Urological and Gynaecological Chronic Pelvic Pain

Current Therapies

Robert M. Moldwin
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To my Jen… Thank you for your wisdom, love, and ability to put up with my craziness.
To my patients who never stop teaching me.
To my colleagues, who have accepted the challenge of unchartered medical waters.

Preface

About 10 years ago, I began a course at the American Urological Association's annual meeting dedicated to the evolving therapies for interstitial cystitis and related pain syndromes. Due to time constraints, the course did away with epidemiology, pathology, and diagnosis and was solely dedicated to current and evolving therapeutic approaches. There was a lot of enthusiasm from our audience who were clinicians dedicated to improving the lives of these patients, but who were frustrated by the frequent underwhelming responses to their recommended treatments. They appreciated the "cut to the chase" concept where all time was spent to hone their clinical skills.

This text was created with the same goal as that course… to focus on the varied therapies that may help our patients. In this case, the scope extends beyond urological practice with topics that would be of interest to primary care doctors, allied health care practitioners, gynecologists, and pain management specialists. My hope and that of our authors is to impart information not only about helpful strategies of care but also the nuances, the appropriate indicated populations, and even the downsides of therapy. The chapters contained herein are not meant to represent a comprehensive compendium of clinical care for the chronic pelvic pain patient. Rather, chapters cover timely topics by authors who are well-established experts in their respective fields.

Finally, some housekeeping issues. The reader should keep in mind that many authors will be discussing off-label strategies, some of which are supported by literature, but others by their specific clinical experiences. You will also see differences in taxonomy and nomenclature from chapter to chapter. One example is interstitial cystitis/painful bladder syndrome (IC/PBS) and interstitial cystitis/bladder pain syndrome (IC/BPS) and even BPS/IC. Another is Hunner's ulcer (HU) and Hunner lesion (HL). These differences have not been edited out of the text as they reflect the changes and the controversies that remain in this field.

Lake Success, NY, USA — Robert M. Moldwin

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The Evolution of Therapy for Chronic Pelvic Pain

1

Jane M. Meijlink and Robert M. Moldwin

Introduction

Ancient texts from China, India, the Middle East and Ancient Egypt document the suffering from urogenital and pelvic pain. Remedies in those times included medicinal herbs, with narcotics to numb the pain. The Italian Renaissance heralded an enhanced interest in the structure and function of the human body that continued to the Enlightenment in the eighteenth century, a time when intense interest developed with regard to nervous system function and pain. The nineteenth century witnessed the emergence of gynaecology and urology as specialties and an increasing interest in women's diseases. Although some progress in pain management was seen with the development of new surgical procedures, anaesthetic agents, antibiotics and aspirin, the addictive properties and easy accessibility of the opioids and cocaine became a medical and social dilemma.

The rise of medical societies and patient support groups in the field of urological and gynaecological chronic pelvic pain, particularly in the twentieth century, led to a new interest in research, diagnosis and treatment and the development of criteria, guidelines, standards and taxonomies.

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Historical Milestones

Pain has dominated the history of medicine and healthcare from the earliest times. Unexplainable physical pain was considered by many cultures and religions to be a sign of possession by demons or evil spirits, and treatment was aimed at exorcism or frightening the evil spirits out of the body. It was infused with magic, sorcery, witchcraft, sorcery and supernatural intervention. Suffering was seen as a punishment for past sins and in some religious cultures continues as such today.

Ancient texts, including the Ancient Egyptian Ebers, Berlin and Kahun medical papyri dating from the second millennium BC, describe bladder, urethral and vaginal pain disorders with treatments that included herbal remedies, honey, milk, oil, resin and even beetle concoctions instilled into the bladder using catheters made of a variety of materials or introduced into the vagina with tampons. Opium poppies were also likely used at that time for pain since opium has been in use for at least 2500 years for medicinal purpose [1]. The use of cannabis by ancient civilisations has been reported in many parts of the world including ancient China, India and the Middle East. Excavations in China of graves dating back to 2700 BC revealed cannabis to have been used for medicinal, psychoactive or ritual purposes. Cannabis for the treatment of pain was introduced in Western medicine in the form of extracts and tinctures around the mid-nineteenth century [2].

Evidence for use of the coca plant for pain treatment in South America can be traced back to at least 1300 BC with sculptures of people chewing coca leaves dating back to 3000 BC, while acupuncture for pain was used as early as 2600 BC in China, according to Sabatowski et al. in their historical overview of pain treatment [3].

A milestone in herbal medicine was *De Materia Medica*, compiled in the first century AD by Pedanius Dioscorides (40–90 AD), a Greek physician, pharmacologist and botanist. This was a five-volume encyclopaedia of medicinal herbs, translated into many languages, and formed the main medicinal herbal reference work of its kind until around the nineteenth century. Remedies for pain included the opium poppy, field poppy, lettuce, belladonna, henbane and black nightshade. A Greek physician and surgeon who practised in Rome and whose influence spanned centuries through his work *De Locis Affectis* (*On the Affected Parts*) was Galen (129–199 AD). He not only had an immense interest in anatomy but also created a classification of different forms of pain. Galenic principles of pain were also presented and adapted by Avicenna (980–1037), a Persian physician and philosopher whose major works *The Canon of Medicine* and *The Book of Healing* were in use up to the beginning of the seventeenth century. Avicenna suggested that the true cause of pain was a change of the physical condition (temperament change) of the organ, whether there was an injury present or not. He also created a much more detailed list of pain descriptor terms [4].

From the Renaissance to the Enlightenment: The Brain and the Nervous System

With the Italian Renaissance came a surge of interest in how the body worked and the concept of pain. While the anatomical drawings and study of the brain by Leonardo da Vinci (1452–1519) served as a major impulse to the study of the nervous system and pain, the French philosopher René Descartes (1596–1650) theorised in his *Treatise of Man* in 1664 that pain was a disorder that passed along nerve fibres until it reached the brain. Descartes was particularly intrigued by phantom pain and felt that it came from the brain.

However, there was probably still little change in actual treatment of pain from ancient times until the Enlightenment in the eighteenth century, when knowledge and understanding of anatomy substantially increased, resulting in great interest in the brain, nervous system and the whole concept of the senses and pain, aided by further development of the microscope [5, 6].

William Cullen (1710–1790), Professor of Medicine at the University of Edinburgh and a prolific writer, also had a special interest in the nervous system, and it was he who coined the term "neurosis" but with a somewhat different meaning than today. In *First Lines of the Practice of Physic*, he writes that he has established a class of diseases under the name of neuroses, or nervous diseases by which he means disorders of senses and motion, caused by nervous disorders and symptoms without a clear organic cause [7, 8]. The meaning of this term was later to be redefined by Jung and Freud, and it was their interpretation of neurosis as a form of hysteria which was to prevail during at least the first half of the twentieth century and to be applied to chronic pelvic and bladder pain of unidentifiable cause, causing many patients with chronic pelvic pain syndromes inestimable harm.

Pelvic Neuralgia

By the early nineteenth century, many books in many languages were appearing on neuralgia (from the French *névralgie*), a term coined by the French anatomist François Chaussier (1746–1828) who endeavoured to classify neuralgic affections in his *Table Synoptique de la Névralgie: suivant la nomenclature méthodique de l'anatomie* (Summary Table of Neuralgia) published in 1802, as noted by Richard Rowland (1798–1854), physician to the City of London Dispensary, in his *Treatise on Neuralgia* in 1838 [9, 10]. Although the term neuralgia was considered the most correct, many other terms proliferated including *tic douloureux*. While these terms originally applied to facial pain, they were soon applied to pain in all parts of the body, including neuralgia of the pelvis, bladder, urethra and even testis.

In *Practical Observations On Strangulated Hernia And Some Of The Diseases Of The Urinary Organs* published in 1836, Philadelphian surgeon Joseph Parrish (1779–1840) used the term *tic douloureux of the bladder*, reporting that "The experience of the medical profession is greatly enlarged on that painful and paroxysmal

affection of the nerves, denominated *tic douloureux*". He explains that the term has been applied until then for afflictions of "the supra- and infraorbital nerves" and that "under the generic name of neuralgia, we have a class of diseases which excite much attention at the present time….I have known instances of great suffering in the urinary organs, from this form of disease". He attributes the use of this term to his mentor, the renowned Philadelphian surgeon Philip Syng Physick (1768–1837) who had studied extensively in Europe [11].

Nineteenth Century, a Time of Medical Impulse

In the first half of the nineteenth century, medical students and doctors with the requisite financial means were travelling to France to study in Paris, a centre of excellence at that time for surgery and anatomy and above all a place for gaining the hands-on experience in anatomy, dissection and surgery that was greatly restricted at other medical centres. Bodies for anatomical dissection were legally available in abundance, unlike London where newly deceased bodies were often stolen from graveyards or even mortuaries ("body snatching"—a lucrative business—was made a criminal offence in the United Kingdom in 1832 by the Anatomy Act). A further advantage of Paris was the apparently unlimited supply of women, pregnant or otherwise, for experience in gynaecological examination (known as "touching") and midwifery, thereby greatly increasing practical knowledge of the diseases of women.

Consequently, new French insights, methods, books in translation and terminology were transmitted to other countries, including America in the decades before the Civil War, and formed a great impulse for development of medical science, instruments and an increasing interest in the urogenital diseases of women in the latter half of the nineteenth century and early twentieth century [12].

However, this emphasis on Paris changed from the 1850s onwards, with medical centres in the German-speaking Austro-Hungarian Empire, particularly Vienna and Berlin, taking over this leading role, along with Prague, London and Edinburgh. Germany introduced the concept of medical specialisms, resulting in the long-standing discipline of obstetrics now being joined by gynaecology, still often known as women's diseases, and the traditional female midwives were gradually being at least in part replaced by male doctors and obstetricians known as accoucheurs. Urology only began to split off from general surgery as a separate discipline towards the end of the nineteenth century.

Medical Education for the Consumer

In Europe and America, the nineteenth century saw the emergence of medical education for the masses. Frederick Hollick (1818–1900) was an American sex educator with a mission to ensure that people understood the anatomy of the human body and how their bodies worked. While many medical books on women's diseases for

physicians were being published during the nineteenth century, Hollick's book *The Diseases Of Woman*, *Their Causes and Cure Familiarly Explained*, with practical hints for their prevention and for the preservation of female health, was one of many "household" books written by him aimed at educating the consumer. This book was highly controversial, even scandalous, at a time when female urogenital (sex) organs were mysterious and taboo and the very idea that women should experience sexual pleasure was unthinkable—in public at least. Nevertheless, his famous book *The Marriage Guide*, *or Physiological and Hygienic Instructor*: *For the Married*, *or Those Intending to Marry*, *Both Male and Female*, *Including Everything Relating to the Philosophy of Generation, and the Mutual Relations of Man and Woman* (1860) was so popular that it ran into hundreds of editions, thereby going some way towards liberating women by educating them about their sexual health [13].

Throughout this period, surgeons, physicians and anatomists were avidly writing textbooks, treatises and manuals on anatomy, physiology, diseases of women, obstetrics, midwifery, bladder, urethra and prostate, including of course every kind of venereal disease. This was an era when venereal disease was rampant, with disastrous consequences in the pelvic organs for infected wives and even babies. Venereal disease was a major cause of urogenital pain disorders in men and a prominent cause of prostatitis. Most medical treatises on the urogenital organs therefore included a strong focus on venereal disease, likewise on urogenital tuberculosis which could affect both men and women.

Suffering and Pain Relief in the Eighteenth and Nineteenth Centuries

The descriptions of the often horrific urogenital and abdominal symptoms and pain in the medical textbooks and the very strong drugs prescribed make one realise how agonisingly people must have suffered in this period, more than anyone today can imagine. Treatment depended on the physician's personal preferences and what limited means were available. The approach at that time was usually "multimodal" and invariably a question of trial and error.

In the eighteenth century, William Cullen was recommending opium and wine as sedatives, while Richard Rowland, in his *Treatise on Neuralgia*, writes that the French surgeon and urologist Jean Civiale (1792–1867) recommends blisters or irritating ointments applied over the pelvis or perineum, although he himself finds nothing so effectual as the application of a few leeches to the groin or sacrum. Rowland interestingly includes a paragraph on "Acupuncturation", noting however that he has never personally had success in curing neuralgia with this treatment and has found that "the needles excited inflammation and all the punctures suppurated" [10].

A milestone in the nineteenth century was the emergence of anaesthesia such as ether and chloroform, offering some relief from the agonising pain of surgery without anaesthetics, followed by the development of anti-inflammatory agents. Nevertheless, opiates continued to be the mainstay of pain treatment. And pain was

indeed commonplace in this century, not helped by the filthy living conditions in the urban slums resulting from the industrial revolution when people from the countryside poured into the cities.

Opiates: Panacea for All Ills

Morphine was discovered in Germany by Friedrich Sertürner who isolated it from opium in 1804 and was commercially marketed some 20 years later. Morphine was much more powerful than opium and turned out to be far more addictive. Codeine followed around 25 years later and cocaine two decades on. All opiates were used indiscriminately in freely available patent medicines, tonics and elixirs for pain relief such as Dover's powder and led to widespread addiction.

Cocaine from coca leaves had been known about for centuries from the Spanish and Portuguese *conquistadores* in South America, but it was not until the mid-nineteenth century that extracts were made for pain relief. It was greatly in use as a local anaesthetic, including in bladder and vaginal instillations and in poultices, but also in patent preparations for everything from toothache to digestive disorders. Coca-Cola® was originally a non-alcoholic patent medicinal drink in the nineteenth century, sold as a cure for headaches and many other diseases but also as a remedy to combat morphine addiction. It was based on coca leaf extracts combined with caffeine extracted from African kola nuts. The cocaine was removed in 1903 [3].

Laudanum was a tincture of opium mixed with alcohol and could be found in every household's medical cupboard in Victorian times. It was a commonly and indiscriminately prescribed drug for diarrhoea and the pain of bowel disorders (remembering that this was a time of rampant cholera and dysentery), for pain from prostatic disorders as well as for "female complaints", including menstrual pain and all kinds of neuralgia, and was used as a sedative for hysteria. Along with opium, it was indeed a panacea for all ills. Since laudanum induces drowsiness, it was also commonly used nightly as a sleeping draught, leading to widespread addiction. Being cheaper than other painkillers and available over the counter, it was widely used among the poorer classes who had no money to consult doctors. However, it was also used in great quantities by the upper classes, including notably the Prince Regent, later George IV (1762–1830), to relieve his severe bladder pain [14, 15].

Unexplainable Bladder Pain

When faced with a patient with pelvic pain, the first thing that many physicians would suspect would have been a bladder stone. However, both Philip Syng Physick of Philadelphia and John Burns (1775–1850), Professor of Surgery in Glasgow, had encountered patients with mysterious bladder pain in whom "the symptoms of stone are met with although none can be found in the bladder". Burns reports that he has "tried many remedies, such as soda, uva ursi, narcotics, anti-spasmodics, tonics and the warm and cold bath, but cannot promise certain relief from any one of these….

If there be much tenderness about the urethra on touching it, or its orifice appear red, it will be proper to commence with the application of leeches to the vulva, and then apply a poultice of linseed meal, with the addition of laudanum" [16].

Chapter 3 of the early edition of *A Practical Treatise on the Diseases and Injuries of the Urinary Bladder, the Prostate Gland, and the Urethra* by Samuel D. Gross (1805–1884) deals with inflammation of the bladder, and here too we have a possible hint of what became interstitial cystitis in a later edition, although at this period the symptoms could have had multiple causes. Gross also notes that there is some mystery since "Dr Louis, of Paris, examined the mucous membrane of the bladder in five hundred subjects, dead of various diseases, without discovering any serious lesion in any of them". He notes that "The chronic form of the malady, on the contrary, is sufficiently common and often entails a vast amount of suffering, which, continuing for months, and perhaps years, finally saps the foundations of life…". Gross emphasises that it is necessary to treat the symptoms rather than the possible cause and recommends "Uva ursi, buchu, balsam of copaiba, Chian turpentine, bicarbonate of soda and potass, nitric acid, muriated tincture of iron, benzoic acid, and hyoscyamus, … either singly or variously combined, and aided by gentle purgatives, with an occasional dose of calomel, a farinacious diet, rest of the genital organs, and avoidance of all excitement, both bodily and mental. If much local distress exists, leeches to the perineum and the inside of the thighs, the hot bath, and anodyne enemata must be prescribed". However, it was not all depressing news as he adds that "Gin, from its specific tendency to the urinary apparatus, appears occasionally to exert a beneficial effect…" [17].

Gin, originally intended as a medicine and known as Jenever, derives its predominant flavour from Juniper berries which were believed to have medicinal properties. Since the Middle Ages, it was renowned as an herbal medicine to cure kidney, bladder and other ailments, as recorded in the sixteenth century by Dr Franciscus Sylvius (1614–1672), a German physician and chemist living and working in the Netherlands. The gin clearly continued to be a popular and trusted treatment for many centuries since the Pittsburgh Post-Gazette of 17 January 1912 recommended medicated gin—mixed with certain other ingredients—as being "splendid for kidneys and bladder", with the proviso that it should be taken in small doses.

Female Disorders

Dysmenorrhoea features extensively in the works of many authors in this period including the aforesaid John Burns who offers a number of suggestions for treatment: "Whenever the pain begins, the patient should go into the warm hipbath, take an opiate, in a full dose, combined with aromatic spirit of Hartshorn [ammonium

carbonate], or with ipecacuanha [a dried root of a plant from Brazil], as in Dover's powder, and drink freely some warm diluents so as to promote perspiration".

In 1887, Dr J. Hutchison physician to Anderson's College Dispensary in Glasgow recommends a fluid extract of *Salix nigra* or pussy willow for dysmenorrhoea which he regards to be part of an irritable nervous system. He has found this extract to be most effective and considerably better than the bromides, valerian, asafoetida, etc. that were commonly used at that time [18]. Although the pain- and fever-relieving qualities of willow bark extract had been known for centuries, at least as far back as the Ancient Egyptians, Romans and Native Americans, aspirin based on salicylin, a chemical found in the bark of the willow tree, was developed in Germany only in the second half of the nineteenth century.

Gynaecological Disorders

In his *A Practical Treatise on the Diseases of Women*, Theodore Gaillard Thomas (1832–1903), a New York gynaecologist who studied in Europe, discusses some of the many pelvic disorders that could affect women, including inflammation of the uterus, endometritis, congestion of the pelvic organs, fistulae, tumours, ulcers, abscesses, vaginitis, vaginismus, diseases of the vulva and much more besides. While noting that there are several different types of vaginitis, he reports that their treatment is similar. "Pain should be relieved by opiate or other anodyne suppositories, placed in the rectum…Every fifth or sixth hour the patient, placing under the buttocks a bed-pan upon which she lies, and between the thighs a bucket of warm water containing boiled starch, infusion of linseed, or infusion of poppies to render it soothing, should by means of a syringe with continuous jet, or an irrigator, throw a steady stream against the cervix uteri for fifteen or twenty minutes, or even for a longer time" [19]. Treatment could be considerably more invasive, and Mathieu Jaboulay (1860–1913), a French surgeon in Lyon, described the treatment of pelvic neuralgia by presacral neurectomy in a paper in which presacral neurectomy was first described [20].

Barbaric Gynaecological Surgery

Alas, there were far worse treatments around for women as illustrated by Samuel D. Gross in 1867 when he quotes remarks made by W.D. Buck of New Hampshire who describes the barbaric treatments by surgeons to which the uterus is subjected: "What with burning and cauterizing, cutting and slashing, and gouging, and spitting, and skewering, and pessarying, the old-fashioned womb will cease to exist, except in history. The Transactions of the American Medical Association have figured 123 different kinds of pessaries, embracing every variety, from a simple plus to a patent threshing-machine, which can only be worn with the largest hoops…. I do think that this filling of the vagina with traps, making a Chinese toy shop out of it, is outrageous" [21, 22].

Female Urology Neglected

Howard Atwood Kelly (1858–1943) played an important role in furthering New World knowledge of (uro)gynaecology and obstetrics. In the 1880s, he travelled extensively to study under the great physicians at the medical centres of excellence in Europe including Leipzig, Berlin and Prague. Appointed as the first Professor of Obstetrics and Gynaecology at the new John Hopkins Hospital in Baltimore in 1889, he was Guy Hunner's chief and as such greatly stimulated research into female urology including interstitial cystitis. Kelly explains that the whole field of female urology had been greatly neglected:

> Previous to the latter half of the nineteenth century but little was known about diseases of the urinary apparatus in women. And while the relatively more urgent and dangerous diseases of the male organs had exacted the closest attention, the modesty of women, as well as the inaccessible nature of the affections, conspired to hinder an earlier scientific investigation of their genito-urinary organs. [23]

Endoscope Creates Focus on Visible Pathology

Another great milestone in history was the invention of the endoscope that led to a gigantic leap forwards in diagnosis and treatment, allowing surgeons to look inside hitherto inaccessible organs without the need for surgery or waiting until the patient was dead (when relatives often refused to allow autopsy). Until this point, diagnosis and examination of the inside of the bladder had been mainly based on sounding with a metal probe through the urethra, surgery and autopsy.

The *Lichtleiter* or light conductor (consisting of only a speculum, candle and mirror and too large to pass through the urethra) was invented by Philipp Bozzini in 1806 in Germany, but it was a French surgeon Antoine Jean Desormeaux who was the first to use a specially adapted *Lichtleiter* endoscope in 1853 to examine the bladder and urethra of patients. Although many tried to develop the concept further, it was Maximilian Nitze (1848–1906) in Germany, a founding father of modern urology, who in 1876 modified Edison's light bulb invention and created the first optical endoscope with a built-in electrical light bulb as the source of light. Endoscopes could also be used for examining the uterus and the rectum, and by 1881 Mikulicz and Leiter had succeeded in constructing the first useful clinical gastroscope.

While the endoscope revolutionised diagnosis, it may have led physicians and surgeons to focus on visible, tangible pathologies to the neglect of the unexplainable pelvic, vulvar and bladder "neuralgias". Chronic invisible pain was caused by psychosocial or sexual stress, it was now claimed. And before long "bladder

neuralgia" had become "bladder neurosis", but now with the psychosomatic and sexual interpretation of neurosis by Freud and Jung [24].

In his treatise *Three Essays on the Theory of Sexuality* first published in 1905, the Austrian neurologist Sigmund Freud (1856–1939) asserted that women were "more prone to neurosis and especially to hysteria". If you can't see it, it doesn't exist was the maxim in the twentieth century. This undoubtedly caused immense damage to patients, especially women, who received no treatment for sexually related genital disorders and were sent home with a "psychosomatic" label. Conversely, the conviction that pain must be caused by organic disease resulted in misdiagnosis and even unnecessary major surgical procedures. This medical misdirection was to continue for decades to come and even today lingers on.

Twentieth-Century Miracle: Antibiotics

Although microorganisms had been discovered in the eighteenth century, it was not until the late nineteenth century that germ transmission was generally accepted as a cause of infection transmission such as cholera, typhus and tuberculosis, the latter also affecting the pelvic organs. However, antibiotics were not generally available until around the mid-twentieth century. Sulfonamides appeared around 1935 and are still used for urinary tract infections, but penicillin—discovered in 1928 by Alexander Fleming—was only available as a treatment around 1950 and was joined by streptomycin. These discoveries would revolutionise the treatment of pelvic, urinary tract and vaginal/uterine infections, saving many lives. It would also help to shed light on a whole new Pandora's box of chronic pelvic pain syndromes, diseases and disorders which now appeared not to be caused by identifiable infection as antibiotics had no effect.

While prostatitis was first identified around 1815, it was only recognised as an entity in the late nineteenth century. Initially believed to be caused by infection and especially gonorrhoea, it was only when the new antibiotics failed to cure many patients that it became evident that non-infectious prostatitis also existed, eventually leading to a classification that splits bacterial from nonbacterial. Together with interstitial cystitis, chronic prostatitis was to become one of the great enigmas in urogenital medicine.

Chronic pelvic pain with no clear cause and which did not respond to antibiotics was now virtually ignored for many decades. The sparse publications on the subject would usually be entitled "psychosomatic" or "psychological" aspects of chronic pelvic pain. Patients would be left to their own devices, with the risk of falling into the hands of charlatans or becoming suicidal. However, this was to gradually change in the last part of the twentieth century, largely due to the rise of professional societies and patient support groups for pain in general and for specific chronic pelvic pain syndromes such as interstitial cystitis, vulvodynia and prostatitis as well as gynaecological pain conditions such as endometriosis. This also led to the realisation on the health provider side that pain should be taken seriously and be adequately treated and on the patient side that they had a right to expect treatment for their chronic pain.

Whereas in the nineteenth century opiates were freely available and consumed like candy with nobody concerned about addiction possibilities, during the twentieth century, the fear of their patients becoming addicted to narcotics discouraged physicians from prescribing strong pain medication for all but the terminally ill. This created an ethical dilemma which still influences pain management today.

Terrible injuries suffered during the Second World War led to a new interest in chronic pain. In the United States, Dr John Bonica began a first multidisciplinary pain clinic in 1946, culminating in publication of the first edition of his milestone book on *The Management of Pain* in 1953 [25].

This was followed by the setting up of the International Association for the Study of Pain (IASP) in 1974. The IASP had developed a classification of chronic pain in 1986; this was later updated to include chronic pain of urogenital origin based on the Chronic Pelvic Pain Guidelines of the European Association of Urology (EAU) of 2003, introducing the concept of chronic pelvic pain syndromes. This meant that scientific attention was at last drawn to chronic pelvic pain syndromes which now acquired an official status [26, 27].

The International Society for the Study of Vulvovaginal Disease (ISSVD), founded in 1970, sparked off research and awareness of vulvodynia, but still nothing existed at either professional or patient level for the interstitial cystitis patients. This was remedied in 1984 with the setting up of the Interstitial Cystitis Association (ICA) in 1984, leading to the involvement of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in the United States in first interstitial cystitis and by the 1990s in chronic prostatitis/chronic pelvic pain syndrome. By this time it was realised that many of these conditions had overlapping symptoms and that they shared many comorbidities.

Guidelines on diagnosis and treatment of chronic pelvic pain syndromes began to emerge from the beginning of the twenty-first century onwards. The 2003 EAU Chronic Pelvic Pain Guidelines included recommendations on diagnosis and management of each individual syndrome, thereby making a start on clarification of what had hitherto been a hit and miss approach to treatment [27]. During the same period, diagnosis and treatment of urological chronic pelvic pain syndromes were also addressed by the International Consultation on Urological Diseases (ICUD) and International Consultation on Incontinence (ICI), including research into neurological aspects, thereby opening up an entire new field for therapies [28]. In 2004, the newly founded European Society for the Study of Interstitial Cystitis (ESSIC, later to become the International Society for the Study of Bladder Pain Syndrome) published a paper on standardised evaluation of interstitial cystitis, followed a few years later by Japanese and East Asian Guidelines on diagnosis and treatment of interstitial cystitis and hypersensitive bladder (HSB) [29, 30].

Although *Campbell's Urology* had contained recommendations for diagnosis and treatment of interstitial cystitis for some years, it was not until 2011 that the American Urological Association (AUA) first published a guideline on interstitial cystitis/bladder pain syndrome (amended 2015) for the purpose of providing "a clinical framework for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome (IC/BPS)". The authors note that there is a growing body of

literature demonstrating that different visceral pain syndromes, as well as pain syndromes in other body regions, and other systemic diseases often occur together in the same patient [31].

When it became clear that little progress was being made in the fields of either IC/BPS and CP/CPPS despite millions of dollars being poured into research, the NIDDK initiated a new approach known as the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) in 2008. The MAPP Network is a multicentre study of urologic chronic pelvic pain syndromes (UCPPS) designed to provide new insights into underlying aetiology, natural history and risk factors for these syndromes and their comorbidities in order to provide a translational foundation for future clinical intervention efforts and improved clinical management. This is a long-term study, which is now into its second phase.

Phenotyping to Reduce Trial and Error Treatment

While multiple treatments of every kind were available, none of them worked for all patients and often for only very small groups of patients. It was becoming increasingly clear that while the patients with all these conditions seemed to have some aspects in common, they were all different, and each patient needed an individual approach. Nickel and Shoskes devised the UPOINT system to phenotype CP/CPPS patients (UPOINT = Urinary, Psychosocial, Organ specific, Infection, Neurologic/Systemic, Tenderness) in 2009. This was later extended to include IC/BPS patients [32, 33]. The aim of phenotyping or subtyping was to try to reduce the trial and error aspect of treatment for these patients and find subtypes that are more likely to respond to specific types of treatment.

Observations and Lessons Learned from History

As has been outlined in this chapter, the treatment of pelvic pain has evolved with our understanding of human anatomy and function. In ancient times, pain therapies were, for the most part, limited to the treatment of symptoms with little knowledge of underlying pathophysiology. The late nineteenth and early twentieth centuries saw a surge in medical knowledge and new instruments and with this the notion, by a considerable number of clinicians, that pain must have an obvious source that can be identified with modern diagnostic technologies. If not identified, "psychosomatic" illness was a likely diagnosis, and this practice was supported by the medical literature! Patients were consequently incorrectly "routed" within the healthcare system and perhaps would have received better care with ancient healers. However, compared to the past two centuries, the attitude of the medical profession to women's pelvic and sexual health has undergone important change, with the Freudian view of women's illness as "hysteria" largely a thing of the past. Furthermore, within the past 15 years, significant progress has been achieved in the field of chronic pelvic pain with the development of patient support groups and dedicated

medical organisations, often working collaboratively. Interdisciplinary therapy and research are currently underway. Efforts have been expanded to define the pathophysiologies that exist, with the goal of developing targeted and personalised therapeutic approaches. As in many other areas of medical practice, much emphasis is now being placed upon not just the pain but also its impact on the quality of the patient's life. Hopefully, this momentum will continue and expand in future years.

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The Changing Role of Organized Patient Support for the Chronic Pelvic Pain Patient

2

Jane M. Meijlink

Introduction

While mutual aid groups and friendly societies were already a popular phenomenon in the nineteenth century at the time of the Industrial Revolution, with the rise in Socialism and Trade Unions [1, 2], modern patient support groups evolved from the mid-twentieth century's member-focused self-help and support group concepts into support and advocacy groups with an increasing range of tasks to meet the demands of today's electronic world and a need for high-quality, reliable information, in addition to providing emotional support and practical information for patients. In recent years, the emergence of the concept of patient empowerment has led to an increasing need for patient advocates to represent their fellow sufferers in the complex and political world of health with the aim of achieving patient-centred healthcare and ensuring that the patient/consumer has a voice in all decision-making about his/her healthcare at all levels. This includes, for example, such diverse issues as education and awareness campaigns for the general public as well as the patient, lobbying authorities in relation to health policy, patient safety, access to social benefits, reimbursement of treatment, patient participation in clinical guidelines and standardization, involvement in research, fund-raising and much more besides.

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Decline in Community 'Umbrella' Led to Rise in Support Groups

Our increasingly mobile society has led to a decline in the close-knit family network with family members now scattered not only all over the country but often throughout the world, while many people no longer know their constantly changing neighbours. In developed countries in particular, this has resulted in a loss of care from the extended family or community 'umbrella' that existed in the past. Furthermore, the family doctor who once knew the entire family has often been replaced by primary care clinics where patients cannot always be sure of seeing the same provider twice. Home visits by the family doctor which formerly played an important role in primary healthcare are now greatly reduced, often applying to emergencies only, while the district nurse has disappeared from the scene in many developed countries. When combined with economic cutbacks in home care services, this means that chronically ill people may often be isolated and left to fend for themselves.

Patient Support Groups in Urological and Gynaecological Chronic Pelvic Pain Syndromes

Patient support groups in the field of urological and gynaecological chronic pelvic pain syndromes really began to emerge with the foundation of the Interstitial Cystitis Association (ICA) in the USA in 1984. By 1993, IC groups were forming in Germany, the UK and the Netherlands and soon began to fan out around the world. In 1994, the National Vulvodynia Association (NVA) was formed in the USA by five vulvodynia patients, followed by the Vulval Pain Society in the UK in 1996. The American Prostatitis Foundation was set up in 1995 and likewise stimulated support groups in this field for men in other parts of the world, notably in the UK.

It was not easy. They were faced with a deep-rooted social taboo or stigma on any discussion of embarrassing disorders between the waist and the knees. While bladders and urine were topics to be avoided in polite society, the very intimate problems of vulvodynia—let alone sexual pain—were completely off limits and only raised in hushed, embarrassed tones in the doctor's office by the bravest of patients. Nevertheless, support groups got off the ground simply because a few very courageous patients were willing to stand on platforms and tell the world that they had a bladder or vulvovaginal pain disorder in order to raise awareness so as to help ensure that other patients would receive the right diagnosis and treatment at the earliest possible stage.

This social taboo still exists today, although in some cultures it is more intense than others. It also creates a problem for support groups with regard to sponsoring since the taboo aspect limits the field of potential sponsors. National enterprises that may be very willing to support, for example, cancer, heart, diabetes and kidney patient associations, are extremely reluctant to have the name of their company linked to embarrassing urological or gynaecological disorders. It is interesting that while prostate cancer has in recent years become an 'acceptable' topic of conversation, interstitial

cystitis (IC)/bladder pain syndrome (BPS) or vulval pain disorders still have not, and patients continue to feel stigmatized and isolated. However, the support groups give them an opportunity to discuss their disorder openly with other patients, and this may in turn also help the patient to be more frank with their doctors about issues they find too embarrassing to discuss.

Support Group Focus: Single Disorders or Combinations?

Although patient support groups traditionally focus on one specific disorder, we have seen the emergence here and there of umbrella organizations covering several chronic pelvic pain syndromes in one association. In practice, however, it is quite difficult to combine groups of disorders where the patients may have completely different symptom priorities while at the same time paying adequate attention to each priority and very importantly ensuring that the support group has sufficient expertise on each disorder. Whereas the trend in recent years has been to look at what the different chronic pelvic pain syndromes have in common, these may not necessarily be the aspects about which patients are specifically concerned. On the other hand, it may be difficult to obtain research or other grants for specific urological and gynaecological chronic pain syndromes, but potentially easier if presented in a wider context of chronic pelvic pain syndromes. Alliances between support groups in this field may therefore be useful.

Awareness, Information, Education

It goes without saying that the less well-known a condition, the more time has to be devoted to raising awareness and providing information since the patient organization may be a main source of practical information about that condition. While a primary objective is to ensure that more patients with symptoms consult a doctor, this is not going to be effective if healthcare professionals have never heard of the condition. This particularly applied to interstitial cystitis/bladder pain syndrome in the early days of the first IC patient support groups. Not only was it virtually unknown among the general public but also little known among healthcare professionals. This even applied to urologists who saw few if any IC/BPS patients since primary care providers were simply not referring patients to them. Consequently, the support groups' campaign to raise awareness at a professional level was initially aimed at both primary care and specialists, but has gradually been expanded to include the allied professions, with urology nurses and pelvic floor physiotherapists later taking a keen interest in chronic pelvic pain syndromes. With an increase in knowledge of comorbidities, attention also had to be paid to raising awareness among gastroenterologists, rheumatologists, neurologists and of course pain consultants and encouraging them to cooperate in multidisciplinary care. This was and still is a challenging task.

Collaborative Action to Raise Awareness

Approached by the ICA, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in the USA played a valuable role in education and science by holding scientific symposiums for interstitial cystitis, attended by patients and professionals from around the world, while the German ICA organized symposiums which formed an important step in raising awareness in Europe and educating both doctors and patients. The Society of Interstitial Cystitis of Japan (SICJ) and a Japanese patient support group were set up in Japan in 2001 and organized a successful series of the International Consultation on Interstitial Cystitis Japan (ICICJ) in Kyoto, involving patients in these scientific meetings. In the meantime, support groups were on the rise around the globe, giving patients the chance to meet each other, share experiences and organize patient gatherings with expert speakers. This was combined with publication of leaflets and brochures, fact sheets on every imaginable topic and treatment, books, videos and ultimately websites in a variety of languages including English, French, German, Spanish, Portuguese, Japanese, Chinese and Russian, to name but a few (see Table 2.1). These activities were assisted by medical advisory boards that played an essential role in helping to ensure that the medical information was absolutely accurate.

Today, much of the information for patients is available for downloading on the patient support group websites, providing reliable information for patients on symptoms, diagnostic procedures, all available treatment modalities and other issues which have an impact on the life of the patient, while both patients and clinicians are kept updated on developments by regular newsletters (see Table 2.2). Webinars are a recent innovation for both patients and clinicians, while Facebook, Twitter,

Table 2.1 Examples of information available from patient support groups

Types of information	Topics covered include
• Brochures, leaflets, fact sheets • Books • Newsletters • Educational videos/DVDs for patients and clinicians • Webinars • Website • Research updates	• Symptoms • Diagnosis • Pelvic and urinary tract anatomy • Individual drugs and therapies • Complementary and alternative medicine and therapies • Natural products • Pain management/toolkit • Comorbidities • Diet • Sexual intimacy • Pregnancy • Self-care/coping/lifestyle changes • Survival strategies • Fitness • Employment and disability • Specific information concerning men, women and children • Information on healthcare providers for patients

Table 2.2 Facilities and services offered by patient support groups include the following (varies greatly depending on the size and resources of the support group)

• Can't wait toilet/restroom cards
• Facebook/Twitter/YouTube/blogs
• Face-to-face meetings/ conferences
• Virtual meetings
• Helplines (telephone and e-mail)
• Online forums
• Online shops
• Online surveys/questionnaires
• Product information
• Toilet/restroom maps per region
• Toolkits for local groups
• Workshops

blogs and YouTube offer new opportunities and challenges. A big change since the Internet revolution is that the information offered by the support groups is no longer restricted to members in a single country, but used by patients, their families and healthcare providers around the world.

This has led to the emergence of the 'expert patient representative' who today reads not only patient information but also scientific literature and attends relevant medical conferences in order to keep the support group members updated on the latest developments and thereby give them hope. A drawback is often a lack of (affordable) access to the scientific literature. Some publishers are offering special patient rates for purchase of articles or open access, but mostly this is not yet the case. Conference registration fees for patient representatives from the support groups can be another financial obstacle.

Increased education and information at both clinician and patient levels have led to the diagnosis and treatment of far more patients worldwide, while the patients themselves have a better understanding of the disease and the different types of treatment. Patient support groups specifically do not encourage patients to self-diagnose, but make sure that patients are well informed so as to allow them to participate fully with their healthcare providers in the process of diagnosis and management. Where necessary, the support groups also provide the patients with information concerning providers with expertise in the field: urologists, urogynaecologists, urology nurses, dieticians, pelvic floor physiotherapists and counsellors, as well as practitioners of alternative forms of treatment.

Emergence of the Internet Presents a New Challenge

The emergence of the Internet, e-health and support group websites with their detailed information is rapidly leading to a changing doctor-patient relationship which, particularly in the case of lesser known conditions, may result in the patient having more up-to-date knowledge than the doctor. Patients not only use the Internet to seek information but also to double-check what the doctor has said and prescribed; patients have

become consumers who now question their doctor's decision, which they never did in the past. This is going to require a new approach by healthcare professionals who will need specific training in medical school to deal with this modern phenomenon so as to be able to communicate and interact with patients arriving at their appointment armed with computer printouts.

Information for Low-Literacy Populations and Non-native Speakers

In this electronic age, it is easy to think of information either on the Internet or in leaflet form as being accessible to all. But of course this is not the case. There are still large parts of the world with a low-literacy or illiterate population where leaflets, brochures and Internet information for patients are going to serve little purpose. Healthcare workers and patient organizations in these parts of the world have been successful in spreading information in the form of cartoons and videos and using music, dance and drama for local rural audiences so as to convey the message in a simple but effective way. With increasing low-literacy migrant populations in the Western world and population groups who do not speak the language of the host country, it may be necessary to make greater use of these methods, including videos with voice-overs in a number of different languages, to make sure that understandable information reaches everyone.

Practical Support

All the forms of support provided by patient groups help to ensure that patients are aware of available treatment, understand why it has been prescribed, share decision-making, learn how to cope, adapt their diet and lifestyle where necessary and play an active role in self-care, thereby improving their quality of life and helping to rehabilitate themselves into society.

Emotional Support and Empathy

An important aspect of the work of support groups has always been to provide personal emotional support through patient-to-patient (peer-to-peer) telephone helplines in the knowledge that a trouble shared is a trouble halved. These helplines provide a listening ear, while patients calling know that the listener is also a patient and therefore has personal experience of the problems and will truly understand. These telephone helplines have in recent years been augmented by email helplines. Sharing a problem helps the patient to overcome the sense of helplessness and hopelessness, combat anxiety and panic, come out of their isolation, accept the new situation and take the first steps towards developing coping strategies, looking at what they can do rather than at what they cannot do. In this way, patients can start to improve their

quality of life. It should be emphasized, however, that suicidal patients need professional counselling and that this task should not be left to patient support groups, as has too often been the case in the past. Some of the larger support groups nowadays have professional counsellors to help man these helplines.

Patient meetings, large or small, give members and their families the opportunity to talk to other people in the same situation and be reassured that they are not alone with this condition. Those who are unable to attend face-to-face meetings benefit from today's online forums that allow members of support groups to exchange experiences, ask questions and discuss day-to-day problems. Support groups encourage patients to openly discuss intimate issues such as sexuality and provide information about professional counselling for their sexual problems. This social interaction with their fellow sufferers helps patients overcome the sense of hopelessness and helplessness that often results from chronic pain and instead regain a feeling of self-confidence and the ability to gradually assume a degree of responsibility for the management of their chronic disorder.

An additional advantage of support group helplines and meetings is that they generate a wealth of feedback, giving patient support groups a comprehensive picture of the whole spectrum of the condition, since patients will tell other patients things they would never tell their doctor. Furthermore, support groups may have personal contact with hundreds and often thousands of patients, making the groups a huge potential source of information for research projects.

Volunteer Participation and Continuity

Many patients have found that the opportunity to participate in the many aspects of running a voluntary support group has given their life new meaning with a positive rather than negative outlook, thereby also helping to improve their own quality of life. Rather than simply passively receiving help, they learn to give help to others too. It is also vital for support groups to involve as many patients as possible, even in the smallest tasks, to ensure that there are people available to take over when chairs and board members retire, and thereby guarantee continuity of the support group. This is one of the biggest challenges faced by support groups. A common problem encountered is that they are often started by one or two patients and everyone expects them to continue forever. When a chair steps down, it is often difficult to find others to take over. While the very large associations often survive better because they may have sufficient resources to be able to take on a paid CEO and/or paid secretary, any sudden cut in funding may have dramatic consequences.

Empowerment

'Empowerment' of patients has been a buzzword in recent years, but not everyone knows exactly what is meant by the term. In its simplest form, it means that patients are no longer bystanders in their own care, but now have the opportunity to play an active

role in their treatment and care. According to the European Network on Patients Empowerment (ENOPE), empowerment is about designing and delivering health and social care services so as to enable patients to take control of their healthcare needs [3]. An empowered patient is an informed patient who understands his/her health condition, is able to make informed choices, can interact with healthcare providers and is capable of making the necessary lifestyle changes. Patient support groups provide their members with the tools to do this. However, this in itself is not sufficient to create patient empowerment: for it to succeed, there needs to be a patient-centred culture in the healthcare system, with an interactive partnership between patients and their clinicians and other stakeholders [4].

Patient Advocacy

With the rise of the expert patient advocate, patient support groups are better able to engage with all stakeholders, including healthcare providers, health insurers, healthcare regulators and industry. While the patients are beginning to gain a voice in decision-making, there is still a long way to go to ensure optimum care and access not only to treatment but also to reimbursement of that treatment and eligibility for a wide range of social and disability benefits.

At present, patient support groups and their representatives are regrettably often involved in decision-making only at the end of the process, as a kind of token window-dressing, when all important decisions have already been taken by the professionals. For patient participation to have any value, patient representatives need to be involved in the entire process.

An additional problem faced by patient organizations is that while many meetings for stakeholders including patients are organized by national and international authorities, with many promises made and declarations signed, there is often little evidence of concrete action by these authorities. Nevertheless, despite these problems, there have been many positive achievements. If the support groups continue with their progress, like the hare and the tortoise, they will find that ‘slow and steady’ eventually wins the race! A strong participating voice for the patient will ultimately lead to more and better patient-centred healthcare.

Participation in Research

Right from the start, patient support groups have actively stimulated research; today, they are also increasingly participating in research projects. Support groups and their members can help to identify and draw attention to areas hitherto neglected by researchers but which patients feel to be of great importance and which directly affect them. In this way, they can help find better treatment and even ultimately a cure for the disease. One practical way in which support groups and all their members play an active role in research is through surveys, both nationally and internationally. This can be of great value to research projects and has become much easier with the emergence of the Internet and online surveys.

Patient Safety

Patient support groups and their umbrella organizations are very involved in all aspects of patient safety including in all areas of healthcare, clinical trials and research projects. The International Alliance of Patients' Organizations (IAPO) has created a useful toolkit to help patients and their organizations engage with stakeholders and have a voice in actions that reduce harm to patients and improve the quality and safety of their healthcare system. This toolkit also provides advice and tips on how to advocate and build partnerships to achieve patient safety goals and on communicating messages to patients and other healthcare stakeholders [5].

Involvement in Clinical Guidelines and Standardization

As already mentioned, patient support groups are a mine of information on the entire spectrum of a syndrome or disease and can therefore make a valuable contribution to clinical guidelines, taxonomies and standardization of terminology and definitions. While healthcare professionals may have a more limited view of just a few links in the chain, support groups have a more comprehensive view all the way along that chain and are likely to be more aware of the impact of additions or changes in terminology and definitions on the patient in practical terms. This means that more patient representatives need training in these fields, including on coding issues, in order to be able to participate fully in this kind of work and not just serve as a rubber stamp at the end of the process. It is particularly important in relation to the International Classification of Diseases (ICD) which may impact their diagnosis, treatment and eligibility for reimbursement of that treatment and the full range of social benefits. The International Continence Society (ICS) has led the way in fully involving patients in standardization processes; more professional societies need to follow this example [6].

Conclusion

While the basic task of a support group has always been one of raising awareness, providing information, offering emotional and practical support to patients and their families and giving patients the opportunity to have contact with each other, the rise of the Internet has greatly increased the possibilities and outreach. Advocacy on behalf of patients at local, national and international levels is now more important than ever in order to achieve patient empowerment and patient-centred healthcare, with patients participating in decision-making as partners. Support groups in the field of chronic pelvic pain syndromes have had to overcome the additional burden of stigmas and taboos; this has made awareness campaigns and fund-raising even more of a challenge for these organizations.

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Practical Psychosocial Management of Urologic Chronic Pelvic Pain Syndromes

3

Dean A. Tripp, Abi Muere, and J. Curtis Nickel

Introduction

Pain has been commonly defined as an "unpleasant sensory and emotional experience associate with actual or potential tissue damage" [1]. This definition is provocative and it opens the door for considering the complexity of pain processing, stating that pain is not purely a somatic nociceptive event. Indeed, pain is considered as much an emotional experience as it can be biological.

The goal of this chapter is to introduce you (the urologist or affiliated health professional) to a current form of empirically supported biopsychosocial intervention for chronic pelvic pain. This chapter should be read as a framework from which you can understand the rationale, research, and practical ways in which pain-associated interventions are considered. The goal of this chapter is not to make you a "uro-psychologist," but simply to highlight important findings in the processes of painful urogenital disease and to provide an example of an office-based mediation that can be helpful in managing your patients' concerns and distress.

In terms of chronically painful conditions, it is well known that various individual factors have an additive negative effect on patients' quality of life. This chapter is not an attempt at replacing medical therapy with psychological therapy, but more about understanding and using the insights of the psychologist in an integrated

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manner to treat this group of patients in the best possible manner. There is a pressing concern in medicine because neither the administration of opiates nor the development of specialty medications, or surgery for certain types of pain, has led to the desired solution for an end to patient chronic pain.

The Cognitive-Behavioral Therapy (CBT) Pain Model

Cognitive-behavioral therapies are not one homogenous process. Rather, they are composed of several intervention methods, each focused on ameliorating specific cognitive or behavioral targets of change. This multidimensional and individualized approach allows for each patient to be considered as an individual. Indeed, a combination of various therapeutic interventions can be effective in treating chronic pain as they address biological, psychological, and social factors, some of which may function independent of the specific pain disorder.

When one considers a psychological perspective of pain, it is presumed that some injury or somatic process, overwhelming patient distress, or a combination of injury and distress causes chronic pain. In all cases, we must remember that physical pain is real but that a dual process may be occurring in which the patient's physiology to the "stress" of pain and subsequent daily life adjustments are reflected in painful muscle tension and thus greater pain sensitivity. It is when the pain moves from acute to chronic for patients (e.g., lasting more than 3 months) that we find the original somatic process might becoming less significant and that the psychosocial risk factors for pain (e.g., anxiety/depression) start to become more pressing issues.

The cognitive-behavioral therapy (CBT) pain model asserts that cognitive and behavioral factors are essential mechanisms in patient well-being as well as improved quality of life [2]. Behavioral strategies provide a backdrop from which patients learn to understand and change the negative thought and behavior patterns associated with pain [3]. Behavioral strategies are designed to educate patients on developing awareness of how their feelings and thoughts are linked to both productive (e.g., exercising, stretching) and nonproductive (e.g., becoming excessively sedentary) behaviors. With a focus on patient education and skill development, there are several common characteristics of CBT programs. For starters, they tend to be problem oriented and extensively teach self-management and communication skills and do this through the use of home practice-based exercises [2, 4, 5]. Importantly, the CBT pain framework is malleable, or patient centered, and can be altered for use in settings of one-to-one therapy or group settings as often found in multidisciplinary pain management programs. In regard to execution, pain therapy often consists of three basic components: (1) helping patients understand how thoughts and behavior affect the pain experience, (2) training patients in cognitive and behavioral coping strategies, and (3) teaching patients how to apply and maintain their newly acquired skills so that they become habitual [6].

The CBT model for chronic pain treatment has been systematically reviewed and shown to be efficacious for many chronic pain conditions (e.g., low back pain, arthritis). Reviews of CBT for chronic pain have found treatment strategies which

aim to reduce negative thinking and emotional responses to pain, decrease perceptions of disability, and promote self-management that are predictive of favorable treatment outcomes such as increased activities and overall functioning [7, 8]. CBT therapies have only recently been proposed and examined for the unique pain urinary symptoms and associated systemic conditions experienced by patients diagnosed with urologic chronic pelvic pain syndromes.

The State of Chronic Pelvic Pain

Urologic chronic pelvic pain syndromes (UCPPS) are a significant healthcare issue. Two prominent conditions are chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in males and interstitial cystitis/painful bladder syndrome (IC/BPS) diagnosed primarily in females.

CP/CPPS has a point prevalence estimate of approximately 16 % among North American males and 14 % among Asian and European males [9, 10]. The National Institutes of Health (NIH) definition of CP/CPPS is that of pelvic pain for 3 of the previous 6 months, with or without voiding symptoms [11], with the hallmark symptom of CP/CPPS identified as persistent pain in the perineum, pelvic area, and/or genitalia [12, 13]. CP/CPPS pain is significant and reported as more severe than other urological conditions such as benign prostatic hyperplasia [12, 14, 15]. The pain experienced in CP/CPPS (i.e., perineal, abdominal, testicular, penile, and ejaculatory pain) can be long-standing, with some patients reporting chronic symptoms without effective or lasting relief for an average of 87 months [16]. As in other pain conditions, CP/CPPS pain does not correspond strongly with medical findings and has no standard pathology [17, 18]. Unfortunately, these symptoms may not remit, and two-thirds of CP/CPPS patients continue to experience life-disrupting symptoms 1 or 2 years later [19, 20].

Interestingly, there is substantial overlap between CP/CPPS and IC/BPS in terms of diagnosis, definition, and symptom profile [21, 22]. Although both conditions include patients with inflammatory findings in the bladder and/or prostate, there are no pathognomonic, histologic, or radiologic findings on which to base a diagnosis for either condition. IC/BPS prevalence estimates in North America range from 2.7 to 6.5 %, and the female-to-male ratio is estimated as high as 9:1 [23, 24], with progressive symptoms suggested for 3–7 years before diagnosis [25]. The NIH, the European Society for the Study of Interstitial Cystitis, and the World Health Organization committees have an accepted definition for IC/BPS. The hallmark characteristic of IC/BPS is persistent bladder pain and the urologic symptoms of urgency, frequency, and dysuria [26, 27], with many patients reporting pain as severe or excruciating [28]. Other medical conditions of chronic pelvic pain (e.g., infection, cancer, etc.) are to be ruled out for both CP/CPPS and IC/BPS.

It has been suggested that urological practitioners regard UCPPS patient management as challenging [29, 30]. As is the case with many chronic pain conditions, CP/CPPS pain does not appear to be strongly associated with biomedical findings [17, 18] and is difficult to manage [31, 32]. Treatment strategies based on

back-to-back application of biomedical monotherapies for patients with severe CP/CPPS may be suboptimal [29, 33]. Further, there are no consistently effective treatments for IC/BPS [34]. Several systematic reviews of pharmacological treatments for IC/BPS found many therapies to be ineffective, of limited efficacy, or to have inconclusive effects [30, 35]. Some researchers have suggested that effective treatment for CP/CPPS, and likely IC/BPS, remains elusive due to the multifactorial nature of its pathogenesis [36]. Unfortunately, both the etiologies and pathogenesis of CP/CPPS and IC/BPS are poorly understood despite the efforts of basic scientists and clinical researchers [36–39].

Societal and Individual Impact

UCPPS symptoms incur large societal costs and present a substantial burden to the healthcare system. CP/CPPS and likely IC/BPS as well are associated with more direct medical costs than that incurred in managing patients with insulin-dependent diabetes [9]. IC/BPS alone is responsible for over four million outpatient physician or clinic visits per year in the United States [40], with associated costs equal to or greater than back pain, fibromyalgia, rheumatoid arthritis, and peripheral neuropathy [22]. It is reported that 50 % of IC/BPS patients report significant work-related disability [41].

UCPPS patients report diminished quality of life (QoL), partially resulting from the physician's frequent inability to offer biomedical treatments for these disabling chronic pelvic pain problems [42]. QoL broadly describes how well people function in life and their subjective perception of their well-being. The impact of CP/CPPS symptomatology on QoL is significant and comparable to other debilitating medical conditions such as active Crohn's disease and congestive heart failure [43, 44]. Reduced QoL is also associated with a variety of comorbidities in CP/CPPS [45]. Increased pain and worsening CP/CPPS symptom severity are associated with poorer QoL [31, 46–48]. More recent studies have found that pain acts as the strongest predictor of poorer QoL when compared with urinary symptoms, age, depressive symptoms, and partner status. Further, females suffering with IC/BPS experience poor QoL due to physical difficulties, emotional regulation issues, and decreased energy levels [49]. IC/BPS has a significant impact on a variety of life areas, such as occupation, social and recreational activities, family and home responsibilities, and sexual functioning [50, 51].

Mental Health Impact

With pain as the cardinal symptom for both CP/CPPS and IC/BPS, it is no surprise that significant psychological comorbidities have long been reported [52–54]. The prevalence of psychological disorders among CP/CPPS and IC/BPS patients is higher than the general population (13 % in CP/CPPS vs. 4 % in healthy controls; 23 % of IC/BPS vs. 3 % of healthy controls) [55]. Past research indicates that

approximately 60 % of CP/CPPS patients meet criteria for major depression and that none had received a diagnosis or were receiving medication for depression [52]. A CP/CPPS internet survey showed that 78 % of patients reported depressive symptoms and 5 % reported thoughts of suicide [14]. These estimates are remarkable because prevalence estimates of depression in the general population range between 5 and 6 % [56]. Suicidal thinking has been found to be more common in patients with CP/CPPS than in healthy men [57]. Depression is associated with early chronic prostatitis-like symptoms [58]. Furthermore, high rates of depression and anxiety in a CP/CPPS sample remained consistent over time [59, 60]. Ku et al. [61] reported that depression in CP/CPPS was correlated significantly with both pain and urinary symptoms. As well, females with IC/BPS tend to report more depression than healthy female controls [62]. A recent history of depression has been associated with higher levels of pain among IC/BPS patients [26], and greater depression was also associated with multiple comorbid body pain sites [63], and is a strong predictor of IC/BPS symptom severity [64]. Recent reports from our research group have also indicated that suicidal ideation is a prevalent problem in as many as 23 % of women suffering from IC/BPS, across urology tertiary care centers in the United States, Canada, India, and Denmark [65].

When discussing mental health in any patient population, it is important to consider gender differences, both in prevalence and in treatment-seeking behaviors. While women are two times more likely than men to be diagnosed with depression [66, 67], underreporting of mental illness among men may account for this discrepancy. Additionally, men may not exhibit the conventionally viewed symptoms of depression [68]; depression symptoms among men may be expressed through fatigue, irritability, loss of interest in work or hobbies, and/or sleep disturbances rather than the traditional depressive affect [69].

To summarize, CP/CPPS and IC/BPS patients report diminished QoL, relatively consistent levels of pain, and considerable psychological comorbidities (i.e., catastrophizing, depression, suicidal thoughts). When considered together, this body of research clearly calls for a psychosocial compliment to ongoing biomedical therapeutic management for CP/CPPS and IC/BPS.

Research on Psychosocial Predictors of Mental Health

There are several important biopsychosocial risk factors that are empirically supported as predictors of UCPPS outcomes such as pain, urinary symptoms, and patient QoL. Cognitive-behavioral factors such as catastrophizing, social support, and pain coping have attracted increasing research and clinical interests in the past 10 years.

Catastrophizing

Everybody knows somebody who is a "*catastrophizer*." Generally speaking, catastrophizing occurs when people perceive or discuss an event/situation as being far

worse than it actually is. Catastrophizing is usually described as an irrational thought where we fear a terrible outcome. Catastrophizing takes a couple of forms. Many people make a "catastrophe" out of a present life situation. For example, if you're a student and you get a grade back on an exam, and you tell yourself (i.e., believe) you are a complete and utter failure and you will lose your ability to get a job when you graduate even though, in reality, it may only be a temporary situation, and there are things that you can do to change this situation. This thought pattern is associated with anxiety and thus catastrophizing gives a situation a truly negative "spin." Other forms of catastrophizing are future oriented, when people anticipate *all* the things going wrong. Catastrophizing can be mild and show up in the form of anxious rumination over a particular stressor, or it can be a trait-like feature with situational stability across a wide range of concerns, such as situations involving pain or worries about upcoming pains.

Described as the tendency to magnify, ruminate, and feel helpless when undergoing or anticipating painful sensations [70, 71], catastrophizing about pain is one of the strongest predictors of greater pain experience in a wide variety of clinical and nonclinical samples [70], including pelvic pain [70, 72–74]. Catastrophizing is a prominent cognitive factor that is associated with chronic pelvic pain and UCPPS patient adjustment. In CP/CPPS, greater pain catastrophizing is associated with greater disability, depressive and urinary symptoms, and worse pain [72]. IC/BPS studies have also found catastrophizing to have significant impact on patients. Catastrophizing is associated with poorer mental health, reduced social functioning, greater disability, greater pain, and greater depression [51, 73]. In particular, the experience of "helplessness" in catastrophizing (i.e., patients' thoughts that they will not be able to manage or that situations are overwhelming and will never improve) is a robust predictor of diminished mental QoL in both CP/CPPS and IC/BPS samples [72, 75–77]. Although not yet substantiated, it is possible that enduring UCPPS symptoms due to attempted but ineffective medical therapy may create feelings of helplessness in patients. It is important to reduce catastrophizing in patients experiencing pain because without intervention it is consistent over time and related to increased emotional distress [20, 70].

Social Support

Another common finding in the distress and pain literature is that greater social support is associated with better patient outcomes. Low social support is associated with diminished QoL, greater depression, disability, pain severity, and pain behavior [78]. In CP/CPPS, though cause and effect are debateable, our lab has shown that when a patient's spouse starts to take over the duties of the patient (i.e., greater solicitous spousal responses to patient pain), patients can become more sedentary, which is associated with greater pain and disability in the patients [72]. Increased distraction resulting from social support reduced the impact of CP/CPPS pain on patient disability, though not its impact on QoL or depression [79]. For IC/BPS, our lab has shown that distraction from spouses in response to patient pain behavior

diminished the impact of pain on mental QoL, but not its impact on physical QoL, depression, or disability [80]. Taken together, this UCPPS research suggests that social support may have a significant impact on patient pain, disability, and QoL and that spousal support may be a key target for interventions.

Pain Coping

Although there are many ways to conceptualize coping, one chronic pain model refers to behavioral coping as illness-focused coping (IFC) or wellness-focused coping (WFC) strategies. WFC strategies, such as task persistence and exercise, are strategies encouraged in the multidisciplinary treatment of chronic pain. In contrast, IFC strategies, such as pain-contingent rest, tend to be discouraged [81]. Pain-contingent rest is a significant IFC strategy in which people avoid movement or activity due to pain, with the prolonged effect of a gradual loss of mobility [82]. Few studies in UCPPS have examined the use of such IFC strategies and their impact on patient outcome, and this research is particularly lacking in the IC/BPS literature. In one of our lab studies in CP/CPPS, pain-contingent rest, not catastrophizing, was shown to be the strongest predictor of disability [72]. Similarly, pain-contingent resting has been shown to be a robust predictor of poorer physical QoL in a CP/CPPS sample, even after controlling for the effects of catastrophizing [75]. Few men with CP/CPPS (9 %) reported finding rest to be a helpful form of coping, with many (42 %) reporting a worsening of symptoms following sedentary behavior [83].

Taken together, the current UCPPS literature unmistakably suggests that a biopsychosocial intervention for pain in CP/CPPS and IC/BPS is warranted. It also highlights specific psychosocial factors as targets for change, such as catastrophizing.

CBT Approach for CP/CPPS

In regard to CBT strategies for UCPPS, there have been no published studies to date regarding the effectiveness of CBT programs for IC/BPS pain and symptom management, with a similar paucity of research evident for CP/CPPS. However, one CBT pilot study has examined the effects of an 8-week psychosocial risk management program for CP/CPPS designed to teach patients to dispute and replace catastrophic thinking with health-focused behaviors [84]. These sessions were designed so a urology nurse or equivalent healthcare worker once trained in the therapy protocol could provide them. As shown in Fig. 3.1, the overall goal of these sessions was to assist patients in identifying, disputing, and replacing catastrophic thinking with health-focused thinking and coping responses. The enrolled patients were instructed in the use of a variety of CBT techniques, with a primary focus on understanding and disputing catastrophic thinking about pain. These sessions also instructed patients on the importance of positive communications and the positive effects of social support. Patients were encouraged to reengage with abandoned

Fig. 3.1 Major treatment modules for the CBT pilot program conducted by Tripp et al. [84]

physical and social activities and add new ones (e.g., walking program). In this pilot study, CP/CPPS symptoms, pain, mood, catastrophizing, and social support were assessed at baseline and then weekly over the course of the program. We found significant and clinically meaningful reductions in pain (50 %), disability (60 %), and catastrophizing (62 %). The reductions in catastrophizing were also strongly associated with reductions in CP/CPPS symptoms. No changes in depressive symptoms or perceived social support were demonstrated. While the findings from this pilot study are promising, no recent replication studies or similar pilot studies for either CP/CPPS or IC/BPS have been published. This is particularly regrettable given the suggestion that UCPPS psychotherapies are given low priority primarily due to surgeons being unfamiliar with the evidence for adjunctive options [85].

Expanded CBT Model

Our research has recently redesigned the previous CBT-based therapy model into an expanded version designed again for UCPPS. This expanded model aims to add several new components to the original program, based partially on patient feedback and the current pain-therapy literature. As shown in Fig. 3.2, one of the first additions was to enhance patient understanding on current theories about "what pain is, how it happens, and what makes it worse." Following this psychoeducational introduction, patients are instructed on the benefits and uses of basic relaxation responses for their pain and stress. The middle sessions are essentially unaltered (i.e., focus on disputing catastrophic thinking about pain, the importance of positive communications and the positive effects of social support, reengagement with abandoned activities), but the final sessions have been added to help patients adjust into a deeper level of disease management. In particular, patients will be instructed on the benefits of mindfulness for pain and stress, as well as focused work on existential questions concerning pain acceptance. Essentially what this expanded model offers patients is sort of a buffet of therapeutic, empirically supported, pain management techniques based on a CBT orientation. These techniques are targeted toward understanding and calming the patients' body as well as understanding and calming one's mind. Each of the new sessions' content is briefly reviewed below.

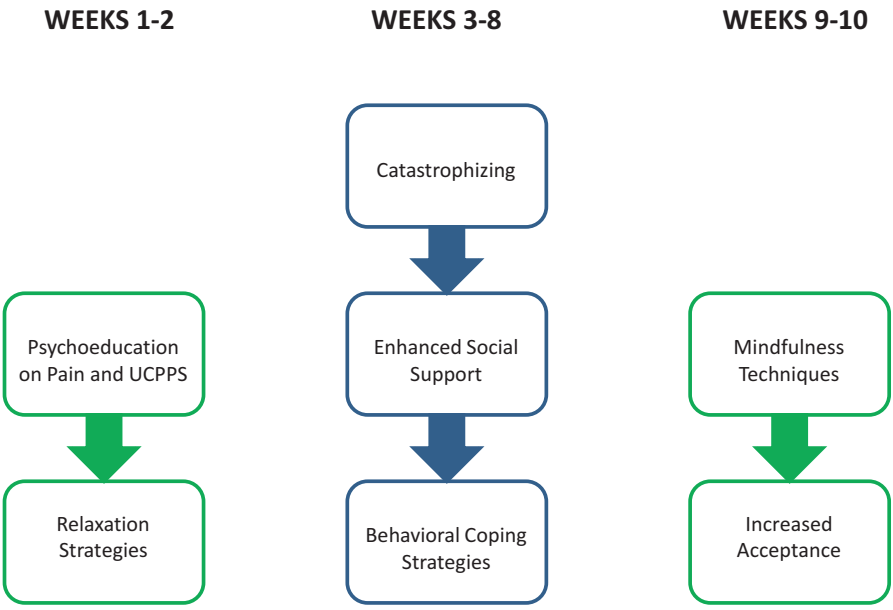

Fig. 3.2 Major treatment modules for the expanded CBT model for UCPPS. Modules in *green* indicate novel additions to the model

Psychoeducation on Pain and UCPPS

During the initial sessions, patients are introduced to the rationale behind this self-management program. They will receive specific education on the central nervous system and how pain and stress are activated and can be diffused through current theories such as a "stress-pain model." They will also learn more about their pain condition, including typical symptoms and prevalence rates, which will allow them to identify the particular aspects of their condition. This session is an important addition to the program because patients often lack correct and self-relevant information on pain and how it relates to their experiences.

Relaxation Strategies

Relaxation techniques are used as a coping response to reduce distress associated with pain and to reduce pain sensations themselves. These strategies tend to focus on repetition of a single sensation or physical activity, such as deep, diaphragmatic breathing, to achieve benefits of a calm physiological state [86]. Further, in combining physiotherapy and paradoxical relaxation training in patients with CP/CPPS, Anderson and colleagues have shown significant improvement in pain, sexual dysfunction, and urinary symptoms at 3 months [87] and 6 months posttreatment [88].

Under the expanded CBT model, patients are instructed in relaxation strategies after their pain education session as to encourage behavioral pain management skills that have psychological benefits as well. By reducing tension in the body related to pain, patients learn that they can also reduce psychological distress.

Mindfulness and Acceptance-Based Strategies

Acceptance and commitment therapy (ACT) is one of the therapies referred to as a "next wave" psychotherapy [89]. ACT is a psychological intervention that employs mindfulness and acceptance techniques. Mindfulness refers to purposeful observation of what is going on in the environment. Mindfulness techniques help patients practice redirecting their attention away from streams of often unhelpful thoughts (e.g., pain catastrophizing thoughts) and toward the present moment [89, 90]. The mindful thinking sessions will focus on training the patient to examine their present experiences with a receptive and nonjudgmental mindset, that is, without automatically evaluating private experiences (e.g., thoughts, feelings, sensations, memories) as good or bad but simply experiencing them as they are. In contrast to CBT techniques that encourage identifying, challenging, and ultimately replacing unhelpful cognitions, mindfulness techniques offer strategies to reduce the impact and influence of unwanted thoughts, feelings, and sensations. As part of the expanded CBT model, patients will use guided home practice of mindful breathing and mindful eating, which are two basic techniques for inducing a calm mind. By practicing mindfulness, the patient is brought full circle back to the earlier relaxation strategies that were used for pain management as well as the cognitive replacement work they practiced during the anti-catastrophizing sessions. The integration of these skills and the repetition allow patients to experience deeper learning.

ACT interventions also focus on developing "acceptance" of unwanted private experiences, as well as promoting commitment and action toward living a valued life [89]. The acceptance-based strategies in this expanded program help patients identify deeply held values, set goals guided by these values, and take action to meet these goals. Here, patients will identify important values in several life areas (e.g., intimate relationships, family, work, etc.) and set practical, obtainable goals for a few of these values. Patients then identify strategies to achieve these goals in order to become closer to these values. These simple home-based exercises are important because they build upon the previous instruction of the program and also the likely successes patients have been able to achieve near the end of the program.

Veehof and colleagues [91] conducted a recent meta-analysis reviewing 25 RCTs comparing mindfulness and acceptance-based therapies for chronic pain with other interventions (e.g., education, medical treatment as usual, CBT). Moderate to large effect sizes were found for pain interference posttreatment and at follow-up.

Clinical Methods

It is understandable that a urologist that has read this far in this chapter might be thinking, "*I cannot do that in my practice*." But the goal of this chapter was to introduce you to the most current form of empirically supported intervention and thus provide you with a framework from which to draw brief, office-based interventions to perform with your patients. Clinicians should consider CP/CPPS and IC/BPS patients good candidates for adjunctive treatments such as CBT for chronic pain, as needed. After reading this chapter it is hoped that you will be able to more easily identify patients' exhibition of anxious or catastrophic thinking about their pain or the pervasive use of passive forms of coping with their pain (e.g., becoming more sedentary). Of course, patients with notable depression must be monitored and followed up appropriately, which is a current standard for care. Given the high prevalence rate of depression among UCPPS patients, a routine screening should be available for all incoming urological patients. Clinicians screening CP/CPPS patients should be aware that in addition to potentially exhibiting nonconventional symptoms of depression, men are generally more likely to self-medicate or engage in excessive working or infidelity than communicate their distress [92]. In addition to providing clients with referrals, clinicians can also open up a dialogue with their UCPPS patients on one of the most robust psychosocial predictors of poor patient adjustment: catastrophizing.

Physician-patient interactions can be critical for improving symptom management as well as providing prized insights to the treating physician in regard to treatment adherence. The physician's understanding of the patient's perspective helps to create productive exchanges of information that will act to enhance patient participation in their own care. In many situations, knowing (rather than supposing) your patients' concerns about their stress and worries, medication complications, and adjustment issues can be essential in shaping the types of information and responses needed from you and the broader treatment needs of your patient.

There are many lists of difficulties associated with poor patient communication [93]. One way to help your patients is to simply talk to them, not for hours but even 3 min during an appointment can be an effective start. You would be surprised what a difference those 3 min can make to your relationship with your patient and how that can guide your care. What we do with these minutes is what is most important. Below we outline steps you can take to establish open lines of communication with your patient, which include consideration of psychosocial concerns:

1. *Work to establish patient trust*. Physicians who value patient trust, satisfaction, and medication adherence try to create open interactions with their patients. One of the key features associated with a trusting relationship is the act of inviting patients to fully participate in their office visit by telling their version of the events or concerns in full, with only limited interruption from the physician for clarification. Patients that are consulted on setting agendas and decision-making options are also more satisfied. Simply stated, the physician who takes time to really listen to what the patient is "trying" to tell you may be considered a high-

performing physician. This act of hearing your patients is essentially the process of gathering data on your patients so that over time you begin to understand their beliefs, fears, and motivations about their health. Some physicians will say to themselves that they do occasionally get the wrong message and take guesses about their patients' experiences. Rather than get the information wrong in the form of supposing, many physicians should simply ask the patient to tell them.

2. *Agree to engage in shared decisions about patient care*. Referred to as a "shared decision-making model" [94], physicians using this model will try to reach agreement on what to do and how to proceed, whether it is a new treatment medication or some psychosocial-based actions (e.g., referral to psychiatrist or psychologist for depression treatment). To ensure shared decisions, physicians should be watchful and responsive to various verbal and nonverbal patient "cues" indicating possible lack of agreement, misunderstanding, or general concern. What this type of interaction establishes is that the physician cares about their concerns of treatment and patient's welfare, especially when the patient seems worried or confused about procedures, etc.
3. *Acknowledge your patients' psychosocial concerns*. Physicians treating UCPPS patients understand that anxiety and depression are common in their patients. But they also need to address the empirically supported mechanisms that drive these end points. Understanding the "context" in which patient health exists is the trick. Are they an anxious person? Are they satisfied with their pain control? Do they have other stressors in their lives (e.g., financial strain)? Do they have supportive people around them? As highlighted in the previous paragraphs on improved communication, engaging, listening, and sharing decisions on next steps can be tremendously helpful for patients. What the patient experiences from such interactions is often labeled as empathy and support.

