):78–80.
9. Rommens PM, Hessmann MH, editors. Intramedullary nailing: a comprehensive guide. London: Springer; 2015. doi:10.1007/978-1-4471-6612-2_31.

Chapter 11
Spinal Cord Stimulation for Chronic Pelvic Pain

William E. Bentley

History

The science behind this technique dates back to 1965 when Melzack and Wall published their Gate Theory of Pain [2]. Melzack proposed that pain signals could be blocked from entering the somatosensory cortex by non-noxious stimuli at the spinal cord level. A few years later, the first spinal cord stimulator (SCS) was successfully implanted in 1967. It has been a commonly used technique for chronic pain treatment since the 1980s. Currently, tens of thousands of implants are performed annually [3]. The exact mechanism of action is not completely understood, but there are a few theories to explain its efficacy. SCS appears to dampen sympathetic activity, increase neurotransmitter activity of GABA receptors, and inhibits A-delta and C-pain nerve fiber transmission by stimulation of the larger A-beta nerve fibers at the level of the dorsal horn (Fig. 11.1).

Procedure

When a patient is deemed a potential candidate for an SCS device, the first step is to schedule a trial. A trial consists of sterilely and percutaneously inserting electrodes into the posterior epidural space under fluoroscopic guidance. These wires are externally attached to a programmable internal pulse generator (IPG) and secured in place for 5–7 days, often with a combination of sutures and dressings. During the trial period, there is daily communication with the patient to evaluate for

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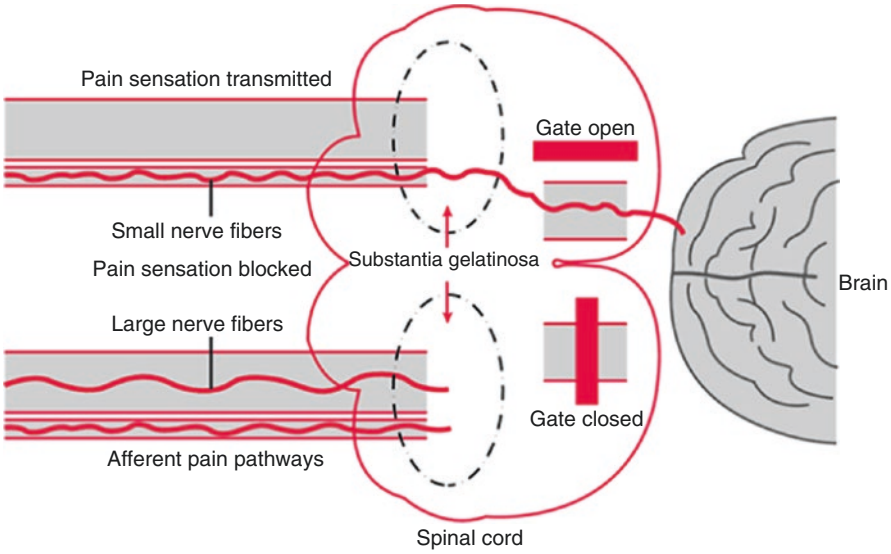

Fig. 11.1 Illustration of the gate control theory of pain

improvements in function (able to walk further, stand longer) and quality of life (improved sleep, better pain control with reduction in pain medications). At the end of the trial, the SCS leads are removed. If the trial is successful, the patient will be scheduled for permanent insertion of the SCS device.

Permanent implantation of the device is a same day surgical procedure. It involves a small thoracic incision to insert percutaneous electrodes or paddle electrodes placed via a laminotomy. The wire leads are then subcutaneously tunneled to the IPG which is typically buried 1–2 cm below the skin, just inferior to the beltline dorsally on the patient's dominant side (Figs. 11.2 and 11.3).

Makes and Models of SCS Devices

SCS devices and their respective IPGs vary in size and function (e.g., rechargeable vs. nonrechargeable). These devices are approximately the size of a pacemaker, but are cosmetically more appealing due to the abundance of soft tissue in the buttocks.

As of January 2016, companies that have Food and Drug Administration (FDA) approval for SCS include Medtronic, Boston Scientific, St. Jude Medical, Nevro, and Greatbatch. Each company boasts a unique device for a specific niche. For example, St. Jude Medical has developed the longest lasting nonrechargeable IPG that is still relatively small in size, the EonC™ Primary Cell IPG. The battery life will vary depending on specific settings, but has an average lifespan of 7 years. This may be an ideal product for patients who are unable or would prefer not to regularly charge their device [4]. Patients who may have difficulty charging their device may

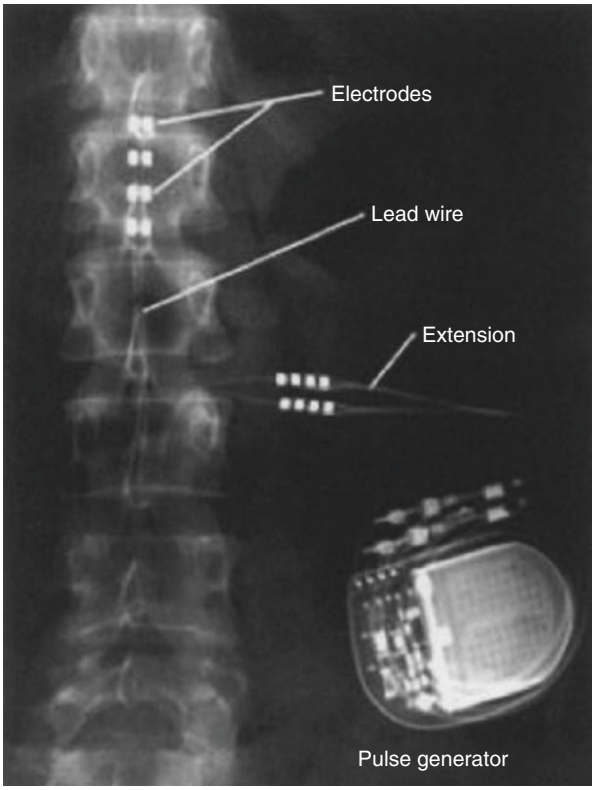

Fig. 11.2 Spinal cord stimulator system labeled

be those who are morbidly obese, elderly, or who have poor upper extremity mobility and or dexterity. The rechargeable IPGs are generally a more popular choice for patients as they are typically smaller in size and therefore more cosmetically appealing. Rechargeable IPGs also boast a longer lifespan that average 9–10 years. That being said, St. Jude has recently unveiled their newest nonrechargeable IPG, the Proclaim™, which is substantially smaller in size in comparison to its antecedent. Below is a visual demonstration of the size of the Proclaim™ as well as its rechargeable counterpart, the Protégé™ [5] (Figs. 11.4 and 11.5).

Some patients with chronic pelvic pain may have a history of gynecologic cancer. If obtaining a pelvic or chest magnetic resonance imaging (MRI) in the future will be clinically important, then one must consider implanting an MRI-compatible SCS. With a traditional SCS device, there is risk for thermal injury at the site of the leads and generator. A recent case series at a tertiary care center identified four patients between 2001 and 2011 ($n = 199$) who had their SCS device explanted due to the primary need for an MRI scan [6].

Medtronic has developed an insulation that allows heat to be dissipated and is the only company that currently offers an SCS that is FDA approved for total body MRI scan. It is important to note that not all Medtronic SCS devices are MRI compatible. Performing an MRI scan with a device or a lead that is not "MR Conditional" is

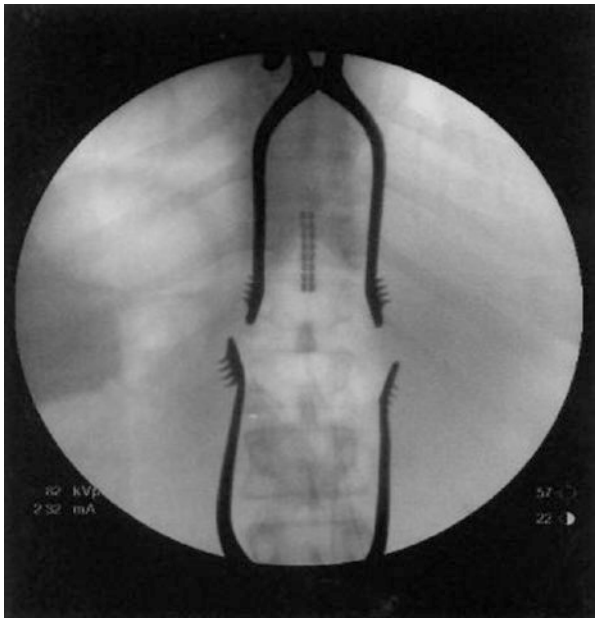

Fig. 11.3 Intraoperative film of thoracic paddle-lead placement via laminotomy

Fig. 11.4 St. Jude Proclaim™ primary cell IPG. (With permission from St. Jude Medical, St. Paul, MN)

unsafe and may cause damage to the implanted leads and/or device. Serious injury may occur to the patient, including death. Prior to any imaging studies, it is necessary to find out the specific make and model of the device and refer to www.medtronic.com/mri to review the most up-to-date guidelines including what Tesla of the MRI machine is deemed safe (1.5 T vs. 3 T).

Historically, patients have struggled with SCS devices that vary in their performance as the body changes position (supine, standing, seated). This may be related to the

Fig. 11.5 St. Jude Medical Protégé™ rechargeable IPG, conditionally MRI safe for head and extremity MRI scan. (With permission from St. Jude Medical, St. Paul, MN)

effects of posture on intracranial pressure that is directly related to changes in cerebrospinal fluid (CSF) volume, as measured by MRI flow studies [7]. Medtronic has also recently introduced AdaptiveStim technology. Using a sensor with a triple-axis accelerometer, the device is able to perceive changes in body position and automatically adjust amplitude, pulse width, and electrode configurations to maintain optimal therapy.

Traditional SCS devices work by a phenomenon known as pain/paresthesia overlap. Patients experience a buzzing or a tingling sensation in the areas in the body that were previously afflicted by neuropathic pain. This sensation is typically described as pleasant. However, it is unsafe to operate heavy machinery while using the device and patients often have difficulty sleeping with the device turned on. As of May 2015, Nevro has entered the SCS market with a device that offers high-frequency stimulation. This technology involves stimulation at a frequency of 10,000 Hz at the dorsal column. Patients with a Nevro SCS achieve similar, if not superior, pain relief without experiencing paresthesias. The pros to this system include the absence of limitation in use of the device as it may be kept on during sleep and while driving. Since the device is always at high frequency, it is recommended that patients must charge this device on a daily basis. It is safe for use with MRI of the head and extremities, but not for abdominal or thoracic MRIs (Fig. 11.6).

Indications

A patient is considered a candidate for an SCS device if they have had chronic pain for greater than 6 months, other treatment modalities have failed or are unsuitable, and the patient has undergone careful screening and assessment from a multidisciplinary team including a psychological evaluation [8]. The FDA has specific indications for the use of each of these devices [9–12]. These indications are not universal, but are similar and are listed in Table 11.1.

Fig. 11.6 Nevro remote control, charging system, and IPG. (Pictures obtained for use with permission from Nevro Corp., Redwood City, CA)

Table 11.1 Common indications for spinal cord stimulation

Post-laminectomy syndrome (previously known as failed back surgery syndrome, or FBSS)
Radicular pain syndrome or radiculopathy
Degenerative disk disease (DDD)/herniated disk pain refractory to conservative and surgical therapies
Epidural fibrosis
Arachnoiditis or lumbar adhesive arachnoiditis
Complex regional pain syndrome (CRPS)
Chronic intractable back pain
Phantom limb pain

Safety

Although rare, there is risk for nerve damage, infection, and/or bleeding into the epidural space. If any of these occur, they may be a medical or a neurosurgical emergency. The most common adverse event to happen following permanent implantation of an SCS is electrode "lead migration," which has been reported to occur in a recent study in up to 12 % of patients [13]. Lead migration may result in an inability of the device to function properly. This may take place following high-impact trauma such as a motor vehicle collision. A surgical revision would be necessary to reposition the electrodes.

Spinal Cord Stimulation for Pelvic Pain

Chronic pelvic pain is unfortunately very common in the United States. Several studies indicate that roughly 15 % of all women of reproductive age are affected [14, 15]. Like all chronic pain syndromes, it is best treated with a multimodal approach. Therapy will often involve a combination of oral medications, physical therapy, cognitive behavioral therapy, and peripheral and/or spinal nerve blocks.

The aforementioned therapies may be definitive; however, many patients with chronic pelvic pain will fail conservative treatments and more often patients will need long-term maintenance therapy. The long-term ramifications of each therapy must always be considered. Since the demographic of chronic pelvic pain patients is almost exclusively young females, most of childbearing age, medical management should be minimized. Specifically in regard to opioid medication, the long-term benefits of therapy for chronic pain patients have never been substantiated.

Electrical neuromodulation with SCS has shown early success in the treatment of chronic pelvic pain. This is not surprising as several studies have demonstrated the relationship between the visceral transmission of pelvic pain and the dorsal column pathways [16, 17].

A case series report by Kapural looked at six female patients with chronic pelvic pain ranging from 4 to 38 years in duration. They were determined to have sympathetically mediated visceral pain based on their response to hypogastric plexus blocks. The patients received an average of 5.3 blocks with significant, but not sustained pain relief following each procedure. Pain relief ranged from 1 to 4 weeks. Three of these patients received a neurolytic hypogastric plexus block with 6 % phenol with moderate prolongation of pain relief, ranging from 3 to 8 months of duration. After a psychological evaluation, all six patients underwent an SCS trial for 7–14 days, and all six trials were successful (>50 % pain relief during the trial period). The lead tip was placed between T11–L1, most commonly at T11. A permanent SCS device was implanted in all six patients with an average follow-up of 2.5 years. Pain as determined by the visual analog scale (VAS) decreased on average from 9 to 2.3 and the pain disability index (PDI) decreased from 58 to 19.7 [16].

In 2003, Whiteside et al. published a case report of a 21-year-old female with a 3-year history of intractable burning bilateral vulvar pain that was exacerbated by sexual intercourse and exercise. This patient failed both conservative and surgical treatments over the ensuing years including topical steroids, topical lidocaine, antifungals, muscle relaxants and neuropathic pain medications, pelvic exercise and biofeedback programs, and three surgical procedures including an uncomplicated partial vulvar vestibulectomy. It is important to note that this patient had no history of sexual abuse or assault. Four years later, the patient had an SCS implanted following a successful trial with the leads covering T10–T11. A 3-year follow-up found the patient to be pain free, married, and able to have pain-free vaginal intercourse. The patient reported that "turning off the spinal stimulator results in resumption of vulvar symptoms over approximately 6 h dissipating over approximately 2 h once the stimulator is reactivated" [18].

Nair et al. wrote up a case study involving a woman with a 15-year history of vulvovaginal burning and deep pelvic pain. This patient had failed conservative therapy and in 2006 this patient was on long-term opioid therapy including oxycodone ER 80 mg every 12 h, oxycodone 10 mg IR every 4 h, and methadone 30 mg three times daily with no improvement in her pain score (10/10 on the VAS scale). Later that year, the patient underwent a successful SCS trial. Ten months following permanent SCS implantation, the patient was off all pain medications with a VAS pain score of 2/10, down from 10/10 [19].

In 2007, Kothari described a technique for implanting peripheral neuromodulation for chronic pelvic pain and coccygodynia. Stimulating electrodes are implanted percu-

taneously in the area of target peripheral nerves, such as the ilioinguinal/iliohypogastric nerves. Similar to SCS, these electrodes would be connected to an external device for a trial period prior to permanent implantation. The promising therapy of peripheral neurostimulation is suggested for patients who suffer from chronic pelvic pain that is visceral in presentation and does not have a dermatomal distribution [20, 21].

Many patients with urge incontinence also suffer from chronic pelvic pain, such as interstitial cystitis. Sacral neurostimulation for urge incontinence has been FDA approved since 1997 [22, 23]. Studies of the sacral nerve stimulator device, Interstim, on patients with urge incontinence have demonstrated the benefit of sacral neurostimulation as an adjuvant pain therapy [24, 25]. In 2006, Brookoff and Bennett described his theory in regard to sacral neuromodulation in intractable interstitial cystitis and related pelvic pain syndromes. His work centered on the theory of neurogenic inflammation in interstitial cystitis. This is described as "the process by which central stimulation of peripheral sensory nerves elicits vasodilatation, plasma extravasation, and other inflammatory changes in peripheral tissue" [23, 26]. In certain disease states, sensory nerve fibers have been found to release neuropeptides through their dendritic terminals, resulting in inflammation.

Patients with pelvic congestion syndrome (PCS) will have symptomatic pain relief with increased blood flow to ischemic areas. This has been demonstrated with vascular surgical intervention [27]. The use of SCSs as a treatment for PCS is currently off label. The authors of this book agree that SCS therapy is a viable treatment option for chronic pain secondary to PCS that fails to respond to conservative treatment; however, the evidence to support this is currently lacking.

Conclusion

To truly demonstrate the benefit of SCSs in the treatment of chronic pelvic pain, there needs to be large, randomized controlled trials. Although these data are lacking, the literature to date supports its use as a viable treatment option. The future of SCS for the treatment of chronic pelvic pain is promising and is likely an underutilized therapy at the current time.

References

1. Barolat G. Spinal cord stimulation for chronic pain management. Arch Med Res. 2000;31:258–62.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
3. Thomson SI. "Spinal cord stimulation's role in managing chronic disease symptoms." Http://www.neuromodulation.com/spinal-cord-stimulation. International Neuromodulation Society, 26 Dec 2013. Web. 26 Sept 2015.
4. "EonC™ primary cell IPG." *St. Jude Medical*. N.p., 19 Nov 2015. Web. 06 Jan 2016. https://professional.sjm.com/products/neuro/scs/generators/eonc-primary-cell-ipg#tech-specs.

5. "Proclaim™ elite recharge-free SCS system for chronic pain." *St. Jude Medical*. N.p., 19 Nov 2015. Web. 17 Feb 2016. https://professional.sjm.com/therapies/proclaim-elite/tech-specs.
6. Moeschler SM, Sanders RA, Hooten WM, Hoelzer BC. Spinal cord stimulator explantation for magnetic resonance imaging: a case series. Neuromodulation. 2015;18(4):285–8. doi:10.1111/ner.12254; discussion 288. Epub 2014 Oct 27.
7. Alperin N, Lee SH, Sivaramakrishnan A, Hushek SG. Quantifying the effect of posture on intracranial physiology in humans by MRI flow studies. J Magn Reson Imaging. 2005; 22(5):591–6.
8. "Position statement on spinal cord neurostimulation." Http://www.painmed.org/files/position-statement-on-spinal-cord-neurostimulation.pdf. Neuromodulation therapy access coalition. 5 Jun 2008. Web. 10 Oct 2015.
9. http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130022a.pdf.
10. http://www.accessdata.fda.gov/cdrh_docs/pdf3/p030017a.pdf.
11. http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130028a.pdf.
12. "Indications safety and warnings." http://professional.medtronic.com/pt/neuro/scs/ind/index.htm#.Vq4fk_krLIU. Medtronic 2016. Web. 21 Nov 2015.
13. Shamji MF, Westwick HJ, Heary RF. Complications related to the use of spinal cord stimulation for managing persistent postoperative neuropathic pain after lumbar spinal surgery. Neurosurg Focus. 2015;39(4):E15. doi:10.3171/2015.7.FOCUS15260.
14. Steege JF. Scope of the problem. In: Steege JF, Metzger DM, Levy BS, editors. Chronic pelvic pain: an integrated approach. Philadelphia: W.B. Saunders; 1999. p. 9.
15. Zondervan KT, Yudkin PL, Vessey MP, Jenkinson CP, Dawes MG, Barlow DH, Kennedy SH. The community prevalence of chronic pelvic pain in women and associated illness behavior. Br J Gen Pract. 2001;51:541–7.
16. Kapural L, Narouze SN, Janicki TI, Mekhail N. Spinal cord stimulation is an effective treatment for the chronic intractable visceral pelvic pain. Pain Med. 2006;7(5):440–3.
17. Palecek J. The role of dorsal columns pathway in visceral pain. Physiol Res. 2004;53:S125–30.
18. Whiteside JL, Walters MD, Mekhail N. Spinal cord stimulation for intractable vulvar pain. A case report. J Reprod Med. 2003;48(10):821–3.
19. Nair AR, Klapper A, Kushnerik V, Margulis I, Del Priore G. Spinal cord stimulator for the treatment of a woman with vulvovaginal burning and deep pelvic pain. Obstet Gynecol. 2008;111(2 Pt 2):545–7. doi:10.1097/01.AOG.0000299879.40565.2d.
20. Kothari S. Neuromodulatory approaches to chronic pelvic pain and coccygodynia. Acta Neurochir Suppl. 2007;97(Pt 1):365–71.
21. Rowe E, Smith C, Laverick L, Elkabir J, Witherow RO, Patel A. A prospective, randomized, placebo controlled, double-blind study of pelvic electromagnetic therapy for the treatment of chronic pelvic pain syndrome with 1 year of follow up. J Urol. 2005;173(6):2044–7.
22. Chancellor MB, Chartier-Kastler EJ. Principles of Sacral Nerve Stimulation (SNS) for the treatment of bladder and urethral sphincter dysfunctions. Neuromodulation. 2000;3(1):16–26. doi:10.1046/j.1525-1403.2000.00015.x.
23. Brookoff D, Bennett DS. Neuromodulation in intractable interstitial cystitis and related pelvic pain syndromes. Pain Med. 2006;7 Suppl 1:S166–84.
24. Bemelmans BL, Mundy AR, Craggs MD. Neuromodulation by implant for treating lower urinary tract symptoms and dysfunction. Eur Urol. 1999;36(2):81–91. Review.
25. MaLossi J, Chai TC. Sacral neuromodulation for the treatment of bladder dysfunction. Curr Urol Rep. 2002;3(1):61–6. Review.
26. Pintér E, Szolcsányi J. Plasma extravasation in the skin and pelvic organs evoked by antidromic stimulation of the lumbosacral dorsal roots of the rat. Neuroscience. 1995;68(2):603–14.
27. Borghi C, Dell'Atti L. Pelvic congestion syndrome: the current state of the literature. Arch Gynecol Obstet. 2016;293(2):291–301. doi:10.1007/s00404-015-3895-7. Epub 2015 Sep 24.

Chapter 12
Intrathecal Drug Delivery Systems

Jasjit Sehdev

Objectives

The objectives of this chapter are as follows

- Basics of intrathecal drug therapy
- Anatomy and physiology of the spinal column
- Approach to the intrathecal drug trial
- Basics of intrathecal pump implantation
- Indications of intrathecal pump/drug therapy
- Complications of intrathecal drug therapy
- Uses in chronic urogenital pain

History of Intrathecal Analgesia and the Development of Implantable Intrathecal Drug Delivery

Intrathecal analgesia has gone through many advancements since its discovery in the nineteenth century. The first documented usage of intrathecal analgesia was seen shortly after the first local anesthetic, cocaine, was discovered. Interestingly, August Bier injected himself and some of his assistants with intrathecal cocaine to demonstrate the analgesia it produces. In 1898, August Bier performed the first documented intrathecal anesthetic on six patients undergoing procedures of the lower extremities. Soon after, Rudolph Matas was one of the first to use intrathecal

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morphine and discover its benefits [9]. Initially, it was used as an adjuvant to decrease the side effects of intrathecal cocaine [10]. Intrathecal morphine had been used as a sole agent as early as the 1940s; however, the mechanism of action of intrathecal morphine was later discovered in the 1970s by Dr. Fields and Basbaum [11–14]. Their scientific research paved the way for our understanding of opioid receptors within the spinal cord, the role of opioids and their ability to inhibit descending pain pathways in the substantia gelatinosa. This ultimately led to Dr. J. Wang reporting clinical benefit of intrathecal opioids for the treatment of cancer pain [15].

Intrathecal analgesic infusions were being performed as early as the 1940s. Opioids were introduced into those infusions in 1979 for the purpose of relieving obstetrical pain secondary to labor [16]. Intrathecal opioids were explored for alleviating pain from other pathologies as well, including cancer. In 1981, the first implantable intrathecal opioid delivery system was performed for chronic malignant cancer pain [10]. Problems were inherent with the pumps system as it required frequent and meticulous maintenance. Each time medication dosing changes needed to be made, the medication infusion would need to be withdrawn from the chamber reservoir via needle aspiration and then replaced with a new infusion. These frequent needle aspirations lead to iatrogenic medication overdose and increased infections. In 1991, externally programmable IDDS were introduced which helped reduce complications and the ease of maintenance and dosing changes with dynamic changes in pain that may be exhibited [10].

IDDS applications were used initially exclusively for malignant cancer pain. With the success of the IDDS, its use was extended for nonmalignant, noncancer pain. However, the use of intrathecal opioid delivery system has become subject for debate and criticism with issues such as drug tolerance, addiction, governmental regulations, and health care professionals.

In this chapter, we will discuss the basics of intrathecal drug delivery systems, the drugs involved in the drug delivery systems, patient selection, process leading to the implant, surgical implantation, complications and management of implants.

The Basics of Intrathecal Drug Delivery System

In order to understand how the intrathecal drug delivery system works, we must first have a basic understanding of pharmacokinetics and pharmacodynamics of drugs within the cerebrospinal fluid (CSF) and the general systemic circulation. Drugs given by mouth (PO), intravenously (IV), intramuscularly (IM), sublingually (SL), and transcutaneously reach systemic circulation at various rates. The circulatory system is responsible for absorption and transportation of the drug to and from the target receptor which ultimately elicits the desired effect. The systemic circulation also delivers the drug to peripheral receptors which often elicits undesired “side” effects. For simplicity, we will use morphine as our example. Morphine is prescribed for the treatment nociceptive pain and less often for neuropathic pain. The

substantia gelatinosa within the spinal column has a high concentration of mu opioid receptors, which is one of the main receptors responsible for producing analgesia. Opioid receptors are also located in other organs such as the intestines and brain that produce unwanted effects such as constipation and sedation, respectively. As patient requirements for morphine increase whether it be due to increased drug tolerance or progression of pathology, the side effect profile can also increase. This can lead to increases in medication intolerance, patient dissatisfaction, morbidity and mortality in extreme cases [6, 9]. Situations where the patient's requirements cannot be met secondary to the intolerable side effects of systemic administration have lead to the niche of intrathecal drug administration for chronic pain.

When morphine is delivered into the CSF intrathecally, a portion of the drug remains in the intrathecal space and acts on opioid receptors producing analgesia. A portion of the drug may also redistribute to produce unwanted side effects [17]. The side effects produced from intrathecal administration are generally less than the side effects produced from intravenous administration. This is because the equianalgesic therapeutic dose of morphine delivered into the CSF is one-hundredth of the equianalgesic dose of morphine delivered intravenously. Since less drug is delivered into the CSF, there is less of the drug that can be absorbed and redistributed systemically. This theoretically leads to a lower side-effect profile for intrathecally delivered drugs versus intravenously delivered drugs [4].

Anatomy of Spinal Canal and Characteristics of the CSF

Understanding the anatomy of the spine and placement of the intrathecal pump is important for patient education, use of the pump, routine management of the pump and diagnosing/treating complications of pump implantation. From the midline of the spine going from superficial to deep are the following layers: skin, subcutaneous fascia, supraspinous ligament, interspinous ligament, ligamentum flavum, epidural space, dura mater, subdural space, arachnoid mater, subarachnoid space, and finally pia mater [6].

The intrathecal space or the subarachnoid space is located between the arachnoid mater and pia mater. The CSF within the subarachnoid space circumferentially coats the spinal cord and nerves. It is responsible for providing transport of nutrients, such as glucose, proteins, immunomodulators, and neurochemicals, within the CSF [6, 9]. The subarachnoid space is continuous from the cranium, lateral ventricles, and the third/fourth ventricles and extends caudally to the level of S2. Approximately 20–25 % of the CSF is located within the spinal column and the rest is located in the cranium and ventricles. Adults have 100–150 cc of CSF located within the subarachnoid space with up to 500 cc of CSF produced daily and the remainder of the fluid reabsorbed [17]. This is important when using the term volume of distribution. Generally, the smaller the volume of distribution of a drug, the less tissue the drug can redistribute to and therefore the higher the concentration within the tissue. The volume of distribution in the plasma is larger than the CSF.

$$V_D = \text{Drug}(\text{dosage}) / \text{Drug}(\text{Concentration})$$
where $V_D = \text{Volume of distribution}$

Therefore, if a small dosage of drug is given intrathecally, the small volume of distribution in the CSF will lead to a more potent effect than if that same dose is given intravenously. Lower protein levels within the CSF, avoiding first pass metabolism and avoiding the blood brain barrier also increases the bioavailability of drugs delivered intrathecally [9].