"Catastrophizing" About Their Pain? Below is an adapted example of how an exchange may be started with a patient about pain and catastrophizing [95]. When you become aware that your patient is reporting high anxiousness about their pain, the following interaction highlights the features of staying engaged with your patient by listening to and summarizing their concerns back to them and by using language that exemplifies a shared decision-making model. In its basic form, the clinician may choose to go over items of a standardized measure of catastrophizing with their patients as to provide a semi-structured approach to introducing pain and its mechanisms. In the example below, it is suggested that physicians have some visual aids when presenting information to patients. If desired, physicians can print a copy of the widely used and publically available Pain Catastrophizing Scale [96] (see Fig. 3.3). Armed with a visual aid or not (depending on your preference), you can start the discussion as suggested below:

> **I have heard you suggest over the past visits that your pain keeps making you feel anxious, that you desperately want it to stop, and that you are feeling like there is little you can do to help yourself? Can you tell me more?** [Pause, listen, you have directed the conversation but now you just need to hear them] [Summarize what they report, like…] **So**

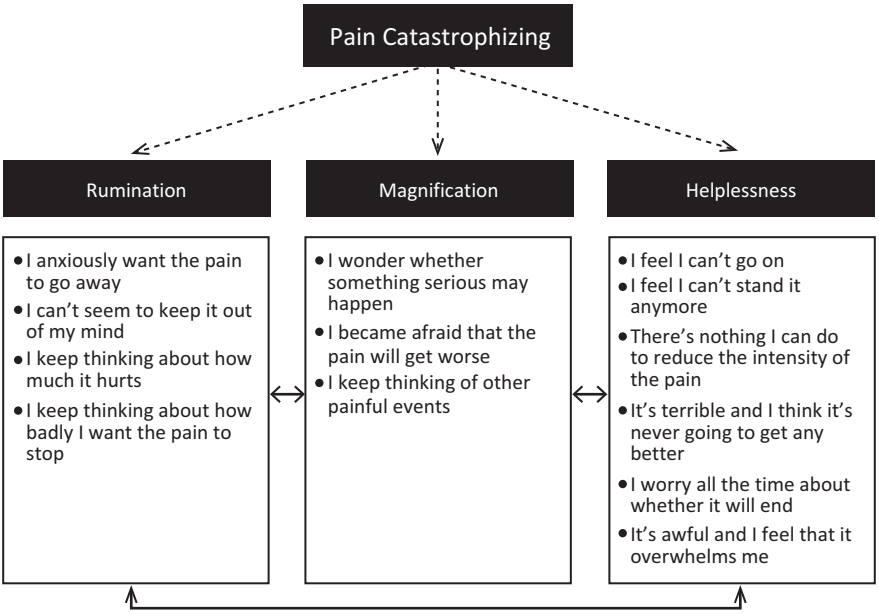

Fig. 3.3 Items of the Pain Catastrophizing Scale [96]

it sounds to me like you are feeling down, worried, etc. [Select terms that apply]. [Further acknowledge their concerns by saying…] **Those types of experiences are not fun, they sound like they can be horrible for you.** [Pause, listen]. [Then proceed to…] **We know that everyone experiences pain at some point in his or her life. They may have headaches, back pain, joint pain, or pain that you have described. Some people experience pain that is really bad, chronic and persistent, whereas others have pain that is far milder at times. Do you know others who have pain?** [Use this social question to deepen the discussion, and to examine potential behavioral models of pain behavior they are exposed to]

We also know that pain creates stress for you. Did you know that stress also creates more pain in your body? [Pause][Acknowledge their response…] **So understanding how stress and pain interact is a key treatment goal in all pain treatment models used today. One that I think we should know more about for your treatment. We know that pain that is left as untreated can become misunderstood and that only leads to more stress, which is not good for your body or your mind.**

Does this connection between pain and stress seem real to you? Can you give me examples where other people you know trying to manage their pain might show this connection? [Pause… listen] **Does this fit with <u>your</u> experience with pain?** [At this point you go back to listening and then offer a summary of what they say to you][Then proceed with…] **This is why I am interested in the types of thoughts and feelings you have when you are in pain—because the connection that exists between pain and stress is not very well described in medicine, would you agree?** [Listen, then proceed to…] **If we can understand how this pain-stress cycle might be affecting you that can be an important step in your care. Here is a list of statements describing different thoughts and feelings people may have when they are in pain** [share Fig. 3.3 with patients or recite some thoughts off the list based on your understanding of the patient's tendencies]. [Looking at

the list, ask…] **Could you tell me how often you have these thoughts or feelings when you are in pain? Or even when you are anticipating pain?** [Listen, then proceed…] **If you had to pick one or two of these types of thoughts that best fit your experience what would they be?** [Pause. Repeat them back to them][Praise them for the effort…] **This is excellent. By understanding your experience this can help us discover the pain pattern you have, and how your pain impacts you. This relationship is important to know because if we understand this pattern, we can look at possible solutions to reduce these negative effects** [Refer to negative effects like mood or social disruption/disability if they have suggested any earlier].

What I would like us to do know is keep track of these types of thoughts over the next while between our visits. When you come back to see me, I want to know what types of thoughts you have the most and what situations or events are mostly associated with these thoughts. Most importantly, you will need to think about how these thoughts make you feel and what you end up doing about that. We call this coping, so in other words, what did you actually do to try to cope in that situation? Whatever that experience is, and whatever you honestly tried to do or not do in that situation, I will be looking forward to hearing more.

What is interesting about the engagement above is that you have set the stage for a collaborative examination of the pain processes experienced by the patient and how they may be promoted. This establishes patient trust, a foundation for a shared decision-making model to care, and a clear acknowledgment that their psychosocial concerns are important to consider.

Conclusions

CP/CPPS and IC/BPS patients have considerable pain and mental health difficulties that are not currently being managed. Patients suffering from these severe and disabling pain syndromes report significantly diminished quality of life. As with other chronic pain conditions, depression and catastrophizing seem to be key players in outcomes in the UCPPS literature. CBT programs designed specifically for UCPPS patients should be considered as adjunctive treatments to biomedical treatments, with a previous pilot study examining a CBT program for CP/CPPS finding promising results in the form of reduced psychosocial risk factors, pain, and disability. A recently expanded model, including empirically supported components of relaxation, mindfulness, and acceptance techniques, is introduced as a treatment option for clinicians. It is hoped that this chapter helps to also bring the idea of physician-patient communication to the forefront of care once again. Better understanding of psychosocial risk factors and how patient engagement can aid in care will only lead to more satisfied and treatment-adherent patients.

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Advanced Practice Nursing Care for the Pelvic Pain Patient

4

Marina Ruzimovsky and Kathleen Donlon

Introduction

Chronic pelvic pain is a mysterious entity, which has been known and has bedeviled medical practitioners for centuries. Vast numbers of men and women suffer from chronic pelvic pain whose etiology is not all that clear. Such conditions may account for a prevalence of greater than 15 million in the United States and include conditions such as interstitial cystitis/bladder pain syndrome, chronic prostatitis/chronic pelvic pain syndrome, endometriosis, vulvodynia, chronic orchalgia, pelvic floor muscle pain, and others. People afflicted with these conditions often experience vague, lingering symptomology punctuated by severe flares in symptoms. The impact on the community from chronic disease in an economic way is astronomical. In 2014 the cost of medical care for an IC/BPS patient was more than $11,000 for a year of treatment [1].

The diagnostic and therapeutic process may be incredibly frustrating for patients and can easily lead to a breakdown in the patient–clinician relationship. Patients often have unrealistic expectations; depression and catastrophizing are common; and patient migration from practice to practice is routinely observed [2]. In order to appropriately treat and then interact with this patient population, the medical team must be cognizant of these comorbidities. The role of the advanced practice nurse is to support, educate, and treat these individuals. The nursing staff also acts as liaison among the other members of the medical team, the patient and their families, or support systems.

This chapter will describe strategies of care for the chronic pelvic pain patients that are commonly employed by members of the advanced care allied health team. *The level of intervention allowable is determined by local and even institutional mandates.*

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Setting Goals and Expectations

Determining the expectation of the patient is a primary goal before establishing a treatment plan. At the initial office visit, the interviewer should ask the patient what is their primary goal in seeking treatment. Patients tend to come with a laundry list of symptoms and complaints, all of which cannot be dealt with immediately; however, they should be reassured that all their concerns will be addressed. Prioritization is key. Ascertain what the most pressing concerns are, and those are the issues that should be dealt with in a stepwise fashion. Patient goals may or may not be realistic. Helping patients set realistic goals and expectations at the first visit is one of the most important and most difficult aspect of treating patients with chronic pelvic pain. It is important they understand that oftentimes there may be multiple treatments and/or changes in their plan of care before they notice any symptom improvement. Helping patients accept the chronicity of their condition and need for individualized treatment plans will facilitate compliance.

The more familiar the practitioner is with the patient (psychosocial background and medical history), the easier it is to set reasonable goals for treatment. Each patient may have a multitude of complaints ranging from irritative voiding symptoms to sexual dysfunction to chronic pelvic pain. Some symptoms are more problematic than others and it's clear that not all complaints may be addressed during one or two office encounters. It's this clinical complexity that makes a cookie cutter approach to patient care doomed to failure. In identifying what a patient will hear and accept, the clinician will encourage more realistic expectations and thus will be more successful in gaining the cooperation of the patient [3–5].

Self-Management and Self-Empowerment

Acquiring self-management skills is a dynamic process for the chronic pelvic pain patient and is generally done in conjunction with help from family, community, and healthcare professionals. They must learn how to manage symptoms, adhere to treatments, and implement lifestyle changes in order to hopefully achieve remission. Along with educating the patient about their illness and teaching them the requisite regimens, skills, and strategies to manage daily illness needs, the advanced practice nurse (APN) is also key to patient self-empowerment [3]. Giving CPP patients skills and resources to manage their condition on their own is a benefit for both providers and clinicians. Whether it is self-care comfort measures prior to sexual activity or doing home intravesical instillations during an IC/BPS flare, these self-empowerment techniques help patients gain some "control" over their lives without being completely dependent on the medical community [6].

Support of family members and friends can be extremely helpful to both the patient and the clinician. Frequently, these people provide encouragement and contribute to positive outcomes. They regularly play an active role by participating in home therapies such as helping the patient with physical therapy exercises, helping with intravesical therapy, and applying topical creams. During periods of flares, these support people

may assist with the patients' daily responsibilities. Conversely, this assistance can go too far, bordering on enabling behaviors which do not provide the patient with autonomy and self-empowerment. This then results in negative patient outcomes [7, 8].

Treatment Strategies

In the daily care of the CPP patient, particularly those suffering from IC/BPS and CP/CPPS, we have found the following treatment strategies to be particularly helpful in promoting self-care and patient empowerment.

UTI Self-Treatment Protocol

Many CPP patients may develop periodic episodes of bacterial cystitis. By immediate therapy being applied, patients can have infections rapidly treated, which may result in faster recovery. The protocol also is a great relief to patients who know that they can receive therapy rapidly no matter whether they are at home or on vacation. Patients are provided with requisitions for urinalysis and culture/sensitivity and are given a urine collection cup with wipes. They are also given a prescription for an antibiotic that they fill and keep the medication at home. When the patient senses that a urinary tract infection is present, they immediately collect a midstream urine specimen. This is refrigerated and brought to a local laboratory (with the requisition) within 48 h [9]. After the specimen is collected, the patient immediately begins the antibiotic. They are instructed to call the office for the culture results in 48–72 h. The timely use of this protocol will help to prevent flares in many interstitial cystitis patients.

Teaching Pearls
Self-treatment protocol for urinary tract infection following the onset of symptoms:

1. Collect clean-catch urine sample.
2. Start prescribed antibiotic.
3. Bring sample to laboratory of choice (may be refrigerated for up to 48 h if necessary).
4. Inform provider of above.

Pelvic Floor Muscle Relaxation Techniques

Hypertonic pelvic floor dysfunction (HTPFD) is a common comorbidity seen in approximately 50–87 % of patients with IC/BPS [10]. HTPFD can exacerbate symptoms and itself can worsen in response to IC flares. Educating the patient about simple

pelvic floor muscle (PFM) relaxation techniques can help break the vicious pain-tightening/spasm-flare cycle that can occur. Some home therapies patients can employ are warm baths with 2 cups Epsom salt or Aveeno® oatmeal for 10–15 min daily, use heated car seats for long drives, avoid constipation and Valsalva maneuvers with defecation and urination, and avoid Kegel maneuvers or tightening of their PFMs [11].

Self-Intravesical Therapy

For those patients in need of intravesical therapies, it's often quite inconvenient to come to the office due to distance, work, or family obligations. To remedy this problem, patients can be taught to administer their instillations at home. The patient and perhaps a support person are instructed in the method of drawing up and mixing the medications necessary for the instillation and then instilling the medication through a small French urethral catheter into the bladder. The patient does not leave the office until having successfully performed the entire process. Phone support is helpful. Written material is always provided and patients are given ample opportunity to ask questions and take notes. The patients are supplied with the appropriate prescriptions for medications and equipment necessary for this procedure at home. These supplies unfortunately are not available in most chain-type pharmacies and often must be obtained from a specialty pharmacy [11, 12].

Teaching Pearls

1. Review written materials with the patient.
2. Review of basic anatomy.
3. Use of appropriate equipment and medications for the treatment.
4. Return demonstration of this entire process from mixing to instillation.

   Advise patient where to obtain supplies and medications.

Therapies Prescribed or Instituted by the APN

Advanced practice nurses can take responsibility for forms of care discussed elsewhere in this book such as managing pharmacotherapy, making appropriate referrals for physical therapy and dietary management. They can often perform myofascial trigger point injections and certain forms of neuromodulation.

Oral and Topical Therapies

The side effects associated with many of the medications used to treat CPP are often related to dosing. Dosing begins at the lower range and is increased slowly to achieve efficacy. Unfortunately, this sometimes can take many weeks during which the patient can become discouraged with the process [7].

Topical medications such as those used for provoked vestibulodynia (PVD) should be first applied in the office to assure that the patient can tolerate it when used at home. Patients are instructed by using a mirror to demonstrate the amount and location of cream application. This is also an opportune time for the APN to educate the patient about their anatomy.

In some cases, the patient might need the assistance of their partners to properly apply the medication; therefore it is important to remember to include those people in these teaching sessions. Again, any medication needs tincture of time to begin to make changes in the patients' symptomology and encouragement is imperative. Clear instructions which have been written for each individual patient can be helpful to their understanding and correct use of these treatments.

Advanced Practice Pearls

1. Monitor patient for potential side effects and interactions between medications.
2. Side effects (and response to therapy) can be dose dependent.
3. Show patients where to apply topical vulvar creams with a mirror demonstration in the office.
4. Encouragement remains key throughout trial of therapy.

   Involve partners in therapy.

Physical Therapy

The role of the APN with regard to physical therapy is initially instructive and supportive to the techniques of the physical therapist. Most of these techniques will be new experiences and can be embarrassing to patients. Patients must be adequately prepared as to what to expect from pelvic floor physical therapy by the clinician prior to their first visit. After the initial evaluation, frequency of visits will be set by the therapist. Patients need to understand that a large portion of their therapy consists of stretching and exercises done daily at home. It is important that patients with a significant other be open and honest with them regarding their physical therapy routine as the significant other may be an integral part of this home therapy in order to achieve the desired positive result. In many cases symptoms will worsen before they improve, and it will fall on the primary medical team to be a sounding board and a cheerleader to encourage these patients to persevere with sometimes difficult and uncomfortable therapy [13–16].

Trigger Point Injection Therapy

Trigger points (TrP), a frequent source of pelvic pain, are hyperirritable regions of skeletal muscle associated with palpable nodules. Trigger point injections, using a variety of agents, most commonly local anesthetics, are used to treat myofascial pain

that has not responded to more conservative approaches and are often employed as adjuvant therapy [17]. These injections can be administered in many locations; however, the most commonly used approaches in our practice for the CPP patient are a paravaginal or transvaginal approach for females and a perineal approach for males. Patients will need to be fully consented of the adverse effects, risks, and benefits of the procedure. Patients are usually awake in order for the practitioner to elicit the exact location of tenderness in the muscle being injected. The patient needs to be fully educated about what to expect as to pain/burning with each injection [14, 18].

Dietary Guidance

Many IC/BPS patients will arrive at your practice with preconceived notions about what they can and cannot eat. Patients have access to information via the internet with regard to effects of certain foods and beverages on various diagnoses. Research is being done in this area and in fact according to some researchers, coffee, chocolate, citrus foods, tomato products, alcohol, cola, and Mexican and Thai foods were among the most commonly reported comestibles that exacerbated IC/BPS symptoms [13, 15, 16, 19]. It is important to remember that not every patient will be food sensitive; and of those patients who have food sensitivities, not all are sensitive to the identical items. Appropriate referral to a nutritionist familiar with IC/BPS is paramount to helping patients maintain a healthy, well-balanced diet (see chapter xx for further information on diet and nutrition) [12, 14–16, 19].

Approach to Telehealth

A responsibility of the APN is telephone triage of the chronic pelvic pain patient. By assessing the patient's needs via the telephone, the APN may be able to change the direction of therapy rather than bringing a patient to the office. Follow-up appointments can then be set to evaluate if the implemented change was successful. Conversely an appointment may be more appropriate after telephone assessment is completed.

Conclusion

Chronic pelvic pain is a complex set of symptoms that is multifactorial and is always a work in progress. This chapter has discussed the complexities of treatment of this underserved group of patients with regard to the advanced practice care. Always apply conservative forms of therapies before radical treatments; a multidisciplinary approach is essential for a positive outcome; and the simultaneous use of more than one treatment modality is often necessary. The care of patients with these diagnoses is a fundamental part of succeeding in changing the lives of these patients and is

generally long term. Engaging the patients' families and support persons along with giving the patients the tools to help them deal with their chronic condition promotes self-empowerment and independence.

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Diet Therapy in the Context of Chronic Pelvic Pain

5

Barbara Shorter and Barbara Gordon

Introduction

The synergistic relationship between food and well-being is beyond doubt. With the discovery that vitamins and minerals eradicate deficiency diseases, the role of these essential nutrients in maintaining health and mitigating disease has been confirmed for centuries. Indeed, there is now abundant evidence that comestibles enhance health through complex biological mechanisms [1–4].

Conversely, the consumption of certain foods and beverages may have a deleterious effect on health, such as the development or potentiation of neoplastic, cardiovascular, or inflammatory disease [5–7]. Furthermore, conditions such as food allergies, celiac disease, and interstitial cystitis/bladder pain syndrome (IC/BPS) warrant the avoidance or limitation of specific comestibles. Historically, urology embraced the role of diet on prostate cancer and nephrolithiasis and gynecology the impact of specific nutrients on pelvic health [8, 9]. More recently, however, studies in both fields focus on diet's effect on chronic pelvic pain (CPP). What has been discovered can profoundly affect a patient's quality of life [10–15].

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Treatment algorithms for CPP conditions, such as interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic pelvic pain syndrome/chronic prostatitis (CPPS/CP), include dietary modification as an integral component of patient care. For other chronic pelvic pain syndromes, such as vulvodynia and pelvic floor dysfunction (PFD), changes in diet may be effective for some patients, suggesting the need for further investigation.

Effect of Foods and Beverages on Chronic Pelvic Pain

Whereas pathogenic mechanisms of CPP remain uncertain, research on the relationship of comestibles to the exacerbation of IC/BPS symptoms spans more than two decades [10, 11, 15–23].

One of the first publications suggesting dietary restrictions compiled patient statements gathered at a women's health clinic for IC/BPS (1984–1985)—Gillespie found that certain foods and beverages increased bladder discomfort in some individuals [18]. Following this, in 1992, Gillespie studied the urine of 240 IC/BPS patients who agreed to ingest offending foods. Most (83 %) reported increased pain and frequency during the study and, when rechallenged, identified the onset of symptoms as soon as 30 min. after ingestion [17]. Later, Koziol determined that acidic and spicy food, alcoholic or carbonated beverages, coffee, and tea affected more than half of 374 IC/BPS patients surveyed [19]. Studies conducted more recently indicate that as many as 90 % of patients report certain foods and beverages definitively and negatively affect their bladders. The most problematic offenders include coffee, tea, alcohol, soda, certain fruits and fruit juices, tomatoes and tomato products, spicy foods, and artificial sweeteners (see Fig. 5.1) [10, 11, 15, 20]. However, symptom management is not consistent with dietary modification, and for unknown reasons dietary pain triggers vary among patients [15, 24].

A case study published in the 1990s suggested a link between the consumption of high-oxalate foods and vulvar pain [25]. Restriction of potentially bothersome comestibles along with calcium citrate supplementation relieved symptoms, pain returned when the protocol ceased, and reintroduction of the treatment once again mitigated symptoms [26]. However, further research suggests that high-oxalate foods are an unlikely causal factor in the onset of vulvodynia [27]. Follow-up studies failed to replicate the original finding; only a small sampling of women found this strategy helpful [27–30]. Without a complete understanding of the etiology of this condition, the potential role of a low oxalate diet remains inconclusive.

Research associates chronic pelvic pain syndrome/chronic prostatitis pain with the intake of certain comestibles. Almost half of the men (44 %), completing a food sensitivity questionnaire, noted that specific foods and drinks elicit symptoms. Top offenders included spicy foods, coffee, hot peppers, alcoholic drinks, and chili; about one-quarter (23 %) of participants noted psyllium, water, and polycarbophil alleviated symptoms [31]. Additional studies also suggest that men restrict coffee, alcohol, and spicy foods [19, 32–36]. Focus groups conducted with CPP patients, however, noted that although some patients tolerated certain types of alcohol, results on specific beverages varied ("champagne but not wine or beer; beer but not wine") [24].

MOST BOTHERSOME	LEAST BOTHERSOME		
Fruits	**Fruits**		
• Cranberry juice • Grapefruit and grapefruit juice • Lemon • Orange and orange juice • Pineapple and pineapple juice • Strawberries	• Apricots • Bananas • Blueberries	• Dates • Melon (honeydew and watermelon)	• Prunes • Pears • Raisins
Vegetables	**Vegetables**		
• Chili peppers • Pickles • Sauerkraut • Tomato and tomato products	• Avocados • Asparagus • Beets • Broccoli • Brussels sprouts • Cabbage • Carrots	• Cauliflower • Celery • Cucumber • Eggplant • Mushrooms • Peas	• Potatoes (white potatoes, yams, sweet potatoes) • Radishes • Spinach • Squash • Turnips • Zucchini
Grains	**Grains**		
	• Oats • Rice		
Protein Foods	**Protein Foods**		
• Processed sandwich meats (salami, bologna) • Soy	• Beef • Fish (shrimp, tuna fish and salmon)	• Eggs • Nuts • Peanut butter	• Pork • Poultry (chicken and turkey) • Lamb
Dairy	**Dairy**		
• Yogurt	• Milk (low-fat and whole) • Cheeses (mild)		
Condiments	**Condiments**		
• Chili • Horseradish • Ketchup • Salad dressings • Soy sauce • Vinegar • Worcestershire sauce	• Herbs • Garlic infused olive oil		
Beverages	**Beverages**		
• Alcohol • Coffee (caffeinated and decaffeinated) • Tea (caffeinated and decaffeinated) • Carbonated drinks (cola, non-cola, diet, and caffeine-free)	• Grain beverages/Coffee substitutes (Cafix®, Pero®, Roma, Postum®) • Water		
Other Foods	**Other Foods**		
• Chocolate • Indian food • Mexican food • Pizza • Spicy foods • Thai food	• Popcorn • Pretzels		
Additives/Artificial Sweeteners	**Additives/Artificial Sweeteners**		
• Artificial sweeteners (Equal® (sweetener), NutraSweet®, Saccharin, and Sweet'N Low®) • Monosodium glutamate (MSG)			

Fig. 5.1 List of least and most bothersome foods for IC/BPS. Sources: Compiled from Shorter B, Lesser M, Moldwin RM, Kushner L. Effect of comestibles on symptoms of interstitial cystitis. J Urol. 2007;178(1):145–52 and Bassaly R, Downes K, Hart S. Dietary consumption triggers in interstitial cystitis/bladder pain syndrome patients. Female Pelvic Med Reconstr Surg 2011;17(1) 36–9

Despite the lack of controlled research, validated questionnaire-based studies provide evidence that the restriction of certain foods and beverages plays a fundamental role in the management of chronic pelvic pain for the vast majority of patients. This corroboration led ten disparate professional associations—geographically spanning three continents—to recommend dietary modifications as the first-line treatment in published guidelines [37–48].

The burgeoning interest in this topic has also yielded an unfortunate plethora of misinformation. Grasping touted generalizations regarding specific groups of edibles, patients frequently eliminate more foods and beverages than necessary. Extensive lists of comestibles to avoid have evolved, often based on inaccurate

anecdotal information. In an effort to alleviate pain, highly motivated patients may unnecessarily abstain from healthy foods, possibly leading to nutritional deficiencies. Limiting nutrients can be damaging and counterproductive to patients who need to fortify immunity, nerve transmission, wound healing, blood flow, and overall nutrition status. Although testimonies indicate certain foods exacerbate symptoms for some and the elimination of offending items can help control CPP, the importance of replacing bothersome foods with nutritious alternatives is inadequately emphasized. This chapter edifies the relationship between comestibles and CPP symptoms and elucidates dietary recommendations for this underserved population.

Potential Contributions of Comestibles to the Pathology of CPP

There is an urgent need for evidence-based research establishing the underlying pathological mechanisms between chronic pelvic pain and the ingestion of certain foods, beverages, and supplements. Nonetheless, several promising theories offer insights on diet and pelvic pain. Popular speculations include alterations in the urothelial barrier, neurogenic inflammation, neural upregulation, and organ cross talk [49–53].

Idiopathic alteration of the glycosaminoglycan mucin layer may enable potentially caustic urine solutes to penetrate deeply into layers of the bladder wall, producing symptoms of chronic bladder pain [50]. Simultaneously, high levels of urinary antiproliferative factor (APF) may inhibit epithelial cell growth [54]. Thereby, a faulty urothelial barrier may contribute to the leaky bladder observed in IC/BPS patients. In turn, this defect may allow noxious substances—perhaps some found in foods—to seep from the urine into sensitive bladder tissue.

Damage to or dysfunction of the peripheral or central nervous system, rather than direct stimulation of pain receptors, may prompt neuropathic pain associated with CPP. Neurogenic inflammation, the release of mediators from sensory nerves, thus, may be a culprit of inflammatory changes. Given that unidentified substances in foods appear to cause sensory nerve endings in the bladder to secrete neurotransmitters, inflammation conjointly with provoked CNS transmissions may account for the sensation of pain [50, 54, 55].

Furthermore, elevated numbers of vanilloid receptor 1 (transient receptor potential cation channel subfamily V member 1 (TRPV1)) are present with bladder pain syndrome [56]. Hot peppers containing capsaicin, identified as particularly problematic in exacerbating pain symptoms in this subgroup of CPP patients, may trigger neural upregulation and bladder reflex activity.

Of note, organ “cross talk” results in the modulation of pain response by visceral inputs distinct from the inflamed site [51]. It is conceivable that the union of stimuli from the gut and the bladder exceeds a threshold, resulting in pelvic pain. Also, long-standing tense holding patterns/excessive straining developed in childhood may lead to chronic constipation and consequently contribute to the onset of pelvic floor dysfunction. [57–60].

Compromised pelvic floor muscle integrity, i.e., hypertonic, dysfunctional muscles can precipitate chronic pelvic pain, including referred pain to the vulvar region

[61–63]. Studies link hypovitaminosis D and chronic musculoskeletal pain [6, 64, 65]. More targeted research suggests a role of vitamin D in maintaining the integrity of musculoskeletal structures, such as the pelvic floor, and links low vitamin D levels with weakened pelvic floor muscles [10, 11, 66–70]. However, further research is needed.

Recommended Dietary Interventions

Clinical experience and published studies, despite being limited, reveal that most CPP patients are sensitive to some and varied comestibles, and, thus, diet manipulation becomes a cornerstone for treatment of chronic pelvic pain. Embracing this tenet, American Urological Association guidelines, for example, suggest the avoidance of certain foods known to be common bladder irritants in patients with IC/BPS. Individual triggers and comorbid conditions necessitate a systematic and thorough process to determine the particular edibles that elicit pain, frequency, and urgency unique for each patient. Equally as important, to ensure adequate nutrition, patients must replace restricted comestibles with alternative foods and beverages and/or supplementation providing the same nutrients that were eliminated. Fruits, particularly citrus, are a food group containing the most problematic edibles. This category typically provides adequate intake of vitamin C. Patients should be advised to consume non-problematic fruits and more vegetables (see Fig. 5.2) to obtain this important nutrient. Balancing metabolic needs with personal palate preferences are essential for successful dietary compliance.

EXCELLENT SOURCES (20% DV)*	GOOD SOURCES (10-19% DV)*
• Bell peppers • Broccoli • Brussels sprouts • Cabbage • Cauliflower • Greens (Swiss chard, spinach, kale) • Melon (honeydew) • Potato • Radishes • Rutabaga • Squash (summer) • Watermelon	• Asparagus • Bananas • Blueberries • Carrot • Celery • Cherries • Corn • Cucumber • Green beans • Peaches

* DV means Daily Value. The daily value recommendation for women is 75mg. and for men is 90mg.

Fig. 5.2 IC/BPS-friendly foods with vitamin C (ascorbic acid)

Elimination Diet

An elimination diet is the most effective, commonly used tool to determine whether or not certain foods may provoke or intensify symptoms. This method will prevent patients from eliminating more foods than is necessary in order to maintain adequate nutrient intake and optimal quality of life. The practitioner begins by collecting a detailed diet history, including any known food allergies and/or intolerances, and assessing individual nutritional needs. A useful tool for identifying trigger foods and beverages for those with IC/BPS and/or CPPS/CP is the Shorter-Moldwin Food Sensitivity (SMFS) Questionnaire, a validated instrument (see Fig. 5.3) [71]. Subsequently, the practitioner must discuss the premise of an elimination diet with the patient—emphasizing the importance of excluding, for 1 month, specific problematic comestibles. There can be no exceptions to foods and beverages allowed/consumed. Successful identification of potentially offending items requires strict adherence. The consumption of even one possible trigger food can undermine the purpose of the plan. Patients addicted to coffee may experience caffeine withdrawal symptoms. They may "sneak" coffee while on the elimination diet, not realizing that coffee is one of the most significant instigators of bladder symptoms. Be prepared to discuss how you can support patient adherence to this and other restrictions. See Fig. 5.4 for step-down approach for eliminating caffeinated beverages.

For those with IC/BPS and CPPS/CP, start with restriction of items that typically trigger symptoms (see Fig. 5.1), as well as any additional edibles the patient finds bothersome per the SMFS [71]. Research found that more than half (50–63 %) of individuals with IC/BPS were cognizant of specific comestibles that trigger bladder symptoms [23]. Of note, some patients may not realize that certain foods exacerbate their pain because symptom improvement may take weeks to appear after a comestible has been eliminated; they expect to experience dramatic improvement in a few days. If the bladder is not given adequate time to calm, problematic foods or beverages may not be obvious. For instance, if coffee is eliminated for a few days and bladder symptoms do not subside, a patient may assume that caffeine is not the bothersome comestible. However, a longer period of elimination may produce a different result.

To test the hypothesis that specific foodstuffs exacerbate bladder pain, urgency, and frequency, after 1 month of bladder-friendly foods, patients must methodically reintroduce a suspected trigger to track its effect on symptoms. Add back no more than one food or beverage at a time. New items should be incorporated slowly across a 3-day period:

- Day 1—try a very small (partial) portion.
- Day 2—if no symptoms appear, consume a slightly larger amount.
- Day 3—if no flaring continues, test a regular size portion.

Reports regarding the onset of symptoms after the ingestion of offending item(s) vary from within a few minutes (anecdotal) to 20 min to 4 h [23, 24, 72]. Focus

group data (57 women with urologic chronic pelvic pain) were unable to provide insights into a specific length of time before a flare onset based on individual dietary triggers [24]. Clinical experience, however, suggests a 3-day waiting period between the introduction of each test food. Do not add any "challenge" foods back into the regular daily diet until completing this testing protocol for all foods. While

a **SHORTER-MOLDWIN FOOD SENSITIVITY QUESTIONNAIRE**

Date:_____

Name: _____

Gender: Male_____ Female_____

Age: _____

Please circle answers

1. Do certain foods and/or beverages worsen your bladder symptoms?
   a. Yes
   b. No
   c. Don't Know

2. If they worsen your bladder symptoms do they:

i. make your urine frequency (the number of times you have to urinate over the course of the day or night)…	Worse	No change	Not Applicable
ii. make your urine urgency (the need to reach bathroom facilities quickly)…	Worse	No change	Not Applicable
iii. make your pain…	Worse	No change	Not Applicable

3. Do you ever eat foods, beverages, or supplements that you know will increase your symptoms?
   a. yes, daily
   b. yes, weekly
   c. yes, monthly
   d. yes, less than once a month
   e. never
   f. don't know

4. Have you modified your diet in any way because of information that you were told by a health care professional or read on a website, in a magazine or newspaper, saw on T.V. or learned from any other media about foods or beverages worsening IC bladder symptoms?
   a. Yes
   b. No

Fig. 5.3 (**a**) Shorter-Moldwin Food Sensitivity Questionnaire. (**b**) Key for IC/BPS Food Sensitivity Questionnaire

5. Read through the following lists of foods. **Check** the box that relates to the effect the food or beverage has on urinary urgency and/or frequency and / or bladder pain.

***Skip this question if you are not food or beverage sensitive**

Effects on Symptoms				
Food	***I Don't Know***	***Worsen Symptoms***	***No Effect***	***Improves Symptoms***
CITRUS FOODS:				
Grapefruit				
Lemons				
Oranges				
Pineapples				
Cranberry Juice				
Grapefruit Juice				
Orange Juice				
Pineapple Juice				
Pears				
SPICY FOODS:				
Chili				
Burritos				
Peppers (hot)				
Mexican Food				
Indian Food				
Thai Food				
ALCOHOLIC BEVERAGES:				
Beer				
Red Wine				
White Wine				
Champagne				
Hard Liquor and Mixed Drinks				
MEAT, FISH, CHICKEN:				
Beef				
Tuna				
Chicken				

Fig. 5.3 (continued)

Effects on Symptoms				
Food	***I Don't Know***	***Worsen Symptoms***	***No Effect***	***Improves Symptoms***
OTHER BEVERAGES:				
Caffeinated Coffee				
Decaffeinated Coffee				
Caffeinated Tea				
Decaffeinated Tea				
Cola Soda				
Non Cola Soda				
Diet Soda				
Milk				
Water				
ARTIFICIAL SWEETENERS:				
Nutrasweet®				
Sweet & Low®				
Equal®				
Saccharin				
OVER THE COUNTER PRODUCTS:				
Prelief®				
Tums®				
Metamucil®/Fibercom®				
Senekot®				
OTHER FOODS/ADDITIVES:				
MSG				
Vinegar				
Horseradish				
Aloe Vera				
Rice				
Tomato/ Tomato Products				
White Potatoes				

Are there any foods not on this list that trigger bladder flares? Yes____ No____
If yes, please list them: _____
_____

Fig. 5.3 (continued)

Key for IC/BPS Food Sensitivity Questionnaire

Recognizing that a common challenge in using any questionnaires may be a tendency of clients to quickly respond without carefully thinking through each question, the following key provides a summary of the findings typical for those with IC/BPS. If results are not consistent with key, you may need to walk through the questionnaire with the patient.

Foods Identified as Most Bothersome to IC/BPS Patients	Foods Identified as Least Bothersome to IC/BPS Patients
Caffeinated Coffee	Water
Decaffeinated Coffee	Milk
Caffeinated Tea	
Decaffeinated Tea	Pears
Cola soda	
Non cola soda	White potatoes
Diet Soda	Rice
Beer	
Red Wine	Chicken
White Wine	Beef
Champagne	Tuna Fish
Hard Liquor and Mixed Drinks	
	Prelief®
Grapefruit	Tums®
Lemons	Metamucil® /Fibercon®
Oranges	Senekot®
Pineapple	
Cranberry juice	
Grapefruit juice	
Orange juice	
Pineapple juice	
Tomato	
Tomato Products	
Hot Peppers	
Horseradish	
Vinegar	
MSG	
Nutrasweet®	
Sweet & Low®	
Equal®	
Saccharin®	
Mexican Food	
Thai Food	
Indian Food	
Chili	
Burritos	

Fig. 5.3 (continued)

Validated questionnaires indicate that coffee (caffeinated and decaffeinated) can be one of the most common bladder flare triggers for IC/BPS patients. This popular habit-forming beverage is regularly consumed because of its' powerful stimulating effect. It "wakes us up" during times of fatigue and stress. For many, morning coffee is also a habit. The addictive drug 'caffeine', found in coffee, is not easy to eliminate from daily intake because it results in withdrawal headaches and fatigue. However, some IC/BPS patients must avoid all coffee products; therefore, the practitioner should be prepared with effective suggestions.

Although going 'cold turkey' is one option, it has uncomfortable side effects and may discourage some from quitting the habit. An advisable approach is to suggest that patients' slowly cut back on coffee; gradually reducing intake as one does when weaning off a drug.

It is helpful to replace the coffee with an alternative. Though tea is not typically a viable option for this patient pool, there are a number of coffee substitutes. For example, available in health food stores and online, are Cafix®, Pero®, Roma and Postum®. These vegetable-based products are generally well-tolerated; however, those with intolerances to wheat and rye should read the food labels. Anecdotal evidence also suggests that these grain beverages may result in less frequent voiding compared to water. Furthermore, patients can carry individual portions with them to mix with hot or cold water when eating out. Keep in mind, that if a particular product does not appeal to or agree with the patient, others should be tried.

Finally, there are other strategies to help patients get energized. Exercise; even a brief, but brisk, 10-minute walk can be an effective stimulant. Not skipping meals and eating throughout the day helps sustain energy levels, as well as eating protein with complex carbohydrate (whole grains) meals to help regulate blood glucose levels. Regular and adequate sleep is also essential to achieve optimal energy level.

Fig. 5.4 Step-down approach for eliminating caffeinated beverages

following the elimination diet, a food/symptom/voiding diary (see Fig. 5.5) may help to determine specific food and beverage triggers [15, 23, 24]. Comestibles could trigger flares directly or exacerbate comorbid conditions, e.g., irritable bowel syndrome (IBS), resulting in a flare [24]. The use of a food diary has been shown to be a very effective tool to enhance a patient's awareness of food intake [73]. This may be valuable to the success of the testing plan and should be encouraged.

Given the severity of pain and impact on quality of life experienced by those with CPP, long-term elimination of offending foods and beverages may be necessary. In addition, for patients with severe CPP triggers, medical management strategies to minimize flaring are advisable during challenge tests. Consider using the elimination diet to test women with vulvodynia for oxalate sensitivity. Restricting

FOOD INTAKE AND VOIDING DIARY

Be sure to include as much information as possible about food eaten (portion sizes, preparation (baked or fried chicken for example), all liquids, all condiments, and all ingredients in mixed dishes. Also, think about your activities for the day to see if there was something you may have missed.

Date	Time	Food	Quantity	Notes on Preparation	Symptoms	Amt. Voided
	Awaken:					

How many times did you get up during the night to urinate? _____

Symptoms: voiding, pain, frequency, urgency

Amount (Amt.) voided: small, moderate, large amou

Sample

Be sure to include as much information as possible about food eaten (portion sizes, preparation (baked or fried chicken for example), all liquids, all condiments, and all ingredients in mixed dishes. Also, think about your activities for the day to see if there was something you may have missed.

Date	Time	Food	Quantity	Notes on Preparation	Symptoms	Amt. Voided
5/1/15	***Awaken:*** *7:00 am*					*Moderate*
	7:30 am	*Mushroom omelet*	*2*	*Cooked in butter, salt*		
		Decaf coffee	*12 oz.*			
		Coffee cream	*2 T.*	*In coffee*		
	9:15 am	*Filtered water*	*16 oz.*	*Sipped through morning*		*Small*
	10:30 am				*Pain*	
	10:40 am					*Small*
	12:40 pm	*Salami*	*4 oz.*			
		Wheat bread	*2 slices*			
		Mustard	*1 tbsp*			*Small*
		Ice water	*16 oz.*	*Splash of lime juice*		
	2:00 pm				*Urgency, Pain*	*Small*
	3:15 pm	*Filtered water*	*16 oz.*			*Small*
		Raw baby carrots	*7*			
	3:45					
	5:00 pm	*Raspberry yogurt*	*6 oz.*	*Low sugar, with Splenda*		*Small*
	6:00 pm				*Urgency, Pain*	*Small*
	7:00 pm	*Pork barbeque*	*6 oz.*	*Grilled*		
		Green beans	*¾ cup*	*Canned, cooked in butter, salt*		
		Cold slaw	*½ cup*	*Store bought*		
		White rice	*½ cup*	*Only salt added*		
	7:30 pm					*Moderate*
	8:30 pm	*Raspberry Crystal Light*	*16 oz.*	*Artificial sweetener*		*Small*
	10:00 pm				*Pain*	
	10:15 pm	*Filtered water*	*12 oz.*			
		Chocolate candy	*2 pieces*			
	10:30pm				*Pain*	*Small*

How many times did you get up during the night to urinate? 3

Symptoms: voiding, pain, frequency, urgency

Amount (Amt.) voided: Small, moderate, large amount

Fig. 5.5 (**a**) Food intake and voiding diary

intake of oxalates may offer relief for a small percentage of patients [29]. However, there are tangible shortcomings with this assessment. A discordance of documented oxalate levels in foods, for example, complicates conclusions [74]. In addition, the form of the oxalate in comestibles, the level of oxalate-degrading bacteria in the individual's gastrointestinal tract, and the calcium and magnesium ratio in a food

and a total meal affect oxalate absorption rates [75]. Food processing also alters oxalate values—processed grains and boiled vegetables typically have less oxalate than whole foods. For better outcomes, suggest the reduction of edibles typically reported to be very high in oxalates, e.g., nuts, spinach, tea, rhubarb, bran, and chocolate (see Fig. 5.6), as well as consumption of adequate fluids to help dilute urine and prevent aggregation of crystals [76]. In addition, consuming dietary calcium with oxalates will bind the oxalate, yielding an insoluble complex that is not absorbed in the digestive tract, hence lowering oxalate absorption [77]. Low oxalate diet advocate, Solomons, suggests also supplementing with calcium citrate to reduce levels of this substance in the body [25].

Collaboratively with the patient, develop menus assimilating the list of least bothersome foods (see Fig. 5.7 for sample 1-day menus), personal preferences, and individual nutritional needs. Also, advise patients to carefully review food labels. To enhance understanding of and conformity to recommendations, employ the behavioral change strategies such as the transtheoretical model developed by Prochaska to assess the individual's readiness to revise dietary patterns [78]. Effective consults must address barriers to change such as the easiness of status quo, ambivalence and/or anxiety about alterations, limiting or avoiding favorite foods, and cost considerations, as well as offer solutions for implementing necessary long-term lifestyle changes (see Fig. 5.8). Of note, other lifestyle adaptations to discuss with patients include additional flare triggers such as skipping meals, medications, chlorinated water, chemically laden laundry products, sitting on cold seats etc. [24].

Comorbidities Needing Consideration

Confounding treatment strategies, a large portion of chronic pelvic pain patients suffer with comorbidities that may exacerbate pain and pelvic symptoms. IC/BPS patients, for example, may present with one or more comorbid conditions including IBS (38.6%), vulvodynia (16–50%), and pelvic floor dysfunction (87%) [79–84]. A quarter of men with CPPS/CP (22%) struggle with IBS [85]. Women with vulvodynia frequently present with IBS and IC/BPS [86]. Individuals with CPP often experience concomitant constipation (21.6%); bloating is another common problem (24.2%) [32, 87–89]. Thus, various strategies must be integrated to account for the numerous dietary considerations of comorbid conditions.

Constipation

For those with chronic pelvic pain and concomitant chronic constipation, the causal relationship is often multifactorial. Dietary patterns and lifestyle factors, physical and mental health conditions, medications, and supplements, among other factors, may influence bowel habits and subsequently the choice of therapeutic interventions [90–92]. Research has indicated causal relationships between constipation and other health conditions such as pelvic floor dysfunction. This, in turn, is often associated with IC/BPS, CPPS/CP, and comorbid IBS [88, 90, 91, 93].

Data sources of oxalate levels in foods vary greatly. The foods below are consistently listed as high in oxalate across reputable food composition references.

- Beets
- Blackberries
- Buckwheat
- Chocolate
- Kidney Beans
- Millet
- Nuts
- Potatoes
- Rhubarb
- Rye
- Sesame Seeds
- Soybeans
- Spinach
- Sweet Potatoes
- Wheat Bran

Fig. 5.6 Foods high in oxalates

MENU FOR IC/BPS	LOW FODMAP MENU FOR CPP AND COMORBID IBS	HIGH FIBER MENU FOR IC/BPS	LOW OXALATE MENU FOR IC/BPS AND/OR VULVODYNIA
Breakfast Raisin Bran Cereal Blueberries Milk Skim or 1% Coffee Substitute with Skim Milk or 1%	**Breakfast** Oatmeal with Chopped Walnuts Banana Lactose-free Milk Coffee Substitute	**Breakfast** Raisin Bran Cereal with Blueberries Whole Wheat Toast Margarine Coffee Substitute with Skim Milk or 1%	**Breakfast** Multigrain Cheerios Milk, Skim or 1% Watermelon Coffee Substitute with Skim Milk or 1%
Mid-Morning Snack Carrots and Celery Peanut Butter	**Mid-Morning Snack** Corn Muffin Rice Milk	**Mid-Morning Snack** Oatmeal Muffin Skim Milk or 1%	**Mid-Morning Snack** Mozzarella Stick Blueberries
Lunch Whole Wheat Bread Turkey Lettuce Avocado Apple Coffee Substitute with Skim Milk or 1%	**Lunch** Grilled Chicken on Oat Bread Spinach Salad Olive Oil and Herb Dressing Almonds Lactose-free Milk Coffee Substitute	**Lunch** Grilled Chicken Brown Rice Garden Salad Olive Oil and Herb Dressing Dates Cucumber Water	**Lunch** Oat Grain Bread Roast Turkey Avocado Spread Lettuce Coffee Substitute with Skim Milk or 1%
Mid-Afternoon Snack Pretzels or Popcorn Water	**Mid Afternoon Snack** Cottage Cheese Blueberries Water	**Mid-Afternoon Snack** Apple Slices Peanut Butter Skim Milk or 1%	**Mid-Afternoon Snack** Popcorn Skim Milk
Dinner Chicken Breast, Baked or Broiled Sweet Potato Peas Salad Olive Oil and Herb Dressing Whole Grain Dinner Roll Dates Coffee Substitute with Skim Milk or 1%	**Dinner** Salmon, Broiled Baked Potato Sautéed Green Beans Cucumber Salad Raspberries Rice Milk Coffee Substitute	**Dinner** Salmon, Broiled Quinoa with Toasted Almonds Roasted Carrots Mixed Green Salad with Chickpeas Olive Oil and Herb Dressing Coffee Substitute with Skim Milk or 1%	**Dinner** Salmon, Broiled White Rice Broccoli Cucumber Salad Olive Oil and Herb Dressing Pears Coffee Substitute with Skim Milk or 1%
Snack (Dessert) Ice Cream Pear Water	**Snack (Dessert)** Pretzels or Popcorn Water	**Snack (Dessert)** Popcorn Prunes Water	**Snack (Dessert)** Cornmeal Crackers American Cheese Water

Fig. 5.7 Sample 1-day menus

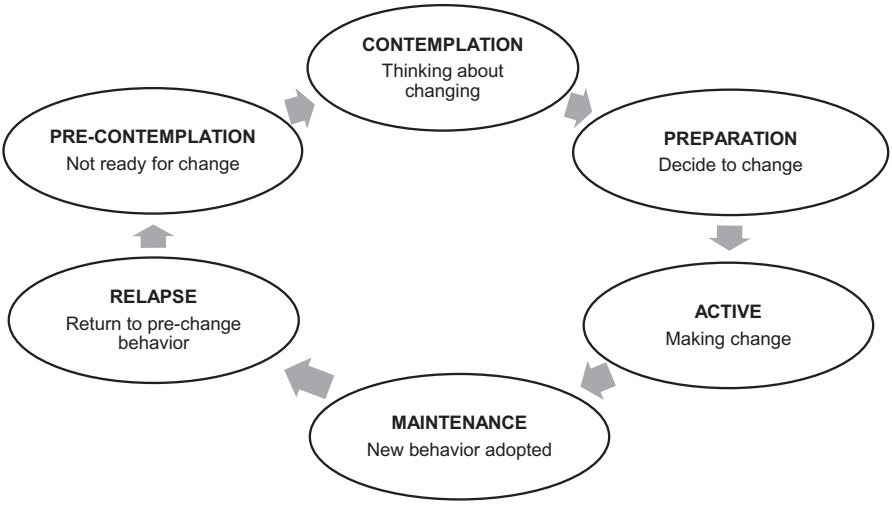

Fig. 5.8 Transtheoretical model for behavioral change

For CPP patients, who follow a typical Western diet, insufficient intake of adequate dietary fiber (e.g., whole grains, legumes, fruits, and vegetables) may be a causal agent for constipation. Indigestible residue from foods is needed to produce fecal bulk and decrease stool transit time [32, 90–92]. This limited fiber intake coupled with self-imposed fluid restrictions, a strategy sometimes used by patients to decrease the frequency of voiding, may exacerbate symptoms of irregularity by further producing dry, hard stools.

Effects of Medications on Bowel Habits

Pharmacological therapeutic agents used by chronic pelvic pain patients may be contributory factors for irregular bowel habits, e.g., antihistamines, narcotic pain medications, nonsteroidal anti-inflammatory drugs, and tricyclic antidepressants can increase the incidence of constipation. Studies have concluded that up to 90 % of those who take opioids for pain experience constipation [94]. Changes in bowel habits may also be associated with the use of dietary supplements, specifically those containing calcium and iron [90, 95]. Figure 5.9 lists medications and supplements that commonly cause constipation.

Nutrition Intervention for Constipation

Query about typical bowel patterns when noting the patient's history [92, 93]. Discuss the individual's usual dietary intake—assess food triggers previously collected with the Shorter-Moldwin Food Sensitivity Questionnaire. In addition, the fullness and bloating produced by constipation may result in a decreased appetite and, substantially, less than optimal dietary intake. These symptoms may contribute to an inadequate intake of nutrients necessary for normal body functioning and extend the chronicity of the condition [95].

MEDICATION / SUPPLEMENT	TYPICAL REASON PRESCRIBED
Antihistamines	Nocturia, daytime frequency, vulvar pain, painful intercourse
Narcotic Pain Medications	Pain
Non-steroidal Anti-inflammatory Drugs	Pain
Tricyclic Antidepressants	Daytime frequency, pain, comorbid depression
Calcium Supplements	Hypocalcemia
Calcium Antacids	Hyperacidity
Iron	Iron insufficiency

Fig. 5.9 Medications and supplements that commonly cause constipation

The typical treatment algorithm for constipation begins with the assessment of dietary fiber, fluid intake, and activity level. The Academy of Nutrition and Dietetics recommends 25–38 g of fiber daily consumed by eating whole grains, legumes, fruits, and vegetables [95]. See Fig. 5.10 for a list of fiber options [96]. Figure 5.7 includes a 1-day sample high-fiber menu for patients with IC/BPS. Some individuals find flaxseed, flax meal, or flax oil helpful for increasing laxation [95, 97]. Palla et al. report a possible mechanism of action, notably, that flaxseed oil stimulates both the cholinergic and histaminergic receptors [97]. For those with concomitant inadequate fluid and fiber intake, it is essential to increase fluids (ideally water consumption) enough to ensure the urine is a pale color [92]. However, increasing fiber without additional fluid intake can worsen symptoms—leading to more severe constipation, abdominal pain, bloating, and gas [92]. Some patients find that a small glass of prune juice daily offers natural laxative effects [95].

Decreased activity levels due to disabling CPP may interfere with regular laxation [90–92, 95, 98]. Encourage patients to attempt to participate in some level of activity daily [92, 95]. A consult with a physical therapist (PT) specially trained in CPP conditions may be helpful in identifying potential options for increased activity. Comorbid conditions such as PFD may influence the specific activities suggested. PT's can also teach massage techniques that help facilitate bowel movements.

If fiber, fluid, and activity are sufficient, further assessment of the underlying causes of the irregularity and additional therapies may be necessary [90, 91, 95, 98]. Some chronic constipation patients may require laxatives [92], such as bulk-forming agents, stool softeners, gastrointestinal stimulants, and bowel lubricants. For individuals with comorbid IBS, bulk-forming agents can be effective [95]. Psyllium, for example, has been found to improve transit time and stool consistency for these patients [90]. Given that opioids inhibit peristalsis of fiber-increased bulk of stool, bulk-forming laxatives are not recommended for those with opioid-induced constipation [99]. For this group of patients, the typical laxative protocol includes a stimulant and stool softener. For other chronic constipation sufferers, mineral oil has been found to be an effective stool lubricant; however, use caution with this treatment as it can impair absorption of fat-soluble vitamins. The addition of pre-/probiotic supplements may also be helpful; research on specific strains, subspecies, and dosages is currently ongoing [95, 100]. Lastly, a bowel retraining program is a recommended strategy for those with stool retention habits [95].

FOOD GROUP	SERVING	GRAMS OF DIETARY FIBER
Breads and Cereals		
All Bran Cereal	½ cup	10
Air-popped Popcorn	1 cup	2.5
Bran Buds	½ cup	7.9
Bran Chex	1 cup	4.6
Cracklin' Oat Bran	½ cup	4.3
Oatmeal (cooked)	1 cup	4.0
Raisin Bran	1 cup	4.0
Whole-wheat Bread	1 slice	1.9
Legumes, cooked		
Kidney Beans	½ cup	5.2
Lima Beans	½ cup	4.5
Navy Beans	½ cup	9.3
Vegetables, cooked		
Broccoli	½ cup	3.0
Brussels Sprouts	½ cup	3.2
Cauliflower	½ cup	2.0
Peas (green)	½ cup	3.3
Potato (with skin)	1 small	2.5
Fruits		
Banana	1 medium	2.0
Blueberries	½ cup	2.0
Dates (dried)	½ cup	1.9
Prunes (dried)	½ cup	3.0
Raisins	¼ cup	2.1

Fig. 5.10 List of fiber foods for patients with CPP

Irritable Bowel Syndrome

Irritable bowel syndrome, a functional gastrointestinal disorder in which either enteral or external stimuli alter gastrointestinal motility, increase GI tract sensitivity, and elevate viscera and/or nervous system responsiveness, is one of the most common comorbidities of IC/BPS [82]. This association is not surprising given the overlapping innervation between the bladder and bowel [101]. Common IBS manifestations include abdominal pain, bloating, cramping, flatulence, and alternating constipation and diarrhea [51, 102]. Food and beverage selection plays a major role in IBS symptom control [13].

Nutrition Intervention for IBS

Therapeutic regimens for CPP patients with comorbid IBS must exclude comestibles aggravating both conditions such as alcohol, caffeine, large loads of fat, and certain indigestible carbohydrates. Alcohol can interfere with absorption of water within the intestinal tract, causing diarrhea [103]. The stimulant caffeine speeds up the movement of the intestinal tract [104]. Large loads of dietary fat can trigger bowel symptoms by increasing muscle movement in the gastrointestinal tract [105].

CARBOHYDRATE	FOOD SOURCES
Lactose (milk sugars)	• Milk from cows, goats and sheep. • Ice cream, soft cheeses, sour cream, custard and other milk products.
Fructose (fruit sugar bonded to glucose, forming the disaccharide sucrose)	• Fruits include apples, pears, watermelon, mangoes, grapes, blueberries, tomatoes and all dried fruits. • Vegetables include sugar-snap peas, sweet peppers, and pickles. • Other foods include honey, agave, jams, dressings and drinks made with high-fructose corn syrup.
Fructans (soluble fiber)	• Bananas, garlic, onions, leeks, artichokes, asparagus, and beets. • Wheat and rye.
Galactans (complex sugars)	• Dried peas, beans, lentils, and soybeans. • Soymilk. • Broccoli, cabbage, and brussels sprouts.
Polyols (sugar alcohols, e.g., isomalt, mannitol, sorbitol and xylitol)	• Fruits like avocados, cherries, peaches, plums, and apricots. • Sweeteners added to sugar-free gum and mints.

Fig. 5.11 Potentially bothersome foods for IBS—FODMAPS

Indeed, Gallo reported that a diet lower in fat (30 % of total caloric intake) appeared to help men manage CPPS/CP [12]. Emerging evidence associates the intake of short-chain carbohydrate (SCC) in certain foods with the onset of IBS symptoms.

FODMAPS: The Indigestible Carbohydrates

Research demonstrates that malabsorptive disorders of individual carbohydrates (lactose, fructose, sorbitol, and gluten) can contribute to symptoms of IBS [106–112]. GI distress stems from altered gut motility due to poor intestinal absorption of specific sugars, as well as their osmotic effect and rapid fermentation by bacteria [113]. By limiting these dietary sugars, 56 % of those with lactose and/or fructose malabsorption improved substantially [108]. In a second study, restricting short-chain carbohydrates eased abdominal symptoms in 75 % of IBS patients [114]. Noting the relationship of carbohydrates with symptom onset, Shepard and Gibson formulated the low fermentable, oligo-, di-, and monosaccharides and polyols (FODMAPS) diet (see Fig. 5.11) [115]. This approach limits FODMAPS for 1 month and slowly reintroduces these comestibles, following the elimination diet protocol [116]. Figure 5.12 provides a list of acceptable food items for individuals with both IBS and IC/BPS; Fig. 5.7 includes a sample low FODMAP elimination diet menu.

Bloating

Bloating, a multifarious condition characterized by both objective and subjective distention of the abdomen [32, 117, 118], has been reported by almost 50 % of men with CPPS/CP particularly after meals [32]. Many patients associate it with the consumption of specific comestibles [98]. Ninety-six percent of these patients experience bloating, 64 % with a diagnosis of constipation-dominant IBS (IBS-C) [98, 117, 119, 120].

FRUITS	DAIRY
• Bananas • Blueberries • Rhubarb (Dried, Small Quantities)	• Cheese (American, Mozzarella, Mild Cheddar) • Milk, Lactose-free • Oat Milk • Rice Milk • Yogurt, Lactose-free*
PROTEINS	**VEGETABLES**
• Beef • Eggs • Fish • Lamb • Pork • Poultry (Chicken, Turkey) • Nuts and Nut Butters—except Pistachios and Cashews • Veal	• Bell peppers • Carrots • Celery • Cucumber • Eggplant • Green Beans • Leafy Greens (Kale, Lettuce, Spinach) • Potato • Pumpkin • Squash • Turnip • Yams
GRAINS	**OTHER ITEMS**
• Breads • Cereal Products (Made with Cornmeal, Millet, Oat, Quinoa, Rice) • Crackers • Gluten free products • Pasta	• Fats (Olive Oil, Garlic-infused Olive Oil) • Herbs (Basil, Coriander, Marjoram, Oregano, Parsley, Rosemary, Thyme) • Olives (Black)
**Potentially bothersome for IC/BPS patients.*	

Fig. 5.12 Acceptable items for individuals with IBS and IC/BPS

Bloating is associated with heightened sensitivity of visceral afferent nerves; thereby, the production and retention of excess abdominal gas may exacerbate the sensation of widespread chronic pelvic pain [121]. Variations in luminal microbiota, for example, are associated with the bloating and gas characteristic of the IBS [121]. Opioid-induced bowel dysfunction, caused by the binding of this narcotic to u-opioid receptors in the GI tract, can also manifest as bloating [122].

Nutrition Intervention for Bloating

Dietary interventions include restricting foods typically known to cause flatulence, such as carbonated drinks and beer, beans, brussels sprouts, cauliflower, and cabbage. For those with symptom onset after the ingestion of dairy products, investigate potential lactose intolerance [98]. The low FODMAP elimination diet may help control bloating associated with IBS [121]. Some reports correlate weight loss with symptom improvement for overweight individuals. Ho et al. noted obese patients more often experienced abdominal pain and IBS symptoms [98, 123]. In addition, recent research suggests further investigation of probiotics for the inhibition of bloating symptoms [98, 119, 121].

The complexity of these confusable conditions presents a great challenge for the practitioner. Clinicians must stress the importance of dietary modifications appropriate for accompanying diagnoses [32, 82]. Therefore, the pelvic pain experienced requires an individualized approach for developing suitable eating plans.

Functional Compounds in Foods

Many studies have examined the use of complementary therapies with chronic pelvic pain management (see Chapter 7: Phytotherapy). Traditional home remedies have included sodium bicarbonate (baking soda) and over-the-counter supplements such as calcium glycerophosphate (Prelief®). However, only a limited number of patients reported these products to be successful at controlling symptoms. Cutting-edge research now focuses on functional compounds in foods such as pre- and probiotics, omega-3 fatty acids, and antioxidants as adjuvant therapies.

Prebiotics and Probiotics

Prebiotics are nondigestible fibers that encourage the growth of beneficial microbes. They help create a colonic environment that is favorable for probiotic vitality [119]. In contrast, probiotics are live colonies of bacteria, which promote a more beneficial balance of intestinal flora [119]. Researchers are currently exploring the positive impact of supplemental pre-/probiotics on microbial alterations correlating with the onset of an array of chronic conditions including IBS. Anecdotally, some CPP patients, especially those with IBS, report that probiotics can be helpful in modulating GI symptoms; however, the science supporting the efficacy of specific species, strains, or combination of strains is lacking. To date, there is much disparity as to the amount and types of probiotics found in various food products, as well as innovative production methods necessary to ensure that live cultures remain viable. Though pre-/probiotics hold promise, evidence supporting these treatment options is sparse. Figure 5.13 summarizes current research on probiotics which may help inhibit CPP symptoms; most of the investigations were done in animal studies and

FOOD SOURCE*	PROBIOTIC STRAIN	PROPOSED MODE OF SYMPTOM INHIBITION
	Lactobacillus (L.)	
• Yogurt** • Kefir • Milk Enriched with Acidophilus • Miso**	L. acidophilus	• Colonic hypervisceral sensitivity
• Sourdough Bread**	L. farciminus	• Visceral hypersensitivity • Colonic hyperpermeability • Pain
• Dairy Products • Kefir	L. paracasei	• Visceral sensitivity and inflammation • Impaired gut permeability
• Cheese • Kefir	L. helveticus (5%) L. rhamnosus (95%)	• Impaired intestinal epithelial barrier • Impaired colonic epithelial barrier
• Sourdough Bread**	L. reuteri	• Pain related to colorectal distension
	Bifidobacterium (B.)	
• Yogurt** • Yogurt Drinks**	B. infantis	• Colorectal distension induced pain • Abdominal pain and/or discomfort bloating/distension

*Strains in comestibles may vary depending upon processing and handling techniques.
**May be potentially bothersome to individuals with IC/BPS.

Source: Theodorou V, Belgnaoui AA, Agostini S, Eutameme H. Effect of commensals and probiotics on visceral senstitivy and pain in irritable bowel syndrome. Gut Microbes 2014 May/Jun;5(3):430-436.

Fig. 5.13 Food sources of probiotics, strains, and CPP symptom inhibition

focus on IBS-related symptoms [124]. Figure 5.14 lists considerations for prescribing pre/probiotics for individuals with CPP. Also, see Fig. 5.15 for a list of CPP-friendly pre-/probiotic food and beverage sources.

Omega-3 Fatty Acids

Research associates the consumption of an ideal balance of anti-inflammatory omega-3 fatty acids (O3FAs) and inflammatory omega-6 fatty acids (O6FAs) with a decreased risk of certain chronic diseases such as CPP [125]. Although the etiology and pathogenesis of chronic conditions like IC/BPS is uncertain, research suggests that CPP may be neuropathic in nature [126–128]. Chronic inflammation is a possible pathway to this enigmatic disease [129–131]. A recent study conducted by Schrepf and the MAPP Research Network suggests involvement of the immune system's toll-like receptor 4 (TLR-4) in the IC/BPS pain symptoms. In addition, the authors highlight a potential association between this relationship and diminished inflammatory control [132]. Furthermore, whether the result of IC/BPS specifically or the result of common comorbid conditions, a cascade of inflammatory mediators have been reported including cytokines, histamines, kinins, complement factors, cloning factors, nitric oxide, and proteases. These intermediaries orchestrate the intrusion of mast cells, eosinophils, macrophages, lymphocytes, and plasma cells leading to irreversible tissue destruction and fibrosis. These cellular changes may lead to fluctuating urinary symptoms including detrusor overactivity and hyperalgesia [129].

1. Though research is ongoing, there is still much unknown about the health benefits and risks of long-term consumption of probiotic products. We do not know, for example, if increased iron absorption promoted by probiotic consumption might increase constipation among those with chronic pelvic pain.
2. Animal research supports the use of probiotics for conditions such as chronic pelvic pain; but, high-level evidence gleaned from robust clinical trials is sparse.
3. Though generally recognized as safe, administration of high doses of probiotics to individuals with compromised immunity may result in complications such as serious infections.
4. Not all strains and species of probiotics have the same effects. High-grade evidence supporting specific strains and species or combinations of these organisms for inhibiting CPP-related symptoms is lacking.
5. Probiotic products are classified as dietary supplements rather than pharmaceutical or biological products. Thus, in the U.S., manufacturers are not required to demonstrate safety, purity, or potency of the products.
6. There is a paucity of studies on appropriate probiotic dosing; therefore, recommendations on specific amounts of probiotic required to achieve specific clinical effects is not known at this time.
7. The amount of probiotic in products may be affected by manufacturing and handling techniques; thereby, the stated level may not reflect the actual level of viable organisms.
8. When possible, recommend foods and beverages with pre/probiotics—this strategy provides patients with access to other nutrients required for optimal dietary intake.
9. Some food sources of pre/probiotics may not be suitable for those with CPP. For individuals with IC/BPS, for example, sauerkraut, soy, and yogurt may exacerbate symptoms.
10. Additional individual food sensitivities may affect choice of prebiotic. For example, though wheat germ is a good source of prebiotics, it may be a CPP trigger for those with comorbid gluten intolerance.

Fig. 5.14 Ten considerations for recommending pre-/probiotics

Additionally, the literature indicates that numerous common chronic inflammatory diseases including cardiovascular disease, hypertension, arthritis, depression, and others share similar urinary markers with CPP such as nerve growth factors (NGF), serum C-reactive protein, nitric oxide, and pro-inflammatory cytokines. Studies demonstrate that adding O3FAs to the diet of patients experiencing these aforementioned diseases (exhibiting the same elevated biomarkers commonly seen in pelvic pain) has resulted in the decrease of chronic inflammation and improvement of the conditions [133–139]. O3FAs, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), found in cold, oily fish, are mediators that trigger the formation of anti-inflammatory,

CPP-Friendly Foods with Functional Compounds

PREBIOTICS*	ANTIOXIDANTS	OMEGA-3 FATTY ACIDS
An ideal daily serving of prebiotics has yet to be determined, however, suggested ranges have been noted: 4 to 8 grams (0.14-0.28 oz) for general digestive health support, >15 grams (0.53 oz) or more for individuals with active digestive disorders. • Raw Chicory Root (9.3 g, 0.33 oz) • Raw Jerusalem Artichoke (19 g, 0.67 oz) • Raw Dandelion Greens (24.7 g, 0.87 oz) • Raw Garlic (34.3 g, 1.21 oz) • Raw Leek (51.3 g, 1.81 oz) • Raw Onion (69.8 g, 2.46 oz) • Cooked Onion (120 g, 4.2 oz) • Raw Asparagus (120 g, 4.2 oz) • Raw Wheat Bran (120 g, 4.2 oz) • Whole Wheat Flour, Cooked (125 g, 4.4 oz) • Raw Banana (600 g, 1.3 lb)	To meet requirements for antioxidants, follow the nutritional goals delineated in at HealthyPeople.gov or ChooseMyPlate.gov. • Apples • Apricots • Artichoke • Blueberries • Broccoli • Brussels sprouts • Dates • Greens (Collard Greens, Spinach, Kale) • Pears • Plums • Pumpkin • Radishes • Raisins • Squash (Winter) • Watermelon • Yams	Aim for two three-ounce servings of Omega-3-rich fish per week and regularly consume Omega-3-rich plant sources. **DHA /EPA Omega 3** • Fish: Salmon, Tuna, Trout, Sardines, Halibut, Herring, Mackerel** • Eggs (fortified) • Milk (fortified) **ALA Omega 3 ***** • Beans (Pinto, Navy) • Brussels Sprouts • Cauliflower • Kale • Nuts (Walnuts, Pecans, Macadamia) • Oil (Canola) • Parsley • Spinach • Squash (Winter)
**Source: Moshfegh AJ, Friday JE, Goldman JP, Ahuga JK (July 1999). "Presence of inulin and oligofructose in the diets of Americans." J Nutr 129 (7 Suppl): 1407S-1411S.* ***These are the best sources. They are most efficiently used by the body.* ****Plant sources of O3FAs are less efficient than those found in fish.*		

Fig. 5.15 CPP-friendly foods with functional compounds

hormonelike compounds called eicosanoids. These substances are valuable in counteracting pro-inflammatory O6FAs, which are predominant in Westernized diets and may play a large role in the formation of chronic inflammation.

As essential cell membrane components, EPA and DHA O3FAs influence biochemical signaling. These polyunsaturated fatty acids may thereby support nuclear receptors involved in gene expression. Conversely, arachidonic acid (AA) O6FA products are thought to be pro-inflammatory mediators, while EPA O3FA products are anti-inflammatory or less pro-inflammatory. Therefore, AA and EPA are competitive substrates. The range of compounds formed from metabolism of O3FAs include EPA and prostaglandin 3 series, leukotriene 5 series, thromboxane 3 series, and resolvin E series, as well as DHA and resolvin D series and protectins. The compounds formed from the metabolism of omega-3, EPA, and anti-inflammatory and antithrombotic resolvins, as well as DHA and protectins, are important anti-inflammatory compounds responsible for beneficial effects of fish oil.

O3FAs have been shown to downregulate or reverse some of the inflammatory mediators and, thus, may offer an alternative or supplemental therapy/treatment for IC/BPS. The ratio of these fatty acids, resulting from our dietary consumption, may be somewhat responsible for decreasing or increasing inflammation. Randomized clinical trials examining the effects of omega-3 fatty acids on bladder symptoms are warranted. Nevertheless, the incorporation of foods high in these anti-inflammatory acids such as salmon, tuna, mackerel, and sardines, three ounces twice a week, can only be an asset to one's diet—they are abundant in various macro- and micronutrients essential to overall health. Figure 5.15 provides a list of IC/BPS-friendly foods high in omega-3 fatty acids.

Antioxidants

Another form of diet therapy gaining much attention because of the relief provided for patients suffering with inflammatory and neuropathic pain is the elevated consumption of antioxidants [140–144]. Studies substantiate that the consumption of high-antioxidant fruits and vegetables improves immune system function and tempers free radical damage to body cells [145]. Common antioxidant products include blueberries, green peppers, spinach, kale, and walnuts (see Fig. 5.15). (A note to keep in mind: deeper-colored pigment foods tend to be highest in these phytochemicals.) Epidemiological data indicates an inverse relationship between high-antioxidant foods and certain chronic inflammatory diseases [146]. Thought by many to be a chronic inflammatory condition, CPPS/CP affects 11 % of Europeans; this is considered to be a significant portion of the population. A prospective epidemiological case-control study determined that men with this condition, compared with controls, tended to consume higher levels of carbohydrates, milk, and milk products and lower levels of fruits and vegetables [32]. Thus, this population does not appear to reap the benefits of a high-antioxidant diet.

For decades we have acknowledged that pain, a primary symptom of CPP, negatively impacts the quality of life of patients. However, only recently have discussions emerged on the emphasis of diet as a therapy for pain. Tall states "infection and injury activate the immune system to produce an inflammatory response, with pain being a consequence of inflammation" [4]. Indeed, evidence is mounting that comestibles provide numerous phytochemicals, micronutrients, and macronutrients, which quell the fires of inflammatory pain. Might the consumption of a wide variety of appropriate comestibles potentially improve quality of life for CPP patients? Only further studies can confirm the preliminary findings discussed above. Incorporating a wide variety of colorful fruits, vegetables, healthy anti-inflammatory fats, numerous whole grains, cold water, oily fish, lean meats and poultry, and low fat dairy products, however, will serve to improve intake of these functional compounds, provide adequate nutrients, and enhance the quality life for the CPP patient.

Optimal Nourishment

This review highlights varied and essential dietary considerations for individuals with chronic pelvic pain. Challenges of achieving this goal may include:

- Identifying all comestibles that may trigger bladder flares
- Developing strategies to help promote compliance with the elimination diet
- Ensuring adequate intake of essential nutrients and fluids
- Highlighting phytochemicals and antioxidants
- Weighing research on the role of anti-inflammatory foods, such as omega-3 fatty acids, establishing the effects and advantages of pre-/probiotics
- Determining the value of oxalate restriction for vulvodynia

- Addressing nutritional considerations for comorbid conditions such as irritable bowel syndrome, constipation, and bloating

One of the most important concepts a professional can suggest is the value of dietary planning. Restriction of comestibles may require carrying snacks and/or backup foods in case acceptable options are not available when eating away from home. Looking at menu choices by going online or contacting restaurants and other eateries ahead of time can enable patients to give thought to potential meal options, perhaps easing the challenges of dining out.

CPP Diet Trivia

As previously mentioned, there is an abundance of misinformation and erroneous statements that abound on the Internet and magazines, causing CPP patient's confusion and frustration. A few brief comments are in order to address six common myths.

Myth 1—Patients should avoid all foods with preservatives: A majority of our food supply contains agents to enhance the characteristics of foods and preserve shelf life. These substances have not been proven to be bladder triggers. Additives with long chemical names (or small amounts of citric acid) are not necessary detrimental. They should be included in the list of challenge foods during the elimination diet.

Myth 2—Anything with acid should be avoided: Although it is true that many problematic foods for CPP patients are high in citric acid, research confirming that acids are the culprits has not been consistent [147]. Furthermore, well-tolerated fruits and vegetables have an abundance of varied acids; many of them, such as citric acid and ascorbic acid, provide high-antioxidant properties. Figure 5.1 provides a list of IC/BPS-friendly foods with vitamin C (ascorbic acid).

Myth 3—Caffeinated coffees and teas should be avoided; however, decaffeinated coffees and teas can be tolerated: Clinical experience has shown that coffees and teas, both caffeinated and decaffeinated, may affect bladder symptoms. Figure 5.4 offers strategies for stepping down from caffeine, as well as alternative CPP-friendly beverages.

Myth 4—Cranberry juice will prevent bladder symptoms: Although some literature indicates that cranberry juice may decrease the incidence of urinary tract infections (UTIs), cranberries have been noted to be a trigger for IC/BPS patients in many survey-based studies.

Myth 5—Allergy testing gives you a positive diagnosis of which foods to restrict: There are limitations with the currently available commercial allergy tests. In addition, these tests may lead to overly restrictive dietary choices [148]. However, the use of allergy testing to identify potential comestibles for short-term restrictions, such as when undertaking the 1-month elimination diet, may be helpful.

Myth 6—Some foods "soothe" the bladder: Though certain foods and beverages appear to trigger flares, at this time, there has been no research conducted that identifies a specific food that physiologically alleviates IC/BPS symptoms.

Variety and Moderation, the CPP Patient Mantra

The guiding nutrition principles for CPP patients should be variety and moderation. These recommendations are, in fact, universal. They should be followed by all individuals. Basic nutritional goals that should be applied when designing healthy eating plans are available at HealthyPeople.gov or ChooseMyPlate.gov. Patients must manage calories, fat (specifically saturated fat, trans fat, and cholesterol from animal and processed products), sugar, salt, and alcohol [149]. Fortunately, the most common comestibles that trigger bladder flares are not essential in our diets; they can all be alternated with other foods and beverages. Therefore, a diet including plenty of fruits and vegetables (fresh, canned, or frozen), legumes, whole-grain products, moderate portions of lean meats and poultry, cold water, oily fish (high O3FAs)—at least two 3 oz servings per week—skim milk products, and adequate fluids, which reflects patient preferences and excludes specific CPP flare trigger foods, is recommended. Considering the current research on the anti-inflammatory properties of O3FAs, increasing these fats in the diet and limiting processed foods (high in O6FAs) would yield a better balance of essential nutrients to decrease chronic inflammation. In addition, individuals with comorbidities may require more complex dietary planning to address confounding nutritional concerns. The value of incorporating a registered dietitian nutritionist on the CPP patient care team emerges.

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The Role of Acupuncture in the Management of Chronic Pelvic Pain

6

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Acupuncture techniques date back almost 3000 years. Over this time, it has not only survived but also grown in popularity, a testament to the value placed on it by patients. Acupuncture uses specialized needles to stimulate specific acupuncture points. The approximately 400 acupuncture points are located along channels also known as meridians. It is an empiric healing art, which has taken millennia to develop. It differs markedly from modern allopathic medicine in that the treatment for a particular presenting complaint, for example pelvic pain, may have variations in treatment due to the emotional, physical, as well as other pathology present in our patient. In other words, no two individuals presenting with similar complaints are necessarily given the same acupuncture treatment. It is this requirement for individualization of treatment that has made acupuncture a powerful technique in the hands of an experienced practitioner of the art and consequently has made evaluation and comparisons of the results challenging.

Acupuncture has been applied to a number of acute and chronic medical conditions such as somatic pain, male and female sexual dysfunction, pregnancy related physiologic changes, cardiovascular disorders, asthma, sports related injuries, and cancer treatment related side effects [1]. Acupuncture has also gained significant support for its role in pain management, particularly in the field of chronic pelvic pain.

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History of Acupuncture

Inscriptions on oracle-bone describing the use of needles on the human have been identified dating back to the twenty first century B.C., although it is unclear whether or not the inscriptions were describing acupuncture [2]. From the twenty first century B.C. to the second century B.C., little historical evidence exists supporting the use of acupuncture in this period, suggesting either poor documentation or its lack of use [3]. The first possible description of instruments employed in acupuncture comes from the writings of a Chinese physician named Fu Xi Shu. He is credited for creating the *Bian Shi* (Stone needle), in approximately 4000 BC; however, the *Bian Shi*'*s* use for acupuncture has only been extrapolated [1–3]. In the second century B.C., a book called *Huang Di Nei Jing* (*Yellow Emperor*'*s Internal Classic*) was published that described the technique of acupuncture that is mirrored in modern-day practice. This book was a compendium of medical writings dating from the fifth century to second century BC that introduced what would later be known as acupressure points and meridians [1, 3].

Following the description of acupuncture in *Huang Di Nei Jing*, this practice gained significant popularity and became a more regimented process. However, toward the middle of the second millennium A.D., acupuncture use declined as its credibility was challenged by a shift in Chinese and Japanese medicine from holistic to allopathic medicine [3]. In the 1800s both nations attempted to ban it from the medical curricula, and toward the beginning of the twentieth century acupuncture was no longer part of the Chinese imperial medical academy [2, 3]. It was not until the cultural revolution of the 1960s that the practice was reinstated and disseminated again [3].

Mechanisms of Acupuncture for Pain Syndromes

The mechanism by which acupuncture affects pain has not been elucidated yet. Traditionally, the thought was that *qi*, the energy of life, was manipulated with the use of acupuncture. There are approximately 400 known acupuncture points, or acupoints, which have been identified [4]. The pathways between the acupoints are known as meridians and the use of acupuncture is to help restore the flow of *qi* through these meridians.

In order to better clarify the mechanisms involved in acupuncture, animal-based biochemical studies have been performed. The mechanisms can be divided into three different locations of action, peripheral, spinal, and supraspinal [5].

Peripheral Effects

Local or peripheral effects are primarily mediated by up and down regulation of certain inflammatory and pain mediators. One of the earliest studies showed an increased rate of release of endorphins during acupuncture by employing naloxone to block the acupuncture effect [6]. Other peripheral mediators involved include

cannabinoids, cyclooxygenase-2, and norepinephrine [5, 7]. Differing immunologic effects have been implicated as well. Natural killer cells, which are thought to play a protective immunomodulating effect in chronic pain and rheumatologic syndromes, are up-regulated after multiple sessions of acupuncture [8]. Acupuncture also alters other cells, such as mast cells, and related cytokines at the peripheral level. In irritable bowel syndrome (IBS), electro-acupuncture decreases the number of mucosal mast cells, as well as levels of tumor necrosis factor-alpha (TNF-α), vasoactive intestinal peptide (VIP), and substance P [9, 10]. There are a myriad of chemokines and mediators that are affected by acupuncture and studies have shown that these effects can vary based on the location of the acupoint and duration of measurement [11].

Spinal Effects

The spinal effects of acupuncture, on the other hand, are primarily mediated by an increase in the level of spinal opioids, norepinephrine, serotonin, and a decrease in glutamate receptor expression [5, 12, 13]. By manipulating endorphinergic cells in the spinal cord, enkaphalin or dynorphin is released causing presynaptic inhibition of neurons in the spinothalamaic tract [1].

Supraspinal Effects

Supraspinal effects of acupuncture have been less studied than the peripheral and spinal effects. Acupuncture has been shown to activate many types of afferent fibers and many nuclei become involved in processing the response [14]. These nuclei include the nucleus raphe magnus, arcuate nucleus, habenular nucleus, periaqueductal gray, locus coeruleus, preoptic area, amygdala, nucleus submedius, accumbens nucleus, caudate nucleus, and the septal area [14]. One of the most understood areas of neuronal involvement is down-regulation of the input through the spinothalamic tract. Normally, noxious stimuli activate A-delta and C-fibers that synapse into the spinothalamic tract. Stimuli are taken to the thalamus and then subsequently to the sensory cortex. Electroacupuncture can modify this communication by activating small myelinated afferent nerves, which stimulate interneurons that down-regulate the effect of the noxious stimulus. These small myelinated afferent fibers can also cause down-regulation of the effect that noxious stimuli have by activating the periaqueductal gray and therefore the raphe nucleus in the medulla. Along with other analgesic effects, this will lead to the inhibition of many of the initial actors and neurons in the spinothalamic tract [1]. This intricate web is still further being defined but the effects of acupuncture are far-reaching and quite complex.

Acceptance of Acupuncture in Alternative Medicine

Acupuncture is still in the field of complementary and alternative medicine (CAM), and therefore, is not always readily accepted by physicians. However, use of CAM

has increased in the United States from 33.8 % in 1990 to 42.1 % in 1997 [15]. Extrapolation of that data placed the number of total visits to CAM centers increasing from 427 million to 629 million which is more than the total number of visits to primary care physicians [15]. Due to this surge in popularity among patients, it is important for physicians to be knowledgeable in the field. A survey in 2007–2008 focusing on pain specialists and those who primarily refer to them was carried out [16]. Although the study was limited by a low response rate of 197 (18.2 %) physicians, it showed that there was a positive view toward acupuncture. Ninety-seven percent of those physicians thought it to be somewhat to very effective while 74 % had made acupuncture referrals [16]. The majority of referrals, 54 %, were initiated from the patient and an almost equal percentage of referrals were made after a trial of conventional pain therapy [16]. Although 13 and 14 % physicians considered their lack of familiarity with the procedure or their perceived lack of evidence in the field to be a barrier, the largest barriers were the lack of insurance coverage and lack of a proper acupuncture center [16]. This survey may be somewhat skewed as this looks primarily at a physician population that treats chronic pain. Another survey in 2010 addressed urologists across three deaneries in England [17]. Approximately 100 urologists responded and stated that 46 % of them rated their knowledge in the field of acupuncture as low [17]. Though most, 54 %, considered themselves neutral toward acupuncture, almost 30 % had acupuncture recommended to them by patients. In order to assess who was more likely to prescribe acupuncture, a multivariable analysis was also undertaken. The only variable that was associated with a urologist suggesting acupuncture was if that urologist had changed their opinion regarding acupuncture during their career [17]. Interestingly enough, half of the urologists had changed their views and when they did it was always either "more positive" or "a lot more positive" [17].

Use of Acupuncture for Pelvic Pain

The practice of acupuncture extends to the early roots of medicine and therefore it has been employed for many chronic pain conditions that were refractory to other methods of treatment. Its surge in popularity and interest as a complement to allopathic treatment modalities has led to more rigorous studies in the field of chronic pain. Multiple meta-analyses of acupuncture studies have shown significant improvement in patients who are afflicted with IBS, fibromyalgia, primary dysmenorrhea, and pregnancy related low back and pelvic pain [18–21]. The effectiveness of acupuncture for these disorders has led to increased interest in exploring and expanding the scope of acupuncture to other chronic pain disorders. Given its efficacy in these fields, naturally acupuncture's role in chronic pelvic pain syndromes was explored.

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by pain in the pelvis, perineum, and/or testicles in the absence of other well-defined pathology and affects the lives of nearly 2–10 % of adult men worldwide and 1.8 % of men in the United States [22–24]. Four categories of CP/CPPS exist depending on

Table 6.1 Classification of types of prostatitis

NIH category	Traditional classification	Definition
Type I	Acute bacterial prostatitis	Acute infection of the prostate
Type II	Chronic bacterial prostatitis	Chronic infection of the prostate
Type IIIA (inflammatory CPPS)	Nonbacterial prostatitis	Chronic genitourinary pain without bacteria but with leukocytes in prostatic secretions, post-prostatic massage urine, or semen
Type IIIB (noninflammatory CPPS)	Prostatodynia	Chronic genitourinary pain without bacteria but without leukocytes in prostatic secretions, post-prostatic massage urine, or semen
Type IV (Asymptomatic Inflammatory Prostatitis)	N/A	No typical chronic pelvic pain but with presence of leukocytes and/or bacteria in prostatic secretions, post-prostatic massage urine, or semen

histopathology of the prostate and acuity (Table 6.1). CP/CPPS remains a challenging condition to treat, as the etiology is unclear in up to 90 % of cases [24]. Although the mechanism of CP/CPPS has not been elucidated, several studies have assessed the role of cytokines in its pathogenesis. Weak correlation, however, exists between the levels of proinflammatory cytokines, such as Interleukin (IL)-1, IL-6, IL-8, and TNF-α, and anti-inflammatory cytokines, such as IL-10 relative to the symptoms of CP/CPPS [25]. Despite IL-10s ability to suppress the immune system by decreasing proinflammatory cytokines (such as TNF-α, IL-2, IL-6, and IL-8) and consequently suppressing the stimulus for the increased production B cells and natural killer cells, low levels of IL-10 have been associated with CP/CPPS [25]. Although the mechanism by which this occurs is not clear, patients with the IL-10 AA genotype, which imparts low IL-10 production, have significantly higher rates of CP/CPPS [26]. In contrast, patients with higher rates of IL-10 in other systemic diseases, such as polymyalgia rheumatica, have a lower incidence of polymyalgia rheumatica symptoms [27].

Moreover, conventional treatment options, such as alpha-blockers and antibiotics, are less efficacious than previously believed [24, 28, 29]. Given the success of acupuncture in the treatment of other pain syndromes such as back pain of pregnancy and fibromyalgia, acupuncture has been utilized as part of a multimodal treatment of CP/CPPS [19, 30]. Promising results have led to a rise in popularity for acupuncture in treating CP/CPPS. In the United States, two million Americans utilized it in 2002 and then in 2007 it rose significantly to three million people [5].

Many early trials were conducted in China showing promise for this modality of therapy specifically for patients afflicted with CP/CPPS [31]. These studies, however, were limited by their poor design. Early studies assessing the efficacy of acupuncture in the treatment of CP/CPPS were plagued with methodological deficiencies, including the lack of randomization and absence of a placebo or control arm, making it

difficult to discern the true treatment effect from placebo. One of these studies was performed by Chen et al. and showed significant improvement in the National Institute of Health Chronic Prostatitis Symptom Index (CPSI) score [32]. This study showed 92 % of men in the study had >50 % response to therapy with CPSI scores decreasing from 28 to 8.5 with significant decreases in pain and quality of life subscores with a durable long-term response to therapy [32]. However, this study was limited by the absence of a control group. Another study of similar size and limitations showed a 50 % reduction of intrapelvic venous congestion as assessed by both transrectal ultrasound and magnetic resonance venography [33]. There were no changes to voiding symptoms but significant improvements in QOL and pain subscores on the CPSI were identified [33]. Posadzki et al. subsequently performed a meta-analysis of many of the strongest studies and a majority of them were earlier Chinese papers [31]. Unfortunately, these earlier studies that they investigated were lacking in methodologic quality, not just because of their lack of control or placebo arms, but because they did not describe blinding, dropout rates, power calculations, adverse events, or inclusion and exclusion criteria [31]. These trials also generally did not use validated instruments to assess patient symptoms [31]. Given the limitations of the individual studies in the review, the authors state that acupuncture's role in CP/CPPS is encouraging; however, currently, there is neither enough quantity nor high quality evidence to allow for a more definitive answer. This led to an eventual series of studies with more standard and strict criteria that are now used to help guide therapy.

Lee et al. performed the first randomized, blinded study comparing acupuncture against sham acupuncture [34]. They created a sham group by having these patients have their needles placed superficially and 15 mm to the left of the respective acupoint. Seventy-three percent of patients in the acupuncture group reached the primary outcome of a drop in ≥6 points in CPSI while the sham group only had 47 % reach that goal. Though there was no difference in the number of patients who had complete resolution of symptoms, 32 % of the acupuncture patients had long-term improvement of symptoms seen 34 weeks after therapy as opposed to a significantly smaller 13 % in the sham group [34]. Another study was performed in which sham and electroacupuncture arms were also compared to controls and patients were assessed using CPSI and prostatic massage urine samples to look for inflammatory mediators [35]. All three groups were given advice and encouraged to exercise while the acupuncture and sham groups were given further therapy. The electroacupuncture group showed significant reduction in CPSI scores, while the sham group and the control arm showed equivalent but nonsignificant improvements in score reductions. Though there were no differences in International Prostates Symptom Scores (IPSS), there was a decrease in prostaglandin E levels in post-prostate massage urine samples in the electroacupuncture arm. This three-arm study highlights the effect that practitioner attention can have with the patient as there were no substantial differences between the placebo sham arm and the control arm. Researchers studying acupuncture in osteoarthritis have shown that it may not matter what therapy the patient received, but that the way the acupuncturist interacted with the patient was what created the difference [36].

Another prospective randomized trial comparing a medical treatment group using levofloxacin and ibuprofen compared to an electroacupuncture group showed that

the acupuncture group had considerably lower CPSI and pain subscores though there was not a significant difference in QOL or urinary symptoms in either group [37]. A review of the current literature was attempted to make definitive conclusions regarding acupuncture and CP/CPPS. The authors, however, were mainly able to conclude that most of the studies were not rigorously designed enough to make definitive claims [31]. They were able to conclude that acupuncture was more efficacious than antibiotics, medications for prostatic hyperplasia, or herbal medicines [31].

Technique and Training

The acupuncture evaluation is similar in structure to that of the standard allopathic medical interview in that the patient provides the history of the present and past conditions, family and social history, and review of systems. Where the interview differs is the inclusion of items that are unique to Eastern medicine and includes seasonal, color, and taste preferences, which are used to fine tune the treatment paradigm. In the case of musculoskeletal pain problems, the pain is localized neuroanatomically according to the acupuncture meridians along which the pain resides.

A focused physical examination follows with addition to the examination of unique microsystems of the tongue, radial pulse, and external ear, which provide insight into the specific contribution of each organ system to the presenting pathology. It also directs treatment design.

The treatment design is responsible for the effectiveness of the treatment. It requires training and experience to master. The treatment design is aimed at first identifying the hierarchy of manifestation of the presenting complaints and then the treatment order. The treatment may consist of simplifying placing needles around the area of a localized site of injury and allowing them to "disperse" what in Eastern medicine is considered to be excess energy or "Qi." Or, the treatment may need to activate multiple meridians by a process called tonification in which heat, electrical, or manual energy is applied to metaphorically create energy movement in a blocked channel.

As is true with all treatments in both Eastern and Western medicine, multiple confounding factors may affect the results. These confounding factors include the patient's age, duration and complexity of the presenting problem, concurrent health issues, medications, prior surgery, lifestyle, as well as the patient's emotional state. What is interesting is that the patient's belief in acupuncture does not affect the outcome.

In the United States there are approximately 3500 physicians and 12,000 non-physician acupuncturists with approximately 90 accredited institutions offering advanced Degrees. There are several programs in the United States that are specially designed for physicians who are interested in obtaining the education and hands on training necessary to use acupuncture effectively in their practice. The American Academy of Medical Acupuncture is the professional society of physicians who have incorporated acupuncture in their practice. Their website (MedicalAcupuncture.org) has references to training programs specifically designed for the practicing physician.

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Phytotherapy in Chronic Pelvic Pain

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Introduction

Chronic pelvic pain syndrome (CPPS) adversely affects the life of many patients, and the management of this syndrome can prove frustrating and dissatisfying to both patient and practitioner. While the body of literature regarding the syndrome is growing, the evidence surrounding conventional medical therapies such as antibiotics is mixed. Public interest has thus increased in phytotherapy, or the use of plant-derived products as medical therapy. Such therapies have been popular in other countries, but their use in the United States has only recently started to increase. At first glance, phytotherapy presents several potential advantages, including low cost, fewer side effects, and unique mechanisms of action. One difficulty with utilizing phytotherapy in practice is the lack of standardization of these products in the marketplace. Unlike pharmaceuticals, phytotherapy products are not regulated by the Food and Drug Administration (FDA). As such, companies selling these products are not required to prove efficacy, safety, or even the actual presence of the advertised active ingredient. As such, patients may be purchasing products that are worthless or, even worse, harmful. However, it is imperative that these treatments receive the same rigorous evaluation as do the more traditional pharmaceuticals to help provide safe and evidence-based medicine for patients with CPPS.

The use of phytotherapy for prostatic disease is not a new idea. Treatments such as saw palmetto (*Serenoa repens*), stinging nettle (*Urtica dioica*), and *Pygeum*

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africanum have at least some clinical evidence in their favor for management of benign prostatic hypertrophy (BPH) [1–4]. Both BPH and CPPS possess an element of lower urinary tract symptoms (LUTS), and consequently these therapies were suggested for both conditions. The literature evidence is accumulating for these therapies as well as other herbal preparations, including pollen extract, quercetin, and traditional Chinese herbal medicine. In this chapter, we will discuss each of these phytotherapies and examine the scientific data supporting or refuting the use of each.

Classification of Prostatitis

Historical classification of prostatitis (i.e., the Meares-Stamey four-glass test) was based on localizing bacteria among urine and expressed prostatic secretion (EPS), and was never formally validated as a classification system [5]. Indeed, its use among urologists was limited given the difficulty in performing and interpreting the test [6]. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) published a new classification system titled the NIH classification system in 1999 [7]. This system was unique in that it changed the focus toward classification based on symptoms and syndromes [7]. The NIH system is summarized briefly in Table 7.1. Notably, this classification has been validated in the literature for use in both research and clinical practice [8]; however, the differentiation of category III into IIIa and IIIb has failed to show clinical relevance. To assess symptom severity, the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) was developed and also can serve as an outcome measure for men with CP/CPPS [9]. This is a validated questionnaire assessing the three main domains affecting men with CP/CPPS – pain, urinary function, and quality of life. Of note, a decrease of ≥6 points on this scale is considered to be clinically significant.

Treatments for Categories I and II, Acute and Chronic Bacterial Prostatitis, are well established. Acute Bacterial Prostatitis is a significant infection with systemic

Table 7.1 Classification of prostatitis

Category I (acute bacterial prostatitis)	Acute bacterial infection of the prostate; notable for pain, positive urine culture, and systemic symptoms of infection
Category II (chronic bacterial prostatitis)	Chronic bacterial infection of the prostate; notable for recurrent urinary tract infections associated with uropathogenic infection noted in the EPS or semen
Category III (chronic prostatitis/ chronic pelvic pain syndrome)	Discomfort/pain in the pelvic region for at least 3 months without the presence of uropathogenic bacteria
Category IIIA (*Inflammatory CPPS*)	*Above with significant leukocytes noted in EPS, post-prostate massage voided urine, or semen*
Category IIIB (*Non-inflammatory CPPS*)	*Above without significant leukocytes noted*
Category IV (asymptomatic prostatitis)	Leukocytes seen in EPS, post-prostatic massage urine, or semen, but without corresponding symptoms. This category is found incidentally during workup for other urologic issues

manifestations requiring urgent antibiotic administration. As such, no phytotherapy or alternative treatment is recommended for use in the treatment of this population. Antibiotic therapy also forms the basis of treatment for Chronic Bacterial Prostatitis patients with documented recurrent bacterial infections. However, patients on prolonged antibiotic therapy may experience perturbations in the gastrointestinal flora, and the use of probiotics (e.g., lactobacilli cultures) may reduce the incidence of side effects related to this [10]. Given the evidence for cranberry juice in urinary tract infections [11, 12], a theoretical benefit may exist for this phytotherapy in Category II prostatitis. However, this has been tested only in animal models, and no data is available for cranberry extract in humans [13]. Further, it has been suggested that that the acidity of cranberry juice may in fact exacerbate symptoms [14]. Category III (Chronic Prostatitis/Chronic Pelvic Pain Syndrome) is the particular subtype in which standard therapy is not well defined, and thus is the particular area in which phytotherapy is most promising and that with the most evidence. The remainder of this chapter will mainly focus on Category III. Category IV (Asymptomatic Prostatitis) is only rarely associated with symptoms or adverse sequelae. Treatment may be warranted in cases of infertility with evidence of inflammation on semen analysis. Antioxidant phytotherapies have been recommended for use in these patients in attempts to maximize fertility [15].

Chronic pelvic pain can also be present in females. Further, the differential diagnosis for these symptoms is much wider in women given possible gynecologic issues. Guidelines have been published by various professional organizations regarding the treatment of chronic pelvic pain in association with such specific etiologies as dysmenorrhea, endometriosis, Interstitial Cystitis/Painful Bladder Syndrome, and Irritable Bowel Syndrome [16–20]. However, the evidence regarding therapies for female chronic pelvic pain in the absence of identifiable etiology is scarce. A comparative effectiveness study by the Agency for Healthcare Research and Quality was not able to definitively draw conclusions regarding available therapies given the lack of quality literature on the subject [21]. When possible, we will note which studies included women in the evaluation of the phytotherapies.

Etiology and Management of the CP/CPPS Patient

The etiology of this syndrome is unclear. However, given the constellation of symptoms found within the diagnosis, it is likely that there are many different etiologies contributing to this symptom complex. Examining these possible etiologies helps rationalize the various phytotherapies used in the treatment of CP/CPPS. While symptoms associated with documented infection fall into other NIH classification categories, several studies have shown evidence of an inflammatory component within Category III prostatitis. The EPS and semen of these men can show elevated inflammatory cytokines and markers of oxidative stress [22–24]. These markers of inflammation may even be present in Category IIIB, or noninflammatory, prostatitis without visualized WBCs in ejaculate. As such, phytotherapies with anti-inflammatory or antioxidant properties are hypothesized to be of benefit. Indeed, the perceived

benefit of antibiotics in CPPS may even be related to the anti-inflammatory properties of these medications rather than the antibacterial properties [22]. Another important etiology of symptoms is pelvic muscle spasm. This may occur as a primary process or as a local reaction to inflammation within the pelvis/prostate. Relieving the spasm via spasmolytic therapies would prove helpful here. Furthermore, spasm of the pelvic muscles may also lead to chronic hypoxia of the tissues. As above, this etiology suggests a role of anti-inflammatory or antioxidant agents in the treatment.

The complex of CP/CPPS can encompass several various symptoms. Once a patient has been tentatively or definitively diagnosed with CP/CPPS, it is important to characterize the phenotype of each individual patient. We have developed a clinical phenotyping system (UPOINT) that can help successfully drive multimodal therapy. By using the UPOINT (Urinary, Psychosocial, Organ-Specific, Infection, Neurologic/Systemic, and Tenderness of Skeletal Muscle) system, the practitioner can further classify each case of a heterogeneous diagnosis. A full discussion of the UPOINT model is beyond the scope of this article, but has been well described elsewhere [25]. This system has been validated to correlate with symptom severity from both a research and clinical practice standpoint [25–27]. The utility of this system in directing therapy will be discussed later in this chapter.

Before deciding on phytotherapies for treatment, the practitioner should consider other supportive treatments that may be more appropriate initially. Examples of alternative therapies include dietary modification, exercise, physical therapy, or behavioral therapy. Dietary modification is a simple and cost-effective method that may prove beneficial. Over 40 % of patients with CP/CPPS may experience food sensitivities, with the most common aggravating categories including spicy foods and caffeinated beverages [28, 29]. Dietary changes were also shown useful in female patients with pelvic pain [30]. Aerobic exercise is another cost-effective modality, and a randomized trial of aerobic exercise resulted in improved NIH scores and QoL over 18 weeks as compared to placebo [31]. Biofeedback and pelvic floor physical therapy are related modalities that address the pelvic floor dysfunction component of CP/CPPS, and several studies have shown benefit [29]. Finally, behavioral therapy is a useful adjunctive therapy that has been suggested to help patients address and cope with the symptoms of their disorder [29].

Treatments in Chronic Pelvic Pain

Traditional treatment of CP/CPPS has included pharmaceutical in various classes, including antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), alpha-blockers, and muscle relaxants. However, the existing evidence is mixed and not particularly strong. A 2012 meta-analysis of treatments for CP/CPPS found no benefit in NIH-CPSI scores with antibiotics, alpha-blockers, or combinations. The same study also showed minimal improvement with NSAID therapy, and identified a significant placebo effect with treatment that confuses analysis of these medications [32]. Given this weak evidence, there is significant interest in the evidence basis for phytotherapies.

Bee Pollen Extract

Bee pollen extract (Cernilton) has anti-inflammatory and antiandrogenic effects that make it attractive for translation to pelvic pain syndromes. The extract is also hypothesized to have effects on smooth muscle spasms which may also contribute to the efficacy. The bee pollen compounds are generally composed of two components, Cernitin GBX and Cernitin T60 [33]. Initial open label studies with this treatment were promising, with one study demonstrating symptomatic improvement in 13 of 15 patients [34]. A subsequent, larger study of 90 patients was then conducted with 90 days of Cernilton treatment and showed similar benefit. While only 1 of 18 patients with complicating factors (prostatic calculi, urethral stricture, bladder neck sclerosis) showed improvement, those patients considered "uncomplicated" saw 36 % cured of symptoms and 42 % with improved symptoms. Further analysis showed improved urinary flow rates, reduced leukocytes in the post-prostatic massage urine, and decreased complement C3/coeruloplasmin in the ejaculate, consistent with proposed anti-inflammatory properties of Cernilton [35].

The efficacy of this therapy was further demonstrated in several randomized clinical trials. Wagenlehner and colleagues conducted a randomized, placebo-controlled study in men with Category IIIA prostatitis. Patients were randomized to either pollen extract (two capsules TID) or placebo for 12 weeks. After 12 weeks of treatment, there were significant improvements in the pollen extract group with respect to NIH-CPSI total scores as well as the pain and QoL subtypes. Overall, 69 % of patients in the pollen extract group versus 49 % of patients in the placebo group experienced >25 % or 6-point decrease in the NIH-CPSI score [36]. It is worth highlighting that the placebo arm demonstrated almost 50 % response rate, although the pollen extract group still performed better. A follow-up analysis was subsequently performed in which the placebo patients crossed over to Cernilton therapy and all patients were followed for an additional 12 weeks. All measurements (NIH-CPSI total score, pain domain, and QoL domain) continued to improve up to week 24, with larger magnitude of effect in patients who had previously been on placebo [33].

Another randomized trial with pollen extract was conducted by Elist and published in 2006. Sixty patients with either Category IIIA or IIIB were randomized to the pollen extract Prostat/Poltit or placebo treatment for 6 months. There was an overall clinical response rate (clinically improved or cured) of 73 % in the pollen extract group versus only 36 % response rate in the placebo group. In addition, LUTS and sexual function were improved in the pollen extract group after treatment [37].

A combination therapy of pollen extract with vitamins (Deprox 500™) was more recently compared to ibuprofen in a randomized phase III study. Patients with either Category IIIA/IIIB prostatitis were randomized to Deprox (two capsules daily) versus ibuprofen (600mg TID) for 4 weeks. The pollen/vitamin group showed improvements in NIH-CPSI overall and pain score subset as compared to ibuprofen. Specifically, over 75.6 % of Deprox patients showed improvement in NIH-CPSI score by at least 25 %, compared to only 41.3 % response rate in patients receiving

ibuprofen [38]. Of note, Deprox was also shown effective in a small pilot study of Category IIIB prostatitis only by the same group of investigators. While this study had no comparator group, 90 % of patients reported improved QoL after 30 days of Deprox treatment [39]. The efficacy of this treatment in non-inflammatory CPPS suggests an additional mechanism of action beyond simply anti-inflammatory effects. In all the above studies, pollen extract compounds were very well tolerated, with minimal adverse effects of treatment.

Quercetin

Quercetin is a polyphenolic bioflavonoid that is found in red wine, green tea, and onions. It has been documented to have antioxidant and anti-inflammatory properties, both of which may be helpful in CPPS. Interestingly, beyond CPPS, quercetin has been investigated in a variety of conditions, including malignancies, cardiac disease, and hypertension. Basic science studies have demonstrated that quercetin inhibits the production of cytokines such as IL-6, IL-8, and TNF, which are elevated in the semen and prostatic fluid of men with CPPS [22]. Further, items naturally containing quercetin (e.g., red wine, green tea) are often avoided by patients, and it has been suggested that they may in fact have a dietary deficiency of quercetin.

The performance of quercetin in the clinical setting was evaluated in a double-blind placebo-controlled trial. Men with Category III prostatitis were randomized to placebo or quercetin (500 mg BID) for one month. Patients receiving placebo did not improve NIH-CPSI scores over the course of therapy (20.2–18.8), while those taking quercetin had a significant improvement in NIH-CPSI scores (21.0–13.1, $p=0.003$). Overall, 20 % of patients in the placebo group and 67% of patients in the quercetin group were noted to have at least 25% improvement in symptom score. An unblinded follow-up arm of the study examined a supplement called Prosta-Q (FarrLabs, El Segundo, CA), which contains quercetin as well as the enzymes bromelain and papain that improve digestion of quercetin. This compound demonstrated further gains in efficacy, as 82 % of patients in this arm showed at least 25 % improvement [40].

Subsequent study has attempted to understand the mechanism of quercetin's action. The ejaculate of men with Category IIIB prostatitis was examined for inflammatory markers before and after treatment with Prosta-Q. Both markers assessed (beta-endorphin, prostaglandin E2) were noted to decrease with Prosta-Q treatment. Further, Shoskes et al. collected blood from CPPS patients and inflammatory cytokine profiles were compared between responders and non-responders. Patients who did not respond to quercetin treatment were more likely to have a low TNF genotype, and they were less likely to have a low IL-10 genotype [41]. Taken together, this suggests that men with a phenotype of less inflammation are less likely to respond to quercetin treatment, which is consistent with the known anti-inflammatory properties of quercetin. Overall, quercetin therapy is very well tolerated. Documented uncommon side effects include nausea, joint pain, and orange pigmentation to the semen [22].

Saw Palmetto

Saw palmetto (*Serenoa repens*) is a phytotherapy derived from the berry of the American dwarf palm tree [3]. There are several proposed mechanisms of action, one of which is decreased conversion of testosterone to dihydrotestoterone [29]. Given the similarity to the mechanism of the 5-alpha-reductase inhibitors finasteride and dutasteride, Saw palmetto has been commonly used as a phytochemical for LUTS and BPH. The commonality of LUTS within both BPH and CPPS suggested a hypothetical use for saw palmetto in patients with CPPS. Saw palmetto was evaluated in a randomized trial versus finasteride, which was the first comparison of phytotherapy against a conventional medical therapy. Patients with Category III CPPS were randomized to finasteride (5mg daily) versus saw palmetto (325mg daily) for 1 year. At one year, the NIH-CPSI scores had decreased in the finasteride group (23.9–18.1), but were essentially unchanged in the saw palmetto group (24.7–24.6). Only 41 % of patients opted to continue saw palmetto at the end of the trial, compared to 66% of patients that elected to continue finasteride therapy [42]. Given the available evidence, there is no recommendation for saw palmetto treatment in patients with CPPS.

Traditional Chinese Medicine

Traditional Chinese medicine commonly utilizes a combination of herbal preparations and acupuncture in treatment of medical disorders. The interpretation of studies of these herbs is difficult given the language barrier, lack of standardized terminology, and heterogeneity of herbal products. However, studies from China have been published suggesting the efficacy of various preparations in both oral and rectal forms [43, 44]. Given recent increases in study of phytochemicals, further study may hopefully examine these herbal treatments in a more standardized fashion. Acupuncture is an associated discipline often prescribed along with herbal treatments. While acupuncture does not fall within the scope of this chapter (please see Chap. 6, "Acupuncture"), several studies have demonstrated efficacy in CPPS [45, 46].

Cannabis

Cannabis use has been demonstrated to be effective in reducing pain symptoms associated with a number of chronic pain conditions. It was thus hypothesized that it may prove similarly beneficial in patients with CP/CPPS. There is a single study in the literature regarding the effect of cannabis use on CP/CPPS. Patients in both a Canadian and American cohort were questioned regarding their use of cannabis as well as prostatitis syndromes. The overall effectiveness of cannabis was noted to be "somewhat/very effective," and many patients reported that use improved their symptoms. While concerns regarding this report include self-reported usage as well as probable bias related to legal issues surrounding cannabis usage in most jurisdictions, these initial results are interesting and deserve further study [47].

Treatment Decisions

The above sections have endeavored to describe the efficacy of several phytotherapies in the treatment of chronic pelvic pain. However, translating this data to the treatment of the individual patients and selecting appropriate therapy can be difficult. Two concepts important in forming treatment decisions are phenotype-directed therapy as well as multimodal therapy as well as phenotype-directed therapy.

As described throughout the chapter, chronic pelvic pain is a heterogeneous disorder with an entire spectrum of symptoms across various domains. The UPOINT system has been utilized to characterize the phenotypes that affect each individual patient, as each patient can have a unique combination of domains that are bothersome. The UPOINT domains and associated clinical features are described in Table 7.2. Once a patient has been evaluated with respect to their phenotype, treatment can be subsequently individualized. For example, pharmaceuticals such as alpha-blockers or anti-muscarinics should be considered in a patient with predominant or significant urinary symptoms.

Some studies on phytotherapy published since the introduction of the UPOINT have been able to elucidate some phenotypic subgroups that benefit from particular treatments. The most substantial evidence in this respect relates to the use of quercetin in men with organ-specific phenotype. A prospective trial of men at the Cleveland Clinic treated according to UPOINT phenotype prescribed men exhibiting organ-specific phenotype with quercetin alone (Prosta-Q) or a combination Quercetin with pollen extract (Q-Urol, Farr Laboratories). Across the entire cohort, treatments regimens including quercetin exhibited the strongest symptom improvement [25].

Table 7.2 The 6 UPOINT domains with associated clinical descriptions (Reprinted with permission from [49])

*U*rinary	– CPSI urinary score >4 – Patient complaint of bothersome urgency, frequency, or nocturia – Flow rate <15 mL/s and/or obstructed pattern – Post void residual urine volume >100 mL
*P*sychosocial	– Clinical depression – Poor coping or maladaptive behavior
*O*rgan-specific	– Specific prostate tenderness – Leukocytosis in prostatic fluid – Hematospermia – Extensive prostatic calcification
*I*nfection	– Exclude patients with evidence of acute or chronic bacterial prostatitis
*N*eurological/systemic conditions	– Pain beyond abdomen and pelvis – Irritable bowel syndrome – Fibromyalgia – Chronic fatigue syndrome
*T*enderness of skeletal muscles	– Palpable tenderness and/or painful muscle spasm or trigger points in perineum or pelvic floor or sidewalls during rectal examination

The above study of UPOINT-directed therapy reported a median of three UPOINT domains positive [25]. As such, it would be highly unlikely to describe one treatment modality that would treat all the symptoms described in this complex. Indeed, a published treatment strategy utilizing sequential monotherapies was associated with disappointing overall outcomes [48]. This review focuses mainly on the evidence for phytotherapies, but the best treatment for each individual may involve several modalities, including pharmacotherapy, phytotherapy, surgical therapy, physical therapy, or other modalities. All patients may benefit from conservative (and noninvasive) therapies such as education regarding the condition, counseling, exercise, stress reduction, and avoiding of symptom triggers [49]. Additional therapies would be added as per the particular phenotypes, as described above. The available evidence for multimodal therapy has been very positive. The previously noted Cleveland Clinic study of multimodal UPOINT-directed regimen demonstrated that 84 % of patients were able to achieve a ≥6 point reduction in NIH-CPSI score after six months of treatment. Further, the efficacy did not decrease in men with multiple positive phenotypes. This not only confirms the utility of the UPOINT system for evaluation and direction of management, but also demonstrates the effectiveness of multimodal therapy.

A large European experience similarly demonstrating the benefits of multimodal therapy was recently published. Men with Category III CP/CPPS were assessed using the UPOINT system to determine the particular disease phenotype, with subsequent combinations of treatments given based on the results. This strategy achieved very favorable results, with 77.5 % of patients achieving a reduction of ≥6 points on the NIH-CPSI scale. Interestingly, while the subgroup of patients with Category IIIA prostatitis had more severe symptoms at baseline compared to the Category IIIB patients, there was significantly greater response to treatment in these patients [50]. Whether this differential response is related to various treatments or different disease subtypes is not clear. Regardless, the literature strongly supports the use of multimodal therapy for treatment of patients with CP/CPPS.

Specific Needs for Additional Research

This chapter has demonstrated the vast gains that have recently been added to the body of literature surrounding phytotherapy for chronic pelvic pain. While these findings have advanced our understanding and management of this troublesome syndrome, there still exist areas in which additional research is still needed. In order to best practice evidence-based medicine, we must subject these therapies to rigorous prospective trials. These have been published with some phytochemicals as quercetin and pollen extracts, but potential treatments such as traditional Chinese herbs and cannabis need to be evaluated in this manner. Further, combination of therapies should be tested to assess for any potentiating or antagonistic effects. Since patients undergoing multimodal therapy receive several treatments at once, it is imperative to maximize the efficacy of the combinations. Finally, there is a distinct lack of literature regarding chronic pelvic pain in females. As a result, this represents a distinct group of patients that is currently not being served by existing therapies.

Conclusion

Chronic pelvic pain is a condition with debilitating effects on patient's quality of life, but unfortunately has not traditionally been treated effectively. Our understanding of chronic pelvic pain syndromes has significantly increased in the past 10–15 years. Specifically, the management has seen vast improvements with clinical phenotyping and use of complementary modalities of treatment. One such modality is the use of plant-derived phytotherapies such as pollen extract, quercetin, and saw palmetto. Both pollen extract and quercetin have been shown to be quite effective in the management of patients with chronic pelvic pain. However, other phytotherapies may soon prove useful within this realm once further research evaluates their efficacy. Practitioners treating chronic pelvic pain should familiarize themselves with the use of the available phytotherapies and incorporate them into phenotype-driven, multimodal therapy.

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Management of Interstitial Cystitis/ Bladder Pain Syndrome with Tricyclic Antidepressants

8

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Introduction

The tricyclic antidepressant amitriptyline (Elavil) has become a staple of oral treatment of IC/BPS (interstitial cystitis/bladder pain syndrome). The 2014 American Urologic Association (AUA) revised Guideline on IC/BPS listed amitriptyline as a second-line treatment of IC/BPS [1]. Other second-line treatments in the AUA Guideline included other oral medications (hydroxyzine, cimetidine, pentosan polysulfate), intravesical instillation (lidocaine, heparin, DMSO), manual physical therapy, and multimodal pain management. The use of amitriptyline to manage IC/BPS is an off-label use; however, clinical experience and data from trials supported its use. The AUA Guideline graded the strength of evidence as Grade B, meaning that there were randomized controlled trials (RCTs) but there were also weaknesses in these RCTs. The use of amitriptyline is designated an Option on the Guideline, which means that there is uncertainty in the balance between benefits and risks/burden of the treatment. **Although amitriptyline may benefit a subset of IC/BPS patients who are able to tolerate the medication at higher doses (50–75 mg at bedtime), it is not possible to identify a priori who the responders might be. Adverse effects, while mostly mild to moderate, are reported by almost all patients and constitute the drawback of this therapeutic approach to manage IC/BPS.** Here, we shall focus the discussion on amitriptyline, the most commonly used tricyclic antidepressant to manage IC/BPS. Other tricyclics (nortriptyline), selective serotonin uptake inhibitors (sertraline), and serotonin norepinephrine update inhibitors (duloxetine) will also be reviewed.

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Mechanisms of Action of Tricyclic Antidepressants

Tricyclic antidepressants possess many pharmacological properties that make it appealing to manage IC/BPS: (1) they have central and peripheral anticholinergic properties, which may help with urinary frequency and urge symptoms; (2) they block the reuptake of serotonin and norepinephrine in the nerve terminals, which may relieve pain by its neuromodulatory effect by increasing the availability of serotonin and norepinephrine neurotransmitters in the central nervous system; (3) they have antihistamine effects; and (4) they have central sedative actions, which may help patients to sleep and rest at night instead of constantly visiting the bathroom. The analgesic action of tricyclic antidepressants is independent of its antidepressant effects.

Efficacy Data on Amitriptyline from Randomized Controlled Trials

There were two randomized controlled trials (RCTs) on amitriptyline: one large multicenter RCT that compared amitriptyline plus standardized education and behavioral modification to placebo plus standardized education and behavioral modification [2], and a smaller single center RCT that compared amitriptyline to an oral placebo [3].

The Interstitial Cystitis Collaborative Research Network (ICCRN) Randomized Controlled Trial

The Interstitial Cystitis Collaborative Research Network (ICCRN) conducted a multicenter, randomized, double-blind, placebo-controlled trial that compared the efficacy of amitriptyline plus standardized education and behavioral modification to placebo plus standardized education and behavioral modification [2]. 271 men and women who had moderate to severe symptoms (pain and frequency ratings of 3 or greater on 0–10 Likert scales) and were treatment naive (no prior significant treatment for IC/BPS) were randomized 1:1 to amitriptyline versus placebo for 12 weeks. Study drug dose was titrated up to 75 mg at bedtime (from 10–25 to 50–75 mg) subject to tolerability. All participants (amitriptyline or placebo) also received standardized education and behavioral modification, which consisted of symptoms and stress management, fluid management, diet modification, and bladder training. The primary outcome was based on the 7-point patient-reported GRA (global response assessment) at 12 weeks. Participants who indicated that they were markedly or moderately improved were considered responders. Participants with the other GRA responses or lost to follow-up were considered nonresponders.

Overall the difference in the primary outcome between the two treatment arms did not reach significance ($p = 0.12$). Fifty-five percent of subjects who received amitriptyline plus standardized education and behavioral modification were responders. Forty-five percent who received placebo plus standardized education and behavioral

modification were responders. Of the subgroup of subjects who achieved a drug dose of at least 50 mg, a significantly higher response rate was observed in the amitriptyline group compared to placebo (66 % vs. 47 %, $p < 0.01$). In the subgroup of subjects who were able to achieve *and* maintain a study drug dose of at least 50 mg to week 12, the responder rate was even greater in the amitriptyline arm compared to control (77 % vs. 53 %, $p < 0.001$). Thus, while on an intent-to-treat analysis there was not significant benefit from amitriptyline, in patients who could tolerate 50–75 mg, the benefits appeared substantial. Although the formal result of this largest amitriptyline RCT to date was negative, having a high percentage of subjects (55 %) reported that they were markedly or moderately improved with amitriptyline plus standardized education and behavioral modification was still a notable result.

Failure to demonstrate efficacy in the primary outcome might be due to the high response rate of the control intervention (standardized education and behavioral modification), and the high drop-out rate in the amitriptyline arm.

The response rate of the control arm (45 % responders) was substantially higher than the majority of previously published randomized trials for IC/BPS (usually in the 30–35 % range for placebo). One might argue that the education and behavioral strategies prescribed in this RCT might actually be an intervention that was effective, and thus was not a "true placebo" [4]. Of note, patient education, self-care practices, behavioral and diet modifications, and stress management are first-line treatments on the AUA Guideline [1]. Theoretically, amitriptyline could still be better than a true placebo, even though adding amitriptyline to education and behavioral strategies did not confer additional benefits, which was what this RCT actually showed. In this trial, the mean decrease in Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI; both secondary outcomes) [5] was 10 in the amitriptyline group and 7.2 in the comparison group. In a previous RCT, the mean decrease in ICSI and ICPI was 8.4 in the amitriptyline group, but the decrease in the placebo group was much lower (3.5) when a true oral placebo was used [3].

The other issue was the high drop-out rate of the amitriptyline arm. Essentially, 1 of 6 subjects (16 %) dropped out of the study by week 12. In the original RCT paper, all subjects who were lost to follow-up were deemed nonresponders (intent-to-treat analysis). This approach might be overly conservative, and may bias the results in favor of the placebo group when there was an imbalance of drop-out rates between the active and placebo groups. Although it is common practice to be conservative and assume that subjects who were lost to follow-up were not doing well and would be nonresponders if they were to remain in the study, in reality subjects dropped out of studies for a variety of reasons besides nonresponse. It was therefore also possible that subjects were lost to follow-up because they felt well and would be responders if they were to remain in the study [6]. To address this possibility, Yang et al. (2014) used an alternative statistical approach (generalized structural mean model) to adjust for both protocol nonadherence and loss to follow-up, and reanalyzing the data from the ICCRN RCT. They found a possible benefit of amitriptyline when administrated at a higher dose level [6].

Only less than half of the subjects in the amitriptyline arm (46 %) were able to achieve the dose of 50–75 mg at bedtime with the dose-escalation strategy, and

stayed on that dose till week 12. And one-fifth of subjects (20 %) were initially able to achieve the 50 mg bedtime dose but reduced the dose to less than 50 mg by week 12. One-third of subjects (34 %) were never able to achieve the 50 mg dose (titration stopped at 25 mg due to intolerability). The first two groups reported higher response to amitriptyline while the third group did not do better than placebo.

The Single Center Randomized Controlled Trial from Germany

The single center, randomized, double-blind, placebo-controlled trial conducted by van Ophoven et al. (2004) in Germany was the only other RTC that compared amitriptyline to placebo [3]. 50 men and women who met the symptom criteria of the NIDDK research definition for IC were randomized 1:1 to amitriptyline versus oral placebo for 4 months [7]. Study drug dose was self-titrated up to higher maximal dose of 100 mg at bedtime (from 25–50 to 75–100 mg). Unlike the ICCRN trial, subjects did not have to be treatment naive, meaning that they were eligible if they had received previous treatments such as hydrodistention, intravesical instillation, and oral medications other than amitriptyline (e.g., anti-histamine, pentosan polysulfate). The primary outcome was the sum of the Interstitial Cystitis Symptom Index and Problem Indexes (ICSI + ICPI) [5]. Overall, there was a significant difference between the two study groups. The mean symptom score-sum (ICSI + ICPI) decreased from 26.9 to 18.5 in the amitriptyline group compared with 27.6 to 24.1 in the placebo group ($p = 0.005$). 63 % of subjects receiving amitriptyline rated the therapeutic outcome as either good or excellent compared to 4 % of subjects in the placebo group ($p = 0.001$, secondary outcome).

The positive primary outcome of this RTC was a contrast to the negative primary outcome of the ICCRN trial. There were a number of notable differences between the two RCTs: (1) there was no standardized education and behavioral modification overlaid onto this RTC—it was a straightforward comparison between amitriptyline and oral placebo here; (2) the primary outcome measures were different (ICSI and ICPI in this trial instead of the GRA in the ICCRN trial); (3) subjects in this trial did not have to be treatment naive; (4) the drop-out rate was significantly lower in this RTC (only 4 % in this trial instead of 16 % in the ICCRN study); and (5) a much higher percentage of subjects in the amitriptyline group were able to achieve and maintain higher bedtime dose of 50 mg or higher (71 % in this trial instead of 46 % in the ICCRN study).

Data from Uncontrolled Clinical Studies of Amitriptyline

Hanno and Wein (1987) first reported a "serendipitous" response to amitriptyline in one of their IC patients being treated for depression [8]. A case report describing a favorable response to another tricyclic antidepressant desipramine was published the next year [9]. Reasoning that a drug that was used successfully at a lower dose for many years in other chronic pain conditions, which also has with anticholinergic,

antihistamine, and sedative properties, might benefit IC, Hanno et al. (1989) conducted the first clinical trial of amitriptyline for IC [10]. Their first case series included 25 IC patients who had failed bladder hydrodistention and intravesical DMSO treatments. A dose of 25 mg amitriptyline was titrated up to 75 mg. Mean follow-up was 16.4 months. Among the 20 patients (80 %) who were able to tolerate 75 mg amitriptyline at bedtime, a significant improvement was observed in pain and urinary frequency, but nocturia did not improve significantly. Eight patients (32 %) had experienced almost complete remission of symptoms and had been on the drug for 4–28 months. A follow-up study by Hanno (1990) reported that among the 28 of 43 patients (65 %) able to tolerate 75 mg amitriptyline for at least 3 weeks, 18 had total remission of symptoms with a mean follow-up of 14.4 months (18 of 43 = 42 %). Five subjects dropped out because of side effects, and five had no clinical benefits [11].

Van Ophoven and Hertle (2005) conducted an open label extension study on 94 IC/BPS patients [12]. Subjects followed a self-titration protocol, but unlike their previous RCT [3], there was no limitation of the maximal daily dose. The mean dose of amitriptyline taken was 55 mg (range 12.5–150). The mean follow-up was 19.0 months, and the mean treatment duration was 16.5 months. The primary outcome was based on the 7-point patient-reported GRA. Subjects who reported that they were slightly improved, moderately improved, or markedly improved were considered responders. Overall, 64 % of subjects were responders using the authors' definition. Using a more stringent definition of response (e.g., consistent with the ICCRN study, those who were markedly or moderately improved were considered success), the response rate was 44 %.

Summary of Efficacy Data from Randomized Controlled Trials and Uncontrolled Studies

The initial single center RCT that compared amitriptyline to placebo drug showed efficacy [3]. A subsequent large multicenter RCT that compared amitriptyline to placebo in treatment naive patients who were also prescribed standardized education and behavioral modification did not show a difference [2]. **However, amitriptyline may benefit a subset of IC/BPS patients who were able to tolerate or maintain amitriptyline at higher doses (50–75 mg at bedtime).** Based on the limited number of RCTs and uncontrolled studies, efficacy rates of 50–66 % can be achieved, with higher efficacy rate (up to 77 %) at sustained higher dose (≥50 mg).

Predicting Clinical Responders to Amitriptyline

Is there any evidence in the literature that IC/BPS patients with certain phenotypes or clinical characteristics might respond better to amitriptyline? Two studies have examined this issue.

In the open label study conducted by Van Ophoven and Hertle (2005), patients who fulfilled the NIDDK research definition of IC (the NIDDK group, $n = 59$, 63 %)

and those who met the exclusion criteria of the NIDDK criteria (the non-NIDDK group, $n=35$, 37 %) were both recruited. The response rates of the two IC subtypes were compared (NIDDK versus non-NIDDK). No difference in the response rate of the two patient subgroups was observed (64 % vs. 63 %) [12].

Sun et al. (2014) examined whether the ESSIC (European Society for the Study of Bladder Pain Syndrome) classification and cystoscopic findings (e.g., presence of glomerulations or Hunner's lesions) influenced the response to amitriptyline in a case series [13]. 30 subjects with ESSIC type I bladder pain syndrome (normal cystoscopy) and 37 subjects with ESSIC types II or III (with glomerulations or Hunner lesions on cystoscopy) were included. Subjects were permitted to self-titrate the dose between 25 and 75 mg and took the medication for 3 months. There was no significant difference of GRA response rate between subjects classified as ESSIC type I versus types II/III (43 % and 49 % of subjects reported moderate or marked improvement at 3 months respectively, $p=0.66$). Type II/III subjects appeared to need higher dose of amitriptyline to relieve their symptoms compared to type I subjects. At 3 months, 72 % of type II/III subjects were taking 75 mg maximal allowed dose compared to 23 % of type I subjects ($p=0.011$). In summary, ESSIC criteria and cystoscopic findings (the presence and absence of glomerulations or Hunner lesions) had no predictive value in the treatment outcome of amitriptyline.

Adverse Effects

Amitriptyline improves IC/BPS symptoms via its known anticholinergic and antihistamine properties. In fact, amitriptyline is one of the most potent tricyclic antidepressants in terms of blocking H1-histaminergic receptors [14]. However, the anticholinergic and antihistamine properties can cause side effects, drug intolerability, and potentially affecting the quality of life.

In the ICCRN randomized trial, 88 % of participants who took amitriptyline reported adverse effects [3]. Most adverse effects were mild (32 %) or moderate (42 %). In descending order, the most common side effects were constitutional symptoms (fatigue, malaise, in 45 % of subjects), gastrointestinal (dry mouth, constipation, in 42 % of subjects), neurological (dizziness, somnolence, in 33 % of subjects), and pain (primarily headache, in 32 % of subjects). Constitutional, gastrointestinal and neurological symptoms were more common in the amitriptyline arm versus placebo ($p<0.05$). Only less than half of the subjects who were randomized to amitriptyline were able to achieve the dose of 50–75 mg at bedtime with the dose-escalation strategy, and stayed on that dose till week 12. Overall, 17 % of subjects in the active arm dropped out of the study, likely due to lack of improvement and/or intolerability.

In the van Ophoven RCT, anticholinergic side effects were noted in almost all subjects (92 %) who took amitriptyline [3]. Dry mouth was the most common side effect (79 %), followed by weight gain (63 %), constipation (46 %), sedation (33 %), and nausea/vertigo (13 %). Most adverse effects were mild. The drop-out rate was remarkably low in that study (only 4 % at 4 month).

In the van Ophoven and Hertle open label study, all 29 subjects who reported no improvement or worsening well-being during amitriptyline treatment dropped out of the study for a 31 % drop-out rate [12]. Cessation of drug intake was reported after a mean treatment period of 6 weeks, at a mean titration dose of 70 mg amitriptyline. Side effect contributed to the decision to drop out of the study in 25 of the 29 patients (86 %), and was the primary reason of drop out in 9 patients. Nonresponse to amitriptyline was the primary reason for drop-out in 20 of the 29 patients (70 %).

It is clear from these and other studies that dose-dependent adverse effects and drug intolerability limited the achievable dose and therapeutic potential of amitriptyline. **Adverse effects, while mostly mild to moderate, are reported by almost all patients and constitute the drawback of this therapeutic approach to manage IC/BPS.** Given that amitriptyline appears to benefit a subset of patients who can tolerate it in the setting of a high likelihood for adverse events, the AUA Guideline designated amitriptyline treatment an Option, meaning that the balance between benefits and risks/burden was uncertain [1].

Clinical Perils on the Use of Amitriptyline to Manage IC/BPS

Due to the constitutional symptoms and dizziness/somnolence side effects, amitriptyline should be taken prior to bedtime (QHS dosing). The usual starting dose is 25 mg orally at bedtime. For patients who are older (age 65 or older), more sensitive to drug side effects, or who are already taking medications with sedation or anticholinergic side effects (it is common for IC/BPS patients to be taking multiple medications with similar side effects), a lower starting dose of 10 mg orally at bedtime should be considered. Patient can self-titrate the dose up on a weekly basis based on the perceived balance between efficacy and tolerability. Slowly titrating the dose on a weekly basis, beginning at 10–25 mg at bedtime and increasing by 10 mg weekly to a target dose of 50–75 mg at bedtime seems to minimize side effects. Patients may also titrate the dose down to identify a tolerated dose if the side effects become bothersome. This approach is preferably to discontinuing the medication prematurely. Six to eight weeks (with 2 weeks at maximum tolerated dosage) is necessary for an adequate trial. Based on data from the two RCTs, a bedtime dose of 50–75 mg should be adequate to achieve response for those who are going to respond [2, 3]. For those who cannot tolerate amitriptyline (a tertiary tricyclic), one might consider switching to nortriptyline (a secondary tricyclic). In a randomized neuropathic pain trial, nortriptyline (an active metabolite of amitriptyline) has an equal analgesic effect on amitriptyline but has less adverse effect [15]. A history of failed tricyclic treatment should not dissuade clinicians from another careful trial since many failures result from high initial dosing, too rapid dose escalation, noncompliance, or inadequate trial (too low a dose or too brief a trial).

For all IC/BPS patients, one should emphasize the importance of patient education, self-care practices, behavioral and diet modifications, and stress management since these are first-line treatments on the AUA Guideline [1]. Multimodal therapy is a mainstay approach for IC/BPS. Prescribing a pill alone without reinforcing the self-help and behavioral strategies is not acceptable. The clinician should also

discuss the expectations, side effects, and dose titration strategy of the amitriptyline treatment. Having a realistic expectation of treatment is important. Explain that complete pain relief is possible but unlikely, and a more realistic goal is to reduce pain by 50 % and to improve function. Inform patients that the effect of dose escalation may not be felt for a week or so. It is important to help patients understand the rationale and clinical value of using amitriptyline so they do not feel stigmatized by taking a "psychiatric" medication or an "antidepressant." Patients should be cautioned about fatigue, sedation, dry mouth, constipation, increased appetite, weight gain, and dizziness. Stool softeners may be prescribed prophylactically for constipation. There are choices among the second-line oral treatments in the AUA Guideline (amitriptyline, hydroxyzine, cimetidine, pentosan polysulfate) [1]. For treatment naive patients, it is reasonable to start with pentosan polysulfate (Elmiron). For those with moderate symptoms who cannot wait weeks for pentosan polysulfate to take effect, adding hydroxyzine or cimetidine (antihistamine) is reasonable, especially for patients with allergies. For those with more severe pain, one can add amitriptyline because it has anti-nociceptive effects. One does not want to initiate or switch more than two medications at a time.

As discussed before, cystoscopic findings, ESSIC classification, and conformation to the NIDDK research definition of IC did not help to identify responders a priori. Considering that amitriptyline and other tricyclic antidepressants have both peripheral and central effects, it seemed suitable for both IC/BPS patients who have localized pelvic/bladder pain, as well as patients who have more centralized pain—those with overlapping chronic pain syndromes including fibromyalgia, chronic fatigue syndrome, vulvodynia, or irritable bowel syndrome [16]. Although IC patients with Hunner lesions in the bladder can respond to amitriptyline at higher therapeutic dose, the AUA Guideline recommends going directly to more effective treatments such as injection of triamcinolone (kenalog) into the Hunner's lesions or fulguration of Hunner's lesions [1, 13]. Men with IC/BPS can also respond well to amitriptyline, as evident in the RCTs and clinical series [2, 3, 12, 13]. Many men who were considered to have chronic prostatitis do, in fact, have IC/BPS symptoms such as painful filling (increase in bladder pain upon bladder filling), painful urgency (urgency to urinate due to pain, pressure, or discomfort), urinary frequency, and nocturia [17]. Thus, it is reasonable to treat men with IC/BPS-like symptoms with amitriptyline. To our knowledge, there was no published study on the use of amitriptyline with chronic prostatitis. Anecdotally, we have success in managing penile, perineal, and genital pain with amitriptyline.

Contraindications and Precautions

Tricyclic antidepressants are contraindicated in patients in the acute recovery phase of myocardial infarction (e.g., within 6 months), with long QT syndrome, significant conduction system disease (bifascicular or trifascicular block), unstable angina, congestive heart failure, frequent premature ventricular contractions, or a history of sustained ventricular arrhythmias. Tricyclic antidepressants should not be given concomitantly with monoamine oxidase inhibitors.

Amitriptyline should be used with caution in patients with a history of seizures (due to atropine-like action), narrow angle glaucoma, increased intraocular pressure (anticholinergic effects), or orthostatic hypotension (adrenergic blockade). It may enhance the response to alcohol, barbiturates, or CNS depressants and should be used in caution in those who consume alcohol excessively. Young adults (aged 24 or less) treated with antidepressants should be observed for worsening of depression, emergence of suicidal ideation and behavior, and unusual changes in behavior. A lower starting dose and slower titration is recommended for elderly patients.

Other Tricyclic Antidepressant: Nortriptyline

Nortriptyline, an active metabolite of amitriptyline, has not been studied specifically in IC/BPS patients. More than two decades ago, Walker et al. (1991) reported findings from a case series of 14 women with chronic pelvic pain who were treated with 100 mg nortriptyline after dose titration [18]. At the 2-month evaluation, six of seven women who remained in treatment reported complete or partial pain relief. The other seven women dropped out of the study due to side effects.

Selective Serotonin Uptake Inhibitors (SSRIs): Sertraline

SSRIs block the reuptake of serotonin neurotransmitter at nerve terminals. SSRIs are the most widely prescribed class of antidepressants to manage depression. Examples of SSRIs include fluoxetine (Prozac) and sertraline (Zoloft). However, there are no published studies on using SSRIs to manage IC/BPS. Engel et al. (1998) conducted a small crossed-over RCT to assess the efficacy of sertraline (50 mg twice daily) in 23 women suffering from chronic pelvic pain. No significant improvement in pain was demonstrated on sertraline compared to placebo [19]. Lee et al. (2005) conducted a small RCT to assess sertraline in 14 men diagnosed with chronic prostatitis. At 13 weeks, there was no difference between active versus placebo group [20]. SSRIs are free of anticholinergic, adrenergic, and histaminergic receptor activities. While SSRIs may have less adverse effects, this pharmacological profile may not be ideal to manage IC/BPS.

Serotonin Norepinephrine Update Inhibitors (SNRIs): Duloxetine

SNRIs block the reuptake of both serotonin and norepinephrine at nerve terminals. One of the known mechanisms of tricyclic antidepressants is to block serotonin and norepinephrine reuptake. SNRIs are commonly used by interdisciplinary pain teams to manage chronic pain syndromes such as fibromyalgia. In fact, duloxetine (Cymbalta) is FDA-approved to manage fibromyalgia (but not for IC/BPS). Van Ophoven and Hertle (2007) reported an observational cohort study to evaluate the efficacy and tolerability of duloxetine for the treatment of IC/BPS. 48 women were

treated for 2 months following up titration to a target dose of 40 mg duloxetine twice daily. Among 48 patients, there were only 5 (10.4 %) who were identified as responders. All five responders reported onset of symptom improvement but not until they had reached the target dose. 17 patients (35.4 %) dropped out of the study exclusively due to side effects, with nausea present in all dropouts. Based on the preliminary data (poor response rate, high dropout, and poor tolerability), the authors did not recommend duloxetine to manage IC/BPS [21].

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Bladder Surface Mucin Analogues

9

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Background

Bladder coating agents are commonly used to treat interstitial cystitis (IC). These agents are thought to address epithelial dysfunction. Lower urinary dysfunctional epithelium (LUDE) describes the defective protective mucous layer of the bladder found in most IC patients [1]. A hydrophilic mucus layer, rich in proteoglycans and glycosaminoglycans, normally covers the bladder luminal surface [2]. Water accumulates in the outer layer of umbrella cells, coating the bladder transitional epithelium. This mucus barrier, called the glycosaminoglycan (GAG) layer, reduces bladder permeability to urinary solutes, such as potassium, creatinine, urea, and ammonia [2, 3]. It also plays a protective role against urinary tract infections, by preventing bacterial adherence to the bladder surface [2]. Thus, bladder coating agents would appear to be a logical approach to address a primary pathophysiologic factor in IC.

IC is a chronic condition, also referred to as bladder pain syndrome. Women are diagnosed ten times as commonly as men. Patients present with urinary urgency, frequency, nocturia, and chronic pelvic pain, which is often increased with bladder filling [4, 5]. Stress, dietary triggers, and sexual intercourse commonly exacerbate symptoms. Many IC symptoms can be explained by a defect in the bladder's protective epithelial layer. The dysfunctional bladder epithelium allows toxic urinary metabolites to penetrate the bladder epithelial barrier [1, 6]. In particular, potassium is highly concentrated in the urine, and its contact with bladder sensory nerves may reproduce IC symptoms. Potassium may cross the epithelium and depolarize submucosal sensory nerves (causing urgency and pain) and cause direct tissue damage to detrusor muscle [1].

Parsons is widely credited for a series of experiments to test the GAG hypothesis that the epithelium is defective and that potassium triggers much of the symptom complex. IC patients have greater epithelial permeability compared to controls [7]. Intravesical

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instillation of potassium reproduces IC symptoms such as urgency and bladder pain [1]. Both asymptomatic controls and IC subjects were tested with both small volumes (50 mL) sterile water and 0.4 M KCl instilled in their bladders. IC subjects were far more likely to report urgency or pain compared to controls when challenged with KCl. Interestingly, when the control subjects were subsequently given a bladder pretreatment of protamine sulfate (effectively to remove the surface GAG layer) and then rechallenged with water and KCl instillations, the control subjects then had much greater urgency and pain compared to their initial baselines. Close to 80 % of IC patients have a positive potassium sensitivity test, compared to only 1.5 % of controls [1, 8]. Although there are controversies in the interpretation of these results (and potassium testing in general), we interpret the data to support the crucial role of epithelial integrity to normal bladder sensation, and its central role when LUDE is present to explain logically and consistently the constellation of symptoms IC patients report.

Admittedly, different explanations for the defect in the bladder lining found in IC patients have been postulated. Abnormal differentiation of urothelial cells into impermeable umbrella cells, or impaired bladder epithelial repair due to the presence of an antiproliferative factor could also be responsible [2, 9].

Despite much evidence supporting the GAG layer hypothesis, some authors postulate that the primary pathophysiological process in IC is mucosal hypersensitivity and neurogenic inflammation. This inflammation could be triggered by a variety of factors, such as infection, autoimmunity, or environmental factors [10, 11].

There are four major groups of glycosaminoglycans (GAGs): heparins and heparin sulfates, chondroitin and dermatan sulfates, hyaluronate, and keratan sulfate [2]. Only the first two are naturally found in the bladder GAG layer [2, 12, 13]. In particular, glycoprotein GP51 and chondroitin sulfate, both produced by urothelial cells, are decreased or absent in IC patients compared to controls [2, 13, 14]. Treatments with intravesical coating agents aim to restore one or more of these defective GAGs.

Defects in the protective GAG layer and chronic exposure of the bladder wall to irritating urinary substances result in a sequence of events including recruitment of inflammatory cells, mast cell degranulation, and neurogenic inflammation [2, 3]. Over time, chronic inflammatory processes and neural activation lead to an increase in local nerve growth factors, nerve ingrowth, and neural sensitization [15, 16]. Neural upregulation is a process that invokes recursive pathways as the body attempts to respond to what it perceives as a localized injury. Regardless of the initial injury, relatively stereotypical inflammatory and neural responses ensue, that if allowed to progress to a chronic state, lead to hypersensitivity and allodynia [17–22]. Ultimately, fibrosis and decreased bladder capacity may also occur if allowed to progress [23].

In an attempt to prevent these potentially irreversible remodeling changes, early diagnosis and treatment should be prioritized [2, 24]. Some initial data using a template called UPOINT has been validated and lends potential support to a multidisciplinary approach [25, 26]. UPOINT is the mnemonic for the six domains included in this IC phenotypic classification system. The domains are: urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic dysfunction, and tenderness of muscles. Therapies can be targeted towards each implicated domain in order to achieve symptom relief [25, 26]. However, in this chapter we only cover bladder mucin surface analogues, which address the organ-specific findings of UPOINT.

Bladder Surface Mucin Analogs

Bladder surface mucin analogues are used in the treatment of IC, with the aim of restoring the integrity of the bladder's GAG layer. The theory behind using those treatments for IC was initially extrapolated from recurrent urinary tract infections studies, as intravesical heparin reduces bacterial adherence to the bladder surface epithelium [1]. Animal experiments demonstrated that exogenous GAG binds to denuded bladder lining, and could reverse some of the pathological processes leading to IC symptoms (Fig. 9.1). Chondroitin sulfate intravesical instillation in a mouse cystitis model adheres to damaged bladder surfaces, but not to normal bladder lining

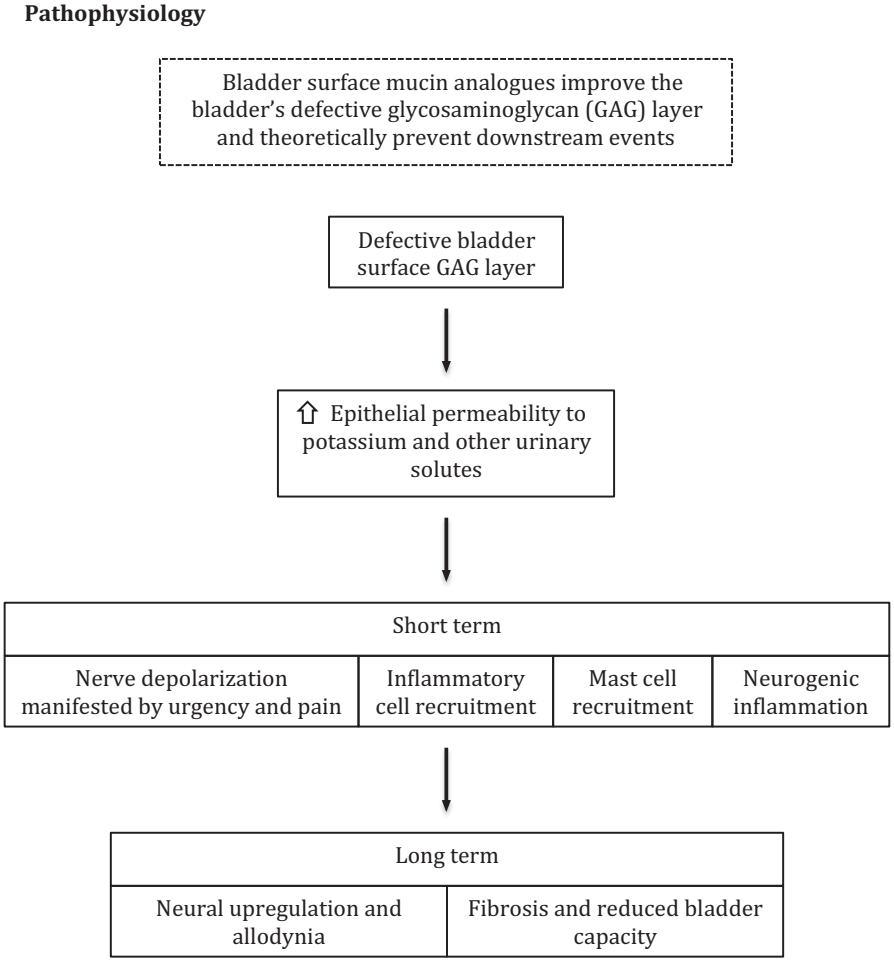

Fig. 9.1 Role of bladder surface mucin analogues in interstitial cystitis pathophysiology

[27, 28]. This restores the GAG layer's impermeability [27]. Rat models also show that chondroitin instillation inhibits inflammatory cell recruitment, including mast cells [29, 30]. Nickel et al. described a rabbit model to compare bladder permeability after treatment with three different types of bladder coating agents. They determined baseline radioactive urea absorption in normal controls, and saw an increase in absorption after protamine wash. After the protamine instillation, rabbits were separated into three groups and treated with one of heparin, PPS, or hyaluronic acid (HA). Heparin and PPS instillations were both successful in reducing urea absorption back to baseline, but HA was not as effective [31].