Drug Distribution Within the CSF

Drugs spread within the CSF spread via several mechanisms including rate and volume of injection, baricity of the injectate, and hydrophilicity. Infusions of drugs do not spread far beyond the area of injection. The drugs stay within the ring in which it is injected [18–20]. Infusions with animal models showed that the dispersion of fluid from the catheter tip was minimal. This was shown with intrathecal infusions performed with methylene blue in pig models. The spread of the dye infused through a catheter was observed and showed that it did not spread more than four vertebral levels above or below the level of the catheter tip [20]. This is because of the relatively stagnant flow of CSF within the spinal canal. The CSF rather has regions of intermixing and stays within a "bubble" or "ring" [21–24]. On the other hand, bolus injections are distributed more widely because they go beyond the ring of an infusion. This is because bolus injections are generally a larger volume injected at a faster rate when compared to an infusion. Properties of the injectate also play a large role in the spread of the injectate. Assuming an upright sitting patient, the more hyperbaric a solution is the more caudad the solution will diffuse. The more hypobaric a solution is the more cephalid the solution will diffuse. Lipid solubility of a drug also affects the extent to which an injectate will diffuse. The more lipophilic (lipid soluble) a solution the less it will diffuse within the CSF. Lipophilic drugs are also more rapidly absorbed and subsequently excreted. The opposite is true of hydrophilic (water soluble) solutions that will spread more widely within the CSF and are less tissue soluble. This leads to a longer duration of action for hydrophilic solution. Hence, morphine (hydrophilic) has a longer duration of action than fentanyl (lipophilic). The size and polarity/ionization of a drug will also impact the spread of a drug. For example, ziconotide which is ionized, large molecule will have more diffuse spread within the CSF than most opioids that are generally small and unionized molecules.

Prior models of the CSF distribution proposed that CSF flow followed a rostral to caudal and subsequently caudal to rostral pattern. This was based off the discovery that the ventricles produced the CSF and resulted in the flow of CSF. This, however, recently has been disputed with a new theory that the CSF flows in a pulsatile fashion. At the level of the spine, the CSF oscillates in relation to the heart rate with areas of turbulence around the exiting nerve roots and walls of the spinal canal.

This is significant and better explains why medications within the spinal CSF and ventricular CSF do not travel readily.

Intrathecal pumps use these principles to treat patients as an alternative to traditional therapy. The success of pumps and the medications used rely on the physiological principles described as earlier. We will discuss the mechanisms of action for specific medications in later subsections.

The Intrathecal Pump

The IDDS consists of a small battery-powered pump/chamber and a spinal catheter that are implanted surgically. The chamber contains a drug or combination of drugs set by the prescriber that are pumped into the intrathecal space via the spinal catheter. The pumps can infuse at constant rates or programmable rates. A constant rate would be prescribed by the physician based on the patient's needs using a radiofrequency transmitter handheld device called a physician programmer. With the constant rate of drug delivery, the assumption is that the patient's drug requirement does not change significantly throughout the course of the day or night.

Programmable rates are variable and set by the prescriber using a physician programmer. The rates are based on the patient's requirements, drugs administered, and concentration of drugs. Variable rates are useful for patients that have requirements that change during the day and/or are much less at night. This can avoid overadministration of drugs and allow for better patient satisfaction. Additionally, some pump systems like Synchromed II by Medtronic, allow for patients to self-administer medication bolus doses within physician prescribed limits. This is generally accomplished with the use of a hand-held device. This allows the patient to take more control over their analgesia and ultimately leads to greater patient satisfaction.

Patient Selection, Indications, and Psychological Screening

The success of any therapeutic modality depends a great deal on selecting patients appropriate for the intervention. The decision to proceed with intervention can be as important as forgoing the intervention and treating the patient via conservative means. Health care providers use guidelines, indications, risks, and benefits to decide if and which therapeutic intervention would be best. The Polyanalgesic Consensus Committee (PACC) in 2012 and the British Pain Society (BPS) in 2008 made the most recent recommendations for the selection and implantation of IDDS. Unfortunately, there are currently no universally accepted guidelines for the use of IDDS. We will use the PACC and BPS recommendations and systematic reviews to discuss patient selection, indications, and expert recommendations. For the purposes of patient selection, we simplify categorizing patients into two categories.

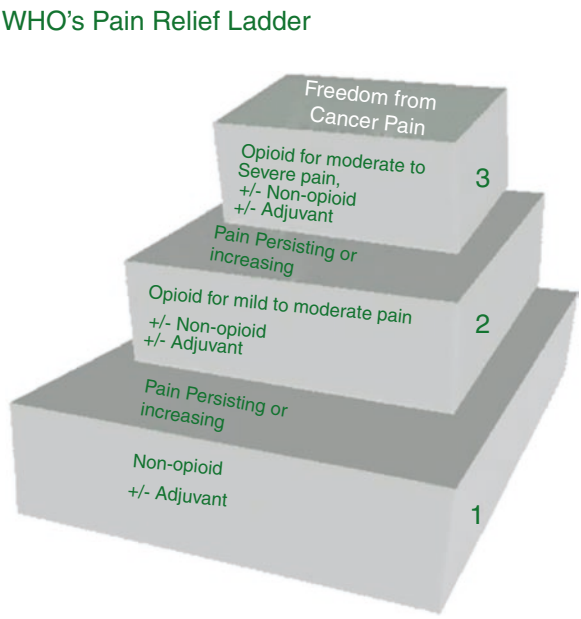

Fig. 12.1 WHO's pain relief ladder showing the stepwise algorithmic approach to chronic cancer pain http://www.who.int/entity/cancer/palliative/en/painladder.jpg

Cancer Pain

According to the World Health Organization's (WHO's) pain relief ladder for patients with cancer, patients are initially treated with nonopioids for mild pain, nonopioids and adjuvants for mild-to-moderate pain and finally opioids, nonopioids and adjuvants for moderate to severe pain [25]. Nonopioids analgesics generally refer to NSAIDs and acetaminophen. Adjuvants analgesics refer to classes of drugs that fall within the antiepileptics or antidepressants class. Conservative treatment generally entails using oral pain medications as listed within the pain relief ladder as well as less invasive therapy. Within the pain community, it is well understood that all pain patients benefit from a multidisciplinary approach from pain physicians, physiatrists, physical medicine and rehabilitation, and psychiatry. In addition to the WHO pain relief model, cancer pain patients may have benefit from other treatment modalities that include but are not limited to physical therapy, behavioral counseling/therapy, relaxation techniques, support groups, and acupuncture (Fig. 12.1).

As a patient's pain progresses with disease pathology, the prescriber can move up the pain relief ladder to tailor the patient's therapy. When an opioid reaches a point where it is no longer producing appreciable analgesia secondary to tolerance or intolerable side effects with increased dosing, then the health care provider should "rotate" the opioids. Opioid rotation is a vital part of the process as some opioids may respond better with certain patients and may not elicit unwanted side effects. Each patient's response to an opioid is not predictable as responses may vary with different opioids. Before escalating medication dosages, the opioids should be "rotated" or changed. Once a medication reaches a

ceiling point where the pain relief is not elicited or is intolerable due to side effects and other forms of conservative therapy have failed, intrathecal pumps can be considered.

Evidence and Recommendations for Patients with Cancer

Traditionally, patients with a prognosis of 3 months or less were not candidates for IDDS. In 2012, PACC revised their previous recommendations and added that patients with a prognosis of 3 months or less can be considered for intrathecal drug therapy [26]. Deer et al. showed that life expectancy can be improved with intrathecal drug therapy and if a patient is not imminently terminal, then they could be a candidate for implantable IDDS [26]. Additionally, IDDS therapy can be useful for patients undergoing chemotherapy/radiation. The first and only randomized controlled trial (RCT) completed to date examining implantable IDDS therapy was done on patients with cancer. In this trial, Smith et al. examined 202 patients that were randomly allocated into conventional medication management treated with morphine and interventional IDDS therapy with morphine infusions. The outcome showed that the IDDS therapy improved pain control, reduced systemic toxicity, and improved survival of patients with cancer [5]. There was a Cochrane review in 2005 evaluating the treatment of cancer pain intrathecal morphine compared to traditional routes. Twenty-eight cohort studies examined opioid intrathecal therapy and showed an 85 % success rate versus a 71 % success rate with traditional morphine therapy [27]. Unfortunately, there is still a paucity of strong literature supporting intrathecal drug therapy. The evidence is level II-C for IDDS therapy for patients with cancer, which means that the evidence is weak and evidence "suggestive" of using IDDS for patients with cancer [28]. The consensus among both PACC and BPS is that patients with cancer that may benefit from IT therapy and should be considered.

Chronic Intractable Nonmalignant Pain

As with cancer pain, refractory noncancer or nonmalignant pain can be treated with IDDS. Some of the more common indications for IDDS are failed back syndrome (postlaminectomy syndrome), spinal stenosis, spondylosis, spondylolisthesis, complex regional pain syndrome (CRPS/RSD), neuropathies, spinal cord related injury, chronic pancreatitis, spasticity, and rheumatoid arthritis [26].

For patients with noncancer or nonmalignant pain, the selection process for proceeding with intrathecal pump implantation can become more complex. Much like the WHO pain relief ladder for cancer pain, the same principles can be applied to other pain patients. Additionally, if a conservative therapy fails (i.e., NSAIDs, opioids, adjuvants, physical therapy, biofeedback, etc.), they can be considered for implantable IDDS [26].

Evidence and Recommendations for Chronic Nonmalignant Pain Patients

The literature for use of IDDS systems for chronic nonmalignant pain patients is less robust than the literature for patients with cancer. Patel et al. reported level II to level III evidence in favor of using IDDS therapy for chronic nonmalignant pain [29]. Moreover, in this systematic review, no randomized controlled trials met the inclusion criteria. Thus far, we have observational and open trial studies that can limitedly support the use of chronic nonmalignant pain.

For spasticity, the literature is slightly more robust for intrathecal therapy. This was shown in a 2006 Cochrane review where Tarrico et al. concluded that intrathecal baclofen produced significant analgesia for patients suffering from refractory spasticity [30]. Two double-blinded studies on spinal cord injury patients suffering from spasticity showed that intrathecal baclofen therapy was beneficial and did not cause significant side effects when compared to placebo [31, 32].

Psychological Screening

Pain can be a manifestation of physical, psychological, or behavioral factors. When treating pain, the health care provider must be cognizant of what can affect pain. The International Association for the Study of Pain defines pain as an "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[33]. Therefore, when considering an intrathecal pain pump, psychological or behavioral sources of pain should be evaluated and treated prior to implanting a pump. The psychological pain and stressors are important to address with terminal patients. Much of their pain and suffering can be treated with behavioral or psychological interventions [26]. Coping with the stressors of impending mortality, disability, and pain which afflicts nearly 30–50% of patients with cancer. The benefit of analgesia outweighs the risk of untreated psychological or behavioral factors that could impact pain perception. Therefore, it is recommended to get psychological screening for IDDS candidates with nonmalignant pain and malignant pain.

Exceptions can be made in select scenarios. For example, in the case of patients with cancer where the prognosis may not be entirely clear, delaying implantable intrathecal therapy for psychological testing or even trialing for that matter may be time consuming and may delay significant analgesia that is much needed. Another instance where exceptions can be made is with stroke or cerebral palsy patients who suffer from spasticity. It is reasonable to continue to move forward with a trial/implant if psychological screening would be unproductive [26].

Expert panel recommendations as well as insurance companies will recommend psychological screening and treatment prior to trial and implantation as is seen with spinal cord stimulator trials. The goal of the screening is to help the patient understand the goal and treatment that will take place. It is to make reinforce the expectations from the intervention.

Indications

One of the main indications for intrathecal pump use is intractable pain that has failed conservative treatment. Failure of conservative treatment can be from ineffectiveness of previously effective medications due to tolerance or medication intolerance due to unwanted side effects. Approximately 10–30 % of chronic pain patients do not respond to conservative traditional oral treatments [34].

Another indication to proceeding with an intrathecal pump is the successful use of a medication for analgesia. This may seem fairly obvious, but it is important to know. The lack of success of parenteral or enteral medication would indicate that intrathecal pump implantation would be unsuccessful. For example, if a patient presents after several months of opioid consumption and has not received significant analgesia or VAS scales of 5 or below, the prescriber must understand that the likelihood of obtaining pain relief from an intrathecal opioid is low. Additionally, if a patient is making frequent emergency room visitations for medication refills or is "prescription shopping", concerns for addiction and inappropriate use of medications should be raised.

Lastly, compliance is important to have with intrathecal pump therapy. Pump implantation, management and maintenance requires strict compliance to help ensure safe and proper use of the pump. There are serious complications that can happen with routine use of the pump. A motivated patient and good support structure help with the success of the intrathecal pump therapy.

Contraindications

Contraindications to IDDS therapy include patient refusal, noncompliance with visitations and refills, patient anticoagulation, hemodynamic instability, sepsis, and abnormal spinal pathology that may lead to increased intracranial pressure or damage to spinal nerves. Relative contraindications include hypotension, untreated psychiatric conditions, chronic lower extremity edema, and emaciation which would interfere with safe implantation of the device [35].

Comorbidities should be controlled prior to implantation to prevent complications around the time of implantation. Some conditions include but are not limited to bleeding disorders, diabetes mellitus, obstructive sleep apnea, history of infection in and around the area of implantation, MRSA, and immunocompromisation. Immunocompromised patients may require additional antibiotic prophylaxis (i.e., vancomycin).

Intrathecal Trial

The trial period is considered to be our best predictor of success with implantable IDDS. Once a patient has been selected to be an intrathecal drug candidate, the health care provider has several questions to answer that will tailor the therapy to the patient. What kind of pain does the patient have? What medication will provide

analgesia? How long should the patient be trialed? Currently, there are no universal recommendations or guidelines on how to proceed. The Polyanalgesic Consensus Committee (PACC) of 2012 and the British Pain Society (BPS) of 2008 have expert panel recommendations on how to proceed with the trial. Recommendations by the PACC and BPS are for providers to develop an algorithm that takes into consideration the method of trialing, the trial drug or drugs, duration of trial, patient safety, adequate monitoring, and goals or criteria for implantation [26, 36].

Trials can be done as single/multiple intrathecal injections and/or epidural/intrathecal infusions. The goals are to observe the analgesic efficacy of the drug and to look for any intolerable side effects. Unfortunately, there is no uniform way of performing a trial for intrathecal drug therapy. The Polyanalgesic Consensus Committee of 2012 recommends that the trialing method be based on the patient symptoms (type of pain) and comorbidities [26]. For example, a cancer patient with nociceptive pain that is effectively treated with a drug administered via a more traditional route can likely be done with a single-shot intrathecal dose or no dose at all if the delay in implanting an IDDS will be significant and may even harm the patient. On the other hand, patients that may not clearly benefit from an implantable IDDS can be considered for longer trials and infusions via percutaneous catheters lasting days to weeks to better assess the clinical benefit of implantable IDDS. Therefore, the duration of the trial should be based on a patient to patient basis. Although trials can be done with epidural injections or infusions, the intrathecal route is preferred by most physicians since it will be more correlative to the patient's physiologic response to the drug.

Intrathecal Trial Drugs

Currently, the three drugs that are approved by the Food and Drug administration (FDA) to be administered as outpatient intrathecal drugs are baclofen (Gablofen), a GABA-B agonist; morphine (Infumorph), a Phenanthrene opioid agonist; and ziconotide (Prialt), a N-type calcium channel blocker [26]. These drugs can be used individually or in combination of each other depending on the goals of therapy. Additionally, there are off-market or off-label uses of other drugs such as local anesthetics (bupivacaine, ropivacaine, levobupivacaine), NMDA antagonists (Ketamine), alpha-2 receptor agonists (Clonidine), and off-label intrathecal opioids (Fentanyl, Sufentanil, Hydromorphone) [26]. Other drugs such as mixed alpha/beta agonists (epinephrine) and acetylcholinesterase inhibitors (neostigmine) can rarely be used as intrathecal analgesics [8, 9].

In order to pick the best drugs that will help the patient, one must first categorize the type of pain the patient is having. Earlier in the chapter, we classified patients into two categories: Chronic cancer pain and chronic nonmalignant pain patients [7]. This is useful in discussing patient selection for intrathecal pumps but is nonspecific when it comes to choosing the drug therapy. For the purposes of selecting drug therapy, we can classify pain into four categories: nociceptive, neuropathic, mixed (nociceptive + neuropathic) and spastic pain [3].

The most predominant type of pain is nociceptive pain. *Nociceptive pain* is a noxious stimuli that elicits sharp, shooting, generally well-localized pain and is a result of tissue damage [6, 9]. Generally, most patients with nociceptive will respond to a single-shot test dose of the drug therapy. The PACC of 2012 first-line agents include morphine, ziconotide, hydromorphone, and fentanyl. The choice of drug will be based on the patient's history of medication use, allergies and intolerances [26].

Neuropathic pain is a noxious stimulus that patients will describe as a burning, lancinating, heavy sensation and/or numbness that is due to nerve damage [3]. A neuropathic pain picture may require a longer trial period to elicit a good analgesic response. This is where percutaneous intrathecal/epidural catheter trials can be useful. These trials could be done as a single/multiple drug bolus trial or an infusion trial lasting a few days to weeks. First-line agents for this setting include morphine alone or with a local anesthetic, most commonly bupivacaine, and ziconotide alone [26]. The decision to use a longer trial will also depend on the patient's preference and if the patient can tolerate a prolonged infusion.

A mixed pain picture is more challenging to treat. It is important to uncover the symptomatology of the patient and delineate goals of therapy with the patient. This will better prepare the patient for what to expect and which symptoms can be relieved with which medications. Patients with mixed pain are usually treated well with a multimodal analgesic approach. This can include opioids, nonopioids, and local anesthetics. It is likely that oral adjuvants will also be helpful.

Refractory spastic pain from spinal cord injury, cerebral palsy, multiple sclerosis, and amyotrophic lateral sclerosis is treated well with subarachnoid baclofen. Baclofen therapy is initially done as a single-shot test dose. Initial bolus doses range from 25 to 50 μg. If the initial bolus does not elicit significant relief from spasticity, a second dose of 75–100 μg can be administered 24 h after the initial dose. A maximum dose of 100 μg can be given after another 24 h if needed [4, 26, 37].

Intrathecal Trial Monitoring

The literature on monitoring for the trial period is minimal and as a result the universal consensus on monitoring protocols does not exist. PACC did offer guidelines to monitoring patients during the trial period. For IT opioids, the panel recommended monitoring for at least 24 h either at an inpatient or similar setting. With Ziconotide, the panelists made a special recommendation to monitor for at least 12 h prior to discharge [26]. If no adverse symptoms were noted than the patient could be discharged home.

The expert panel recommendation for 24-h monitoring is one that has not been substantiated by evidence [26]. In clinical practice, experienced practitioners may have different methods for monitoring depending on the method of trialing (bolus, IT catheter, epidural catheter), drug(s) trialed or the patient's comorbidities. Therefore, it is important these factors are kept in mind when trialing a patient. For example,

patients with obstructive sleep apnea, diabetes, immunosuppression, cardiovascular disease, pulmonary disease, and/or a history of infection should be optimized and treated appropriately prior to a trial. Antibiotics for infections should be completed. Patients with diabetes should have their blood glucose levels controlled. Elevated levels of glucose can predispose patients to inflammation and infection. Patients with coagulation disorders or bleeding disorders should have anticoagulants stopped if that can be safely done. These measures will help prevent trial complications.

Trial Complications

During the trial period, monitoring is recommended by PACC and BPS during the first 24 h to monitor for more immediate complications such as respiratory depression/arrest and hypotension [1]. The use of IT opioids is usually the most common culprit of respiratory depression. Morphine is more hydrophilic and has a longer duration of action then more lipid soluble drugs such as fentanyl [2, 6, 9]. Therefore, the respiratory depression from morphine will usually present later than with fentanyl. Hypotension can happen with the use of IT opioids and local anesthetics via venodilation and arteriodilation [2, 6, 9].

Post dural puncture headaches can occur after trials or intrathecal pump implantation. Though rare with the use of a 22G–25G spinal needle, they can develop immediately and up to several days after the trial. Typically, a postdural puncture headache will be described as a bifrontal or posterior occipital headache that worsens with the sitting or standing position and alleviated by the supine position [6, 9, 38]. Other sources of headaches should be ruled out. Treatment includes caffeine, hydration, NSAIDs and other nonopioid analgesics.

Meningeal infections are a rare but significant complication that can occur with trialing or implantation [26, 37]. Since the complication is so rare, the use of antibiotics has not shown significant benefit and is indicated or recommended. For trials involving epidural/intrathecal catheter infusions, antibiotics are routinely given by physicians but there is no evidence substantiating its use.

Other less severe complications or adverse effects are urinary retention, sedation, orthostatic hypotension, and peripheral edema (associated with IT opioids and its effects on antidiuretic hormone). The presence of these adverse effects indicates a lower dosage may be required or a change in medication can be considered.

Opioid Management

During the trial and pump implantation, opioids can be managed in three general ways. One option is to maintain opioid usage throughout the trial and measure results based off the addition of IT opioids. Opioids would be weaned then after pump implantation. A second option would be to partially wean opioids prior to IT

opioid trial and implantation. The third option is to completely wean the patient off of opioids prior to trialing and implantation.

Weaning patients partially or completely off of opioids can help determine if a patient is experiencing opioid induced hyperalgesia (OIH) [39]. OIH is a sensitization to nociception induced by the use of opioids. With prolonged use of opioids, the nervous system can develop a paradoxical response to painful stimuli. While the exact molecular mechanism is not well understood, the notion is that the sensitization can occur through five mechanisms; central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms, and decreased reuptake and enhanced nociceptive response [39].

Since OIH may be a cause of opioid failure, it is reasonable to reduce the amount of opioid usage prior to IT pump trial and implantation. This may help deduce if OIH is the cause of chronic pain and implantation may not be necessary. Additionally, the reduction of opioid usage may help with the success of IT drug therapy.

Pump Implantation

Implantable intrathecal drug delivery systems are implanted surgically with two sets of incisions. The first incision is done posteriorly along the midline of the back superficial to the spinous processes. A Tuohy needle is then inserted into the intrathecal space using a midline or paramedian approach. Once the subarachnoid space is accessed and good CSF flow is observed, an intrathecal catheter can then be threaded into the space to the desired level.

A second incision is made along the anterior flank, above the iliac crest and below the costal margin which will be the location of the drug reservoir. The laterality is decided based off patient preference and prior incision/surgeries. Ideally, the position of the incision should be in an area that is accessible for needle aspiration and injection into the reservoir. The depth of the reservoir should be about 1.5–2.5 cm below the skin.

A tunneler is then used to make a subcutaneous track for the intrathecal catheter from the posterior incision to the flank incision. During the tunneling, care must be taken not to cause injury to intra-abdominal structures. In some instances, a small 1 cm incision can be made at the apex of the flank in cases where tunneling is difficult.

Complications

Intrathecal pump implantation complications can be divided into surgical complications, drug side effects and complications, mechanical complications, refill complications, and patient-specific complications.

Surgical complications include bleeding, epidural/intrathecal infection, pocket infection, seroma formation, spinal cord injury, catheter damage, and malpositioned/

flipped drug reservoir. Surgical site infections and infections in general have been largely reduced due to the use of sterile equipment, sterile gloves and gowns, and perioperative use of antibiotics. Most infections can be treated conservatively with monitoring and antibiotics. Surgical pocket infections may occur and do require decompression and antibiotics. Pocket infections do not necessarily require the complete removal of the intrathecal system. Infection in the subarachnoid or epidural space does necessitate removal of the entire system. Superficial infections range from 2 to 5 % in case study of 100 patients [40]. Deep infections including epidural and subarachnoid infections range from 0 to 0.5 % in the same series of 100 patients.

Drug side effects and complications are the most common complication from implantable IDDS [41]. The complications that can occur are due to physiological and pharmacokinetic properties of the drug itself. General complications which can occur with all drugs include anaphylaxis, meningitis/infection from contaminated solutions/preservatives, sedation, altered mental status and respiratory depression [1]. Additionally, withdrawal from abrupt cessation of drug administration can precipitate complications.

Mechanical complications are either catheter or pump related. More commonly, complications occur with the catheter (65 %) versus the pump (35 %) [42]. The catheter can leak at any point prior to entering the subarachnoid space. A leakage can occur at the interface of the pump and catheter. The adapter can be faulty or the catheter may be incompletely interfaced with the adapter allowing for areas of leakage. The catheter may be compromised or broken at any point along the catheter. Potential causes of breakage could be trauma, surgery with inadvertent ligation of the catheter, or shearing of the catheter during insertion of the catheter. During the implantation process, the access port is aspirated to see if there is good flow of CSF retrograde from the catheter. This however does not test for a leak. The best way to test for a leakage is to kink the catheter distally and attempt to inject saline through the access port and look for a source of leakage. Finally, the last cause of leakage can be malposition or migration of the catheter tip out of the subarachnoid space. Vice versa, the catheter can have an obstruction due to a kink or bend. The pump itself does not require “flip” in the pocket which would require surgical correction to properly manage refilling and accessing the pump. The annual risk of surgery secondary to mechanical complications is 10 % [26, 37].

During the drug filling or refilling process, iatrogenic complications can occur. Complications can occur during the refill process due to inappropriate volume, inappropriate drug administration (wrong drug), programming errors (wrong rates), and iatrogenic drug deposition outside the drug reservoir which can lead to systemic toxicity and overdose from the drug and less commonly withdrawal from the drug [4, 26].

There are some patient-specific complications that can occur with the long-term use of IDDS. With long-term use of IDDS and specifically with opioids, hormonal changes in growth hormone, luteinizing hormone, follicle-stimulating hormone, and testosterone [4, 26]. This may lead to changes in libido, fatigue, and sexual dysfunction. When educating patients, it is important to include this into the discus-

sion regarding informed consent since these changes may not be well appreciated and do warrant periodic monitoring by a physician.

Lastly, a rare and unique complication to IDDS is the growth of a granuloma, a noninfectious mass of inflammatory cells at the catheter tip. The offending mass can occlude the lumen of the catheter and obstruct flow which could precipitate drug withdrawal or could cause cord compression and damage. The etiology of granulomas appears to be an inflammatory reaction due to the offending agent being infused. Case reports have most commonly reported opioids being involved specifically morphine. Lipophilic opioids have not been found to be associated with granulomas. The incidence increases with the duration of the infusion with the incidence being 0.04 % for the first year and 1.16 % by year 6 [4, 43]. Presentation of granulomas is most commonly reduced effectiveness of the drug therapy. Treatment of granulomas was outlined by the PACC guidelines [26]. If a patient has neurological complications from the granuloma, immediate surgical evaluation and treatment should be done. If there are no neurological complications, the offending agent should be changed to a nonopioid such as ziconotide or replacement of the offending agent with a saline infusion and supplementation with oral analgesics.

Intrathecal Pump Devices

In order to provide patients with the best treatment options, the physician must understand the details of each IDDS company, limitations of each device, and differences in features. Implantable IDDS systems can be divided into two categories, fixed rate and variable rate or dynamic rate.

Codman 3000 makes a MRI safe titanium intrathecal pump that works through a pressure regulated bellow system with a flow restrictor within the catheter that regulates the flow of the medication into the intrathecal space. The rate is fixed when implanted and cannot be changed. Since the system does not require batteries, it can effectively last a lifetime and does not require pump changes due to battery depletion. Because of its features, this system is appealing as a low cost and low maintenance system that does not require battery changes. Since it is a fixed rate system, its disadvantage is for patients that may have dynamic or anticipated elevated requirements for analgesia. For example, cancer patients with advanced disease that have escalating analgesic requirements or patients undergoing chemotherapy that have may have varying levels of pain. Another disadvantage is since there is no electronic portion of the pump, there is no way to know how much medication is left in the reservoir other than by calculation and manual aspiration. Battery-powered pumps have devices that calculate how much fluid is left which can prevent calculation errors that may occur if doing it manually [44].

Medtronic Synchromed II and Flowonix Prometra systems make variable rate IDDS pumps. Both pumps are battery powered and programmable with a clinician programmer. This provides ease of rate changes without intervention. The Codman system requires aspiration and reinjection with a solution at a new dosage for dose

changes. Synchromed II and Prometra have the programmers which can change the dosage of the medication delivered to the patient. This provides more comfort by avoiding needle sticks and potentially lower rates of infections when compared to the Codman system. Additionally, this allows for modification of doseages with relative ease with patients that have increased requirements for analgesia, that is, cancer patients. Both systems are battery powered and require a new pump every 4–7 years. The drug chamber reservoirs for both Synchromed and Prometra are smaller than the Codman System and therefore require more frequent refills.