Oral pentosan polysulfate sodium (PPS) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of IC since 1996. PPS can also be used for intravesical instillations. Heparin sulfate is used off-label as instillation treatment for IC. Other intravesical agents, not available in the USA, include hyaluronic acid and chondroitin sulfate.

According to the 2015 American Urological Association amended guideline on the treatment of interstitial cystitis and bladder pain syndrome, first-line treatments include stress reduction techniques, pain management, patient education, and behavioral modifications. Oral PPS and intravesical coating agents are considered second-line treatments [32]. However, in the senior author's practice, we often initiate treatment with PPS and/or intravesical compounds at the patient's first visit, once the diagnosis of IC is highly suspected. In fact, we commonly use a combination of lidocaine, heparin, and sodium bicarbonate intravesically for two purposes: to confirm our diagnosis, and to initiate a fast-acting treatment for symptom relief. Since the diagnosis of IC is most frequently delayed by months to years, due to its vague symptomatology and poor recognition, we feel that by the time patients get to our clinic the disease has been present for years, and should be addressed directly [4, 5, 33]. We will take time during this first visit to educate the patient, and discuss conservative managements options listed above, while also initiating intravesical alkalinized lidocaine with heparin for immediate onset of symptom relief [34].

Physicians should however be cognizant of the fact that the quality of evidence for bladder surface mucin analogues is not ideal. Trials have been difficult to complete. IC patients are often reluctant to be enrolled in treatment protocols that could potentially assign them to a placebo [35]. A distinct phenotype of IC patients with multiple sensitivities has also been reported [36]. These patients commonly experience sensitivity and bothersome side effects to various medications, and are likely to be less compliant with treatment due to these effects. Multiple studies use the "last observation carried forward" analysis to compensate for high loss to follow-up rates. This analysis assigns the last patient observations to the end of the follow-up period, which may lead to bias [37]. In addition, the placebo effect is strong in this population, similar to many populations with chronic pain or fatigue. In order to ensure adequate case selection, multiple studies have strict inclusion and exclusion criteria, which could affect generalizability. Finally, many studies to date have few patients, questionable design, and short follow-up [12, 38]. Despite these limitations, treatments discussed below have demonstrated some relief in symptoms. However, size of effect on urinary frequency and pain is mild-to-moderate. The various bladder surface mucin analogues to be discussed are presented in Table 9.1.

Table 9.1 Bladder surface mucin analogues

Name	Route of administration	Dose	Schedule of administration	Grade of recommendation for use		
				AUA grade 2014	EAU level of evidence	EAU grade 2015
Pentosan polysulfate sodium	1. Oral	100 mg TID to 200 mg BID	Daily for minimum 6 months	B	1a	A
	2. Intravesical instillation	200–300 mg	Twice weekly for 6 to 12 weeks	N/A	1b	A
Heparin	1. Intravesical instillation	20,000 U heparin, 8 mL 2 % lidocaine, and 4 mL 8.4 % sodium bicarbonate	One to three times per week for 12 weeks	C	3	C
	2. Sub cutaneous injections	5000 U TID for 2 days then BID × 12 days	With concomitant oral PPS, repeat if symptoms recur	N/A	1b	A
Chondroitin sulfate	Intravesical instillation	400 mg	Weekly for 6 weeks, followed by monthly instillations	N/A	2b	B
Hyaluronic acid	Intravesical instillation	40–120 mg	Weekly for 4–12 weeks	N/A	2b	B
Hyaluronic acid and chondroitin sulfate	Intravesical instillation	800 mg HA and 1 g chondroitin sulfate	Weekly for 4–8 weeks, then bi-weekly	N/A	N/A	N/A

AUA = American Urological Association
EAU = European Association of Urology

Pentosan Polysulfate Sodium (PPS)

Oral PPS

PPS is the only oral IC treatment approved by the U.S. Food and Drug Administration (FDA). Available under the trade name Elmiron®, PPS is a semi-synthetic low molecular weight heparin-like derivative, with weak anticoagulant properties. Its mechanism of action is presumed to involve restoration of the protective mucus barrier of the bladder. However, PPS has multiple potential mechanisms of action. PPS was found to correct potassium sensitivity in 60 % of subjects, supporting the bladder coating mechanism of action [39].

Treatment with oral PPS has been studied extensively. A total of eight randomized trials have been published on oral PPS, as well as one unpublished trial, which

was halted due to nonsignificant results [32, 40]. In the six published trials comparing PPS to placebo, three showed a benefit to PPS, two showed no difference, and one was underpowered to show a difference [35, 41–45]. Overall, clinically significant symptom improvement with PPS averages 21–56 % versus 13–49 % with placebo [32]. A pooled analysis of five of the six randomized trials comparing oral PPS to placebo (performed prior to publication of the latest trial) found global symptom improvement after PPS therapy (RR 1.78, 95 % CI 1.34–2.35) [38]. The most recent randomized placebo-controlled trial published in 2015 by Nickel et al. compared the effect of 300 mg or 100 mg PPS daily versus placebo in 368 patients, and found no effect difference between the three groups at 24 weeks. The authors acknowledged that their inclusion criteria were not as strict as those used in most PPS effectiveness studies, and reinforce the need to further study the specific effect of various treatments on each IC phenotypes [45]. Two other randomized trials did not include a placebo group. A dose-effect study, which will be discussed in more detail later, showed that PPS response was not dose-dependent [46]. A second trial showed a benefit to cyclosporine A over oral PPS [47].

PPS reduces pain, as well as urinary urgency and frequency, but its impact on reducing nocturia may be less pronounced [42–44]. Voided volumes also increase, albeit slightly [43, 44]. Obvious limitations of the available literature include variable disease definitions between studies, and a mean follow-up of only 15 weeks [38]. Due to these weaknesses, the American Urological Association classifies the evidence for PPS as Grade B, or moderate [32]. The European Association of Urology recommends its use (Grade A: evidence from level 1 studies) [48].

There may be a better response to PPS in patients with non-ulcer IC compared to patients with Hunner's ulcers [49]. IC patients in whom ulcers are seen on cystoscopy tend to be older, and have a smaller bladder capacity [50–52]. Hunner's ulcers arguably may represent severe disease playing out in a relatively ischemic bladder compared to younger patients [50–52]. One study found a more pronounced decrease in urinary frequency, and increase in voided volume after PPS treatment in the group of patients without ulcers [49].

In the early era of PPS, there was a belief that higher doses might prove to be more efficacious. To test that hypothesis, Nickel et al. randomized patients to different daily PPS doses. Patients were assigned to 300 mg (the standard FDA approved dose), 600, or 900 mg daily for 32 weeks (each cohort received drug in three divided doses, e.g., 300 mg daily was given as 100 mg orally three times per day). After 32 weeks, close to 50 % of patients reported 50 % or more global improvement in their symptoms [46]. Interestingly, response to treatment was not dose-dependent. Instead, duration of therapy was more important. The longer patients were on PPS therapy, regardless of dose, the more likely they responded to therapy. Some patients reported improvement as early as 4 weeks, but the median time to response was approximately 5–6 months. Although treatment response was not dose dependent, side effects were. Diarrhea and rectal bleeding were more common at increasing doses. Patients were also more likely to discontinue treatment due to adverse effects in a dose dependent manner (discontinuation increased from 18 to 31 %) [46]. Patients beginning PPS therapy should be informed that it might take up to 6 months

for symptom improvement to commence. What should be done if a patient has no response by 6 months? Some authors advise PPS be stopped and to change to a different treatment option [53]. A contrary view from one open label study shows ongoing new responders between 6 and 24 months of continuous therapy, demonstrating that some additional responders may be expected with long-term PPS [54]. Treatment must be individualized.

The pharmacokinetics of PPS has been described, with approximately 6 % of the orally ingested dose being absorbed, and excreted into the urine, mostly in the form of metabolites. It is metabolized both in the liver and by the renal system. The only contraindication to PPS therapy is an allergy to PPS or related compounds. However, caution should be taken when using PPS in patients with conditions that place them at an increased risk of bleeding complications, such as active anticoagulation, thrombocytopenia, hemophilia, aneurysms, and gastrointestinal lesions, as well as in patients with a history of heparin-induced thrombocytopenia, and those with hepatic insufficiency (due to lack of data) [55]. PPS was initially studied for the indication of using it as an oral anti-coagulant. Its anti-coagulant effect was so weak as to be considered a failure. Anecdotal reports of hematologic complications include one case of life-threatening coagulopathy [56], and two cases of thrombocytopenia and venous thrombosis [57].

PPS is generally well tolerated. Most common side effects include rectal bleeding in 6 %, and alopecia in 5 % (generally limited to a single area of the scalp). Other side effects, not significantly more common than with placebo, include nausea, diarrhea, abdominal pain, headache, and rash. Mild increase in liver enzymes could occur in 1 % of patients, at levels up to 2.5 times normal. This increase is usually seen within the first year of treatment, and is self-limited in most cases. Increased PTT and PT, or thrombocytopenia is rare [55]. Anecdotally, patients who experience bothersome gastrointestinal side effects while taking PPS often seem to tolerate the medication better when it is taken out of its gelatin capsule. When our patients complain of abdominal pain, or other digestive symptoms associated with PPS ingestion, we commonly suggest that they empty the content of the capsule in a small glass of water (a shot glass is suitable to avoid them drinking with a large volume of water that would otherwise dilute it) prior to ingesting it.

The recommended dosage for PPS is 300 mg daily, taken in three divided doses [55]. Our clinical experience reveals better patient compliance with twice daily dosing. Expert opinion suggests considering either 100 mg in the morning and 200 mg in the evening, or to simplify patient instructions, 200 mg twice daily, albeit at higher cost [17]. Even though a total daily dose of 400 mg is off label, it is our preferred regimen.

The expense associated with oral PPS therapy is often a limiting factor. Some physicians may begin with less expensive options, such as amitriptyline and hydroxyzine [9]. However, those do not directly address the fundamental defect in the bladder's protective barrier, but rather act on downstream pathways of the disease. We believe that a combination therapy incorporating some type of bladder coating agent is appropriate for adequately treating IC.

Intravesical PPS

In order to improve delivery of PPS to the bladder lining, intravesical administration has been reported. Systemic side effects could theoretically also be minimized with this approach. However, with this modality, absorption is still poor, despite the defective GAG layer. Repeated dosing is also required due to continuous urine washout [53]. The European Association of Urology considers intravesical PPS as effective and may augment response to oral PPS. Based on 1b level of evidence (evidence from an individual RCT), they recommend intravesical PPS for use in the treatment of IC with or without concurrent oral PPS (Grade A recommendation: evidence from level 1 studies) [48].

Two trials compared intravesical PPS with placebo. Bade et al. in 1997 treated 20 patients, and found that intravesical PPS was more effective than placebo. The response rate was twice as high in the treatment group. Effect also increased over time from the 3 month to the 18 months follow-ups [58]. Davis et al. in 2008 randomized 40 women to oral PPS and concomitant intravesical PPS versus oral PPS and intravesical placebo. In all patients, lidocaine (8 mL of 1 % solution) and sodium bicarbonate (3 mL of 8.4 % solution) were first instilled for a period of 5 min to provide some immediate relief, prior to the instillation of PPS or placebo. Intravesical PPS was administered twice weekly for the first 6 weeks of protocol with concomitant oral PPS, followed by oral PPS alone for the remainder. After the treatment period of 18 weeks, the group treated with both oral and intravesical PPS saw a much greater decrease in their symptoms compared to the group receiving oral PPS and intravesical placebo (62 % vs. 25 % had 50 % or more symptom improvement). Quality of life was also most improved with intravesical PPS [59].

In Europe, a PPS solution is available, with 100 mg PPS per mL. Otherwise, the content of two to three capsules of PPS can be mixed with normal saline for the instillation [59]. Some authors recommend an initial 6 weeks of twice-weekly instillations, followed by a slow tapering with 4–6 weeks of weekly treatments, then reduced to twice monthly, prior to discontinuing treatment [60]. Although evidence for intravesical PPS is limited to small trials, it appears to be beneficial and it remains a possible treatment option for IC patients.

Heparin and Alkalinized Heparin Cocktails

Intravesical Heparin

Intravesical heparin has been used off-label in the treatment of interstitial cystitis for over 20 years. Evidence for its use consists mainly of observational studies. The American Urological Association suggests that it may benefit patients, and could be used as second-line treatment. The evidence for its use is graded as category C, by both the American and European societies, due to the low quality of available studies [32, 48].

Parsons et al. reported intravesical heparin's use in 48 patients. After 3 months of receiving three instillations per week, 56 % of patients were significantly improved. Sixteen patients continued treatment up to 1 year, with 15 of them still having

symptom relief [61]. Improvement with this therapy may also be gradual, with its full effect not seen until months after treatment initiation [17, 34]. Urodynamic evaluation in 29 patients before and after a 3-month course of heparin instillations revealed increased first filling sensation (96 ± 46 mL vs. 146 ± 55 mL) and cystometric capacity (262 ± 90 mL vs. 304 ± 85 mL) after treatment [62].

In order to combine the long-term effectiveness of heparin with immediate relief, Parsons reported the combination of intravesical heparin with lidocaine and sodium bicarbonate. Lidocaine is poorly absorbed through the bladder lining. The addition of sodium bicarbonate to alkalinize the urine to a pH of eight or more renders lidocaine more lipid-soluble. This improves its absorption across the bladder mucosa. The use of this combined instillation preparation resulted in immediate relief in 75–94 % of patients, depending on the dose of lidocaine used, and 50 % had relief for 4 h or more. Sixteen patients continued to receive instillations three times weekly for 2 weeks, with persistent symptom control. Relief was maximal within the first 48 h after each treatment [34]. A single cross-over, randomized placebo-controlled trial of 18 patients compared a combination of heparin, lidocaine, and sodium bicarbonate instillations to sodium bicarbonate alone. Twelve hours post-instillation, pain and urgency were more significantly reduced in the active treatment group [63]. One single-arm study administered combined heparin and lidocaine weekly for 3 months. Treatment effect was maintained for 2 months after the last instillation in up to 50 % of patients, and decreased afterwards [64]. IC patients with a positive potassium sensitivity test may respond better to intravesical heparin, compared to those with a negative test [65].

Nickel et al. randomized 102 IC subject to daily instillations of alkalinized lidocaine or placebo for 5 days. Three days after the end of treatment, symptomatic improvement was more significant in the lidocaine group, with 30 % of subjects (vs. 10 % in the placebo group) reporting moderate or marked improvement. In most cases, this effect persisted for at least 1 week [66]. Thus, both heparin alone and alkalinized lidocaine alone seem to have some effect in IC patients. At the time of writing, it is still unknown what the relative contribution of each component of the heparin cocktail is versus the others.

Dyspareunia and sexual dysfunction have been reported in up to 87 % in women with IC [67, 68] A 3-week course of three-times weekly instillations with heparin, lidocaine, and sodium bicarbonate improved sexual function and treated dyspareunia in 57 % of subjects, with results persisting on average 3 weeks after the last instillation [69]. In practice, some patients experience mostly short-term relief from these instillations, and benefit from more frequent treatments. For those with dyspareunia, we occasionally recommend an instillation of this combined preparation in the 2-h period immediately preceding sexual intercourse, to take advantage of the anesthetic action of lidocaine on bladder sensory afferents.

In the studies mentioned, dosages of the various preparation components varied from 10,000 to 50,000 U of heparin per treatment, 80–200 mg of lidocaine, and 250–420 mg sodium bicarbonate in 10–15 mL water. Instillation duration also varied between 30 and 60 min, and treatment frequencies were reported between one to three times weekly [34, 61, 63, 69]. Our usual protocol consists of 20,000 U heparin, 8 mL

2 % lidocaine, and 4 mL 8.4 % sodium bicarbonate, which should be kept in the bladder for ideally 60 min. We will vary the administration schedule based on the severity of each patient's symptoms. Typically, we gradually taper down the frequency of instillations as patients respond and their symptoms abate. Treatment can also be taught such that patients may be able to do self-catheterization and self-treatment.

Side effects with intravesical heparin are usually minimal. Urethral and bladder sensitivity, during the instillation and when voiding the instilled solution, have been reported with concomitant lidocaine administration. This can be minimized with the use of hydrophilic catheters [63, 64, 70]. Some patients complain of severe urethral "burning" when they void the alkalinized lidocaine and this burning sensation persists for days. In these patients, we catheterize them instead of letting them void the solution. The presumption is that their urethra is sensitive to the alkaline pH, but as yet, this presumption is unproven. Apart from occasional treatment-related hematuria, bleeding complications associated with intravesical heparin have not been reported [64]. Serum PTT and PT are usually not affected [63].

Subcutaneous Heparin

Using subcutaneous heparin in the treatment of IC was first introduced in the 1980s, at a time when the disease was still very poorly understood. Much more recently, a group of 40 patients, who already responded to oral PPS, received 3 months of subcutaneous low-dose heparin. Only 24 % showed symptom improvement with this route of administration. Improvement after subcutaneous heparin was more significant in patients with a lesser response to PPS [71]. Due to the potential risks of bleeding complications and heparin-induced thrombocytopenia, the risks likely outweigh the benefits of subcutaneous heparin administration for most IC patients. However, the European Association of Urology recommends the use of subcutaneous heparin in addition to oral PPS for low responders to oral PPS (Grade 1b) [48].

Chondroitin Sulfate

Chondroitin sulfate is another natural component of the bladder GAG layer. As mentioned earlier in this chapter, animal studies demonstrate adherence of chondroitin sulfate to defective bladder mucosa, which leads to decreased local inflammation [27–29]. Available in Canada and European countries since the early 2000s, but not approved in the USA, sodium chondroitin sulfate is available under the name of Uracyst® (Tribute Pharmaceuticals Canada Inc., Milton, ON, Canada, and LIDDE Therapeutics, Essex, UK). Chondroitin sulfate was omitted from the American Urology Association guidelines, but included in the European Association of Urology guidelines, due to its presence on the European market. Evidence was graded as 2b, as nonrandomized studies showed effectiveness, and published randomized controlled trials were underpowered. They provide a grade B recommendation to consider this treatment modality prior to more invasive treatments [48].

Nickel et al. conducted two RCTs comparing intravesical chondroitin sulfate to placebo for 8–12 weeks. Both trials failed to show a difference between the groups,

but were underpowered to do so [72, 73]. A meta-analysis pooled data from those two RCTs and a prospective study, and concluded that a small difference in symptoms was in fact present. The analysis included a total of 213 patients, and demonstrated an overall global response of 43.2 % (95 % CI: 35.0–51.5) with chondroitin sulfate compared to 27.4 % (95 % CI: 17.6–37.2) with placebo. The pooled RR for benefit of chondroitin over placebo was 1.55 (p = 0.014, 95 % CI: 1.09, 2.22). However, ICSI score (used to quantify IC symptom severity) and urinary frequency were not different between the groups [74]. Nordling and van Ophoven reported on a prospective observational multicenter European study of 286 chronic cystitis patients. Fifty-one percent of patients had a diagnosis of IC. Other diagnoses included radiation cystitis, chronically-recurring cystitis, and overactive bladder. Three-month follow-up, after a mean of eight instillations, revealed overall significant improvement in frequency, urgency, and pain, as well as increased maximal bladder capacity. Seventy-seven percent of IC patients reported a fair to excellent response to treatment [75].

In women with overactive bladder, not interstitial cystitis, intravesical chondroitin sulfate was found to be more beneficial than anticholinergic therapy in a randomized trial, at 1 and 2 years after treatment initiation [76, 77].

Sodium chondroitin sulfate is available in two formulations, 0.2 % (40 mL) and 2 % (20 mL), depending on the country [12]. The recommended dosage is 400 mg weekly for 6 weeks, followed by monthly instillations. Treatments are continued until symptom resolution. Side effects are minimal and include urethral and bladder discomfort, rare incidence of rash, as well as risk of urinary tract infection, like other instillation treatments [74, 75].

Hyaluronic Acid (HA)

Hyaluronic acid, or hyaluronan, is a mucopolysaccharide. Its intravesical instillation is thought to result in regeneration of the GAG layer, as well as inhibition of mast cell degranulation [78]. Also known under the trade names Cystistat® (Bioniche Pharma Group, Geneva, Switzerland) and Hyacyst® (Syner-Med, Surrey, UK), HA has been approved by Health Canada, Health Authorities of the European Union, and China, among others. However, the FDA did not approve its use in the United States. HA use is supported by observational studies only. HA was not discussed in the most recent American Urological Association guideline. However, the European Association of Urology examined the available data and recommended its use as second-line, prior to resorting to more invasive treatments (Recommendation grade B: from level 2 studies) [48]. We do not routinely use HA, due to lack of evidence.

No randomized controlled trial support the use of intravesical HA instillations. In fact, three randomized placebo-controlled trials revealed nonsignificant results, but none of those were published in peer-reviewed journals [79]. In a cohort study of 126 patients treated with an average of 12 weekly instillations, 55 % of patients had significant improvement in their symptoms, including 35 % who had successfully resumed treatment for symptomatic recurrence, after 6 months. Overall, 84 % of patients reported quality of life improvement [80]. A long-term follow-up of the

same study population showed an overall 68 % response rate at a mean of 4.9 years. Fifty percent of the sample had symptom resolution with no further treatment, and the rest received additional instillations of HA and/or oral PPS therapy [81]. As a positive potassium test denotes a defective bladder GAG layer, this test has been used to assess response to treatment with HA. HA was shown to reverse a positive potassium test in close to 50 % of treated women [82]. In fact, some experts advocate that a potassium sensitivity test be used to select candidates for HA therapy. Some authors have noted a better response, of up to 80 % in patients with a positive potassium test, compared to 22 % in patients with a negative potassium test [80, 83, 84].

Hyaluronic acid instillation was evaluated for use after bladder hydrodistention and proved beneficial [85]. Bladder hydrodistention with cystoscopy under analgesia can be used to assist in making a diagnosis of IC, and was also found to improve symptoms in some patients [4, 86]. In an open-label trial, 47 patients were divided into three treatment groups. The first group received HA after their hydrodistention. Fifty percent of subjects had maintained symptomatic improvement for up to 9 months. The second group did not receive instillations after hydrodistention, and had short-term improvement of symptoms, with return to baseline symptoms at 3 months. A third group of patients, who received heparin instillations after hydrodistension, had their symptoms recur after 6 months. In summary, the group that received HA instillations after hydrodistention had the longest symptom relief period. Apart from an effect on pain, HA reduced voiding frequency, and improved bladder capacity in that setting [85].

HA has also been combined with an alkalinized lidocaine solution to reduce pain and symptoms acutely from IC. One study in 45 patients who previously failed oral treatments compared HA instillations alone, HA with alkalinized lidocaine instillations, and alkalinized lidocaine instillations alone. HA with lidocaine provided immediate relief that lasted up to 48 weeks in some patients. HA alone provided relief that usually started more than 2 weeks after treatment initiation. Lidocaine without HA showed a quick response that was not persistent. Cystoscopic exam demonstrated improvement of submucosal ectasia in all patients who exhibited them initially [87].

One prospective trial of 103 women treated with HA showed improvement in sexual function. In particular, dyspareunia and negative reactions were reduced by approximately one third [68].

HA is available in vials of 50 mL containing 40 or 120 mg of HA. The recommended administration consists in weekly instillations for 4–12 weeks, followed by monthly instillations until symptom resolution. One study showed no difference in outcomes between weekly and biweekly treatments [88] Duration of instillation varied among studies, between 30 and 120 min [80, 84, 85]. It may be difficult for patients with a small bladder capacity to hold this amount of fluid for a prolonged period of time. Patients with such severe symptoms may not be appropriate candidates for this treatment regimen [80].

Adverse events with HA instillations are rare, and include mild irritative symptoms and urinary tract infections [68, 80, 85]. It is contraindicated in people with known hypersensitivity to one of the components of the solution.

Combination of Hyaluronic Acid and Chondroitin Sulfate

Hyaluronic acid and chondroitin instillations can be administered concomitantly for the treatment of IC. In Europe, a formulation of the two products combined is available under the name Ialuril® (Aspire Pharma Limited, Petersfield, UK). It contains HA 1.6 %—800 mg and chondroitin sulfate 2.0 %—1 g in 40 mL of 0.9 % saline. Small observational studies reported significant improvement in urgency, frequency, voided volume, and pain after 3–6 months of treatment [89, 90]. A prospective trial of 53 patients assigned to either HA-chondroitin sulfate or HA alone found improvement in symptoms in both groups, without any statistically significant difference between them [91]. A group of 12 patients continued to receive monthly instillations for up to 3 years after the initial treatment regimen, and symptom improvement remained stable during the first 9 months of treatment [92].

Reported dosing of the HA-chondroitin sulfate combination is the content of one vial of 40 mL instilled weekly for 4–8 weeks, then bi-weekly. Some authors then taper down the treatment to monthly prior to stopping [89, 91].

Considerations for Intravesical Instillation of Bladder Mucin Analogues

Prior to an instillation, the patient is instructed to void completely. We then usually administer 10 mL of 2 % lidocaine gel through the urethral meatus for 5–10 min [59]. A small catheter (usually 8 or 10 Fr) is used for the instillation. In patients who complain of severe discomfort with instillation treatments, or urethral burning, we advocate a hydrophilic catheter. Those special catheters reduce friction during catheterization, and alleviate insertion-related symptoms in many cases [69]. They are available from multiple suppliers depending on the region. The bladder is first drained with the catheter. The desired solution is then instilled in the bladder, and the catheter is removed. The patient is instructed to ambulate for 30–60 min, and then void.

Multiple authors recommend antibiotic prophylaxis at the time of instillation to prevent urinary tract infections [80]. With low reported rates of urinary tract infections with instillations (as low as 0.4 %) [59], we do not routinely administer antibiotics, except in patients with a positive history. If one was to administer antibiotics, a single dose of nitrofurantoin 50–100 mg should be appropriate [80].

Conclusions

Interstitial cystitis is a chronic syndrome that requires a prolonged treatment course, and frequent re-treatments. Due to its complex pathophysiological process, therapeutic options are often not as effective alone, as they are in combination [53]. Bladder surface mucin analogues address the main pathophysiological process at the root of IC symptoms. However, their efficacy is not immediate, as it takes time

to allow the bladder to heal. Considering the addition of other treatment modalities, such as anti-histamines and possibly tri-cyclic antidepressants, can concomitantly address downstream reactions, such as mast cell degranulation, and neural inflammation and upregulation [32]. The remodeling of neural pathways once the pain's inciting event disappears takes time [3]. This explains why most treatments show a gradually increasing benefit with longer treatment courses. We also commonly use intravesical instillations to acutely reduce bladder symptoms, while also initiating oral PPS therapy. The intravesical treatments then act as a bridge until oral PPS has reached its full therapeutic potential, which takes months. Parsons suggests that for mild cases, months of therapy are usually needed, and that up to 2 years of treatment are likely required for more severe cases [3]. Hence, bladder-coating agents should hold an integral part of a multimodal approach to the management of IC. Future avenues in the treatment of IC include the use of different techniques to improve drug delivery, and efficacy. This includes the use of nanomedicine, tissue engineering, and mucoadhesive delivery systems [93].

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Neuroleptic Agents for Chronic Pelvic Pain

10

Rachel Frank Schnall and Michel A. Pontari

Abbreviations

AE	Adverse event
BPS	Bladder pain syndrome
CNS	Central nervous system
CPP	Chronic pelvic pain
FDA	Food and Drug Administration
GABA	Gama-aminobutyric acid
ICSI	Interstitial Cystitis symptom index
Mg	Milligram
NNT	Number needed to treat
NSAID	Nonsteroidal anti-inflammatory drug
PDA	Painful diabetic neuropathy
PHN	Post herpetic neuralgia
TCA	Tricyclic antidepressant medication
Tid	Three times per day
VAS	Visual analog scale

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Part I. Background

Despite their more widely applicable uses at present, the neuroleptic drugs gabapentin (Neurontin©) and pregabalin (Lyrica©) were initially developed as antiepileptic medications. Gabapentin was originally developed as an adjunctive therapy for partial seizures without secondary generalization in patients above the age of 12 years. It was FDA approved for adults with this condition in 1993. The approval was extended to children with partial seizures in 2000 [1]. Later, in 2002, it was approved for use in the United States for treatment of post-herpetic neuralgia [2]. Beyond these approved indications, physicians have been using gabapentin for numerous off-label pain-related conditions with marked improvement of symptoms with minimal adverse effects [3, 4]. For example, gabapentin is a first-line treatment, despite current off-label status, for use in the management of diabetic neuropathic pain [5]. It is also prescribed for conditions such as trigeminal neuralgia, fibromyalgia, menopausal hot flashes, restless leg syndrome, as well as numerous other forms of neuropathic pain [2, 6-8].

In 2004, pregabalin was approved by the European Commission for use in peripheral neuropathic pain and adjunctive management of partial seizures [9]. It was also approved for use in the United States by the FDA for the treatment of diabetic neuropathic pain and postherpetic neuralgia [9, 10]. Pregabalin was not approved for use in partial seizures until 2005 [11]. This drug is now FDA approved for use in other neuropathic pain, such as that associated with spinal cord injury and fibromyalgia [1, 8, 9]. Its off-label uses include management of menopausal hot flashes and restless leg syndrome [12, 13].

Currently, investigations into the various uses of these drugs continue in an effort to prove medication safety, to demonstrate efficacy, and to gain a more complete understanding of the mechanism by which these drugs alleviate or eliminate the symptoms of chronic and neuropathic pain. The need for quality randomized control trials is paramount as most available research is either retrospective or lacks the statistical power to drive true changes in clinical practice.

Part II. Mechanism of Action and Pharmacology

Both gabapentin and pregabalin have analgesic, antiepileptic, anxiolytic, and sleep-modulating activity. They act mainly as an antagonist of the alpha-2-delta ($\alpha_2\delta$) subunit located on voltage-sensitive calcium (Ca^{2+}) channels and thereby modulate Ca^{2+} influx. These channels appear to be located in highest concentration in the dorsal horn of the spinal cord. Antagonism of these channels results in inhibition of excitatory neurotransmitters, such as glutamate, calcitonin-related gene product, and substance P. This, in turn, reduces pain signal transmission within the central nervous system (CNS) and acts to minimize pain associated with central sensitization, a term used to describe pain receptor activity and signal transduction that continues despite termination of the inciting stimulus [14, 15]. These nociceptive nerve fibers also respond at a level out of proportion to the strength of stimulation, also known as hyperesthesia. Gabapentin acts to minimize hypersensitivity of these pain

Table 10.1 Pharmacologic properties of gabapentin and pregabalin [1, 3, 15, 21]

–	Gabapentin	Pregabalin
Administration	PO	PO
Absorption	Saturable, non-linear Proximal small intestine	Saturable, non-linear Proximal small intestine
Time to peak plasma concentration	3–4 h	1 h
Half-life	5–7 h	6–7 h
Bioavailability	Inversely proportional to dose: 60 % with 900 mg daily dose 33 % with 3600 mg daily dose	>90 % regardless of dose
Bound to plasma proteins	No	No
Excretion	Renal, unmetabolized	Renal, unmetabolized

fibers following surgery, nerve injury, or inflammation [16, 17]. The type of pain that neuroleptic medications target is described as paroxysmal pain that is burning or stabbing in quality. Gabapentin and pregabalin are less likely to be effective on dull or aching pains [18].

Gabapentin has also been shown to have peripheral effects. It minimizes signaling through C and Aδ nerve fibers, the former is responsible for burning pain while the latter transmits sensations of sharp pain [17]. Strangely enough, despite its structural similarity to the neurotransmitter gamma-aminobutyric acid (GABA), as its drug name suggests, gabapentin has not been shown to interact with any inhibitory GABA receptors [19, 20].

Pregabalin works in a very similar manner, but with greater binding affinity and potency. It has been shown to be six times more potent than gabapentin and is more rapidly absorbed into systemic circulation. Gabapentin achieves maximal plasma concentration in three to four hours while pregabalin does so in roughly 1 h [11]. Both gabapentin and pregabalin are absorbed in the proximal small intestine in a saturable, nonlinear, manner [1]. Neither drug binds to plasma proteins within the circulation. Both are excreted by the kidneys in an unmetabolized form and must, therefore, be used with caution in patients with renal impairment. However, age-related changes in kidney function do not affect elimination of these drugs [19] (Table 10.1).

Part III. Use in Chronic Pain Syndromes

Neuroleptic drugs such as gabapentin and pregabalin have been approved for patients with various chronic pain syndromes [1]. These disorders are described as nociceptive pain arising from peripheral sources that results in abnormal stimulation of the central somatosensory system that serves no physiologic purpose [19]. These medications have been shown to improve muscle relaxation, which encourages use of proper musculature and minimizes pain associated with chronic muscle spasm [22].

Table 10.2 Efficacy of outcomes with gabapentin postherpetic neuralgia vs. painful diabetic neuropathy [15, 23]

–	Substantial improvement (at least 50 % pain reduction)	Moderate improvement (At least 30 % pain reduction)
Postherpetic neuralgia	NNT = 8 (95%CI = 6.0–12)	NNT = 6.5 (95%CI = 4.0–16)
Painful diabetic neuropathy	NNT = 5.9 (95%CI = 4.6–8.3)	NNT = 9.4 (95%CI = 2.6–29)

Overall, gabapentin has been demonstrated to be effective in one third of patients suffering from chronic pain syndromes. In these cases, gabapentin is associated with a fifty percent reduction of pain intensity. Response rates have been noted to be highest among patients with diabetic neuropathy and postherpetic neuralgia [1]. Between 9 and 17 % of patients treated with either gabapentin or pregabalin experience a 50 % reduction in pain with a number needed to treat (NNT) of 5.9. In regards to postherpetic neuralgia, 13–25 % of patients experience a 50 % reduction in pain symptoms after being treated with these neuroleptic medications. For this condition, gabapentin is associated with a NNT of 8 while pregabalin has a NNT of 4 [1, 23] (Table 10.2). Success rates have proven to be lower in patients with central pain syndromes and fibromyalgia. Therefore, though all of these various pain conditions have a similar pathophysiologic mechanism, they should be treated separately from one another. It seems that there is no effective way to predict which patients will respond best to these medications. Current evidence suggests that a short trial with gabapentin or pregabalin is the best way to determine individual success [1].

Neuroleptic medications have also been shown to be useful in the management of psychosomatic symptoms. They have been noted to have beneficial effects on insomnia, fatigue, depression, quality of life, work, depression, and anxiety [21]. They are considered to be first-line pharmacologic treatment for patients with fibromyalgia and have also been used in the management of neuropathic pain associated with irritable bowel syndrome [1, 9, 24]. Patients generally require at least 6 weeks of treatment with pregabalin or 8 weeks with gabapentin to truly assess response [1, 19, 23, 25].

Part IV. Use in Urologic and Gynecologic Chronic Pelvic Pain Syndromes

Neuroleptic treatments in men with chronic pelvic pain (CPP) syndromes act to improve muscle relaxation and encourage proper use of pelvic floor musculature [14]. They have also been shown to improve, by nearly 50 %, symptoms associated with neurogenic bladder. Patients have reported significant reductions in urinary frequency, urgency, and noted fewer episodes of urge incontinence after only 1 month of treatment with gabapentin. Also, neuroleptic medications produce a delay in the first desire to void by decreasing detrusor over activity and increasing bladder maximum capacity. Researchers attribute these improvements to a decrease in detrusor over activity through modulation of bladder afferent fibers as well as minimizing sacral reflex center excitability [17, 25].

The mechanisms by which neuroleptic medications improve symptoms of CPP in women mimic those of their male counterparts. Studies specifically examining the improvement of symptoms in women have assessed generalized CPP as well as bladder pain syndrome, and vulvodynia. There has also been research into the use of gabapentin for pain associated with transvaginal mesh insertion for pelvic floor prolapse repair. Similar to studies targeted at male CPP, researchers assess improvement of symptoms using various standardized surveys. A common study employed for female CPP is the Visual Analog Scale survey (VAS), which is designed to measure changes in pain intensity over time [18, 26-30].

Vulvodynia is caused by an increase in the number of pain receptors present within the vaginal vestibule and some degree of central sensitization. Both of these pathophysiological mechanisms are associated with CPP. Therefore, treatment with neuroleptic medications is appropriate. Various studies have reported between a 50–80 % improvement of symptoms after treatment with gabapentin, with 64 % of patients reporting a complete resolution of symptoms [31-33].

One study examined the efficacy of either gabapentin or pregabalin compared to first-line treatment of pelvic neuropathic pain, the tricyclic antidepressants (TCAs). Researchers have studied the effects of TCAs compared to gabapentin and even studied the effects of combined therapy for symptoms of CPP. Although all treatment arms experienced significant improvement in pain symptoms at all investigated time points, after 24 months of treatment, patients who received gabapentin, either alone or in conjunction with TCAs, showed superior improvement of symptoms, based on the VAS survey scores, compared to those patients who received only TCAs. Also, patients receiving either gabapentin alone or in combination with TCAs reported fewer bothersome adverse effects. Those side effects that were reported were more likely to subside during the follow-up period while patients with similar complaints using TCAs were less likely to experience symptom relief [18].

Neuroleptic medications have also been shown to be beneficial in the treatment of bladder pain syndrome. A prospective, nonrandomized study by Lee et al. (2010) examined the use of gabapentin, as part of a three-drug regimen for women with this condition. This study found that use of nonsteroidal anti-inflammatory drugs (NSAIDs) with TCAs and gabapentin allowed for a significant improvement in symptoms. Patients reported a 73 % improvement in VAS score after only 1 month of therapy. The Interstitial Cystitis Symptom Index (ICSI) score, a measurement of pain, urgency, and overall interstitial cystitis symptoms over time improved by 64 % after only 1 month of treatment [22]. A second study by Kwon et al. (2013) examined this triple therapy for overactive bladder. This study demonstrated a significant improvement in symptoms of urgency, urge incontinence, frequency, nocturia, and bladder pain after 1 month of treatment. Patients reported a 34–58 % improvement in overactive bladder symptoms. This study also demonstrated significant improvement based on ICSI and VAS symptom scores, 44–63 % and 53–75 %, respectively [29]. These two studies demonstrate the benefit of triple therapy: patients can achieve significant symptom improvement while minimizing dosing of each individual drug and, therefore, reduce the incidence of undesired adverse effects.

In studies that have included patients with all types of CPP, results have been promising but, generally speaking, they have proven to be difficult to interpret. Primary outcomes of these studies tend to be a generalized improvement in pelvic pain symptoms. Many studies rely on standardized surveys to measure patient improvement. These surveys assess pain, urinary symptoms, and quality of life. Though gabapentin and pregabalin have proven to significantly improve symptoms in certain areas assessed by these surveys, namely pain and urinary symptoms, these drugs do not appear to improve all aspects of pelvic pain. Therefore, their impact on symptom improvement, as measured by these surveys, may be more difficult to measure and may appear to lack statistical significance [7, 12, 21 22, 27, 36].

As of now, most patients, both men and women, who are treated with neuroleptic medications for CPP have already failed numerous other medications. That being said, new approaches to treating this condition may encourage use of these medications earlier in disease presentation. A recently developed treatment method, called UPOINT (urinary, psychosocial, organ specific, infection, neurologic/systemic, tenderness of musculature), takes the position that a single treatment modality is insufficient for maximal symptom relief on the basis that the disease process itself is driven by numerous pathophysiological mechanisms. Therefore, multimodal treatment is necessary. For example, urinary symptoms are treated with alpha blockers such as tamsulosin while psychosocial issues (such as depression, anxiety, and chronic fatigue) should be treated with stress reduction and cognitive behavioral therapy. According to UPOINT, neuroleptics such as gabapentin and pregabalin are among the therapies that have been recommended for the treatment of neuroleptic pain associated with CPP [22, 34, 35].

Overall, these medications should be used when patients have a neurologic basis for their symptoms. The research that has been conducted as of this point is difficult to interpret as these drugs were likely used as a catchall for patients who have proven to be refractory to first-line treatments. Therefore, the statistical significance of patients who report satisfactory improvement in their symptoms may be falsely low due to the fact that many patients treated with neuroleptic medications did not have an underlying neurologic basis for their pain and, thus, these drugs were unlikely to provide relief in the first place. Also, according to UPOINT, proper treatment of the disorder involves employment of numerous medications and therapies. One cannot expect neuroleptics to resolve all symptoms of a multimodal disease. Despite this, most studies have reported results that show promise for symptom improvement. Therefore, in order to maximize the benefit of neuroleptic medications on patients with CPP, these drugs should only be given to patients' pain symptoms that are neuropathic in origin and should be given in conjunction with other treatment modalities [22, 34, 35].

Part V. Dosing and Adverse Effects

Much of the current research regarding the efficacy of neuroleptic medications focuses on identifying the proper dosing regimen for optimal pain relief. Other studies have examined the effectiveness of various routes of administration of the drugs,

such as oral compared with topical preparations [36]. At present, it appears that no single most appropriate dosing schedule has been identified. As with most medications, treatment with neuroleptic medications involves initial administration of lower doses with upward titration until desired effectiveness is achieved. Patients who may require higher doses for optimal symptom management are also more likely to experience adverse effects. Dosing must be somewhat individualized to balancing patient-reported pain relief with undesired symptoms [19, 37].

Various drug preparations have been designed to maximize efficacy and improve drug availability. An extended release, gastro-retentive capsule has been designed to provide continuous delivery at optimal absorption sites over the course of 8–10 h. Similarly, an extended release pro-drug of gabapentin, gabapentin encarbil, can be absorbed more rapidly throughout the gut and is then converted to the active metabolite, gabapentin, once in circulation [19].

Backonja and Glanzman (2003) reported that most patients experienced maximal improvement of symptoms, with minimal adverse effects, at a dose of 1800 mg daily. They demonstrated that most dosing regimens span from a starting dose of 900 mg daily and are titrated to a maintenance dose of 1800–3600 mg daily. Gabapentin is usually administered three times per day. Initiation of treatment to starting dose is typically achieved over the course of 3 days with subsequent titration and dose maintenance (Table 10.3). Maintenance dose is determined by at least a 50 % reduction in pain symptoms. After termination of treatment, mean daily pain scores were significantly decreased in the gabapentin group compared to the placebo group (21 % vs. 14 %, $p < 0.048$). Therefore, the authors recommend that upward titration and maintenance of gabapentin be individualized for optimal efficacy [19].

Other studies have escalated dosing at different rates. An open-label study initiated gabapentin at 100 mg per day and titrated to 2700 mg daily over the course of 6–12 days. Even with escalation of dosage at this rate, there was no occurrence of serious or life-threatening side effects. Only 10 % of patients experienced some temporary drowsiness that limited upward titration. With this dosing regimen, 65 % of patients reported a moderate to excellent response [19].

Pontari et al. (2010) examined the efficacy of pregabalin compared with placebo on patients with chronic pelvic pain syndromes. Treatment was initiated with 150 mg daily followed by upward titration with 300 mg daily for 2 weeks.

Table 10.3 Proposed dosing schedules for gabapentin [3][a]

Initiation	Day 1—300 mg QD Day 2—300 mg BID (600 mg/day) Day 3—300 mg TID (900 mg/day)
Titration	Days 4 → 14—900 mg to 1800 mg/day Doses administered on a TID schedule
Maintenance	Days 15 → drug course completion—1800 to 3600 mg/day Doses administered on a TID schedule

[a]Dose escalation has been simplified by the production of 300, 600, and 800 mg formulation tablets

Table 10.4 Proposed dosing schedules for pregabalin [34]

Initiation	Days 1 → 14—50 mg TID (150 mg/day)
Titration	Days 15 → 28—100 mg TID (300 mg/day)
Maintenance	Days 29 → 42—200 mg TID (600 mg/day)

Maintenance dose was 600 mg daily (Table 10.4). Compared with the placebo group, men receiving pregabalin experienced reductions in all pain assessment scores studied [34].

Patients suffering from pudendal neuralgia following vaginal mesh insertion have been shown to benefit from treatment with both gabapentin and pregabalin. Gyang et al. (2014) found that patients experienced symptom relief after only 1 week of treatment. Gabapentin doses ranged from 100 to 1800 mg daily. Pregablin dosing ranged from 50 to 300 mg daily [27].

Freynhagena et al. (2005) studied the efficacy of flexible-dosing regimens of pregablin. The authors hoped to demonstrate improved medication tolerability without compromising adequate pain relief compared with a fixed dosing schedule. Flexible-dosing involves escalating doses of pregabalin on a weekly basis according to individual responses and tolerability. Overall, after 12 weeks of treatment, the average administered dose in the flexible-dosing study arm was less than that of the fixed-dosing group (372.2 mg/day and 481.5 mg/day, respectively). Both flexible-dosing and fixed-dosing were significantly superior to placebo in terms of improvement of pain symptoms. The NNT in order for one patient to experience at least a 50 % reduction in symptoms in the fixed dosing group was 3.6 while the NNT for the flexible-dosing group was 3.8. Therefore, flexible dosing did not prove to provide superior pain relief compared to fixed dosing though it did however, delay the onset of bothersome adverse effects. This study suggests that individualized, flexible, twice-daily dosing of pregabalin may enhance drug tolerability while optimizing efficacy of pain relief [37].

In the treatment of neurogenic bladder, studies have demonstrated that symptom relief can be achieved at much lower doses of gabapentin. Carbone et al. (2006) demonstrated significant symptom relief with initial dosing at 300 mg daily and a maximum dose of 900 mg daily. Patients reported nearly a 50 % reduction in urinary symptoms (frequency, urgency, incomplete emptying, hesitancy, etc.), a significant increase in bladder capacity, and improved urodynamic parameters [25].

Bladder pain syndromes (BPS) with associated overactivity may also be treated with neuroleptic medications. Most studies have explored the use of multidrug therapy in the management of these patients. Two studies prescribed triple therapy with etodolac, amitriptyline, and gabapentin. Etodolac was dosed at 600 mg daily. Initial doses of amitriptyline and gabapentin were 5 mg and 300 mg, respectively. In one of the studies, the TCA and gabapentin dosage could be increased, gradually, to maximum doses of 75 mg amitriptyline and 900 mg gabapentin as needed for satisfactory relief of BPS symptoms. Results demonstrated that improvements in all pain scale indexes studied were statistically significant, ranging from 44.2 to 73.1 %, depending on the questionnaire employed, after only 4 weeks of treatment. These results suggest potentially improved symptom relief with simultaneous minimization of adverse effects, as lower doses of each individual drug are administered [29, 30].

Patients with vulvodynia experienced pain relief with gabapentin at slightly lower doses than those used for conventional neuropathic pain syndromes. Numerous dosing regimens have been examined, with variable efficacy and responsiveness. Some studies recommend initiating gabapentin treatment orally at 50 mg daily but most studies have recommended an initial dose of 300 mg daily with a slow upward titration to a maintenance dose of 1200 mg daily [31-33].

It may also be helpful to use a topical formulation of gabapentin for the treatment of vulvodynia. Of those patients given topical gabapentin, 80 % reported a greater than 50 % improvement in pain scores. After only 8 weeks of use, 29 % of patients reported a complete resolution of symptoms. The benefits of topical cream include a reduced requirement for active drug and reduced systemic absorption, minimizing the incidence of adverse effects. Available preparations include high-dose (6 % gabapentin), intermediate-dose (4 % gabapentin), and low-dose (2 % gabapentin). Boardman et al. (2008) found no significant reduction in pain scores when comparing dosing regimens. Therefore, in an effort to minimize adverse effects and maximize patient compliance, it would be recommended to initiate treatment with low-dose topical gabapentin with upward titration of cream strength as needed [36].

Chronic pain syndromes may develop following surgical procedures. Early identification and treatment of postoperative pelvic pain with neuroleptics may minimize long-term effects of surgical instrumentation. Three case reports by Oefelein and Bayazit (2003) examined the use of gabapentin in patients following laparoscopic radical nephrectomies. These patients received 300 mg gabapentin TID postoperatively for at least 3 months with adequate resolution of symptoms [38].

A Cochrane review (2014) of gabapentin for treating neuropathic pain recommend that dosing begin at 300 mg daily with upward titration by increments of 300 mg until pain relief is achieved or adverse effects make taking the drugs intolerable to a maximum dose of 3600 mg daily. It is recommended to achieve a dose of at least 1200 mg daily to maximize the likelihood of adequate pain relief [1]. Other studies recommend an ideal dose of 1800 mg [19].

Clearly, no consensus has been reached regarding proper dosing of neuroleptic medications in the treatment of neuropathic pain, especially in the cases of chronic pelvic pain syndromes (Table 10.5). This wide variation is due, in part, to the incidence of adverse events (AEs) as the administered dose increases. Typically, AEs are mild and do not necessitate withdrawal from neuroleptic treatment. In fact, many studies have demonstrated no statistical significant difference between withdrawals from neuroleptics compared with placebo [19]. Rather, there are limitations in upward titration of daily dosage [18, 37].

The likelihood that patients being treated with neuroleptics will experience an undesired or bothersome side effect is quite high. Some studies have reported that up to 59 and 66 % of patients receiving pregabalin and gabapentin respectively will experience at least one AE [1, 23, 37]. That being said, the side effect profile for neuroleptic medications is quite favorable and AEs are frequently temporary in nature even with continued use [37]. Most patients experience only mild to moderate AEs [15, 23]. The most common AEs that occur with use of neuroleptics are dizziness and somnolence. Dizziness occurs in 19 % of patients while somnolence

Table 10.5 Neuroleptic dosing regimens, compared

Study authors	Study design	Population studied	Follow-up period	Dosing regimen	Adverse effects
Backonja and Glanzman (2003) [19]	Review of four randomized clinical trials (RCTs), placebo-controlled study	Men and women with neuropathic pain	7–8 weeks follow-up	Gabapentin – Initial dosing at 900 mg daily – Stepwise upward titration to maximum dose of 3600 mg daily	– AEs reported were generally mild to moderate (most commonly dizziness and somnolence) – Withdrawals were comparable in both gabapentin and placebo groups
Freynahgena et al. (2005) [37]	RCT, double-blind, placebo-controlled, parallel-group study	Men and women with painful diabetic neuropathy or postherpetic neuralgia	12 weeks follow-up	Pregabalin – Flexible, twice daily dosing (escalating doses 150-300-450-600 mg daily) – Fixed dosing (600 mg daily)	– 66.3 % of all subjects experienced atl east one AE – 20.9 % of all pregabalin users discontinued the drug due to dizziness, nausea, vertigo, or somnolence – 17% of patients receiving flexible dose pregabalin discontinued treatment compared with 25% of patients receiving fixed dose pregbalin
Pontari et al. (2010) [34]	RCT, double-blind, placebo-controlled	Men with chronic prostatitis/chronic pelvic pain syndromes	6 weeks	Pregabalin – Initiation with 150 mg daily for two weeks – Titration with 200 mg daily for two weeks Maintenance with 600 mg daily for two weeks	– 59 % of all patients reported at least one AE of primarily mild or moderate severity – The pregabalin group had more neurologic AEs (38.5 %) – The placebo group experienced more pain related AEs (33.3 %) – There was no statistical difference in AE incidence between the two groups
Boardman et al. (2008) [36]	Retrospective study	Women with generalized or localized vulvodynia	5 year follow-up	Gabapentin – High-dose cream (6 % gabapentin) -Intermediate-dose cream (4 % gabapentin) – Low-dose cream (2 % gabapentin)	– 14 % of patients receiving topical gabapentin discontinued treatment for local irritation – 8 % of patients receiving topica gabapentin discontinued treatment due to urinary complaints (transient retention, frequency, or recurrent UTIs)

Lee et al. (2010) [14]	Prospective, nonrandomized study	Men and women with BPS	3 year follow-up period	Triple therapy (etodolac plus amitriptyline plus gabapentin) – Initial treatment with 600 mg etodolac plus 5 mg amitriptyline plus 300 mg gabapentin – If not symptom-free after two weeks: increase TCA to 20 mg and gabapentin to 600 mg – Upward titration was performed, as necessary, to maximum dose TCA 75 mg and gabapentin 900 mg	– AEs with triple therapy included drowsiness and dry mouth – No patients withdrew from treatment
Kwon et al. (2013) [29]	Prospective, open-label study	Men and women with BPS and/or interstitial cystitis	12 weeks follow-up	Triple therapy – 600 mg etodolac plus 5 mg amitriptyline plus 300 mg gabapentin	–
Sator-Katzenschlager et al. (2005) [18]	Open-label, prospective, RCT	Women with CPPS	2 year follow-up	Gabapentin – Initiation with 300 mg daily with weekly upward titration by 300 mg to a maximum dose of 3600 mg daily	–

occurs in roughly 14 % of patients. Less commonly reported effects include peripheral edema (7 %), nausea (6.1 %), ataxia (8.8 %). Compared with controls, patients receiving pregabalin are more likely to report neurologic symptoms [23, 37]. Generally speaking, all of these AEs occur with higher frequency at doses of gabapentin exceeding 1200 mg daily [1, 15, 37].

Interestingly, many studies did not find a statistical difference between the incidence of AEs between controls and patients receiving neuroleptics [23, 34, 37]. The method of administration may also impact the likelihood that patients will experience AEs. Patients were more likely to not only experience AEs but to withdrawal from treatment when enrolled in fixed-dosing schedule compared to those undergoing flexible-dose administration [37]. Patients using topical gabapentin preparations for the treatment of vulvodynia did not experience any of the systemic AEs associated with oral formulations [36].

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Anti-Allergic Compounds in Chronic Pelvic Pain

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Introduction

Probably, the most common cause of chronic pelvic pain (CPP) is interstiticail cystitis/bladder pain syndrome (IC/BPS), a disorder of mostly young and middle-aged women characterized by at least 3–6 months of pain, pressure, or discomfort over the supra-pubic area or the bladder, along with day frequency of urination and nocturia, in the absence of a urinary tract infection (UTI) [1–6]. The location of the pain or discomfort is 80 % abdominal, 74 % urethral, and 65 % low back [7]. The pain is strongest perimenstrually [8] and many patients report pain with intercourse [9].

The prevalence of IC/BPS has increased significantly over the last 30 years [10] with those studies based on symptoms reporting higher rates than those using research criteria. An office survey in the USA reported a prevalence of 575/100,000 women [11], and a study of self-reported adults with IC/BPS in an urban US community reached an estimate of 4 % [12].

IC/BPS remains a diagnosis of exclusion [1, 3]. The "O'Leary-Sant" Symptom and Problem Index measures urinary and pain symptoms, as well as quality of life [13]. The "Pain, Urgency and Frequency" (PUF) questionnaire also assesses sexual function [14], but it does not predict either disease or its severity [15]. History of sexual, physical, or emotional abuse is important because as many as 50 % of IC/BPS women report having been abused, half of them sexually [16]. The *severity* of

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the need to void is more consistent with IC/BPS than a sudden urge to void more typical of overactive bladder [17]. Spicy foods [18] and smoking may also exacerbate symptoms [19].

In addition to physical and urogynecologic examination, digital and manometric pelvic floor muscle examination should be performed to evaluate pelvic floor dysfunction [20]. Cystoscopy following bladder distension (preferably with isotonic saline or isotonic glycine to avoid hypotonic damage to the urothelium) under spinal or general anesthesia [21] permits visualization of urothelial "glomerulations" and "Hunner lesions, but "glomerulations" may occur even in normal bladders [22]. Nevertheless, cystoscopy could also allow for biopsies that may reveal increased number of mast cells [23]; a count of >28 tryptase-positive detrusor mast cells/mm^2 may identify a subgroup of IC/BPS patients [21, 24].

Allergies and Inflammation

Unfortunately, IC/BPS is often misdiagnosed [25–27] at least partly because patients often experience comorbid diseases [26–28], such as panic disorder [29] and allergies [26, 27], especially mastocytosis [30] and "mast cell activation syndrome" [31], chronic fatigue syndrome (CFS), fibromyalgia and irritable bowel syndrome (IBS) [32–34], as well as endometriosis and vulvodynia [35–37], all of which have an atopic basis [28]. In fact, fibromyalgia [38] and "brain fog" [39] may be the most common presenting symptoms other than frequency and pain. Symptoms can worsen with physical or psychological stress [40–42]. We reported that biopsies from respective tissues in patients who had both IC/BPS and endometriosis had evidence of inflammation, mast cell activation, and increased expression of the stress-associated corticotropin-releasing hormone (CRH) [43]. CRH can stimulate selective mast cell release of vascular endothelial growth factor (VEGF) [44], which increases vascular permeability [45]. Importantly, both CRH [46] and VEGF [47] have been reported to be increased in the bladder of IC/BPS patients.

The cause of IC/BPS is still unknown hampering the development of effective treatments [48]. The bladder glycosaminoglycans (GAG) may be compromised [49], due to loss of GAG components chondroitin sulfate (CS) and hyaluronate sodium (HS) [50]. Bladder inflammation is variable and more often associated with the presence of Hunner lesions [51, 52]. Recent findings indicate that inflammation correlates with increased bladder, urine and serum levels of nerve growth factor (NGF) [53, 54], and a monoclonal humanized antibody against NGF showed significant benefit in IC/PBS [55]. Moreover, TLR-4 stimulation of peripheral blood mononuclear cells was strongly associated with all symptoms [56].

The importance of bladder mast cells has been discussed repeatedly [57, 58] and could explain the pain and some histologic aspects of IC/BPS [40]. However, it is mast cell *activation* [59] that is important and not the actual number of mast cells as also recently discussed for IBS [60, 61]. For instance, the cytokine IL-1 was shown to stimulate selective mast cell release of IL-6 [62] and stress-induced serum IL-6 increase was entirely dependent on mast cells [63]. These findings are important since IC/PBS patients have higher plasma IL-6 levels [56].

Treatment Approaches

Unfortunately, there are no curative drugs for IC/PBS and recent reviews do not even mention the possible use of immune modulators [5, 6, 10, 64–66], see Table 11.1.

Bladder Lining Replenishing

Sodium pentosanpolysulfate (PPS, Elmiron) is an oral synthetic polysaccharide reported to be beneficial in an early study with an unusual low placebo arm [67]. However, a large randomized, double-blind, placebo-controlled, multicenter trial using PPS (300 mg/day for 3 months) had no significant effect ($p < 0.064$) over placebo [68]. Similarly, a subsequent randomized study of 300 mg/day PPS for 6 months was indistinguishable from placebo [69]. Any small beneficial effect of PPS may be due to its weak ability to inhibit mast cells [70].

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs), such as amitriptyline (Elavil) and doxepin (Sinequan), also have antihistaminic actions [71]. In fact, doxepin was reported to be 800 times as potent as diphenhydramine in antagonizing the histamine-1 receptor [72]. In one randomized, double-blind, placebo-controlled, clinical trial ($n = 50$) amitriptyline (self-titrated up to 100 mg/day for 4 months) produced a 64 % response rate [73]. Another multicenter, randomized, placebo-controlled trial of amitriptyline reported that only those IC/BPS patients ($n = 207$) who took more than 50 mg/day had a significantly higher ($p = 0.01$) response rate at 7 weeks [74]. However, sedation and weight gain often decrease patient compliance. The beneficial action of amitriptyline

Table 11.1 Oral medications used for IC/BPS

Agent	Dose
Drugs	
Amitriptyline (Elavil)	25–50 mg po at bedtime
Hydroxyzine (Atarax)	25–75 mg po at bedtime
Montelukast (Singulair)	10 mg po daily
Omalizumab (Xolair)	150 mg sc every 2–3 weeks
PPS (Elmiron)	100 mg po three times daily
Prochlorperazine (Compazine)	10 mg po three times daily
Rupatadine (Rupafin)	10 mg po twice daily
Supplements	
CS, HS, quercetin (CystoProtek)	2 capsules po twice daily
Luteolin, quercetin (FibroProtek)	2 capsules po twice daily

po per oral
sc subcutaneusly

may be associated with its ability to inhibit mast cells [75]. The antiemetic phenothiazine, prochlorperazine (Compazine), may be useful because it also has both histamine-1 receptor antagonists and mast cell inhibitory properties [75].

Antihistamines

Hydroxyzine (Atarax) is a first generation histamine-1 receptor antagonist. In an open label study ($n=37$) using 75 mg at bedtime (titrated up from 25 mg at bedtime over 1 month) for 4 months reduced symptoms by 55 % [76]. In another open-label, nonconsecutive case series ($n=140$) hydroxyzine had a 55 % success rate [77]. Hydroxyzine is sedating, but daily use at bedtime minimizes its sedative effect during waking hours while retaining its antihistaminic actions [78].

Rupatadine (Rupafin) is a second generation histamine-1 receptor reverse agonist that also blocks the action of platelet-activating factor (PAF) [79] and has additional anti-eosinophilic properties [80]. Rupatadine may also be useful because it inhibits histamine release from mast cells [80, 81]. In contrast, even though the first generation histamine-1 receptor antagonist ketotifen (Zaditen) was reported to inhibit conjunctival mast cells [82], it did not inhibit skin mast cells, but it actually stimulated them at high doses [83].

Histamine-2 receptor antagonists, such as famotidine (Pepcid) or ranitidine (Zantac), are often used together with histamine-1 receptor antagonists [84].

Anti-leukotrienes

The cysteine-leukotriene receptor antagonist montelukast (Singulair) [85] was reported to be successful in one male patient with IC/PBS and allergic rhinitis [86] and in ten female patients with detrusor mastocytosis [87].

IgE Neutralization

In one case report of an IC/PBS patient with asthma and allergic rhinitis, use of the anti IgE monoclonal antibody omalizumab (Xolair), which is approved for asthma and chronic urticaria [88], was successful in also treating IC/PBS symptoms [89].

Mast Cell Blockers

Disodium cromoglycate (cromolyn), called “a mast cell stabilizer,” improves gastrointestinal symptoms in patients with mastocytosis [90], but had no effect on IC/PBS [91]. This is not surprising as cromolyn is a weak in vivo inhibitor of human mast cells [92–94].

Flavonoids

The structure of cromolyn resembles the backbone of some naturally occurring flavonoids, mostly found in green plants and seeds, with potent antioxidant and anti-inflammatory actions [95]. Quercetin (5,7-3′5′-pentahydroxyflavonol) and its structurally related luteolin (5,7-3′5′-tetrahydroxyflavone) are mast cell inhibitors [96–98]. We showed that quercetin is a more potent mast cell inhibitor than cromolyn [94] and tetramethoxyluteolin (5,7-3′5′-tetramethoxyflavone) is a more potent inhibitor of human cultured mast cells than luteolin [99]. A skin lotion (GentleDerm) containing tetramethoxyluteoin was recently made available and may be used by patients with vulvodynia or vulvar vestibulitis.

In one open label study ($n=17$), the dietary supplement CystoProtek containing the natural anti-oxidant and anti-inflammatory flavonoid quercetin (150 mg/capsule) together with the GAG components CS (150 mg/capsule) and HS (10 mg/capsule, three times daily for 6 months) improved IC/PBS patients with allergies by 55 % ($p<0.05$) [100]. In another open label study of IC/BPS patients ($n=227$), CystoProtek produced a 52 % response rate ($p<0.0001$) [101]. The benefit of the oral GAG components in CystoProtek is supported by long treatment results of intravesical CS and HS that were apparent for 3 years [102]. CS may not only help replenish the damaged bladder lining, but it also inhibits mast cells [103].

A more recent study using CystoProtek together with another dietary supplement, FibroProtek, which contains a combination of quercetin (170 mg/capsule) and luteolin (255 mg/capsule), had a response rate of over 75 % (unpublished).

Luteolin may even protect against damage of bladder nerves since it was also shown to induce the synthesis and secretion of neurotrophic factors [104] and the related flavonoid 7,8-dihydroxyflavone mimicked the activity of brain-derived neurotrophic factor (BDNF) [105]. Moreover, the related flavonoids 4′-methoxyflavone and 3′,4′-dimethoxyflavone were reported to be neuroprotective [106].

Unfortunately, less than 10 % of orally ingested flavonoids in powder are absorbed [107, 108] and are extensively metabolized to inactive ingredients in the liver [109]. In order to increase intestinal absorption, the flavonoids in CystoProtek and FibroProtek are mixed with olive kernel oil. It is interesting that olive oil [110] and flavonoids [111] have been reported to inhibit cyclooxygenase, which is responsible for the production of proinflammatory prostaglandins.

Conclusion

The prevalence of IC/BPS has increased significantly and is a major source of CPP leading to significant disability. Early diagnosis and management with a combination of anti-allergic compounds can lead to substantial symptom reduction and improved quality of life.

Disclosures Dr. Theoharides has lectured for Algonot, LLC, and is the inventor of the US patent 6,635,625 and of the trademarked (US registration 2,840,956) dietary supplement CystoProtek.

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Opioids and Related Medications

12

Timothy J. Atkinson and Jeffrey Fudin

Role of the Specialist in Prescribing Opioids

Specialty physicians and collaborating providers sometimes place themselves in awkward patient situations when prescribing opioids. Rather than performing risk assessments and monitoring individual patients, standardized prescriptions for procedures or symptom flares are thought to be sufficient to mitigate risk. A keen understanding of the issues surrounding opioid therapy will aid the specialty provider to recognize risk in the treatment of severe pain unresponsive to standard protocols yet respond appropriately and compassionately to legitimate pain complaints.

When addressing pain complaints, it is the primary responsibility of specialty providers to communicate with the primary care provider (PCP) and/or pain provider. This should include assessment of pain severity, causality, and treatment recommendations. When pain complaints result in consults for specialty care, PCP and/or pain providers often require both confirmation of a diagnosis as well as an indication of pain severity or whether pain complaint is biologically plausible. When pain is not addressed among treatment recommendations, it may create confusion and frustration with referring providers. An indication of severity is critical for the understanding of other providers and can be communicated simply, for example, "Condition xyz can cause fairly severe pain but is routinely managed with moderate analgesics and physical therapy."

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Various medical and surgical specialties may need pain services. For example, rheumatologists, neurologists, and orthopedists commonly suggest and prescribe medications for pain. Nephrologists working with dialysis patients often find themselves being asked to address pain complaints as well since they may see these providers up to three times per week. All prescriptions for pain medications should be coordinated with PCP even if prescriptions are standard prescriptions for postoperative pain. Specialty providers who elect to assume pain management responsibilities are to be commended; however, they should have a sound understanding of the concepts of opioid prescribing and implement universal precautions [1].

Concepts of Long-Term Opioid Prescribing

Managing pain chronically differs in significant ways from acute pain and palliative pain management. The length of time that patients are treated introduce new risks that must be accounted for and monitored. The decision to utilize opioids for pain management changes therapy and elevates risk. Only one practitioner should be in charge of prescribing pain medications. While this is usually a primary care provider, there are cases where specialty providers have assumed this role. Opioids are unequaled in their ability to relieve pain and suffering. They also are associated with serious long-term and dose-dependent side effects. Combined with their potential for addiction, tolerance, physical dependence, and street value, these risks require that opioids should be reserved for severe pain unrelieved by other means and after failure of alternative modalities.

This chapter discusses basic concepts of long-term opioid prescribing for pain including implementation of universal precautions, short vs long acting opioids, opioids in the treatment of neuropathy, common adverse effects associated with opioid therapy including emerging evidence on risk to mothers during pregnancy and neonates, and hormonal imbalances related to suppression of the hypothalamic-pituitary-adrenal axis.

Universal Precautions

Universal precautions for opioid prescribing are a system of safeguards that attempt to mitigate the risks of chronic opioid therapy. These precautions are the minimum standard or core recommendations of pain management guidelines many of which are evidenced-based and validated while others are practical recommendations based upon clinical experience [2–7]. Table 12.1 is a quick summary of universal precautions for opioid prescribing.

Pain patients have often been seen by multiple providers previously so obtaining records particularly from their most recent prescriber is critical and will save compassionate providers from enormous heartache and hassle by recognizing early warning signs of problem patients before assuming care. At a minimum, prior to assuming care for a patient's pain management, records should be received along

Table 12.1 Universal precautions for long-term opioid therapy [1]

Precaution	Explanation
Pain/medical history	Permission to contact previous providers, obtain, and review records
Physical assessment	Physical exam and imaging explain pain complaint? Know what you are treating!
Consider all treatment options	Weigh risks vs benefits of opioid therapy; alternative therapies; previous trials
Risk assessment	Age, mental health, family and personal history of sexual and/or substance abuse
Informed consent	Discuss risk vs benefits and expectations of patients receiving opioid therapy
Trial of opioid therapy	Start lowest effective dose of short-acting opioid for temporary period
Monitoring	Urine drug testing; state PMP, pill counts, functional assessment
Escape Plan	Define treatment failure, taper and discontinue, referral to specialist

Adapted from CDC's common elements in guidelines for prescribing opioids for chronic pain

with a letter of good standing and/or permission obtained to contact their previous provider. Patients desperate to receive pain medications may misrepresent their pain/prescription history so behaviors that should raise red flags include refusing permission to contact previous provider, letter stating aberrant behaviors resulting in discharge from clinic (failed "pill counts," inappropriate urine drug screens, lost/stolen medications) and requirement for high dose opioids. The above should serve to warn practitioners that a patient may not be a good candidate for opioid therapy in this setting and a referral for pain management or substance abuse services may be advisable depending on the situation. Notwithstanding, patients are sometimes mislabeled by previous providers especially if urine drugs tests by immunoassay yielded a false-negative or positive test that was not confirmed by liquid or gas chromatography and mass spectrometry.

Physical assessment is a key component and an opportunity to assure that the pain level reported is consistent with pathology demonstrated on imaging and exam. Providers should identify physiologically plausible causes for pain severe enough to warrant opioid therapy. Exaggerated pain behaviors and esoteric pain complaints that cannot be easily verified are red flags that should delay utilizing opioids until additional testing has been completed. Consider all treatment options before deciding to utilize opioid therapy. Evaluate evidenced-based recommendations for the specific pain complaint and assure all non-opioid and non-pharmacologic options are being utilized or have been utilized. Retrials of non-opioid options are advisable if pain severity warrants opioid trial even if previously attempted. If patients focus on opioids and will not consider utilizing alternative treatment options, then opioid therapy should be reconsidered and their history should be reexamined and gaps identified and addressed. Beware of requests to treat pain complaints outside your specialty.

If a practitioner is leaning toward prescribing opioids a formalized risk assessment is recommended to evaluate the risk of abuse/misuse and potential addiction.

There are a number of validated risk assessment tools available including Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients in Pain (SOAPP), Current Opioid Misuse Measure (COMM), Diagnosis Intractability Risk Efficacy (DIRE), Pain Assessment Documentation Tool (PADT), Addiction Behaviors Checklist (ABC), and Brief Risk Interview (BRI) [8–14]. Most of these tools are free and available online with several versions available. Each examines the patient's history and attitudes toward taking pain medications that predict risk associated with opioid therapy. Key indicators of increased risk that have been validated are personal history of substance abuse with alcohol, illicit drugs, and prescription drugs. A family history of substance abuse increases risk but not to the same extent as personal history [8]. There is also increased risk with young patients [15–44] compared to elderly populations. A personal history of sexual abuse increases risk particularly in women. The presence of certain mental health disorders clearly increases risk including bipolar disorder, schizophrenia, obsessive-compulsive disorder (OCD), attention deficit disorder (ADD), and to a lesser extent depression and anxiety [8]. To be clear, identified high-risk patients may be best managed in a pain specialty practice where frequent visits, increased monitoring, and functional testing are available.

Once the decision has been made to treat with opioids, a discussion between the provider and the patient is recommended with a review of associated risks versus benefits and expectations of care. This is now called the informed consent process and replaces former opioid agreements or contracts that were frequently misunderstood by patients and perceived as binding legal instruments. This change is disconcerting to some providers, however, because they believe it makes it more difficult to withdraw therapy from noncompliant patients. This concern is easily allayed if providers make it crystal clear during the informed consent process that they will only provide opioid therapy if they are comfortable that doing so is safe and effective.

A trial of opioid therapy should be attempted prior to committing to long-term opioid therapy. For this to be successful, a predefined end date to the opioid trial is established up front with clear goals for therapy. For example, if by providing opioids pain decreases by 20–30 % but activity remains the same and no progress is demonstrated toward goals of functional improvement, then the trial may be considered a failure. Goals should be discussed and agreed upon in advance and progress assessed after trial period has ended. An escape route, or preplanned strategy to taper and discontinue opioid therapy, is necessary when an opioid trial fails for various reasons including: aberrant behavior arises, side effects outweigh benefits, much higher dosage requirement necessary to control pain than anticipated, or lack of functional improvement. An opioid taper should be initiated to decrease impact of withdrawing therapy and reasons for discontinuation explained along with recommendations for alternative treatment.

Monitoring during opioid therapy is the key to successful management and should be individualized to each patient's unique level of risk. Urine Drug Testing (UDT) should be a routine part of monitoring for opioid therapy at a frequency that reflects their risk. Ideally, UDT should be observed to avoid adulteration or substitution. Positive or unexpected results should be sent for confirmation testing (LC-MS or GC-MS) to assure accurate results to guide clinical decision making. "Pill"

counts might be helpful when patients are suspected of overusing their medications but are of little help if stockpiling or diverting their medications. It is fairly easy for a patient drug-dealer to obtain illegal opioids in a hurry in order to fill their prescription bottle to an acceptable or believable quantity for a provider's viewing. State prescription monitoring programs (PMP) are helpful to assure patients are not receiving multiple prescriptions for pain medications from different providers and should be checked routinely. Functional assessments should be incorporated into a monitoring plan to assure that sufficient progress toward goals of therapy is being pursued and achieved.

Short-Acting Versus Long-Acting Opioids

The appropriateness of long-acting versus short-acting opioid formulations is a constant source of debate within the pain management community. There is no evidence that either long-acting or short-acting opioids are more effective in treating pain but there are significant differences that should influence treatment decisions [2]. Long-acting opioids include various formulations encompassing controlled-release, extended-release, sustained-release, and transdermal options. Those with long half-lives such as methadone and levorphanol should not be assumed to have continuous ongoing analgesia with long dosing intervals—in fact, methadone most frequently requires dosing three or four times daily even though it has the longest half-life compared to other long-acting opioids [15, 45]. Short-acting opioid formulations are also diverse and include oral, sublingual, intranasal, and IV options. While some of these formulations are abuse deterrent, most are not.

Long-acting opioids are indicated when patients have persistent pain that lasts throughout the day. Extended or controlled-release formulations are a higher risk of drug overdose in treatment naive patients and such risk is substantially increased by 2.3 times as demonstrated in a recent study [16]. It is recommended that opioid naive patients should receive short-acting medications prior to conversion to long-acting for dose-finding purposes even if the intent is to convert to long-acting [2, 4]. Long-acting medications are often higher doses that are slowly released over 8–12 h making them more difficult to reverse if the amount is excessive. The majority of long-acting medications are also not abuse deterrent and therefore can be crushed and either snorted or put into solution and injected resulting in a massive dose delivered at once. In clinical practice, patients often report decreased recognition of benefits with long-acting compared to short-acting and it may take a longer trial to evaluate benefits. Advantages to long-acting options include more consistent drug delivery and steady serum levels often leading to decreased side effects, possible diminished cognitive impairment, and more restful consistent sleep over several hours [17, 18].

Short-acting opioids are indicated for acute intermittent, postsurgical, and/or episodic or breakthrough pain. Short-acting opioids have a quicker onset and a higher peak serum level that is associated with more euphoria and therefore greater addiction potential. In clinical practice, patients often prefer them over long-acting opioids because they can "feel" them working with their rapid onset and higher peak.

They are favored by addicts which is reflected by both likeability studies and street value [19]. Short-acting opioids are designed to last 3–6 h but with the development of tolerance this decreases to 2–3 h or less as only the peak level results in analgesia [18]. Despite the fact that short-acting opioids are not designed for consistent coverage, in clinical practice most patients tend to schedule their short-acting opioids in an attempt to simulate a long-acting opioid. Therefore, as tolerance increases these patients begin to ride the pain roller coaster with more ups and downs as gaps where their pain is uncontrolled continue to widen between doses.

The decision to utilize short or long-acting opioids should be made on an individualized basis weighing all the risks and benefits. The pathology should be severe enough to warrant opioid therapy. A patient's history should be taken into account including substance abuse, aberrant behavior, psychiatric comorbidities and stability, and noncompliance with treatment and follow-up. Specialty providers usually prescribe short-acting opioids due to the short amount of time they follow a patient but occasionally take over prescribing opioids for a period of time and in either case should be familiar with clinical considerations discussed herein.

Opioids in Neuropathy

Neuropathic pain is one of the most common types of pain and can be particularly difficult to treat. Neuropathy is often the result of a lesion, compression, and/or damage to a nerve either peripheral or central. Nociceptors become more sensitive to pain stimuli, are activated longer, and result in abnormal firing at the nerve ending [20, 21]. Neuropathy symptoms are described as burning, shooting, electric, and often associated with tingling or numbness. Neuropathy often results in sharp lancinating pain that travels from one location to another and/or radiates outward. There are numerous causes of neuropathic pain but some of the most common types of neuropathy are diabetic peripheral neuropathy and postherpetic neuralgia. Neuropathy is often a key component to mixed or complex pain syndromes such as spinal stenosis, radiculopathies, and complex regional pain syndrome.

The effectiveness of opioids for the treatment of neuropathy is one of the core debates in pain management. Since the subject has not been studied extensively, we are left with only short-term clinical trials that demonstrate opioids can be effective in treating neuropathy. For clinicians who treat pain patients for more than 12 weeks, however, it is clear that traditional opioids are only temporarily effective in addressing neuropathic pain complaints and monotherapy with opioids is problematic and routinely leads to rapid dose escalations as the original pain level returns after a brief period of efficacy. Opioids depend on altering pain perception through afferent pathways of the central nervous system but do not affect neuronal firing or transduction that partially explains the temporary nature of opioid efficacy [21]. This has finally been recognized in treatment guidelines for neuropathy which no longer recommend opioids as first-line options for neuropathy [22, 23].

Clinical Pearl: When opioid monotherapy is utilized for the treatment of neuropathy, it is common to see patients on very high dose opioids.

For the successful long-term management of neuropathic pain, adjunct medications need to be utilized appropriately to address this pain and to avoid unnecessary escalations in opioid therapy. At times, neuropathic pain is severe enough to warrant opioid therapy in combination with adjunct therapies but clinicians should keep in mind the limitations of opioid therapy in addressing neuropathy. Atypical opioids are one possible exception due to alternative mechanisms that can make them highly effective at treating neuropathy but not for their inherent opioid properties.

Opioids in Pregnancy

Between 1999 and 2010, opioid overdose deaths increased by 400 % and prescriptions for opioids increased the nearly same margin [24]. The increase availability of opioids resulted in more women of child-bearing age using opioids which are pregnancy category C, indicating that animal studies have shown significant harm to fetus, and their use should be avoided unless benefit outweighs potential harm. Opioid use during pregnancy is the primary cause of neonatal abstinence syndrome (NAS), which is a withdrawal syndrome in newborn babies following birth. The incidence of NAS over the same time period above has increased by three times previous rates and opioid abuse during pregnancy has increased nearly five times [25]. A national survey reported that illicit drug use including opioid use was 16.2 % in teenage pregnancy compared to 7.4 % of pregnancies of women aged 18–25 [26]. Complications of NAS include preterm birth, low birth weight, respiratory distress, feeding intolerance, seizures, and increased mortality. Symptoms of NAS may develop in roughly 60–80 % of babies whose mothers were using opioids during pregnancy, which, in addition to complications previously mentioned, may result in increased hospital length of stay in the neonatal ICU for an average of 30 or more days [25, 27]. It is therefore critical that women of child-bearing age are screened and educated regarding the risks of opioid therapy during pregnancy.

Opioids and Adrenal Suppression

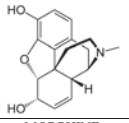
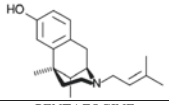
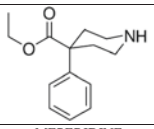
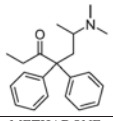
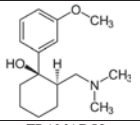
The effects of opioids on the hypothalamic-pituitary-gonadal axis are well known and characterized by a decreased release of sex hormones from direct effects at both the hypothalamus and inhibition of gonads [28–31]. Less well known, however, is the opioid-induced suppression of the hypothalamic-pituitary-adrenal axis [32]. Opioids binding at the hypothalamus result in reduced release of corticotropin-releasing hormone (CRH) which reduces pituitary secretion of adrenocorticotropic hormone (ACTH) [33, 34]. Opioids also interfere with the adrenal glands' ability to produce cortisol, a hormone that is physiologically important for the stress response [32, 35, 36]. Adrenal androgen, dehydroepiandrosterone (DHEA), production and release is reduced and may be severe enough to cause symptoms of weakness, fatigue, depression, and sexual dysfunction [35]. Opioids appear to antagonize the

entire hypothalamus-pituitary axis and through multiple combined mechanisms, result in decreased androgens partially explaining why prevalence of opioid-induced hypogonadism is much higher than previously believed (40–60 %) [28, 37, 38].

Traditional Opioids

Opioids primarily act as agonists at endogenous opioid receptors [21, 39]. Entire volumes have been dedicated to the complexity of these agents and their impact on patient care. The goal of this section is to discuss general characteristics of opioids, highlight unique characteristics of individual opioids, and provide clinically meaningful strategies for use in every-day practice. First, rather than thinking of opioids as natural, semisynthetic, or synthetic, it is enormously helpful to separate them into their pharmacologic classes (see Fig. 12.1). The pharmacologic classes of opioids are phenanthrenes, benzomorphans, phenylpiperidines, and diphenylheptanes. Committing this chart to memory provides a wealth of practical and clinically significant information on relationships between different opioids, incomplete cross-tolerance, UDT interpretation, and chance of cross allergy between opioids.

Phenanthrenes are the largest class of opioids with morphine, the prototypical opiate, from which nearly all others are derived explaining their structural similarity. One key difference between morphine and the other opioids in this class is dihydroxylation at the 6′ position which is believed to decrease the GI side effects (nausea, vomiting, and constipation). The majority of the drugs in this class are dehydroxylated phenanthrenes (i.e., oxycodone, hydrocodone, hydromorphone,

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	MEPERIDINE	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Morphine Nalbuphine Naloxone* Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanil Sufentanil	Methadone Propoxyphene	Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK
*Agents lacking the 6-OH group of morphine, possibly decreases cross-sensitivity within the phenanthrene group				

Revised and reprinted from paindr.com.

References:
Fudin J. (2011), paindr.com
Updated 2015 by Dr. Thien C. Pham

Fig. 12.1 Pharmacologic Classes of Opioids. *Agents lacking the 6-OH group of morphine, possibly decrease cross-sensitivity within the phenanthrene group. Revised and reprinted from paindr.com. References: Fudin J. (2011), paindr.com; Updated 2015 by Dr. Thien C. Pham

oxymorphone, buprenorphine, levorphanol, etc). While dihydroxylation may decrease the risk of cross allergy within the class to some extent, it is probable that patients with a true allergy to morphine will have a similar reaction to other agents in this class. Common causes of opioid intolerance are nausea, vomiting, sedation, somnolence, and pruritus. While severity may vary, these are common side effects of initiating and/or titrating opioid therapy and are typically transient. If these are severe or persistent, then many can be treated, for example, antihistamines for pruritus, and anti-emetics for nausea/vomiting. Due to structural similarity of agents within the phenanthrene class, it is very common for patients complaining of pruritus with morphine to experience a similar reaction with hydrocodone or oxycodone although the severity may vary. A true allergy to opioids is very rare and characterized by angioedema and anaphylaxis. A true allergy to any opioid in the phenanthrene class would preclude utilizing alternative agents within the same class due to high risk or probable cross allergy risk. In these rare cases, an opioid from a different pharmacologic class should be selected, for example fentanyl (phenylpiperidine) or methadone (diphenylheptanes) that have very different chemical structures and therefore are much less likely to be recognized by the body and induce an allergic reaction. Similarly, a history of meperidine may indicate that a patient can tolerate fentanyl, and previously tolerating propoxyphene potentially predicts tolerability to methadone. Therefore, when patients report allergies to multiple opioids, additional questions should be asked to ascertain the severity of the reaction or intolerance and determine if this may have been transient if therapy had continued. Education should be provided so patients will consider alternative opioid therapy if necessary. The clinician should be suspicious for medication misuse/abuse when patients are adamant that only one opioid is effective for their pain and are unable to tolerate other options. This may lead to high dose opioid therapy as tolerance develops and patients remain unwilling to switch to alternative options.

Clinical Pearl: Patients should not have a "favorite" opioid. If they are emphatic that only one opioid works for their pain, this should serve as a red flag; although we do need to consider that sometimes patients just don't like change.

Tolerance to individual opioid therapies is a common occurrence in clinical practice and at some point requires change to another opioid for improved analgesia at equal or decreased doses. When considering an opioid rotation to an alternative opioid, the patient's history should be considered. Some portion of developed tolerance from the previous opioid is expected to transfer over and this is called incomplete cross tolerance. Selecting an opioid from a different pharmacologic class may increase efficacy in some cases as no tolerance has been developed to the new chemical structure.

A keen understanding of pharmacologic classes of opioids is enormously helpful when interpreting UDT results. For example, most UDT are immunoassay-based tests returning results for opiates. This actually tests for morphine and due to structural similarity, other phenanthrenes are included by default. This is a critically important concept because this test easily detects morphine but typically requires higher concentrations of related drugs (hydrocodone, hydromorphone, oxycodone, etc) to return a positive result. Whether or not a positive result is

returned often depends on the cross-sensitivity of the reagent and concentration that determine detection limits. Since UDT specifically tests only for morphine, then opioids from different pharmacologic classes like fentanyl, meperidine, methadone, tapentadol, and tramadol are not detected and require specialized testing. When providers do not understand this concept, patients often have their opioids discontinued for negative results when the test was not capable of returning a positive result. Utilizing the correct UDT test is critical both for initial and follow-up testing. Immunoassay testing is vulnerable to false positives such as PPIs, NSAIDs, and some HIV medications that routinely report false positives for cannabinoids. Amphetamines have numerous false positives including decongestants, beta blockers, and levodopa/carbidopa among other compounds with catecholamine-like structures. For these reasons, positive results should be sent for confirmation testing with liquid or gas chromatography/mass spectrometry with definitive results. Of note, newer designer drugs of abuse such as spice (synthetic cannabinoids), bath salts (synthetic cathinones), Kratom, and Ecstasy (3,4-methylenedioxy-methamphetamine [MDMA]) do not routinely show up on UDT without specialized testing [40].

Clinical Pearl: There are currently 19 subreceptors of the μ-opioid receptor that have been identified. Genetically we express different subreceptors which is one mechanism believed to explain why some patients respond better to one opioid over another [39].

Table 12.2 lists the pharmacokinetic and pharmacodynamics profiles of commonly prescribed opioids for easy comparison. While there are similarities particularly within pharmacologic classes, there are also differences that become important to clinical practice. The unique features of various opioids are discussed below.

Morphine

Morphine is the standard that all other opioids are compared against for potency, efficacy, and adverse effects. It is available in nearly all dosage forms. Morphine may cause higher incidence of nausea/vomiting compared to alternative opioids. It has a relatively low bioavailability (20–40 %), short half-life, and therefore reaches steady state quickly. Morphine is metabolized hepatically via phase II metabolism through glucuronidation into morphine-3-glucuronide (inactive) and morphine-6-glucuronide (active) [41, 42]. Clinically, morphine (parent) accumulates in hepatic dysfunction and dose decreases may be necessary to avoid adverse effects. The glucuronide metabolites are significant in renal dysfunction as they accumulate and can result in neurotoxicity; therefore, morphine should not be utilized in patients with poor renal function (CrCl < 30 ml/min) [43].

Clinical Pearl: Euphoria associated with opioid use relates to quick onset and potency. IV opioids are more desirable than oral opioids because of a much higher peak serum concentration and rapid onset of effect. IV opioids should therefore be avoided in high risk patients if possible.

Table 12.2 Pharmacokinetic and pharmacodynamic properties of commonly prescribed opioids

	μ-Opioid Rec BA	Equivalent doses		Duration of action, h	Half-life ($T_{1/2}$), h	Time to steady state, h	Metabolism
		IV, mg	PO, mg				
Phenanthrenes							
Morphine	+	10	30	IR: 4	2–4	24	Morphine-3-glucuronide, Morphine-6-glucuronide-active, Normorphine, 7,8-dihydromorphinone
Hydrocodone	+	N/A	30	4–6	4	20	Major: Norhydrocodone (3A4)-inactive
							Minor: Hydromorphone (2D6)-active, 6-alpha and 6-beta hydrocodol
Hydromorphone	++	1.5	7.5	3–5	1–3	20	Major: hydromorphone-3-glucuronide
Oxycodone	+	N/A	20	3–6	2–3	24	Major: noroxycodone (3A4)-weak active
							Minor: oxymorphone (2D6)-active
Oxymorphone	+	1	10	4–6	7–9	36	Major: oxymorphone-3-glucuronide
							Minor: oxymorphone-6-glucuronide
Buprenorphine	++++	0.3	N/A		24–42	120–294	Norbuprenorphine (3A4)-weak active
							Glucuronidation of both parent and metabolite
Levorphanol	++	2	4	6–15	11–16	80	Levorphanol-3-glucuronide
Phenylpiperidines							
Fentanyl	+++	0.1	[a]		IV: 2–4	IV: 24	Major: norfentanyl (3A4)-inactive (99%)
					Patch 17–22	Patch 90 h	
Diphenylheptanes							
Methadone	++	3.75	7.5[b]	4–8	8–59	40–295	Major: EDDP (3A4, 2B6, 2C19)
							Minor: EDMP
Misc							
Tapentadol	−[c]	N/A	75–100	4–6	4	24	Major: tapentadol-O-glucuronide-inactive
							Minor: *N*-desmethyl-tapentadol (2C9/2C19)-inactive

BA binding affinity, *Rec* receptor

[a]See package insert for conversions from morphine to Fentanyl

[b]Methadone conversions are complex variable depending on morphine equivalent dose

[c]Eighteen times less affinity for μ-opioid Receptor binding affinity

Hydrocodone

Hydrocodone is a dehydroxylated phenanthrene with potency considered equivalent to morphine. Until recently, it was only available in the United States as a short-acting combination product usually combined with either acetaminophen or ibuprofen. It was originally believed that combining hydrocodone with mild analgesics would have an opioid-sparing effect by increasing relief and discourage potential abuse. Over the past two decades, hydrocodone combination products have consistently been the most prescribed opioid and often the most prescribed drug in the United States [44]. Until October 2014, hydrocodone combination products were Schedule III controlled substances allowing five refills in a 6-month period. The DEA concluded that hydrocodone combination products do not reduce abuse and very high prescription rates do not seem to support any opioid-sparing properties [46]. As a result, all products containing hydrocodone have been rescheduled into Schedule II with the other opioids requiring monthly prescriptions. While hydrocodone does have appeal in likeability studies, the high prescription rates are believed to be the result of convenience as hydrocodone was the only opioid of substantial potency that was available with refills. New long-acting hydrocodone formulations (Zohydro®, Hysingla®) have recently been approved in the past couple of years amid some controversy as many associated their high prescription rates with abuse potential. The impact of rescheduling hydrocodone will be under heavy scrutiny over the next decade as will the abuse potential and street value of new long-acting formulations.

Clinical Pearl: The United States uses 99 % of the world's supply of hydrocodone, but that's because other countries choose to use either morphine or dihydrocodeine instead and not because we're keeping it for ourselves. It is still available in Canada as a cough syrup.

Hydrocodone undergoes extensive hepatic metabolism via CYP450 system primarily through 3A4 into its major metabolite norhydrocodone (inactive), and via 2D6 into its minor metabolite hydromorphone (active) including 6-keto reduction into 6-alpha and 6-beta hydroxyl metabolites. CYP 3A4 inhibitors have been shown to increase hydrocodone concentrations by nearly double normal serum concentrations [47]. In studies of patients with severe hepatic dysfunction, hydrocodone concentrations accumulated to a significant extent but not for mild or moderate hepatic dysfunction. Only slight accumulation was observed in renal dysfunction likely because >90 % of hydrocodone had already been converted to its metabolites which do not significantly affect analgesia or contribute to adverse effects.

Hydromorphone

Hydromorphone is a dehydroxylated phenanthrene and minor active metabolite of hydrocodone. It has ten times higher affinity for the u-opioid receptor compared to morphine (heroin is only seven times higher) but is only four times more potent as an oral formulation [48]. Hydromorphone has poor oral bioavailability

(24 %) requiring higher dosages in oral formulations for effect particularly compared to its potent IV form. Compared to other traditional opioids, hydromorphone has a quick onset achieving peak serum concentrations rapidly (48–60 min) and has the shortest half-life (1–3 h) [49]. Similar to many other active metabolites repurposed as unique drugs, hydromorphone does not pass through oxidative metabolism again (i.e., CYP 450) and is metabolized almost exclusively via phase II metabolism by glucuronidation which yields a 3-glucuronide and 6-glucuronide metabolites. Hydromorphone does accumulate in hepatic and renal dysfunction and dose decreases may be necessary. However, hydromorphone has been recommended as a first-line medication for severe pain in dialysis patients for years because the glucuronide metabolites accumulate but have not been shown to cause neurotoxicity [49–51].

Clinical Pearl: The increased affinity, rapid onset, and high potency make IV hydromorphone a "favorite substitute" for heroin addicts who routinely present to the ER with severe pain complaints.

Oxycodone

Oxycodone is a dehydroxylated phenanthrene with increased potency compared to morphine. It is available in several oral formulations. Oxycodone is consistently favored in "likeability studies" and reported by the DEA to have a high street value suggesting it is a favorite among abusers [19]. Oxycodone CR was the most abused oral opioid on the market until 2012 when it was reformulated with abuse deterrent technology. Now, short-acting oxycodone is favored [52]. Similar to morphine, oxycodone has a short half-life and achieves steady state quickly but has a much higher bioavailability (60–87 %) than morphine. Oxycodone may be slightly activating compared to sedating properties of alternative opioids. Oxycodone is hepatically metabolized via CYP 450 isoenzymes 3A4 for conversion into its major but inactive metabolite noroxycodone, and 2D6 into its minor active metabolite oxymorphone [53]. Oxymorphone has higher potency compared to oxycodone but represents less than 10 % of the administered dose so is not considered a clinically significant contributor to analgesia [54, 55]. Utilizing the CYP 450 system and 3A4 in particular makes oxycodone a fairly high risk for drug interactions. Oxycodone serum concentrations are increased in hepatic dysfunction and may require dose reduction. While metabolites do accumulate in renal dysfunction, there is no known toxicity and may be used with caution in patients with poor renal function.

Clinical Pearl: Oxycodone IR 30 mg tablets are currently the most abused prescription drug formulation with a consistently high street value and appeal to abusers as a large amount of drug in a small tablet is easy to crush, chew, or inject. More potent options like hydromorphone and oxymorphone have the highest street value but are not prescribed as often. Patients requesting regimens of oxycodone IR 30 mg tablets, or other potent options, should raise red flags.

Oxymorphone

Oxymorphone is a dehydroxylated phenanthrene and the minor active metabolite of oxycodone. Oxymorphone has two to five times higher affinity for the μ-opioid receptor than oxycodone and twice as potent [54, 55]. Oxymorphone has very poor oral bioavailability (10 %) but is available in an IV formulation that is ten times more potent than IV morphine. Oxymorphone has a faster onset (30 min) but longer half-life (7.2–9.4 h) and delayed arrival at steady-state concentrations (3 days) compared to its parent oxycodone [56]. Oxymorphone is metabolized via phase II glucuronidation into its major but inactive metabolite oxymorphone-3-glucuronide and minor active metabolite oxymorphone-6-glucuronide which makes up less than 1 % of administered dose [41, 56]. Oxymorphone significantly accumulates in hepatic and renal dysfunction (65 %) and dose reductions may be necessary. Serum concentrations in hepatic dysfunction increased 12-fold due to a large increase in bioavailability and prompting an FDA warning for patients with moderate to severe hepatic dysfunction [56]. While medications metabolized via glucuronidation typically have fewer drug interactions and are less affected in hepatic dysfunction, the large increase in bioavailability of oxymorphone precludes recommending it to patients without additional studies to clarify safety concerns.

Fentanyl

Fentanyl is a phenylpiperidine that is 100 times more potent than morphine which is why it is dosed in micrograms (mcg) and not milligrams (mg). Fentanyl also has many dosage forms including IV, transmucosal, lollipop, and transdermal. Fentanyl is highly lipophilic and distributes into bodily tissues extensively. There is no oral dosage form because oral bioavailability is too low to utilize clinically [57, 58]. The most common dosage form is the transdermal patch as the transmucosal and lollipop formulations have enormous abuse potential and therefore have required REMS and are usually reserved for cancer pain. Equianalgesic conversions from other opioids to transdermal fentanyl are troubled by high interindividual variability with erratic and unpredictable absorption due to skin permeability, thickness, cachexia, and other genetic factors.

Fentanyl undergoes phase I metabolism via CYP450 almost exclusively through 3A4 (99 %) into its major metabolite norfentanyl (inactive). Such a high percentage metabolized through 3A4 results in fentanyl being highly vulnerable to drug interactions since 85 % of all drugs are metabolized in this pathway [55, 59, 60]. 75 % of fentanyl dose is excreted in the urine with 10 % excreted unchanged.

Clinical Pearl: Beware of cachectic, frail, or elderly patients on fentanyl patches because they may not be receiving the full dose and/or benefit and therefore switching them to an alternative opioid often results in an accidental overdose.

Fentanyl patches are often recommended clinically for nonadherent patients because the patches are more difficult to abuse. Fentanyl patches are, however, vulnerable to extraction of the drug by abusers determined to remove the drug. Fentanyl

patches were originally formulated as a reservoir system to a drug-in-matrix system which makes extraction and dose-dumping through application of heat more difficult than before [61]. A common adverse effect of fentanyl patches is actually related to the patch adhesive which in some patients results in dermatitis. While this is sometimes severe enough to warrant discontinuation, in the majority of cases an aerosolized steroid applied to the area and allowed to dry before patch placement will alleviate or substantially decrease symptoms and therefore allow continuation of therapy.

Clinical Pearl: Fentanyl patches release approximately 89% of their drug in the first 48 h and some individuals describe it wearing off the third day. If the patient complains of these phenomena, it is reasonable to allow patch change every 48 h instead of every 72 h.

Buprenorphine

Buprenorphine is a dehydroxylated phenanthrene and semisynthetic derivative of the naturally occurring opium alkaloid thebaine [62, 63]. It is classified as a partial agonist/antagonist because it demonstrates antagonist activity at δ and κ-opioid receptors and partial agonism at the μ-opioid receptor [64–66]. The only dosage forms available are IV, SL, and transdermal because buprenorphine undergoes extensive first-pass metabolism (95%) making oral dosage forms impractical [65, 67]. It is highly lipophilic with extensive distribution into bodily tissues and is primarily metabolized and eliminated hepatically via CYP 3A4 into an active metabolite that is weak and not considered clinically relevant [65, 68]. With chronic administration, buprenorphine has a half-life of 24–48 h which combined with the highest affinity of all opioids for the μ-opioid receptor, means it is capable of blocking the effects of other opioids for a tremendous period of time [67, 69–71]. These properties make buprenorphine useful for treating opioid dependence and pain but if administered to a patient already on opioids, it may induce withdrawal symptoms. At the time of chapter submission, three FDA-approved products exist that are specifically indicated for analgesia. These include formulations by injectable, transdermal, and buccal routes of administration available respectively as Buprenex, Butrans, and Belbuca.

Atypical Opioids

Atypical opioids have a unique place in therapy due to their ability to provide multimodal analgesia in one medication. Similar to traditional opioids, atypical opioids are full agonists at μ-opioid receptors but also boast an additional mechanism that increases analgesic efficacy in neuropathic pain conditions. Since neuropathic pain is often a key component in complex, or severe pain conditions, the unique pharmacology of these agents can be highly effective. Atypical opioids have additional clinical considerations due to complex pharmacokinetics that must be considered and sometimes make practitioners feel nervous or uncomfortable prescribing them due to unfamiliarity. Atypical opioids include methadone, levorphanol, tapentadol, and tramadol.

Methadone and Levorphanol

Methadone and levorphanol are atypical opioids with unique pharmacology and pharmacokinetics. They originate from different pharmacologic classes and therefore have very different chemical structures as methadone is a Diphenylheptane while levorphanol is a dehydroxylated Phenanthrene of the morphinan type [72]. Despite these differences in their chemical structure, their in vivo activity is nearly identical. They are both potent agonists of the μ-opioid receptor, noncompetitive antagonists at the *N*-methyl-D-aspartate (NMDA) receptor, and both inhibit the reuptake of serotonin (5-HT) and norepinephrine (NE) [21, 73–75]. Levorphanol is a full agonist at the Kappa (κ) opioid receptor which also results in analgesic activity primarily at the $Kappa_3$ receptor for which it has high affinity. NMDA receptors are upregulated in many severe chronic pain conditions and activated NMDA receptors can result in allodynia, hyperalgesia, and potential neuroplasticity [76, 77]. Antagonizing NMDA receptors can potentially reverse neuronal hyperexcitability and developed opioid tolerance [72, 77–80]. The NMDA antagonism in particular makes these agents unique and extremely useful in severe chronic pain conditions where other analgesics fail and potentially explains their increased potency compared to morphine [76, 80]. Methadone's potency compared to morphine increases at higher doses, for example, studies show that methadone is four times as potent as morphine at doses less than 90 mg per day but increases to 8 or 12 times as potent compared to morphine at higher doses [81]. Levorphanol is roughly four to eight times more potent than morphine but little information is available on equianalgesic dosing compared to morphine at higher doses [21, 82].

Methadone and levorphanol have been approved for use since the early 1950s but their use has never been widespread particularly compared to other opioids a result of their complex pharmacokinetics. Table 12.3 compares characteristics of methadone and levorphanol relevant to clinical practice. The half-lives of both methadone (15–59 h) and levorphanol (11–16 h) are longer than their duration of analgesia resulting in accumulation that can lead to delayed onset of serious adverse events (i.e., respiratory depression) particularly when combined with breakthrough pain medication or rapid dose increases. A cautious approach to dose increases is therefore required when considering dose increases to maintain safety, and should be delayed until after each drug achieves steady-state concentrations which for levorphanol is 4 days (80 h) and for methadone is 7–10 days (150 h). Clinically, the lack of familiarity with titration and equivalent dosing strategies are the most common reasons these agents are avoided. As a result, pain management guidelines recommend methadone be reserved for practitioners intimately familiar with its unique pharmacokinetics [2–7].

Clinical Pearl: "As needed" dosing of methadone or levorphanol are not appropriate because of the long half-life and their reliance on accumulation for maximum effect.

Methadone has serious risks associated with therapy beyond drug accumulation, and cautious dose adjustments are not sufficient to mitigate these risks. Methadone is a high risk of drug interactions because it undergoes 3A4, 2B6 (and other isoenzyme) extensive cytochrome P450 (CYP450) and P-gp metabolism that can decrease

Table 12.3 Comparison of methadone and levorphanol

	Levorphanol	Methadone
Pharmacology		
Opioid chemistry[a]	Dehydroxylated phenanthrene	Diphenylheptane
Opioid agonist activity[b,c]	μ, κ3 ≫ κ2, κ1	μ
NE reuptake blockade	✓	✓
NMDA inhibition	✓	✓
Pharmacokinetics		
Volume of distribution (Vd)	10–13 L/kg	1–8 L/kg
Protein binding	40 %	90 %
Half-life[b,c]	11–16 h	15–60 h
Metabolic pathway[b,c]	Phase II glucuronidation to levorphanol-3-glucuronide	3A4, 2B6, 2C19 mediated N-demethylation to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP)
Elimination (primary)	Renal	Hepatic
Dosing		
PO equivalent dose to 30 mg/day of PO morphine[b,c]	4 mg	7.5 mg
Duration of action[b,c]	6–15 h	4–8 h

[a] http://paindr.com/wp-content/uploads/2012/05/Opioid-Chemistry-09-2011.pdf
[b] http://opioidcalculator.practicalpainmanagement.com
[c] http://paindr.com/wp-content/uploads/2012/05/Pharmacodynamic-and-Pharmacokinetic-Properties-of-Commonly-Prescribed-Opioids_Fudin-Perkins.pdf

serum concentrations subtherapeutic levels or increase to unsafe or dangerous levels [83, 84]. Methadone can prolong the QTc interval leading to life-threatening cardiac arrhythmias particularly if taking other proarrhythmic medications [83, 85]. Routine screening for drug interactions and monitoring with EKGs are therefore recommended. Levorphanol has no known cardiac toxicity and relatively low risk of drug interactions because it is not metabolized via CYP450 system but rather undergoes glucuronidation instead. Despite these advantages, levorphanol continues to be the "forgotten opioid" for most practitioners and lack of studies utilizing levorphanol explains why clinically methadone is normally used first line in the absence of contraindications even for practitioners familiar with levorphanol [82, 86].

In clinical practice, it is common for patients being treated for opioid dependence to report taking methadone or buprenorphine for pain rather than dependence. Since both of these medications are utilized for chronic pain and treatment of opioid dependence caution is warranted and a few additional questions need to be addressed. Methadone dosing regimens are the best indicator of treatment type, methadone maintenance programs dispense a large daily dose (80–120 mg) once daily and patients usually must show up each day to receive it whereas methadone utilized for

pain is prescribed three or more times daily at much lower doses in most cases. Twice daily dosing for methadone in hepatic dysfunction or the elderly is routine. For buprenorphine, the dosage form prescribed is the best indicator of treatment, for example, sublingual buprenorphine (Suboxone, Subutex) is only FDA approved in the United States for the treatment of opioid dependence and not utilized for pain. SL buprenorphine was utilized in Europe for chronic pain before being used for opioid dependence, but in the United States this would be off-label and rare. The only available FDA-approved buprenorphine product for chronic pain is the buprenorphine transdermal patch (Butrans®).

Clinical Pearl: Methadone or buprenorphine dispensed for opioid dependence at maintenance facilities may not show up when checking a State Prescription Drug Monitoring Program because they are not considered pharmacies and have different reporting requirements.

Tapentadol (Nucynta®) and Tramadol (Ultram®)

Tapentadol (Nucynta®) and tramadol (Ultram®) are unique opioids that combine weaker μ-opioid agonist effects with neuroamine reuptake for increased synergy. While tapentadol is a relatively new drug with approval in 2009 (IR) and 2011 (ER), tramadol has been on the market since 1995. Both of these agents are a result of research efforts in the 1990s on the effects of centrally mediated monoaminergic transmission on descending pain inhibitory pathways [72, 73, 87, 88]. Norepinephrine (NE) was found to be the monoamine primarily responsible for attenuating pain signals and particularly useful in neuropathic pain [89, 90]. Clinically, it seems combining an opioid agonist with a NE reuptake inhibitor has an opioid-sparing effect that should increase pain relief and minimize side effects [73, 87, 91, 92]. *As of this writing, tapentadol is the only opioid currently FDA approved for use in patients with neuropathic pain* [93].

While both tramadol and tapentadol have similar pharmacology and were created with similar intent, they are profoundly different agents. In reality, tapentadol was intentionally designed to overcome tramadol's barriers to efficacy [87]. Tapentadol has 18 times less affinity for the μ-opioid receptor (MOR) than morphine compared to tramadol that has 6000 times less affinity for the same receptor [87]. Tramadol is essentially a prodrug because its analgesic effects are highly dependent on metabolic activation to its major active metabolite, *O*-desmethyl-tramadol (M-1), which has 200 times greater affinity for MOR and produces six times more analgesic effects than tramadol itself [94–96] For these reasons, tramadol is recommended for moderate pain and is slightly more potent than codeine (Table 12.4).

Racemic tramadol is nonselective and possesses both NE and 5-HT reuptake inhibition in relatively equal amounts which increases the potential risk of serotonin syndrome when combined with other serotonergic agents (i.e., antidepressants, triptans, etc.) and may therefore limit its utility [97–99]. In contrast, tapentadol is highly selective for NE with an affinity and potency compared to venlafaxine that increases clinical utility and decreases risk [87]. Tapentadol's combined synergy

Table 12.4 Tapentadol and tramadol differences compared

Properties	Tramadol	Tapentadol
Mu binding $^{\text{Affinity}}$	6000× less than morphine	18× less than morphine
Metabolism	Significant CYP ^{450}	Conjugation, O-glucuronide
Risk of drug interactions	High	Low
Neuroamine activity	5-HT/NE	NE, almost no 5-HT

results in functional analgesia of only two to three times less potency compared to morphine and in clinical trials tapentadol 100 mg was equivalent to oxycodone 20 mg. There are also key differences in metabolism of tramadol and tapentadol that may influence treatment. Tapentadol is metabolized primarily through glucuronidation with low risk of drug interactions and only 13 % entering the CYP 450 system which is not considered clinically relevant [100]. Tramadol is metabolized by the CYP450 system to a significant extent and requires metabolic activation via 2D6 into its active metabolite M-1. Unfortunately, CYP2D6 is highly polymorphic and 5–15 % of Caucasians lack a functioning enzyme and concurrent drug therapy with agents that inhibit 2D6 can prevent tramadol from converting into its active form and from receiving the intended analgesic benefits [98, 99].

Tapentadol's dual mechanism of action has several clinical advantages over traditional opioids. Tapentadol shows delayed development of tolerance compared to morphine (tolerance developed to morphine 2.5 times faster than tapentadol) [87]. Furthermore, although tapentadol has similar CNS side effects (somnolence, dizziness, headache) to typical opioids, it has roughly 50 % fewer gastrointestinal (GI) side effects (nausea, vomiting, constipation). This effect is particularly helpful to patient populations sensitive to adverse GI effects of opioid therapy, especially the elderly [101]. Tapentadol and tramadol are unique agents that are often best used clinically for mixed or complex pain complaints with both musculoskeletal and neuropathic pain to take advantage of their unique mechanisms.

Pharmacogenetics

Pharmacogenetics is truly individualized medicine where specific genetic markers hold the key to success or failure and should therefore guide drug selection for critical therapies [102, 103]. The impact of advances in pharmacogenetics for cancer and HIV diseases are transforming treatment and extending into many other areas of clinical practice. Pharmacogenetic testing can be classified into two major types, genotyping and metabolic mapping. Genotyping identifies the genetic expression of specific genes that predict clinical response and may guide effective treatment or serve as a red flag to life-threatening adverse effects [104–109]. Metabolic mapping provides crucial information on how individuals metabolize drugs differently based upon the expression of certain genes. This may enable prediction of drug response and have a potential role in dose adjustment [55, 110, 111]. Metabolic mapping has identified deficiencies in CYP 2D6 that is highly polymorphic and can substantially

impact drug therapy. These polymorphisms can be broadly defined into Extensive Metabolizer (EM), Poor Metabolizer (PM), and Ultra metabolizer (UM). EM is considered normal metabolism while PM indicates a deficiency or nonworking enzyme that may lead to accumulation and/or decreased requirement for medication. UM indicates accelerated metabolism and potentially a higher requirement of medication for adequate response [55]. CYP 2D6 is a minor metabolic pathway for oxycodone and hydrocodone and major pathway for codeine and tramadol which rely upon 2D6 for metabolic activation into their active forms. Oxycodone and hydrocodone each have active metabolites converted utilizing CYP 2D6 but are not considered clinically relevant as this compromises less than 10 % of administered dose [112]. Tramadol and codeine, however, have the potential for profoundly different results with expression of CYP 2D6 variants [113–115]. UM convert codeine into morphine and tramadol into its M-1 metabolite at much higher concentrations than the general population and has been associated with a higher risk of infant and child overdose with codeine in particular. On the other hand, when PM receive codeine or tramadol it may never be converted into its active metabolite and therefore may result in very poor analgesia. Similar to genetic influences, drug interactions may also play a role when inducers or inhibitors of CYP 2D6 are used concomitantly with these opioids. Codeine and tramadol in particular then will have enormous variability between individual patients depending on their genetics and other medications. One of the most appealing aspects of metabolic mapping is that identification of affected pathways becomes a permanent part of their genetic profile in their medical record.

Genotyping has yet to yield results relevant to clinical practice but research over the past two decades has identified at least 299 pain-relevant genes [116, 117]. Specific gene variants of OPRM1 (μ-opioid receptor), COMT (regulates neurotransmitters and expression of μ-opioid receptors), and MC1R (modulation of descending pathways in gray matter) are a few among many that have shown promise for predicting response to opioid therapy [116, 118]. Each variant by itself has a small to moderate effect size and nearly everyone expresses at least one functional variant making clinical response difficult to predict at best. The most profound results have been combinations of known genetic variants or expression of extremely rare variants with loss-of-function or dramatically increased activity [116, 118, 119]. Pain genotyping is now considered a multigenetic model with the majority of individual genes having mild to moderate effects. In short, while genotyping now predicts drug response in the treatment of cancer and HIV, similar success in the field of pain management has been elusive and will require significant advances in research before this becomes clinically relevant.

Conclusion

The importance of specialty physicians and other appropriate specialty clinicians in pain management cannot be overstated. Referring providers rely on specialists for assessment, diagnosis, pathology of pain, and treatment recommendations.

Specialists providing pain management services requiring opioid therapy should adhere to universal precautions to appropriately assess, monitor, and mitigate risk. Drug selection should be guided by knowledge of unique characteristics of each opioid including pharmacokinetics, pharmacodynamics, and pharmacogenetics likely to influence efficacy and safety. Emerging evidence on opioid adverse effects should be considered in perspective with previous medial history and balanced with potential benefits to provide individualized care.

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Hormonal Therapy for Pelvic Pain

13

Alexandra King and Sonia Bahlani

Introduction

There are multiple pathophysiological pathways involved in chronic pelvic pain (CPP). One such mechanism involves the role of sex steroid hormones (androgens, estrogens, and progestins) in the structure and function of genital tissues. Despite the high prevalence of CPP, there are very few comprehensive guidelines examining hormonal therapy for management of these patients. Currently, there is no consensus regarding measurement of hormones during evaluation and treatment of CPP. It is, however, important to understand how types of hormonal therapy can be used in management of pelvic pain. This chapter provides an overview of various causes of pelvic pain in which incorporating hormonal therapy can be effective.

Genitourinary Syndrome of Menopause (Atrophic Vaginitis)

An estimated 10–40 % of postmenopausal women have symptoms related to vulvovaginal atrophy [1]. Unlike vasomotor symptoms that typically accompany menopause, these symptoms are generally progressive and are unlikely to spontaneously resolve [2]. Despite this high prevalence, vulvovaginal atrophy is an underreported and underdiagnosed condition; only 20–25 % of affected women seek medical treatment for relief of their symptoms, leaving a large population of women suffering without treatment [3].

During reproductive age, serum estradiol levels typically range from 30 to 40 pg/mL in the early follicular phase to more than 200 pg/mL during ovulation. In menopause, these levels fall to less than 20 pg/mL [4]. Estrogen receptors A and B are expressed throughout the female urogenital system, including the squamous epithelium,

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connective tissue, and smooth muscle of the vulva, vagina, urethra, and bladder trigone. As such, these tissues are dependent upon estrogen support for facilitation of numerous biochemical and physiologic functions [3, 4]. Loss of this estrogen stimulation causes profound changes in the vulvovaginal and urogenital mucosa. The vaginal epithelium becomes thin and pale with fewer rugae and an accompanying progressive loss of vascularity in the vaginal mucosa. Pubic hair grays and becomes sparse, subcutaneous fat in the mons pubis and labia majora decreases, and the introitus becomes pale, shiny, and dry with signs of inflammation such as patchy erythema and increased friability. In the dermal layer, collagen fibers swell, fuse, and undergo hyalinization while elastic fibers fragment. This causes the vagina to lose elasticity and distensibility with secondary shortening and narrowing of shape [2, 4]. Loss of vascularity leads to vaginal dryness, as the vagina relies principally upon transudate from surrounding vessels to produce secretions [4]. Cytologic examination of the vaginal mucosa in menopausal women shows shifts in the vaginal maturation index (VMI) with a decrease in the proportion of superficial cells and an increase in the proportion of parabasal cells [3].

Diminished estrogen levels are also associated with decreases in the population of lactobacilli, shifting vaginal pH toward a neural or alkaline environment; this change in colonization increases the likelihood of vaginal discharge, odor, and infection [3, 4]. The urethra, bladder, and pelvic floor musculature are also affected by estrogen loss. Urinary complaints from genital atrophy include urethral discomfort during voiding, dysuria, urinary frequency, hematuria, urge incontinence, and increased risk of prolapse due to weakness in the urogenital diaphragm [4, 5]. Thus, patients with atrophic vaginitis present with a constellation of symptoms that greatly affect their quality of life, including dryness, irritation, discomfort, itching, discharge, dyspareunia, post-coital pain and spotting, urinary complaints, with increased susceptibility to infection and secondary inflammation [3–6].

Treatment of vulvovaginal atrophy focuses on symptomatic relief as well as reversal of atrophic anatomic changes that have resulted from decreased estrogen levels. Estrogen therapy, either systemic or locally administered, is the current standard of care [3]. For women with isolated vulvovaginal symptoms, local vaginal therapy is the treatment of choice and should be used in the lowest effective dose for the shortest duration consistent with treatment goals and risks for individual women [5, 6].

The primary impact of vaginal estrogen is its local effect on the vulvovaginal and urogenital mucosa [4]. Administration of exogenous estrogen has been shown to restore normal vaginal pH levels, as well as to thicken and revascularize the epithelium and increase lubrication. Positive effects on VMI are also seen through an increased number of superficial cells and decreased parabasal cell frequency. Existing subjective symptoms of atrophy including dryness, irritation, pruritis, urinary frequency, and dyspareunia are also alleviated [2, 3].

Local administration of estrogen allows for avoidance of systemic side effects secondary to low dosage requirements in addition to bypass of the first pass effect of the GI system. In fact, the increased risk of VTE seen with oral estrogen therapy has not been found with these lower doses of local estrogen [3]. Oral estrogen therapy is often supplemented with progesterone therapy to prevent endometrial hyperplasia and cancer. This adverse effect is a concern in patients who have not had a hysterectomy. However, a recent Cochrane review found no significant differences

in endometrial hyperplasia or incidence of proliferative endometrium when vaginal estrogen therapy was compared to placebo [7]. Additionally, current recommendations state that it is unnecessary to prescribe a progestin in combination with low dose vaginal estrogen to prevent endometrial hyperplasia, and furthermore that endometrial surveillance is not recommended in asymptomatic low risk women [3, 4]. Results of a WHI study showed no increased risk of breast cancer in women receiving oral estrogen monotherapy; there is currently lack of evidence on the risk of breast cancer associated with vaginal estrogen therapy [2].

Vaginal estrogen therapy may offer better symptom relief than oral estrogen [3]. A meta-analysis of ten clinical trials showed that vaginal estrogen therapy provided the greatest symptom relief and improvement of vaginal/vulvar atrophy despite lower serum estradiol levels [2]. All local estrogen therapies have been shown to be equally effective for the relief of symptoms of vaginal atrophy and, specifically, dyspareunia in addition to acidification of vaginal pH and increased VMI in favor of mature squamous cells [6, 7]. Most women will experience relief of symptoms within the first few weeks of starting therapy, although complete renewal of genital tissue integrity and comfort may take up to 4–6 weeks [8]. Approximately 10–25 % of women on local estrogen therapy will continue to have symptoms and require additional therapy [4]. Local therapy is most commonly administered in the form of a cream, tablet, or intravaginal ring.

A. Estradiol (Estrace®) and Conjugated Estrogen (Premarin®) Creams

Estrace and premarin creams are the most common choice of vaginal product for the treatment of atrophic vaginitis. Estrace contains 0.01 % estradiol and is indicated for the localized treatment of vulval and vaginal atrophy. General dosage is 2–4 g daily for 1–2 weeks followed by a gradual taper to a maintenance dose of 1 g one to three times per week after restoration of the vaginal mucosa has been achieved. Studies have shown that even at low 10 μg dose, all patients responded symptomatically to treatment with estrace, with vaginal cytology and pH showing improvement and serum estradiol levels remaining in the postmenopausal range [9].

Premarin is a conjugated equine estrogen (CEE) cream (0.625 mg CEE/g) indicated for treatment of general symptoms of atrophic vaginitis in addition to the specific treatment of moderate to severe dyspareunia. General dosage is 0.5–2 g in a cyclic regimen, daily for 21 days then off for 7 days. It has been shown to be as effective as both the estradiol ring and tablet in decreasing symptoms of vulvovaginal atrophy [7]. Increased levels of serum estradiol have been reported with use of CEE when compared to other local estrogen therapy [3]. Adverse events such as endometrial proliferation, uterine bleeding, perineal pain, and breast pain and tenderness have been reported more often with the use of the CEE cream than with other therapy; however, these events have been relatively mild [2].

Creams may have an advantage over tablets or rings for some patients as they are soothing, can be directly applied to the vulval and vaginal area, and also providing flexibility in dosing and frequency of administration as required by the individual patient. They are also low in cost. On the other hand, compliance rates are often low

among these patients as many see the creams as messy, causing leakage and irritation, and also inconvenient, as the user must measure amount of cream used by themselves [6].

B. Estring/Femring

Estradiol rings have also been found effective in relieving signs and symptoms of vulvovaginal atrophy and improved dyspareunia in comparison to placebo [3, 10]. The Estring contains 2 mg of estradiol, which is released at a steady rate of 7.5 μg every day for 90 days. Similarly, the Femring releases either 0.05 mg or 0.1 mg estradiol every day for 90 days. A burst release of the hormone is often obtained before the release is stabilized with maximal estradiol plasma concentrations obtained within the first 3 h after insertion [2]. In multiple studies the vaginal estradiol ring was as effective as the estradiol tablet in alleviating vaginal symptoms of estrogen deficiency while maintaining low systemic absorption, with serum estradiol levels between 21 and 28 pg/mL [11].

Vaginal estradiol rings have been associated with very few side effects. In a 12-week study comparing the vaginal estradiol ring with CEE cream, 6 % of women using the ring and 8 % of women using the cream reported mild vaginal bleeding with no reports of endometrial hyperplasia in either group [12]. Studies in elderly women have also shown increases in bone density and beneficial effects on user's lipid profiles showing decreases in total cholesterol and LDL as well as increases in HDL with use of Estring [13, 14]. Vaginal estradiol rings are generally easy to use and convenient for patients due to their 3-month efficacy and reliability with lack of discharge and other adverse effects. Disadvantages may include difficulty in ring insertion, displacement of the ring, and potential complaints from partners who may feel the ring during coitus.

C. Estradiol Vaginal Tablet (Vagifem®)

Vagifem is an estradiol tablet for intravaginal insertion that is generally inserted with an applicator daily for 2 weeks followed by twice weekly for therapeutic maintenance. It comes in two doses, 10 and 25 μg. Trials have shown vagifem to be effective in relieving patient symptoms of dryness, irritation, itching, and dyspareunia with statistically significant changes in VMI while maintaining low systemic absorption [3]. In a 12-week placebo-controlled trial, vagifem showed improvement in symptoms at week 2 and maintained through week 12 [15]. An additional study established noninferiority of vagifem compared to CEE cream and found patients to prefer the tablet over the cream due to ease of use [16]. Recently, a 12-week randomized, double-blind, placebo-controlled study demonstrated efficacy of both 25 and 10 μg vaginal tablets in the relief of vaginal symptoms and urogenital atrophy, including VMI and vaginal pH. While improvements were greater with 25 μg than with 10 μg estradiol tablet, both doses were shown to be effective in treatment of atrophic vaginitis [5].

Adverse effects seen with use of vagifem are mild but include breast pain, vulval and vaginal itching, vaginal discharge, and skin rash. Additionally, the tablet can be

prematurely expelled if not inserted high enough into the vaginal vault or in patients with prolapse [3]. Advantages of vagifem include its ease of use with a biodegradable applicator, no need for daily treatment, and lack of association with vaginal leakage [6].

D. Testosterone Cream

Testosterone cream has been used experimentally in the treatment of vaginal atrophy in patients on aromatase inhibitors for breast cancer treatment, as controversy has long existed on vaginal estrogen interference with aromatase inhibitor efficacy. A 4-week pilot trial of 20 postmenopausal women with breast cancer found that vaginal testosterone (150 and 300 μg) improved dyspareunia, vaginal dryness, and VMI without increasing estradiol levels [17]. This is insufficient to recommend the use of vaginal testosterone for atrophic vaginitis at this time; however, further studies are warranted [18].

E. New Therapies

Estrogen agonists and antagonists are a potential therapeutic alternative to current therapy as nonsteroidal compounds with estrogen-like activity in some tissues and anti-estrogen activities in others [3]. Lasfoxifene and ospemifene in particular have shown a positive impact on vaginal tissue in postmenopausal women [19]. Intravaginal administration of dehydroepiandrosterone (DHEA) is also emerging as a new therapeutic option that permits the biosynthesis of androgens and estrogens only in specific targeted tissues that contain the required enzymes, such as tissues in the vagina [20].

Endometriosis

Endometriosis is a major contributor to pelvic pain. It is characterized by the presence of endometrial-like tissue outside the uterus, primarily on the pelvic peritoneum, ovaries, and rectovaginal septum, and in rare cases on the diaphragm, pleura, and pericardium. Endometriosis affects 6–10 % of women of reproductive age and 50–60 % of women with pelvic pain [21]. A unifying theory regarding the pathogenesis of endometriosis has remained elusive; however, it is currently believed that this etiology is multifactorial, involving retrograde menstruation, progesterone resistance, immune dysfunction, and a proinflammatory environment with a dysfunctional peritoneum.

According to this theory, eutopic endometrium is sloughed via patient fallopian tubes into the peritoneal cavity during menstruation. These tissues and cells attach to peritoneal surfaces, establish a blood supply, and invade nearby structures, aided by the expression of extracellular adhesion molecules and upregulation of anti-apoptotic factors such as BCL-2 [22]. They are then infiltrated by sensory, sympathetic, and parasympathetic nerves and elicit an inflammatory response. These implants secrete estradiol as well as PGE2, which activates aromatase to further

increase estrogen levels and attract macrophages and other inflammatory cells, ultimately effecting the secretion of pro-angiogenic and pro-inflammatory factors such as VEGF, IL-8, IL-1B, and TNF-a. This inflammatory response leads to angiogenesis, adhesions, fibrosis, and scarring, which can lead to the clinical syndrome of pain and infertility [21, 22]. However, not all women with retrograde menstruation have endometriosis. Normally, refluxed endometrial tissue is cleared by the immune system; dysregulation of this mechanism has been implicated in the predisposition to implantation and growth of endometrial cells. This theory is supported by the high concordance found with other autoimmune diseases such as lupus and rheumatoid arthritis in these patients [22].

Additionally, endometrial progesterone resistance characterized by alterations in progesterone responsive gene and protein expression is now considered a central element in disease pathophysiology. Chronic inflammation may play a role in epigenetic modifications that promote the development and progression of endometriosis [23]. Eutopic and ectopic endometrial progesterone resistance enhances survival and implantation of refluxed endometrium by preventing a complete transition of endometrium from proliferative to secretory phase [22] and promotes further inflammation via failure of progesterone-mediated NFKB suppression. This allows continuous expression of pro-inflammatory cytokines in endometrial tissue [23]. Overall, it is clear that the pathophysiology of endometriosis is multifactorial, with genetic, anatomical, endocrine, immunological, and possible environmental factors all influencing the risk of endometriosis development.

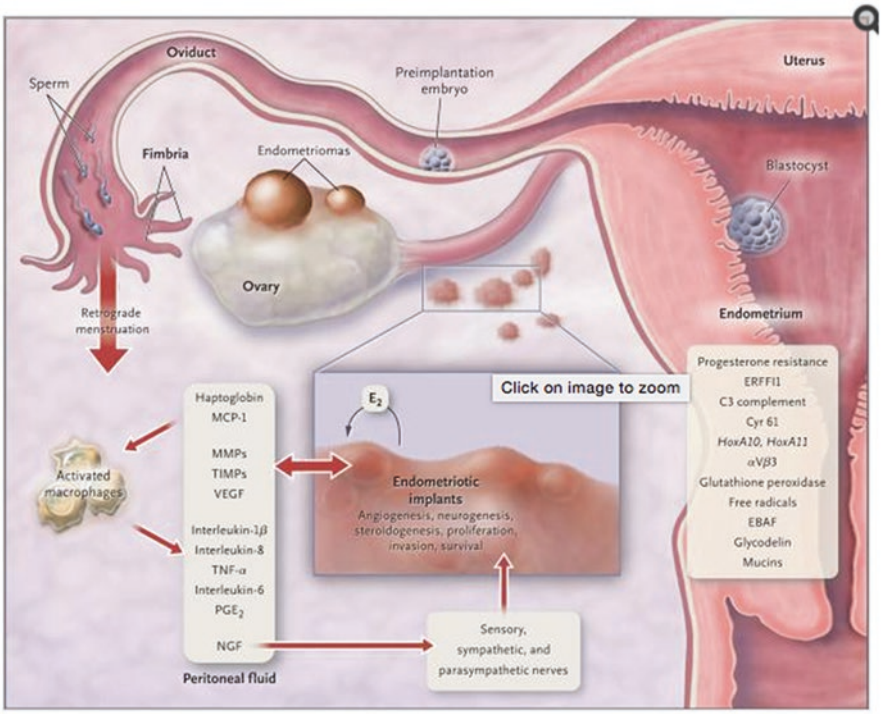

Diagram of pathogenesis of endometriosis from Giudice [21].

The most common symptom found in women with endometriosis is pelvic pain associated with progressive dysmenorrhea (50–90 %), which is often accompanied by dyspareunia, dyschezia, and/or dysuria. Pain generally begins before menses and continues throughout the duration of menstrual flow, but pain can also be intermittent or continuous throughout the menstrual cycle in some cases [24]. Many women also have referred flank or low back pain. Additionally, endometriosis is one of the most common causes of infertility, with monthly fecundity rates at 0.02–0.10. These fertility problems are likely due to mechanical interference with sperm-egg union or zygote transport as a result of pelvic adhesions and disruption of normal anatomy, but also likely to an endometrial environment hostile to implantation secondary to progesterone resistance [21, 25].

Long-term treatment of patients with endometriosis involves medical therapy and surgical therapy. In most cases, pain recurs 6–12 months after treatment [21]. Surgical intervention can be used as first-line therapy or initiated after failed medical therapies [26]. It generally involves excision, fulguration, or laser ablation of endometriotic implants. Laparascopic ablation of endometriotic implants has been shown to be 65 % effective in reducing pain, as compared with a 22 % rate of pain reduction associated with diagnostic laparascopy alone [27]. Adjunctive medical therapy post surgery with a GnRH agonist, danazol, or combined oral contraceptive (OCP) compared with no postoperative treatment has revealed a significant reduction in pain scores at the conclusion of therapy [28]. First-line medical therapy involves NSAIDs for dysmenorrhea relief in combination with combined OCPs in the absence of contraindication to the use of OCPs. If pain persists, continuous OCP use or installation of a levenorgesterol intrauterine system is indicated. If this is not effective, GnRH agonist therapy with estrogen and progestin add back therapy can be considered as well as surgical intervention for persistent pain [21]. The major goal of the current medical therapy is to create an acyclic hypoestrogenic environment through blockade of ovarian estrogen secretion, creation of a pseudopregnancy, or local inhibition of estrogenic stimulation of the ectopic endometrium [29].

A. Estrogen-Progestin Contraceptive

Combined OCPs are now considered first-line therapy for patients with endometriosis except when contraindicated in smokers greater than 35 years of age due to increased risk of MI, stroke, and VTE [21]. The use of cyclic OCPs has recently been advocated as practical and inexpensive long-term treatment for chronic endometriosis either as a strategy to avoid surgery or as postoperative adjuvant therapy to prolong the symptom-free interval [30]. Long-term regimens of OCPs have been shown to reduce the frequency and severity of recurrent dysmenorrhea, as well as anatomic relapse of endometriosis postoperatively [31].

Combined OCPs inhibit gonadal estrogen production via negative hypophyseal feedback. This suppression of ovarian activity may also reduce prostaglandin production, thus decreasing inflammatory status [30]. A recent randomized controlled trial showed superiority of OCPs over placebo in decreasing baseline pain scores ($p<0.001$) and volume of ovarian endometriomas ($p=0.04$) [32]. Additionally,

other studies have shown OCPs to promote statistically significant improvement in dysmenorrhea, non-menstrual pelvic pain, and size of endometriomas when compared to controls [33]. When compared to leuprolide acetate, a GnRH agonist, in a 48-week randomized, double-blind, controlled trial, reduction of pain from baseline was equal between the two treatment groups, with a significant reduction in financial burden over the year for users prescribed OCPs [34].

In women with severe dysmenorrhea, a switch to continuous from cyclic OCP use has reduced pain scores by 58 % within 6 months and 75 % after 2 years [35]. Continuous use also has potential to reduce dysmenorrhea and reseeding of endometriosis, making it an ideal candidate for long-term therapy [34]. Side effects of OCP use are generally mild, but can include nausea, weight gain, fluid retention, depression, breakthrough bleeding, breast tenderness, headache, and decreased menstrual flow. Continuous OCP therapy is associated with amenorrhea [21]. Alternative routes of administration such as the contraceptive ring or patch should also be considered in this patient population, as they provide constant plasma drug levels while avoiding first pass metabolism and have shown higher rates of compliance due to ease of use [30].

B. Progesterone-Based Therapy

a. Progestin

Progesterone has an anti-mitotic effect on endometrial cells and has been shown to suppress inflammation of the endometrium in vitro, making it a natural candidate to treat endometriosis [30]. Dienogest, a synthetic selective progestin with the absence of androgenic activity at a dosage of 2 mg daily, has been shown to reduce endometriotic lesions through a number of biological mechanisms. Dienogest induces a hypoestrogenic, hypergestagenic local endocrine environment that allows decidualization of endometrial tissue followed by atrophy of endometriotic lesions. It may also reduce plasma estradiol levels directly through apoptosis of granulosa cells in the ovary [36]. It may also inhibit angiogenesis, an essential stage in the development of endometriotic lesions [37].

Dienogest at a dose of 2 mg daily for 12 weeks was shown to be significantly more effective than placebo [29]. Studies of dienogest in Germany, Japan, and Argentina all showed sustained decrease in endometriosis-associated pelvic pain, dyspareunia, and dysmenorrhea with a favorable safety profile [38–40]. In Japan, daily 1, 2, and 4 mg dienogest therapy for 24 weeks improved baseline symptomatology by 63.8, 66.7, and 73.2 %, respectively [39]. Further studies have since concluded that dienogest treatment for up to 65 weeks is associated with symptom relief in endometriosis and this effect lasts for at least 24 weeks after the end of treatment, suggesting dienogest sustains improvement that exceeds the period of active treatment [41]. When compared to GnRH agonists such as leuprolide acetate, dienogest was found to be noninferior, with fewer hypoestrogenic side effects such as decreased bone mineral density (BMD) [42]. Serum estradiol levels of patients on dienogest were stable, in support of the estrogen threshold theory put forth by

Barbieri in 1992, which proposes that optimal endometriosis therapy provides a suppression of estrogen levels sufficient to inhibit endometrial stimulation but moderate enough to prevent hypoestrogenic adverse effects such as BMD [42]. Side effects of dienogest and other progestin treatments include weight gain, acne, breast tenderness, erratic bleeding, and headache [42, 43]. Additional reports of affected lipoprotein levels and hepatotoxicity have also been put forth with use of other synthetic progestins such as norethindrone acetate, but have not been found with dienogest use [29].

b. Medroxyprogesterone Acetate

Medroxyprogesterone acetate (MPA) is another synthetic progestin indicated for use in dysmenorrhea and noncyclic chronic pelvic pain [21]. It is available as a pill and as a depot injection once every 3 months. Similar to dienogest, MPA helps prevent the implantation and growth of the endometrium in retrograde menstruation in addition to its anti-inflammatory effects on the endometrium [44]. Studies have shown MPA to be as effective in controlling endometriosis-associated pelvic pain as OCPs [45]. Menstrual irregularity and bone loss with prolonged use due to creation of a hypoestrogenic state are common issues that have arisen with long-term use of MPA [44]. Other side effects include nausea, weight gain, fluid retention, breakthrough bleeding, depression, and amenorrhea. Additionally, delayed resumption of ovulation after depot MPA injections makes MPA use in women who may wish to conceive in the near future a relative contraindication [21].

c. Levonorgestrel Intrauterine System (Mirena®, Skyla®)

The levonorgestrel intrauterine system (LNG-IUS) provides an alternative route of delivering the progestogen levonorgestrel directly into the uterine cavity at a steady rate of 20 μg/day during a 5-year period. LNG-IUS affects the endometrium, where concentrations of levonorgestrel induce atrophy and pseudodecidualization of the endometrium. It also causes depletion of estrogen and progesterone receptors to anti-proliferative effects and increases expression of Fas, a pro-apoptotic molecule [43, 44]. While literature on use of LNG-IUS in endometriosis is relatively limited, recent studies have shown LNG-IUS to diminish endometriosis-associated pain and dysmenorrhea as compared with regular follow-up with no treatment or treatment with a GnRH agonist after conservative surgery [21].

In a study of LNG-IUS versus depot MPA, mean pain score was significantly reduced 3 months into therapy in both groups, and LNG-IUS use was associated with higher mean DEXA *t*-scores over the lumbar spine when compared with the depot MPA group [44]. When compared to leuprolide acetate, a GnRH agonist, improvement in pain was seen in months 1, 3, and 6 in both groups, but at 1 year, follow-up pain scores in the LNG-IUS group had returned to pretreatment levels while scores in the leuprolide acetate group remained significantly reduced, supporting noninferiority as short-term therapy with unclear long-term benefits [43]. Additional studies have also shown the greatest improvement in symptoms to occur in the first year of LNG-IUS therapy, with no significant changes occurring in the remaining 24 months of study [29].

However, other studies support long-term use of LNG-IUS, reporting follow-up periods of up to 3 years revealing a statistically significant reduction in dysmenorrhea scores with up to 87.5 % of patients reporting improvement in pain according to VAS [30]. Basu et al. cite high rates of anovulation in the first 3 months of LNG-IUS insertion as a possible explanation for good initial response in patients. Additionally, decreased endometrial load secondary to reduced menstruation may also explain relief in symptoms with LNG-IUS insertion [47]. A recent Cochrane review in 2013 cited studies showing significant reduction of painful periods in LNG-IUS treatment groups as compared to control and GnRH agonist groups in postoperative treatment. Overall, there is limited but consistent evidence that postoperative LNG-IUS use reduces the recurrence of painful periods in women with endometriosis but that further study is needed to confirm these findings [48]. Side effects associated with LNG-IUS are generally mild, but include bloating, weight gain, headache, breast tenderness, irregular vaginal bleeding in the first few months postinsertion, and abdominal pain [21, 43, 44]. Advantages of LNG-IUS use for the treatment of endometriosis include avoidance of repeat administrations, increased long-term compliance, few side effects, favorable safety profile, and cost effectiveness as compared to other treatments commonly used for long-term symptom control [44].

d. Etonogestrel Contraceptive Implant (Implanon®)

Implanon is a single rod etonogestrel-containing contraceptive implant that provides an alternative way of delivering progestogens. It is applied subdermally with contraceptive action achieved via inhibition of ovulation for at least 3 years and has been shown to improve dysmenorrhea [29]. In a pilot study comparing implanon to depot MPA injections, average decrease in pain was 68 % in the implanon group as opposed to 53 % in the depot MPA group [49]. Side effects reported were comparable in both groups and included weight gain, decreased libido, acne, hair loss, breast tenderness, headache, depression, and hot flashes. The main reason for dropout in the implanon group was spot bleeding episodes. However, implanon was not associated with any change in cholesterol, making it a good choice for patients with preexisting high BMI and impaired metabolic profiles [49].

C. GnRH Agonist

Treatment with GnRH agonists such as leuprolide acetate was the standard treatment for endometriosis in the 1990 s [48]. Unfortunately, its unfavorable side effect profile and need for “add-back” estrogen-progesterone therapy has led it to fall out of favor in recent years [43]. However, it is still an important component of endometriosis treatment, especially in patients refractory to OCPs or progestins. GnRH agonists deplete the pituitary of endogenous gonadotropins and inhibit further synthesis, thus interrupting the menstrual cycle and creating a hypoestrogenic state with endometrial atrophy and amenorrhea. The hypogonadotropic, hypogonadal state generated deprives existing endometriosis, while secondary amenorrhea prevents new seeding

of the peritoneum, relieving endometriosis-associated pain and decreasing the size of current endometriomas [30]. Improvement in pain scores for dysmenorrhea with the use of GnRH agonists is 60–100 %, similar to improvement found with the use of antiprogestins, danazol, and OCPs [50]. GnRH agonist use is associated with considerable side effects including bone loss, vasomotor symptoms, vaginal dryness, decreased libido, hot flashes, irritability, and worsening serum lipoprotein cholesterol distribution [21, 51]. In a study comparing GnRH agonist use to dienogest, patients on leuprolide acetate showed BMD of 1.070 at baseline and 1.014 after 6 months of treatment. Additionally, at baseline patients reported hot flashes 0.78 days per week, increased to 4.70 days per week after 6 months of treatment [51].

As such, treatment with GnRH agonists is limited to 6 months in the absence of estrogen-progestin (norethindrone acetate) add back therapy, which allows treatment to be prolonged for up to 2 years [51]. In support of the estrogen threshold theory, maintaining estradiol between 30 and 45 pg/mL will maintain bone mineral density without stimulating disease, as concentrations of estradiol over 50 pg/mL are needed to support the growth of endometriotic lesions. However, even with sufficient add back therapy, careful consideration should be taken in the use of GnRH agonists in younger women who have not yet reached maximum bone density [52].

D. Aromatase Inhibitor

A novel therapeutic option for the treatment of endometriosis is aromatase inhibitors such as anastrozole and letrozole. Endometriotic lesions express aromatase and synthesize their own estradiol; prevention of this synthesis via aromatase inhibitor has been shown effective in reducing pelvic pain, with effects similar to other hormonal therapies [21, 30]. Pain reduction has been reported in human trials with a clear effect on dysmenorrhea and dyspareunia in addition to physical and social functioning. Side effects reported include irregular bleeding, weight gain, and joint pain [53, 54]

E. Danazol

Danazol is a synthetic androgen with mild androgenic but strong anti-estrogenic activity that induces the inhibition of gonadotropin release, determines the competitive inhibition of steroidogenic enzymes, modulates immunologic functions, and suppresses cell proliferation [30]. It has been shown to have effects equivalent to GnRH agonists in the reduction of pain after surgical treatment and was a standard of therapy for endometriosis in the 1980s [33, 48]. Danazol use is characterized by adverse changes in lipid metabolism and androgenic adverse effects, including weight gain, edema, acne, hirsutism, vaginal atrophy, and oily skin, which lead to low compliance with therapy [51]. Recent associations of danazol with a 3.2-fold increased risk of ovarian cancer have made it an unpopular treatment choice among physicians [55].

Vulvodynia

Vulvodynia is a common multifactorial, heterogenous, and chronic gynecological disorder with an estimated prevalence of up to 16%. Women with vulvodynia experience severe physical pain resulting in psychological distress, sexual dysfunction, and significant reduction in quality of life [56]. Affected individuals generally have proinflammatory cell migration to the vulva and/or vestibule, local production and release of proinflammatory pain inducing substances, hyperinnervation of C-fibers, central sensitization with lowered thresholds, anatomic dysfunction, sexual dysfunction, and hypercontractibility of the pelvic floor causing myofascial pain. Pelvic floor dysfunction is likely secondary to chronic inflammation of the mucosa and thus reactive in nature [57].

There are two major categories of vulvodynia: provoked and generalized. Localized provoked vulvodynia (LPV) presents as a characteristic pattern of mechanical allodynia localized to a specific area such as the vulvar vestibule (vestibulodynia), whereas generalized vulvodynia (GVD) shows a more diffuse pain pattern involving part or all of the pudendal nerve distribution [57].

Vulvodynia can be primary, defined as dyspareunia from the first attempt of sexual intercourse, or secondary, in which dyspareunia appears after a period of pain-free sexual intercourse [57]. The vulva is innervated by the pudendal nerve (S2, S3, S4), genitofemoral nerve, ilioinguinal nerve, and iliohypogastric nerve. Patients most commonly complain of discomfort at the separation of the labia minora, dyspareunia at the vestibular introitus, and tenderness at the orifices of vaginal glands and/or pain surrounding the entire vulva and vestibule [56]. The health care cost in regards to management of vulvodynia in the USA is estimated to be between 31 and 72 billion per year. Unfortunately, there remains a relative paucity of research despite this large impact on women and society, and the etiology of vulvodynia remains elusive [58]. Possible etiologies are manifold:

1. Embryologic developmental defect in the primitive urogenital sinus

Patients with vulvodynia commonly have comorbidities such as IBS, fibromyalgia, and IC/BPS, all with the shared embryologic origin of the urogenital sinus that may represent a unifying mechanism for pain these patients experience [57, 58].

2. Dysfunctional immune response to infection

An inability to clear infections such as vulvovaginal candidiasis and the subsequent inflammation produced has been proposed to lead to the development of this condition [57]. However, fluconazole has been shown to not resolve patient's symptoms, making this theory unlikely [58, 59].

3. Neurological disease with neuropathic pain

Neuropathic or neurogenic mechanisms include neural hyperplasia, inflammation, central or peripheral nociceptive dysfunction, and abnormal secretion of

neurotransmitters and/or neuropeptides and other inflammatory mediators. Central anatomical and biochemical modifications can occur after peripheral nerve damage, including sensitization, spinal and supraspinal reorganization, and alterations in inhibitory pathways. GABA and glutamate are key neurotransmitters involved in neuropathic pain pathways; glutamate released by C fibers leads to an increased response of dorsal horn neurons [56].