Both Synchromed II and Prometra systems are MRI compatible; however, each company has different guidelines for management of the pump. The synchromed system is a peristaltic pump roller system that stops when the magnetic field of an MRI is sensed and is designed to restart after the MRI on its own. Medtronic recommends investigation of the pump before and after the MRI to ensure proper functioning of the pump. The prometra system, on the other hand, is a valve gated dose-regulated system that does not require investigation before or after the MRI but does require removal of the drug from the pump reservoir [26, 44].

The Synchromed II system offers a patient therapy manager which allows the patient to self-administer boluses within clinician set limits. This is a feature unique to the Medtronic system. The purpose of it is to treat breakthrough pain via a hand-held device. This is an effective way to avoid unnecessary increases in flow rates for variable spikes of pain patients can experience throughout the day. This can also help prevent patients from becoming tolerant to the therapy (Fig. 12.2).

Intrathecal Drug Therapy

We will discuss algorithms presented by the PACC of 2012 intended to guide practitioners. These algorithms are based off clinical experience, clinical, or preclinical literature. As with the trial, when choosing appropriate medications to administer for long-term intrathecal drug therapy, one must identify the type of pain the patient is having. Is the patient experiencing nociceptive pain or neuropathic pain? Is it a combination of both? Does the patient have spastic pain? The PACC guidelines identify algorithms for neuropathic and nociceptive pain.

Neuropathic pain can be treated with a multimodal analgesic approach. First-line therapy can be morphine, ziconotide or morphine, and bupivacaine. Second-line agents include the use of morphine plus clonidine or hydromorphone in lieu of morphine with or without the addition of clonidine or bupivacaine. Third-line agents include clonidine as a sole agent, ziconotide plus an opioid, or the use of fentanyl with or without the use of bupivacaine or clonidine. Fourth-line agents for neuropathic pain are the combination therapy of bupivacaine and clonidine with or without the use of an opioid. Finally, last line agent for neuropathic pain is the use of baclofen [3, 4, 26, 44].

Nociceptive pain can also be treated with a multimodal analgesic approach. First-line agents include the use of morphine, hydromorphone, fentanyl, or ziconotide.

Fig. 12.2 Medtronic Synchromed II system with variable rate IDDS. Beginning on the *left* is the front view of the Intrathecal Pump with reservoir port (center) and access port (top) of the device. The *middle* image shows the lateral view of the device. The leftmost image is the current physician manager device that allows for modification of the intrathecal drug therapy. (Reproduced with the permission of Medtronic)

Second-line agents are the first-line agents as listed plus the use of bupivacaine. Third-line agents for nociceptive pain are the opioid of choice with the use of clonidine. Fourth-line agents include the use of opioids, clonidine, and bupivacaine or the use of sufentanil with the use of clonidine or bupivacaine. Finally, the fifth-line agents are a combination therapy of sufentanil, bupivacaine, and clonidine [44].

Management of mixed pain can be a combination of the therapies outlined earlier. Spastic pain generally is limited to baclofen and can be added with some of the modalities above.

Monitoring During Intrathecal Drug Therapy

According to the PACC 2012 guideline, it is recommended to routinely monitor patients in the inpatient setting during initiation of IT drug therapy, reinitiation of IT drug therapy or IDDS revision. During the immediate phase after initiation or reinitiation of IT drug therapy, literature review shows that there is an increased risk of mortality [45]. Patients with certain comorbidities, such as chronic obstructive pulmonary disease, obstructive sleep apnea, and certain psychiatric conditions, may require more vigilant monitoring. Monitoring during this crucial period can lead to improved patient safety and potential prevention of devastating complications.

Uses for Chronic Urogenital/Pelvic Pain

Chronic urogenital and pelvic pain syndromes are being highlighted more and more over the past 15–20 years [47]. Previously, it has gone unrecognized and has been underappreciated. We are learning more and more about these syndromes as we gain more data. What we have learned is that chronic urogenital pain seems to afflict more females than males. Epidemiological data show that 14.7 % of women of childbearing age suffer from chronic pelvic pain which estimates to about nine million women within the US [46, 47]. The ratio of women to men who suffer from these pain syndromes is as high as 9–1 in some epidemiological data. The vast majority of chronic urogenital pain syndromes are also accompanied by pain syndromes in other regions of the body. Additionally, we also appreciate that approximately 50 % of patients with pain syndromes also have psychological effects, such as depression and/or anxiety, that can potentiate their pain perception [47].

The approach to chronic urogenital and pelvic pain syndromes is generally approached in a multimodal fashion. The data highlighting the use of intrathecal pumps are weak for urogenital pain syndromes. However, the approach to the treatment of urogenital pain can include the use of implantable IDDS with the use of analgesics as highlighted earlier. With more data and research and further advancements in our pharmacological arsenal to treat pain, we can hopefully help patients by helping deduce the best treatment modality for each individual patient.

References

1. American Society of Interventional Pain Physicians Fact Sheet. American Society of Interventional Pain Physicians. 2011. https://www.asipp.org/documents/ASIPPFactSheet101111.pdf. Accessed Jan 2016.
2. Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's management of pain. Philadelphia: Lippincott Williams & Wilkins; 2001.
3. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: results from a cross-sectional survey. Eur J Pain. 2006;10:127–35.
4. Knight KH, Brand FM, Mchaourab AS, Veneziano G. Implantable intrathecal pumps for chronic pain: highlights and updates. Croat Med J. 2007;48(1):22–34.
5. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol. 2002;20:4040–9.
6. Barash PG, Cullen BF, Stoelting RK, Cahalan M, Stock MC, Ortega R. Clinical anesthesia. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
7. Steams L, Boortz-Marx R, Du Pen S, Friehs G, Gordon M, Halyard M, Herbst L, Kiser J. Intrathecal drug delivery for the management of cancer pain: a multidisciplinary consensus of best clinical practices. J Support Oncol. 2005;3(6):399–408.
8. Medtronic. Urgent medical device safety notification: use of unapproved drugs with the SynchroMed implantable infusion pump. 2012. http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@neuro/documents/documents/synch-ii-final-hcp.pdf. Accessed Jan 2016.

9. Miller RD, et al. Miller's anesthesia. 6th ed. Philadelphia: Elsevier/Churchill Livingstone; 2004.
10. Onofrio BM, Yaksh TL, Arnold PG. Continuous low-dose intrathecal administration in the treatment of chronic pain of malignant origin. Mayo Clin Proc. 1981;56(8):516–20.
11. Pert CB, Snyder SH. Opiate receptor: demonstration in nervous tissue. Science. 1973;179:1011–4.
12. Atwek SF, Kuhar MJ. Autoradiographic localization of opiate receptors in Rat brain. 1. Spinal cord and lower medula. Brain Res. 1977;124:53–7.
13. Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. Science. 1976;192:1357–8.
14. Basbaum AI, Clanton CH, Fields HL. Opiate and stimulus-produced analgesia: functional anatomy of a medullospinal pathway. Proc Natl Acad Sci. 1976;73:4685–8.
15. Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology. 1979;50:149–51.
16. Alper MH. Intrathecal morphine: a new method of obstetric analgesia. Anesthesiology. 1979;51(5):378–9.
17. Hocking G, Wildsmith JAW. Intrathecal drug spread. Br J Anaesth. 2004;93(4):568–78.
18. Stockman HW. Effect of anatomic fine structure on the flow of cerebrospinal fluid in the spinal subarachnoid space. J Biomech Eng. 2006;128(1):106–14.
19. Degrell I, Nagy E. Concentration gradients for HVA, 5-HIAA, ascorbic acid, and uric acid in the cerebrospinal fluid. Biol Psychiatry. 1990;27(8):891–6.
20. Bernards CM. Cerebrospinal fluid and spinal cord distribution of baclofen and bupivacaine during slow intrathecal infusions in pigs. Anesthesiology. 2006;105(1):169–78.
21. Battal B, Kocaoglu M, Bulanski N, Husman G, Tubal Sanal H, Tayfun C. Cerebrospinal fluid flow imaging by using phase-contrast MR technique. Br J Radiol. 2011;84(1004): 758–65.
22. Bulat M, Klarica M. Recent insights into the hydrodynamics of the cerebrospinal fluid. Brain Res Rev. 2011;65(2):99–112.
23. Henry-Feugeas MC, Idy-Peretti I, Baledent O, et al. Origin of subarachnoid cerebrospinal fluid pulsations: a phase-contrast MR analysis. Magn Reson Imaging. 2000;18(4):387–95.
24. Friese S, Hamhaber U, Erb M, Keuker W, Klose U. The influence of pulse and respiration on spinal cerebrospinal fluid pulsation. Invest Radiol. 2004;39(2):120–30.
25. WHO's pain relief ladder. World Health Organization. 1986. http://www.who/int/cancer/palliative/painladder/en/. Accessed 02 Feb 2016.
26. Deer TR, Prager J, Levy R, et al. Polyanalgesic consensus conference 2012: recommendations for the management of pain by intrathecal drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2012;15:436–66. doi:10.1111/j.1525-1403.2012.00476.x.
27. Ballantyne JC, Carwood CM. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. Cochrane Database Syst Rev. 2005;1:CD005178.
28. Hayek SM, Deer TR, Pope JE, Panchal SJ, Patel VB. Intrathecal therapy for cancer and non-cancer pain. Pain Physician. 2011;14(3):219–48.
29. Patel VB, Manchikanti L, Singh V, Schultz DM, Hayek SM, Smith HS. Systematic review of intrathecal infusion systems for long-term management of chronic non-cancer pain. Pain Physician. 2009;12(2):345–60.
30. Taricco M, Pagliacci MC, Telaro E, Adone R. Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review. Eura Medicophys. 2006;42(1):5–15.
31. Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Parke B, Kroin JS. Intrathecal baclofen for severe spinal spasticity. N Engl J Med. 1989;320(23):1517–21.
32. Hugenholtz H, Nelson RF, Dehoux E, Bickerton R. Intrathecal baclofen for intractable spinal spasticity – a double-blind cross-over comparison with placebo in 6 patients. Can J Neurol Sci. 1992;19(2):188–95.
33. Bonica JJ. The need of a taxonomy. Pain. 1979;6(3):247–8. doi:10.1016/0304-3959(79)90046-0.

34. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, Mercadante S, Pasternak G, Ventafridda V, Expert Working Group of the European Association of Palliative Care Network. Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol. 2001;19(9):2542–54.
35. Smith TJ, Coyne PJ. How to use implantable intrathecal drug delivery systems for refractory cancer pain. J Support Oncol. 2003;1(1):73–6.
36. The British Pain Society. Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for the best clinical practice. August 2006. https://www.britishpainsociety.org/static/uploads/resources/files/book_ittd_main.pdf. Accessed 03 Feb 2016.
37. Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice. The British Pain Society. 2008. https://www.britishpainsociety.org/static/uploads/resources/files/book_ittd_main.pdf. Accessed 10 Feb 2016.
38. Munts AG, Voormolen JH, Marinus J, Delhaas EM, van Hilten JJ. Postdural puncture headache in complex regional pain syndrome: a retrospective observational study. Pain Med. 2009;10:1469–75.
39. Lee M, SIlcerman S, Hansen H, Patel V, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. http://www.painphysicianjournal.com/current/pdf?article=MTQ0Ng%3D%3D&journal=60. Pain Physician. 2011;14:145–61.
40. Kumar K, Nath R, Wyant GM. Treatment of chronic pain by epidural spinal cord stimulation: a 10-year experience. J Neurosurg. 1991;75(3):402–7.
41. Bhatia G, Lau ME, Koury KM, Gulur P. Intrathecal drug delivery (ITDD) systems for cancer pain. F1000Res. 2013;2:96.
42. Koulousakis A, Kuchta J. Intrathecal antispastic drug application with implantable pumps: results of a 10 year follow-up study. Acta Neurochir Suppl. 2007;97:181–4.
43. Miele VJ, Price KO, Bloomfield S, Hogg J, Bailes JE. A review of intrathecal morphine therapy related granulomas. Eur J Pain. 2006;10:251–61.
44. Bottros MM, Christo PJ. Current perspectives on intrathecal drug delivery. J Pain Res. 2014;7:615–26.
45. Coffey RJ, Owens ML, Broste SK, et al. Medical practice perspective: identification and mitigation of risk factors for mortality associated with intrathecal opioids for non-cancer pain. Pain Med. 2010;11(7):1001–9.
46. Ledger W, Schlaff WD, Vancaillie TG. Chronic pelvic pain. Cambridge: University Printing Press; 2015.
47. Ballantyne JC et al. Chronic pelvic and urogenital pain syndromes. International Association for the Study of Pain. 2008. http://iasp.files.cms-plus.com/Content/ContentFolders/Publications2/PainClinicalUpdates/Archives/PCU08-6_1390262181984_2.pdf. Accessed 20 Feb 2016.

Chapter 13
Psychiatric Aspects in Chronic Pain and Utility of Yoga and Mindfulness-Based Cognitive Behavioral Therapy for Pain (Y-MBCT Pain) as a Translational Model

Basant Pradhan

> Insofar as psychotherapy or counseling is effective and produces long-term changes in behavior, it presumably does so through learning, by producing changes in gene expression that alters the strength of synaptic connections and structural changes that alters the anatomical pattern of interconnections between nerve cells of the brain. As the resolution of brain imaging increases, it should eventually permit quantitative evaluation of the outcome of psychotherapy.
>
> —Nobel Laureate Eric Kandel ([49], p.460)

Introduction

One may agree that under-treated pain is an epidemic and over-treated pain is a nightmare for clinicians. It is a major public health problem. Chronic pain in the United States has a national economic cost of approximately $600 billion per year [57]; pain costs society $2000 per year for every individual living in the United States [113]. Chronic pain involves many complex aspects including persistent pain, anxiety, depression, difficulty moving, muscle weakness due to lack of use, and, of course, reduced quality of life—requiring further healthcare resources [3]. Pain is necessary to handle the danger signal that invoked it; however, due to the unpleasantness of pain, it is something that is consciously avoided: this adds to its complexity. In addition, the fear of pain in these patients more often than not leads to the avoidance of important activities such as exercises and thus creates a vicious cycle of avoidance, disability, depression, and more enduring pain. Prolonged pain, through the various feedback mechanisms, may lead to changes in the structure of the body and functions of the nerves that perpetuate these symptoms even after the tissue has had adequate time to heal [21]. It is not only the cost of health care or

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disability that is impacted by chronic pain; actually, the type of care that a patient receives and responds to is greatly impacted by chronic pain as well. No wonder that chronic pain is a leading cause for absence from work, reducing labor productivity, patient's income and insurance coverage, and increasing the need for workers' disability [71]. Also important to note that although many therapies are available for chronic pain, up to two-thirds of patients are inadequately treated [92].

One needs to distinguish here c*hronic pain* from *acute pain* which differ from each other in a number of ways. In general, acute pain tends to be adaptive because it is purported to result in survival actions (such as escaping behaviors which protects from the danger), whereas chronic pain eventually becomes maladaptive, causes great deal of suffering and a great reduction in quality of life, etc. By definition, chronic pain is enduring and goes beyond the expected period of healing, regardless of its origin, that is, trauma, surgery, or as part of a degenerative disease, just to name a few. The typical time frame used for defining chronic pain is defined, rather arbitrarily, as *pain that persists beyond a 6-month window period* [101]. Another characteristic that distinguishes chronic from acute pain is the associated emotional component of the perceived suffering which becomes important in the assessment and subsequent treatment of chronic pain. Also chronic pain, more often than not, results in depression and in fact is one of the leading causes of suicidality in this population. Studies have revealed high rates of suicidal ideation and suicide attempts in patients suffering from chronic pain, which amounts to rates as high as 50 % in some studies [91]. Of note, in pain literature, the terms "constant pain," "frequent pain," and "persistent pain" are rather used interchangeably and the reported prevalence for constant or frequent pain in the US population has been quite variable: ranging from as low as 11 % to as high as about 47 %, due in part to the inconsistent criteria for defining chronic pain. Nonetheless, these prevalence estimates in all studies highlight the enormous public health issue of chronic pain. Often, "persistent pain" is defined arbitrarily as self-reported pain "every day" or "most days" for the past 3 months [51]. Using these criteria, a 2010 National Health Inventory Survey (NHIS), which queried about 35,000 households, found that approximately 19 % (39.4 million adults) of American adults suffer from "persistent pain" [51]. Alarmingly, more than 60 % of these patients reported that their pain is constantly present: a number huge enough to trump the sum of patients suffering from heart disease, diabetes, and cancer combined [41].

It is important to understand that in chronic pain no single therapy can adequately treat the many components involved in it. This leads to a growing call for integrated care that improves patient outcomes and reduces long-term costs. Ironically, despite the appeal of the integrated-care approaches like the biopsychosocial models, medical pain specialists often do engage in "pain as functional or structural abnormality," an "either-or" dichotomous approach while damaging their patients with chronic pain. This becomes further complicated by the focused quest for a "pain generator" as well as predominance of purely medical/physical modalities suggested as first-line treatment options in published treatment guidelines from professional medical societies. Integrated-care strategies are available for the treatment of chronic pain and were accepted practice in the late twentieth century [92].

However, over time, changes in the healthcare system resulted in barriers to implementation of these collaborative approaches. An integrated-care approach engages a variety of healthcare professionals in order to address the multiple problems that characterize chronic pain. In this multidisciplinary approach, in addition to pain medications, exercise, injection procedures, and psychological therapies including cognitive–behavioral therapies (CBTs), Yoga and mindfulness-based interventions need to be integrated into a broader framework of pain management. Incorporated into an integrated-care program, these and other evidence-based therapies can be geared toward improvements not only in pain but also in daily functioning of these patients, making it imperative to remove the barriers that currently discourage their effective use. The various portions of this chapter will focus on an integrated-care model that consists of a standardized module of *Yoga and mindfulness-based cognitive behavioral therapy for pain* (Y-MBCT pain) that attempts to bridge some of the existing gaps in treatment. For implementation of this holistic and integrated approach, a comprehensive understanding of the biopsychosocial model of development and maintenance of chronic pain is necessary. Especially important to understand is the role of emotional factors and the long-standing negative memories of the chronic pain experience, laid out layer after layer and mediated by the conditioned learning mechanisms that make these experiences more ingrained. Also important is the sensitization of the crucial brain areas that provide fertile nidus for perpetuating this complex learning process and creates the complex pain hologram.

Psychiatric Aspects of Pain and Need for Integrated Models of Care

Researchers tend to agree that except for malingering and factitious pain, chronic pain should be regarded as genuine [31]. Mind plays a big role in constructing the pain experience and psychological factors can significantly influence the experience of pain. Thus, acknowledging that psychological factors are involved in the pain experience does not necessarily mean that the pain is not real or patient is faking it. It is well known that the associated anxiety, fear, and stress have modulatory influences on pain and tend to exacerbate the pain experience by manifold. Fear and anxiety can enhance responses to and interpretation of the pain-producing events [40, 59, 68–70, 80, 82]. Also measures to reduce anxiety can reduce pain—this is true for both behavioral (cognitive) interventions and anxiolytic drugs [8]. As Andrew Miller [67] diligently writes: “All pain is real enough to those who have it; all stand equally in need of compassion.”

Many individuals with chronic pain have comorbid psychiatric disorders and they form a heterogeneous group. In some patients, many of these varied disorders may be secondary to chronic pain, but in others they predate the onset of pain or reflect alternative expressions of the same underlying psychobiological disorder. As comprehensively reviewed by many researchers [26, 31], chronic pain is commonly

comorbid with psychiatric disorders as well as some chronic physical conditions that account for a substantial proportion of the disability associated with them. The common psychiatric conditions that often feature pain as part of the illness are somatization disorder, hypochondriasis, factitious physical disorders, pain associated with psychological factors, and malingering. Among these psychiatric disorders, even though depression is the most commonly studied comorbid one, other entities, especially anxiety disorders, are quite common. In particular, depression, anxiety, panic, and posttraumatic stress disorders (PTSDs) may strongly influence chronic pain without directly causing it.

The frequent occurrence of mental disorders among patients with chronic pain has great implications for the management of these patients. Whatever their etiological significance, each of these psychiatric disorders may exacerbate the pain condition and impede recovery. A comprehensive understanding of the complexity of these not only provides opportunities for designing appropriate interventions but also raises new questions for further research. Their effective management requires psychiatric as well as biological considerations. At the same time, clinicians must be careful not to presume that chronic pain complaints that cannot be accounted for readily by physiological findings are due to psychiatric disorders. Current standards of care and treatment modalities for chronic pain pose numerous difficulties. The non-steroidal anti-inflammatory drugs (NSAIDs), like naproxen, ibuprofen, and aspirin, which can be purchased over the counter, lack the potency to alleviate chronic and moderate to severe pain. While opioids and steroids have proven more effective at alleviating pain, they each pose their own unique set of shortcomings and risk factors. Prolonged use of steroids often results in important side effects like muscular atrophy, electrolytes (mostly potassium) deficiencies, and renal problems just to name a few. For patients with chronic pain who do receive opioid treatments, the quick rate of tolerance and need for increased dosages pose fiscal and dependency concerns. These important issues have led the American Association for Family Physicians (AAFP) to recommend that physicians follow strict clinical guidelines. These guidelines include not only screening and monitoring patients with annual drug urine samples and reviewing all documentation of their medical history for positive indicators for addictions but also referring patients to and requiring patients to participate in adjunctive programs and therapies [41]. The recent guideline for prescribing opioids for patients with chronic pain, released by the Center for Disease Control (CDC) [24], includes 12 recommendations among which the first recommendation is to use nonpharmacologic (e.g., physical therapy, CBT) and non-opioid therapies (e.g., NSAIDs, acetaminophen), which are preferred for chronic pain. The CDC recommends that clinicians should consider opioid therapy only if expected benefits outweigh risks to the patient, and if they are used they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Another important fact is that in the treatment of chronic pain, pharmacological agents when administered alone often fail to mitigate the cognitions, memories, and emotions related to pain perception, and primarily address pain as a mere physical sensation instead which indeed is erroneous and is an oversimplification. As a result, there is an increased need for integrated and inno-

vative treatment models for pain management. However, such an all-encompassing, biopsychosocially informed and patient-centered treatment model for chronic pain is rare to see in clinical situations, if nonexistent. Below, I describe some important concepts related to chronic pain.

Pain Biography (Pain Memory) Constructs the Chronic Pain Experience

Pain is not just a physical sensation, rather it is a complex phenomenon in which one's perception and memory play crucial roles [61]. The pain experience as a whole and the associated pain behaviors are especially important because these behavioral adaptations reduce global quality of life and increase the risk for exaggerated pain perception that can lead to depression, anxiety, and panic disorders, as well as insomnia [17].

Nociception, the Pain Experience, and Gate Control Theory of Pain Transmission

It is important to distinguish between *nociception* and *pain experience*. Nociception is not exactly the pain experience. Nociception is caused by the stimulation of pain receptors (nociceptors), whereas pain experience is a product of pain processing by the higher brain centers. Nociception is better conceptualized as a danger signal that alerts the brain that something potentially threatening has just occurred. In the process of nociception, information about peripheral stimuli gets transmitted upstream by primary afferent nociceptors to the spinal cord, brainstem, thalamus, and subcortical structures. By contrast, the experience of pain can result only when there is an activity of thalamo-cortical networks that process the information conveyed by neural pathways of nociception [72]. Nociception does not always result in pain experience, whereas pain perception/pain experience can happen without nociception (as seen in phantom-limb pain). Neurons at many levels of the neuraxis respond to noxious stimuli, but that response does not necessarily indicate or lead to the pain experience. For example, the spinal cord of an individual who suffered a complete spinal cord transection can still process information transmitted by nociceptors, but because this information cannot be transmitted upward to higher centers beyond the level of transection, stimulus-evoked pain experience is unlikely.

Physiologically, pain experience can be said to be composed of four processes: *transduction* (transforming the pain stimulus which can be thermal, mechanical, or chemical energy to electrical energy by the sensory mechanisms of the body that includes nerve endings), *transmission* (passage of a nerve impulse across nerve endings and synapses by the activation of a specific chemical mediators that stimulate or inhibit the process transmission), *modulation* (regulation of intensity and

expression of pain), and *perception* (the conscious mental elaboration of the pain stimulus). The perception/experience of pain is a complicated phenomenon as it combines dynamic interplay between the peripheral and central nervous system. The magnitude of pain is determined to a great extent by the strength of descending inhibitory (usually they are inhibitory) and facilitatory pathways that regulate the processing of the nociceptive messages. Thus, human pain conditions present in a multitude of biological and psychological phenotypes and add to the difficulties in correctly diagnosing and treating them.

From ancient time, numerous theories of pain have been proposed; however, one can see mostly a fragmented or dichotomous approach rather than comprehensive and integrated approach. Many have focused on pain as a physical sensation and most, if not all, have failed to define a comprehensive mechanism of pain perception that accounts for the diversity of patient reports. Interestingly, the early Greek philosophers like Plato and Aristotle conceptualized pain as an emotional phenomenon or a "passion of the soul" whereas Rene Descartes, the eminent French philosopher of seventeenth century, replaced these by his reductionist and mechanistic theory of pain [19]. The Cartesian model in which pain was considered to result from a tissue damage and subsequent transmission of information in a mechanical process in which nerve fibers carried signals from the periphery to the brain (rather than the heart)—culminating in unpleasant physiological sensations [64]—stood uncontested for about 350 years. While models like these accounted for some dimensions of pain perception, eventually they proved problematic and failed to account for the diversity of patients' pain reports, which are often made in the absence of noxious stimuli, as in the experience of phantom-limb pain. This has important therapeutic implications. For example, when we understand that pain does not equal tissue damage, but instead it is a warning signal, it can help to remove some of the worry that often accompanies pain.

The gate control theory of pain transmission [65, 66] proposes that there are gates at the level of spinal cord which regulate pain transmission. The non-painful inputs close the gates to painful inputs, thus preventing the pain sensation from traveling up to the central nervous system. Therefore, stimulation by non-noxious input is able to suppress pain. The gate control theory [65] starts with a gate at the spinal cord, opening it allows pain signals to ascend, and the various aspects come into play during ascension to reduce the pain. The A-delta and C-fibers (smaller diameter fibers) in the dorsal horn of the spinal cord help open these gates, whereas the A-beta fibers (larger fibers) coming down or coming in help close these gates and thus reduce the pain transmission and *rub the pain away* [64]. This theory attributes the pain experience to not only sensory factors, but cognitive, emotional, interpersonal, and cultural ones, as well. Pain involves complex interactions between central and peripheral nervous system and involves both ascending and descending pathways, which are influenced by pain history, attention, and emotional and affective states [64]. Unlike in the case of Cartesian models of pain, the gate control theory postulates that painful stimuli transmit signals to specific "nerve gates" in the spinal cord, and either remain closed or open, allowing for the perception of pain [56]. Below, I describe the various brain areas involved in the perception and memories of the chronic pain experience.

Role of the CNS and Brain in Chronic Pain, Sensitization, and Neuroplasticity

The chronic pain experience is definitely multilayered and the mechanisms that contribute to its development are indeed complex compared to those of acute pain. Chronic pain experiences are not merely instances of momentary pain that do not resolve quickly or in due course of time; rather, they involve changes in the properties of nociceptors as well as of the pain circuits that exist in the spinal cord and at other levels of the neuraxis [6, 7, 43, 103]. These changes are called in the neural circuitry and are broadly categorized under neuroplasticity and closely linked with other terms like pain sensitization, long-term potentiation (LTP), and conditioned learning [11]. Pain sensitization generally enhances signals in pain transmission circuits by decreasing the pain threshold needed for eliciting the pain response. Pain sensitization results from an increase in the excitability of nociceptors at the site of the insult (e.g., the site of an incision) or at the peripheral nerve endings (called peripheral sensitization) or due to changes in the excitability of neurons in the spinal cord and supraspinal sites in the brain (called central sensitization). Sensitization happens due to the neuro-plastic nature of the pain circuits which, mediated by conditioned learning, results in alterations of pain transmission. Central sensitization is a considerably more complicated process that can result from changes in the amount of neurotransmitter released from nociceptor terminals in the spinal cord or brainstem, notably glutamate and the neuropeptide substance-P [6, 7, 52], from loss of inhibitory regulation exerted by inhibitory interneurons in the spinal cord and at supraspinal loci, and from biochemical changes in the pain transmission neurons that increase their responsiveness to peripheral inputs. Pain sensitization results in a pathological state called hyperalgesia which is defined as an increased response to a noxious stimulus and manifests as an increased sensitivity to pain [12, 100]. There are two types of hyperalgesia, primary and secondary, each associated with different mechanisms. Primary hyperalgesia is largely attributed to peripheral sensitization of nociceptors and secondary hyperalgesia with central sensitization. At the injury site, primary hyperalgesia is induced by the release of numerous inflammatory mediators including the products of cyclooxygenase enzyme activation. Also in many cases, through conditioned learning, it also leads to another pathological state called allodynia in which innocuous or non-noxious stimuli evoke behaviors indicative of pain.

The role of pain memory, in creation of the chronic pain experience, cannot be over-emphasized. Resonating to some extent with the earlier Platonic and Aristotelian concepts that regard pain as a perception and not just a sensation, recent research (a comprehensive review can be found in National Research Council Committee on Recognition and Alleviation of Pain in Laboratory Animals [72]) suggests that the perceptual dimensions of the pain experience are mediated in large part by the memory. Pain catastrophizing, a common pain behavior, demonstrates this point well. Those who exhibit this particular catastrophizing behavior struggle with pain-related thoughts and memories when just anticipating or actually experiencing a painful

encounter. These thoughts and memories can result in the development of exaggerated and negative emotional and cognitive schema that amplify the perceived threat of painful stimuli and result in feelings of helplessness, fear, and anxiety [56]. Not surprisingly, a tendency toward pain catastrophizing is often accompanied with maladaptive behaviors like avoidance of activities and situations associated with past painful experiences [17]. Also, there are instances when individual perceives pain in the absence of the actual noxious stimuli, as in the experience of phantom-limb pain. Multiple conditions such as surgery, diabetes, fibromyalgia, etc. may change the properties of the nociceptive systems, which could lead to the amplification of pain or even spontaneous pain.

Recent studies suggest that the perception of pain in the absence of tissue or nerve damage that characterizes chronic pain states (as in the experience of phantom-limb pain) may develop in part as a result of long-term neuroplastic changes in the activity of N-methyl-D-aspartate (NMDA) receptors, a type of glutamate receptor intimately involved in the various learning and memory mechanisms [22, 23]. Persistent activation of nociceptive pathways up-regulates the activity of glutamate (NMDA) receptors of dorsal horn synapses in spinal cord, and cause central sensitization by strengthening and amplifying the ascending nociceptive pathways to the brain through synaptic neuroplasticity mechanisms that include long-term potentiation (LTP) and long-term depression (LTD), two main processes involved in pain memory formation that modulates the pain perception or pain experience of the individual. After injury, glutamate-induced neuro-plasticity (also called activity-dependent central sensitization) is a key step in the increased synaptic efficacy occurring in the dorsal horn of the spinal cord at the synapse between primary afferent terminals and second-order neurons. This mechanism shares comparable features with the hippocampal LTP, which is an important mechanism for memory consolidation and contributes to the development of post-injury pain hypersensitivity [15].

Thus, it is important to understand how brain areas process the complex pain experience and how some brain areas can generate pain (mostly the emotional aspects of pain) even in the absence of noxious pain stimuli. Better understanding of these mechanisms will eventually lead us for their manipulations in therapeutic ways to alter these pathological experiences [20]. The prefrontal cortex (PFC) is such an important brain area that has expanded greatly in primate evolution, with the ventral and medial PFC (vmPFC) specialized for the regulation of emotion (internal states), while the more dorsal and lateral regions of the PFC (dlPFC) mediate cognition (external states) [5, 34]. The circuits in the ventral and medial PFC can represent the emotional value of an event, while circuits in the dorsolateral regions generate representations of external space and sensory features. Brodmann area (BA) 24 (anterior cingulate cortex, ACC), BA 25 (subgenual cingulate, which is actually a part of the ventromedial PFC, also called as the subgenual vmPFC), and the insular cortex are all key parts of a circuit that processes the emotional aspects of pain [11, 107]. The ACC has been postulated to attenuate pain by employing cognitive control mechanisms to modulate pain through the activation of the descending opioid system via the peri-aqueductal gray in the spinal cord.

The cognitive modulation of pain is influenced by a number of factors ranging from attention, beliefs, conditioning, expectations, mood, and the regulation of emotional responses to noxious sensory events. The sensory versus the emotional aspects of pain are processed by parallel pathways [109, 110], where the arousing and suffering aspects of pain are processed by diffuse projections that arise through the brainstem and medial thalamus, which then projects to the insular cortex and the anterior cingulate BA24 [90, 110]. Both insular cortex and BA 24 project to BA25 which in turn projects to a number of brain structures that mediate emotional responding [33], including the amygdala (unconscious primitive emotional associations) [54], hypothalamus (vegetative functions) [13], and nucleus accumbens (changes in emotional habits, loss of feeling of reward) [28], and to the brainstem for control of reflexes and the autonomic nervous system [73], thus completing the body–brain–body loop that can maintains the vicious cycling. These regions all interconnect to provide a holistic mental state [77]. Within the vmPFC, BA 25 (subgenual vmPFC) is of particular interest, as this region is the "head ganglion" of the visceromotor system [76], and is positioned to control much of the limbic and autonomic nervous system, and interestingly this is the area overactive in patients with major depressive disorder and also has an exceptional density of serotonin transporters [62]. BA25 projections to the brainstem can excite columns of neurons in the peri-aqueductal gray that generate coordinated responses to painful events, for example, the freezing response ("mental paralysis"), or other body-wide responses to pain and stress [73]. Importantly, neurons in many of these areas are capable of representing information in the absence of sensory stimulation. Interestingly, this medial pain system is overactivated in depression in which one can have the generation of mental suffering (normally caused by a painful stimulus) even in the absence of an actual sensory event (like in the phantom pain experience). This view explains why patients with depression report more somatic symptoms like pain even in the absence of physical pain stimulus.

Because of the many systems involved in processing chronic pain, combining both pharmacological and nonpharmacological therapies (that take into account environmental factors that contribute to pain) may be the best approach to solving the problem of chronic pain. An in-depth understanding of the pain experience and the processes involved in this are indeed critical and will lead to a comprehensive view that may set the stage for more integrated and multidimensional model of pain management that may eventually replace the rather fragmented treatment models that exist currently. The scientific advances in areas of the various mechanisms of chronic pain, the processes involved in the transition from acute to chronic pain, and better understanding and implementation of the various evidence-based components of pain management with an interdisciplinary and more integrated approach could result in a quantum leap in the care of chronic pain conditions. Development of novel and more integrated pain management protocols that has multidimensional (biological, psychological, spiritual/quality of life, etc.) components could unburden some of the current public health burden in the treatment of chronic pain states.

CBT in the Treatment of Chronic Pain

Given the fact that chronic pain is often difficult to treat pharmacologically, the role of nonpharmacologic strategies like CBT (cognitive behavioral therapy) is important to explore. In a recent article [29], the authors reviewed data from six randomized controlled trials examining CBT for pain and found that CBT improved pain-related functional outcomes such as pain interference and disability. The authors argue for expanding on these findings with larger-scale clinical trial research, as well as more comprehensive pain assessments with longer-term follow-up. Since early 1980s, treatment approaches based on CBT strategies began to address the treatment of chronic pain [102].

Since then, traditional CBT for chronic pain has been very successful in many ways. There are two core principles at the heart of CBT approaches to chronic pain. The first is that psychological (cognitive and emotional) factors can influence the experience of pain itself. The second principle is that problems with client's functioning related to the pain can be addressed even if the pain is not targeted directly or even if it remains unchanged. There are at least five systematic reviews relevant to current CBT for chronic pain, each generally concluding that these approaches can produce significant benefits, such as reduced pain and improved daily functioning [37, 39, 69, 96]. However, when a similar meta-analysis was published by the same group 10 years later [25] in which 40 trials were analyzed and stricter inclusion criteria were applied in order to identify the studies for analysis, the overall conclusion was positive but less emphatic. These analyses showed that cognitive and behavioral treatments produced small effects on pain and disability and a small effect on mood, particularly at follow-up which led the authors to conclude that the evidence for cognitive and behavioral treatments for chronic pain is "weak" and that the quality of treatments, or the reporting of these treatments, apparently is not improving over time [25].

Another problem with CBT for pain is that there is a lack of clarity in treatment process within CBT for chronic pain [63]. Here, process means the directly targeted, theoretically based, psychological elements deemed to affect improvements in treatment outcome variables. This is sometimes called therapeutic mechanism. When one can identify processes of change that are both sufficient and necessary for the benefits observed in treatment, and identify the methods that impact these processes, then one is able to optimize treatment impact. It is quite difficult to precisely define the theory or theories behind current psychological treatments for chronic pain, including CBT, and this leads to several problems. There are many different treatments, some are based on theoretical models and some are not, and the current view is that not one model seems to explain most of these [42]. It has been argued that if not one theoretical model encompasses all treatments, and if each treatment only targets finite subsets of psychological factors, then any choice of theory will exclude some of these factors and could result in suboptimal treatment for some patients [42]. These important issues compel researchers to identify a potential pathway for progress for psychological treatments for chronic pain so that we can in this complex process both actively recognize the successes of the past and embrace

the areas where progress is insufficient. These areas include in particular the identification of therapy process and, perhaps more important, the explicit linking of theoretical assumptions, therapy processes, and clinical technique.

Yoga and Mindfulness-Based Interventions in the Treatment of Chronic Pain

Pain is a basic and probably one of the biggest human suffering. From ancient times, beginning with ancient India and later globally, Yoga and mindfulness methods have been used for transcending human sufferings including pain. Chronic pain is multidimensional. At the various levels, that is, physical as well as mental, beyond the nociceptive pathway, there are somatic and hyperarousal components mediated by the autonomic nervous system, which negatively influences muscular tension, posture, patterns of breathing, mood states, etc., all of which further exacerbate the accompanying distress and dysfunctions. Yoga and mindfulness practices integrate physical discipline, mental training, and moral principles to encourage a healthy and holistic way of living.

The term mindfulness is used to describe both a set of methods and the psychological processes impacted by these methods, processes that include non-defensive, moment-to-moment, and "non- judgmental" awareness [2]. In the USA, the use of mindfulness in chronic pain was pioneered by John Kabat-Zinn [44, 45, 47]. A comprehensive review about the utility of mindfulness in chronic pain can be found in books by Kabat-Zinn [46] and Gardner-Nix [32] that describe holistic approaches to help people manage and cope with their daily pain. These interventions are deemed effective for chronic pain in terms of both symptom reduction and improved emotional functioning [36]. In a study of 174 participants, mindfulness-based stress reduction interventions (MBSR; [46]) were found effective for problems with stress, chronic pain, or anxiety [14]. A similar result was demonstrated in another study of MBSR specifically focused on treatment for chronic pain [94]. After the initial studies on chronic pain, later on researchers have studied these interventions in other pain conditions like chronic migraine and chronic headaches as well [60, 108].

Several other studies, including randomized controlled trials, have directly examined Yoga as a potential treatment for pain and found evidence for the beneficial and safe use of Yoga to alleviate different painful conditions (reviewed by [4, 104, 112]). Apart from its therapeutic effects on the musculoskeletal system (e.g., increase in strength and flexibility), Yoga also involves focused attention (FA) and has been shown to improve mood and depression [53, 97, 111]. Both attentional and emotional factors influence pain perception [93, 105]. Furthermore, Yoga practitioners are encouraged to adopt an emotionally detached observation of the present moment which is a core component of mindfulness/meditation practice. The emotional and cognitive tools developed in Yoga practice could potentially alter a person's relationship with pain, particularly by strengthening control over affective

reaction to pain. Apart from studies supporting their empirical efficacy, the use of Yoga and mindfulness interventions for pain has been supported by neuroimaging data as well. Mind–body practices like Yoga and meditation seem to have the opposite effect on the brain compared to the brain effects of chronic pain. Yoga and meditation practice exert a protective effect on brain gray matter that counteracts the neuroanatomical effects of chronic pain [11, 106]. Yoga practitioners have more gray matter than controls in multiple brain regions, including in the insula or other parts of the cerebral cortex that are involved in pain modulation. However, the effects of long-term and regular Yoga practice on experimental pain perception and more precise knowledge illuminating the underlying neuroanatomical basis of altered pain perception are yet to be explored.

Limitations with Traditional CBT and Mindfulness-Based Interventions

Yoga and meditation interventions are heterogeneous and more often than not are not being used in a standardized manner. So its therapeutic effects are often difficult to compare across studies. Also as far as the use of Yoga and mindfulness interventions are considered, more so in the Western world, unfortunately, many concepts are rather mystified and add to the existing misconceptions. For example, although conceptually the term "Yoga" is inclusive of "meditation" (and also includes many other things like lifestyle, physical aspects, etc.) and "mindfulness" is a type of meditation, these three terms are often used interchangeably adding to the already-existing confusion. In the West, Yoga and mindfulness are used in rather dichotomous way, that is, Yoga is used as a mere physical exercise and meditation as a mental technique or a breathing exercise. Also often Yoga is used in piecemeal, that is, only its physical aspects are used and if mental aspects are used, they are used in isolated rather than the integrated manner as proposed in the original schemes. In the ancient schemes that advocated for the use of Yoga in its entirety, Yoga originally comprised of eight limbs that include meditation as its sixth and seventh steps (i.e., concentrative-type meditation [Pali. *samatha*], and mindfulness-type meditation [Pali. *satipatthana* or *vipassana*], respectively) [74, 75, 83]. The ancient Indian scriptural scheme of Yoga (in Vedic traditions, this is known as the *Eight-limbed Yoga* [Sanskrit: *Astanga Yoga*, [95]]; in the Buddhist traditions, this is called the *Noble Eightfold Path* [Pali. *Atthangika Magga*, [74]]) actually advocated for the holistic and sequential use of all eight steps of Yoga. Yoga in those traditions used to be all-encompassing and tends to span from one's lifestyle and life views to one's physical aspects that include one's body, breathing, postures, and eventually culminates in liberation of the individual from the sufferings of life by the use of meditation [18, 27]. The fragmented use of Yoga, as seen in the West, restricts its scopes as well as utility, and makes the integration between body and mind far from being complete. In this context, an interesting finding emerging from a review done in Vietnam veterans with PTSD is worth mentioning [10]. These studies find that

although the physical aspects of Yoga, such as physical postures (Sanskrit. *asana*), reduced some symptoms of comorbid depression in patients with PTSD, they had no impact on the hyperarousal symptoms, panic, or anger outbursts until meditative interventions including meditative breathing methods (Sanskrit. *pranayama*) and FA (focused attention) meditation were added. Thus, Yoga is more effective when its many elements are used in combined, synergistic, and targeted ways.

Despite the success of mindfulness interventions in pain, as seen in studies described earlier, there is clearly room for improvements. One area for development in mindfulness studies is the examination of the issue of treatment process. Given the relatively large number of outcome studies of mindfulness-based approaches for chronic pain, there have been surprisingly few directly addressing mindfulness per se as a process of change and even fewer are the studies that have attempted to separate component processes within mindfulness although in some studies a relationship has been shown between the time spent in home practice and improvements in distress symptoms and general health [14]. Nonetheless, neither of these studies showed a specific causal role for facets of mindfulness processes or methods. Another particular area for further development in studies of mindfulness-based treatment methods for chronic pain is activity-related outcome. Previous studies of mindfulness have focused predominantly on mental health outcomes, such as symptoms of anxiety and depression, and rarely on activity-related outcomes, such as physical activity and social role performance [9, 16, 50]. As a result, evidence is not clear if these mindfulness-based interventions can change behavior patterns in ways that translate into improved physical and social functioning. Also, the limited data linking specific mindfulness-related processes to improvements in outcomes have been noticed. There have been attempts to identify specific processes within mindfulness, for example, re-perceiving, de-centering, and intimate detachment [98], yet these do not seem to achieve a quality of greater precision or direct manipulability compared with mindfulness itself. They also do not link with a theoretical framework or a comprehensive set of behavior-change principles. It may enhance the overall effect of mindfulness methods, and help produce results of greater practical importance, to combine these methods with methods that more directly aim to improve engagement in wider patterns of daily activity. One such approach is the dialectical behavior therapy (DBT; [58]) but to the best of our knowledge, there are no controlled trials of DBT for chronic pain. The other approach that blends mindfulness-related processes and direct behavior-change methods is acceptance and commitment therapy (ACT; [38]), which has some efficacy data in chronic pain [63].

The strength of CBT is its pragmatism, its targeted approach, and the measurability of its effects. However, as one can see, there is a clear need for developing new all-encompassing models of pain treatment which bridge across the biological, psychological, as well as spiritual domains. Such translational treatment models need to reflect the authenticity of the ancient scriptural traditions of Yoga and meditation, and at the same time need to bridge across these ancient methods with the methods of modern science without losing the fidelity and essence in this process of standardization and adaptation. The *Yoga and mindfulness-based cognitive therapy* for pain (Y-MBCT pain, described in detail later), a translational model developed

by Pradhan, is his humble attempt to address some of these issues and provide more broader and integrated approach for pain management. Based on the insights from his *translational mindfulness* research [83–89] and recognizing the strengths and limitations of traditional CBT as well as problems with piecemeal use of Yoga, in this model Pradhan in addition to CBT for pain uses a broader scheme of Yoga which involves its all eight limbs that includes meditation (sixth and seventh limbs), cultivation of a balanced lifestyle (*that of moderation* rather than of extremes, otherwise called as the *Middle Way* constituted by the first and second limbs of Yoga; [18, 83]), and the psychosomatic preparatory stages (third to fifth limbs that includes Yogic postures, Yogic physical exercises and Yogic procedures called *kriyas,* meditative breathing, and detachment; [99]) which make oneself ready for meditation which is considered as the central aspect of Yoga. Of note, when Yoga is used with its all eight limbs in order to target a distressing symptom, resolution of the symptom and amelioration of the attending suffering are considered as the eighth limb of Yoga [83]. This translational model combines the neurobiology of pain experience with its psychology, that is, the five-factor model of pain experience which in an all-encompassing manner incorporates all five fundamental components of pain. These five components are one's thoughts about pain, the feelings the pain brings in the person, the associated sensations/perceptions, the invoked memories, and the urges/will/energy that result in the various actions or behaviors by the individual in the context of chronic pain. The pain symptom inventory (described later), based on these five factors of pain experience, is akin to the thought record of CBT and goes beyond the thoughts or feelings of client. Of note, traditional *CBT* includes only three components of the pain experience, that is, thoughts, feelings, and behavior. Conceptually and methodologically, the *Y-MBCT pain*, like the DBT, ACT, or MBCT, could be categorized under the broader rubric of the third-wave cognitive therapy [48]. Adherent to the methods described in the monastic traditions of ancient India, in the Y-MBCT-pain model, meditation practice usually begins with cultivation of one's attention and induction of detached and non-judgmental awareness in which one learns how to maintain and shift flexibly one's attention at will onto an object of choice, while disengaging oneself from the elaborative processing of these objects by one's mind. These objects of choice can be physical (such as one's body parts and the pain in it), physiological (such as one's change in breathing, heart rate, etc. as induced by the pain), or mental (such as one's thoughts, feelings, or emotional experiences about the pain).

Meditation and Medication Have Different Mechanisms for Pain Relief and Thus Can Be Combined and Integrated

About the precise mechanism by which mindfulness interventions relieve pain has not been entirely clear to researchers. There is debate whether mindfulness interventions do so by the release of naturally occurring opiates or by other mechanisms of pain relief. A new study [116] conducted by researchers at the Wake Forest

School of Medicine and Cincinnati Children's Hospital Medical Center and funded in part by the National Center for Complementary and Integrative Health demonstrates that mindfulness meditation does not rely on the endogenous opioid activity to reduce pain, which is an important consideration for using meditation to treat chronic pain. In this randomized control study, researchers recorded pain reports in 78 healthy adults during meditation or a non-meditation control in response to painful heat stimuli and intravenous administration of the opioid antagonist naloxone (a drug that blocks the transmission of opioid activity) or placebo (saline injection). Participants were randomized to one of four treatment groups: (1) meditation plus naloxone, (2) control plus naloxone, (3) meditation plus saline, or (4) control plus saline. People in the control groups were instructed to "close your eyes and relax until the end of the experiment." The researchers found that participants who meditated during saline administration had significantly lower pain intensity and unpleasantness ratings compared to those who did not meditate while receiving saline. Importantly, data from the meditation plus naloxone group showed that naloxone did not block meditation's pain-relieving effects. No significant differences in reductions of pain intensity or pain unpleasantness were seen between the meditation plus naloxone and the meditation plus saline groups. Participants who meditated during naloxone administration also had significantly greater reductions in pain intensity and unpleasantness than the control groups. These findings demonstrate that mindfulness meditation reduces pain independently of opioid neurotransmitter mechanisms. The researchers noted that because opioid and non-opioid mechanisms of pain relief interact synergistically, the results of this study suggest that combining mindfulness-based and pharmacologic/nonpharmacologic pain-relieving approaches that rely on opioid signaling may be particularly effective in treating pain.

Y-MBCT-Pain Model, Its Uses of Yoga and the Pragmatism of Brief CBT

Y-MBCT pain is a treatment approach within the family of CBT but goes beyond it. As mentioned earlier, meditations are stylistically two types: concentrative or focused attention (FA) type and mindfulness or open-monitoring (OM) type. Given the differences in the neural processes with different forms of mindfulness meditation, it is likely that FA and OM practices influence pain in different ways [115]. Specifically, FA is proposed to involve repetitive cognitive reappraisal and to promote sustained attention, whereas OM is proposed to involve non-judgmental appraisal of salient sensory events [83]. Studies on Zen meditation practitioners [35, 81] show that an FA meditation does not significantly reduce pain, and also that OM meditation is more effective at reducing pain after meditation training, as compared to FA. It has also been shown that the meditation styles that use either FA-only or OM-only approaches are not that effective at pain reduction and take many long hours of practice, whereas the combined meditation types, which have elements of

both FA and OM, are effective at reducing behavioral and neural mechanisms of pain after brief mental training [114]. Thus, cognitive practices employing attentional stability (FA) in conjunction with nonevaluative awareness of sensory events (OM) can reduce pain, even after brief mental training [115]. The Y-MBCT-pain model uses these insights from recent scientific research and combines not only both types of meditations but also incorporates in a standardized way the meditative lifestyle (Middle Way) and the elements of CBT for chronic pain. Its pragmatic and targeted approach, its time-limited format (six to eight individual therapy sessions, 30 min each in duration), and its generalizability by user-friendly yet standardized style of home practice make it an effective brief therapy for chronic pain.

The theoretical foundation of the Y-MBCT model for pain derives from the three original scriptural schools of Yoga and mindfulness, that is, the Eight-Limbed Yoga (*Ashtanga*) of Patanjali (circa. fourth century BC), the mindfulness (*satipatthana*) model of Buddha (circa. sixth century BC), and the standardizations of the technique-rich style of *Tantra* (second century CE). The main meditation methods used in these models are the *samyama* (the combination of sixth, seventh, and eighth limbs of Yoga) combined with the Buddhist *satipatthana* method using the tripartite model of human experience and the five-factor model of mind. As a pain- or disorder-specific model, this is an extension of the wellness model (called *Standardized Yoga and Meditation Program for Stress Reduction*: SYMPro-SR©, [83]). This models combine all three main aspects of Yoga (Yogic philosophies, techniques, and practice) packaged together for their symptom-specific use in client's daily life. The results of this holistic practice are not only stress relief, symptom amelioration, or sustained calmness in daily life but also lifestyle modifications in the form of creation of a balanced lifestyle and balanced life views (collectively known as the *Middle Way* in the Buddhist meditative traditions). This broader and integrated approach increases not only the scope of these interventions but also their efficacy and generalizability. Apart from many important standardizations, in the Y-MBCT models, heavy emphasis is placed on personalization of the meditative interventions by using the data about each client obtained from the use of standardized instruments. These include the *Assessment Scale for Mindfulness Interventions* (ASMI©), the five-factor inventory based on the five-factor model of human experience (elaborated later) and *home practice log* (for detailed descriptions, please see [83]). These instruments help in enhancing adherence to the practice of the tools as well as generalization of the therapeutic gains to the daily life situations of the clients. In the Y-MBCT for pain model, the five-factor inventory serves as a personalized inventory for the therapist and client to elicit and quantify client's normal experiences as well as the psychopathology and pave the way to apply techniques and principles of brief CBT in targeted ways.

Y-MBCT-pain module is the modification of TIMBER (trauma interventions using mindfulness based extinction and reconsolidation of trauma experience) psychotherapy, which was designed by Pradhan and has been successfully applied to change expression of fear and trauma memories in patient with chronic and refractory PTSD. For detailed discussions on the memory extinction and memory reconsolidation processes and clinical use of translational treatment methods (e.g., TIMBER) based on these learning mechanisms, please see Pradhan [83] and Pradhan et al. [85, 86]. As done in TIMBER psychotherapy, the interventions in the

Y-MBCT-pain psychotherapy aim to change the expression of pain memories, the pain perceptions, and the associated meanings in patients suffering from chronic pain. In Y-MBCT pain, after initial detachment from pain experience is established using meditative methods, the brief CBT interventions informed by the five-factor pain inventory are applied to induce change of the pain experience and to enhance better coping. Y-MBCT-pain module includes a combination of Yoga and mindfulness methods along with elicitation of the arousal response to pain experience and the behavior-change methods using the five-factor inventory, standardized meditation protocols, and brief CBT techniques.

The Cornerstones in the *Y-MBCT-Pain* Module: Five-Factor Inventory of Pain, Buddha's Middle Way and Staged Meditation Protocols

Based on the fundamental concepts about human mind and human experiences, the five-factor inventory for pain, Buddha's Middle Way and standardized meditation protocols (SMPs) form the cornerstones in the *Y-MBCT-pain* module. These are succinctly described in the scriptures on Yogic/mindfulness philosophies, that is, the *Yoga Sutras*, the primary source (in Sanskrit language) textbook of Yoga [95], and the *Visuddhi Magga*, the primary source (in Pali language) Buddhist encyclopedia of meditation [74]. The five-factor inventory provides a rich database on the personalized pain experience of the client. In the Y-MBCT for pain module, these pathological experiences are changed toward normalcy by using the staged meditation protocols (SMPs) which, through *i*nduction of mindful state, enhances detached observation, monitoring, and reappraisal of the complex pain experience. Subsequently, elements of brief CBT are used to change the contents of the attending dysfunctional thoughts, feelings, behaviors, and also enhance coping. The use of the philosophy of Buddha's *Middle Way* (this philosophy, as the name suggests, advocates to stay away from extreme behaviors or extreme views and adopt instead a path of moderation that comprises of balanced lifestyle and balanced views on life experiences, [83]) enhances meditation practice, prevents *strivings* (i.e., endless struggle to do the perfect meditation) in the client, and provides the perfect matrix for generalization of the meditations into client's daily life. Of note, striving has been described as one of the main obstacles that comes in the way of achieving the mindful state during meditation.

Below I describe some of these concepts that form the basic foundations of the Y-MBCT-pain module:

- *Mind*, *the creator of all human experiences*, *is a bundle of five things*: One's mind, in mindfulness philosophies, is just another sense organ and is known as the *inner apparatus* (Sanskrit: *antah karana,* [83], p.46). Mind is the creator and locus of all human experiences which are co-created by the five components, otherwise called as *aggregates* (Sanskrit: *skandhas,* Pali: *khandas*), that is, one's thoughts, feelings, sensations/perceptions, memories, and urge/will/impulses which result in actions or behaviors (see Fig. 13.1).