Pain can result from peripheral sensitization in the skin, central sensitization in the spinal cord, or, most likely, both. Cascades of inflammatory cytokines can sensitize nociceptors and induce nerve growth factors resulting in hyperinnervation and prolonged activation of nerve fibers that may produce chronic release of neuroactive substances. This perpetuates a cycle that results in central sensitization, an increase in the excitability of neurons within the CNS, such that normal input produces an abnormal response. Central sensitization allows perpetuation of symptoms after the triggering factors are resolved [56]. Chronic inflammation therefore results in proliferation of C-fibers with altered receptor expression and decreased sensory threshold, resulting in allodynia and hyperalgesia that activates inflammatory cells to release more pro-inflammatory factors, perpetuating the cycle [60].

4. Trauma, musculoskeletal disease
5. Hormonal deficiency

The focus of this section on vulvodynia will be in regards to possible alterations in hormonal milieu, specifically resulting from hormonal birth control [58]. Some of the symptoms of genital estrogen deficiency atrophy such as sensitivity to touch in the vulvar area and complaints of burning and itching sensation associated with touch, are common in patients with vulvodynia as well as in postmenopausal women [61]. Additionally, vestibular biopsy specimens from 30 women with vulvodynia who had been symptomatic for at least 6 months showed a significant decrease in estrogen receptor expression: 50 % of sample tissue exhibited no receptor expression compared with only 17 % of samples from the healthy, premenopausal control group [62].

In a Canadian study of OCP use, relative risk for vestibulodynia, a vulvodynia subtype, in women who have begun to use OCPs early in life (≤17 years old) was higher than in those who had never used OCPs. In an interview of 138 women with vestibulodynia compared to 309 age matched controls, only 4 % of women with vestibulodynia had never used OCPs compared with 17 % of controls. Relative risk of vestibulodynia was 6.6 for ever users compared with never users, and this risk increased with OCP use up to 2–4 years [61]. Additional studies have suggested that first use of OCPs at a young age is strongly related to the development of vestibulodynia (RR: 9.3). The strength of this relation may vary according to the hormonal composition of OCPs [63]. A chart review of 50 premenopausal women presenting with vestibulodynia while on OCPs showed that upon cessation of OCP use and subsequent topical estrogen cream treatment, vestibular pain scores decreased significantly from 7.5 to 2, further supporting the presence of hormonal influence on vestibulodynia [64].

Multiple mechanisms have been proposed to explain the potential relationship between OCP use and development of vulvodynia. One proposed mechanism is that the decreased content of estrogen and relatively stable contents of progesterone in OCPs may cause significant structural changes in the vagina in response to sex steroid hormone deprivation and replacement, which may be associated with vaginal mucosal changes that lead to vulvodynia [61]. It is also possible that via OCP inhibition of LH, decreased testosterone and increased sex hormone binding globulin (SHBG) levels may induce changes in hormone receptors as well as alter the morphological pattern in the vulvar and vestibular mucosa. OCPs have also been shown to lower the pain threshold of the vulvar vestibule [64]. Panzer et al. have suggested that prolonged exposure to synthetic estrogens in OCPs can induce gene imprinting and increased gene expression resulting in biochemical and morphological changes in the mucosa that increase vulnerability to external exposures or irritants that ultimately cause an increased local inflammatory response, pain at touch, and dyspareunia [63, 65].

Proposed treatment involves replacement of estrogen; treatment with local application of estrogen cream has been reported beneficial for some women with vulvodynia [61]. In a study of 50 premenopausal women using OCPs with secondary vulvodynia, improvement in posttreatment pain scores was found following discontinuation of OCPs and local application of topical estradiol and testosterone twice daily for an average duration of 20 weeks [58]. Ultimately, however, management of vulvodynia must be multifactorial to reflect the many components of this complex illness. Treatment requires attention to each factor including pelvic floor dysfunction, neuropathic pain, hormonal abnormalities, and psychological factors as well as background abnormalities such as overwashing and irritating topical agents [59].

Conclusions

The use of hormonal therapy as part of the armamentarium in the clinical management of chronic pelvic pain can be extremely beneficial. It is important to address hormonal components of pelvic pain. Utilization of such therapies is part and parcel of treatment of chronic pelvic pain syndromes.

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Non-surgical Management of Vulvar Pain

14

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Definition

At the Fourth International Consensus of Sexual Medicine (ICSM) in 2015, experts representing the several international societies dedicated to the study of vulvar and sexual pain established revised nomenclature for these conditions, based upon current research and clinical expertise. These new terminologies acknowledged vulvar pain and vulvodynia as a complex, multifactorial pain syndrome with varied etiologies, and imply that treatment should be tailored to each individual based upon their clinical presentation [1] (see Tables 14.1 and 14.2).

[In this chapter, the term *vulvodynia* refers to idiopathic, chronic vulvar pain; *provoked vestibulodynia (PVD)* refers to provoked vestibular pain; and *dyspareunia* refers to a symptom of genital pain conditions, including vulvodynia, during penetrative sexual activities].

Assessment

Assessment of the Vestibule

A complete pain and sexual history is mandatory in the assessment of the vulvodynia patient (See Table 14.3).

A thorough physical exam is essential to the diagnosis and treatment of women with vulvodynia. The cotton-swab, or q-tip, touch test is standard care for the

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Table 14.1 2015 Consensus terminology and classification of persistent vulvar pain and vulvodynia: clinical presentation [1]

(a)	Vulvar pain caused by a specific disorder (women may have BOTH a specific disorder AND vulvodynia)
	• Infectious
	• Inflammatory
	• Neoplastic
	• Neurologic
	• Trauma
	• Hormonal deficiencies
(b)	Vulvodynia (vulvar pain of at least 3 months duration, without a clear identifiable cause, which may have associated factors)
	Descriptors of vulvodynia
	• Localized, generalized, or mixed
	• Provoked, spontaneous or mixed
	• Primary or secondary
	• Intermittent, persistent, constant, immediate, or delayed

Table 14.2 2015 Consensus terminology and classification of persistent vulvar pain and vulvodynia: possible associated factors [1]

• Comorbidities and other pain syndromes
• Genetics
• Hormonal factors
• Inflammation
• Musculoskeletal
• Neurological mechanisms (central and peripheral)
• Psychosocial/psychosexual factors
• Structural defects

diagnosis of PVD [2]. The cotton-swab test is the most common test used for diagnosing localized, provoked pain of the vestibule. This test involves palpation of genital areas with a cotton-tipped applicator, in particular the vulvar vestibule. This test is performed in various ways depending on the health care provider; for instance, some will moisten the cotton-swab tip, whereas others do not; some providers palpate in a consectutive order, while others palpate in a nonconsectutive order [3]. The primary areas of the vestibule that are palpated are the Skene glands at 11 and 1 o'clock and minor vestibular glands at 5 and 7 o'clock, all the while applying consistent pressure [4, 5]. Pain is then rated on a numerical scale or subjectively classified as mild, moderate, or severe [3, 4].

It has been demonsrated that the amount of pressure applied during the cotton-swab test varies according to providers; therefore, Pukall et al. described the use of the vulvalgesiometer to standardize pain genital pain assessment and quantify levels of sensitivity [6]. Use of the device allows for palpation of the vulva at a consistent, standardized pressure, thus allowing for greater reliabiltity in evaluation [3].

Table 14.3 Obtaining a thorough pain and sexual history

• Develop a timeline
– Has intercourse always been painful?
– Has tampon use always been painful?
– Did the pain start acutely or gradually?
– Is the pain there all the time or only with provocation?
– Since the pain began, have there been episodes of completely pain free sexual activity?
• Determine the location of the pain
– Is there pain upon insertion?
– Is there pain inside the vagina?
– Is there deep pain (with thrusting)?
– Is there pain with clitoral stimulation?
– Is there pain with orgasm?
– Is there post-coital/post-orgasmic pain/burning?
• Elicit symptoms
– Burning, rawness, cutting, tearing, searing, aching, dull, throbbing, tearing, dryness, pruritus?
– Is there the feeling of clenching or "hitting a wall"?
– Is there urinary hesitancy, urgency, frequency, dysuria, the feeling of incomplete emptying?
– Is there constipation, diarrhea, anal/rectal fissures?
• Additional questions
– History of physical, sexual or emotional abuse?
– Did the pain start while on oral contraception?
– History of allergies to creams, soaps, medications? History of contact dermatitis, allergies, eczema, asthma, thyroid dysfunction, diabetes?
– History of positive vaginal cultures (STIs, vulvovaginal candidiasis (VVC), bacterial vaginitis (BV))
– History of vulvar dermatoses (lichenoid derm: LSC, LSA, ELP)
Previous vulvar biopsy?
Are there oral lesions?
Are there any fissures? Is there bleeding/tearing with penetration?
Does she wake up in the middle of the night scratching?
– Peri- or menopausal symptoms?

Women with vulvodynia and dyspareunia tend to have high levels of anxiety associated with the physical exam of their genitals. This is an opportune time to educate the patient about their anatomy and attempt to assuage their fears. Providing the patient with a hand-held mirror during the exam can aid not only as an education tool, but also help validate the patient's pain as "real" if the clinician can reproduce it on exam and show the patient its origin [3]. Using a mirror to demonstrate how to apply a topical cream can also facilitate compliance. This helps to decrease the anxiety of pain associated with any contact to the vulva, clarify the location of the pain, as well as facilitate compliance of topical therapies.

Assessment of the Pelvic Floor

Internal evaluation of the pelvic floor muscles (PFMs) in women with vulvodynia is crucial. The relationship between hypertonic pelvic floor dysfunction (HTPFD) and vulvodynia has been discussed in the literature [7–10]. While it is unclear if HTPFD results from chronic vulvar pain or if it is a precipitating factor, HTPFD can exacerbate the symptoms of vulvodynia and can itself worsen with vulvodynia or PVD flares. For those women with comorbid vulvodynia and HTPFD, referral to a physical therapist who specializes in pelvic floor physical therapy for a comprehensive evaluation and treatment program is essential.

Evaluating the superficial pelvic floor muscles begins by evaluating the patient's response when downward pressure placed on at the introitus (stretching the transverse pereneii muscle) and a widening/stretching maneuver is performed superficially at the labial minora (stretching the bulbocavernosus and ishiocavernosus muscles). Pain in response to palpation of these muscles often indicates myofascial restrictions within the superficial muscles and the urogenital triangle that may at least in part be the cause of superficial introitual pain and pain at the vestibule. Next, the left and right deep levator muscles (pubococcygeus, iliococcygeus and cocygeus), along with the obturator internus muscles are palpated. Myofacsial restrictions in these muscles are often related to deep penetrating discomfort with entry and/or thrusting [11]. Pelvic floor muscle (PFMs) strength on the left and right sides can be evaluated by having the patient squeeze the examining finger (Kegel maneuver), hold for a count of five, and then release the muscle. Women with sexual pain and pelvic floor dysfunction often have weak PFMs upon squeeze and have difficulty maintaining the contraction and relaxing the muscle to baseline.

Baseline Lab Assessment

Wet prep and vaginal cultures are done to rule out chronic candidiasis, bacterial infection, and atrophic changes.

Management

There is a paucity in the literature of randomized, placebo-controlled trials for the treatment of vulvodynia. The majority of the studies done to date have been small, open-label, or placebo-controlled studies with a sample size too small to render useful data [12]. Most often, clinicians rely on clinical experience and expert opinion in conjunction with useful information gleaned from research, to devise an individualized treatment plan. Treatment options for vulvodynia can be divided into five categories: behavioral modification, medical, surgical, alternative, and psychosocial. Treatment of vulvar pain is most successful when it is multimodal and involves an interdisciplinary team consisting of a medical clinician, a physical therapist, and a psychobehavioral and/or sex therapist.

Behavioral Modification

Behavioral modification begins with patient education. Setting realistic goals and expectations right from the outset of care is essential in the treatment of women with vulvar pain. It should be made clear that vulvodynia is a chronic condition, in which symptoms are managed but may be ongoing, characterized by periods of remission and symptom flare. Women should understand that improvement can be a slow, arduous process and because there is not a "one size fits all" treatment, finding the correct treatment for them may take some trial and error, time, and patience.

Good vulvar hygiene is the first and easiest step women can take to alleviate irritation and discomfort (see Table 14.4). Soaking in warm baths with either Epsom salt or Aveeno oatmeal can be soothing as well as the application of ice for 10–15 min at a time every 4–6 h can help mitigate burning sensations.

Data suggest when compared with healthy controls, women with vulvodynia have higher levels of stress and anxiety than healthy controls [13–17]. It has been postulated that stress can exacerbate symptoms of vulvodynia and that symptoms tend to worsen stress. Stress reduction and relaxation techniques should be encouraged.

Table 14.4 Vulvar hygiene

• Avoid scented soaps, detergents, body washes, bath gels and bubble baths
• Wear non-constricting, cotton underwear during the day
• Avoid pantyhose and tight pants
• Use mild, hypo-allergenic soap for bathing and water-only for cleansing the vulva and vagina
• Avoid douching, over-the-counter vaginal wipes, deodorants and other commercial products
• Use unscented pads and tampons
• Use a water-based, unscented, hypoallergenic lubricant for sex play. Coconut oil or all natural vitamin E oil may also be used
• Avoid the use of fabric softener and dryer sheet on underwear
• Apply ice or cold packs to the vulva for 10–15 min up to 6×/day and before or after sexual activity. To decrease deeper vaginal irritation, to fill a glove with water and freeze it, rip off a finger and insert it into the vagina
• Warm baths twice a day with either Epsom salt or Aveeno® oatmeal helps relieve irritation and/or vulvar itching
• Avoid activities that place pressure directly on the vulva such as bicycling
• Apply topical lidocaine 10–15 min to the vulva prior to sexual activity. Make sure to wipe off the excess, avoid oral contact, and/or have male partner use a condom to avoid penile numbing. If there is increased irritation after sexual activity, topical lidocaine may also be applied at that time for additional relief. Care should be taken to avoid overuse and to only apply a fingertip amount to the introitus
• White Crisco® or coconut oil may be used as a topical barrier to decrease irritation and burning associated with exercise, urination and/or swimming (due to irritation from chlorine). They can also be soothing to mitigate the burning sensation experienced during episodes of flares

Medical

Nonsurgical medical therapy for the treatment of vulvodynia includes the use of topical preparations, oral medications, and injection therapy. The reader must remain cognizant of the fact that these treatment options are not FDA approved for the treatment of vulvodynia and therefore used off-label and without standard preparation or dosing.

Topical Medications

Topical medications are commonly used in the treatment of vulvodynia, often times as first line or in conjunction with oral medications. There are numerous topical medications available and used in clinical practice, but few controlled trials have been done to verify their efficacy. Many patients prefer topical preparations due to their low incidence of systemic side effects. As with application of any topical agent to the vulva and vestibule, care must be taken to avoid irritating components. A knowledgeable compounding pharmacist can be an important member of the treatment team, suggesting hypoallergenic bases for creams and ointments and avoiding vehicles that may exacerbate symptoms, while still achieving maximum therapeutic effect.

Lidocaine

Lidocaine 2 or 5 % ointment is typically used to mitigate some of the pain and discomfort associated vulvodynia; however, there has only been one double-blind, placebo-controlled randomized trial of topical lidocaine. Foster et al. compared the efficacy of topical lidociane monotherapy, oral desiprimine monotherapy, and lidocaine-desiprimine combined therapy for 12 weeks, with patient assessment through 52 weeks. They found no effect of the interventions when compared to placebo [18]. A recent large, prospective study of 520 women with vulvodynia evaluated daily pain and the ability to achieve intercourse after treatment with 5 % xylocaine applied overnight (8 or more hours) to the vestibule for 6–8 weeks. After 6-month follow-up, 88 % (458/520) of the women were able to have intercourse compared with 34 % (171/520) at the initial visit. The mean daily pain as rated by visual analogue score (VAS) was also reduced from pretreatment compared to posttreatment (8.6 (6–10) vs. 2.5 (0–5), respectively) [19]. Most other trials that looked at topical lidocaine were noncontrolled and efficacy rates varied from no better than placebo to about 50 % [20, 21] leading the ICSM to not recommend lidocaine as a treatment for vulvodynia.

Hormonal

The role of hormones and their association to vulvodynia remain an enigma. Vulvodynia in menopausal women is frequently misdiagnosed with the attendant dyspareunia attributed solely to vulvovaginal atrophy and decreased lubrication [22]. Despite treatment with topical estrogen, menopausal women with concomitant vulvodynia and dyspareunia had persistent vulvar pain [23, 24]. While vulvodynia is thought to be more prevalent in premenopausal women, a small, retrospective

histopathologic analysis of pre- and postmenopausal women with vulvodynia found that 71 % of women with postmenopausal vulvodynia correlated their symptoms to a drop in estrogen levels and 50 % reported their pain began with menopause. Additionally, 22 % of the women with secondary vulvodynia reported their pain started in the postpartum period [25]. The National Vulvodynia Association (NVA) and expert opinion support treatment of women with vulvodynia who demonstrate atrophic changes in the vulva and vestibule with topical estrogen therapy [26, 27].

There is conflicting evidence on the use of oral contraceptives and development of vulvodynia. Burrows et al. reported the risk of provoked vestibulodynia symptoms with the use of combined oral contraceptive (COC) use ($n=50$). The use of topical estradiol 0.01 % and testosterone 0.1 % in addition to discontinuing their COCs improved VAS scores significantly from 7.5 to 2.0 ($p=0.001$) [28]. Conversely, a population-based study by Reed et al. showed no correlation between developing vulvodynia symptoms and COC use ($n=906$) [29].

Gabapentin

Gabapentin 2–10 % topical preparations have been used in the treatment of vulvodynia (both localized and generalized) with good tolerability and low incidence of systemic effects. A retrospective review of 51 women with vulvodynia (19 with generalized and 32 with localized) was conducted to evaluate the efficacy and tolerability of 2, 4, and 6 % topical gabapentin. Results showed that 80 % of the patients improved by at least 50 % and 29 % of the patients achieved full improvement. Furthermore, topical application of all doses was well tolerated without any side effects associated with oral gabapentin in any of the 51 women [30]. It should be noted that this review lacked a comparison group and did not account for various concurrent treatments [31].

Amitriptyline-Based Topical Preparations

The use of topical amitriptyline for vulvodynia is preferable for patients who wish to avoid untoward side effects of oral tricyclic antidepressants such as fatigue, weight gain, constipation, and drying of mucous membranes. Amitriptyline 2 % cream was evaluated in a prospective trial of 150 women with vulvodynia of which 84 (56 %) reported some level of benefit; 15/150 (10 % of the total number of participants) reported intercourse as comfortable and pain free [32]. A small, retrospective review of 38 women with refractory vulvodynia treated with amitriptyline 2 %/baclofen 2 % cream established improvement in symptoms in 71 % of subjects. Although none of the participants experienced any systemic side effects of either oral amitriptyline or baclofen, local burning occurred in 29 % of women, but only 8 % discontinued treatment as a result [33]. Finally, combination amitriptyline 1–2 %/ketamine 0.5 % cream has been used for the treatment of genital, rectal, or perineal pain. A retrospective chart review was done to identify diagnosis, efficacy, and adverse effects. The authors found of 13 patients prescribed amitriptyline/ketamine cream, one (8 %) had complete relief, ten (77 %) had some to moderate relief, and two (15 %) had no response. Only one patient experienced local burning pain when using an amitriptyline/ketamine preparation in a lidocaine base. Otherwise, no local or systemic adverse effects were reported [34].

Cromolyn

A double-blind, placebo-controlled study of cromolyn 4 % in 34 women with refractory vulvodynia showed no statistically significant improved efficacy over placebo in dyspareunia and vulvar vulvar pain [35]. However, the authors note that even though they did not reach statistical significance, 53.8 % of women using cromolyn cream had at least 50 % improvement in the aforementioned parameters, compared to 38.5 % using placebo factors such as subjective patient symptom reporting, fluctuations in symptoms, and refractory patient population [35]. It is not uncommon for clinicians to use cromolyn 5–10 % in petrolatum base to treat some patients with vulvodynia.

Cutaneous Fibroblast Lysate

A placebo-controlled, crossover study, of 30 women with vulvodynia found the topical cream with cutaneous fibroblast lysate had a statistically significant, albeit clinically modest (20–30 %) reduction in dyspareunia and decreased focal erythema compared to placebo [36]. The cream was well tolerated without any adverse or systemic effects.

Capsaicin

Women with vulvodynia are found to have increased vanilloid receptors (VR1) in the peripheral terminals of nociceptors. Topical capsaicin has an agonist effect on VR1 (TRPV1), thereby producing desensitization to burning and decreased pain [37, 38]. Two trials with topical capsaicin for the treatment of vulvodynia, one prospective and one retrospective, have attempted to determine the efficacy and tolerability of the treatment [39, 40]. In both studies, women premedicated with topical lidocaine prior to application of capsaicin; therefore, it was impossible to elucidate if improvement was due to either cream or a combination of both. The prospective study demonstrated 59 % improvement in symptoms; however, once the women discontinued use of capsaicin, their vulvar pain symptoms recurred. Symptom improvement was once again achieved with return to using the cream [39]. All participants reported severe burning with capsaicin application.

Other Topicals

Topical therapies that have not shown significant benefit in the treatment of vulvodynia include topical: antifungals, steroids, nifedipine, and progesterone.

Intralesional Injections

The use of injectable agents has not been well studied; however, many experts in vulvodynia add this treatment modality to their armamentarium to be used as adjuvant therapy or when other therapies fail. Risk-benefit ratio must always be assessed and discussed with the patient when deciding to employ this treatment option.

Steroids

Submucosal injection of corticosteroids, typically mixed with lidocaine, is thought to have anti-inflammatory effects and improve pain in women with vulvodynia [41]. A small, prospective study ($n=22$) of women with provoked vestibulodynia treated

with submucosal injections of lidocaine and methylprednisolone ascertained that 15 of 22 women (68 %) responded favorably to treatment: 8 of 15 (36 %) had marked improvement in dyspareunia and pain with q-tip test; 7 of 15 (32 %) had complete resolution of symptoms. Failure to respond was seen in 7 of 22 (32 %) of participants [42]. Lidocaine and betamethasone submucosal injections were reported in two separate case reports ($n=1$) as a successful treatment option for vulvodynia resulting in total relief from pain and dyspareunia [43, 44]. These are all small, uncontrolled studies lacking a placebo arm; therefore, it is hard to determine whether or not steroidal intralesional injections are efficacious in the treatment of vulvodynia.

Botulinum Toxin A

Botulinum toxin A (Botox®) has been used in the treatment of other pain syndromes such as migraine headaches and TMJ [45]. Botox® inhibits the release of glutamate and substance P from nociceptive neurons that may in turn decrease peripheral and central sensitization associated with vulvodynia [45–47]. Moreover, it is also thought to decrease the hypertonicity of the pelvic floor musculature and peripheral neuropathy, thereby reducing vulvar pain and dyspareunia and improving sexual function [48]. Historically, it was difficult to evaluate the efficacy of Botox® for vulvodynia due to the lack of RCTs and standardization of treatment. Furthermore, publications mainly consisted of small case series or individual case reports [5]. These small, open-label, prospective studies have mostly shown improvement in symptoms using Botox® at doses of 20–100 U in varying injection sites (vestibule, levator ani, perineum), with or without electromyographic (EMG) guidance [49–57]. To date, there has been one prospective, placebo-controlled, RCT of Botox® for provoked vestibulodynia ($n=64$). At 6-month follow-up, both the Botox® ($n=32$) and placebo ($n=32$) cohorts had significant pain reduction ($p<0.001$); however, median VAS scores failed to illustrate a significant difference in pain reduction between the two groups ($p=0.984$). Likewise, no significant difference in improvement in sexual functioning or quality of life was observed between the two cohorts [58].

Although adverse effects of botulinum toxin A are extremely rare, they have been reported. Botox® is not a permanent treatment and positive results vary, lasting from 3 months to up to 12 months in some cases. Adverse effects are self-limiting and typically resolve as the Botox® begins to lose its potency. Patients must be thoroughly consented to all possible adverse effects and reactions prior to injection with this medication (see Table 14.5).

Oral Therapies

Oral pharmacotherapy for vulvodynia primarily consists of antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs); and anticonvulsants: gabapentin and pregabalin. Treatment with oral medications is often second-line therapy despite the lack of evidence for this approach [48]. As with all other medical

Table 14.5 Potential complications of Botox® injections

• Infection
• Hematoma
• Syncopal episode
• Intravascular injection leading to systemic toxicity
• Intraneural injection leading to nerve damage
• Spread of toxin effect weakening nearby muscles
• Allergic reaction
• Increased risk of clinically significant adverse effects from therapeutic doses in patients with peripheral motor neuropathic diseases, neuromuscular junction disorders or amyotophic lateral sclerosis
• Aminoglycosides, anticholinergic agents, muscle relaxants and other agents that interfere with neuromuscular transmission should be used with caution, as untoward adverse effects can be potentiated with concomitant use of Botox®
• Botox® may not work immediately and may take 1–3 weeks for patients to see clinical improvement; patients may not have adverse effects for the same time period and potentially may develop them at any time while the drug remains active

treatments for vulvodynia already discussed, most oral pharmacotherapy trials are without standardized dosing, are nonrandomized, not placebo-controlled, and do not control for concurrent therapies.

When prescribing antidepressants or anticonvulsants, it is important to remember to start at a low dose and slowly titrate every 7–10 days to give the patient ample time to acclimate to any adverse effects (see Table 14.6). Once they reach their therapeutic dose, they may not appreciate their desired pain response for 4–6 weeks.

Antidepressants

Antidepressants are used successfully in the treatment of chronic pain syndromes by effecting serotonin, norepinephrine as well as having adjuvant therapeutic influences through histamine receptors and modulating sodium channels [59]. Tricyclic antidepressants are first-line in the treatment of most neuropathic pain syndromes. Pain relief is independent of antidepressant effects of TCAs and therefore may be achieved at much lower doses than those needed to treat depression [59]. The most common TCA used in the treatment of vulvodynia is amitriptyline starting at doses between 10 and 25 mg increasing by 10 mg every 7–10 days to an average of 50–75 mg/day. (Maximum dose is 150 mg/day; however, over 100 mg/day there is a higher risk of sudden cardiac death [60].)

Reed et al. prospectively evaluated 271 women diagnosed with vulvodynia, 201 (77.1 %) were treated with a TCA for 3 months at which time 162 (59.8 %) were reevaluated. Eighty-three women were taking a TCA, of whom 49 (59.3 %) reported more than 50 % improvement in pain compared to 30 of 79 women not taking a TCA (38 %) [61]. Additional small, retrospective chart reviews or single case reports reveal varying results ranging from 27 % improvement to 100 % or complete remission [62–68]. On the contrary, two double-blind, randomized, placebo-controlled trials were unable to show therapeutic difference in pain relief between TCA and placebo [18, 69].

Table 14.6 Oral therapies for vulvar pain

Drug	Typical dosing for treatment of vulvar pain	Adverse effects
Antidepressants		
Tricyclics		
Amitriptyline/ Nortriptyline	10–75 mg/day	Dry mouth, dizziness, fatigue, constipation, urinary retention/ hesitancy, weight gain, palpitations, vivid dreams Increased risk of sudden cardiac death in doses over 100 mg/day
SNRIs		
Duloxetine	30–90 mg/day	Nausea, vomiting, dyspepsia, drowsiness, weight gain, weight loss, urinary retention, dry mouth, decreased libido, headache
Venlafaxine	150–225 mg/day	
Milnacipran	50 mg two times/day	
Anticonvulsants		
Gabapentin	100–1200 mg three times/day	Drowsiness, dizziness, headache, weight gain, depression
Pregabalin	25–150 mg two times/ day	Fatigue, dry mouth, dizziness, weight gain, peripheral edema, constipation

Reference [1]

There are no controlled data on SSRIs in the treatment of vulvodynia and they are generally not recommended in the treatment of other chronic neuropathic pain syndromes as other types of antidepressants provide superior pain relief with less side effects [59, 60].

There are evidence-based data that show SNRIs such as venlafaxine, duloxetine, and milnacipran to demonstrate good efficacy with less side effects than TCAs in treating neuropathic pain [59, 60]. Milnaciprin has recently been evaluated in a 12-week open-label trial of 22 women with PVD and was found to significantly reduce vulvar pain in women with PVD ($p < 0.001$). 79 % of those receiving milnaciprin reported at least one adverse effect, most commonly nausea (47.6 %), headache (42.9 %), hot flushes (23.8 %), and dizziness (19.0 %). No one participating in the study discontinued due to adverse effects [70].

Anticonvulsants

Anticonvulsants are FDA approved to treat other forms of neuropathic pain, and gabapentin has been the most studied and utilized anticonvulsant in the treatment of vulvodynia. It is thought to work on calcium channels to block the release of glutamate and substance P [71]. Dosing for gabapentin can range between 100 and 3600 mg/day. The dose is typically started low, 100–300 mg at bed, and slowly titrated every 7–10 days into three divided doses of 300 mg 3×/day (Max dose 1200 mg 3×/day). As with TCAs, patients should be forewarned that once they reach a therapeutic dose, they should be prepared to remain there for at least 4–6 weeks before determining efficacy.

There are no RCTs on the use gabapentin for vulvodynia; however, observational studies and case reports show efficacy range between 50 and 82 % [50, 66, 72–75]. Brown et al. are in the process of conducting the first double-blind, placebo-controlled, RCT of extended release gabapentin in 120 women with provoked vestibulodynia [76]. An open-label, prospective, randomized trial of 56 women with either gabapentin ($n = 20$), amitriptyline ($n = 20$), or a combination of both ($n = 16$) evaluated their pain at 6, 12, and 24 months. Results showed that all participants experienced significant pain relief; however, the groups receiving gabapentin alone or in combination with amitriptyline had significantly better pain relief than the group receiving amitriptyline monotherapy [77]. Finally, Jerome presented a single case report of a patient with refractory vulvodynia who was successfully treated with pregabalin with an 80 % reduction of pain [78].

Other Therapies

The use of other treatment modalities has been shown to be an effective option for women with vulvar pain. These alternative treatments include psycho-behavioral therapy, physical therapy, and alternative therapies.

Physical Therapy

Women with dyspareunia related to chronic vulvar pain commonly exhibit increased muscle tension and myofascial trigger points in the pelvic, abdominal, back and pelvic floor muscles, and have increased restrictions and decreased mobility in these areas. Pelvic floor physical therapy (PT) utilizes a variety of modalities, including: pelvic and core mobilization and stabilization; connective tissue, visceral and neural mobilization; internal and external myofascial trigger point release, biofeedback and electrical stimulation [8, 79, 80]. PT restores the proper length of the pelvic floor muscles and tissues, reduces neural tension, and decreases pain, which facilitates sexual comfort [81–83]. The utility of pelvic floor muscle therapy for improving sexual function in cohorts of women with vulvodynia has been demonstrated in the literature [10, 81, 84, 85]. When compared to topical lidocaine in the treatment of vulvodynia-rated pain, PT and biofeedback resulted in symptoms improvement in improvement in 66 % of patients, which was maintained at 12-month follow-up [20]. Finally, a prospective study of 11 patients with vulvodynia concluded that PT led to normalization of pelvic floor muscles, significant reduction in pain during vaginal palpation, during gynecologic exams, and during sexual intercourse [8].

Although more research is warranted, data suggests that pelvic floor muscle physical therapy treatment can be a key element toward alleviating vulvar pain [86].

Psycho-Behavioral Therapy

Cognitive-Behavioral Therapy (CBT)

CBT is one of the most commonly used and studied psychological interventions for vulvar pain and dyspareunia. In this treatment, the woman and or partner are given psycho-education on the multidimensional impact of pain on an individual and the relationship. Concepts including the role of psychological and relationship factors in coping with pain and in the maintenance of pain are explored [87]. Bergeron and colleagues investigated the efficacy of a combination of group CBT in two different randomized trials of women with PVD. In the first study, which compared vestibulectomy surgery, biofeedback, and CBT, participants who received CBT reported significant improvements in pain at a 6-month follow-up. At a 2.5-year follow-up, their ratings of pain during intercourse were equivalent to those of women who underwent surgery [88]. Once again, Bergeron et al. looked at women with provoked vestibulodynia ($n=97$) who were randomly assigned to either use a topical corticosteroid cream or to group CBT for a 13-week treatment period. Intent-to-treat multilevel analyses showed that participants of both groups reported statistically significant reductions on pain measures from baseline to posttreatment and 6-month follow-up, although the CBT group reported significantly more pain reduction at 6-month follow-up. At posttreatment, women in the CBT condition were significantly more satisfied with their treatment, displayed significantly less pain catastrophizing, and reported significantly better global improvements in sexual functioning than women assigned to the topical application. Findings suggest that CBT may yield a positive impact on more dimensions of sexual pain than does a topical treatment [89].

In addition to CBT, couple therapy interventions and mindfulness-based psychoeducational intervention have also been shown to decrease vulvar pain, anxiety, and catastrophizing [90–93].

Alternative Therapies

Acupuncture

Acupuncture is well reported in the literature to decrease chronic pelvic pain. Multiple studies have demonstrated acupuncture decreases vulvar pain, improves quality of life, and increases overall mental and sexual health [94–96]. A recent randomized controlled study of 36 women with vulvodynia showed that compared to controls, vulvar pain and dyspareunia were significantly reduced in the group receiving acupuncture [97].

Hypnosis

Hypnosis typically involves suggestions for changes in thoughts or behaviors, perception, sensation, emotion, or subjective experience. Treatment for pain often begins with relaxation followed by specific suggestions to change how the pain is perceived. To date, one preliminary study and one case report, both of women with

vulvodynia employing the use of hypnotherapy as a treatment option, elucidated reduction in pain and improved sexual function [98, 99]. Considering that these options are devoid of adverse effects, more rigorous studies are warranted.

Transcutaneous Electrical Nerve Stimulation (TENS)

An emerging approach to treating vulvodynia by modulating the peripheral nervous system is transcutaneous electrical nerve stimulation (TENS). TENS has been shown to be effective in other pain conditions largely resulting from the hypothesized release of endogenous opioids by stimulation of afferent and motor fibers [48]. TENS has shown to improve vulvar pain in women with vulvodynia [100, 101]. A double-arm, randomized, placebo-controlled trial of 40 women demonstrated significant improvement in the treatment group vs. placebo as evidenced by improved visual analogue scale (VAS) and pain questionnaire scores pre- and post-treatment ($p = 0.004$, and $p = 0.001$; respectively) [101].

Conclusion

Vulvar pain, including provoked vestibulodynia and dyspareunia, are highly prevalent forms of chronic pelvic pain in women. More information regarding assessment and treatment is needed. A comprehensive assessment is essential to understand the location and extent of the pain of women presenting with vulvar pain. Additionally, treatment should progresses from less invasive to more invasive, and several treatment options are available. Due to its complex nature, the treatment of chronic vulvar pain is often multimodal, incorporating treatments from different disciplines. Multidisciplinary treatment is essential and members should include medical clinicians, physical therapy, psycho-behavioral therapy, and/or sex-therapy. In the future, improvements in patient phenotyping will hopefully lead to targeted therapies with better outcomes.

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Immunomodulators for Interstitial Cystitis/Bladder Pain Syndrome

15

Deborah R. Erickson and Eric M. Blalock

Introduction and History

This chapter will focus on systemic medicines that modulate the immune system (bladder instillations are covered in other chapters). The literature can be confusing because the definition of "interstitial cystitis" (IC) has changed over time. To help orient the reader, we will start with a brief history of the relevant terms and definitions.

Approximately 100 years ago, Hunner described small cohorts of women with bladder pain and bleeding "ulcers" on cystoscopy [1–3]. While not the first to report this entity, his papers were the most compelling at the time and made the disorder more widely known [4–6]. The name "Hunner ulcer" persisted for decades, but "Hunner lesion" is generally preferred now.

After Hunner's reports, the terms "interstitial cystitis" (IC) and "Hunner ulcer" became essentially synonymous [6]. Later, however, IC patients were identified without Hunner lesions. For example, in 1949, Hand reported 223 cases of IC, of whom >70 % lacked Hunner lesions. He used the term "Grade 1 IC" for patients who had normal bladder capacity under anesthesia and small submucosal hemorrhages after distention [7]. These small petechiae were later termed "glomerulations" and were thought to be a diagnostic hallmark of IC.

In 1987, Fall et al. described their categories of "classic" and "nonulcerative" IC based on cystoscopy: the former had Hunner lesions and the latter had glomerulations

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but no Hunner lesions [8]. Comparing bladder biopsies from these two groups, the "classic" patients had more severe inflammation and higher mast cell counts than the "nonulcerative" patients [8, 9]. Many subsequent studies confirmed that Hunner lesions involved bladder inflammation. A complete list of these papers is beyond the scope of this chapter, but those relevant to treatment will be cited where appropriate.

For patients without Hunner lesions, the etiologic theories and diagnostic criteria continued to evolve. Glomerulations lost their role as a diagnostic hallmark because they were found not to be sensitive or specific for IC. The current European Society for the Study of IC (ESSIC) and American Urological Association (AUA) guidelines do not require glomerulations for diagnosing the disorder now called Bladder Pain Syndrome (BPS) and IC/BPS, respectively [10–12].

In summary, the relevant definitions have changed over 100 years. At first we had IC, which involved bladder erythema and inflammation. Now we have BPS or IC/BPS, a chronic pain syndrome that may not involve any cystoscopic abnormalities or bladder inflammation. Unlike the original IC, this chronic pain syndrome is not rare. A recent epidemiologic study using a high-specificity definition estimated the United States prevalence as 2.70 % of women >17 years old [13]. Within this large and diverse patient population, only a small subset will have a pathology amenable to immunomodulation.

Patient Selection

As noted above, there is little rationale for systemic immunomodulation unless the patient has inflammatory bladder pathology. Therefore, correct patient selection is essential.

Patients with Hunner lesions have bladder inflammation and are appropriate candidates, but systemic immunomodulation is too risky to be a first-line treatment. The first-line treatment is cystoscopy with lesion fulguration or injection of triamcinolone (a long-acting synthetic corticosteroid) [11, 12]. After this, most patients have excellent symptom relief. Unfortunately, the underlying inflammatory pathophysiology continues and the lesions eventually recur. If the recurrence follows a long symptom-free interval, then repeat cystoscopic treatment is indicated. On the other hand, if the lesions recur quickly or are too extensive initially, then immunomodulation would be considered.

Patients without Hunner lesions might be candidates, because some of them have bladder inflammation. For example, in a Belgian cohort with 48 patients lacking Hunner lesions, 14 had medium or severe inflammation on bladder biopsy [14]. As another example, in a United States cohort of 63 patients without Hunner lesions, 17 had severe inflammation on bladder biopsy [15].

Although intravesical treatments are not the topic of this chapter, it is interesting to note that DMSO and/or corticosteroid cocktails can improve symptoms for both types of IC/BPS, with or without Hunner lesions. The responders in the latter group may have bladder inflammation despite the lack of visible lesions, or these agents may have other effects that improve IC/BPS symptoms besides their anti-inflammatory properties.

In summary, the best candidates for systemic immunomodulation are patients with Hunner lesions who have rapid recurrence after cystoscopic treatment, or whose lesions are too extensive for cystoscopic treatment. (Patients with long symptom-free intervals between cystoscopic treatments should have periodic treatments, because those are less risky than long-term systemic immunomodulation.) One might also consider immunomodulation for patients who have inflammation on bladder biopsy, even without visible Hunner lesions. For patients without biopsy-proven inflammation, systemic immunomodulators are unlikely to help and the risk/benefit ratio may be too high.

Specific Agents

Glucocorticoids

Glucocorticoids act in the cell nucleus to modulate gene transcription. They affect numerous genes and thus have numerous effects. Their immunosuppressive effect is due, at least in part, to facilitated transcription of I-KB, the endogenous inhibitor of NF-KB, a key component of the activated adaptive immune response.

From the 1950s to the 1970s, several authors described corticosteroid injections into IC patients' bladders. Results were variable [6, 16]. Decades later, Cox et al. reported significant improvement in 21 of 30 patients after injecting triamcinolone into Hunner lesions [17]. Their high success rate may reflect improvements in patient selection and/or cystoscopic instruments compared to the early reports. As noted above, the AUA guideline recommends cystoscopy with fulguration or triamcinolone injection for treatment of Hunner lesions [11, 12].

Oral corticosteroids also had variable results in early trials [5, 6, 16]. More recently, two centers targeted oral corticosteroids specifically for patients with Hunner lesions [18, 19]. Each study enrolled 14–15 patients. Response rates were 64 and 47 %, respectively. The latter trial also followed bladder nitric oxide as a marker of inflammation; it decreased by 50 % in the responders but was unchanged in the nonresponders [19]. While these results add to the evidence for inflammation in Hunner lesions, the AUA guideline recommends against long-term systemic corticosteroids due to the high side effect profile [11, 12].

Chloroquine Derivatives and Azathioprine

Chloroquine and its derivatives are antimalarial drugs that also have immunosuppressive properties. Currently, hydroxychloroquine is used for malaria, rheumatoid arthritis, and lupus erythematosus. Azathioprine is a purine analog used for immunosuppression in several disease states.

In 1976, Oravisto and Alfthan described their cohort of IC patients who had failed bladder distention and were then randomized to (1) chloroquine or oxychloroquine, with most patients also taking as much salicylate as they could tolerate, or (2) azathioprine [20]. Patients who failed the first arm were tried on the other arm.

Thirty-eight patients received azathioprine. The authors did not specify how many patients received azathioprine first, or had already failed the chloroquine/salicylate arm. Of the 38 patients, 22 (58 %) had complete pain relief. Because all responders noted improvement in 1–2 weeks, and a brief trial would be fairly low-risk, this appears to be a valid option to try. On the other hand, almost 40 years later, there are no subsequent publications on azathioprine for IC/BPS. The lack of follow-up articles raises doubt about azathioprine's long-term efficacy.

Twenty-two patients received chloroquine or oxychloroquine, usually with salicylate. The authors did not specify how many patients were in this arm first or after failing azathioprine. Of the 22 patients, 11 (50 %) had complete pain relief. In contrast to azathioprine, which had a rapid effect, chloroquine/oxychloroquine/salicylate response required 4–6 months. Due to this long delay, plus the lack of subsequent literature on chloroquine with or without salicylates, this form of treatment seems unlikely to have a useful role in IC/BPS treatment.

Methotrexate

Methotrexate is an antimetabolite that prevents the synthesis of folate and may also suppress the immune response by other mechanisms. It is used to treat several types of autoimmune disease.

Moran et al. had a patient whose IC symptoms improved dramatically after starting methotrexate for psoriasis [21]. Therefore, they did a prospective study with nine IC patients. Four improved and wished to continue, four had little change and one worsened. The authors noted that all patients had failed bladder distention and DMSO, but did not describe selecting patients with Hunner lesions or with inflammation on bladder biopsy. Therefore, it is unknown whether these suboptimal results indicate low efficacy of methotrexate for the inflammatory pathophysiology, inclusion of patients who did not have an inflammatory pathophysiology, or both. This paper was published in 1999 and there are no subsequent publications on methotrexate for IC/BPS.

Mycophenolate

Mycophenolate suppresses inosine monophosphate dehydrogenase, an enzyme on which T and B lymphocytes are uniquely dependent for guanosine nucleotide synthesis. It is used for immunosuppression in kidney, heart, or liver transplant recipients.

The IC Collaborative Research Network conducted a multicenter trial of mycophenolate vs. placebo [22]. Of 210 planned subjects, only 58 were randomized before the study was halted due to a new black box warning. On interim analysis, the response rates for mycophenolate and placebo were 15 and 16 %, respectively.

In this study, the entry criteria required cystoscopy to show glomerulations and/or ulcerations. However, the authors did not indicate how many subjects had Hunner lesions; also there was no mention of bladder biopsies. Therefore, it is unknown whether the low response rate was due to low efficacy of mycophenolate for the inflammatory pathophysiology, inclusion of patients who did not have an inflammatory pathophysiology, or both.

Adalimumab

Adalimumab is a monoclonal antibody against tumor necrosis factor-alpha (TNF-a). It is used for inflammatory arthritis, inflammatory bowel disease, and psoriasis.

Bosch had a patient whose IC symptoms resolved after starting adalimumab for Crohn disease [23]. Therefore, he did a randomized trial of adalimumab vs. placebo. The article does not state how many patients were originally planned, but the study was terminated early for humanitarian reasons because half of the 43 enrolled patients had shown a dramatic clinical improvement. Surprisingly, unblinding revealed success rates of 53 and 50 % in the active drug and placebo groups, respectively.

Due to three design flaws in the study, we still do not know whether adalimumab would be an effective treatment for the subset of IC/BPS patients (if any) whose pathophysiology is mediated via TNF-a.

First, all patients in this study received education and support in addition to the active drug or placebo. Education has well-known efficacy, is a first-line treatment in the AUA guideline, and likely contributed to the 50 % success rate in the placebo group. A high success rate in the placebo arm makes it more difficult to demonstrate a significant difference with an active drug. The same phenomenon occurred in the IC Collaborative Research Network's trial of amitriptyline vs. placebo, in which all subjects also received standardized education [24]. Moderate to marked improvement occurred in 55 % of patients in the active drug group, not significantly higher than the 45 % success rate in the placebo group. However, when the authors analyzed the subset of patients who could tolerate at least 50 mg amitriptyline a day, their success rate of 66 % was significantly higher than the placebo group's.

Second, the adalimumab dose in this study may have been too low. It was similar to the usual dose for arthritis, but lower than the usual dose for inflammatory bowel disease. Inflammatory bladder disease may require the higher dose.

Third, the patients in this study were recruited based on symptoms. Without cystoscopy or bladder biopsy, there is no evidence that these patients had any immune-mediated pathology, with or without TNF-a involvement.

Future research is needed to determine whether adalimumab or other anti-TNF agents would be effective if given to IC/BPS patients who had demonstrable inflammation mediated by TNF-a. For clinicians at the current time, adalimumab might be considered if the patient has an approved indication for adalimumab (e.g., inflammatory arthritis or bowel disease) in collaboration with the appropriate specialist.

Cyclosporine A

Cyclosporine A (CyA) suppresses T lymphocyte proliferation by binding cyclophilin and inhibiting calcineurin, preventing calcineurin-activated transcription of the pro-inflammatory cytokine interleukin-2. Systemic CyA is approved in the United States to prevent kidney, heart, or liver transplant rejection, also to treat severe rheumatoid arthritis and psoriasis. Topical CyA is used for certain inflammatory eye disorders.

The pioneering research on CyA for IC was conducted in Finland. In 1996, Forsell et al. published their open-label pilot study of CyA for IC patients who had previously undergone bladder distention with either no relief or temporary relief [25]. Of 11 patients, ten had relief of bladder pain and nine had voiding frequency decrease by 5–26 voids per day. The article does not specify whether the patients had Hunner lesions or bladder biopsies. Based on the pilot study, additional patients were recruited and the long-term study was published in 2004 [26]. Of 23 patients who received CyA for at least 1 year, 20 were totally free of pain. Mean voiding frequency decreased from 21 to 10 voids a day.

Unable to acquire an appropriate placebo, the investigators next performed a 6-month randomized trial of CyA 3 mg/kg/day in two daily doses vs. pentosan polysulfate (PPS) 300 mg/day in three daily doses [27]. Each arm had 32 patients. Three patients in the PPS arm withdrew for hematuria (1) or lack of benefit (2). Three patients in the CyA arm withdrew: one had emesis, one had gastrointestinal pain and gingival hyperplasia, and one had headache, paresthesias, and gingival hyperplasia. For the 58 patients who completed the trial, CyA significantly outperformed PPS for all outcomes measured as means: 24-h frequency, nocturia, voided volume, awake bladder capacity, IC symptom and problem index scores, and pain visual analog scale. Success rates, defined as at least moderate improvement on global response assessment, were 75 % for CyA and 19 % for PPS. When success was defined as much better or completely cured, the corresponding rates were 59 and 13 %. Hunner lesions were present in five and ten patients randomized to CyA and PPS, respectively. The authors did not state whether presence of Hunner lesions was associated with outcome. Bladder biopsy was not mentioned.

Based on the above data, the original AUA guideline listed CyA as a Tier 5 treatment option (of six tiers) with caveats: it is not approved by the United States Food and Drug Administration for IC/BPS, adverse event rates were high and it should be used only by providers experienced with IC/BPS and willing to provide long-term care after intervention [11].

After the original guideline, two additional articles were published. The first was a combined series of 44 patients by three IC/BPS experts at tertiary centers [28]. All patients had failed at least two oral medications and at least one type of bladder instillation or cystoscopic treatment. CyA was started at 2–3 mg/kg/day in two daily doses, maximum150 mg twice a day. The dose was reduced as needed for adverse events, also was gradually decreased as tolerated after achieving good symptom response.

The report did not mention bladder biopsies, but the authors noted that 34 patients had Hunner lesions. For these patients, 85 % had initial success but six later stopped due to adverse events, for a final success rate of 68 % with Hunner lesions. In contrast, for the ten patients without Hunner lesions, only three (30 %) had success. All responders had a notable improvement within 4 months. Adverse events included increased serum creatinine, hypertension, exacerbation of chronic bronchitis, alopecia, bacterial cystitis, oral ulcers, thrush, diarrhea and hypomagnesemia, gout and cutaneous lymphoma.

The second report described 16 patients who all had Hunner lesions [29]. Patients received CyA 3 mg/kg/day in two daily doses for 12 weeks, then 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks. One patient was excluded for UTI and five withdrew due to side effects such as diarrhea, abdominal pain, and hyperbilirubinemia. After 12 weeks the mean IC symptom score decreased from 16 to 8, and only one patient had a symptom score above 11. If the other nine patients are defined as responders, the response rate is 90 % for the patients who completed the study and 56 % (9 of 16) overall. The investigators also measured bladder nitric oxide (NO) as a marker for inflammation. Mean NO concentration decreased from 489 to 3 parts per billion by 8 weeks on CyA. After stopping CyA, symptom scores and NO levels increased.

Including these two new articles, the updated AUA guideline kept CyA as a Tier 5 option [12]. The guideline emphasized that serious adverse events can occur and only few patients had long-term follow-up, so it remains uncertain whether the benefits of CyA outweigh the risks. Clinicians inexperienced with CyA were strongly encouraged to seek expert guidance for dosing and monitoring.

Summary and Practical Considerations

To date, the systemic immunomodulators with published trials for IC/BPS are corticosteroids, azathioprine, chloroquine derivatives, methotrexate, mycophenolate, adalimumab, and CyA. Of these, CyA is the only agent with more than two supporting publications and the only agent listed as an option in the AUA guideline.

In our practice we offer CyA to patients with Hunner lesions that are too extensive for cystoscopic treatment or that recur quickly after cystoscopic treatment. We also would offer it to a patient without Hunner lesions if he/she had failed the less risky options and if bladder biopsy showed inflammation.

When discussing CyA, we emphasize the risks including renal damage, serious infections, and malignancy, especially lymphoma and skin cancers. We make sure that none of the less risky options have been overlooked, including frequent instillations with high doses of analgesic and anti-inflammatory agents. We offer urinary diversion, which seems drastic but avoids the serious infectious and cancer risks of CyA, and usually leads to pain resolution in patients with Hunner lesions.

If the patient desires to proceed with CyA, we check blood pressure and lab work including complete blood count, liver and renal function, electrolytes, serum magnesium and uric acid levels, urinalysis and culture. We start with 3 mg/kg/day in two equal doses. CyA comes in 25-mg pills and we round down to make the dose fit. For example, for an 80-kg patient, 3 mg/kg/day would be 240 mg a day. We would round down to 200 mg a day and prescribe 25-mg pills, take four pills twice a day. The rationale for rounding down comes from Forrest, who routinely started with 2 mg/kg/day and also had good results [28]. Regardless of patient weight, our maximum starting dose is 150 mg twice a day.

We see the patient back in 1 month and check blood pressure, also the same lab work plus CyA level. If symptoms are improving and blood pressure and lab work

are normal, then we continue the same. If symptoms are improving and blood pressure or lab work is abnormal, we decrease the dose by one or two pills (i.e., 25 or 50 mg) a day. If symptoms are not improving, we do not increase the CyA dose unless the serum level is subtherapeutic.

We see the patient back in 3 months for the same evaluation. This visit (4 months on CyA) is a decision point: does the symptom relief justify continuing CyA? If no, we stop. The rationale for stopping comes from the two most recent articles, in which all responders had notable benefit by 3–4 months [28, 29].

If the patient has significant benefit and decides to continue at the 4-month visit, we encourage him/her to decrease his/her dose gradually (e.g., decrease by one pill a day every 3–4 weeks) and increase if the symptoms return. Most patients end up at about 50 mg twice a day and most need to continue a low dose indefinitely. We continue the same monitoring every 3 months (every 4 months for long-term stable patients).

Future Research

Should other immunomodulators besides CyA be considered (or, if previously studied, reconsidered)? Possible reasons to use a different immunomodulator instead of CyA would be better efficacy, lower toxicity, or (assuming adequate efficacy) lower expense.

To date, no other systemic immunomodulator has demonstrated better efficacy than CyA. However, with some of the prior trials, the selection criteria may have allowed patients without inflammation to be enrolled. If so, the studied agents may have failed due to inappropriate patient selection. If any of these agents is significantly less toxic than CyA, then one might consider a randomized trial of CyA vs. the alternate agent, restricted to patients with Hunner lesions or biopsy-proven bladder inflammation.

In two prior studies limited to patients with Hunner lesions, oral corticosteroids had response rates of 64 and 47 %, respectively [18, 19]. These are similar to the success rates for CyA in patients with Hunner lesions (68 and 56 %) if withdrawals are included in the denominators [28, 29]. It remains unknown whether the adverse event profiles for corticosteroids vs. CyA, each given long-term at the lowest dose needed to control bladder symptoms, would favor one agent over the other.

Tacrolimus as a similar mechanism of action to CyA may involve less toxicity. A prior abstract described good results in IC [30]. A prospective comparison of CyA vs. tacrolimus would provide useful guidance for future patients.

Due to design flaws in the prior study of adalimumab, we must be careful not to dismiss it prematurely. It is unclear whether the differing toxicity profiles would justify a formal comparison of adalimumab vs. CyA, but at least it could be considered for patients with comorbid conditions that are appropriately treated with adalimumab. Also, if there were a method for identifying IC/BPS patients with TNF-alpha mediated pathology, those patients may be appropriate for a future trial of adalimumab.

Future research may reveal more specific information about the specific cell types and mediators that promote the pathophysiology of inflammation (when

present) in IC/BPS. Elucidating these details may allow development of future treatments that are more restricted and have less toxicity. For example, if B cells were found to have a major role in some patients, then rituximab might be effective for them. Another area for future research would be to use low doses of more than one agent in combination, as is currently done for certain organ transplant and cancer chemotherapeutic regimens.

Conclusions

It is profoundly gratifying to help an IC/BPS patient resolve his/her debilitating symptoms and resume a normal life. For some patients, immunomodulation is the treatment that provides this gratification. However, it is neither a panacea nor a miracle cure. Success requires proper patient selection: patients without an immune-mediated pathophysiology are unlikely to respond; also some patients may have refractory end-stage bladders. Even when effective, the current agents are limited by side effects and risks. Patients must be counseled and monitored carefully. Future research may lead to new agents, alone or in combination, to provide effective relief with fewer risks.

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Other Oral Agents for Chronic Pelvic Pain

16

Christopher J. Dru and Jennifer T. Anger

Anesthetics

Bladder anesthetics are orally administered medications that provide topical local anesthesia to the bladder upon excretion into the collecting system. There are no FDA-approved medications to effectively treat IC/PBS or CP/CPPS; however, bladder anesthetics are routinely used as a first-line therapy for the urgency/frequency and irritative voiding symptoms caused by these disease processes. The two most frequently used bladder anesthetics are phenazopyridine and methenamine, sodium phosphate monobasic, phenyl salicylate, methylene blue, hyoscyamine sulfate (Uribel™).

Phenazopyridine

Phenazopyridine is an azo-dye oral bladder anesthetic commonly used in the treatment of irritative voiding symptoms for many genito-urinary ailments. It is typically administered in combination with other nonsteroidal anti-inflammatory medications or antibiotics at the time of an episode of bacterial cystitis. The most common and marked side effect is a vivid red/orange color change in the urine and other bodily secretions. For this reason, it is usually prescribed as a short-term medication. The change is color is harmless, but it can permanently damage fabrics, clothing, and contact lenses. Other less common side effects are headaches, dizziness, renal dysfunction, yellowing of the skin, and confusion. Patients with glucose-6-phosphate dehydrogenase deficiency should not use phenazopyridine because it can exacerbate oxidative stress causing intravascular hemolysis. The mechanism of action of phenazopyridine is not clearly understood, but it is thought to act directly on the bladder mucosa as a topical anesthetic.

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Methenamine, Sodium Phosphate Monobasic, Phenyl Salicylate, Methylene Blue, Hyoscyamine Sulfate (Uribel™)

Uribel™ is another oral bladder anesthetic used in the treatment of irritative voiding symptoms. Similar to phenazopyridine, it is commonly administered in combination with other oral analgesics or antibiotics for the treatment of symptomatic genito-urinary infections. Also similar to phenazopyridine, it is not FDA-approved for the treatment of IC/PBS or CP/CPPS but does help treat irritative symptoms. Each component of the medication has a specific mechanism to help alleviate bladder pain. Methanamine acts as an antiseptic and bactericidal agent when it degrades into formaldehyde in acidic urine. Methylene blue has weak antibacterial properties that are not well characterized but require acidic urine for activation. Sodium phosphate monobasic is an acidifying agent that aids in the activation of methenamine and methylene blue. Phenyl salicylate produces topical analgesia of the bladder mucosa via weak inhibition of cyclooxygenase enzymes. Hyoscyamine is a parasympatholytic that aids in the relaxation of bladder smooth muscle to reduce spasms. The side effect profile of Uribel™ is minimal and it can be taken four times daily for long-term use. Uncommon adverse reactions include tachycardia, flushing, blurred vision, and shortness of breath.

Although evidence in the literature is lacking regarding the use of phenazopyridine in IC/PBS and CP/CPPS, it can be quite effective for patients with milder bladder pain symptoms. Men and women, usually those with mild or intermittent symptoms, can take phenazopyridine as needed for symptom exacerbations. However, long-term usage can result in the side effects as mentioned above. Methenamine, sodium phosphate monobasic, phenyl salicylate, methylene blue, hyoscyamine sulfate, on the other hand, is safe to take regularly or as needed, and also provides relief for patients with mild or intermittent symptoms.

Alpha-1 Receptor Antagonists

The alpha-1 receptor is a G protein-coupled receptor involved in the central and peripheral nervous systems. Norepinephrine and epinephrine are the neurotransmitters utilized in this signal transduction pathway. Alpha-1 receptor activation is primarily involved in smooth muscle contraction and vasoconstriction. Alpha-1 receptor antagonists have been used in the treatment of benign prostatic hyperplasia for many years, and there are several additional genitourinary indications for this class of medications. Several studies were performed to demonstrate the potential efficacy of alpha-1 receptor antagonists—alfuzosin, doxazosin, tamsulosin, and terazosin—in the treatment of CP/CPPS. However, there is scant literature supporting the use of alpha-1 receptor antagonists in IC/PBS. Theoretically, alpha-receptor blockade might help in men and women with pelvic floor dysfunction/voiding difficulty that results from their pelvic pain condition.

Alfuzosin

In 2003, Mehik et al. randomized seventy men with CP/CPPS to either alfuzosin 5 mg PO twice daily, placebo, or their current oral medication therapy (with the understanding that alpha-1 receptor antagonists were not included). These patients were followed for 6 months. There was a statistically significant decrease in pain symptoms in the alfuzosin group (65 % of study patients had a >33 % improvement in National Institutes of Health, Chronic Prostatitis Symptom Index (NIH-CPSI) total score; $p=0.01$). However, there was no improvement with alfuzosin in voiding symptom scores or quality of life scores. In addition, once the treatment study was over and the medication was stopped, patients treated with alfuzosin had symptom deterioration back to baseline. The authors concluded that alfuzosin therapy was safe and well tolerated but only provided a modest improvement in pain-predominant CP/CPPS patients [1].

Several years later in 2008, Nickel et al. conducted a multicenter, randomized, double-blind, placebo-controlled trial to reevaluate the efficacy of alfuzosin in the treatment of men with CP/CPPS. Two hundred seventy two men were randomized to either alfuzosin 10 mg PO daily or placebo for a 12-week period. At the end of the study period, there was no significant difference between patients who received alfuzosin versus placebo in terms of global response assessments (34.8 % versus 33.6 % respectively; $p=0.90$). In both study groups, there was a 4-point decrease in total NIH-CPSI scores. The authors' findings did not support the use of alfuzosin in the treatment of CP/CPPS [2].

Doxazosin

Evliyaoğlu et al. investigated the efficacy of doxazosin therapy in the treatment of CP. Sixty men were randomized to either doxazosin 4 mg PO daily or placebo for a 3-month period. There was a statistically significant difference in IPSS score in terms of overall pain and quality of life scores. In fact, patients who were randomized to doxazosin demonstrated a 37 % improvement in quality of life over that 3-month time period [3].

As a follow-up study several years later, Tuğcu et al. performed a prospective, placebo-controlled trial to compare the efficacy of doxazosin monotherapy to triple therapy with doxazosin, anti-inflammatory medications, and muscle relaxants. This study showed no significant difference in NIH-CPSI total score between the treatment groups [4].

Tamsulosin

Nickel et al. randomized 58 men with moderate/severe CP/CPPS to either tamsulosin 0.4 mg PO daily or placebo for 6 weeks. Men who received tamsulosin had an improvement in NIH-CPSI total score of approximately 3.6 points ($p=0.04$). The authors concluded that tamsulosin was superior to placebo in helping patients who suffer from severe forms of CP/CPPS [5].

Terazosin

Cheah et al. randomized 100 men with CP/CPPS to either dose-escalated terazosin (1–5 mg) PO daily or placebo for 14 weeks. In men who received terazosin, there was a reduction in symptoms as evaluated using the NIH-CPSI questionnaire. However, the authors found no difference in the velocity of urinary flow or post-void residual bladder volumes. It was concluded that terazosin was superior to placebo in the treatment of CP/CPPS [6].

In summary, alpha-1 receptor antagonists may be a useful adjunct in men who have failed other mainstays of therapy for chronic pelvic pain. Though not ideal first-line monotherapy, they are effective in some groups of patients. Alpha-1 receptor antagonists may potentially be of benefit in the subset of men and women with concomitant pelvic floor dysfunction who may benefit from relaxation of the bladder neck. It is important to note the side effect profile on this class of medications, and differences in effect of men versus women. Hypotension is a rare but significant side effect that effects both genders. For this reason this medication is typically given before bedtime. The other significant side effects, seen only in men, are retrograde ejaculation and anejaculation. In a randomized trial, tamsulosin was shown to have a 90 % decrease in ejaculate volume, with complete anejaculation in 35 % of patients. In contrast, retrograde ejaculation and anejaculation were not observed in men randomized to alfuzosin vs. placebo [7]. In men concerned with retrograde ejaculation or anejaculation and in men who are or will be attempting to conceive children, it is of the utmost importance to counsel them on these side effects. Alfuzosin may be a preferred agent in this patient population.

Nonsteroidal Anti-inflammatory Agents

Nonsteroidal anti-inflammatory drugs (NSAIDS) help reduce pain and inflammation through the inhibition of cyclooxygenase enzymes, type 1 and type 2 (COX1 and COX2, respectively. COX1 and COX2 catalyze the formation of thromboxane and prostaglandins from arachidonic acid. Aspirin is an example of a nonselective, irreversible inhibitor of COX1 and COX2. COX1 is a constitutively expressed housekeeping enzyme that has several roles in maintaining physiologic homeostasis. Inhibition of COX1 is associated with gastrointestinal bleeding and gastric ulcers by decreasing prostaglandin production. Given the morbidity associated with inhibition of COX1, a class of COX2-selective inhibitors was developed. In the CP/CPPS patient population, two COX2-selective inhibitors were studied—rofecoxib and celecoxib. No randomized trials have shown a benefit of NSAIDS in the treatment of IC/PBS; however, NSAIDS are commonly used early in the management of patients who present with painful urinary urgency and frequency who may later be diagnosed with IC/PBS. The side effect profile of COX2-selective inhibitors includes cardiovascular events such as stroke and myocardial infarction, gastric/intestinal ulcer disease, headache, nausea, vomiting, indigestion, and anxiety.

Rofecoxib

In 2003, Nickel et al. conducted a randomized, controlled, double-blind study of 161 men with chronic nonbacterial prostatitis to receive rofecoxib 25 mg PO daily, rofecoxib 50 mg PO daily, or placebo for 6 weeks. NIH-CPSI total, domain, and pain scores decreased in all groups; however, no significant difference was found between the groups who received placebo and the groups who received rofecoxib. In a subset analysis, there was a significant difference for men who had a six points or greater improvement in symptoms based upon the NIH-CPSI pain scale on rofecoxib 50 mg PO daily (vs. control, $p<0.05$). This study represented the first randomized trial of COX2 inhibitors in the treatment of CP/CPPS, and the authors concluded that there may be a beneficial effect of rofecoxib but that additional studies were needed [8]. Given the cardiovascular side effect profile, Rofecoxib was removed from the market and is no longer available.

Celecoxib

In a follow-up study several years later, Zhao et al. conducted a randomized blinded controlled trial of 64 men with CP/CPPS to receive either celecoxib 200 mg PO daily or placebo for 6 weeks. All men were followed with NIH-CPSI scores. At the end of the treatment, men who received celecoxib had an average decrease in NIH-CPSI total score from approximately 24 to 16. Men who received placebo had an average decrease in NIH-CPSI total score from approximately 24 to 19.5. This decrease between groups was statistically significant ($p<0.015$). In addition, there was a significant improvement in pain subscores ($p<0.006$) and quality of life ($p<0.032$) in men who received celecoxib. However, there did not appear to be a lasting improvement in symptoms once the medications were stopped. The authors concluded that celecoxib provides significant symptomatic improvement in men with CP/CPPS [9].

In summary, there does appear to be a useful role for NSAIDs, mainly COX2-selective agents, in the treatment of CP/CPPS. Although there remains a paucity of literature surrounding the use of NSAIDs in IC/PBS, a 2-week trial of NSAIDs may be effective in some patients with early onset IC/PBS who have relatively mild symptoms. However, the significant side effect profile of these medications must be considered. Rofecoxib was removed from the market given an association with significant cardiovascular events, but celecoxib remains available.

Cholinergic Antagonists

Cholinergic antagonists are classically used for the treatment of overactive bladder symptoms, including frequency, urgency, nocturia, and urge incontinence. Response to anticholinergics was once considered exclusion criteria for IC/PBS [10, 11]. However, many people who have pain associated with frequency and urgency may

actually respond well. These agents work by binding to acetylcholine receptors, mainly in smooth muscle, to reduce muscle tone. This aids in improved bladder filling and decreased frequency of micturition. While the mechanism of CP/CPPS is not clearly understood, a component may be attributed to the increased frequency of bladder contraction and relaxation. Cholinergic antagonists can be efficacious, but they do have a significant side effect profile. The most common side effects experienced by patients are dry mouth, blurred vision, constipation, and urinary retention. Cholinergic antagonists are divided into two chemical variants: quaternary and tertiary amines. Tertiary amines are associated with a more significant side effect profile as they are able to cross the blood–brain barrier. Solifenacin, a tertiary amine, is the only cholinergic antagonists studied in a randomized fashion in CP/CPPS. Oxybutynin has been shown to help alleviate the bothersome urinary urgency and frequency associated with IC/PBS and overactive bladder but does not treat the disease process itself [12, 13].

Solifenacin

In 2011, Lim et al. conducted a randomized, single-blinded study of 96 men with CP/CPPS to receive either ciprofloxacin 1000 mg PO daily or ciprofloxacin 1000 mg PO daily and solifenacin 5 mg PO daily in combination for 8 weeks. Men treated with ciprofloxacin in addition to solifenacin had statistically significant improvement in symptoms observed via the NIH-CPSI total score and in the pain and urinary subset scores compared to men who received ciprofloxacin alone. The authors concluded that solifenacin is a useful adjunct in the treatment of CP/CPPS, especially in those with urinary frequency and urgency [14].

Overall, cholinergic antagonists are a useful adjunct in the treatment of CP/CPPS. Although there is a relative lack of data using these agents in IC/PBS, they can be effective in alleviating the bothersome urinary frequency and urgency associated with bladder pain. Oxybutynin is a mainstay in the treatment of overactive bladder-associated urgency and frequency and is utilized often when these symptoms predominant in IC/PBS. In one study, approximately 6 % of women with IC/PBS were taking oxybutynin to alleviate frequency/urgency symptoms [15]. Additional studies are needed to determine the true efficacy of these agents in IC/PBS.

Mirabegron, a beta-3 agonist, is a relatively new medication used to treat urgency and frequency associated with overactive bladder. Activation of the beta-3 receptor in the detrusor results in muscle relaxation with a subsequent increase in bladder capacity. In randomized trials, it has been shown to improve many of the bothersome symptoms of overactive bladder [16]. Given the efficacy of cholinergic antagonists in the treatment of CP/CPPS and symptomatic relief in IC/PBS, there may be a future application of mirabegron in both of these patient populations. Preliminary data is promising, but randomized placebo-controlled studies are needed to assess the specific role of mirabegron in treating IC/PBS.

Pentosan Polysulfate Sodium

Pentosan polysulfate sodium (PPS) is one of the few FDA-approved medications for the treatment of IC/PBS. PPS is administered as either an oral agent or as an intravesical infusion. It is thought to protect and coat the damaged bladder mucosa and prevent permeability by maintaining the glycosaminoglycan (GAG) layer. Increased bladder permeability and breakdown of the GAG layer with subsequent irritation of the underlying bladder mucosa is one of the proposed mechanisms of IC/PBS. Patients receiving PPS should be assessed at 3 months. If pain symptoms have not improved, then PPS can be continued for three additional months; however, no benefit was shown in continued use of PPS when there was no symptom improvement after the first 3 months of treatment [17].

In 2005, Nickel et al. conducted a randomized, double-blinded, placebo-controlled trial of 100 men with CPPS to receive either pentosan polysulfate sodium 300 mg PO three times daily or placebo for 16 weeks. Patients who received pentosan polysulfate sodium therapy had improvement in the Clinical Global Improvement (CGI) symptom score index ($p=0.04$); however, the mean CGI scores were not significantly different. Additionally, there was also a trend toward improvement in symptom score when utilizing NIH-CPSI total scores ($p=0.068$). The authors concluded that pentosan polysulfate sodium was more likely than placebo to help provide relief of the symptoms associated with CPPS, though the effect found was minimal [18].

Conclusions

There is a range of medications that can be helpful in the management of patients with urologic chronic pelvic pain. Most have a relatively small impact on symptoms overall, though may lead to significant improvement in pain for certain subsets of patients. To date, studies reveal how little we know and how many more studies are needed, particularly in the case of IC/PBS, to help us improve care for the pelvic pain patient.

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Therapy for Interstitial Cystitis/Bladder Pain Syndrome and Other Forms of Pelvic Pain During Pregnancy

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Peter Van Eerden and Saila Moni

Introduction

Pelvic pain is a common condition in women and has a prevalence ranging from 16 to 25 % [1]. There are several potential etiologies of chronic pelvic pain in women and they include disorders of the gynecologic, urologic, gastrointestinal, musculoskeletal, and nervous systems [2]. Pelvic pain unique to pregnancy is even more common, occurring in 48–56 % of all pregnancies [3]. More specifically, a recent cross-sectional study in the United States demonstrated that two thirds of a cohort of pregnant patients reported back and pelvic pain [4]. The pain often starts in the first trimester of pregnancy and worsens as the pregnancy progresses [5]. Many healthcare providers are apprehensive about treating pain in pregnant patients due to risks associated with the various therapeutic interventions during pregnancy; it is estimated that over 50 % of the women receive little or no intervention from their healthcare providers [4]. However, for many pregnant patients, pain can interfere with daily activities, disturb sleep, and can lead to disability/sick leave. Subsequently, for physicians, familiarity with common pain problems as well as the maternal and fetal risks associated with the therapeutic interventions will prevent and ameliorate these outcomes and achieve a more comfortable pregnancy. The intent of the present chapter is to focus on management options in women with preexisting chronic gynecologic and urologic pain syndromes who subsequently become pregnant. We will discuss the treatments options of chronic pain syndromes in pregnancy, as well as highlight

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issues that need to be taken into consideration when dealing with pain therapy in pregnancy. Important to acknowledge is that every attempt was made to make the discussion that follows to be evidence-based however, there is paucity of research in this domain due to the subjective nature of the condition, lack of universally recognized classification system, and limited research in pregnant population [6].

Urologic Causes of Pelvic Pain

Our focus will primarily be on urologic causes of pelvic pain that exists prior to any potential future pregnancy and the treatment options available and how they can be used/altered/adjusted/discontinued with pregnancy. A common painful syndrome of the urinary system is interstitial cystitis/bladder pain syndrome (IC/BPS). Hallmark features include perceived bladder pain, urinary frequency, urinary urgency and without evidence of infection.

Interstitial Cystitis

There is very little literature on pregnancy in women with a history of interstitial cystitis/bladder pain syndrome (IC/BPS). The most common theory for the cause of IC/BPS is deficiency of the bladder urothelium. This may be the primary problem or it may be secondary to bladder inflammation. Pregnancy is associated with changes in estrogen and progesterone that may affect bladder urothelium. Both estrogen and progesterone have been shown to stimulate growth of cultured urothelial cells [7, 8]. Another proposed mechanism of IC/BPS is the destruction of the glycosamnioglycane-GAG-layer of the bladder urothelium which then exposes the submucosal nerve filaments making them accessible to noxious substances of urine [9]. Dysfunction of urothelium resulting in altered production of growth factors such as heparin binding epidermal growth factor has also been implicated in IC/BPS [9]. As mentioned, inflammation and mast cell activation plays a key role in the pathophysiology of IC/BPS. In fact, histological examination of ulcers among patients with IC/BPS has shown pan-cystitis and perineural infiltrates of lymphocytes as well as having a tenfold increase in mast cell counts compared to controls [9]. Important to note that these findings are not seen among non-ulcer IC/BPS patients. Other possible etiologies include autoimmune dysfunction, autonomic nerve changes, and hypoxia. All the possible theories discussed above can be modified by pregnancy due to hormonal changes; more specifically, the gonadal hormones have been shown to influence these mechanisms and thus influence symptoms and manifestations of IC/BPS during pregnancy [10]. More recently, IC/BPS has been termed a neuroimmunoendocrine disorder with complex pathogenetic interactions, which is probably most accurate; studies have shown that mast cells in close proximity to nerve terminals can be influenced by estradiol and corticotropin releasing hormone [9]. This finding illustrates that pregnancy through the gonadal hormones can indeed influence IC/BPS. The search for an exact pathogenesis model for IC/BPS remains to be developed and research is ongoing.

In the context of pregnancy, IC/BPS symptoms may go into remission or improve, and some suggest may worsen as the pregnancy progresses, i.e., in the third trimester. In 1989, the Interstitial Cystitis Association did a survey on how women who have mild, moderate, and severe forms of the disease and became pregnant fared [11]. The survey revealed that women who had mild symptoms often got worse and their symptoms remained worse for up to 6 months after delivery [11]. Women with severe symptoms often seemed to improve, and remained that way for up to 6 months after delivery [11]. Women with moderate symptoms appeared to remain much the same [11]. As for pregnancy outcome, there was no significant difference in the number of cesarean deliveries and the disease did not appear to have any impact on the general health of the infant [12]. Notably, the worsening of symptoms with progression of pregnancy from baseline may be due to enlargement of the gravid uterus or from women stopping their oral therapy due to perceived risks to the fetus (Interstitial Cystitis Association 2010) [13]. However, pregnant women with IC/BPS should not stop treatments as the disease can have significant effect on the quality of their lives; one database of all IC/BPS patients reported that nearly 40 % of patients reported urinating 15 times or more during awake hours, more than 20 % reported voiding at least four times per night, almost half (47.9 %) reported constant urgency, and 23.6 % reported having severe pain [14]. Thus, therapy in pregnancy should be tailored based on patient's symptoms and taking maternal/fetal risks into consideration.

Treatment Options for Interstitial Cystitis/Bladder Pain Syndrome

A wider array of treatment options are available for patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Treatment options for IC/BPS include conservative therapy that includes patient education/empowerment, behavioral modification, physical therapy, stress reduction, and dietary manipulation [9]. Oral therapy includes many oral drugs such as penton polysulfate sodium, amitriptyline and tricyclic antidepressants, antihistamines analgesics, cyclosporine A, and others [9]. Intravesical therapy includes infusion therapy with lidocaine, heparin and dimethylsulfoxide, corticosteroids, endoscopic injection of botulinum toxin type A, and others. Surgical interventions include sacral neuromodulation, denervation surgery, bladder modifying surgery, and total cystectomy/urethrectomy. Initial treatment type and level should depend on symptom severity, clinician judgment, and patient preferences.

First-Line Therapy for Interstitial Cystitis/Bladder Pain Syndrome

The first step in the management of patients with interstitial cystitis/bladder pain syndrome (IC/BPS) is to provide education about the condition, including the diagnostic criteria, variability of symptoms, and chronic nature of the condition [15]. Patients should be counseled that adequate symptom relief is achievable, but that this may require multiple trials of different types of therapies. Acute conditions that

may exacerbate IC/BPS symptoms should be treated promptly, including genitourinary disorders (e.g., urinary tract infection, vulvovaginitis).

Initial options for treating IC/BPS present minimal risks to the pregnant woman and can be offered to all patients. In patients with mild IC/BPS symptoms, first-line therapy may be effective alone. Self-care practices and behavior modification include local heat or cold over the bladder or perineum, avoidance of activities or food or beverages that exacerbate symptoms, such as caffeine, alcohol, artificial sweeteners, and hot pepper and bladder training based on your voiding patterns to alleviate symptoms; these changes also incorporate dietary modifications [See chapter 5: Diet in the context of Chronic Pelvic Pain] [9]. Care should be taken to avoid excessive heat in the first trimester as exposure to heat in the form of hot tub, sauna, or fever in the first trimester of pregnancy has been associated with an increased risk of neural tube defects [16]. Avoiding exercises, recreational activities, sexual activities, or body positions that seem to worsen the bladder symptoms may be helpful. Women may find that increasing fluid intake is helpful. Others experience pain with bladder filling and may find that moderate fluid restriction provides some relief. Patients should be instructed to avoid extremes of fluid intake. In most patients, it is not necessary to drink more than 2 L of fluid per day. The Institute of Medicine recommends that pregnant women drink about 10 cups of fluids daily as significant fluid restriction can lead to constipation, hemorrhoids, excessive swelling, urinary tract or bladder infections and promote preterm uterine contractions. While there is no conclusive literature to show it, common sense and clinical judgment dictates that stress reduction and normalization of life will improve overall quality of life [9]. However, despite these interventions, many women will require additional therapy for adequate symptom control.

Second-Line Therapy for Interstitial Cystitis/Bladder Pain Syndrome (Medical Management)

Second-line therapy in the management of interstitial cystitis/bladder pain syndrome (IC/BPS) includes appropriate manual physical therapy techniques, oral medications, and intravesical treatment [17]. These interventions are more invasive compared to the first-line therapy, which can be administered to both pregnant and nonpregnant patients indiscriminately [17].

Physical therapy may be beneficial to women with IC/BPS who have pelvic floor muscle tenderness on examination. Pelvic physical therapy includes treatment of the pelvic muscle tender points, trigger points, connective tissue restrictions, and muscular abnormalities of the soft tissues [17]. Typical therapy utilizes a transvaginal approach and often includes myofascial release. This type of treatment is provided by a physical therapist with specialized training in pelvic soft tissue manual manipulation and rehabilitation. While more invasive than first-line treatment, there is limited data of this intervention on pregnant patients. Transvaginal therapies limited to the pelvic muscles are likely safe in pregnancy. Some practitioners also apply electrical stimulation, for which there is little to no data in the context of pregnancy. Extrapolating from low quality data of pregnant patients with low back pain and

pelvic pain undergoing physical therapy, one can conclude that physical therapy when done appropriately is efficacious and safe in pregnancy [6].

Second-line oral medications and intravesical therapy are amitriptyline, cimetidine, hydroxyzine or pentosan polysulfate and dimethyl sulfoxide, heparin, and lidocaine respectively [17]. While not part of the American Urological Association's (AUA) protocol specific for IC/BPS management, analgesic medications such as acetaminophen, NSAIDs, and opioids may be needed to be used intermittently for pain management at any point of treatment. There are no comparative studies of oral medications for IC/BPS; the choice of agent depends upon the risk of adverse effects and patient preference. Usually, for the nonpregnant patients, the strategy is to try different medications empirically and decision to continue is based on efficacy and side-effect profile. For the pregnant patient, the fetal risks associated with various medications are weighed against the degree of symptom relief provided. These decisions should be made in a multidisciplinary fashion with the obstetrician, maternal fetal medicine physician, urologist, and the patient. One important fact to keep in mind is that the baseline risk for fetal malformations is approximately 2–4 % in the general population [11]. The following sections will discuss various medications and interventions and risks associated with pregnancy.

Medication Use in Pregnancy

The basic principles of teratology were described by James G. Wilson in the early 1970s [18]. Susceptibility to teratogens depends on the genotype of the conceptus and its interactions with the environment. It also varies with the developmental stage at the time of exposure. Teratogens act in specific ways to initiate abnormal embryogenesis. The final manifestations of abnormal development are malformation, growth restriction, functional disorder, and death. The effective dose of an agent is that dose biologically available to the embryo or fetus. Finally, there is a dose response for all exposures, a threshold dose below which no effect is detected.

In 1989, the Food and Drug Administration (FDA) established a widely used pregnancy category system that has been incorporated into the product label. The FDA risk classification in pregnancy consists of categories A, B, C, D, and X, indicating potential risk of drug exposure to the fetus if taken by the woman during pregnancy. They were amended in 2001. The intent of the pregnancy drug categories was to inform both clinicians and pregnant women about the teratogenic risks associated with specific mediations and was intended to be an easy way to gauge drug safety. The limitations of this categorization are that it provides a false sense of security, is highly reliant on animal studies, includes too few data in humans, and focuses on overt fetal injury. It is preferable that experimental animal data be supplemented by data obtained in humans. Additionally, there are no timely updates, there is inadequate post marketing surveillance and silence about dosing changes required in pregnancy. This system has recently been replaced by a system that relies on plain text information about specific medications.

In December 2014, the Food and Drug Administration (FDA) amended its regulations governing the content and format of the "Pregnancy," "Labor and delivery,"

and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drug and biological products. The FDA published the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule) [19].

The PLLR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The final rule requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling. For human prescription drug and biological products subject to the Agency's 2006 Physician Labeling Rule, the final rule requires that the labeling include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help healthcare providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The PLLR also requires the label to be updated when information becomes outdated. The final rule creates a consistent format for providing information about the risks and benefits of prescription drug and/or biological product use during pregnancy and lactation and by females and males of reproductive potential. These revisions are intended to facilitate prescriber counseling for these populations. This rule became effective on June 30, 2015. Prescription drugs and biologic products submitted after this date will use the new format, while labeling for prescription drugs approved before June 30, 2015 will be phased in gradually.

There are other avenues for information available for clinicians which provide summary information in a variety of ways. Online databases include TERIS, Reprotox, Briggs, and Shepard. OTIS (Organization of Teratology Information Specialists) MotherToBaby is a service of the nonprofit Organization of Teratology Information Specialists (OTIS) and is dedicated to providing evidence-based information to mothers, health care professionals, and the general public about medications and other exposures during pregnancy and while breastfeeding (http://www.mothertobaby.org). Pregnancy registries, case reports of adverse events, observational cohort studies, database cohorts, case–control studies, and summary of data sources provide additional resources.

With these thoughts in mind with regards to regulations and labeling, we will now discuss specific medications and interventions.

Analgesics in Pregnancy

Acetaminophen

Acetaminophen is an analgesic and antipyretic used frequently in pregnancy. Acetaminophen has no known teratogenic properties and is hepatotoxic only in extreme overdosage [20]. As with most drugs, there are no controlled studies in

pregnant women in the first trimester. The Danish National Birth Cohort consisting of 88,142 patients who had information on acetaminophen use during the first trimester of pregnancy demonstrated that ingestion of acetaminophen during pregnancy is not related to an overall increased prevalence of congenital abnormalities or to an increased prevalence of the most frequent abnormalities. [21]. For pain management during pregnancy, acetaminophen is a safe and effective first-choice agent.

NSAIDs

NSAIDs have both analgesic and anti-inflammatory properties and are commonly used for pain management. The proposed mechanism of action of NSAIDS is by acting as nonselective inhibitors of cyclooxygenase and thus inhibiting prostaglandin synthesis. During pregnancy, prostaglandins modulate many key processes, including stimulating uterine activity, maintaining patency of the fetal ductus arteriosus (essential for adequate in utero blood flow), and promoting fetal urine production (which contributes to the level of amniotic fluid in the second and third trimesters) [20]. Consequently, alteration of prostaglandin metabolism by NAIDS can be expected to have varied effects on the pregnancy, depending on the timing and duration of use.

NSAIDs are among one of the most frequently used drugs during the first trimester of pregnancy because it is an over the counter medication routinely used for pain management. There is controversy regarding risks associated with maternal exposure in the first trimester. Several studies found an association with higher rates of miscarriage while others found no such associations; possible mechanism is the NSAIDs interference with placental circulation and implantation [20]. Similarly, data on congenital malformation associated with NSAID use in the first trimester is inconsistent; some observational studies have shown increased rate of cardiac defects and gastroschisis while others did not show such a relationship [20]. The Collaborative Perinatal Project suggests that first-trimester exposure to aspirin does not pose appreciable teratogenic risk nor does ibuprofen or naproxen, the most commonly used NSAIDs [22].

The effects of fetal exposure to NSAIDs in the third trimester are well documented. NSAIDs use in the third trimester is associated with premature narrowing of the ductus arteriosus, which can lead to pulmonary hypertension in the newborn and decreased fetal urine production leading to oligohydramnios. For example, Indomethacin is very effective for pain caused by degenerating fibroids; however, its use for long periods, defined as greater than 48 h, has been associated with narrowing of the ductus arteriosus and oligohydramnios [21]. Therefore, if NSAID use is indicated, the duration should be short. More importantly, all NSAID use for pain should be discontinued by 34 weeks' gestation to prevent pulmonary hypertension in the newborn [23].

Summarizing the data, NSAID use in pregnancy must be done with caution to achieve benefit and avoid fetal risk. NSAID use in the first and second trimesters has

shown inconsistent pregnancy outcomes and thus it is prudent to use the lowest dose for the shortest duration to ameliorate symptoms. In the third trimester, if NSAID use is indicated, the duration should be short (less than 48 h) in the absence of monitoring of fetal ductus flow and amniotic fluid volume and should be stopped at 34 weeks of gestation.

Opioids

Opioids are often prescribed and used for the management of pain in the antepartum, intrapartum, and postpartum periods. Much of our present knowledge about the effects of chronic opioid exposure during pregnancy is derived from the study of opioid-abusing patients. While further studies need to be done and some studies show inconsistent results, there has been an association linked to opioid exposure and birth defects. The Collaborative Perinatal Project monitored 50,282 mother-child pairs and studied exposure to codeine, propoxyphene, hydrocodone, meperidine, methadone, morphine, and oxycodone and only codeine was found to have an association with respiratory malformation (respiratory) [20]. Also, a study using data gathered from the National Birth Defects Prevention Study (1997–2005), which consisted of an ongoing multisite, population-based, case–control study of more than 30 types of major structural birth defects, reported that opioid treatment from 1 month before pregnancy through the first trimester was associated with a greater risk for conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida, and gastroschisis; codeine and hydrocodone represented 69 % of all reported exposures [24]. It is important to understand that increase in relative risk for rare birth defects translates into only a modest absolute increase in risk above baseline in population. According to the FDA guidelines, all opioid analgesics are now teratogenic risk category C when used for a short time. Healthcare providers should have an open discussion with their patients regarding opioid use and patients should make an informed decision.

Chronic opioid use in pregnancy has been associated with low birth weight and decreased head circumference, although there may be confounding factors such as polysubstance abuse and smoking [20]. It is important to note that all opioid medications are risk category D when used for long periods of time during pregnancy [20]. This labeling is due to the risk of neonatal opioid dependence when mothers are treated with opioid medications for prolonged periods during pregnancy. For opioid-dependent patients, acute cessation should never be done as it may cause fetal withdrawal in utero resulting in fetal tachycardia and death [25]. Furthermore, acute opioid withdrawal carries an increased risk of miscarriage, placental abruption, and preterm labor. Hence, for pregnant patients who are opioid dependent, regardless of whether the use is prescription or illicit, the recommendation is to continue narcotic medication for prescription use or opioid substitution therapy such as methadone or buprenorphine plus entry into treatment programs for women using illicit drugs [20]. Neonates exposed to opioid medications can develop neonatal abstinence syndrome (irritability, increased tone, poor feeding, and seizures) in

the first few days of life. Recognition and supportive measures typically result in few short-term consequences for the neonate and there are no studies evaluating the long-term effects of in utero opioid exposure. Notably, recently data has shown that buprenorphine compared to methadone results in higher birth weight, lower prevalence and severity of the neonatal withdrawal syndrome, and shorter hospital stay for the newborn [26].

Parenteral opioids are often used in the perioperative period. There are not many comparative studies evaluating the various parenteral opioid analgesics. Important to note that these medications may lead loss of normal variability in the fetal heart rate and may cause respiratory depression in the neonate. Of the parenteral opioids, meperidine, which has a very long half life of 18 h, can lead to accumulation to toxic levels and its active metabolite normeperidine can cause excitation of the nervous system leading to tremors and seizures; as such, it is not recommended in repeated doses in pregnancy [25]. Fentanyl, morphine, and hydromorphone are all safe and effective alternatives when a potent opioid is needed for parenteral administration.

Opioid analgesics can also be administered into the intrathecal or epidural spaces to provide analgesia. Such neuraxial administration of opioids provides excellent analgesia. Spinal or epidural delivery of opioids can be used to minimize maternal plasma concentrations, thereby reducing placental transfer to the fetus or exposure of breastfeeding infants [25].

Gabapentin

Many of anticonvulsants have been used in the management of chronic pain syndromes. Gabapentin or 1-(aminomethyl)cyclohexaneacetic acid, a newer anticonvulsant marketed as Neurontin, is used for chronic and more specifically neuropathic pain syndromes. Gabapentin inhibits dopamine release in parts of the central nervous system. It is a category C drug according to FDA [20].

There is limited and inconsistent data on pregnancy outcomes and gabapentin use. Experimental animal data have shown some adverse effects. In the manufacturer's data reported to the FDA, it was noted that the offspring of mice and rats exposed to doses of 1–4 times the maximum recommended human dose (MRHD) experienced delayed ossification at numerous sites in the skeleton, including the skull, vertebrae, and limbs as well as hydroureter and/or hydronephrosis [27]. In contrast to the manufacturer's data, a published study in mice, rats, and rabbits did not report any developmental toxicity of gabapentin at comparable maternal doses (3000, 1500, and 1500 mg/kg/day, respectively) [28]. Similarly, the data among humans reveal case reports of normal and abnormal pregnancy outcome after gabapentin therapy. There are case reports involving gabapentin-exposed infants born with defects such as cyclopic holoprosencephaly in one instance [29], the absence of an opening for one ear canal in another instance [30], pyloric stenosis, and inguinal hernias [31]. However, in each of these cases the mothers were also receiving other drugs and no conclusion can be drawn regarding what role if any gabapentin

might have played in their development. This confounding effect is further demonstrated in a multinational collection of reports from teratogen information services, which identified 223 women who were taking gabapentin during the first trimester and compared their outcomes with a control population exposed to other medications [32]. In this study, there were seven children with major malformations, including two with ventricular septal defect, and one each with anencephaly, pyloric stenosis, clubfoot, cryptorchidism, and a combination of macrocephaly, micro-retrognathism, and cutis marmorata. However, all women with affected children were also exposed to other medications and three of them smoked cigarettes. There were more elective abortions and more intensive care nursery admissions in the gabapentin-exposed infants. Contrasting this data are findings from the Danish record linkage study, which also evaluated birth defect diagnoses in women who filled a prescription for an anticonvulsant medication during the presumed first trimester of pregnancy [33]. They reported no association to congenital anomalies among the 59 pregnancies with exposure to gabapentin (odds ratio 0.71, 95 % CI 0.10–5.10). Similarly, a Swedish Medical Birth Registry study reported that there was no effect on birth-weight-adjusted head circumference in 56 infants exposed to gabapentin monotherapy compared to the general population not exposed to antiepileptic drugs [34]. Furthermore, the Gabapentin Registry Study has not shown an increased risk for adverse maternal and fetal events [35].

In summary, there are conflicting data with regards to gabapentin use and pregnancy outcomes and thus difficult to make recommendations. It is prudent to discontinue gabapentin if one is able to tolerate discontinuation during pregnancy, particularly during the first trimester and possibly resuming afterward if it had yielded excellent results.

Second-Line Therapy of Interstitial Cystitis/Bladder Pain Syndrome

Penton Polysulfate Sodium (PPS)

Pentosan polysulfate sodium (PPS), which goes by the trade name of Elmiron, has been found to have a modest benefit for symptom reduction in interstitial cystitis/bladder pain syndrome (IC/BPS) based on randomized trial data [15]. PPS is the only oral medication approved by the US Food and Drug Administration (FDA) for treatment of IC/BPS. The typical regimen is 100 mg three times daily.

It is classified by the older FDA categorization as a Class B drug. There are no adequate or well-controlled studies of pentosan polysulfate sodium use in human pregnancy. The effects on the developing fetus, if there are any, are unknown. In one study, hemostasis in fetuses between 18 and 23 weeks' gestation remained similar to unexposed controls 30 min after a single PPS injection. Exposed fetuses had been previously selected for abortion between weeks 18 and 23 of gestation due to chromosomal abnormalities or hemoglobinopathies [36]. However, changes in maternal hemostasis occurred within 30 min of PPS injection suggesting that PPS may not

cross the placenta [36]. Reproductive studies involving pregnant rats/mice and rabbit given doses 15 and 7.5 mg/kg of pentosan polysulfate sodium, respectively, did not result in evidence of fetal harm [37]. However, until more data is available, pentosan polysulfate sodium should only be used during pregnancy if the maternal condition justifies the potential risk to the fetus.

Amitriptyline

Amitriptyline is a tricyclic antidepressant, marketed under the brand names Elavil and Endep. Amitriptyline is the most widely used agent for initial pharmacologic therapy of IC/BPS, since the effects can be observed soon after therapy. Amitriptyline appears to be most effective at higher doses, but use of these doses is limited by bothersome or dangerous adverse effects. Tricyclic antidepressants are believed to have analgesic properties and also to relieve the depressive symptoms associated with chronic pain. FDA lists it as a category C drug.

Amitriptyline crosses the human placenta and had adverse fetal effects in some animal models but not others. Amitriptyline was associated with teratogenic effects in the hamster, especially when the benzodiazepine chlordiazepoxide was coadministered [38, 39]. Cranial malformations and encephalocele were predominant among the anomalies reported. In humans there has been concern that amitriptyline and other tricyclic antidepressants might cause congenital malformations [40] with specific attention focused on limb reduction defects [41, 42]. However, retrospective studies of large populations have failed to show a preponderance of amitriptyline users among mothers of children with congenital limb defects [43]. Furthermore, studies have shown no developmental effect among the young children exposed in utero in follow-up; neurobehavioral testing of 80 children with antenatal exposure to tricyclic antidepressants (of whom 29 had been exposed to amitriptyline) did not demonstrate differences in IQ or behavior compared to 55 children with exposure to fluoxetine or 84 children without antidepressant exposure during gestation [44]. There are few case reports of withdrawal symptoms exposed to tricyclic antidepressant in pregnancy, but no such reports exist specifically for Amitriptyline [11]. Nortriptyline, a metabolite of amitriptyline, was associated with urinary retention in one newborn [45–48]. As such, the pediatrician can be notified in advance that the mother has been taking amitriptyline in pregnancy. Summarizing the overall experience, while there are some poor outcome associations, amitriptyline is relatively safe in pregnancy and seems to have a low risk profile.

Hydroxyzine

Hydroxyzine (Atarax; Vistaril) is a benzhydrylpiperazine antihistamine used as a sedative, antianxiety agent and as an antipruritic. A major active metabolite of hydroxyzine is cetirizine, which is also a commercial antihistamine. Hydroxyzine is the most commonly used antihistamine for the treatment of IC/BPS. Hydroxyzine is listed as a category C drug by the FDA.

Gestational effects of hydroxyzine have been equivocal. In rats, hydroxyzine and other antihistamines, including meclizine and buclizine, produced malformations of the palate and skeleton when administered during sensitive periods of gestation [49, 50]. Hydroxyzine was associated with malformations in beagle puppies [51] and dose levels of 5.5 mg/kg were associated with abortion in pigs and monkeys [52]. The hydroxyzine metabolite norchlorcyclizine is the proximate toxicant transferred to the rat fetus [53]. However, rodents might not be suitable for studying the human developmental effects of this and other histamine antagonists, because histamine constricts arterioles in rodent tissues but dilates arterioles in human tissues [54]. Fetal edema caused by antihistamines in rats was suggested as the mechanism by which these drugs induce orofacial malformations [55]. Data on the gestational effects of hydroxyzine exposure during human pregnancy include four reports involving 240 pregnancies. In the oldest of these reports, no significant increase in anomalies or pregnancy loss was found among 100 women who used oral hydroxyzine (50 mg/day) for nausea and vomiting [56]. The Collaborative Perinatal Project identified 50 women with first trimester exposure to hydroxyzine, five of whom gave birth to malformed children [43]. The possible increase of congenital anomalies (10% of the exposed infants) did not reach statistical significance, and no pattern of defects was identified. No increase in the incidence of major or minor defects was detected in a third report involving 53 exposed women [57]. The fourth report involved follow-up of 37 pregnancies with hydroxyzine exposure [58]. One child was stillborn with renal aplasia and a shortened femur and tibia.

Like many sedatives, hydroxyzine can decrease the response rate of the fetal heart, but this effect has not been associated with clinical significance in terms of fetal well-being [59]. Two cases of neonatal withdrawal syndrome primarily involving neonatal seizures were associated with hydroxyzine after maternal use of this compound as an antipruritic throughout pregnancy and as a sedative for 4 weeks before delivery [60]. One pregnancy also included prenatal exposure to phenobarbital during the three weeks before delivery [61]. No long-term developmental effects were reported in either case.

In summary, due to adverse events that were observed in animal reproduction studies and some human studies and concern for possible withdrawal syndrome, hydroxyzine, if used in pregnancy, must be done with caution. Given these concerns, some physicians advocate using cetirizine (active metabolite of Hydroxyzine), which is a category B drug as it was not teratogenic in animal studies, and in human studies the relative risks of fetal malformations were low [62]. However, antihistamines also have antiinflammatory and analgesic effects and thus hydroxyzine and cetirizine may differ in their mode of action resulting in different effects.

Intravesical DMSO (Dimethyl Sulfoxide)

Dimethyl sulfoxide (DMSO) is a solvent that has been used medicinally as a topical skin preparation and as a bladder irrigant. DMSO was approved by the FDA for use in IC/BPS in 1997 and it was found to be efficacious in two randomized control trials [63, 64]. Intravesical DMSO is administered via bladder catheter with instillation of 50 mL

DMSO weekly for 6–8 weeks, then every 2 weeks for 3–12 months. DMSO has been associated with teratogenic and embryotoxic effects in several animal models [65–68]. In the hamster, the injection of 500–800 mg/kg on the eighth day of gestation was associated with exencephaly, microphthalmia, bone and limb abnormalities, and cleft lip. However, the findings are not always consistent as some investigators have reported no increase in defects, or only few defects, when even higher dose levels of DMSO were administered to mice and rats. Furthermore, some studies found DMSO produced teratogenic effects when administered parenterally but not when administered orally [69, 70]. Interestingly, DMSO promotes the systemic uptake and alters the bioavailability of a variety of compounds [71], and a number of reports have demonstrated that the simultaneous administration of DMSO can alter the teratogenicity and toxicity of other agents [72, 73]. Additionally, in vitro DMSO increased the uptake of adsorbed DNA by cells in culture [74], a feature that may be associated with an increase in viral infectivity and persistence in embryonic cells [75, 76]. It is uncertain, however, whether this activity is important as a possible mechanism of reproductive toxicity.

There is no published experience with DMSO and human pregnancy. DMSO has been used as a cryoprotectant in the freezing of early experimental animal [77, 78] and human embryos [79–81]. It has been studied for possible use to preserve immature testicular tissue in the hope of preserving the fertility of boys exposed to gonadotoxic therapies [82, 83]. The viability and apparent normalcy of frozen embryos after thawing suggests that DMSO exposure is not toxic to the early embryo. An investigation on the viability of whole rat embryo culture found DMSO to inhibit growth at a concentration of 2.5 vol.% but to be relatively nontoxic at 0.5 vol.% and entirely nontoxic at 0.1 vol.% [84]. How this concentration-effect information may apply to human in vivo pregnancy is unknown. A 2013 study of cryoprotectants found that 6 % DMSO combined with 3 % ethylene glycol resulted in greater chromatin damage of cryopreserved Eastern Anatolian red bull sperm than six other cryoprotectants tested; however, a cryoprotectant of 3 % glycerol and 3 % DMSO was among the least damaging to chromatin [85]. However, an unpublished study of DMSO in male and female rats exposed by inhalation at dose levels up to 2.783 mg/L for 90 days showed no effects on sperm count, sperm motility, or sperm morphology and no effects on the female estrous cycle. No adverse effects were noted on reproductive organs of either sex [86].

In summary, due to adverse effects seen in some animal models, inconsistent data on DNA damage, and nonexistent data on human subjects, it is usually recommended to avoid DMSO in pregnancy. However, if a pregnant patient on this intervention has excellent control of her symptoms, it may be continued after a thoughtful conversation with the patient.

Intravesical Lidocaine

Lidocaine is a class B drug. For IC/BPS therapy, the treatment requires bladder catheterization and lidocaine is instilled to relieve bladder discomfort. Absorption of intravesical lidocaine is pH-dependent. An injection of lidocaine has a pH of 6.5

and at this pH, greater than 90 % of the lidocaine is in the acid form and its absorption from the bladder is minimal [87]. In contrast to the acid form, the base form of lidocaine is nonionized and lipid soluble, so it does get systemically absorbed from the bladder. [87]. When lidocaine gets absorbed systemically, it crosses the placenta, reaching fetal serum concentrations 0.5–1.3 times the maternal concentration [88]. The effects of lidocaine on the fetus are not well known. Lidocaine caused no fetal harm when given to pregnant rats [88]. However, important to note, most human studies are about use of lidocaine as an anesthetic for labor and delivery, not about chronic use during pregnancy. In summary, the safest choice of lidocaine use during in pregnancy for IC treatment is non-alkalinized lidocaine and avoids the issue of systemic absorption. The disadvantage of course is that non-alkalinized lidocaine does not penetrate the bladder epithelium well and thus may not relieve pain as effectively.

Intravesical Heparin

Heparin is class C drug mainly due to no adequate and well-controlled studies on heparin use in pregnant women; however, it is considered safe in pregnancy. Heparin is a large, highly negatively charged molecule that is unlikely to be absorbed from the bladder after intravesical administration. Furthermore, even systemic heparin is considered to be safe in pregnancy, since it is thought not to cross the placenta for the same reasons [89]. A pregnant patient whose symptoms have improved with intravesical heparin administration should probably continue doing so in pregnancy.

Third-Line Therapy for IC

AUA recommends cystoscopy under anesthesia with short duration, low pressure hydrodistention if first and second-line treatments have not provided acceptable symptom control and quality of life. Furthermore, if Hunner's lesions are present, then fulguration (with laser or electrocautery) and/or injection of triamcinolone should be performed.

Bladder Hydrodistention/Treatment of Hunner's Lesions

Bladder hydrodistension is more advanced therapy requiring cystoscopy, usually performed in the operating room under deep sedation or general anesthesia. Hydrodistention has traditionally been used for diagnostic purposes for IC/BPS, but has also been considered therapeutic because some patients report prolonged relief of symptoms after the procedure. This effect is possibly due to the disruption of sensory nerves within the bladder wall. There is no standard technique for hydrodistension. Treatment of the Hunner lesions is usually done in the same procedure if the lesions are present via resection, electrical cauterization, or injection of these lesions with a corticosteroid.

The maternal/fetal risks associated with this intervention are those related to use of anesthesia and surgery in pregnancy, which we will discuss here briefly.

There is no data specifically on hydrodistension during pregnancy and outcomes. Due to absence of objective data, it is difficult to make recommendations. Patients should be counseled to weigh the benefits of symptom relief against the risk of anesthesia/deep sedation in pregnancy.

Surgery Requiring Anesthesia in Pregnancy

Whenever a pregnant woman undergoes nonobstetric surgery requiring anesthesia, a multidisciplinary approach with her obstetrical team, surgeon, anesthesiologist, and neonatologist is prudent to coordinate management.

Surgery in Pregnancy

With regards to surgery in pregnancy, there is no strong evidence that miscarriage, teratogenesis, and adverse outcomes such as vaginal bleeding are increased among women undergoing surgical intervention [90]. However, the underlying condition promoting surgery must be taken into consideration as studies have shown women with peritonitis in the setting of appendicitis have higher rates of fetal demise, miscarriage, and preterm labor [90]. If possible, surgeries should be performed during the second trimester as the risk of preterm labor may be lower in this trimester compared to third trimester.

Anesthesia in Pregnancy

Anesthesia appears to be safe in pregnancy [91]. There is currently no compelling evidence that any specific anesthetic agents should be avoided during pregnancy. There is no strong evidence of increased risk of miscarriage in patients who received anesthetic agents for surgery during early pregnancy while some studies did show an association [91]. Currently used anesthetic agents have no known teratogenic effects, and multiple large retrospective studies have not shown an increase in congenital defects in infants born to mothers who had surgery and anesthesia during pregnancy [92]. There is some concern about fetal brain development in the setting of exposure to inhalational anesthetic agents as laboratory and animal studies have shown increased neuronal apoptosis and negative effects on neurodevelopment; further studies need to evaluate this association [93]. Important to remember all anesthetic induction and maintenance agents cross the placenta and neonate when delivered emergently during such a surgical case may require ventilatory support, i.e., intubation and mechanical ventilation due to the respiratory depressant effects of residual anesthetic agents. However, these effects are transient, requiring no additional measures other than ventilatory support until the effects of the medications wear off.

Injection of Triamcinolone of Hunner's Lesions

Corticosteroids are listed as category D in the first trimester and category C thereafter. Systemic corticosteroids are teratogenic in humans and animals.

A recent study noted that in humans, the main fetal anomaly associated with maternal corticosteroid use was cleft lip or palate, and the risk was increased from a baseline of about 1/1000 to about 3/1000 [94]. In treating pregnant IC/BPS patients, intravesical corticosteroids are used and there are no data describing the extent of systemic absorption. With this lack of knowledge, if a patient is already using this treatment with good results, she may continue, especially after the first trimester when palate formation is complete.

Fourth-Line Therapy for Interstitial Cystitis/Bladder Pain Syndrome

Neuromodulation and intradetrusor botulinum toxin A are fourth-line therapies for interstitial cystitis/bladder pain syndrome (IC/BPS) [17]. These therapies should be administered only by clinicians who have experience with use of these approaches in patients with IC/BPS and with management of the adverse effects that may occur.

Sacral Nerve Stimulation

Neurostimulation or neuromodulation of the sacral nerve is a minimally invasive surgical treatment used for lower urinary tract dysfunction and chronic pain. The device consists of an implanted lead that lies along a sacral nerve root (usually S3 nerve root) and is attached to an implanted pulse generator. Currently, FDA approved neuromodulation of sacral nerve for the treatment of urinary urgency and frequency, but not for the treatment of IC/BPS but is known to be efficacious in the management of IC/BPS. The safety of neurostimulation for use during pregnancy or delivery has not been established. Little is known about the effects of sacral nerve stimulation (SNS) on uterocervical function. One study evaluating six premenopausal and postmenopausal patients was evaluated for uterine activity and the study demonstrated that in premenopausal women SNS seems to exhibit no effect or an inhibitory effect rather than an excitatory effect on uterine activity [95]. There are case reports of successful term pregnancy without any complications with SNS as well as having poor outcomes such chronic motor tic disorder, preterm birth, and a neonate with a pilonidal sinus at birth [96–98]. In summary, because the effects of sacral nerve stimulation on the fetus, mother, and pregnancy are completely unknown, the Medtronic company recommends that a pregnant patient turns it off for the entire duration of pregnancy.

Intradetrusor Injection of Botulinum Toxin

The efficacy of intradetrusor injection of botulinum toxin in alleviating IC/BPS symptoms stems from its ability to temporarily inhibit acetylcholine release and cause flaccid paralysis and analgesic properties [99]. Important to note, there is a risk of urinary retention with injection of botulinum toxin, which may be particularly devastating for a patient with a painful bladder. Any patient considering this treatment must be willing and able to perform intermittent self-catheterization. Use of botulinum injection for IC/BPS management is not approved by the US Food and Drug Administration (FDA).

There is good evidence regarding the use of botulinum toxin in myofascial pain syndrome, neuropathic pain, and joint pain. The data available in the literature regarding the use of botulinum toxin in pregnancy are case reports of women who received the toxin without knowing that they were pregnant. There were no harmful effects for the fetus in these cases where the application occurred during the first trimester [100]. There is paucity of data, however, botulinum toxin does not appear to be associated with teratogenicity or poor pregnancy outcomes.

Fifth-Line Treatment for Interstitial Cystitis/Bladder Pain Syndrome

Cyclosporine

Cyclosporine A, a calcineurin inhibitor, widely used immunosuppressive drug in organ transplantation, is efficacious in managing symptoms of some patients with IC/BPS, especially those with Hunner lesions [101]. Of note there are significant adverse effects associated with this medication, including nephrotoxicity, hypertension, immunosuppression, hair growth, gingival hyperplasia, paresthesias, abdominal pain, flushing, and muscle pain. With regards to pregnancy, there is paucity and inconsistent data. In rodents, there is little or no transplacental passage of cyclosporine [102] and in pregnant rats, cyclosporine has no effect on organogenesis. Data on humans is more conflicting as some reports found little to no transfer while others found levels that were equivalent to those in maternal serum [103, 104]. Extrapolating data from organ recipient patients, the risk of teratogenicity among the offspring of women treated with cyclosporine appears to be low, but premature labor and infants who are small for gestational age have been reported as well as maternal hypertension, renal disease, and diabetes; notably, the underlying medical condition may be a confounding factor in these associations [105–107]. In summary, the long-terms effects of cyclosporine on infants are not known but based on current data cyclosporine can be used in pregnancy but should be used at lowest dose for symptom relief; maternal blood pressure and renal function should be monitored during administration.

Sixth-Line Therapy in Interstitial Cystitis/Bladder Pain Syndrome

Major surgeries (i.e., substitution cystoplasty and urinary diversion with or without cystectomy) are historic treatments of last resort for patients with interstitial cystitis/bladder pain syndrome. These surgeries have significant morbidity and have been described in the past in carefully selected patients for whom all other therapies failed to provide adequate symptom control and quality of life [15]. Today, most urologists would consider bilateral nephrostomy tubes before considering these procedures with high morbidity even in the non-gravid population.

Gynecologic Causes of Pelvic Pain

Gynecologic conditions that result in pelvic pain primarily include pelvic inflammatory disease (PID), endometriosis, adnexal pathologies, uterine fibroids, pelvic congestion syndrome, and pain from vulvar /clitoral etiologies. We will not focus on infectious causes such as PID/Sexually transmitted diseases or adnexal pathology such as ovarian cysts in this chapter.

Endometriosis is the presence of endometrial tissue (stroma and glands) outside the uterus, which induces a local inflammatory response [108]. It is an estrogen-dependent chronic condition associated with pelvic pain and infertility affecting reproductive-age women [109]. The prevalence in the general population is up to 10 %, and however can be as high as 87 % among women with chronic pelvic pain [110]. More specifically, the pain can manifest as dysmenorrhea (cyclical pain associated with menstruation), dyspareunia (pain with or following sexual intercourse), and pelvic or abdominal pain. Pain symptoms due to endometriosis often disappear or improve significantly during pregnancy, making interventions unnecessary. This is thought to be due to anovulation and amenorrhea preventing bleeding of endometriotic tissue but also to different metabolic, hormonal, immune, and angiogenesis changes related to pregnancy [108]. Briefly, pain management for endometriosis can be divided into medical therapy and surgical interventions. Medical therapy includes combined oral contraceptive pill, nonsteroidal anti-inflammatory drugs (NSAIDs), gonadotrophin-releasing hormone analogues, progestins, androgens, aromatase inhibitors, anti-TNF (tumor necrosis factor), and selective estrogen receptor modulators [109]. Surgical interventions include laparoscopic surgery (excisional and/or ablative), abdominal surgery (excisional and/or ablative), and surgical interruption of the nerve pathways [109]. Again, these interventions are usually not required in pregnancy because pain symptoms resolve or improve spontaneously. Furthermore, epidemiological study has demonstrated that higher parity and increased duration of lactation is associated with decreased risk of endometriosis among parous women [110]. Therefore, pregnant women with endometriosis can be reassured about the benign course of their pregnancies by their physicians.

Uterine fibroids or leiomyomas are benign smooth muscle tumors and they are the most common solid pelvic tumors found among women [111]. The prevalence

can be as high as 35 % among the reproductive-age women [112]. More specifically among pregnant patients, the prevalence ranges from 0.9 to 4 % of the population [112]. The natural history of fibroids in pregnancy, contrary to the common notion that they grow in size, is that they in reality stay the same size; prospective studies have demonstrated that most uterine fibroids (49–60 %) had minimal change in volume throughout pregnancy defined as <10 % change, whereas 22–32 % of the fibroids showed an increase in growth, and 8–27 % of the fibroids exhibited a decrease in size [112]. Fibroid growth mostly occurs in the first trimester and among larger fibroids (>5 cm) [112]. Many antepartum, intrapartum, and fetal complications have been associated with fibroids such as pregnancy loss, dysfunctional labor, and fetal anomalies/intrauterine growth reduction; the evidence on these poor outcomes has been controversial and inconsistent [112]. However, one of the most uncontroversial outcomes of fibroids is pain. Pain is one of the most frequent complications of fibroids in pregnancy and studies show that 5–15 % of women who have fibroids require hospitalization at some point during their pregnancy for the management of pain [112]. It is theorized that fibroid pain likely results from poor perfusion in the setting of rapid growth of the fibroid leading to degeneration (i.e., ischemia and necrosis) with release of prostaglandins [112]. This hypothesis is supported by the observation that fibroid pain usually presents in the late first or early second trimester, the period of greatest rate of fibroid growth. Along with pain localized to the fibroid, pregnant patients may present with mild leukocytosis, fever, and nausea and vomiting [112]. The management of fibroid pain during pregnancy begins with symptomatic relief, which includes rest, hydration, and pain control with routine analgesics such as Tylenol and/or narcotic analgesia. Severe fibroid pain not relieved by this regimen necessitates other interventions, including nonsteroidal anti-inflammatory drugs, antepartum myomectomy, and termination of pregnancy [112]. More specifically, indomethacin, a NSAID, administered 25 mg every 6 h is very effective in resolving fibroid pain and is more efficacious than opioid analgesics [113]. Therapy with NSAIDs should be limited to pregnancies less than 32 weeks of gestation because of the possibility of inducing premature closure of the ductus arteriosus, neonatal pulmonary hypertension, oligohydramnios, and fetal/neonatal platelet dysfunction [113]. Similarly, Ibuprofen when compared to opioid medications resulted in greater reduction in the length of hospital stay among hospitalized pregnant patients [114]. In rare situations, there have been successful case reports of epidural anesthesia use for management of fibroid pain [115]. Antepartum myomectomy is usually not recommended in pregnancy and should only be reserved for women who have subserosal or pedunculated fibroids and severe fibroid pain not relieved by medical therapy and who are in the first or second trimester of pregnancy; numerous case studies have demonstrated that this can be done safely [112]. Interestingly, one prospective study enrolled 106 pregnant women with fibroids to either conservative management or to surgical management for more severe disease resulting in 18 patients undergoing antepartum myomectomy and 88 patients being managed conservatively [116]. Spontaneous abortion rate, preterm birth rate, puerperal hysterectomy were all higher among the conservatively managed group, whereas the rate of cesarean delivery was higher among

the myomectomy group and the fetal outcomes were comparable among the two groups [116]. The findings from this study raise the possibility that surgical management in selected patients may be safe and result in better outcomes; however, larger and randomized trials need to be done for further and more comprehensive investigation. Finally, termination of pregnancy is an option for patients who have failed all therapies and the specific method of termination depends on gestational age and patient preference. Other interventions, i.e., contraceptive steroids, gonadotropin-releasing hormone agonists, aromatase inhibitors, and uterine artery embolization, while appropriate on nonpregnant patients are not plausible interventions for pregnant patients. Notably, physicians taking care of patients with fibroids should discuss preconception myomectomy when appropriate and provide anticipatory guidance and proper management of fibroid pain during pregnancy.

Pelvic congestion syndrome (PCS) is a common condition among women with chronic pelvic pain that results in poor physical, psychological, and sexual function. PCS occurs when varicose veins develop around the ovaries in a setting of chronic pelvic pain and can account for approximately one third of cases of chronic pelvic pain in some studies [117]. Typical symptoms include noncyclic lower abdominal or pelvic pain, usually described as a dull and achy or fullness that lasts for >6 months [117]. Other associated symptoms include headache, bloating, nausea, vaginal discharge, vulvar swelling, feeling of leg fullness, lower backache, rectal discomfort, urinary urgency, generalized lethargy, and depression [117]. This pain is usually worsened by prolonged standing, sexual intercourse, menstruation, and pregnancy. Specifically, during pregnancy pelvic vein capacity increases by 60 % owing to the mechanical compression of the gravid uterus and the vasodilator action of progesterone leading to venous distention, venous hypertension, and retrograde flow; all these changes can worsen PCS in pregnancy [117]. Furthermore, the weight gain and positional changes of the gravid uterus that occur during pregnancy can cause kinking of the ovarian veins and result in venous congestion, which also can worsen PCS [117]. Interestingly, pregnancy provides an important protective effect among PCS patients as pregnancy quiets the estrogen hyperstimulation that has been implicated in the pathophysiology of the disease [117]. Thus, contrary to the notion that pregnancy will always worsen symptoms of PCS, often the symptoms are improved due to the hormonal changes resulting in greater impact than the physical changes of pregnancy. Treatments for this condition hence are medical management with hormone analogues and analgesics, surgical ligation of ovarian veins, hysterectomy with or without bilateral salpingo-oophorectomy, and transcatheter embolization [118]. Specifically, medical treatment includes progestins, danazol, gonadotropins receptor agonists (GnRH) with hormone replacement therapy (HRT), and NSAIDS [118]. Because majority of these medications achieve what pregnancy achieves naturally, they are not used in pregnancy. After the advent of embolotherapy, which is more efficacious than open and laparoscopic interventions, surgical interventions have been abandoned due to anesthetic and surgical risks to the mother and developing fetus [118]; 60–100 % of patients report significant relief with embolotherapy [117]. Physicians taking care of pregnant patients with PCS can reassure them that symptoms usually improve in pregnancy and intervene for symptomatic relief with usual analgesic medications.

Conclusion

It is important to remember that pain in pregnant women is not always obstetric in nature. Pregnant women receiving treatment for chronic pain must continue to be treated, even during labor and delivery. The comprehensive management of the conditions that may be a source of pain during pregnancy requires the use of medications that are not always 100 % safe. Treatment must be multidisciplinary and humanized, bearing in mind the implications for the mother and the fetus. Most of the medications and therapies used for the treatment of pain have not been tested in controlled trials during pregnancy. Existing data suggest that the use of any of them, even those classified under category B, must be weighed against the potential short- and long-term risk for the fetus. There are websites that can be used for registering adverse events from drugs during pregnancy; based on the entries, the risk categories are then updated. It is important to visit those websites periodically to learn about the potential risks when initiating or continuing any form of therapy. Aside from the teratogenic risk, it is important to consider the effects on fetal development during the rest of the pregnancy as well as during breastfeeding.

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Nerve Blocks

18

Andrew Baranowski and Luke Mordecai

Chronic Pelvic Pain (CPP) may have its origin from any structure in the pelvis, which includes the abdominal and pelvic walls as well as being a primary condition; recent epidemiological studies indicate a staggeringly high population prevalence of 14.7% in the USA [1], 24% in the UK [2] and 25.4% in New Zealand [3]. Furthermore, the seminal paper on the topic, published in 1996, suggested that the direct and indirect economic costs ran into billions of dollars even then [1]. Therefore, the correct management of CPP is of great significance to health systems and society and the nerve blocks discussed in this chapter have an important role.

CPP can be utterly debilitating and many interventions have been attempted. Nerve blocks are based on the first principle of arresting transmissions from an area of pathology, be it organic or functional, to the brain using a Cartesian model of human nervous anatomy. However, the origins of chronic pain as an illness are far more complex than one nerve "mis-firing" as is reflected in the importance of the biopsychosocial model; the poorly localised nature of visceral pain only serves to further complicate matters in the context of CPP. The latter is important as it pertains to patient selection for interventions. There should be multidisciplinary agreement regarding the lack of a surgical cure and a transparent discussion regarding the likely risks and benefits of a nerve block.

There is evidence that many individuals with CPP also suffer from psychological difficulties although it would appear that the latter has no impact on the success or failure of interventions. Therefore, patients should never be denied nerve blocks solely on psychological grounds. However, clinical practice acknowledges that we

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should be careful in distressed patients as expectations may not be appropriate and a failed procedure may add to their distress.

Injections around nerves in the context of CPP are perceived to have three major usages which are: (1) to aid in diagnosis, (2) as a treatment for the pain itself and (3) in the management of cancer pain. It is often important to only perform one intervention at a time as the diagnostic element is negated if more than one intervention is performed simultaneously as direct effect cannot be determined independently. Doubts over the long-term efficacy of neurolytic blocks, in combination with the potential disastrous complications, have led to a general unwillingness to perform these procedures except in the context of the palliative management of cancer pain [4].

Reasons to perform nerve blocks in chronic pelvic pain
1. Diagnostic
2. Therapeutic
3. Management of cancer pain, palliative care

Anatomy

Important nerves and structures in CPP
1. Ilioinguinal nerve
2. Iliohypogastric nerve
3. Genitofemoral nerve
4. Pudendal nerve
5. Lumbar plexus
6. Superior hypogastric plexus
7. Cluneal nerves (superior, middle, inferior)
8. Ganglion impar

Despite a growing acceptance that the cause and effect Cartesian model of nervous transmission is by no means fully explanatory regarding CPP an understanding of the anatomy is still vital for all practitioners in the area, especially in the context of performing nerve blocks.

To further complicate matters, the pelvis is innervated by both somatic and visceral sources and an appreciation of both is required in the complex management of often poorly localised CPP.

The neurology has embryological origins and so derives its innervation from the thoracolumbar spinal and sacral levels. Many of the afferents from the reproductive organs share a similar course to the sympathetic nerve bundles and have cell bodies positioned between T10 and L3, there are also a significant number that travel with parasympathetic fibres to the sacral dorsal root ganglion.

Both male and female genitals give rise to afferents that follow the same path via the hypogastric plexus, to the hypogastric nerve, then the superior hypogastric plexus terminating in the thoracolumbar sympathetic chain where they then join the spinal cord by way of the dorsal routes. Some anatomical areas share multiple innervations, and afferents from the upper vagina, cervix, uterine body, upper bladder, urethra and some bowel also travel in the pelvic splanchnic nerves (S2–S4) via the inferior hypogastric plexus. The ovaries, outer fallopian tube and ureter have afferents that join the sympathetic chain at L4 but do not communicate with the spinal cord until about T9.

Whilst the parasympathetic nervous system has a well-documented function in control of the bladder, bowel and reproductive reflexes its role in the transmission of pelvic visceral in poorly understood.

The somatic innervation of the pelvis and its structures arise from Thoracolumbar and sacral nerve roots. The **iliohypogastric**, **ilioinguinal** and **genitofemoral** nerves arise from L1 and L2 and innervate the lower anterior abdominal wall, the anterior vulva/anterior scrotum, the urethra and shaft of penis and the possibly clitoris. The **Pudendal** nerve, arising from S2–S4, provides sensation for the anal canal, perineum, lower vagina/vulva/posterior scrotum and also the clitoris/glans penis.

The dual, or triple innervation of, many structures, superficial and deep within the pelvis is a major contributory factor regarding poor localisation. Furthermore, visceral and somatic afferents both have connections with the dorsal horn, thereby further confusing second order neurons as to the origin of any transmission.

We will review in detail the anatomical course of the nerves in order to identify the locations in which they are amenable to block.

The **pudendal** nerve is paired and formed from the three nerve roots S2-S4. The roots emerge from the sacrum usually medial to the origins of the piriformis (but can be caught up in the digitations of the piriformis). The lower two roots merge into one cord and proceed to then join the upper cord just prior/posterior to the sacrospinous ligament, hence forming the pudendal nerve. This then passes between piriformis and ischiococcgyeus muscles and exits the pelvis via the greater sciatic foramen before winding around the lateral part of the sacrospinous ligament and reentering the pelvis by way of the lesser sciatic foramen. The nerve then follows the lateral wall of the ischiorectal fossa whilst contained within the obturator fascia, known as the pudendal or eponymously as, Alcock's canal. Within the canal the pudendal nerve divides into the inferior anal nerve, the perineal nerve and either the dorsal nerve of the penis or clitoris. It needs to be noted that the separation off of the inferior anal nerve from the pudendal is highly variable in position.

The **Lumbar plexus** is predominantly formed from the first four lumbar nerve routes but may also have contributions from T12 or above. The plexus itself is closely approximated to the psoas major, anterior to the transverse process' of the second to fifth lumbar vertebrae and it gives rise to some important nerves in the context of CPP.

The **iliohypogastric** nerve is formed from the L1 nerve root (as well as others) and courses lateral to the psoas on the lumbar fascia, posterior to the inferior pole of the kidney and over quadratus lumborum. It travels above the iliac crest before directing in between transversus abdominus and inferior oblique, before crossing through the latter muscle at the level of the anterior superior iliac spine. It gives off motor branches before terminating in the sensory innervation of the mons pubis skin and penile shaft/clitoral hood.

The **Ilio-inguinal** nerve is also formed from the L1 nerve root and follows the same course as the iliohypogastric nerve up until it pierces the internal oblique muscle. Its terminal branches pass into the inguinal canal and through the superficial ring to supply sensory innervation to the skin over the pubic symhysis, the upper medial thigh and the skin of the root of the penis and anterior scrotum or labia majora.

The **Genitofemoral** nerve is formed from the L1 and L2 nerve roots and lies on the anteromedial surface of psoas posterior to the ureter where it then divides into genital and femoral branches. The **genital** nerve crosses the external iliac artery and passes through both deep and superficial inguinal rings. In males it runs in the spermatic cord and supplies sensory innervation to the scrotal skin and motor innervation to the cremaster muscle. In females it runs in the inguinal canal with the teres uteri ligament and supplies sensory innervation to the labia majora.

The **Superior hypogastric plexus** is usually positioned at the level of the bifurcation of the aorta and lies anterior to the body of the L4 vertebra. It gives off sympathetic fibres in two trunks, the paired hypogastric nerves, which travel on into the ovarian and ureteric plexi via the inferior hypogastric plexus. The superior hypogastric plexus usually receives input from the two lower lumbar splanchnic nerves (L1–2), and parasympathetic fibres arising from the pelvic splanchnic nerve (S2–4). Blockade of this plexus can be used in the context of pain originating from the cervix, uterus or fallopian tubes and by avoiding sacral innervation will not interfere with bowel of bladder control. It has been described as being especially useful in cancer pain [5].

The **Cluneal** nerves are divided into superior, middle and inferior and collectively supply cutaneous innervation to the buttock. The **Superior Cluneal** nerve is formed from the terminal ends of the posterior rami of lumbar spinal nerves L1–3. A branch of this nerve may become entrapped between the iliac crest and the thoracolumbar fascia giving rise to marked spot tenderness over the iliac crest and buttock pain radiating down the ipsilateral leg. The **Inferior Cluneal** nerve is a branch of the posterior femoral cutaneous nerve originating from the sacral plexus. It travels directly under the ischium to innervate the lateral anus and lateral labia majora in females. It lies close to the pudendal for a part. Compression or entrapment of this nerve can lead to pain in the buttock, posterior thigh, particularly when sitting on a hard seat, the perineal region.

The **Ganglion Impar**, or **Ganglion of Walther**, is the termination of the left and right sympathetic chains where the latter merge in the midline at the level of and anterior to the sacrococcygeal junction. Blocking this ganglion can give excellent results in the management of coccydynia [6] and in the treatment of neoplastic pain of sympathetic origin [7].

The two diagrams below illustrate the important structures discussed that are most commonly involved with chronic pelvic pain.

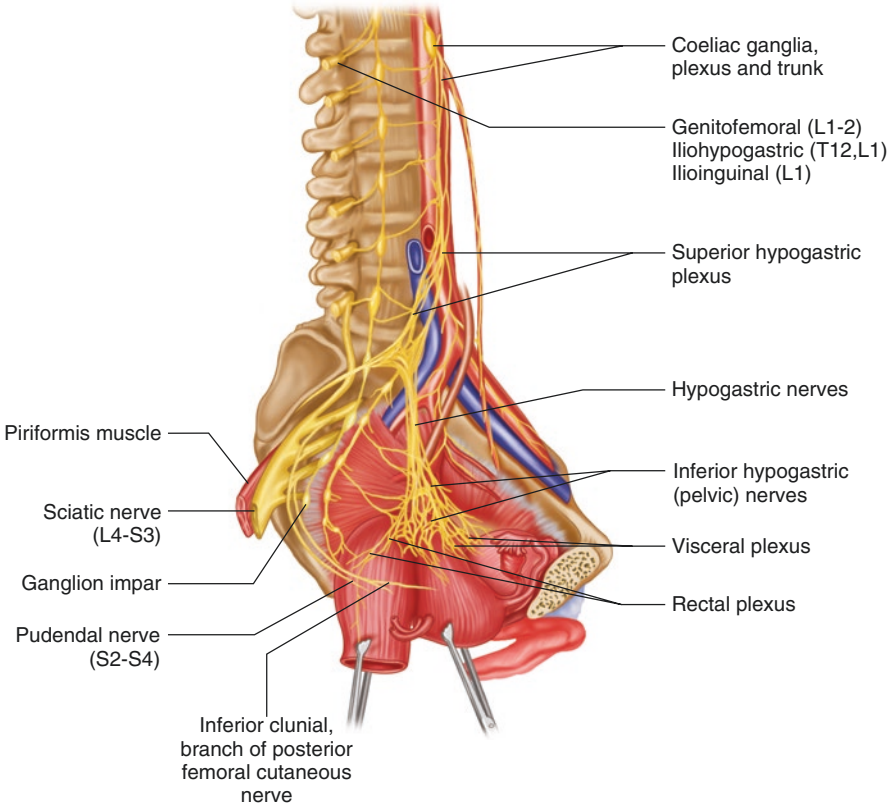

Fig. 18.1 Unilateral alcock's canal pudendal nerve block

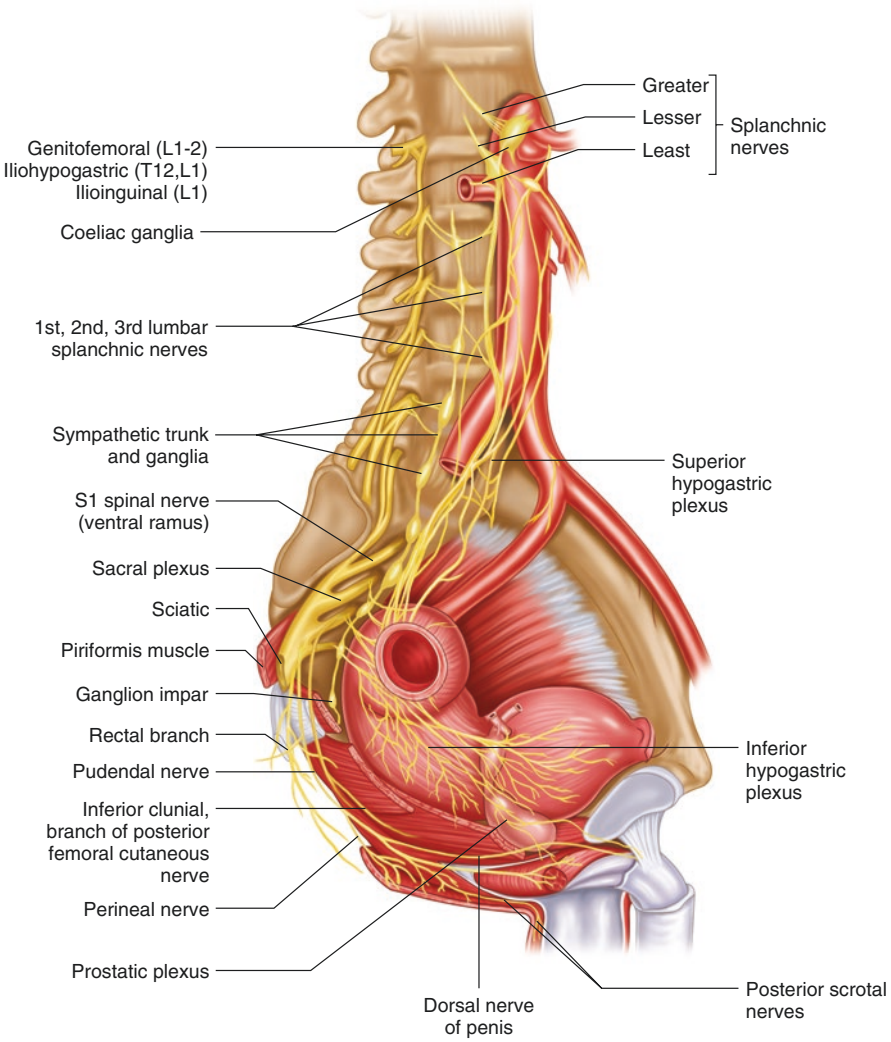

Fig. 18.2 Bilateral obtuator internus injections with contrast

General Notes on Chronic Pelvic Pain Interventions

Chronic pelvic pain may originate from the musculoskeletal, nervous, genitourinary, gastrointestinal or gynaecological system; therefore, it is of seminal importance to involve a multidisciplinary team to ensure correct diagnosis and appropriateness of any treatment before commencing. The corollary of that fact is that to increase the likelihood of nerve blocks being effective they should be performed as soon as indicated. Irrespective of the underlying aetiology, once

neuropathic pain mechanisms have become established the prospect of cure becomes more unlikely.

The same general contraindications exist for all nerve blocks regardless of site or aetiology. Clotting should be normal, anti-coagulants should be stopped or bridged and known coagulopathies should be corrected pre-procedure. Similarly, procedures should not be performed in the presence of local or systemic infection. Written consent should be obtained and careful consideration should be given by the practitioner regarding the likely potential benefit, as unrealistic hopes can be holistically damaging in the context of psychological states associated with chronic pain. Consent should be clear about risks, particularly the risks of increased pain and nerve damage from the injections.

Essential criteria to be met before an intervention
Multidisciplinary team involvement
Agreement regarding underlying diagnosis
Appropriate patient selection especially regarding expectations

Procedures

Nerve Blocks used in the treatment of CPP
1. Pudendal Nerve blocks
2. Inferior Cluneal block
3. Lumbar plexus block
4. Superior hypogastric plexus block
5. Ganglion Impar block

The authors will now discuss the practical steps involved in carrying out nerve blocks in the context of CPP. Given the limited scope of this chapter we will restrict discussion to specialist procedures thus whilst many procedures may be beneficial, such as sub-arachnoid, epidural and caudal blocks, they are adequately described in the general literature already.

It is not the aim of this chapter to provide a detailed approach to the procedures and the procedures should only be performed by appropriately trained persons as a part of a MDT.

Pudendal Nerve Blocks

Prior to the procedure, and in addition to the general complications already discussed, specific risks should be elucidated which include perforation of an adjacent viscus, and in the case of sacrospinous ligament infiltration, sciatic nerve

involvement manifesting as a weak leg or pain. There is the potential for bladder or bowel incontinence, though such complications would be considered rare sexual dysfunction has been noted on occasions following nerve blocks, but the mechanisms are complex.

The pudendal nerve can be blocked via transperineal infiltration using a landmark technique; however, this will not be discussed as it has been discounted as useful in the context of CPP [8].

An **ultrasound technique** may be adopted to block the pudendal nerve at the level of the ischial spine; however, at this point the nerve is thin, 4–6 mm, and deep, about 5 cm, which may explain why it is visualised only 47.2 % of the time [9]. The pudendal vessals next to the nerve may act as a landmark.

A low frequency (2–5 MHz) curvilinear probe is required and the patient is placed in the prone position. The probe is first placed transversely over the posterior superior iliac spine (PSIS) to visualize the sacroiliac (SI) joint before being slid laterally to identify the iliac wing. After the latter is seen, the probe is rotated into the expected plane of the pyriformis muscle and moved caudally to view the ischium at which level the latter muscle and gluteus maximus should be seen. Continuing caudally the sacrospinous ligament appears as a hyperechoic structure running from the ischial spine to the sacrum. The pudendal artery is positioned just medial to the ischial spine and pudendal nerve is medial to the artery. The injection is performed at this level between the sacrospinous and sacrotuberous ligaments, the latter seen deep to gluteus maximus. As with all blocks relying on an ultrasound guided technique the needle tip should be clearly visualised in the correct location before any injection. A 15 cm block needle is appropriate, allowing for normal ranges of body habitus, and a total volume of up to 10 ml of local anaesthetic, usually lignocaine 1 %, and steroid, 40 mg triamcinolone, may be used.

A combined **fluoroscopy and nerve stimulator** approach is more routinely used by the authors for blocking the pudendal nerve at the level of the ischial spine. Once again the patient is position prone and using surface landmarks and fluoroscopy the ischial spine is identified in a straight line between the tip of the coccyx and then greater trochanter. A 15 cm nerve stimulating needle is inserted aiming for the ischial spine (the nerve locator is switched on to identify the nerve early and prior to the risk of damaging it). Upon contact of the ischeal spine the needle is re-directed medially between 5 and 10 mm to identify the sacrospinous ligament. The operators should feel the latter as a definitive resistance and possibly pop if it is entered. As the nerve is superficial entry is often not necessary. At this point the operator should increase the current down the needle and enquire as to whether that reproduces or exacerbates the patient's normal pain. The patient should be in a plane of sedation adequate to tolerate the procedure as well as answer the latter question. Upon successful replication of symptoms, the operator may assume correct needle tip positioning and inject a similar volume of local anaesthetic and steroid as previously described. A motor end point of anal twitch is also usefully in certain cases.

For deeper pudendal nerve blocks in the region of Alcock's canal using **Computed Tomography (CT)** is the gold standard as they allow the most precision at varying levels. CT may also be used for injections at the IS level, but the higher

radiation dose must be considered and with a nerve stimulator is probably not necessary.

The patient is placed prone, head first in the CT scanner in all the following nerve blocks.

McDonald first described infiltration of the sacropsinous ligament using CT scan [10]. An appropriate CT slice is identified at the level of the mid acetabulum and a 10 cm needle is placed about 2–3 cm lateral to the midline, perpendicular with the skin. The needle should penetrate through to the anterior border of gluteus maximus where the ligament in question lies. The position of the needle tip may be repeatedly checked using a low radiation, scanning mode until deemed correctly positioned. Positioning is formally checked with 2 ml of contrast (diluted appropriately) which one would expect to see as an ellipsoid shape running medially and posteriorly, before injecting between 6 and 10 ml of local anaesthetic and steroid mix.

Infiltration of **Alcock's Canal** using **CT** was first described by Bensignor and requires an anatomically more more caudal slice in the scanner. The ideal image should demonstrate Alcock's canal positioned in the "V" formed by the muscles obturator internus and puborectalis. The pudendal nerve itself will not be identifiable however. Prior to the scan a small radiopaque wire should be taped vertically over the midline of the patient at the presumed level of the block, which can then be used to mark guiding measurements on the images. These measurements are hence transferred onto the patient's skin so as to identify accurate skin puncture sites. Having done this a 15 cm nerve block needle is dropped in a slightly medial direction until in contact with the ischial tuberosity. The needle is then walked off this structure medially and then advanced towards the measured depth of Alcock's canal, checking progress with repeat CT scans as necessary. Needle tip position is again confirmed with injection with 1–2 ml of diluted contrast before injecting 4–8 ml of local anaesthetic and steroid mix. Figure 18.1 shows an ideal needle tip position for this block with spread of contrast.

Exactly the same scan slice and procedure may be used to inject obturator internus and puborectalis muscles. To inject the former, after walking the 15 cm needle off of the ischial tuberosity, the tip is directed more laterally and into the body of the muscle. Puborectalis normally only requires a 10 cm needle which is dropped vertically and perpendicular to the skin usually 1–2 cm from the midline. The procedure regarding repeat scans to check needle position and contrast to confirm remains. Suitable volumes of local anaesthetic and steroid mix are 4 ml for puborectalis and 6 ml for the larger obturator internus. Figures 18.2 and 18.3 demonstrate needle tips positions that correspond to these blocks respectively.

The **Inferior Cluneal nerve** may also be injected using CT guidance (or x-ray fluoroscopy). A CT slice demonstrating the ischium is required and a 10 cm needle is directed towards the posterior lateral aspect, where the nerve runs, although cannot be directly visualised. Contrast is again injected to confirm position, before 4–5 ml of anaesthetic, steroid mixture.

The **lumbar plexus** may be blocked at source or the individual nerves targeted distally. Multiple techniques have been described to block the lumbar plexus, although it is most often approached under x-ray guidance using 15 cm needles with

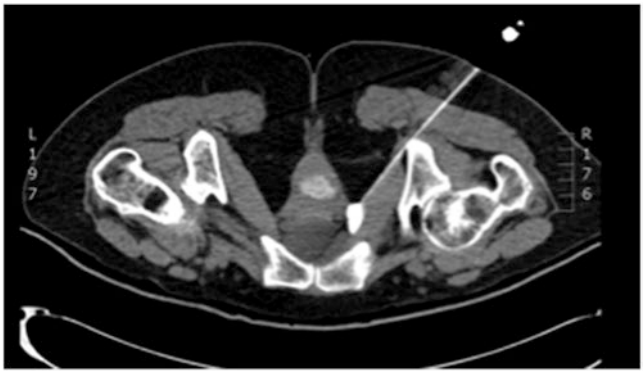

Fig. 18.3 Bilateral puborectalis injections with contrast

the patient in the prone position. The body of L2 is identified using x-ray and a spot is marked on the skin 5 cm lateral to this on one or both sides as appropriate. The block needle punctures the skin at this point and is angled 30–45° cephalad until contact is made with the transverse process. The needle is then walked inferiorly and medially until contact is made with the vertebral body, which in turn is walked off anteriorly until a pop is felt as psoas fascia is pierced. An anterior-posterior (AP) view should then be acquired demonstrating the needle tip half way between the lateral edge of the vertebral body and the spinous process. The position of the needle tip should be confirmed in two x-ray planes clearly showing a linear longitudinal spread and the absence of lateral of posterior extension. A total volume of 10 ml anaesthetic and steroid may then be injected per side. Assessment of the temperature of the ipsilateral feet will rapidly determine success of the block due to the sympathetic interruption and the patient and recovery staff should be warmed about the potential for postural hypotension.

The **ilioingiunal** and **hypogastric nerves** may be blocked together distally. Whilst a landmark technique relying on the haptic feedback from fascial puncture is widely used and accepted, the authors advocate the use of ultrasonography to ensure accurate placement of injectate.

A spot is marked approximately 2 cm medial and superior to the anterior superior iliac spine (ASIS). An ultrasound probe is then placed in this region, parallel and superior to the inguinal ligament. The three fascia of external oblique, internal oblique and transversus abdominus should be easily identifiable. Under in plane ultrasound guidance, up to 20 ml of anaesthetic-steroid mixture may be placed in each of the two planes sandwiched between these three fascia.

The **superior hypogastric plexus** may be blocked to alleviate pain thought to originate from the uterus, cervix or fallopian tubes. This procedure is carried out upon x-ray guidance, with the patient in the prone position with the lumbar lordosis minimized as far as possible. After identification using x-ray, 15 cm needles are introduced bilaterally at the level of L4/5, approximately 5-7 cm from the midline and aimed medially and caudally towards the antero-lateral body of L5, avoiding both the iliac crest and the L5 transverse process. The needle is then walked off the

body of L5 and advanced about 1 cm, at which point a pop should be perceived. As always the position of the needle tip should be confirmed with x-ray just anterior to the vertebral bodies of L5 and S1 and injection of contrast should demonstrate a gentle curve in the paramedian line in the lateral view. The needle tip will be sitting directly adjacent to the iliac bifurcation so extreme caution should be taken to avoid intravascular injection. A volume of 10 ml is customarily injected bilaterally.

Finally, a **ganglion Impar** block may be performed, most commonly under x-ray guidance, with the patient in the prone position. There are various methods for accessing the ganglion but the trans-sacrococcygeal approach is the most popular due to its simplicity and efficacy as well as low risk of rectal perforation. A 5 cm, 22-G needle is inserted at the sacral cornu and should pierce the sacro-coccygeal ligament in the midline before being advanced through the vertebral disc until the tip is ventral to the sacro-coccygeal ligament. Position should then be confirmed using contrast and x-ray images in the lateral view, which should demonstrate a reverse comma distribution before 10 ml of local anaesthetic and steroid mixture is introduced.

Conclusion

Nerve blocks have a well-documented role in the management of CPP and should be considered alongside pharmacological, psychological and lifestyle treatment options. These often-complex patients should have integrated multidisciplinary input and as described earlier, patient selection is of paramount importance.