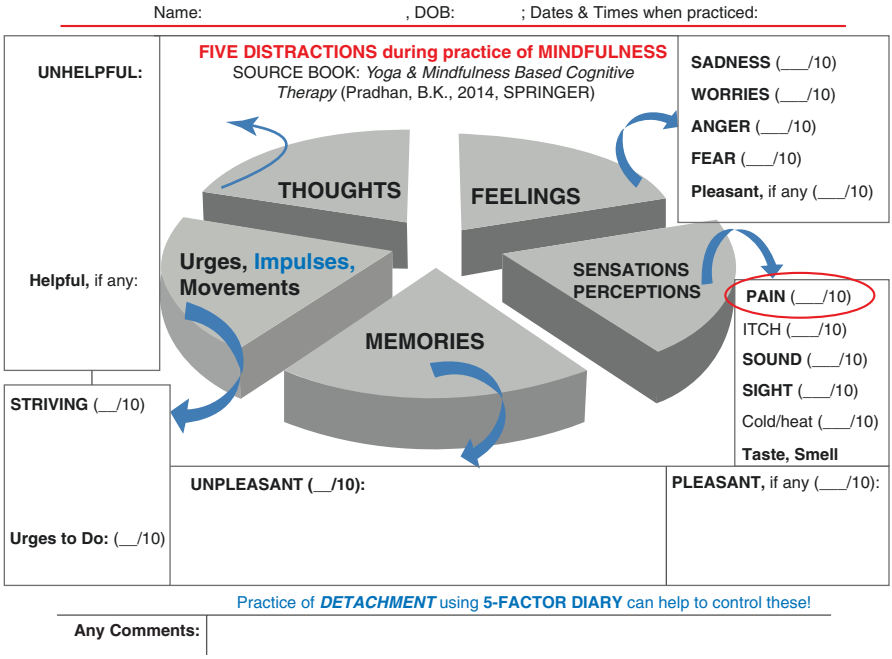

Fig. 13.1 Five-factor model of any human experience

These components are cemented together in a composite form by the attending memories, which provide a personalized context to the other four components which engage in a dynamic interplay and build up the total experience in a composite manner. Thus, these five components, by their dynamic interplay, co-create all the experiences including the experience of stress, happiness, sadness, or the pain experience, etc. Importantly, by changing these individual components of the experience, the composite experience as a whole can change. Of note, memory (Sanskrit. *smriti*, *pratyaya*) is a crucial factor in this five-factor model because it tends to color the other four components, provides a contextual and temporal matrix for their expressions in an ongoing manner, and thus heavily influences one's learning processes.

The Five-Factor Inventory for Pain (Pain Symptom Inventory)

This inventory (Fig. 13.2) was developed by Pradhan [83], based on the five-factor model of any human experience created by the mind. This comprehensive inventory serves as a main tool in the Y-MBCT-pain psychotherapy and is used to generate data on the content as well as the sequence of the five components as they come up

during expression of the pain experience in client's daily life or in therapist's office during the trial practice of meditation. Also, this inventory helps to delineate the cognitive distortions, to identify maladaptive feelings, memories, or life experiences including the client's maladaptive urges/impulses, safety behaviors, and avoidance behavior that maintained the symptoms and dysfunctions in a vicious cycle. This helps people identify and develop skills to change all the five key components that form the core of the pain experience, that is, negative thoughts, feelings, memories, and behaviors. Based on the scriptural concepts on human mind and any human experience, this model emphasizes that individuals—not outside situations and events—create their own experiences, pain included. And by changing their negative thoughts and behaviors, people can change their awareness of pain and develop better coping skills, even if the actual level of pain stays the same. This pain symptom inventory provides rich and personalized information on the pain experience of the patient and helps the therapist to target the individual components of this experience using the brief CBT interventions in an individualized yet symptom-specific and structured way. Pain symptom inventory and interventions in the Y-MBCT-pain module help the individual getting detached from all components of the pain and then to reappraise them in less emotional if not entirely neutral way. This provides a new perspective on pain experience and subsequently these individual components (the thoughts, emotions, and behaviors related to pain) are changed using brief CBT and also improve coping strategies, and thus put the discomfort in a better context to be able to be reappraised. This helps individuals recognize that the pain interferes less with their quality of life, and therefore can function better.

All experiences are representations which can be changed by promoting new learning. Mindfulness philosophies assert that all of the information derived by the mind based on the five components of human experience are just representations in the mind [83]. These representations, as the name suggests, are symbolic (akin to map rather than territory) and dependent on the quality/state of the mind and brain during their acquisition and subsequent expressions. Also, they change with change of the conditions that invoked these representations and thus are amenable to new learnings that result in new memories. This is true for the pain experience as well, which is amenable to new learning that provides new meanings or new associations to the existing information. Recent research from cognitive neuroscience upholds this view and asserts that memory is state dependent and changeable [78, 79] and thus experience is prone to change as well. Meditative wisdom informs us that amelioration of stress and healthy reappraisal of situations are possible by modification of the internal representations: this is done by achieving the meditative insight about the nature of these representations so that premature actions or cognitions (judgments, conclusions or biases, etc.) are prevented. Y-MBCT-pain model utilizes these principles for the treatment of chronic pain. Thus, breaking down the individual pain experience, which is a composite of the five basic components as mentioned above, and eliciting the details of their sequence, form, and contents by using the quantitative five-factor inventory, paves the way for modifying them further with mindfulness tool and the brief CBT interventions. The targeted and specific *Y-MBCT-pain*

Name: **DOB:** **Highest Level of Education:**

PAIN SYMPTOM(S) INVENTORY (PSI©, Based on the *Five Factor Model* of Human Experience)

Current MAIN SYMPTOM(s) *that you want to use mindfulness for*: PAIN, Sadness, Anger, Panic, Compulsion, Others_____

DATES & TIMES when PAIN/associated symptoms were recorded using the Five Factor Model	INTENSITY (0-100%)	THOUGHTS aronsed in you by the PAIN/associated symptoms	FEELINGS arouned in you by the PAIN/associated symptoms	What kind of MEMORIES the PAIN/associated symptoms brings in you?	BODILY SENSATIONS or Movements or Visuals or Sounds etc, if any, that get arouned by the PAIN/associated symptoms	What ACTIONS/ BEHAVIORS the PAIN/associated symptoms make you do? PLEASE ELABORATE
1.						
2.						
3.						
4.						

COPING SKILLS that you're using to handle the Main Symptoms:_____

What other things can help?_____

COMMENTS, if any:_____

Source Book: ***Yoga & Mindfulness Based Cognitive Therapy: A Clinical Guide*** (Pradhan, B.K., 2014; SPRINGER International Publishers)

Fig. 13.2 The pain symptom inventory

tools help in de-escalation of arousal or avoidance symptoms in response to the pain experiences and also help to deconstruct the pain experience by inducing the detached observation and reappraisal of the five components of pain. This detached observation helps the individual to move from the reactive state to a responsive state and also prevents the client from acting on the pain experience. This provides the

insight (Pali. *nanna*) into the pain experience and thus provides new learnings and new meanings which eventually becomes no longer distressing or dysfunctional.

How Y-MBCT-Pain Sessions Are Actually Conducted?

Y-MBCT-pain interventions are applied for the patients in five steps in a sequence and perfected initially by six to eight therapist-assisted individual sessions (30-min duration each) followed by home practice daily. These five steps are as follows:

1. *Psychoeducation phase*: This involves educating patient on factors maintaining chronic pain, how five-factor model is relevant to the pain experience, and how mindfulness-based detached mental state can be cultivated using the scriptural philosophy, technique, and practice of Yoga and mindfulness.
2. *Skill acquisition phase*: In this phase, patients are trained on practice of Yoga-based *kriyas,* Yogic postures that are relaxing to the pain condition, how to attain the FA state using meditation, how to achieve the mindfulness-based detached monitoring (MBDM) of the pain experience using meditation, and, how to use Middle Way in daily life.
3. *Pain-specific home practice phase*: In this, home practice of Y-MBCT pain is initiated using home practice log and the pain symptom inventory. Patients are trained on how MBDM can be used at home to detach them from the pain experience.
4. *Training on Brief CBT and the five-factor pain inventory phase* (*cognitive–behavioral rehearsal phase*): In this phase, various brief CBT interventions are used to enhance coping and modify patients' dysfunctional thoughts, feelings, and behavior. Also after initial training during therapist-assisted sessions in therapist's office, mindfulness-based graded exposure therapy (MB-GET, [84, 89]), a specific CBT intervention, which is highly successful in anxiety and avoidance problems, is used for the pain situations so that the patient is able to better cope with these situations without using the avoidance mechanisms.
5. *Generalization and maintenance phase using home practice and Middle Way:* This is the final phase of therapy in which daily home practice of meditation and its generalization to patient's daily life are ensured. The meditative lifestyle based on the philosophy of Middle Way greatly facilitates this step.

These above interventions are done in two stages, and over six to eight individual therapy sessions (30 min each) as described below:

- *STAGE-1* (*Context rather than content approach*): In this, the patient is encouraged to take a detached and 'bird's eye view' of the five components of pain without elaborating on the details of each thoughts, feelings, sensations, memories, and movements/urges related to the pain experience. Instead, the patient is encouraged to use just neutral words for these five components (mentally saying "just a thought" or "just a feeling," etc.) and shift the focus from the pain experience to the standardized breathing meditations to establish an FA state. This helps

to focus on *context* rather than the contents of the pain (these contents usually exacerbate the pain experience). Sustained attention and suspension of peripheral awareness using body (*kriya*) and breathing along with FA facilitate reduced awareness of unwanted stimuli like pain and begins to induce detachment from the pain experience, which becomes ready to be appraised in the next stage

- *STAGE-2* (*Content and sequence approach followed by corrections with meditative reappraisal and brief CBT interventions*): In this, after the detachment is established by using the MBDM mental state, the patient is able to feel pain in a detached way rather than in first person. Then, MBDM with the use of five-factor pain inventory focuses on the *content* of each of the five factors of pain and the sequence in which these five factors build up the complex pain experience. Then once detached appraisal of the pain experience is done, the contents of these five factors are changed by using brief CBT interventions so that the thoughts and associated feelings are changed and thus new learning is induced. Also, this helps to enhance coping and pain tolerance.

How Y-MBCT Pain Is Different from Psychological Therapies for Pain?

Y-MBCT pain can be distinguished from other approaches within CBT or other mindfulness treatment approaches in the philosophical assumptions and the scientific strategies it adopts. Y-MBCT pain has roots in learning theory and in the learning and memory processes (extinction and reconsolidation processes) that influences the multilayered experience of chronic pain and in laboratory studies of basic behavioral processes. It includes an emphasis on cognitive processes and affective-behavioral experiences, just as in other CBT approaches but in more inclusive ways. Y-MBCT-pain module uses extensively the five-factor inventory and tends to "normalize" human suffering to a certain extent by seeing the pain experience as a continuum from the normal day-to-day pain experience to grossly dysfunctional pain experience. As one can see in the five-factor inventory and the Y-MBCT-pain model, pain and suffering as inherent in the human condition are built into the design of human experience and behavior. In this approach, the therapist practices meditation with the client in-session, thus establishes better empathic connection with the client and his/her pain and suffering. These approaches reflect an emphasis on qualities in the behavior of the treatment provider and on the experiential methods rather than on didactic ones (which are mere verbal jargons). Also, it focuses on changing the responses to the pain and its associated symptoms rather than focusing on the symptoms themselves (care, not cure approach). It tends to focus more on the process rather than just on contents. The pain symptom inventory based on the five-factor model is akin to the thought record of traditional CBT but is more inclusive. The triadic model of thought record used in traditional CBT focuses primarily on one's thoughts, feelings, and behavior, whereas the pain symptom inventory touches upon all five components.

The experiential data obtained from the trial-breathing meditation during eliciting the five-factor response to pain and from the use of the ASMI (Assessment Scale

for Mindfulness Interventions) [83] emphasize on the patient's psychological flexibility (or inflexibility) aspects and attempts to enhance the flexibility in non-judgmental and empathic ways. *Psychological flexibility* is the capacity to continue with or change behavior, guided by one's goals, in a context of the various interacting psychological processes [63].

The psychosomatic adaptations for therapeutic use of the Y-MBCT pain are based on *two major themes in Yoga*: Yoga as a profound psychosomatic science and meditation as a science of attention. Y-MBCT pain relies on the fact that pain is the ultimate psychosomatic phenomenon. Pain is composed of both somatic signal (something wrong with the body) and interpretation of the meaning of that signal (this meaning is learning dependent and can be changed by the five-factor model). Pradhan's model uses the five-factor model and ASMI scale to use brief CBT to decrease and alter the meaning of pain by new learning. Pain experience = tissue damage/pain sensitization of the body combined with the emotional reaction to it that is brought by the five factors in one's mind: Mindfulness interventions change emotional reaction to it (via five-factor inventory), FA and detachment from pain experience. Of note, *detachment (disassociation)* is different from dissociation and should not be confused with it [83]. Dissociation is a rather primitive defense mechanism of mind, whereas detachment is a higher-order psychological function that can be cultivated through mindfulness interventions.

Thus, the Y-MBCT for pain model, beginning with the physical body, eventually influences all aspects of the person: physical, mental, emotional, and spiritual. It offers various levels and approaches to relax, energize, remodel, and strengthen body and mind. The postures (Sanskrit: *asanas*) and meditative breathing (Sanskrit: *pranayama*) harmonize the physiological system and initiate a relaxation response in the neurohumoral system by effecting a reduction in the existing metabolism, establishing a quieter breathing, stabilizing the blood pressure, reducing muscle tension, lowering heart rate, and slowing and synchronizing the brain wave pattern, all of which contribute to one's stress arousal pattern in response to pain. As these pain response patterns get modulated, hyperarousal of the nervous system and the static load on postural muscles get reduced and the function of viscera improves with the sense of relaxation and sleep gets deeper and sustained, fatigue diminishes. Also, when somebody gets established in a regular schedule of meditation, the personalized meanings of pain and suffering change and the preexisting conditioning and identification with chronic pain reduces: all of these change the context and meanings of the pain and its associated dysfunctions in the sufferer's daily life. Meditation and *pranayama*, along with relaxing and physically nondemanding postures can help individuals deal with the emotional aspects of chronic pain, reduce anxiety and depression effectively, and improve the perceived and actual quality of life.

Conclusion and Future Considerations

In pain management, considering the low resources and difficulties in the implementation of multidimensional treatment, it is important to develop treatment models that are easy to implement, that can be combined with other treatment modalities,

and most importantly can be done via self-help. Y-MBCT pain is a self-help module and this model can be used alone or in combination with pain medications or other therapies as well depending upon the severity of pain, and the need of the individuals. It relieves a burden from clinicians as well. Yoga and mindfulness have been shown to increase one's level of control by enhancing the self-efficacy [60]. Self-efficacy is defined as the individual's perceived capacity to exercise self-control over their cognitive, behavioral, and affective responses to stressful events, and is considered as an important psychological resource buffering the impact of stress on the individual. Also, mindfulness changes one's perception of pain and the meanings attached with these perceptions. The combination of pain and the perceived uncontrollability of pain mutually influence each other and serve to amplify the pain experience. The element of the ability to control is a critical component of pain management, and mindfulness provides an excellent opportunity for many to modulate or even eliminate the pain.

Compared to the often nonstandardized and piecemeal use of Yoga, as just a physical exercise or as a breathing technique or as an isolated meditation technique, as typically seen in the Western world, Y-MBCT pain uses standardized and sequential use of all eight steps of Yoga in flexible, personalized, and pain experience-specific manner. These interventions in the Y-MBCT pain combine all three aspects of Yoga, that is, philosophy, technique, and practice. These include the Yogic lifestyle (*Middle Way),* the physical aspects of Yoga such as postures and physical exercises (Sanskrit. *asanas* and *kriya respectively*), and standardized breathing techniques, meditation techniques (both FA meditation and mindfulness meditation, which belong to the fifth and sixth steps of Yoga) targeted toward individual symptoms and accompanying dysfunctions, and most importantly includes personalized counseling of the clients about the mindfulness philosophy that elucidates the workings of the human mind in normal and pathological states, as described in the scriptural traditions of Yoga. This model is holistic and translational in its development, targeted and standardized in its use, and can be flexibly combined with other evidence-based treatments including medications and psychotherapeutic or cognitive–behavioral interventions for the management of pain. In near future, as an extension of our research work in population with chronic PTSD to those with chronic pain [87], we intend to use the Y-MBCT-pain model in a randomized control trial, which will compare the efficacy of this treatment with other treatments (e.g., pain medications like NSAIDs, opiates or ketamine, and other therapies like CBT for pain). Of note, ketamine is a glutamate (NMDA) receptor antagonist and is a novel analgesic. In pain conditions, it works through two main mechanisms: analgesia (by mu receptor agonism) and also by the alteration of pain perception and pain memory (by glutamate antagonism) [1]. Also as a pharmacological agent, ketamine is being increasingly used in stress-related conditions like depression, PTSD, which are often comorbid in patients with chronic pain. Thus in future we also intend to develop ways in which Y-MBCT pain can be used alone or in combination with beneficial elements of other treatment modalities in a "tiered approach" depending

on the severity and complexity of the pain and of course preference of the individuals with pain.

References

1. Afridi SK, Giffin NJ, Kaube H, Goadsby PJ. A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. Neurology. 2013;80(7):642–7.
2. Baer RA. Mindfulness training as a clinical intervention: a conceptual and empirical review. Clin Psychol Sci Pract. 2003;10:125–43.
3. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163(20):2433–45.
4. Balasubramaniam M, Telles S, Doraiswamy PM. Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Front Psychiatry. 2013;3:117. doi:10.3389/fpsyt.2012.00117.
5. Barbas H, Saha S, Rempel-Clower N, Ghashghaei T. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. BMC Neurosci. 2003;4:25.
6. Basbaum A, Jessell T. The perception of pain. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 4th ed. New York: McGraw-Hill, Health Professions Division; 2000.
7. Basbaum AI, Woolf CJ. Pain. Curr Biol. 1999;9:R429–31.
8. Belzung C. The genetic basis of the pharmacological effects of anxiolytics: a review based on rodent models. Behav Pharmacol. 2001;12(6–7):451–60.
9. Bohlmeijer E, Prenger R, Tall E, Cuijpers P. The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis. J Psychosom Res. 2010;68:539–44.
10. Brown RP, Gerbarg PL. Sudarshan kriya yogic breathing in the treatment of stress, anxiety, and depression: clinical applications and guidelines. J Altern Complement Med. 2005;11(4):711–7.
11. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci. 2013;14(7):502–11.
12. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron. 2006;52(1):77–92.
13. Carmel PW. Vegetative dysfunctions of the hypothalamus. Acta Neurochir (Wien). 1985;75(1–4):113–21.
14. Carmody J, Baer RA. Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. J Behav Med. 2008;31:23–33.
15. Chiechis S, Nicoletti F. Metabotropic glutamate receptors and the control of chronic pain. Curr Opin Pharmacol. 2012;12:28–34.
16. Chiesa A, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review. J Altern Complement Med. 2011;17:83–93.
17. Crombez G, Vlaeyen JWS, Heuts PHTG, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. Pain. 1999;80(1–2):329–39.
18. Dalai Lama. The middle way: faith grounded in reason. (Jinpa T, Trans.). Boston: Wisdom Publications; 2009.
19. De La Forge. Treatise on the human mind, International archives of the history of ideas. Boston: Kluwer Academic Publishers; 1997.
20. Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. Nat Neurosci. 2014;17(2):192–200.
21. Deyo RA, Von Korff M, Duhrkoop D. BMJ. 2015;2015:350. http://dx.doi.org/10.1136/bmj.g6380.

22. Dickenson A. The neurobiology of chronic pain states. Anaesth Intensive Care Med. 2011;14(11):484–7.
23. D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. Br J Anaesth. 2008;101(1):8–16.
24. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. MMWR Recomm Rep. ePub: 15 Mar 2016. doi: http://dx.doi.org/10.15585/mmwr.rr6501e1er.
25. Eccleston C, Williams AC, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2009;2009(2):CD007407. doi:10.1002/14651858.CD007407.pub2.
26. Eisendrath SJ. Psychiatric aspects of chronic pain. Neurology. 1995;45(12 Suppl 9):S26–34; discussion S35-6. PMID 8538883.
27. Eliade M. Yoga: for immortality and freedom. 2nd ed. Princeton: Princeton University Press; 1969.
28. Everitt BJ, Belin D, Economidou D, et al. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philos Trans R Soc Lond B Biol Sci. 2008;363(1507):3125–35.
29. Finan PH, Buenaver LF, Coryell VT, Smith MT. Cognitive-behavioral therapy for comorbid insomnia and chronic pain. Sleep Med Clin. 2014;9(2):261–74.
30. Furini C, Myskiw J, Izquierdo I. The learning of fear extinction. Neurosci Biobehav Rev. 2014;47:670–83.
31. Gureje O. Psychiatric aspects of pain. Curr Opin Psychiatry. 2007;20(1):42–6.
32. Gardner-Nix J. The mindfulness solution to pain: step-by-step techniques for chronic pain management. Oakland: New Harbinger Publications; 2009.
33. Ghashghaei HT, Hilgetag CC, Barbas H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. Neuroimage. 2007;34(3):905–23.
34. Goldman-Rakic PS. Circuitry of the primate prefrontal cortex and the regulation of behavior by representational memory. In: Plum F, editor. Handbook of physiology, the nervous system, higher functions of the brain. Bethesda: American Physiological Society; 1987. p. 373–417.
35. Grant JA, Courtemanche J, Rainville P. A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. Pain. 2011;152:150–6.
36. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits: a meta-analysis. J Psychosom Res. 2004;57:35–43.
37. Guzmán J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: systematic review. BMJ. 2001;322:1511–6.
38. Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: an experiential approach to behavior change. New York: The Guilford Press; 1999.
39. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. Health Psychol. 2007;26:1–9. doi:10.1037/0278-6133.26.1.1.
40. Hunt SP, Mantyh PW. The molecular dynamics of pain control. Nat Rev Neurosci. 2001;2(2):83–91.
41. Institute of Medicine of the National Academies. Relieving pain in America – a blueprint for transforming prevention, care, education, and research. Pain Res 2011 Rep Br. 2011;2011:4. Available at: www.iom.edu/relievingpain.
42. Jensen MP. Psychosocial approaches to pain management: an organizational framework. Pain. 2011;152:717–25.
43. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413:203–10.
44. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. Gen Hosp Psychiatry. 1982;4:33–47.
45. Kabat-Zinn J, Lipworth L, Burney R. The clinical use of mindfulness meditation for the self-regulation of chronic pain. J Behav Med. 1985;8:163–90.

46. Kabat-Zinn J. Full catastrophe living. New York: Delacorte Press; 1990.
47. Kabat-Zinn J, Massion AO, Kristeller J, Peterson LG, Fletcher KE, Pbert L, Lenderking WR, et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry. 1992;149:936–43.
48. Kahl KG, Winter L, Schweiger U. The third wave of cognitive behavioral therapies. Curr Opin Psychiatry. 2012;25(6):522–8.
49. Kandel E. A new intellectual framework for psychiatry? Am J Psychiatry. 1998;155:457–69.
50. Keng SL, Smoski MJ, Robins CJ. Effects of mindfulness on psychological health: a review of empirical studies. Clin Psychol Rev. 2011;31:1041–56.
51. Kennedy J, Roll JM, Schraudner T, Murphy S, McPherson S. Prevalence of persistent pain in the U.S. adult population: new data from the 2010 national health interview survey. J Pain. 2014;15(10):979–84.
52. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10:895–926.
53. Lavey R, Sherman T, Mueser KT, Osborne DD, Currier M, Wolfe R. The effects of yoga on mood in psychiatric inpatients. Psychiatr Rehabil J. 2005;28:399–402.
54. LeDoux J. Fear and the brain: where have we been and where are we going? Biol Psychiatry. 1998;44(12):1229–38.
55. Ledoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155–84. New York.
56. Lethem J, Slade PD, Troup JDG, Bentley G. Outline of a fear-avoidance model of exaggerated pain perception-I. Behav Res Ther. 1983;21(4):401–8. doi:10.1016/0005-7967(83)90009-8.
57. Lewis SS, Loram LC, Hutchinson MR, Li CM, Zhang Y, Maier SF, Huang Y, Rice KC, Watkins LR. Naloxone, an opioid-inactive toll-like receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats. J Pain. 2012;13(5):498–506.
58. Linehan MM. Cognitive-behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
59. Linton SJ. A review of psychological risk factors in back and neck pain. Spine. 2000; 25(9):1148–56.
60. Marlowe N. Self-efficacy moderates the impact of stressful events on headache. Headache. 1998;38:662–7.
61. Marchand S. The phenomenon of pain. Seattle: IASP Press; 2012.
62. Mayberg HS. Targeted electrode-based modulation of neural circuits for depression. J Clin Invest. 2009;119(4):717–25.
63. McCracken LM, Vowles KE. Acceptance and commitment therapy and mindfulness for chronic pain: model, process, and progress. Am Psychol. 2014;69(2):178–87.
64. Melzack R, Katz J. The gate control theory: reaching for the brain. In: Craig KD, Hadjistavropoulos T, editors. Pain: psychological perspectives. Mahwah: Lawrence Erlbaum Associates Publishers; 2004. ISBN 0-8058-4299-3.
65. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971–9.
66. Melzack R. Pain and the neuromatrix in the brain. J Dent Educ. 2001;65(12):1378–82.
67. Miller A. Ingenious pain. London: Scepter; 1997.
68. Morley JS. New perspectives in our use of opioids. Pain Forum. 1999;8(4):200–5.
69. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain. 1999;80:1–13. doi:10.1016/S0304-3959(98)00255-3.
70. Munro G. Dopamine D(1) and D(2) receptor agonism enhances anti-nociception mediated by the serotonin and noradrenaline reuptake inhibitor duloxetine in the rat formalin test. Eur J Pharmacol. 2007;575(1–3):66–74.
71. Natl. Cent. Heal. Stat. 2006. Available at: http://www.cdc.gov/nchs/data/hus/hus06.pdf.
72. National Research Council (US) Committee on Recognition and Alleviation of Pain in Laboratory Animals. Recognition and alleviation of pain in laboratory animals. Washington, DC: National Academies Press; 2009.

73. Neafsey EJ. Prefrontal control of the autonomic nervous system: anatomical and physiological observations. Prog Brain Res. 1990;85:147–65.
74. Nyanamoli B. The path of purification (Visuddhimagga). Kandy: Buddhist Publication Society; 1975.
75. Nyanaponika T. The heart of Buddhist meditation. Kandy: Buddhist Publication Society; 1954.
76. Ongür D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex. 2000;10(3):206–19.
77. Opler LA, Opler MGA, Arnsten AFT. Ameliorating treatment-refractory depression with intranasal ketamine: potential NMDA receptor actions in the pain circuitry representing mental anguish. CNS Spectr. 2015;21(1):12–22.
78. Pally R. How the brain actively constructs perceptions. Int J Psychoanal. 1997;78:1021–30.
79. Pally R. Non-conscious prediction and a role for consciousness in correcting prediction errors. Cortex. 2005;41:643–62.
80. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: a review of predictive factors. Anesthesiology. 2000;93(4):1123–33.
81. Perlman DM, Salomons TV, Davidson RJ, Lutz A. Differential effects on pain intensity and unpleasantness of two meditation practices. Emotion. 2010;10:65–71.
82. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PMRawlins JN, Tracey I. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci. 2001;21(24):9896–903.
83. Pradhan BK. Yoga and mindfulness based cognitive therapy: a clinical guide. Cham: Springer; 2014.
84. Pradhan BK, Pumariega AJ, Barnes A. Successful use of mindfulness based graded exposure therapy (M-BET) in adolescents with PTSD: a case series. Presented in the 21st World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP), Durban; 2014.
85. Pradhan BK, Gray RM, Parikh T, Akkireddi P, Pumariega A. Trauma Interventions using Mindfulness Based Extinction and Reconsolidation (TIMBER©) as monotherapy for chronic PTSD in adolescents: a pilot study. Adolescent Psychiatry. 2015;5(2):125–31.
86. Pradhan BK, Parikh T, Makani R, Sahoo M. Ketamine, transcranial magnetic stimulation (TMS) and depression specific Yoga-mindfulness based cognitive therapy (DepS Y-MBCT) in management of treatment resistant depression: Review and some data on efficacy. Depress Res Treat. 2015;2015:842817. doi:10.1155/2015/842817, Hindawi Publishing Corporation.
87. Pradhan BK, D'Amico JK, Makani R, Parikh T. Non conventional interventions for chronic post-traumatic stress disorder (PTSD): ketamine, repetitive transcranial magnetic stimulation (rTMS) and alternative approaches. J Trauma Dissociation. 2016;17(1):35–54.
88. Pradhan BK, Parikh T, Sahoo M, Pumariega A. Successful use of yoga-mindfulness based cognitive therapy (Y-MBCT) in comorbid panic and generalized anxiety disorders (GAD): a pilot study. Presented in Philadelphia in the annual conference of the Anxiety and Depression Association of America (ADAA); 2016. doi:10.13140/RG.2.1.2245.4163.
89. Pradhan BK, Sabia M, Jean S, Wainer I, Pumariega AJ. Ketamine and mindfulness based cognitive therapy in refractory PTSD: comparison of efficacy and metabolomics profiles (ongoing study at departments of Psychiatry and Anesthesiology at Cooper University Hospital, NJ and the Bio-analytic and Drug Discovery Division of the National Institute on Aging); 2016 unpublished data.
90. Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science. 2000;288(5472):1769–72.
91. Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. Clin J Pain. 2008;24(3):204–10.
92. Reuben DB, Alvanzo AA, Ashikaga T, Bogat GA, Callahan CM, Ruffing V, Steffens DC. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. Ann Intern Med. 2015;162(4):295–300.

93. Rhudy JL, Meagher MW. The role of emotion in pain modulation. Curr Opin Psychiatry. 2001;14:241–5.
94. Rosenzweig S, Greeson JM, Reibel DK, Green JS, Jasser SA, Beasley D. Mindfulness-based stress reduction for chronic pain conditions: variations in treatment outcomes and role of home meditation practice. J Psychosom Res. 2010;68:29–36.
95. Satchidananda S. The yoga sutras of Patanjali: translations and commentary. Yogaville: Integral Yoga Publications; 1978.
96. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology. 2008;47:670–8.
97. Shapiro D, Cook IA, Davydov DM, Ottaviani C, Leuchter AF, Abrams M. Yoga as a complementary treatment of depression: effects of traits and moods on treatment outcome. Evid Based Complement Alternat Med. 2007;4:493–502.
98. Shapiro SL, Carlson LE, Astin JA, Freedman B. Mechanisms of mindfulness. J Clin Psychol. 2006;62:373–86.
99. Sivananda S. Kundalini yoga. 10th ed. Himalayas: Divine Life Society Publication; 1994.
100. Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. Prog Neurobiol. 1992;38(4):397–421.
101. Trestman RL, Appelbaum K, Metzner J, editors. Psychiatric aspects of pain management. New York: Oxford University Press; 2015.
102. Turk DC, Meichenbaum D, Genest M. Pain and behavioral medicine: a cognitive-behavioral perspective. New York: Guilford Press; 1983.
103. Urban MO, Gebhart GF. Supraspinal contributions to hyperalgesia. Proc Natl Acad Sci U S A. 1999;96:7687–92.
104. Vallath N. Perspectives on yoga inputs in the management of chronic pain. Indian J Palliat Care. 2010;16(1):1–7.
105. Villemure C, Bushnell MC. Cognitive modulation of pain: how do attention and emotion influence pain processing? Pain. 2002;95:195–9.
106. Villemure C, Ceko M, Cotton VA, Bushnell MC. Insular cortex mediates increased pain tolerance in yoga practitioners. Cereb Cortex. 2014;24:2732–40.
107. Vogt BA, Sikes RW. The medial pain system, cingulate cortex, and parallel processing of nociceptive information. Prog Brain Res. 2000;22:223–35.
108. Wells RE, Burch R, Paulsen RH, Wayne PM, Houle TT, Loder E. Meditation for migraines: a pilot randomized controlled trial. Headache. 2014;54:1484–95.
109. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol. 1997;14(1):2–31.
110. Willis WD, Al-Chaer ED, Quast MJ, Westlund KN. A visceral pain pathway in the dorsal column of the spinal cord. Proc Natl Acad Sci U S A. 1999;96(14):7675–9.
111. Woolery A, Myers H, Sternlieb B, Zeltzer L. A yoga intervention for young adults with elevated symptoms of depression. Altern Ther Health Med. 2004;10:60–3.
112. Wren AA, Wright MA, Carson JW, Keefe FJ. Yoga for persistent pain: new findings and directions for an ancient practice. Pain. 2011;152:477–80.
113. Yang W, Dall TM, Halder P, et al. Economic costs of diabetes in the U.S. in 2012. Diabetes Care. 2013;36(4):1033–46.
114. Zeidan F, Gordon NS, Merchant J, Goolkasian P. The effects of brief mindfulness meditation training on experimentally induced pain. J Pain. 2010;11:199–209.
115. Zeidan F, Grant JA, Brown CA, McHaffie JG, Coghill RC. Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain. Neurosci Lett. 2012;520(2):165–73.
116. Zeidan F, Adler-Neal AL, Wells RE, et al. Mindfulness-meditation-based pain relief is not mediated by endogenous opioids. J Neurosci. 2016;36(11):3391–7.

Chapter 14
Complementary and Alternative Medicine

Robert G. Gessman

Complementary and Alternative Medicine Definitions and Classification

Alternative medicine is by definition a non-mainstream practice used in place of conventional medicine, whereas complementary medicine is used together with conventional medicine. Truly alternative medicine by this definition is rare in the United States. Complementary and alternative medicine (CAM) treatments, however, have become sufficiently popular that it seems inappropriate to continue grouping these modalities outside of the definition of "orthodox" or conventional practice. Integrative medicine may provide a more inclusive term given the expansion of evidence of treatments taking into account the body, mind, and spirit [2, 3].

History and Modern Perspective on Selected CAM Approaches

History of CAM in the USA

In 2007, a Center for Disease Control (CDC) National Health Statistics Report found that 38 % of US adults reported using CAM over the past year with the majority of use for the intention of overall wellness and pain management [4]. CAM treatments are perceived by patients to incorporate a balanced approach to overall wellness and the patient holism without the need to hyperfocus on potential underlying pathology. While there is no formal classification for CAM therapies, according to the National Health Interview Surveys (NHISs) the most popular CAM

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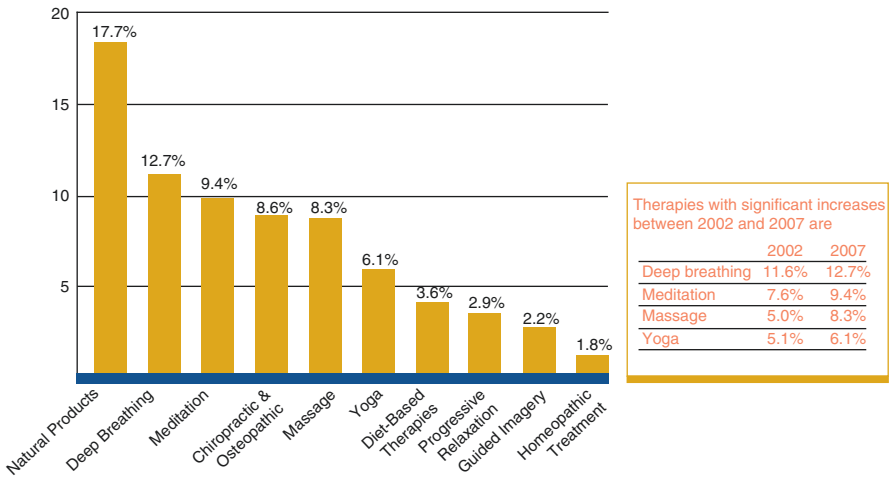

Fig. 14.1 Ten most common CAM therapies among US adults who reported CAM use within 1 year of being surveyed in the 2002 National Health Interview Survey on CAM from: Barnes et al. [4]

therapies in the USA are dietary supplements, mind–body practices including deep breathing, yoga, meditation, and manipulative practices including massage, chiropractic/osteopathic manipulation, and acupuncture. While urogenital pain is not among the most frequent conditions for which CAM therapies are utilized in the USA, CAM therapies are most commonly attempted for musculoskeletal conditions including back pain, neck pain, joint pain, and arthritis Figs. 14.1 and 14.2.

Acupuncture Analgesia

Traditional acupuncture is a Chinese medicine that has been practiced for thousands of years, dating back to 100 BC involving penetrating the skin at specific points of the body with thin, solid, metallic needles that can be attached to electrical stimulation [5]. Integral to the practice of acupuncture is the fundamental concept of Qi (pronounced *Tchee*) as the vital energy circulating the body through flow channels called meridians. Written during the Ming Dynasty (1368–1644), *The Great Compendium of Acupuncture and Moxibustion* was created to include 365 acupuncture points where the flow of Qi could be manipulated. This doctrine acts as the modern foundation of acupuncture practice [6].

Neurochemical Basis of Acupuncture and Electroacupuncture

While acupuncture was first considered for its use in anesthesia in the USA in the 1970s, it initially proved to be ineffective in this role as a means of surgical anesthesia [7]. However, the effects of acupuncture analgesia in humans were discovered to

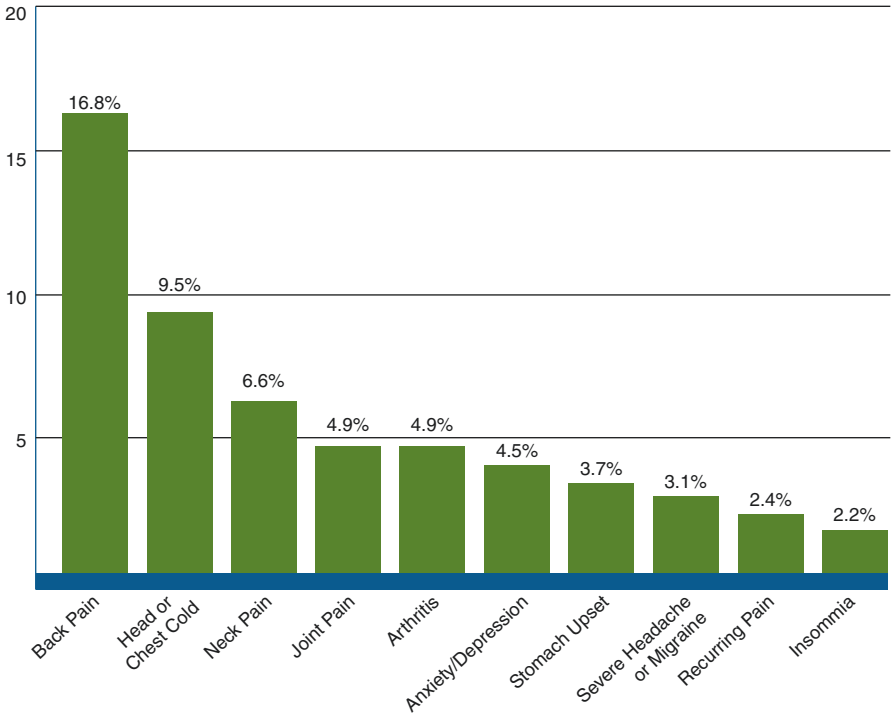

Fig. 14.2 Conditions for which CAM was most commonly reported among US adults who reported CAM use within 1 year of being surveyed in the 2002 National Health Interview Survey on CAM from: Barnes et al. [4]

be blocked by procaine infiltration at specific acupuncture points. It was further revealed that this peripheral afferent transmission pathway of acupuncture analgesia was not present in paraplegic/hemiplegic patients [8–10]. Studies by Pomeranz et al. suggest the importance of "De Qi" for successful analgesia and effective propagated sensation along acupuncture channels, where De Qi is described as the sensation felt by acupuncturists of the needle grab by muscle or by patient as a feeling of electrical activity or aching. This sensation was attributed to group III muscle afferent fibers given a study that acupuncture analgesia is blocked by injection of procaine into the muscle underneath the acupuncture point, whereas analgesia was not blunted by procaine injection at the subcutaneous layer of the acupuncture point [11]. To demonstrate the central nervous system's neurochemical role of acupuncture using an animal model, the cerebrospinal fluid from rabbits was removed after receiving finger acupuncture and was then transferred into the cerebral ventricles of rabbits that received no acupuncture, increasing the pain threshold of the recipient rabbits [12]. Human studies soon revealed the analgesic effect of acupuncture to be partially reversed with naloxone, indicating endogenous opioid involvement in acupuncture analgesia [13–15]. These results were verified through the study of healthy volunteers and patients with chronic pain [16, 17].

Research on the mechanism of the analgesic effect of electroacupuncture indicates that different neuropeptides are released using electroacupuncture with selected frequencies. Through compelling evidence, acupuncture shows effective stimulation of the production of endorphins, serotonin, and acetylcholine in the central nervous system, ultimately intensifying analgesia. Acupuncture has the ability to harmonize autonomic nervous system (ANS) and decrease inflammation within the inflammatory reflex located in the autonomous nervous system. Studies suggest that "electroacupuncture of 2 Hz accelerates the release of endogenous enkephalin, b-endorphin and endomorphin, while 100 Hz selectively increases the release of dynorphin. However, a combination of the two frequencies produces a simultaneous release of all four opioid peptides, resulting in a maximal therapeutic effect" [18].

Auricular Acupuncture

Auricular acupuncture is founded upon the principle that ear tissue has unique embryologic and neurologic derivations providing auricular points to serve as a microsystem referred to as a "reflex somatotopic systems" which acts as a microcosm of the whole body, perhaps through the modulation of reticular formation activity. Starting in the 1950s, Paul Nogier started scientific exploration and mapping of the auricular somatotopic microsystem illustrating a homuncular arrangement of the auricular reflex somatotopic systems with little divergence from the traditional Chinese auricular acupuncture charts as shown in Fig. 14.3 [19]. In the USA, a blinded experiment showed that 92 medical diagnosis could be identified by tenderness and examination of auricular somatotopic point pathology [20]. As with the somatotopic mapping of the brain, auricular somatotopic mapping indicates there is a disproportionately larger area dedicated to the head and hands compared to other parts of the body.

Auricular acupuncture is most frequently utilized for acute traumatic problems and superficial lesions, but is increasingly used for withdrawal and detoxification as well. It is also recommended for chronic conditions in conjunction with body acupuncture needling [21]. Preliminary evidence on the specificity of two auricular acupoints has been studied in a small group of humans using functional magnetic resonance imaging (MRI) to show that brain-specific activation patterns are indeed associated with the different auricular acupoints [22].

Acupuncture for Urogenital Pain

According to the Shao Yin energy axis method of acupuncture, the kidney is a vital organ, acting as the root of life, the root of Qi, the foundation of the Yin and Yang, as well as Water and Fire balances within the body. Kidney Yin is suggested to moisten and nourish while kidney Yang is suggested to warm and activate. The Kidney Principal Meridian depicted in Fig. 14.4 is a specific grouping of 27 points

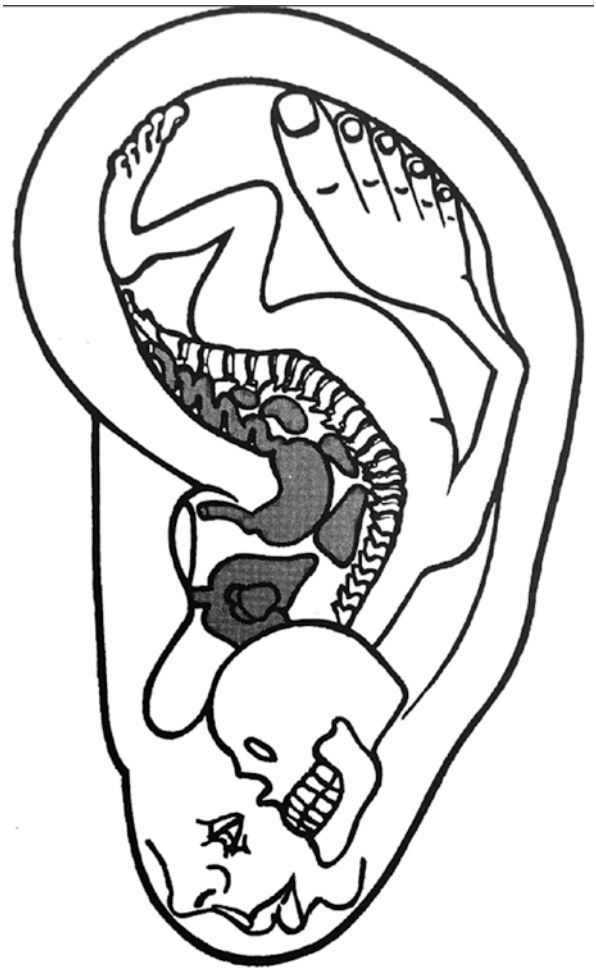

Fig. 14.3 Image of auricular somatotopic mapping illustrating a homuncular arrangement of the auricular reflex somatotopic systems (From: Helms [11])

that starts on the plantar surface of the foot (KI-1), travels to the medial surface of the ankle, and encircles the medial malleolus. It ascends along the medial leg to cross the pubic tubercle (KI-11), then travels parallel to the midline of the abdomen, along the costosternal border to its final point at the inferior border of the sternoclavicular junction (KI-27) [23]. Among these points, the most common points utilized and their related pathologies are listed below:

- KI-3: urinary frequency, menstrual disorders, sexual dysfunction, lumbar pain, edema of lower extremities, arthritic, and degenerative disease.
- KI-5: nephritis, renal colic, kidney failure, difficult urination, uterine prolapse, edema.
- KI-6: urinary retention, impotence, sterility, lower abdominal pain.
- KI-7: cystitis, orchitis, impotence, lumbar pain, edema.
- KI-10: nephritis, renal colic, cystitis, prostatitis, urination difficulty, deep lumbar stiffness and pain, lower abdominal pain, colitis, hemorrhoids.

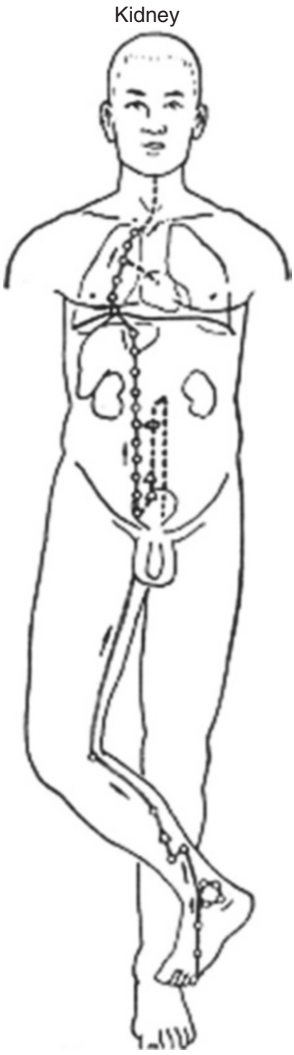

Fig. 14.4 Kidney principle meridian is a specific grouping of 27 points utilized for relief of an array of urogenital pain conditions (see text) (From: Alberta College of Acupuncture & Traditional Chinese Medicine: Kidney meridian (foot shao yin) Pathway)

The bladder principal meridian is a group of 67 points depicted in Fig. 14.5 starting at the inner canthus (BL-1) and climbs the orbit, then from forehead to occiput (BL-10) in parallel to midline. At BL-10, the meridian bifurcates into medial and lateral branches which travel parallel to the vertebral column along the sacrum. They cross the buttocks and meet at the popliteal fossa, then travel between the heads of gastrocnemius to the lateral border of the achilles tendon, then along the dorsal-plantar skin border to the lateral nail angle of the fifth toe (BL-67). Acupuncture of these points is typically utilized for symptoms of head, neck, back, groin, and buttock pain [24].

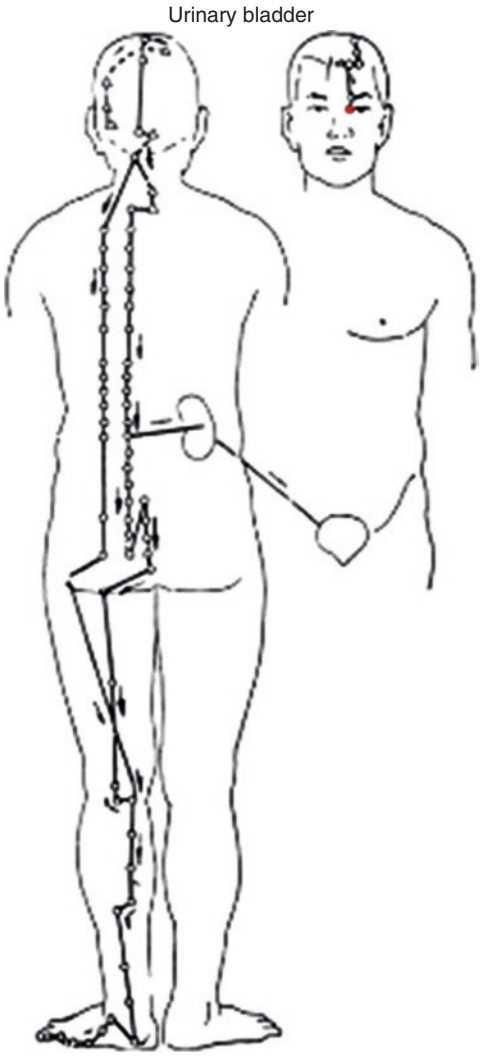

Fig. 14.5 Bladder meridian is a specific grouping of 27 points utilized for relief of an array of urogenital pain conditions (see text) (From: Alberta College of Acupuncture & Traditional Chinese Medicine: Urinary Bladder meridian (foot tai yang) Pathway)

Evidence for Acupuncture in Pain Management Practice

Acupuncture as an analgesic approach to acute pain, chronic pain, and specific pathologies, which continues to be scrutinized to determine if the effects are statistically significantly compared to placebo or "sham" acupuncture. "Sham" acupuncture refers to a variety of techniques which mimic acupuncture but either do not pierce the skin or do not use specific/traditional acupoints on the body. Table 14.1 summarizes modern western evidence regarding the use of acupuncture as it relates to pain management for specific conditions.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive, nonpharmacologic technique applying low-voltage electrical currents to the skin. TENS can be used solely as an intervention for mild to moderate pain or an adjunct to pharmacotherapy for moderate to severe pain. It can be applied with varying frequencies, from low (<10 Hz) to high (>50 Hz). Intensity may also be varied from sensory to motor intensities. The main techniques are acupuncture-like TENS (high intensity, low frequency), intense TENS (high intensity, high frequency), and conventional TENS (low intensity, high frequency), which is most commonly used in clinical practice.

History of TENS

Hieroglyphs dating as early as 3100 BC depicted electrogenic catfish as a method practiced by Ancient Egyptians to potentially treat ailments. In the first century AD, Roman Scribonius Largus used electricity from a large Mediterranean electric ray, *Torpedo marmorata*, to treat headaches and gout pain. Greek physician Galen also wrote that this fish may have been the best remedy known for epilepsy at the time. Electrostatic generators increased the use of electricity in medicine in the early 1900s, but lack of portability and increased focus on pharmacologic therapy lead to decreased use for pain management [25]. In 1965, Melzack and Wall published a paper summarizing literature on pain pathways, theorizing a gate-control system for pain perception (see Fig. 14.6) mediated by both peripheral and central input that can be modulated for analgesia by decreasing small fiber nerve input (Aδ) or activation of large fiber input (Aβ) [26]. Wall and Sweet went on to test this theory in humans and found that chronic pain could be modulated using high-frequency percutaneous electrical stimulation to activate large-diameter peripheral afferents (Aβ) to produce focal analgesia [27]. Central analgesic pathway in rats was demonstrated by Reynolds et al. with direct focal electrical stimulation of the periaqueductal gray region of the midbrain [28]. In 1967, neurosurgeon Dr Norman Shealy performed one of the first dorsal columns stimulation procedures in a human case report, showing this was a potential analgesic benefit, human application, and safety [29]. In 1974, the first portable TENS machine was patented in the United States by Don Maurer, one of the founders of the neurological division of Medtronic [30]. TENS was used as a predictive test in patients to determine the potential for success of dorsal column stimulation implants; however, many of these patients found relief with the TENS modality without necessity of an implant [31].

Table 14.1 Summary of modern evidence for acupuncture use for conditions causing urogenital pain

Pathology	Type of study	Number of Individuals	Conclusions
Back and neck pain, osteoarthritis, shoulder pain, or chronic headache	Meta-analysis of 29 randomized control trials	17,922	Acupuncture was superior to both sham and no-acupuncture control for each pain condition ($P<0.001$ for all comparisons)
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	Randomized control trial	89	After 10 weeks of treatment, acupuncture proved almost twice as likely as sham treatment to improve CP/CPPS symptoms. Participants receiving acupuncture were 2.4-fold more likely to experience long-term benefit than were participants receiving sham acupuncture
Chronic pelvic pain secondary to pelvic inflammatory disease	Prospective uncontrolled case series	30	Twenty-nine of the 30 patients (99.6 %) responded to acupuncture treatment and their pelvic pain resolved clinically with total resolution of pelvic pain and no new attack following 6 months of acupuncture therapy
Category IIIB chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	Prospective cohort study	93	Following six sessions of acupuncture to the BL-33 acupoints once a week statistically significantly decrease in all of the subscores evaluated at all periods compared with the baseline. Eighty-six out of 93 patients (92.47 %) were NIH-CPSI responders (more than 50 % decrease in total NIH-CPSI score from baseline) at the end of the treatment
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	Three-arm randomized control trial	39	At 6 weeks, the NIH-CPSI total score had decreased significantly in the electroacupuncture (EA) group compared with the sham EA and no EA control groups ($P<0.001$). Mean prostaglandin E(2) level in the post-massage urine samples had significantly decreased in the EA group ($P=0.023$)

(continued)

Table 14.1 (continued)

Pathology	Type of study	Number of Individuals	Conclusions
Premenstrual syndrome	Meta-analysis of ten randomized control trials	756	Acupuncture is superior to all controls (eight trials, pooled risk ratio (RR): 1.55, 95 % confidence interval (CI): 1.33–1.80, $P < 0.00001$). Effects of acupuncture compared with different doses of progestin and/or anxiolytics supported the use of acupuncture (four trials, RR: 1.49, 95 % CI: 1.27–1.74, $P < 0.00001$). Acupuncture significantly improved symptoms when compared with sham acupuncture (two trials, RR: 5.99, 95 % CI: 2.84–12.66, $P < 0.00001$). Note that most of the included studies demonstrated a high risk of bias in terms of random sequence generation, allocation concealment, and blinding
Adult cancer pain	Meta-analysis of 11 randomized control trials	–	No large trials were identified that had low risk of bias and positive results. The most common reasons reviewers assigned high risk of bias were problems with blinding patients and small sample size
Adult cancer pain	Meta-analysis of six randomized control trials	–	Effectiveness of acupuncture in palliative care for cancer patients is promising, especially in reducing chemotherapy or radiotherapy-induced side effects and cancer pain. Acupuncture may be an appropriate adjunctive treatment for palliative care
Adult cancer pain	Meta-analysis of three randomized control trials	204	One study showed acupuncture had lower pain scores at 2-month follow-up than either acupuncture at placebo auricular points or noninvasive auricular placebo group. The other two studies showed positive results favoring acupuncture compared to medication they were viewed suggested to be limited methodologically with small sample sizes, poor reporting, and inadequate analysis

Table 14.1 (continued)

Adult cancer pain	Meta-analysis of 15 randomized control trials	–	Acupuncture alone was not significantly better for pain management when directly compared to drug therapy ($n=886$; RR: 1.12; 95% CI: 0.98–1.28; $P=0.09$); however, acupuncture with concomitant drug therapy significantly improved pain compared to drug therapy alone ($n=437$; RR: 1.36; 95% CI: 1.13–1.64; $P=0.003$). High risk of bias and low methodological quality were noted in the meta-analysis
Primary dysmenorrhea	Meta-analysis of ten randomized control trials	673	Improvement in pain relief from acupuncture compared with a placebo control (OR: 9.5, 95% CI: 21.17–51.8), NSAIDs (SMD: −0.70, 95% CI: −1.08 to −0.32) and Chinese herbs (SMD: −1.34, 95% CI: −1.74 to −0.95). Results were limited by methodological flaws
Uterine fibroids	None of six randomized control trials met inclusion criteria for meta-analysis	–	Currently no high-quality adequate evidence available to allow assessment of the efficacy of acupuncture in the treatment of uterine fibroids
Dysmenorrhea/endometriosis	Meta-analysis of one included RCT	67	Dysmenorrhea scores were lower in the acupuncture group (mean difference: −4.81 points, 95% CI: −6.25 to −3.37, $P<0.00001$) scale. The total effective rate ("cured," "significantly effective," or "effective") for auricular acupuncture and Chinese herbal medicine was 91.9 and 60%, respectively (RR: 3.04, 95% CI: 1.65–5.62, $P=0.0004$). The improvement rate did not differ significantly between auricular acupuncture and Chinese herbal medicine for cases of mild to moderate dysmenorrhea, whereas auricular acupuncture did significantly reduce pain in cases of severe dysmenorrhea

(continued)

Table 14.1 (continued)

Pathology	Type of study	Number of Individuals	Conclusions
Primary dysmenorrhea	Meta-analysis of 27 randomized control trials	2960	The SP6 acupoint was commonly selected in 17 trials. Compared with pharmacological treatment or herbal medicine, acupuncture was associated with a significant reduction in pain. Three studies reported reduced pain within groups from baseline; however, two RCTs did not find a significant difference between acupuncture and sham acupuncture. Results were limited by methodological flaws and risk of bias
Provoked vestibulodynia (PVD)	Case series	8	Statistically significant improvements in pain with manual genital stimulation. Findings require replication in a larger, controlled trial before any definitive conclusions on the efficacy of acupuncture for PVD can be made

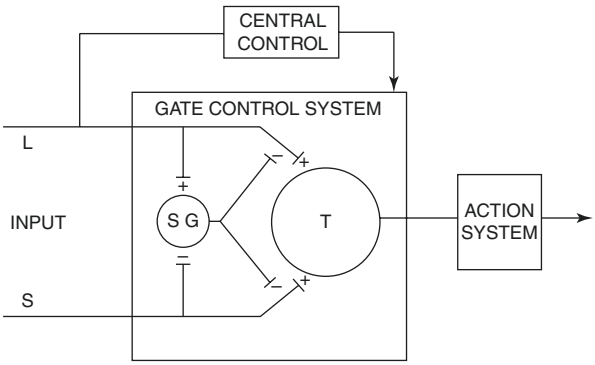

Fig. 14.6 Diagram of the gate-control theory of pain. Large-diameter nerve fibers (*L*) and small-diameter nerve fibers (*S*) project to the substantia nigra (*SG*) and first central transmission cells (*T*). S decreases inhibitory effect of SG on T and L increases inhibitory effect of SG on T. Excitation is indicated by (+) and inhibition by (−). Central control trigger is represented by a line running from L to central control mechanisms (From: Melzack and Wall [26])

TENS Mechanism of Action

Animal studies initially showed TENS analgesia to be mediated through both peripheral and central mechanisms. Centrally, the dorsal column of the spinal cord and brainstem utilizes opioid, serotonin, and muscarinic receptors to mediate TENS

analgesia, while peripherally opioid and α-2 noradrenergic receptors are involved [32]. The central mechanism of TENS activation was shown in animal studies through reduction of hyperalgesia with the application of TENS contralateral to the site of injury [33, 34]. TENS-induced small-diameter afferent (Aδ) activation causes long-term depression of central nociceptive cell activity for up to 2 h mediated by the activation of the midbrain periaqueductal gray and rostral ventromedial medulla (i.e., descending inhibitory pathways) and inhibition of descending pain facilitatory pathways [35].

Peripherally, the blockade of cutaneous afferents with EMLA cream (lidocaine and prilocaine emulsion) during TENS application had no effect on analgesia after induction of painful stimuli into the knee joint of rats, showing the importance of deep-tissue afferents at the site of TENS application (see Fig. 14.7). However, when local anesthetic was injected into the knee joint during TENS application, there was a complete blockade of the analgesic effects of TENS, showing TENS analgesia was mediated by large-diameter primary afferents from deep somatic tissues [36]. Human studies on pressure pain threshold at the dorsal interosseous muscle using an electronic algometer found that maximal TENS-induced hypoalgesia is obtained when high-intensity, "strong but comfortable" current is applied regardless of frequency [37].

Evidence for TENS Use for Analgesia

Patient experience and satisfaction suggest that TENS is useful as an analgesic modality as solitary treatment for mild to moderate pain or in combination with pharmacotherapy for moderate to severe pain. Systematic reviews of randomized controlled trials (RCT) on the clinical application of TENS as an analgesic modality for various types of pain have been inconclusive. This section summarizes modern literature on TENS as an analgesic intervention.

TENS for Postoperative Pain

An RCT of 100 women undergoing major gynecological, lower abdominal surgery with a standardized general anesthetic technique showed that TENS decreased postoperative opioid analgesic requirements and opioid-related side effects when utilized as an adjunct to patient-controlled analgesia (PCA) after lower abdominal surgery. The use of TENS at mixed (2- and 100-Hz) frequencies of stimulation produced a slightly greater opioid-sparing effect than either low- (2-Hz) or high (100 Hz)-frequencies alone [38].

Despite an earlier systematic review that showed no significant benefit from TENS on postoperative pain, a subsequent meta-analysis of 21 RCTs published in 2003, which included 11 trials and a total of 964 patients, found a mean reduction in analgesic consumption of 35.5 % (range 14–51 %) better than placebo. Of note,

inclusion criteria for TENS stimulus parameters for this meta-analysis were TENS titration to optimal treatment, defined as "strong, sub noxious electrical stimulation with adequate frequency at the site of pain." The median frequency of TENS usage from this study was 85 Hz. Patients in this meta-analysis were assumed to have free access to additional analgesics for supplementation to achieve a tolerable level of pain intensity [39].

TENS for Labor Pain

TENS electrodes are applied to the lower back over T10–L1 dermatomes 1.5–3 cm lateral to the spinous process bilaterally for the first stage of labor with a second set of electrodes placed over the S2–S4 dermatomes for the second stages of labor. Despite studies that have shown maternal satisfaction [40, 41] with TENS versus placebo, a systematic review of seven RCTs with a total sample size of 1168 on TENS for labor pain did not support the theory that TENS significantly provides more analgesia than placebo (sham TENS). It is worth noting that TENS was noted to show no mention of significant effect on fetal monitoring during this study [42].

TENS for Dysmenorrhea

In a case series on patients with primary dysmenorrhea, 102 nulliparous women previously being treated with pharmacologic agents were additionally treated with an experimental TENS device (Freelady, Life Care, Tiberias, Israel) to the lower abdomen: 56.9 % reported marked pain relief, 30.4 % reported moderate pain relief with the addition of TENS intervention, 58 % of patients reported self-discontinuation of other analgesic interventions, and 31 % reported decreased use of other analgesics. This study had no placebo control and was not randomized [43].

A Cochrane meta-analysis published in 2002 included 7 RCTs involving 164 women with primary dysmenorrhea high-frequency/conventional TENS, 50–120 Hz, was shown to be more effective for pain relief than placebo TENS (odds ratio (OR): 7.2; 95 % confidence interval (CI): 3.1–16.5) whereas low-frequency TENS (1–4 Hz), also referred to as acupuncture-like TENS, was found to be no more effective in reducing pain than placebo TENS (OR: 1.48; 95 % CI: 0.43–5.08) [44].

TENS for Acute Pain (<12 weeks)

A Cochrane meta-analysis published in 2015 included 6 of 19 analyzed RCTs (1346 patients) on the effects of TENS versus placebo (sham TENS without current) as a sole treatment for acute pain. The types of acute pain included in this

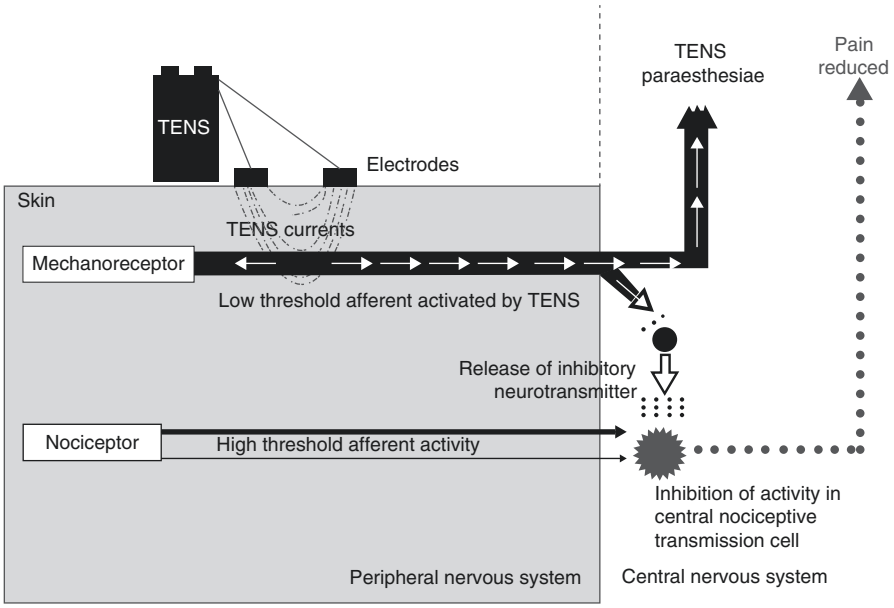

Fig. 14.7 Postulated mechanism of action for TENS-induced analgesia. TENS generates nerve impulses that will collide and extinguish noxiously induced impulses arising from peripheral structures (From: Jones and Johnson [109])

Cochrane review were procedural pain, for example, cervical laser treatment, venipuncture, screening flexible sigmoidoscopy, and nonprocedural pain, for example, postpartum uterine contractions, and rib fractures. The analysis provides tentative evidence that TENS reduces pain intensity greater with placebo (no current) TENS when administered as a stand-alone treatment for acute pain in adults. The authors noted that the quality of evidence was weak due to a high risk of bias associated with inadequate sample sizes and unsuccessful blinding; however, TENS should still be considered as a treatment option solely or in combination with other treatments for acute pain [45].

TENS for Chronic Pain

Nonrandomized controlled clinical trials have found benefit for many types of chronic pain but systematic reviews remain inconclusive for chronic pain. Meta-analyses for chronic musculoskeletal pain suggested that TENS is superior to sham TENS for pain and stiffness and patients may need to administer TENS throughout the day to achieve best effects [46]. A Cochrane meta-analysis on RCTs with consideration of TENS use for chronic neuropathic pain is pending investigation and additional studies for adequate powering [47].

TENS for Chronic Low Back Pain

A Cochrane qualitative synthesis of four high-quality RCT studies with 585 patients concluded that the evidence from the small number of available placebo-controlled trials does not support the use of TENS in the routine management of chronic low back pain. Consistent evidence in two trials (410 patients) showed that TENS did not improve back-specific functional status. There was moderate evidence that work status and the use of medical services did not change with TENS treatment [48].

TENS for Cancer-Related Pain

A Cochrane review of three RCTs (88 participants) showed no significant differences between TENS and placebo in women with chronic pain secondary to breast cancer or bone pain related to different types of cancer treatment. In the other RCT, there were no significant differences between acupuncture-type TENS and sham in palliative-care patients. The review concluded that there remains insufficient evidence to judge whether TENS should be used in adults with cancer-related pain and that additional large multicenter RCTs are necessary to assess the value of TENS for cancer-related pain [49].

TENS for Urogenital Pain

In a retrospective cohort of 100 patients at a urogenital pain clinic at The Institute of Urology and Nephrology in London, TENS was found to have benefit in some patients with interstitial cystitis, testicular pain, and dysmenorrhea. [50] No RCTs or reviews were found on literature review.

Contraindications of TENS

- Allergy to the pad contact material (tape/gel).
- Pad placement over broken, damaged skin, open wounds, skin with active dermatologic pathology, skin with diminished sensation or nerve damage.
- Pad placement over pacemaker.
- Pad placement over eyes.
- Pad placement over the anterior neck near or the carotid sinus.
- Pad placement in patients with active seizure disorders (can obfuscate identification of clinical seizure activity).
- Pad placement on abdomen in laboring patient if TENS interferes with fetal monitoring.
- Inability to understand/follow TENS instructions.

Yoga

In Sanskrit, the word "Yoga" comes from the root *yug* (to join), or yoke (to bind together or to concentrate). The modern definition of yoga is a mind and body practice with a focus on exercise, breathing, and meditation that originates from ancient Indian philosophy driven by the desire for improvement of personal health, awareness, freedom, and longevity [51].

Brief History of Yoga

Origins of Yoga techniques date back to stone carvings found at archaeological sites in the Indus Valley dating back more than 4000 years, predating written history [52]. Since this time, the tradition of Yoga practices has evolved as they have passed from teacher to student through direct instruction and demonstration. The Vedas is the sacred scripture of Brahmanism dating to the twelfth to tenth centuries BCE that is the basis of modern-day Hinduism, which may contain the oldest documented Yoga teachings [53]. Later, around 500 BCE the Bhagavad-Gita was a scripture dedicated to yoga and has served as a philosophical inspiration for Hindu religion. Buddhism and Hinduism incorporate aspects of yoga and meditation as a means to quiet the mind and create a sense of space in the body, striving to achieve enlightenment through transcendence of the limitations of the mind [54].

Patanjali, considered "the father of yoga," compiled oral traditions into "The Yoga Sūtras" around 400 CE creating the collective foundation of what is now Classical Yoga or "Ashtanga" (eight-limb) Yoga, providing guidance on how to master the mind to achieve spiritual growth [51]. According to the American Yoga Association, Yoga was first practiced in the USA in the 1800s by a select few but was not commonly practiced until the 1960s when interest grew for Eastern philosophy and culture. Americans travelled to India to learn Yoga and invited yogis to the USA such as B.K.S. Iyengar and Pattabhi Jois to teach yoga workshops [55]. Today, over 100 different schools of yoga are now practiced worldwide. Most of these schools fall under the "Hatha Yoga" umbrella, which emphasizes *Asana* [posture] and *Pranayama* [breath control] techniques sometimes practiced without the broader philosophic focus of the other more spiritual limbs of yoga [51]. Yoga is now commonly performed in western culture without religious intention [56]. Instead, yoga is often practiced as a preventative health measure with benefits such as reducing stress and improving overall physical fitness, strength, and flexibility, but it can also have deleterious health effects if practiced improperly. Table 14.2 summarizes some yoga positions that have shown benefits for urogenital pain conditions. While some schools of yoga incorporate rapidly transitioning, self-guided poses, Iyengar Yoga is a particular school of yoga that may be better suited for chronic pain patients, offering customized poses and use of props such as blankets, belts, blocks, and chairs to assist students in optimizing benefits while preventing injury. Iyengar Yoga emphasizes individualized attention and emphasis on the

Table 14.2 Urogenital conditions and yoga postures that may be beneficial [106]

Clinical presentation and sample beneficial postures for urologic conditions [8, 12]			
Pelvic floor hypotomicity	Stress urinary incontinence, cystocele, rectocele, vaginal prolapse, uterine prolapse	Frog prose (with kegels)	Strengthen pelvic floor, realignment of coccyx and sacroiliac joint, loosen tight pelvic muscles
		Sitting forward bend	Improves back muscle strength, increases back flexibility, increases flexibility in hips
		Shoulder stand/ fish-pose set	Strengthens pelvic floor muscles (PFM), increases neurotransmitter production, decreases muscle tension in back, greatly increases torso muscle strength
		Locust pose	Increases upper body strength and back flexibility
		Plank pose	Increases upper body strength, especially good for patients who are very weak in their upper body
		Bird pose	Improves hip and shoulder flexibility
		Seated twist	Improves hip and spine flexibility
		Basic deep breathing, lying flat on back	Provides cool down, helps reduce tension
		Resting pose, lying flat on back	Provides cool down, helps reduce tension
Pelvic floor hypertonicity	Prostatodynia, vulvodynia, chronic orchitis, chronic epididymitis, interstitial cystitis	Bridge pose	Restores flexibility in hips, strengthens torso and leg muscles
		Cobra pose	Reduces muscle tension in back
		Cow pose	Relaxes tension in hips, back, and shoulders
		Crocodile pose	Increases upper body and back strength
		Downward-facing dog	Improves sacroiliac joint function, strengthen upper body
		Frog pose	Realigns sacroiliac and coccyx, stretch and relieves tension in PFM

Table 14.2 (continued)

Clinical presentation and sample beneficial postures for urologic conditions [8, 12]			
		Half-shoulder stand/fish-pose set	Teaches pelvic floor muscle awareness, decreases tension in lower back and PFM, strengthens torso muscles
		Kegels (very gentle version)	Decreases muscle tension in hips/pelvis
		Locust pose	Increases upper body strength and back flexibility
		Side leg lifts	Reduces side hip and waist muscle tension, strengthens side hip and waist muscles, stretches PFM
		Squatting pose	Greatly increases hip, pelvic, and leg strength and flexibility
		Twist (seated)	Improves hip and spine flexibility
		Wind reliving	Improves leg, hip, and pelvic flexibility Aids in concentration, helps reduce stress
		Alternate nostril breathing sitting	Cool down, helps reduce stress, releases tension in lower back and pelvic muscles

Adapted from: Ripoll and Mahowald [106]

alignment and precision of postures for particular pain pathologies. One example of Iyengar poses recommended for urogenital pain is shown below in Fig. 14.8, which depicts extended triangle pose, suggested to tone abdominal and pelvic organs and help relieve menstrual pain. This form of yoga also has the most robust certification process in the USA, requiring a minimum of 3 years of continuous training before one can begin the mentoring and teaching education process required to apply for certification to teach Iyengar Yoga [57].

Role of Yoga in Pain Management

According to the 2007 NHIS, yoga is the sixth most common complementary health practice among adults in the USA. This survey conducted between 2002 and 2007 found that over 13 million adults practiced yoga in the previous year [58]. As yoga has grown in popularity in the USA, western medicine has increasingly researched the ancient practice for evidence of health benefits including pain management. Many of the studies to date have been limited by

Fig. 14.8 Extended triangle pose, suggested to tone abdominal and pelvic organs and help relieve menstrual pain [107] (From: Sorosky et al. [107])

heterogeneity related to intervention content and delivery, specifically lack of standardization of yoga postures/practice. A bibliometric review of available publications on yoga research between 1967 and 2013 found a threefold increase in the number of publications in the last decade, signaling that yoga research is a field undergoing substantial growth and interest. The distribution of disorder categories for which yoga has been studied is shown in Fig. 14.9 with a limited number specific to urogenital pain syndromes. The top three disorders addressed by yoga interventions were mental health, cardiovascular disease, and respiratory disease [59].

Despite heterogeneity limitations, a meta-analysis of 16 controlled clinical studies including 1007 participants on the effectiveness of yoga on pain and pain-associated disability suggests that yoga has a moderate effect on pain and associated disability from several conditions including back pain, headache/migraine, and rheumatoid arthritis [60]. A systematic review of ten RCTs including 967 patients with chronic low back pain found strong evidence for short-term and long-term effects of yoga on pain and short-term pain-associated disability. This study also found moderate evidence for long-term effect on pain-associated disability [61]. A meta-analysis of nine RCTs performed in 2011 suggested that yoga leads to

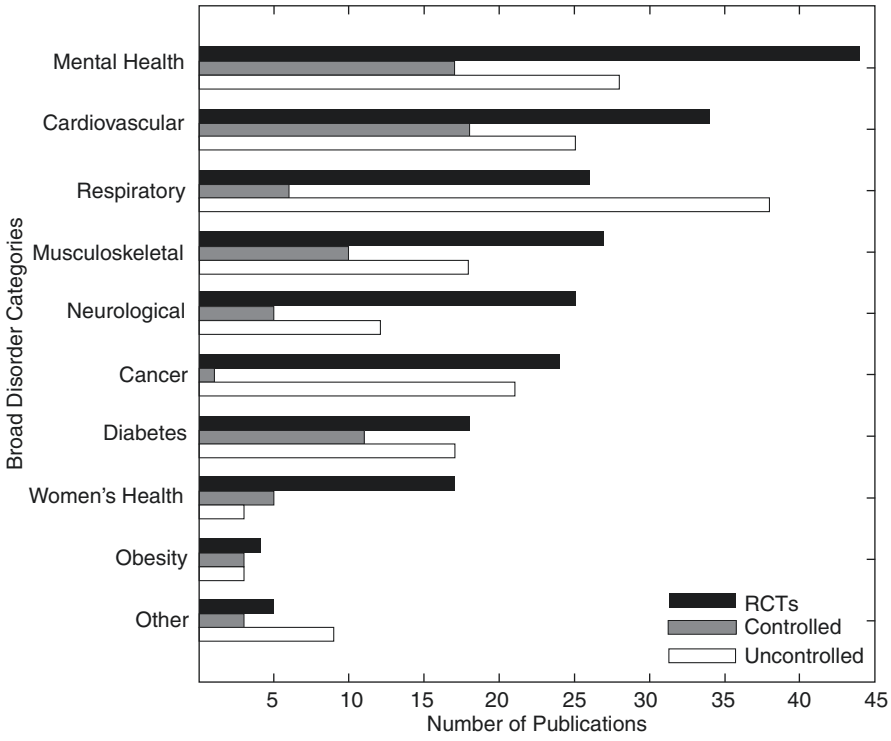

Fig. 14.9 Distribution of disorder categories for which yoga has been researched in publications between 1967 and 2013 [59] (From: Jeter et al. [61])

a significantly greater reduction in pain when compared to control interventions such as standard care, self-care, therapeutic exercises, relaxing yoga, touch and manipulation, or no intervention [62].

Benefits of yoga for the management of pain may have a more central foundation beyond the musculoskeleton. A cross-sectional study published in the *Cerebral Cortex* submitted 14 experienced yoga practitioners, as well as 14 people who did not practice any mind–body techniques to a cold-pain tolerance test in which a hand was immersed in cold water until it could no longer be tolerated while brain imaging was being performed on the participants. The researchers found that yoga practitioners tolerated cold pain more than twice as long as the controls and yoga practitioners had greater mid-insular cortex gray-matter volume, an area known to be related to pain processing, pain regulation, and attention. The volume of insular gray matter in yoga practitioners also correlated positively with the duration of yoga practice [63]. A review of the effect of meditation on pain perception incorporating neuroimaging studies and neurophysiological studies such as functional MRI, magnetoencephalography, and electroencephalography suggests that meditation reduces pain-related neural activity in the anterior cingulate cortex, insula, secondary somatosensory cortex, and thalamus [64].

As more studies on the effects of yoga continue to be conducted, many physicians cite not just scientific results but a wealth of anecdotal information suggesting that yoga helps people feel more in control of their physical well-being and more capable of overcoming causes of pain. Practitioners also report greater relaxation which can help increase tolerance to pain sensations. Yoga can instill an overall perception of health and balance, which can mitigate feelings of limitation and disappointment associated with physical discomfort.

Herbal-Based Treatments

Introduction

Since antiquity, plants and their by-products have been primary sources of food, shelter, clothing, medicine, and numerous other uses for mankind. Many of the modern medicines we have today find their roots in plants from which therapeutic compounds have been isolated, concentrated, replicated, and sometimes altered. Early civilizations including Americans, Hindus, Babylonians, Persians, Romans, Chinese, and Greeks utilized plant resins and fragrances for cultural, ritualistic, and religious activities to soothe both humans and appease their gods [65]. In modern times, herbal-based treatments have become the most popular form of CAM therapy in the USA, with the most commonly utilized products shown in Fig. 14.10 (note: urogenital pain was not one of the more common conditions for which herbal therapy use was reported according to this study) [4]. According to a 2007 NHIS, "non-vitamin, nonmineral, natural products" accounted for almost 44 % of out-of-pocket costs for CAM therapy in the USA, amounting to approximately $14.8 billion [66]. This section focuses on the anti-inflammatory and analgesic properties of herbs with the most common use and robust support in the literature for urogenital conditions including *Boswellia*, *Arnica*, Capsaicin, and Chinese Herbal Medicine and their utility for pain management and application for urogenital pain.

Boswellia serrata

Boswellia serrata tree resin, commonly referred to as Frankincense or Olibanum, is native to Arabia and India. Resin contains mono-, di-, triterpenes, tetracyclic triterpenic acids, and four major pentacyclic triterpenic acids known as β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid, and acetyl-11-keto-β-boswellic acid, responsible for the inhibition of pro-inflammatory enzymes. Of these compounds, the most potent inhibitor of 5-lipoxygenase and also the most potent anti-inflammatory enzyme is acetyl-11-keto-β-boswellic acid (AKBA). *Boswellia* resin has shown to have significant anti-inflammatory effects in animal models and human studies on osteoarthritis and rheumatoid arthritis [65]. *Boswellia* is also one

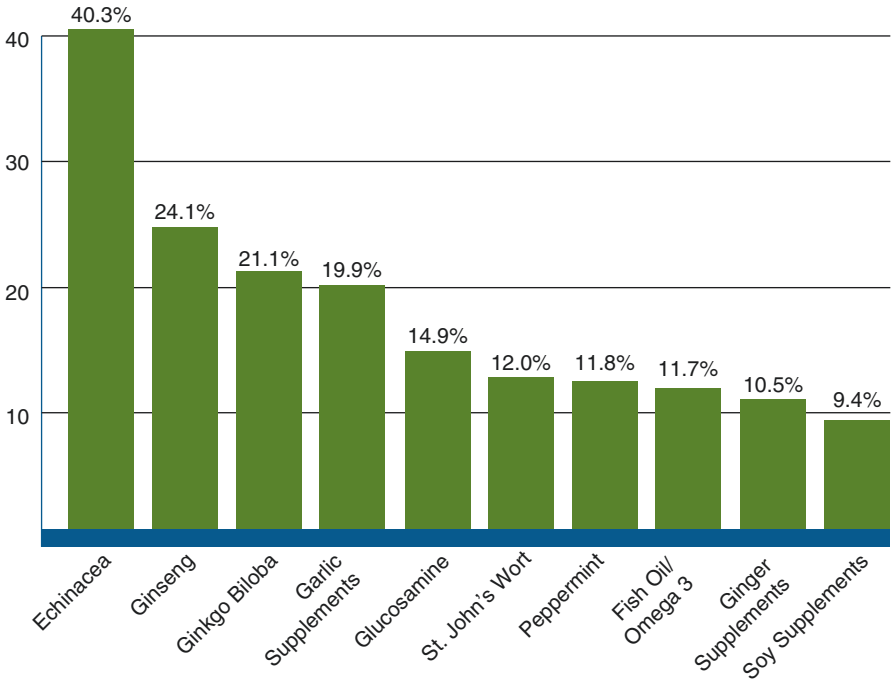

Fig. 14.10 Ten most common natural products utilized by adults who reported the use of a nonvitamin, nonmineral, natural products within 1 year of being surveyed in the 2002 National Health Interview Survey on CAM [4] (From: Barnes et al. [4])

of the more thoroughly studied herbs, likely due to its efficacy in vitro and in early in vivo investigations.

AKBA has also been shown to potently inhibit human prostate tumor growth through inhibition of angiogenesis induced by vascular endothelial growth factor receptor 2 (VEGFR2)-signaling pathways [67]. Some of the branded formulations containing *B. serrata* are available for purchase in the USA. A meta-analysis of seven RCTs on the medical effectiveness of *Boswellia* resin found that *Boswellia* is clinically effective for conditions caused or maintained by inflammatory processes including asthma, rheumatoid arthritis, Crohn's disease, osteoarthritis, and collagenous colitis. In the included trials, no serious, long-term, or irreversible adverse effects or drug interactions were noted [68]. A systematic review of plant food supplements with anti-inflammatory properties concluded *Boswellia* to show the best efficacy in treating pain (308 patients in 6 studies noted benefit after treatment vs. no benefit in 72 patients) and inflammatory conditions but additional, well-designed RCTs are needed to determine the efficacy of other herbal preparations [69].

In relation to urogenital pain, Chinese herbs of Myrrh and Frankincense are often combined for treating some inflammatory pain diseases with synergistic therapeutic effects. Analgesic activity of frankincense was compared to myrrh extract versus the combination for oxytocin-induced dysmenorrhea in mice by measuring writhing

times. This study concluded that the combined herbs significantly reduced the writhing times and prolonged the latency period ($P<0.01$) indicating improvement in dysmenorrhea analgesia in mice [70].

A systematic review of three RCTs showed that *Capsicum frutescens* (Cayenne) reduces acute and chronic low back pain more than placebo in humans in the short term. There was less evidence available to support that *Harpagophytum procumbens*, *Salix alba*, *Symphytum officinale* L., *Solidago chilensis*, and lavender essential oil reduce pain more than placebo [71].

In an RCT of *Boswellia* (900 mg daily divided in three daily doses) versus sulfasalazine in 30 patients with chronic colitis over 6 weeks, 70% in the *Boswellia* treatment group went into symptom remission versus 40% of those treated with chronic colitis gold-standard treatment, sulfasalazine. Ninety percent of the patients treated with *Boswellia* showed an improvement in laboratory or histopathology measurements of inflammation versus 60% in the control group that received sulfasalazine [72]. A randomized, placebo-controlled, double-blind trial of *B. serrata* in maintaining remission of Crohn's disease showed no significant benefit versus placebo. However, the mean time to diagnosis of relapse was decreased to 171 days for the *Boswellia* group and 185 days for the placebo group ($P=0.69$). No advantages of *Boswellia* were detected in laboratory measurements of inflammation versus placebo but *Boswellia* displayed a good safety profile [73].

A small study of $n=12$ healthy human adults compared analgesic activity of single oral dose (125 mg, two capsules) of *B. serrata* to placebo using mechanical pain analgesiometer (by Randall–Selitto test) and found that pain tolerance had increased significantly ($P\leq0.01$) with *B. serrata* when compared to placebo at 1, 2, and 3 h [74].

Arnica

Arnica montana is a member of the sunflower family shown in Fig. 14.11 also known by the names "Mountain tobacco," "Leopard's bane," or "Mountain arnica" and has been one of the most popular homeopathic remedies to treat bruises, sprains, arthritic pain, and muscle aches in the USA and Europe [75]. While in vitro studies have shown *Arnica* to contain antimicrobial and anti-inflammatory properties, a systematic review of homeopathic arnica studies determined *Arnica* to have no statistically significant effect in these uses compared to placebo [76]. In relation to urogenital pain, Hart et al. conducted a double-blind placebo controlled investigation of oral arnica for the treatment of pain and infection prevention after hysterectomy in 73 women. Patients were randomized to receive 2 doses of arnica 30 C or placebo the day prior to hysterectomy and three daily doses postoperatively for 5 days. No significant difference was observed between *Arnica* and placebo on infection rate or postoperative pain [77]. Recently, the action of one of the Brazilian *Arnicas*, *S. chilensis*, was evaluated in treating lumbago in a double-blind placebo control trial in which 10 g of 5% *S. chilensis* extract in glycol gel was applied twice

Fig. 14.11 *Arnica montana* is a member of the sunflower family also known by the names, "Mountain tobacco," "Leopard's bane," or "Mountain arnica" [108] from Wikipedia: Arnica

daily to skin of ten volunteers with lumbago for 15 days and compared to the application of 10 g of placebo gel in ten volunteers also with lumbago. Analog visual pain scores and flexibility measured by the modified Schober method were recorded in both groups. The study concluded that the *Arnica* gel application group showed a significant improvement in pain perception and lumbar flexibility after 15 days of treatment compared to placebo gel [78].

While some evidence exists in support of the use of *Arnica* as a medical therapy for specific pathologies, at this time the majority of randomized clinical trials suggest that homeopathic arnica is no better than placebo in treating bruising, swelling, and pain. Further trials involving larger cohorts are needed to support the benefit of *Arnica* for inflammation or pain management [75, 79].

Capsaicin

Capsaicin is the active component derived from the fruit of capsicum, also known as cayenne pepper. While oral formulations are generally not utilized for pain management, capsaicin has been used as an active ingredient in topical remedies for its anti-inflammatory properties to relieve muscle and arthritic types of pain, neuropathic

pain, and psoriasis. The analgesic mechanism of action of capsaicin has been linked to depolarization of C-fiber polymodal nociceptors, release of substance P, and agonism of transient receptor potential vanilloid subfamily member 1 (TRPV1) [80, 81]. The initial painful, burning sensation has been attributed to the initial increase in substance P. Following this initial neuronal excitation, a refractory period creates long-term nerve terminal defunctionalization [82, 83].

There is weak to moderate evidence to support its efficacy over placebo as an adjunct for musculoskeletal pain (0.025 % cream four times daily), diabetic neuropathic pain (0.075 % cream three to four times daily for 8 weeks), and painful human immunodeficiency virus (HIV)-associated sensory neuropathy (high-concentration 8 % transdermal patch in a single application lasting either 30, 60, or 90 min) [84, 85]. The high-concentration 8 % transdermal capsaicin patch was also shown to be safe and effective compared to placebo for the treatment of postherpetic neuralgia; however, it is less effective than its utility for musculoskeletal or diabetic neuropathic pain [84, 86]. Studies also support benefits of topical low-concentration capsaicin for psoriasis, while its utility for rheumatoid arthritis remains inconclusive [87, 88]. There is insufficient evidence to support the use of capsaicin specifically for urogenital pain etiologies.

Herbal Treatments and Chinese Herbal Medicine for Female Urogenital Pain

Herbal preparations are commonly used alternatives or supplements for the treatment of female urogenital pain caused by pathologies including uterine fibroids, dysmenorrhea, endometriosis, premenstrual syndrome, and recurrent urinary tract infections. The first book of Chinese medicine devoted to obstetrics and gynecology topics dates back as far as 1237 A.D. [89]. Mechanisms of action of Chinese medicine for female urogenital disorders are suggested to stem from the regulation of endocrine and immune systems, improvement of blood circulation, and anti-inflammatory activity [90].

A Cochrane systematic review of 21 randomized clinical trials involving 2222 women with uterine fibroids found insufficient evidence to support or refute the effectiveness of herbal preparations for symptomatic relief due to study design flaws. However, the review noted that there are some small, low-quality studies that support the use of *Tripterygium wilfordii* and Guizhi Fuling in reducing the volume of uterine fibroids [91]. A similar Cochrane systematic review of two low-quality RCTs including 158 women found that oral plus enema administration of Chinese herbal medicine (Nei Yi Wan, composed of turtle shell, vinegar-treated rhubarb, and succinum) following endometriosis surgery showed a greater reduction in pain scores and adnexal mass size compared to danazol treatment with fewer side effects than conventional danazol or gestrinone therapies [92].

Herbal Treatments for Male Urogenital Pain

Benign prostatic hypertrophy (BPH) is one of the most common prostate problems encountered by men over age 50 and can result in significant discomfort and even pain in this population. As such, numerous studies have been performed to evaluate the efficacy of natural treatments for this condition. *Pygeum africanum* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures versus placebo with those in the treatment group more than twice as likely to report an improvement in overall symptoms. [93] A review found that beta-sitosterol treatments were well tolerated and improved urinary symptoms and flow measures in men with mild to moderate BPH; however, treatment did not significantly reduce prostate size compared to placebo [94]. On the contrary, systematic review on the effects of the saw palmetto plant extract, *Serenoa repens*, at double and triple doses, did not improve urinary flow measures or prostate size in men with lower urinary tract symptoms consistent with BPH despite initial studies that suggested some benefit [95].

Future of Herbal-Based Treatments

While herbal-based treatments account for the majority of CAM therapy utilized in the USA and evidence is emerging to support its use within western medicine, additional research is needed to elucidate the precise benefits and roles of individual therapies.

Reiki Therapy

Definition and Brief History

The word Reiki is derived from the Japanese words “Rei” which represents “God’s Wisdom or the Higher Power” and “Ki” which represents “life force.” [96] Reiki is a 2500-year-old treatment encompassing both spiritual and physical healing suggested to work by optimizing flow of “life force,” through either physical contact or from a distance through pathways such as chakras and meridians as well as flowing around the body in a field of energy called the aura. Reiki does not associate with religious beliefs but one of the accepted definitions of Reiki is “the energy of life that is being guided by the Great Universe (the Universal Being of Wisdom and Love)” [97]. Reiki theory describes how life force can be disrupted by negative thoughts or feelings and how Reiki therapy can raise the vibratory level of the energy field to improve flow of life force [96]. Reiki is estimated to be practiced by over four million around the world with over one million Reiki Masters on record [98].

The Role of Reiki for Pain Management

Although noted as an ancient practice, Reiki has grown in national acceptance and incorporation into western medicine. The Center for Reiki Research website lists 68 hospitals in the USA that offer Reiki therapy to their patients and quotes a 2007 American Hospital Association survey that reported 15 % or over 800 American hospitals offered Reiki as part of hospital services [99]. The Society for Integrative Oncology (SIO) recommends Biofield therapies for cancer patients based on the safety profile, but have yet to promote the use due to limitations of available evidence [100].

Preliminary evidence continues to expand for Reiki and other Biofield therapies. In a laboratory study, Reiki performed at a distance using rats significantly reduced stress response as measured by rise in heart rate with loud noise exposure relative to Sham Reiki [101]. A review of available RCTs indicates that there is evidence to suggest that Reiki therapy may be effective for pain and anxiety; however, many of these trials are inadequately powered or controlled [102]. A phase II trial of Reiki versus rest on patients with cancer pain showed lower visual analog scale (VAS) pain ratings and improved quality of life as assessed by questionnaire but no reduction in opioid use [103].

With regard to the application of Reiki therapy for urogenital pain management, Reiki has been studied for menopause-related pain and pain following elective cesarean sections (C-sections). A systematic review of 12 RCTs evaluating Reiki treatment for the management of menopause-related pain found that nine of the 12 trials detected a significant therapeutic effect of the Reiki intervention but noted that these studies were limited by the lack of blinding or randomization [104]. In a study of women undergoing elective C-section, distant Reiki was compared to usual care but distant Reiki had no significant effect on opioid consumption or the area under the VAS-time curve but resulted in a significantly lower heart rate and blood pressure post C-section [105].

Future of Reiki for Pain Management

While promising evidence is emerging in support of Reiki therapy for pain management, additional high-powered, high-quality studies are needed to evaluate the potential clinical benefits and limitations of this type of Biofield therapy.

Future of CAM in the USA

As western medicine and culture continues to repopularize historically utilized modalities and adopt a more holistic approach to health care, research continues to expand our knowledge on the benefits of CAM therapies. The evidence put forth in this chapter suggests the benefits of many CAM therapies with little potential for

harm noted in the available literature. While some US medical schools are beginning to incorporate education on CAM therapies as elective curriculum to introduce students to the philosophy of integrative medicine, the future may see evidence-based CAM therapies incorporated into required curriculum as patient preferences continue to drive the evolution and scope of health care and its offerings. Perhaps, the future of CAM therapy will see new systems of accreditation and standards of quality for these treatment modalities as they continue to be scrutinized and researched. Interestingly, therapies may at some point reach popularity that they are no longer complementary or alternative, but rather part of the accepted standard of care for the treatment of specific pain condition.

References

1. Furnham A, Forey J. The attitudes, behaviors and beliefs of patients of conventional vs. complementary (alternative) medicine. J Clin Psychol. 1994;50(3):458–69.
2. National Center for Complementary and Integrative Health. Complementary, alternative, or integrative health: what's in a name? https://nccih.nih.gov/health/integrative-health, Accessed 27 Dec 2015.
3. Rakel D. Integrative medicine. 3rd ed. Philadelphia: Saunders; 2012. p. 2–11.
4. Barnes PM, Bloom B, Nahin R. CDC National health statistics reports #12. Complementary and alternative medicine use among adults and children: United States, 2007. Dec 10, 2008. https://nccih.nih.gov/sites/nccam.nih.gov/files/news/nhsr12.pdf. Accessed 27 Dec 2015.
5. NIH: National Center for Complementary and Integrative Health. Acupuncture https://nccih.nih.gov/health/acupuncture. Accessed 27 Dec 2015.
6. White A, et al. A brief history of acupuncture. Rheumatol/Br Soc Rheumatol. 2004; 43:662–3.
7. Dimond EG. Acupuncture anesthesia. Western medicine and Chinese traditional medicine. J Am Med Assoc. 1971;218:1558–63.
8. Chiang CY, Chang CT, Chu HL, Yang LF. Peripheral afferent pathway for acupuncture analgesia. Sci Sin. 1973;16:210–7. 3. Research Group of Acupuncture Anesthesia,Peking Medical College. Effect of acupuncture on the pain threshold of human skin. Nat Med J China. 1973;3:15 1–57 (In Chinese, English abstr).
9. Research Group of Acupuncture Anesthesia, Peking Medical College. Comparison of the analgesic effect of acupuncture and transcutaneous electric stimulation. In: Selected papers on theoretical studies of acupuncture anesthesia. Shanghai: People's Press; 1973. p. 12–8. 264 pp. (In Chinese).
10. Department of Physiology, Shanghai First Medical College, Shanghai First Tuberculosis Hospital and Shanghai Institute of Acupuncture and Moxibustion. The effect of acupuncture on the pain threshold of normal humans. Selection of research on acupuncture anaesthesia, Shanghai People's Press. 1973. pp. 33–39 (in Chinese).
11. Helms J. The science of acupuncture. In: Acupuncture energetics: a clinical approach for physicians. 1st ed. Berkeley: Medical Acupuncture; 1995. p. 33.
12. Research Group of Acupuncture Anesthesia, Peking Medical College. The role of some neurotransmitters of the brain in finger-acupuncture analgesia. Sci Sin. 1974;17:112–30.
13. Mayer DJ, Price DD, Rafii A. Acupuncture hyperalgesia: evidence for activation of a central control system as a mechanism of action. First World Congr. Pain, Florence; 1975. p. 276 (Abstr.).
14. Mayer DJ, Price DD, Rafii A. Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. Brain Res. 1977;121:368–72.

15. Pomeranz B, Chiu D. Naloxone blocks acupuncture analgesia and causes hyperalgesia: endorphin is implicated. Life Sci. 1976;19:1757–62.
16. Jiang ZY, Ye Q, Shen YT, Zhu FX, Tang SQ, Liang NJ, Zeng XC. Effects of naloxone on experimental acupuncture analgesia evaluated by sensory decision theory. Acta ZooL Sin. 1978;24:1–8. In Chinese, English abstr.
17. SjOlund B, Eriksson M. The influence of naloxone on analgesia produced by peripheral conditioning stimulation. Brain Res. 1979;173:295–301.
18. Han J-S. Acupuncture and endorphins. Neurosci Lett. 2004;361:258–61.
19. Helms J. Auricular acupuncture. In: Acupuncture energetics: a clinical approach for physicians. 1st ed. Berkeley: Medical Acupuncture; 1995. p. 135–7.
20. Oleson TD, Kroening RJ, Bresler DE. An experimental evaluation of auricular diagnosis: the somatotopic mapping or musculoskeletal pain at ear acupuncture points. Pain. 1980;8(2): 217–29.
21. Helms J. Auricular acupuncture. In: Acupuncture energetics: a clinical approach for physicians. 1st ed. Berkeley: Medical Acupuncture; 1995. p. 138.
22. Romoli M. Ear acupuncture and fMRI: a pilot study for assessing the specificity of auricular points. Neurol Sci. 2014;35 Suppl 1:189–93. doi:0.1007/s10072-014-1768-7.
23. Helms J. Auricular Acupuncture. In: Acupuncture energetics: a clinical approach for physicians. 1st ed. Berkeley: Medical Acupuncture; 1995. p. 315.
24. Helms J. Auricular acupuncture. In: Acupuncture energetics: a clinical approach for physicians. 1st ed. Berkeley: Medical Acupuncture; 1995. p. 331–5.
25. Finger S. Origins of neuroscience: a history of explorations into brain function, vol. 36. New York: Oxford University Press; 1994. p. 807. doi:10.1002/ana.410360532.
26. Melzack R, Wall P. Pain mechanisms: a new theory. Science, N Ser. 1965;150:971–9.
27. Wall PD, Sweet WH. Temporary abolition of pain in man. Science. 1967;155:108–9.
28. Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science. 1969;164:444–5.
29. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg. 1967;46:489–91.
30. Maurer D. Transcutaneous stimulator and stimulation method. U.S. Patent 3,817,254. Publication date June 18, 1974. https://www.google.com/patents/US3817254. Accessed 27 Dec 2015.
31. Long DM. Electrical stimulation for relief of pain from chronic nerve injury. J Neurosurg. 1973;39:718–22.
32. Sluka KA. The Neurobiology of pain and foundations for electrical stimulation. In: Robinson AJ, Snyder-Mackler L, editors. Clinical electrophysiology. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 107–49.
33. Sabino GS, Santos CM, Francischi JN, de Resende MA. Release of endogenous opioids following transcutaneous electric nerve stimulation in an experimental model of acute inflammatory pain. J Pain. 2008;9(2):157–63.
34. Ainsworth L, Budelier K, Clinesmith M, Fiedler A, Landstrom R, Leeper BJ, Moeller L, Mutch S, O'Dell K, Ross J, Radhakrishnan R, Sluka KA. Transcutaneous electrical nerve stimulation (TENS) reduces chronic hyperalgesia induced by muscle inflammation. Pain. 2006;120(1–2):182–7.
35. Sluka K. TENS mechanism of action. In: Schmidt RF, Willis WD, editors. Encyclopedia of pain (muscle pain management). Berlin: Springer; 2007. p. 2406–9.
36. Radhakrishnan R, Sluka KA. Deep tissue afferents, but not cutaneous afferents, mediate transcutaneous electrical nerve stimulation-Induced anti hyperalgesia. J Pain. 2005;6(10): 673–80.
37. Claydon LS, Chesterton LS, Barlas P. Effects of simultaneous dual-site TENS stimulation on experimental pain. Sim J Eur J Pain. 2008;12(6):696–704.
38. Hamza MA, White PF, Ahmed HE, Ghoname EA. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. Anesthesiology. 1999;91(5):1232–8.

39. Bjordal JM, et al. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. Eur J Pain. 2003;3:181–8.
40. Thomas IL, et al. An evaluation of TENS for pain relief in labour. Aust NZ J Obstet Gynaecol. 1988;28:182–9.
41. Van der Spank JT, et al. Pain relief in labor by transcutaneous electrical nerve stimulation. Arch Gynecol Obstet. 2000;264:131–6.
42. Halpern SH, Douglas JM. The use of transcutaneous electrical nerve stimulation for labor pain. In: Halpern SH, Douglas JM, editors. Evidence-based obstetric anesthesia. Malden: Blackwell; 2005. p. 30–7. doi:10.1002/9780470988343.
43. Kaplan B, Rabinerson D, Lurie J, Pelea Y, Royburt H, Neri A. Clinical evaluation of a new model of a transcutaneous electrical nerve stimulation device for the management of primary dysmenorrhoea. Gynecol Obstet Invest. 1997;4(4):255–9.
44. Proctor M, Farquhar C, Stones W, He L, Zhu X, Brown J. Transcutaneous electrical nerve stimulation for primary dysmenorrhoea. Cochrane Database Syst Rev. 2002;27(1):132–41. doi:Art. No.: CD002123.
45. Johnson MI, Paley CA, Howe TE, Sluka KA. Transcutaneous electrical nerve stimulation for acute pain. Cochrane Database Syst Rev. 2015(6):CD006142. http://www.cochrane.org/CD006142/SYMPT_transcutaneous-electrical-nerve-stimulation-tens-to-treat-acute-pain-in-adults.
46. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. Pain. 2007;130:157–65.
47. Claydon LS, Chesterton L, Johnson MI, Herbison GP, Bennett MI. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. Cochrane Database Syst Rev. 2010(10):CD008756.
48. Khadilkar A, Odebiyi DO, Brosseau L, Wells GA. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. Cochrane Database Syst Rev. 2008(4):CD003008.
49. Hurlow A, Bennett MI, Robb KA, Johnson MI, Simpson KH, Oxberry SG. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. Cochrane Database Syst Rev. 2012(3):CD006276.
50. Baranowski AP, Mallinson C, Johnson NS. A review of urogenital pain. Department of Pain Management, Department of Anaesthetics and Department of Urology, University College London Hospitals, London, UK. Pain Rev. 1999;6:53–84.
51. Garfinkel M, Schumacher RH. YOGA. Rheum Dis Clin North Am. 2000;26(1):125–32.
52. Riley D. Hatha yoga and the treatment of illness. Altern Ther Health Med. 2004;10:20–1.
53. Witzel M. Vedas and Upanisad. In: Flood G, editor. The Blackwell companion to Hinduism. Oxford: Blackwell Publishing; 2003. p. 68–101.
54. Feuerstein, Georg (translator). The Yoga-Sutra of Patañjali: a new translation and commentary, inner traditions. 1989.
55. Internation Infopage for Ashtanga Yoga: the who's who of the Ashtanga Yoga tradition http://www.ashtangayoga.info/ashtangayoga/tradition/traditionsroots. Accessed 27 Dec 2015.
56. American Yoga Association. http://www.americanyogaassociation.org/general.html. Accessed 27 Dec 2015.
57. Inyengar Yoga National Association of the United States. https://iynaus.org/iyengar-yoga. Accessed 27 Dec 2015.
58. National Center for Complementary and Integrative Health: Yoga for Health. https://nccih.nih.gov/health/yoga/introduction.htm. Accessed 27 Dec 2015.
59. Jeter PE, et al. Yoga as a therapeutic intervention: a bibliometric analysis of published research studies from 1967 to 2013. J Altern Complement Med. 2015;21:586–92.
60. Büssing A, et al. Effects of yoga interventions on pain and pain-associated disability: a meta-analysis. J Pain. 2012;13(1):1–9.
61. Cramer H, et al. A systematic review and meta-analysis of yoga for low back pain. Clin J Pain. 2013;29(5):450–60.

62. Posadzki P, et al. Is yoga effective for pain? A systematic review of randomized clinical trials. Complement Ther Med. 2011;19(5):281–7.
63. Villemure C, et al. Insular cortex mediates increased pain tolerance in yoga practitioners. Cereb Cortex. 2013;24:2732–40.
64. Nakata H, et al. Meditation reduces pain-related neural activity in the anterior cingulate cortex, insula, secondary somatosensory cortex, and thalamus. Front Psychol. 2014;5:1489.
65. Siddiqui MZ. Boswellia serrata, a potential antiinflammatory agent: an overview. Indian J Pharm Sci. 2011;73:255–61.
66. Nahin RL, Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. National health statistics reports; no 18. Hyattsville: National Center for Health Statistics; 2009.
67. Pang X, Yi Z, Zhang X, Sung B, Qu W, Lian X, et al. Acetyl-11-keto-β-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. Cancer Res. 2009;69:5893–900.
68. Ernst E. Frankincense: systematic review. BMJ. 2008;337:a2813.
69. Di Lorenzo C, et al. Plant food supplements with anti-inflammatory properties: a systematic review (II). Crit Rev Food Sci Nutr. 2013;53(5):507–16.
70. Su S, et al. Evaluation of the anti-inflammatory and analgesic properties of individual and combined extracts from commiphora myrrha, and Boswellia carterii. J Ethnopharmacol. 2012;139(2):649–56. doi:10.1016/j.jep.2011.12.013.
71. Oltean H, Robbins C, van Tulder MW, Berman BM, Bombardier C, Gagnier JJ. Herbal medicine for low-back pain. Cochrane Database Syst Rev. 2014;12.
72. Gupta I, et al. Effects of gum resin of Boswellia serrata in patients with chronic colitis. Planta Med. 2001;67(5):391–5.
73. Holtmeier W, Zeuzem S, Preiss J, et al. Randomized, placebo-controlled, double-blind trial of Boswellia *serrata* in maintaining remission of Crohn's disease. Inflamm Bowel Dis. 2010;17(2):573–82.
74. Prabhavathi K, et al. A randomized, double blind, placebo controlled, cross over study to evaluate the analgesic activity of Boswellia serrata in healthy volunteers using mechanical pain model. Indian J Pharm. 2014;46(5):475–9. doi:10.4103/0253-7613.140570.
75. Kouzi SA, et al. Arnica for bruising and swelling. Am J Health-Syst Pharm. 2007;64:2434–43.
76. Ernst E, Pittler MH. Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials. Arch Surg. 1998;133(11):1187–90.
77. Hart O, Mullee MA, Lewith G, et al. Double-blind, placebo-controlled, randomized clinical trial of homeopathic arnica C30 for pain and infection after total abdominal hysterectomy. J R Soc Med. 1997;90:73–8.
78. Da Silva AG, et al. Evaluation of an extract of Brazilian arnica (Solidago chilensis Meyen, Asteraceae) in treating lumbago. Phytother Res. 2010;24(2):283–7. doi:10.1002/ptr.2934.
79. Lannitti T, et al. Effectiveness and safety of Arnica Montana in post-surgical setting, pain and inflammation. Am J Ther. 2016;23:e184–97.
80. Marsh SJ, Stansfeld CE, Brown DA, et al. The mechanism of action of capsaicin on sensory C-type neurons and their axons in vitro. Neuroscience. 1987;23(1):275–89.
81. Lynn B. Capsaicin: actions on nociceptive C-fibres and therapeutic potential. Pain. 1990;41(1):61–9.
82. Sharma SK, et al. Mechanisms and clinical uses of capsaicin. Eur J Pharmacol. 2013;720(1–3):55–62. doi:10.1016/j.ejphar.2013.10.053.
83. Brooks SH. Capsaicin-based therapies for pain control. Prog Drug Res. 2014;68:129–46.
84. Mason L, et al. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ. 2004;328:991.
85. Phillips TJC, Cherry CL, Cox S, Marshall SJ, Rice ASC. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One. 2010;5(12), e14433. doi:10.1371/journal.pone.0014433.
86. Zhang WY, et al. The effectiveness of topically applied capsaicin: a meta-analysis. Eur J Clin Pharmacol. 1994;46(6):517–22. doi:10.1007/BF00196108.

87. Ellis CN, Berberian B, Sulica VI, et al. A double-blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol. 1993;29(3):438–42.
88. Richards BL, Whittle SL, van der Heijde DM, et al. Efficacy and safety of neuromodulators in inflammatory arthritis: a Cochrane systematic review. J Rheumatol Suppl. 2012;90:28–33.
89. Zhou J, Qu F. Treating gynaecological disorders with traditional Chinese medicine: a review. Afr J Tradit Complement Altern Med. 2009;6(4):494–517.
90. Xu M, Si TY, Lao YR, Guo XF, Wen ZH, Lai SL. A literature review of clinical trials on Chinese medicine for endometriosis. J Guang Univ Tradit Chin Med. 2004;21(5):399–402.
91. Liu JP, Yang H, Xia Y, Cardini F. Herbal preparations for uterine fibroids. Cochrane Database Syst Rev. 2013(4):CD005292. doi:10.1002/14651858.CD005292.pub3.
92. Flower A, Liu JP, Lewith G, Little P, Li Q. Chinese herbal medicine for endometriosis. Cochrane Database Syst Rev. 2012(5):CD006568. doi:10.1002/14651858.CD006568.pub3.
93. Wilt TJ, Ishani A. Pygeum africanum for benign prostatic hyperplasia. Cochrane Database Syst Rev. 1998(1):CD001044. doi: 10.1002/14651858.CD001044.
94. Wilt TJ, Ishani A, MacDonald R, Stark G, Mulrow CD, Lau J. Beta-sitosterols for benign prostatic hyperplasia. Cochrane Database Syst Rev. 1999(3):CD001043. doi:10.1002/14651858.CD001043.
95. Tacklind J, MacDonald R, Rutks I, Stanke JU, Wilt TJ. *Serenoa repens* for benign prostatic hyperplasia. Cochrane Database of Syst Rev. 2012(12):CD001423. doi:10.1002/14651858.CD001423.pub3.
96. The International Center for Reiki Training: What is Reiki. http://reiki.org/FAQ/WhatIsReiki.html. Accessed 27 Dec 2015.
97. Rand, WL. Reiki Before Usui. In: Rand, WL editor. An evidence based history of Reiki: a selection of articles from Reiki New Magazine. Southfield: International Center for Reiki Training. p. 39–42.
98. Rand, WL. History of Reiki. In: Rand WL editor. An evidence based history of Reiki: a selection of articles from Reiki New Magazine. Southfield: International Center for Reiki Training. p. 16–31.
99. Center For Reiki Research: Hospital List. http://www.centerforreikiresearch.org/HospitalList.aspx. Accessed 27 Dec 2015.
100. Deng GE, et al. Integrative oncology practice guidelines. J Soc Integr Oncol. 2007;5(2):65–84. doi:10.2310/7200.2007.002.
101. Baldwin AL, Wagers C, Schwartz GE. Reiki improves heart rate homeostasis in laboratory rats. J Altern Complement Med. 2008;14(4):417–22. doi:10.1089/acm.2007.0753.
102. Thrane S, et al. Effect of Reiki therapy on pain and anxiety in adults: an in-depth literature review of randomized trials with effect size calculations. Pain Manag Nurs. 2014;15(4):897–908. doi:10.1016/j.pmn.2013.07.008.
103. Olson K, et al. A phase II trial of Reiki for the management of pain in advanced cancer patients. J Pain Symptom Manage. 2003;26(5):990–7.
104. Nedrow A, et al. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. Arch Intern Med. 2006;166(14):1453–65. doi:10.1001/archinte.166.14.1453.
105. Vandervaart S, et al. The effect of distant reiki on pain in women after elective Caesarean section: a double-blinded randomised controlled trial. BMJ Open. 2011;1(1), e000021. doi:10.1136/bmjopen-2010-000021.
106. Ripoll E, Mahowald D. Hatha Yoga therapy management of urologic disorders. World J Urol. 2002;20:306–9. doi:10.1007/s00345-002-0296-x.
107. Sorosky S, et al. Yoga and pilates in the management of low back pain. Curr Rev Musculoskelet Med. 2008;1:39–47. doi:10.1007/s12178-007-9004-1.
108. Wikipedia: Arnica Montana. https://commons.wikimedia.org/wiki/File%3AArnicamontana.jpg. Accessed 1 Jan 2016.
109. Jones I, Johnson MI. Transcutaneous electrical nerve stimulation. Contin Educ Anaesth Crit Care Pain. 2009;9(4):130–5. http://ceaccp.oxfordjournals.org/content/9/4/130.full.pdf. Accessed 27 Dec 2015.

Index

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