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Intravesical Therapy for Bladder Pain Syndrome/Interstitial Cystitis: Dimethyl Sulfoxide

19

Dena Moskowitz and Gamal Ghoniem

Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) represents a major health burden in the United States and around the world. A recent study (RAND Interstitial Cystitis Epidemiology) estimated that 6.5 % of American women suffer from the disease [1]. Women who were younger or college-educated had greater symptom persistence [2]. Treatment options are broad, from behavioral modification, to oral pharmacologic agents, to intravesical treatments. Intravesical therapy is popular because it spares patients from the systemic effects of oral agents. In this regard, intravesical Dimethyl sulfoxide (DMSO) has been used for many years by urologists in managing these challenging patients.

DMSO was first approved by the FDA for the treatment of BPS/IC in 1978. It was in that year that urologists from the Cleveland Clinic first published promising results in a group of patients with inflammatory GU disorders [3], and it has remained a mainstay of treatment for BPS/IC since that time. The popularity of its use lies in long-demonstrated safety with minimal morbidity as compared to other types of treatments. It has proven in multiple studies to have "success" rates consistently above 60 %. Two small randomized studies have shown its safety and efficacy [4, 5]. The most recent guidelines published by the American Urologic Association include intravesical DMSO, along with other intravesical treatments, as a second-line treatment option for BPS/IC [6].

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Mechanism of Action

DMSO is an organic compound with the formula $(CH_3)_2SO$. It is used as a solvent, and it dissolves both polar and nonpolar compounds. Although proven to be clinically effective, there is still some mystery surrounding the mechanism of action for DMSO. Multiple theories and mechanisms have been hypothesized in both in vivo and in vitro models.

Effects on ATP Release

It has been demonstrated that adenosine triphosphate (ATP) is released from the serosal surface of the bladder in response to stretch, and that this may provide a mechanism for afferent signaling of urgency and/or pain [7]. Indeed, it has been shown that urine from patients with BPS/IC has increased levels of ATP, providing a possible mechanism for their upregulated sensory inputs [8]. In another study, urothelial cells from patients with BPS/IC were grown and cultured and compared to controls. Urothelial cells in BPS/IC patients showed significantly increased release of ATP as compared to controls in response to stretch. DMSO abolished this response in preparations from BPS/IC patients, but had no effect upon the amount of ATP released from control cells [9].

Bladder Wall Contractility

BPS/IC is thought to be distinct from detrusor over activity (DO) in that the former is primarily a sensory problem, with the latter a motor problem. However, DO is commonly found in conjunction with BPS/IC, and it follows that the relief of uninhibited contractions may offer some relief of this syndrome. A study of rat bladder strips demonstrated completely abolished contractions to stimulation after exposure to 40 % DMSO [10]. Shiga et al. also demonstrated a relaxation of sustained contraction in rabbit bladder strips in the presence of DMSO [11]. They further showed that the mechanism behind this finding may be due to the ability of DMSO to decrease the sensitivity of myofilaments to calcium. Therefore, some of the effects of DMSO to relieve the symptoms of BPS/IC may come from its ability to decrease DO.

Anti-inflammatory Actions

One notable recent study demonstrated multiple anti-inflammatory properties of DMSO [12]. This study used a transgenic mouse model of autoimmune cystitis and treated the animals with 50 % DMSO solution. They found improvement in bladder histopathology, decreased production of inflammatory factor mRNAs, and a reduction in CD8+ T cells. Inflamed bladders demonstrated prominent cellular infiltration,

edema, and hyperemia in the lamina propria. These effects were decreased in bladders treated with DMSO. The improvement in bladder histopathology was present in both the acute and chronic models of autoimmune cystitis.

Soler et al. also demonstrated an anti-inflammatory action of DMSO. In this study, the authors created a model of BPS/IC by inducing cystitis with intravesical protamine sulfate. Rats were then treated with 50 % intravesical DMSO and histopathologic sections were examined for inflammatory changes. The rats treated with DMSO showed decreased edema, vascular congestion, and inflammatory infiltrates. Interestingly, when DMSO was infused in rats with normal bladders there was an increase in edema and inflammatory cells, possibly providing an explanation for the temporary flare in symptoms after initial instillation that some patients experience [13].

Histamine Release

Histamine release from mast cells is thought to be play a role in the development of BPS/IC symptoms, hence a potential role for antihistamines to treat this condition. Although it has been hypothesized that DMSO assists with mast cell stabilization to prevent histamine release, this has not been shown. In fact, one group showed that the histamine:creatinine ratios did not change at all in women with BPS/IC treated with DMSO [14]. However, these authors do consider that the cell-membrane stabilizing properties of DMSO prevented mast cell degranulation, thereby preventing histamine release in the urine. It is speculated that prevention of mast cell degranulation is responsible for the symptomatic relief, as this would decrease histamine levels in the tissues.

Other Mechanisms

DMSO is thought to have a multitude of other mechanisms that can help relieve symptoms of BPS/IC. Notably, membrane penetration is important in its delivery to the urothelium and even submucosa. Secondly, membrane transport that enhances other chemicals to reach the tissue is important in cases when used in combination with other medications. These properties combined make it an excellent choice for use in multiagent administration, as discussed below.

Technique

Many treatment regimens exist for instillation of DMSO. In a standard fashion, DMSO is administered intravesically as a 50 % solution (RIMSO-50®). Frequently, it is used in the form of an intravesical “cocktail,” being mixed with other agents such as heparin, sodium bicarbonate, or steroids. A general treatment regimen for DMSO alone consists of weekly instillations of 50 mL of 50 % DMSO solution for 6–8 weeks, followed by a maintenance program of 50 mL every 2 weeks for 3–12

months [15]. Prior to starting treatment a urine analysis with reflex culture is obtained to rule out infection [16] All patients should be counseled extensively on what to expect prior to beginning treatment. Patient's understanding that there may be a flare in dysuria, pelvic pain, and urinary frequency over the course of the first 3–4 instillations with DMSO is paramount to their willingness to complete treatment and ultimately find relief.

In patients with BPS/IC, the catheterization required to administer intravesical treatments can be distressing. It is important to provide the patient with a comfortable environment, as well as a physician and staff with whom the patient is familiar. To start, 2 % lidocaine jelly is used to anesthetize the urethra and make catheterization more comfortable. A lidocaine uroject is used, and a gentle SLOW pressure given on its applicator. This gentle pressure allows some of the lidocaine jelly to reach the inside of the bladder and perhaps provide relief from potential discomfort of the medication itself. A 10-min wait period is important to achieve a good topical anesthetic effect. A 12-French catheter is used to instill the medication slowly. The patient is encouraged to keep the medication in the bladder for 15 min prior to voiding. If they are unable to tolerate the holding period, the catheter may be clamped during this time period, and the medication emptied at the end of the session. If patients experience bladder spasms with instillation they may be premedicated with sublingual 0.125 mg hyocyamine. This has a fast onset as well as a short duration of action, which is ideal for this situation. Other options are premedication with oxybutynin or belladonna with opium.

Although response rates to DMSO are known to be good, there is a significant chance of recurrence of symptoms after initial treatment. Recurrences can also be treated with DMSO with good success. However, over time, this can become a burden financially and socially if patients require repeat office visits for catheterization. An alternative is to teach patients to do self-intermittent catheterization and instillation of DMSO at home. This method was studied by Biggers, who noted a 90 % response rate with self-administered treatment at the time of symptoms onset over a 6–24 month period [17]. This is a good option for patients who feel comfortable with catheterization and have difficulty coming to repeat clinic appointments. Like office instillations, home instillations should follow a schedule of one instillation weekly for 6 weeks, followed by a reassessment in the office.

Side Effects

Side effects of intravesical treatment are usually minor and do not cause discontinuation of treatment. The most common side effect noted is urethral irritation, which in one study was noted to occur in 48 % of patients after the first instillation [18]. This same study, however, showed that side effects are transient, with a statistically significant reduction in side effects between the first three and second three treatments. These irritative symptoms can be treated with oral medications, and are responsive to anticholinergic as well as tricyclic antidepressant medications [19].

DMSO is also known to cause a garlic-like odor to the breath and taste to the mouth. It is thought to be caused by a small percentage of the DMSO that is excreted

through the lungs as dimethyl sulfide. This effect is temporary and self-resolving, lasting for 24–48 h after treatment [16]. Patients should be counseled as to this side effect prior to treatment so that they may plan appropriately, as it can cause social distress. Often the authors will give the instillations on a Friday, so that this particular side effect will wear off prior to the patient returning to work on Monday.

There has been some concern for development of cataracts with long-term use of DMSO. This side effect has not been demonstrated in randomized studies. Still, some recommend ophthalmologic referral for patients who undergo long-term use [18].

Multiagent Therapy

Patients should be reassessed for treatment response at each visit. In general, there is at least a 60 % response rate to DMSO, and a 2-month trial period of instillations is generally adequate. If patients show no or inadequate response to treatment, multiagent therapy can also be considered. It is believed that DMSO can cause a temporary inflammatory response of the bladder, and that this allows better penetration of other agents, such as anti-inflammatories and antibiotics [13, 20].

Ghoniem et al. [19] showed a 92 % remission rate lasting an average of 8.1 months with this approach. Their intravesical solution consists of 50 mL of 50 % DMSO, 40 mg of methylprednisolone, and 5000 units of heparin sulfate. Patients received an initial instillation in the operating room after hydrodistension and measurement of bladder capacity. They then returned weekly for 5 additional weeks. 36 % of patients experienced one or more relapses. For these patients a second course was initiated. One to two instillations per month over a 3-month period was usually enough to induce another remission.

Another study of multiagent therapy by Hung et al. [21] also showed promising results for this treatment. These authors used a DMSO cocktail as a first-line treatment for BPS/IC. Their solution consisted of 50 mL of 50 % DMSO, 100 mg of hydrocortisone, and 25,000 IU of heparin sulfate. Patients received weekly instillations for a total of eight sessions. 65.5 % of patients showed at least a satisfactory response to treatment. The authors identified three risk factors for an inadequate response to treatment-advanced cystoscopic glomerulations, microscopic hematuria, and urodynamic detrusor underactivity.

The authors currently use a slightly different cocktail than the one described above, and it is given as a primary therapy among second-line treatments for BPS. The mixture consists of 50 mL of 50 % DMSO, 40 mg methylprednisolone, 10,000 units of heparin, and 80 mg of gentamicin. Gentamicin was added due to the finding that gram-negative bacteria may play a role in the pathogenesis of BPS [22]. An algorithm for treatment is shown in Fig. 19.1. While our algorithm adheres to the AUA guidelines, using intravesical instillations as a second-line treatment for BPS/IC, we generally use instillations prior to initiation of systemic pharmacologic therapy. This affords patients the opportunity to try a localized treatment and avoid the systemic side effects associated with medications such as tricyclic antidepressants and antihistamines.

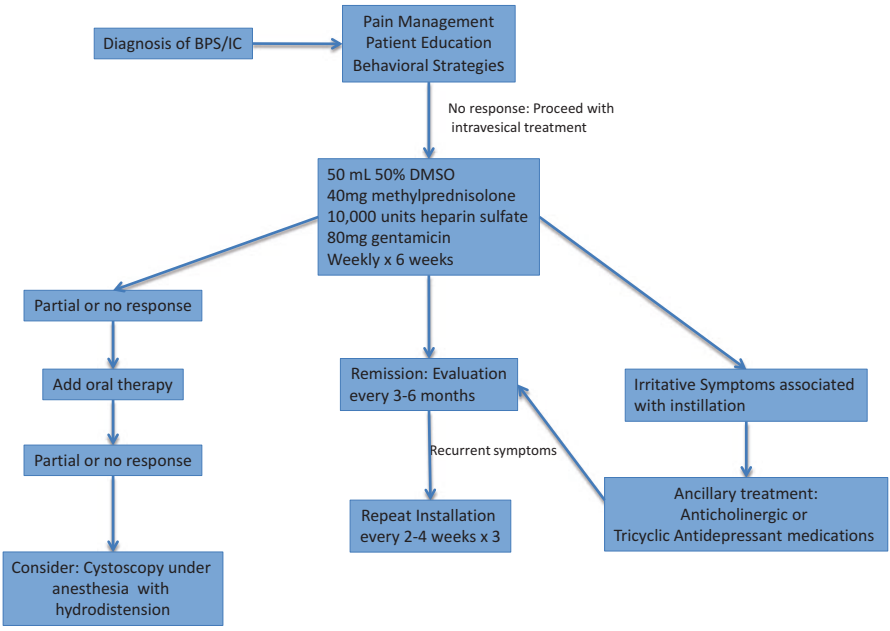

Fig. 19.1 Algorithm outlining the use of DMSO cocktail in a patient care setting. It may be necessary to add ancillary treatments for partial or no response group as shown on the left side of the graph

Studies of DMSO

Randomized Controlled Trials

Two randomized controlled trials have studied the effectiveness of DMSO. The first, by Perez-Marrelro et al., was published in 1988 [4]. This study compared the use of a 50 % DMSO solution ($n=15$) to a placebo ($n=17$, saline only) every 14 days for 2 months. The response rate was 87 %, and patients demonstrated improvement in pain, urgency, bladder capacity, and subjective improvement of symptoms.

The second of these randomized trials was published in 2000 by Peeker et al. [5]. They randomized patients to treatment with 50 % DMSO ($n=11$) versus BCG ($n=10$). Treatments were given weekly for a total of 6 weeks. Patients who did not respond to initial treatment were then crossed over to the other group after a washout period. Results were stratified by type of IC, either classic or non-ulcer type. Patients treated with DMSO showed a significant reduction in urinary frequency, though only in those with Hunner lesions. Pain was significantly reduced in both types of IC, but there was no difference in bladder capacity in either group. No benefits were shown in the BCG group.

Nonrandomized Studies

Multiple prospective studies of DMSO have been published since the 1970s. Stewart et al, in1972, demonstrated improvement after instillation every 14 days in 21 patients [23]. The same group went on to show effectiveness for DMSO in one prospective [24] and one retrospective study [3]. These and several others were able to demonstrate consistent improvements in pain and urinary urgency; however, the results for improvement in bladder capacity were mixed. Response rates in these studies very, with the lowest being 65 % [3], and the highest 95 % [25]. This last study, by Fowler, looked only at patients with "early" IC, without significant ulceration or scarring on cystoscopic examination. Indeed, this would correlate with more recent studies of multiagent therapies, where the effectiveness of intravesical treatment is more pronounced when bladder capacity is greater and ulcerations are less prominent [19, 21].

Outcomes

Although the reported response rates are high with intravesical DMSO, the evidence for its use remains weak. The existing randomized trials have small numbers of subjects. The prospective trials also have small numbers and rely heavily on subjective reports of improvement. Because of this, the most recent AUA guideline has assigned a grade of C to the use of DMSO in BPS/IC and its designation as an option for treatment [6]. Due to its high level of absorption the guidelines advise a dwell time of not longer than 15–20 min; however, they acknowledge that very few adverse events are reported. In addition, a Cochrane review of all intravesical treatments for BPS/IC did not find strong enough evidence to recommend any of them [26]. Despite this, DMSO continues to be among the most commonly used treatments.

Future

In moving forward with intravesical treatments for BPS/IC, further research will be needed to prove their effectiveness. The ideal intravesical treatment is effective in treating symptoms, easy to administer, and has minimal morbidity. DMSO has shown promise in all of these areas, yet there is still hesitation for its strong recommendation due to the lack of scientific evidence. Future randomized controlled, multi-institutional studies will be needed to prove its true value for patients with BPS/IC.

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Intravesical Lidocaine in Interstitial Cystitis/Bladder Pain Syndrome

20

Nicole Golda and J. Curtis Nickel

Introduction

The etiology of interstitial cystitis/bladder pain syndrome (IC/BPS) has been described as related to inflammation, mucosal defects, permeability problems, neuro-endocrine abnormalities, genetic disturbances, and/or infection, but the end result becomes a hypersensitivity of the urinary bladder with hallmarks that include exaggerated and abnormal sensory and motor reactions to the presence of urine in the bladder. In some patients, the symptoms progress to debilitating hyperalgesia and allodynia.

For many patients with IC/BPS, instillation therapy has been an integral part of the therapeutic management strategy. Multiple agents have been studied, alone or in combination, for instillation into the bladder for the treatment of IC/BPS. The American Urologic Association (AUA) IC/BPS guidelines list intravesical therapies as a treatment option when first-line conservative therapy fails; used alone, or in conjunction with physiotherapy techniques and oral agents [1]. The advantage of intravesical instillation is that therapy is directed to the bladder, allowing establishment of high concentrations of the agent locally, and minimizing systemic side effects.

The rationale for the use of local anesthetic instillation is to alter the process of neurogenic inflammation and hypersensitivity. Short-acting lidocaine and long-acting bupivacaine are the commonly used anesthetics instilled alone, or as part of a "cocktail" with therapies that aim to replenish the deficient glycosaminoglycan (GAG) layer in the bladder (heparin sulfate, hyaluronic acid, chrondroitin sulfate). In addition to providing relief of bladder pain, intravesical anesthetic instillation can be used as a diagnostic tool for IC/BPS to distinguish the pelvic pain related to the bladder from that of non-bladder-related pain [2].

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Mechanism of Action

The heterogeneity of the IC/BPS population suggests that the pathophysiology of IC/PBS is likely multifactorial. However, the common belief is that any prolonged noxious stimuli leads to neuroplasticity of the nervous system and development of chronic pelvic pain that is shared by all IC/BPS patients. Characteristic features of the neuropathology and resulting pain that IC/BPS patients experience include: pain that seems inappropriate to degree of tissue pathology, exaggerated pain experience (hyperalgesia), and pain from normally non-noxious stimuli (allodynia) [3].

Sensory information from the bladder comes from peripheral nociceptors carried by afferent fibers of the pelvic and hypogastric nerves. The afferent transmission is via a combination of thinly myelinated A (alpha) fibers and unmyelinated C fibers. Under physiologic conditions, the normally silent type C nerve fibers require high threshold noxious chemical, mechanical, and/or thermal stimuli to generate an action potential. However, damage or injury to these fibers triggers local neurogenic inflammation allowing sodium to enter the nerve ending. This causes an electric signal to build up in the nerve, passing along the peripheral nerve to the dorsal horn of the spinal cord and then upward into the brain, where the signal is interpreted as pain [3].

Repetitious stimulation of a nerve leads to a general increase in excitability of type C nerve fibers and sensitization of peripheral and central sensory nociceptive nerve endings. This process lowers the threshold required to incite nociceptive stimuli transmission and can result in neuronal "wind up" and neuroplasticity with resulting chronic pain, regardless of the initiating etiology. It is this process that may explain bladder hyperalgesia and allodynia, even after the inciting event is controlled [4].

Anesthetic agents work by temporarily blocking sodium from entering the nerve ending; therefore, the electric signal buildup is prevented from passing along the nerve pathway to the brain and the pain signal is stopped. Lidocaine and bupivacaine also possesses anti-inflammatory, anti-histamine, and immunomodulating properties, and may also allow for C fiber desensitization [5, 6]. At lower blood concentrations, sensory neurons are primarily affected, while at higher concentrations the effects become generalized.

Side effects are typically not serious and may include temporary discomfort, dysuria, urethral irritation, hematuria, and urinary tract infection. To improve tolerance to the procedure, the use of an 8-Fr pediatric feeding tube combined with intraurethral lidocaine may help [7]. Although local anesthetics are generally safe, systemic toxicity can occur after administration of an excessive dose. The pharmokinetics of intravenous lidocaine have been well studied and the majority of studies indicate that signs and symptoms of toxicity appear at serum levels of greater than 5 μg/mL [8]. Once absorbed into the bloodstream, the central nervous system (CNS) and cardiovascular system (CVS) are susceptible to the local anesthetics effects.

When systemic exposure exceeds the maximum safe dose, manifestations of toxicity typically appear within 5–10 min after the injection; however, onset may range from 30 s to as long as 60 min [9, 10]. The first signs and symptoms are usually

Table 20.1 Signs and symptoms of local anesthetic toxicity

Central nervous system (CNS)	Cardiovascular system (CVS)
Initial: • Circumoral and/or tongue numbness • Metallic taste • Lightheadedness • Facial tingling • Dizziness, vertigo • Restlessness, anxiety • Visual disturbances • Tinnitus • Disorientation • Drowsiness Late: • Respiratory muscle twitching • Convulsions • Unconsciousness • Coma • Respiratory depression and arrest • Cardiovascular depression and collapse	Initial: • Hypertension • Tachycardia • Chest pain • Shortness of breath • Palpitations • Lightheadedness • Diaphoresis Late: • Hypotension • Bradycardia • Syncope • Atrioventricular block • Ventricular arrhythmias • Cardiac arrest

neurologic with perioral numbness and tinnitus. A patient may feel lightheaded, and report visual and auditory disturbances, which can progress to seizure and cardiac and respiratory arrest. Signs and symptoms of local anesthetic toxicity can be found in Table 20.1 [9, 10].

The amount of drug administered as well as the route of administration influences the side effects of local anesthetic agents. Studies have demonstrated that intravesical anesthetic agents can provide local anesthesia to the bladder, without extensive absorption by the urothelium to significantly increase serum levels [11]. Furthermore, in a study to determine safe dosing of intravesical lidocaine, Henry et al. found that the serum lidocaine levels after intravesical instillation were similar to those achieved when infiltrating a comparable dose of lidocaine subcutaneously [12].

When dose administration follows local anesthetic dosing guidelines (for lidocaine using a maximum of 4.5 mg/kg, or up to 300 mg total dose), the authors believe that intravesical anesthetic instillation is a safe treatment option for patients with IC/BPS. Certainly doses of 100–200 mg appear to be a safe dose.

Intermittent Lidocaine Monotherapy

Anesthetics have been used intravesically for many years to provide adequate local anesthesia to allow for minor bladder cauterization, small biopsy procedures, and intradetrusor Botox™ injections [11, 13, 14]. Intravesical lidocaine has been shown in two uncontrolled studies to have a beneficial effect on the treatment of pain and urinary frequency in patients with IC/BPS. The earliest reported use was in 1989 by Asklin and Cassuto, who administered 10 mL of 2 % lidocaine

mixed with 40 mL of normal saline for bladder instillation in a patient with ulcerative IC/BPS daily for 2 weeks, and then twice weekly for 4 weeks. The patient reported improvement in symptoms, including cessation of pain, and an increase in bladder capacity; however, the symptoms returned 3 months after ending intravesical lidocaine instillation [15].

Another case study from Greece in 1992 demonstrated a similar favorable effect of relieving pain in a patient with a 5-year history of IC/BPS. The treatment included 8-weeks of repeated intravesical treatment of 15 mL of 2 % lidocaine mixed with 50 mL normal saline and was found to be safe with no adverse reactions reported with 2-year follow-up [16].

Bupivacaine-Based Therapy

Although lidocaine has been successfully used in providing analgesia for bladder procedures of short duration, the goal of treatment in patients with IC/BPS is to provide longer duration of treatment effect. In an attempt to achieve this goal, bupivacaine is sometimes used in patients (20 mL 0.5 % bupivacaine), as it is more lipophilic and longer acting. Quillin and colleagues reviewed their experience of patients who received a single instillation of 20 mL 0.5 % bupivacaine after failing lidocaine-based cocktails. Although only transient, 27 % of patients had complete pain relief and 53 % had partial relief. Furthermore, for patients doing self-instillation they recommended adding 40 mg gentamicin (1 mL) to prevent infection [17].

Bupivacaine-based cocktails are first line for some experts: 20 mL 0.5 % bupivacaine, 20 mL 2 % lidocaine jelly (Moldwin [18]) or 10,000 U heparin, 80 mg gentamicin, 50 mL 0.5 % bupivacaine, 50 mL 8.4 % sodium bicarbonate, 100 mg hydrocortisone (Lukban [19]). However, the authors of this chapter do not advocate bupivacaine because of lack of safety data, inconsistent and unpredictable absorption, particularly with bicarbonate and the increased risk of cardiovascular toxicity when compared to lidocaine.

Alkalanized Lidocaine Therapy

Initial uncontrolled observational studies demonstrated a short-term benefit of intravesical lidocaine instillation in patients with IC/BPS. However, the effects were not prolonged and it was hypothesized that the pharmacokinetics of alkalinized lidocaine may allow for a sustained benefit.

The physiologic activity (onset of action, potency, and duration of action) of local anesthetics is a function of the percent ionization at physiologic pH, with the nonionized form more readily capable of diffusing across nerve membranes and blocking sodium channels. With a pKa of ±8.0, lidocaine is almost entirely ionized in typically acidic urine. Therefore, by alkalinizing lidocaine with sodium bicarbonate to increase the urine pH, the equilibrium shifts toward the hydrophobic,

nonionized form, which allows for better drug penetration of the urothelium. For an excellent and comprehensive review of the pharmacokinetics of alkalinization and review of the literature on this topic, we refer the reader to an excellent review article by Henry et al. [20].

Although no published studies have directly compared lidocaine with and without alkalinization, there have been studies demonstrating significant improvement in efficacy with alkalinization. Henry et al. found that IC/BPS patients had a significant reduction in bladder pain after intravesical administration of 5 % lidocaine at a dose of 5 mg/kg alkalinized with 20 mL 8.4 % sodium bicarbonate. The authors concluded that this was a safe dose in inflamed bladders, as the amount of absorbed lidocaine from bladder urothelium in IC/BPS patients was the same as that of healthy volunteers. The peak serum lidocaine concentration reached 1.3 μg/mL at 30 min, well below the toxic serum threshold of 5 μg/mL [12].

In a phase II multicenter randomized, double-blind placebo-controlled industry-sponsored study by Nickel et al., 10 mL solution of 2 % lidocaine alkalinized with sequential instillation of 8.4 % sodium bicarbonate (to prevent precipitation in a syringe/catheter) was instilled for 5 consecutive days in 102 patients (held for 1 h). Significant improvement in symptoms (Global Response Assessment (GRA) scale) was reported compared to placebo, 3 and 10 days after completing this course of alkalinized lidocaine instillations, 30 % vs 10 %, $p=0.012$ and 24 % vs 12 %, $p=0.102$, respectively. Furthermore, this treatment was demonstrated to be safe, with minimal side effects and peak serum lidocaine concentrations remaining below 2 μg/mL [21].

Some patients describe dysuria when voiding the instilled alkalized preparation. This might be secondary to the actual alkalization rather than the lidocaine. If this turns out to be a problem, the authors have found that leaving the instillation foley catheter in situ, but clamped or plugged for 20 min and only removing it after draining the preparation, usually solves this problem.

Multiagent Lidocaine Therapy

In an effort to improve response rates and provide sustained relief of IC/BPS symptoms, various agents have been tested in combination with lidocaine for intravesical instillation. The hypothesis being that lidocaine may provide immediate relief of bladder symptoms, allowing additional agents more time for efficacy. Anesthetic cocktails have added agents to target regeneration of the integrity of GAG layer, such as hyaluronic acid (HA), pentosan polysulfate (PPS), or heparin sulfate.

Several studies have reported that instillation of HA provides improvement for some patients with IC/BPS [22, 23].

Recognizing that HA has a modest and slow onset of action, Lv et al. proposed addition of lidocaine to aid in immediate relief of bladder symptoms. They divided 48 patients with IC/BPS who failed oral medications into one trial and two control groups (HA alone, alkalinized lidocaine alone). The trial group received 40 mg HA, 10 mL of 2 % lidocaine, and 5 mL of 8.4 % sodium bicarbonate intravesically on a weekly basis

for 8 weeks and then monthly for 4 months (held for 1 h). At study end, the GRA of the trial group patients reached 73.3 % and the results from the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI) demonstrated a statistically significant improvement in symptoms and problems, respectively. Furthermore at 24-weeks, the HA alone and HA+alkalinized lidocaine groups had response rates of approximately 68 %, while there was no improvement noted in the group treated with alkalinized lidocaine alone (8 % response rate) [24].

PPS is the only oral agent approved for IC/BPS by the FDA; however, its disadvantage is that its concentration in the urine is very low, resulting in up to a 6-month lag before clinical benefits are realized. To achieve more rapid results, Davis et al. compared alkalinized lidocaine with or without intravesical PPS. All 41 patients in the study received oral PPS for a total of 18 weeks, and twice weekly instillations for 6 weeks. They were randomized to receive 8 mL of 1 % lidocaine and 3 mL of 8.4 % sodium bicarbonate plus either 200 mg PPS intravesically or placebo (30 mL saline). Overall response rates were approximately 90 % in both groups; however, the treatment group had a statistically greater reduction in ICSI/ICPI scores compared to placebo (46 % reduction vs. 24 % reduction; $P=0.04$) [25].

Heparin sulfate instillation has been shown to be effective in ameliorating symptoms in some patients with IC/BPS [26]. Parsons evaluated the efficacy of heparin as part of multiagent therapy at varying concentrations in 82 patients using 40,000 U heparin and 3 mL 8.4 % sodium bicarbonate plus either 8 mL 1 % lidocaine or 2 % lidocaine. Immediate relief of pain and frequency after one 8 mL instillation improved when the concentration increased from 1 to 2 % (94 % *vs.* 75 %; $P<0.01$). A further six instillations of 2 % lidocaine were given over 2 weeks and 80 % of patients had symptom relief lasting >48 h after the last treatment [27].

Similar results were shown by Welk et al., who administered 2 mL (20,000 U) heparin, 8 mL 2 % lidocaine, and 4 mL 8.4 % of sodium bicarbonate in 23 female IC/BPS patients complaining of dyspareunia. Patients were treated with intravesical instillation three times per week for 3 weeks (held for 1 h). Sixty-five percentage of patients reported a positive response at 3-week follow-up [28].

Nomiya et al. showed improved duration of effect in a study of 32 patients treated with intravesical instillations of 20,000 U heparin, 5 mL 4 % lidocaine, and 25 mL 7 % sodium bicarbonate (held for 30 min) on a weekly basis for 12 weeks. On GRA, response increased with further therapy (33 % post first instillation, 77 % at end of study, 90 % 1 month after the last instillation); however, then the response rate declined to 46 % at 2 months and 16 % at 6 months following cessation of treatment [29].

In a multicenter prospective, double-blind, crossover trial, Parsons et al. randomized 28 patients to receive a lidocaine cocktail to compare its efficacy and safety to placebo. The active drug included 50,000 U heparin, 1.3 % lidocaine (200 mg), and 420 mg sodium bicarbonate in 15 mL of water versus the control of sodium bicarbonate only (held for 30 min). In this single-dose randomized trial, the lidocaine cocktail was more effective than placebo on global assessment of symptoms (GAR) six-point questionnaire, which showed significant improvement in patients on active drug vs. control: 50 % vs. 13 % ($P=0.013$), respectively.

There were no adverse events and serum lidocaine concentrations ranged from 0.24 to 2.0 μg/mL [30].

Observational studies report successful outcomes for 65–94 % of patients after treatment with heparin combined with alkalinized lidocaine [27–30]. These promising results showed that the local anesthetic activity of lidocaine can provide immediate relief of bladder symptoms, which can then be maintained with the addition of heparin.

Continuous Lidocaine Exposure

The recent development of a continuous drug delivery system for lidocaine (LiRIS® or lidocaine-releasing intravesical system) has promising results and is currently undergoing further trials. The size of a tiny pretzel, the device is inserted cystoscopically and is retained in the bladder, releasing solid lidocaine minitablets slowly over a period of 2 weeks. In its single arm phase I trial, Nickel et al. enrolled 16 women with IC/BPS and bladder hemorrhages or Hunner's lesions who received either LiRIS® 200 mg or LiRIS® 650 mg for 2 weeks. Cystoscopic examinations were performed at study end (day 14 device removal) compared with day 1 and objective improvement was noted, including total resolution of Hunner's lesions in five of six patients with baseline lesions. At study end, the GRA reached 64 % and was maintained for 2 weeks [31].

Electromotive Lidocaine Administration

Electromotive drug administration (EMDA) is a modality used to enhance drug absorption by the urothelium through application of an electric current to drive molecules. Several studies have evaluated bladder hydrodistention in patients with in IC/BPS using EMDA, the first reported in 1992. This initial case study instilled 80 mL of 1 % lidocaine with 1:100,000 epinephrine intravesically in a patient to perform hydrodistention. The bladder was distended to a final volume of 600 mL, with 16 mg of dexamethasone added at the end of instillation, and the patient's bladder symptoms were improved for 6 weeks [32].

Using a similar technique, 100 mL of 2 % lidocaine, 1.5 mg epinephrine, and 16 mg dexamethasone installation with EMDA followed by hydrodistention in 21 women with IC/BPS demonstrated distention from a discomfort level of 200 mL to an average volume of 600 mL. At 6 months after instillation, patients reported a 25 % success rate (pain score of 0) [33]. Riedl et al. reported complete resolution of bladder symptoms in 61 % of patients ($N = 13$) with IC/BPS using EMDA of 100 mL of 2 % lidocaine, 16 mg epinephrine, and 16 mg dexamethasone [34].

Rose et al. conducted the first study to compare the efficacy of EMDA of lidocaine versus instillation of alkalized lidocaine alone to provide local anesthesia for bladder distention. Ten patients had instillation of 5 mg/kg alkalized lidocaine before hydrodistention, versus a second group of 11 patients who had EMDA of

lidocaine anesthesia prior to distention. There was a greater increase in bladder capacity using EMDA versus alkalized lidocaine, 135 % vs. 70 %, respectively. The authors concluded that lidocaine EMDA is superior to alkalized lidocaine, allowing for greater distention of the bladder for a longer period of time [35]. However, there is a need for a randomized blinded comparison of lidocaine with and without EMDA.

Patient Self-Directed Therapy

For patients who are capable of self-catheterization, an anesthetic cocktail can be self-administered at home as maintenance therapy. We would suggest that weekly or biweekly instillation of 5 cc of 1 % lidocaine mixed with 5 cc saline (total volume 10 cc) after voiding would be a very safe recommendation for patients who have had successful clinic-based treatment. Patients can be taught techniques to perform home instillation and this cocktail can be mixed by their pharmacist.

Intravesical Lidocaine as a Diagnostic Tool

In addition to providing relief of bladder pain intravesical lidocaine instillation is a useful diagnostic tool for IC/BPS. This concept was first published by Taneja et al. to differentiate between pain from the urinary bladder versus pain originating in other pelvic organs. The authors treated 22 women with pelvic pain with 20 mL of 2 % intravesical lidocaine solution. Sixty-eight experienced a reduction of pain by 50 % or greater (visual analogue scale (VAS) for pain). All nonresponders were subsequently diagnosed with nonbladder pathology causing their pelvic pain. The authors found value in performing intravesical instillation of lidocaine to aid in diagnosis, but also to identify patients who should not be treated with intravesical therapy and possibly be referred to other specialists for further work-up of a non-urologic source of pelvic pain [2].

We recommend that patients with equivocal findings (usually those with severe pelvic floor pain in whom it is difficult to decide if the problem is bladder pain, pelvic muscle pain/spasm, or both) be assessed before and after an anesthetic challenge test, as described below.

To begin the test, perform and document a focused pelvic examination to assess for pain when palpating the bladder, urethra, perineum, and pelvic floor trigger points. Then insert a lubricated 12 or 14 Fr Foley catheter into the bladder and drain any residual urine. Fill the bladder with saline through the catheter by gravity (80 cm water pressure) until the patient has discomfort and/or pain. Document that volume as the functional bladder volume/capacity and then drain the bladder. Then instill 5 mL of 4 % lidocaine (200 mg) into bladder followed directly by 5 mL 8.4 % sodium bicarbonate (10 mL total), and then clamp the catheter for 10–15 min. After the solution is drained, refill the bladder by gravity (as above) and ask the patient to hold the volume at capacity for 5 min (hydrostatic bladder dilation) before draining

the bladder. This bladder volume after anesthetic challenge is calculated and compared to the pre-anesthetic volume. Then perform cystoscopy and document glomerulations, Hunner's ulcers etc. and lastly, repeat and document the focused pelvic examination.

If one, two, or all of these conditions are met, we believe the bladder can be confirmed as the origin of pain (organ specific).

1. The post-anesthetic bladder capacity is considerably greater. While the actual increase in volume to confirm the bladder as a source of pain has not been validated, we suggest that it should be at least a 50 % increase.
2. The pelvic examination after the anesthetic challenge results in significant reduction or amelioration of perceived bladder pain (anterior vaginal wall and bimanual examination). This will further allow for better assessment of contributions of other perineal/pelvic muscles and trigger point contributions to pelvic pain (both bladder pain and dysfunctional pelvic floor pain can coexist in individual patients).
3. The presence of significant glomerulations (controversial as these can be observed in normal bladders), submucosal and/or mucosal bleeding, and/or Hunner's ulcers confirms bladder pathology.

Some urologists simplify this procedure by instilling the local anesthetic (with or without alkalizing agent) at the end of the procedure and determine if that improves the pain. However, that does not allow assessment pain impact on functional bladder capacity, assessment of bladder mucosa after hydrodistention, or evaluation of pelvic floor before and after bladder anesthesia.

Conclusion/Recommendations

Intravesical lidocaine in the assessment and treatment of IC/BPS disease symptoms (refractory or for flare-ups) is recommended for patients willing to accept catheters and bladder instillations. Instillation of lidocaine on a daily or weekly basis is an option for short-term, and possibly longer-term relief IC/BPS bladder pain. Treatments may be administered in the clinic setting or at home in some cases.

Alkalinized lidocaine has been safely used in clinical trials. If a clinician chooses to administer an alkalinized preparation, then he or she must keep in mind the benefit of enhanced absorption may come with a risk of potential lidocaine toxicity.

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Innovative Intravesical Therapies

21

Austin G. Hester and Robert J. Evans

The American Urological Association guidelines for the treatment of interstitial cystitis/bladder pain syndrome have proven to be beneficial to many patients. There is a subset of patients who respond poorly to the standard treatment options. Given the continued pain and voiding dysfunction seen in this patient population, innovative therapies have been pursued to alleviate the symptomatology resistant to standard treatment regimens.

Immunosuppressants

Bladder pain syndrome/interstitial cystitis is a syndrome commonly felt to be associated with inflammation within the bladder. For example, it has been shown that in patients with interstitial cystitis, mast cell release is associated with release of the cytokine interleukin-8 (IL-8), a marker of inflammation, and there is a documented alteration in the production of cytokines IL-6 and cGMP as well in these patients [1]. Hunner lesions, which are seen in the ulcerative forms of interstitial cystitis, result from inflammatory changes in the bladder mucosa and submucosa [2, 3]. Given the large degree of inflammation seen on biopsy of these lesions, systemic immunosuppression has been tested for potential therapy. Systemic corticosteroids have been studied and noted to be efficacious, but with the long list of side effects noted with this therapy, the AUA has actually recommended *against* this treatment option [2, 4, 5].

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Cyclosporine A is a well-known immunosuppressant used in a wide variety of medical conditions, including transplant recipients, dermatologic disorders, autoimmune disorders (such as systemic lupus erythematosus), and in diseases of chronic inflammation [2, 6–9]. Given the fact that interstitial cystitis/painful bladder syndrome is potentially autoimmune in nature, the AUA guidelines recommend Cyclosporine A as a fifth-line treatment for patients who have failed simpler options [4].

The mechanism of action has been well-studied and is known to inhibit calcineurin, a critical element in the activation of T-cells [2]. Calcineurin has phosphatase activity which is inhibited by cyclosporine when it forms a complex with cyclophylin, thus inhibiting the natural nuclear translocation and activation of NFAT transcription factors [9, 10]. Importantly, cyclosporine inhibits the transcription of interleukin-2, an important step in T-cell activation [9].

Prior to 2005, the only studies used to evaluate the efficacy of cyclosporine in the treatment of bladder pain syndromes were retrospective analyses [11]. However, a randomized control trial performed in Finland in 2005 was able to successfully study the efficacy of cyclosporine A in comparison to pentosan polysulate sodium (PPS). Overall, the researchers found that cyclosporine A produced a superior result to PPS in all elements of the study. They reported a significant ($p < 0.001$) difference in subjective resolution of symptoms (per a global response assessment), with 59 % of patients treated with cyclosporine demonstrating improvement of symptoms versus only 13 % of those treated with PPS. Objectively, they noted an improvement in micturition frequency with cyclosporine in comparison to PPS. Despite the significant side effects patients in the cyclosporine arm experienced (see below for more details), there was a similar drop-out rate noted between the two groups. The researchers hypothesized this may be due to the improvement in symptoms in these patients from the treatment itself, thus outweighing any side effect profile [12].

Due to the small sample sizes used in previous studies, a more recent study evaluated three tertiary centers in a retrospective review [2]. This study was able to combine a total of 44 subjects (14 men and 30 women), 34 of whom were noted to have Hunner lesions on biopsy. They noted a significant symptom improvement in patients with Hunner lesions, but due to a substantial dropout rate secondary to side effects of cyclosporine, the success rate dropped to 68 %. Prior to those patients leaving the study, the initial response rate was noted to be 85 %. There was a much lower success rate of 30 % in those subjects without Hunner lesions. This was not a surprising finding given the appearance of Hunner lesions in the subset of patients who also have other diseases of chronic inflammation, including Sjögren's syndrome, inflammatory bowel disorders, hypersensitivities/allergies, and rheumatoid arthritis [13]. In fact, an autoantibody receptor studied extensively in the pathogenesis of Sjögren's syndrome has been seen in bladder wall biopsies, suggesting that these autoantibodies may be associated with interstitial cystitis [14]. As anticipated, these patients had an adequate response to an immunosuppressive agent. Given the response in some patients without Hunner lesions, there may be some underlying chronic inflammation in these patients' bladders or there are other unknown effects of cyclosporine A on the bladder lining [15, 16]. Erickson et al., found markers of inflammation in patients without ulcers, indicating ulcers were not a sensitive marker of inflammation on bladder biopsy [1].

The retrospective review of the three centers also evaluated dosing of cyclosporine A in the treatment of interstitial cystitis. Two centers used an initial dose of 3 mg/kg whereas the third group used 2 mg/kg. They found similar response rates despite different dosing regimens. This has not yet been evaluated with a randomized control trial, but use of the 2 mg/kg dose may help to reduce the side effect profile associated with cyclosporine use [2].

Cyclosporine use in interstitial cystitis/bladder pain syndrome has been limited by its adverse event profile. Elevated serum creatinine has been seen and half of the patients who experienced this effect required a lower dose of cyclosporine whereas the other half required stopping cyclosporine altogether. Hypertension can also occur, but these patients all improved with either stopping cyclosporine or with the addition of an antihypertensive medication. Other adverse events include alopecia, wound infections, cutaneous lymphoma, thrush, and mouth sores [2]. The Sairanen trial reported a similar side effect profile with the addition of gingival pain and hyperplasia, paresthesias, abdominal pain, flushing, muscle pain, and shaking [12]. Cyclosporine A has long been used in the transplant population and has been associated with secondary malignancies such as skin cancers [17]. Despite this significant side effect profile, Forrest et al., noted that many of the patients were unwilling to stop therapy due a significant improvement in their bladder pain symptoms and quality of life [2].

There has also been one reported small trial exploring mycophenalate, another immunosuppressive agent, in the treatment of interstitial cystitis [18]. This trial had to be terminated early due to a black box warning classifying the drug as a pregnancy category D (evidence of fetal harm), as well as an increased risk of infection and lymphoma. As many of the patients were young women of childbearing age, the study was terminated early.

More recently there has been interest in the nerve terminals or nocireceptors which transmit the painful stimuli to the brain. Nerve growth factor (NGF) is responsible for the transmission of pain secondary to inflammation in visceral organs such as the bladder. Inhibition of this growth factor has been shown to be potentially beneficial in the treatment of acute and chronic pain syndromes, including pain syndromes involving visceral organs [19–22]. Tanezumab is a monoclonal antibody developed to inhibit the binding of NGF to its receptor, reducing the natural response to painful stimuli. In a randomized, double-blinded, placebo-controlled phase 2 study to evaluate safety and efficacy of Tanezumab in the treatment of interstitial cystitis/painful bladder syndrome, 36 % of patients treated with the antibody had a 50 % or greater reduction in pain scores versus only 9 % of the placebo group. It also demonstrated a significant decrease in urgency symptoms, but not frequency or Interstitial Cystitis Symptom Index score. Several side effects were noted from the tanezumab treatments. The most common were headaches, paresthesias, and hyperesthesias, but most were mild and improved by the end of the treatment period. Overall, the anti-NGF antibody was found to be preliminarily effective in the treatment of interstitial cystitis [23].

The FDA terminated the trials of Tanezumab in the treatment of multiple pain syndromes due to avascular necrosis seen in trials related to osteoarthritis. However, this has been attributed to the possibility that these patients were having such

adequate pain control that they were causing further damage to their joints via uninhibited repeat usage [24]. The use of Tanezumab is now being reevaluated for the treatment of visceral pain syndromes.

Additionally, given the hypothesized autoimmune nature of the disease, TNF-α inhibitors such as adalimumab, which are used in the treatment of other autoimmune disorders [25, 26], have been explored in the treatment of interstitial cystitis/bladder pain syndromes. It has previously been shown that TNF-α is overexpressed in the urothelium of those with interstitial cystitis [27]. A recent phase III, randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy of adalimumab for bladder pain. Of the 43 patients evaluated, 21 received adalimumab for 12 weeks. Despite the significant improvement in symptoms in the patients receiving adalimumab, there was no significant difference in comparison to the placebo group, thus failing positive proof of concept [28].

A new, novel immunosuppressant agent, AQX-1125, is currently under investigation and has demonstrated significant promise. AQX-1125, developed by Aquinox, is a small molecule that activates the enzyme SHIP1, a modulator of inflammatory activity. By increasing SHIP1 activity, the end-result is to decrease immune cell activation and chemotaxis [29]. The results of the Phase 2 trials were recently released. The Phase 2 LEADERSHIP trial, a randomized control trial of AQX-1125 versus placebo, demonstrated a greater than two point improvement of average daily pain on an 11-point scale recorded in an eDiary. This is felt to be clinically significant, but was not quite statistically significant (0.061). However, several secondary endpoints studied over 6 weeks reported at clinic visits demonstrated a significant improvement in pain score ($p=0.006$) and both O'Leary-Sant IC Symptom/Problem Indices (ICSI/PI) and Bladder pain/IC Symptom Scale (BPIC-SS) showed improvement by 4.4 (0=0.008) and 4.8 ($p=0.012$), respectively [30]. This data is very promising, but of course further study is necessary before this drug is marketed.

Intravesical Lidocaine

Lidocaine, a local anesthetic, has long been studied in the treatment of interstitial cystitis/bladder pain syndrome [31]. This was initially reported in 1989 with a case report by Asklin and Cassuto, who reported that multiple instillations of a 0.4% solution of 200 mg lidocaine over a several week period resulted in a significantly improved symptom score and histologic findings in a patient with interstitial cystitis. These changes were only temporary and were noted to recur after cessation of treatment [32]. A later study demonstrated that twice monthly instillations were possible to maintain the benefit of lidocaine treatments [33].

Electromotive drug administration, which uses electrical charge to drive a drug through visceral tissue, was first studied in the bladder using intravesical lidocaine. Lidocaine was instilled into the bladder and a current was applied for 10 min. Using a probe to deliver a constant electrical current into the bladder, the bladder was slowly hydrodistended to full capacity and a steroid was instilled. These patients experienced relief of symptoms for up to 6 weeks following the procedure [34].

Lidocaine is potentially toxic if absorbed systemically from intravesical instillations. The safety of lidocaine instillations was exhibited by instilling the local anesthetic into the bladder for 1- and 2-h durations and measuring blood levels. On average, the maximum concentration was reached at 60–90 min and the maximum level noted was still less than 30 times the toxic level of lidocaine. Intravesical usage of lidocaine is considered safe [35].

Heparin, which is thought to enhance the glycosaminoglycan layer of the bladder wall, has been added to solutions of lidocaine and shown to improve symptoms of patients with interstitial cystitis. Given the continued symptom relief past the expected time for the topical application of lidocaine, the researchers hypothesized the solution could be affecting the local neural pathways by downregulation [36]. They performed a second study using a higher concentration of lidocaine, demonstrating similar symptom relief of pain and urgency [37]. A similar solution of lidocaine, heparin, and sodium bicarbonate was used to study the effect of intravesical installations on dyspareunia, demonstrating that 65 % of patients rated a greater than 50 % improvement in all symptoms with 57 % stating their dyspareunia had completely resolved [38].

Given the overall success of lidocaine as a treatment option for interstitial cystitis/bladder pain syndrome, a novel drug delivery device is under development to allow for the slow release of lidocaine into the bladder. This continuous lidocaine-releasing intravesical system (LiRIS) is currently under investigation as an innovative treatment option for bladder pain. The LiRIS device is a small, coiled double-lumen tube filled with "mini-tablets" of lidocaine. As urine diffuses into the system, the mini-tablets dissolve, creating a highly concentrated lidocaine solution which is slowly released into the lumen of the bladder. Approximately 60–70 % of the lidocaine in the tubing is released over a 2-week span. An empty LiRIS device has been evaluated in healthy volunteers, and it is felt to be well tolerated with the most common side effects noted to be dysuria and hematuria [39].

A Phase 1b clinical trial in a small sample of patients with interstitial cystitis/bladder pain syndrome was used for another point of concept. Patients received either LiRIS 200 mg or LiRIS 650 mg for 2 weeks, then were re-evaluated using validated questionnaires and cystoscopy. Patients experienced an improvement in their bladder pain symptoms, including pain, urgency, and frequency. Additionally, these patients were noted to have improvement in Hunner's lesions, with five of the six patients noted to have the lesions pre-operatively experiencing complete resolution. Additionally, many of these patients continued to have reduction in their symptoms for up to several months following the trial [39]. These are very encouraging findings, and LiRIS is currently under further investigation.

Liposomes

The purpose of the wall of the urinary bladder is to form a watertight surface to prevent passage of urine and blood transmurally. The layers of the bladder form a tight junction to prevent passage of molecules in either direction, including typically easily passed molecules such as water, urea, and potassium [40]. There are

natural mechanisms in place to allow passage of certain structures via "transcellular" or "paracellular" pathways [41]. The ability to surpass or modify these mechanisms is used for intravesical therapies. While certain medications, such as some antibiotics, protamine sulfate, and dimethyl sulfoxide (DMSO), change the permeability of the wall of the bladder, more recent therapies have demonstrated the ability to actually cross the wall of the bladder itself.

Intravesical therapies utilize the idea of direct instillation of medications into the urinary bladder with the intent of direct uptake. Given the mechanisms listed above, the direct uptake into the bladder is limited by the natural tight junctions of the urothelial cells. The constant "washout" of directly injected therapies which necessitates repeated installments of concentrated drugs limits efficacy of instillation therapy [42]. Nanocarriers have been studied to enhance uptake of drugs by the local cell walls and improve the response to instillations.

One potential way to improve penetration is through the use of nanocarriers known as liposomes. Liposomes are artificial constructs with an aqueous core formed using the natural phospholipid layers of a cell wall to make a spherical structure for transport. These structures have been extensively used for transport of drugs, including capsaicin [43, 44]. With a lipophilic outer layer and an aqueous core, they are capable of carrying both hydrophobic and hydrophilic molecules [42].

The ability to carry hydrophobic molecules allows for passage through the membranes of the urothelial cell wall and delivery of an agent that may not otherwise penetrate the bladder wall. This mechanism of assisted passage has been important for drugs like capsaicin where the previous mechanism of entry was using ethanolic saline, a toxic molecule to the bladder wall [42]. In fact, Tyagi et al., demonstrated that replacing the mediator with a more benign structure such as a liposome allows for a safe but equally efficacious delivery of capsaicin for the inhibition of the micturition reflex in rats [44]. This technology has already been shown to be efficacious topically with the application in vaginitis using clotrimazole and metronidazole [45].

The utility of liposomal therapy in the treatment of chronic pelvic pain has been demonstrated. Peters et al., evaluated the use of liposomes in the delivery of intravesical sphingomyelin. Their study involved instilling treatments of a preliposomal sphingomyelin liposate into the bladders of 14 patients with interstitial cystitis/bladder pain syndrome. The solution was allowed to sit in the bladder for approximately 30 min before being emptied by voiding. This was repeated for three more instillations for each subject. Results of this study demonstrated a significant decrease in pain and urgency scores in these patients at 4 weeks post-treatment, but was limited by a lack of a controlled arm of the study [46].

It has been proposed that one mechanism of action for the development of bladder pain syndromes is the leaking of potassium and other irritants through the bladder wall, thus instigating a nerve potential and causing pain [47–49]. Oral pentosan polysulfate sodium (PPS) has long been used for the treatment of interstitial cystitis, specifically targeting the glycosaminoglycan layer of the bladder wall [50]. It is hypothesized that PPS acts by coating the bladder wall in a structurally similar matrix (PPS) to the natural glycosaminoglycan layer to decrease permeability and thus prevent passage of solutes which could result in pain [51]. In fact, it is the only

oral FDA-approved treatment for interstitial cystitis [12, 52]. A 2009 study evaluated the efficacy of oral PPS versus topical PPS via liposomal delivery. They were able to use a lower dose of PPS for direct instillation (80 mg weekly) as opposed to the oral regimen (100 mg three times daily) given the direct interaction with the bladder lining. They determined that the instillation of PPS directly into the bladder per urinary catheter achieved a similar rate of control of bladder pain symptoms as an oral PPS regimen with a lower risk of systemic side effects (thus possibly reducing allergic responses) [41, 52].

Stem Cell Therapy

Epithelial cells make up the lining of most viscera, including the bladder. These cells have natural processes to allow for regeneration under toxic conditions such as chemical or mechanical stresses. This replacement process is known as "tissue homeostasis" and is able to be carried out through the presence of stem cells, which by definition have the ability to differentiate into cells of their particular lineage; for example, the liver is a remarkable example of the ability to regenerate after a significant proportion of the organ is damaged through the regeneration of hepatocytes from stem cells [53]. Unlike many other cell layers in other viscera in the human body, the urinary bladder generally stays in a quiescent phase. As it does not frequently require rapid turnover, the stem cells found in the basal layer of the epithelium remain largely dormant. Naturally, given an insult to the lining of the bladder, these cells may activate for repair and have been noted to be exceptionally proliferative when there is a need to regenerate [54, 55].

The urothelium is composed of three layers, which include the basal layer, an intermediate layer, and the terminally differentiated layer, also known as the "umbrella layer," and has been noted to be in varying stages of differentiation in interstitial cystitis, including a squamous-like variant [56–60]. Similar to other cell linings in the body, the urothelium is differentiated by activating a series of cascades, including the Sonic hedgehog (Shh) and Wnt pathways [54]. Between the signaling pathways, the stem cells ultimately have control over the rest of the urothelium, aiding in regeneration of damaged tissue. Generally, the urothelium is a quiescent layer, not prone to rapid turnover. In the setting of damage and inflammation, a mechanism is in place to regenerate the protective lining. Mechanical or chemical injury to the epithelium results in the production of Shh from the basal stem cells, initiating a cascade of signals, ultimately resulting in expression of the Wnt protein. This allows for the production of urothelial and stromal cells in the area of injury resulting in the renewed integrity and restoration of function of the lining of the bladder [55]. This pathway has been studied as a constitutively active mutation in certain cancers [61].

An important recent study by Song et al., studied the ability to utilize this knowledge of stem cells to treat interstitial cystitis/bladder pain syndrome [54]. The inflammatory and symptomatic changes seen in interstitial cystitis were created in rat bladders by instilling a solution of 0.1 M HCl into the bladders (and PBS into

controls). The HCl instilled bladders were noted to have denuded epithelium, inflammatory changes, neural cell activation, and angiogenesis, comparable to the histologic changes seen in interstitial cystitis. Human umbilical cord blood-derived mesenchymal cells (UCB-MSC) or controls (PBS) were injected into the submucosal layer of the bladder. The rats that received the UCB-MSC injection were noted to have a significant improvement in voiding dysfunction characterized by the interval between detrusor contractions. The rats injected with UCB-MSC were noted to essentially be cured of almost all symptoms and histologic changes noted with interstitial cystitis, including the denuded epithelium, inflammatory changes, and neural and vascular genesis. However, the fibrosis that is occasionally seen in an interstitial cystitis-affected bladder was noted not to be significantly reduced in the bladders treated with mesenchymal stem cells, although there was a slight decreased in fibrosis noted. They were also able to show how the stem cells were able to differentiate into normal urothelium via stimulation of the Shh and Wnt signaling pathways, thereby indicating their ability to regenerate where the tissue was damaged. This study is limited by the fact the rat interstitial cystitis model does not exactly reflect the changes seen in human patient, but the results are promising [54].

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Endoscopic Procedures for Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)

22

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a complex clinical entity that remains difficult to diagnose and treat. Although the pain associated with IC/BPS may be multifaceted, those patients who suffer from true bladder allodynia may be aided with the use of local therapies such as intravesical agents or endoscopic procedures. This chapter will focus on the later approach, one that would be contemplated when more conservative measures fail.

A Role for Hydrodistention for Bladder Pain?

Hydrodistention has played a significant and varied role in the history of IC/BPS. The procedure entails over-distending the bladder under anesthesia with the use of an irrigant. Many techniques have been described, but there remains no singly accepted method [1–3]. Hydrodistention was originally described by Frontz in 1922 and was later incorporated into Messing and Stamey's definition of IC in 1978 [4]. At that time, the procedure was considered the "gold standard" to diagnose the condition. Further studies, such as the one performed by Waxman and colleagues, demonstrated the lack of specificity for diagnosis by prospectively showing 45 % of completely asymptomatic women having cystoscopic findings consistent with IC after hydrodistention [5].

Though its diagnostic ability is unclear, many still recommend hydrodistention in the workup of IC/BPS [3, 6]. The most current recommendations by the American Urologic Association (AUA) at the time of this publication state that cystoscopy and/or urodynamics may be used when the diagnosis is unclear but are not necessary in uncomplicated cases [7]. In our practice, we rarely perform hydrodistention

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Table 22.1 Some technical aspects of hydrodistention

1. General or spinal anesthesia is commonly used
2. Hydrodistention is usually carried out to 60–80 cm H_2O pressure for a short duration, usually 2–4 min
3. *The bladder surface should be viewed while hydrodistention is being performed.* If bladder mucosal tears are identified, continue filling with extreme caution or discontinue filling
4. Prepare electrocautery equipment before hydrodistention in the event of persistent focal bleeding
5. Although controversial, we tend to avoid hydrodistention in the face of a Hunner lesion. If identified at the time of procedure, we will biopsy to rule out pathology, i.e., CIS
6. Consider leaving an intravesical anesthetic, i.e., 2 % lidocaine, postoperatively for patient comfort

for diagnostic purposes. Office cystoscopy is, however, often performed particularly when there is concern for the presence of a Hunner lesion.

Since its inception, hydrodistention has been employed as a therapeutic tool for the IC/BPS patient [4, 8–10]. Success rates are highly variable and change based upon the duration of follow-up and the metric used to quantify success. Success rates vary from 56 to 100 % in modern studies, and duration of pain control is generally 6 months or less [11–13]. It is unclear which patient population will benefit from hydrodistention. Attempts have been made to predict which patients will respond to this therapy based upon their predominant urinary symptom. The results, however, showed no significant difference seen in post-distention variables such as glomerulations or anesthetic capacity [13]. The AUA considers a short duration, low pressure hydrodistention a third-line treatment (Table 22.1). The lack of strong evidence of hydrodistention as a therapeutic option led to a Grade C recommendation by the AUA and consideration as a limited therapeutic option by the European Association of Urology [7, 14]. The Japanese Urologic Association, on the other hand, has recommended hydrodistention as part of the diagnostic workup of IC/BPS and has given a grade B recommendation for the use of hydrodistention in treating IC/BPS. However, they too concede that there is a considerable lack of high quality evidence demonstrating the effectiveness of therapeutic hydrodistention [6]. It is important to note that though complications are rare with short duration, low pressure hydrodistention, there are descriptions of bladder perforations and necrosis [4, 10, 15, 16]. Long duration, high pressure hydrodistention should not be offered to patients based upon AUA guidelines.

Hunner Lesions (Formerly Termed Hunner's Ulcers)

A Hunner lesion (HL), formerly termed Hunner "ulcer" and originally described by Dr. Guy Hunner almost 100 years ago, is an area of reddened mucosa which often has a central pale scar with vessels that converge to its epicenter [4, 17]. The prevalence of HL varies significantly depending on the series analyzed. It ranges from as low as 5–10 % of cases while as high as 50 % [18, 19]. Patients with HL clinically tend to be older with decreased bladder capacities and greater frequency.

Histologically, HL are wedge shaped with either absent urothelium or one that is intermixed with acute and chronic inflammatory cells and fibrin [20–23]. These changes are seen deeper in the lamina propria and muscularis propria where significant edema and fibrosis can be present [20]. There are no pathognomonic histological findings. Classic architecture of an ulcer is not uniformly found; hence the recent change in terminology from *ulcer* to the nonspecific term, *lesion*.

The patient with a Hunner lesion likely represents a unique variant where local bladder pain is not only present, but the pain that the patient experiences is directly related to the inflammatory process. In general, HL can easily be identified upon office cystoscopy. Others feel that these lesions may also be identified by the presence of focal inflammation that occurs during bladder hydrodistention through the use of narrow band imaging [24]. Hunner lesions are easily differentiated from glomerulations, where glomerulations are rarely seen without bladder distention and are typified by the presence of multiple punctate submucosal bleeding points (Fig. 22.1).

Attempts have been made to find predictive surrogate markers or clinical features that could identify which patients have HL without the use of cystoscopy [21]. There were no demographic characteristics or genitourinary symptom characteristics that were predominantly associated with one subtype as opposed to the other [25]. The only differences seen were that there was a higher incidence of pyuria in classic IC disease and that there were different disease associations between HL and

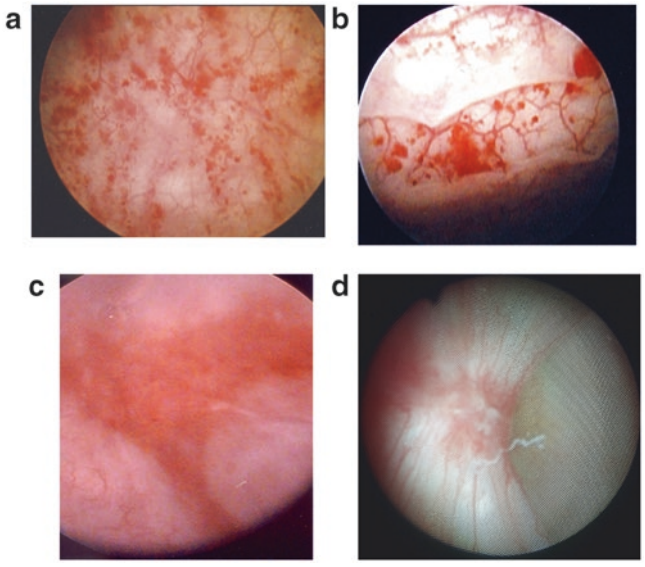

Fig. 22.1 (**a**) Glomerulations noted during hydrodistention under anesthesia. (**b**) Glomerulations and mucosal tears identified during hydrodistention. These tears often occur near the bladder neck. (**c**) Hunner lesion. Note the diffuse hyperemia and difficulty differentiating this from neoplastic disease. (**d**) Hunner lesions are often associated with bladder wall scarring and a loss of bladder capacity

non-HL disease [21, 25]. Of 31 patients with HL in Peter's analysis, none of them had an association with Sjögren's disease, multiple sclerosis, or lyme disease. There was also a significantly higher proportion of patients with fibromyalgia, migraines, and temporomandibular joint disorder in patients without HL [25].

Resection of Hunner Lesions

Soon after the original description of the HL, resection was proposed as a means to provide symptomatic relief. Hunner himself proposed this treatment; however, the long-term results were not promising. There was the thought that denervation procedures could offer symptomatic control and this theory was further investigated. However, it was noted that the more centralized the denervation, the higher the rate of recurrence and sensory disorder [22].

Multiple studies have retrospectively evaluated the efficacy of treating IC/BPS patients with HL with transurethral resection (TUR). Several investigations examined the effect of TUR of the HL and the surrounding rim of edematous tissue. These studies focused on larger resections of the lesions without resecting more than half the muscular layer in order to prevent fibrosis. Peeker et al showed that there was approximately a 90 % increase in duration of symptom relief compared to hydrodistention, and it averaged a length of 23 months [22]. They were able to group patients into four distinct populations. Groups 1 and 2 were by far the most preponderant and included patients who were undergoing long periods of remissions and those who were short-term good responders requiring multiple TURs. The other two smaller groups included those who developed bladder contractures and those who had rapid progression to end-stage disease. There were no differences in the number of lesions or the age at diagnosis among these groups, but those patients who were likely to rapidly progress had a significantly decreased bladder capacity under anesthesia [22]. Chennamsetty performed a similar study showing that 89.6 % of patients noted symptom improvement and that the procedure itself did not change the patient's bladder capacity [26].

Fulguration of HL has become more commonly employed for the treatment of HL, likely due to its theoretically lower risk of bladder perforation and scarring. In this instance, deep fulguration is usually performed with a resectoscope rollerball or bugbee electrode. Table 22.2 outlines some clinical pearls that are useful in the surgical management of HL (Table 22.2). Both Hillelsohn and Ryu examined patients treated in this manner demonstrating that 25 (78 %) of patients reported improved or stable symptoms while 27 (45.8 %) required repeat treatment and fulguration [27]. The average number of fulgurations was 4.3 for those who required repeat TUR and the mean time between these fulgurations was 20.3 months. Interestingly, after 48 months, the repeat fulguration rate plateaued at 57.2 %, indicating that interaction between the disease process and this treatment truly comes to head at that time. Unfortunately, no clinical characteristics predicted the chance of repeat fulguration [27, 28]. However, a similar rate of success and no differences in functional bladder capacity were noted between patients who received single versus

Table 22.2 Suggestions for endoscopic hunner lesion fulguration

1.	Hunner lesions may be indistinguishable from carcinoma in situ. Rule out neoplastic disease before proceeding
2.	The finding of a HL does not absolutely mandate surgical intervention. Other conservative measures still need to be considered
3.	Apart from a standard discussion of risks and benefits, patients should understand that these procedures do not usually provide cure. HL are very likely to recur
4.	Ablative procedures are rarely successful in the face of widespread, diffuse inflammatory disease. In these instances, we have found it best to resort to other forms of care, i.e., intravesical instillation therapy, immunosuppressive therapy, etc.
5.	Although some practitioners perform hydrodistention at the time of fulguration, we have found this to frequently produce significant bleeding from these friable lesions. These areas are also more prone to tear during the filling process. Furthermore, the distention of the bladder will often produce secondary edematous changes and extension of the hyperemic effect, thus obscuring the region of interest
6.	Consider the intravesical instillation of a topical anesthetic when fulguration is completed to facilitate postoperative comfort
7.	Consider instituting a bladder retraining protocol 3–4 weeks postoperatively to optimize bladder capacity

multiple fulgurations. It is important to note that the procedure itself is tolerated very well by most patients. Most patients note significant relief of pain 24–48 h postoperatively (Table 22.2). One study showed that 98 % of those surveyed would undergo repeat electrocautery therapy of their ulcers again [26].

Another endoscopic procedure that has shown success in the treatment of HL is laser ablation. In the 1980s studies showed that HL responded to Neodynium:YAG (Nd:YAG) laser ablation with a response rate of 50–65 % [29]. That series, however, had two delayed cases of small bowel perforation, which raised the question of safety with this procedure. Nd:YAG treatment was once again revisited in 2001 by Rofeim et al. They specifically chose the laser modality because of its 5 mm low depth of penetration and its low degree of tissue heating [30]. With the use of this laser, the tissue heat rises to approximately 60–70 °C and spares the underlying elastic fibers and subsequently is thought to prevent loss of bladder capacity. In order to prevent thermal damage to the small bowel, this trial had a few procedural differences from the previous study that reported associated bladder perforations. The patients in the older study were hydrodistended prior to laser ablation and the entirety of their trigone was treated except the ureteral orifices. Instead, the newer trial did not have hydrodistention performed, and the bladder was minimally filled with sterile water. The filling period was between 1 and 3 s and the power of the laser was limited to 15 W. They considered a treatment to be complete when the lesion was blanched and the surrounding mucosa was not treated if it appeared normal.

Laser ablation of HL under these limitations was tolerated and no complications were noted. The results were significant with mean pain scores decreasing from 9.1 to 1.2. Similar improvements were seen in the severity of urgency, frequency, and nocturia. The typical time from intervention to improvement was 2–3 days. However, similar to electrocautery, 11 of 24 patients (45.8 %) required repeat laser ablation.

Endoscopic steroid injection directly into HL has recently gained popularity. The theoretical advantage of steroid injection versus an exclusively ablative procedure is the potential for decreased associated bladder wall scarring. Another theoretical advantage is the dissolution of scar that had previously been laid down. Cox prospectively assessed patients who underwent endoscopic injection of triamcinolone acetonide into the HL [31]. Triamcinolone was chosen due to its prolonged duration of action that tends to last several weeks and because it is an agent used for postoperative inflammation. 10 ml of triamcinolone acetonide injectable suspension was diluted to a 40 mg/ml ratio and divvyed up into 0.5 ml portions to be injected in the center and periphery of the ulcers. 28/30 (93%) showed improvement while 21 (70%) showed much improvement. All the aspects of the IPSS showed significant improvement, and no complications were experienced.

Injections are typically performed with an endoscopic injection needle under cystoscopic control (Fig. 22.2). Injection depth may need to be adjusted based upon the angle of needle penetration, but is most commonly performed to 2–3 mm. As noted with fulguration, we will avoid performing this procedure with hydrodistention (although this is a controversial topic). We do not recommend performing endoscopic injection in the office setting as one might do for Botox® injection in the overactive bladder patient. Firstly, HL patients are exquisitely sensitive to bladder filling and rarely tolerate even the small amount of bladder distention needed to perform accurate injections (even in the face of premedication with an intravesical anesthetic). Perhaps more importantly, bleeding, sometimes fairly brisk, is frequently encountered after injections. Therefore, one needs to use sterile water or glycine as an irrigant and have electrocautery at the ready.

Electrocautery fulguration, laser ablation, and triamcinolone injections have shown to provide significant improvement in both pain and lower urinary tract symptoms. These three methods have been recommended by the American Urologic Association for the treatment of IC with HL and have been given a grade C evidence level [7].

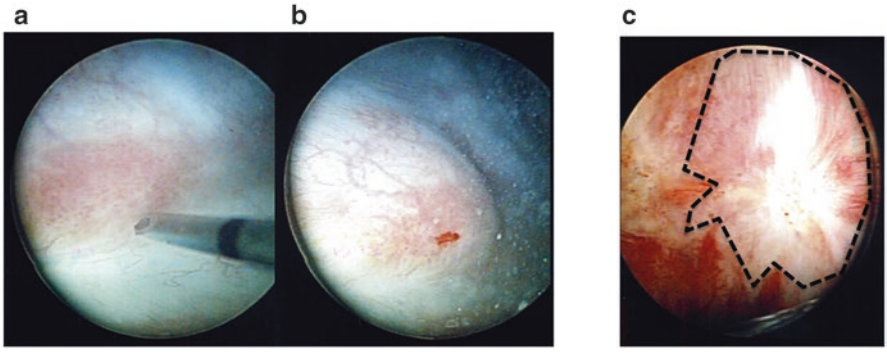

Fig. 22.2 (**a**) Small HL prior to injection. (**b**) Same patient after injection. Note the raised mucosa. (**c**) Different patient with recurrent symptoms 16 months after initial injection. Note the region of previous injection devoid of inflammatory disease (*inside dashed line*), but peripheral region of recurrent inflammation

Bladder Wall Incision

Unfortunately, for some HL patients, chronic inflammation and bladder wall fibrosis ultimately results in unremitting pain and/or a severe reduction in bladder capacity. These patients with what some might term "end stage bladder" have few options beyond urinary diversion. Bahlani and Moldwin studied two such patients whose surgical history precluded them from pursuing urinary diversion [32]. Both had decreased bladder capacities (30 and 120 ml) and significant scarring that caused severe bladder wall tethering and loss of compliance. Using homium laser, these bands were incised and divided at multiple regions to the level of the perivesical fat. An indwelling catheter was left for 1 week and a cystogram was performed at that time prior to removal of catheter. A bladder holding protocol was then started postoperatively in which the patient would attempt to postpone voiding for 15–20 min in order to improve on bladder capacity. After a mean follow-up of 4.2 years, there was an increase in bladder capacity of approximately 50 %, improvements in time between voids, and amelioration of pain with bladder filling. This process of endoscopic lysis of bladder scars can prove to be an effective supplemental method of improving bladder symptoms in those IC patients who otherwise are restricted in surgical options. The value of homium laser energy was the precise application of energy without significant scatter effect.

Conclusion

Endoscopic management is an evolving tool for the clinician treating IC/BPS. Patients who are the most suitable candidates for such procedures are those who have failed more conservative forms of care and have well-defined bladder-based pain. In the future, we hope to see the further development of minimally invasive procedures so that the recommendation of urinary diversion for these patients becomes a footnote in urological history.

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Botulinum Toxin Endoscopic Injection for Pelvic Pain

23

Christopher P. Smith and Michael B. Chancellor

Abbreviations

aboBoNT-A	AbobotulinumtoxinA
AUA	American Urological Association
BoNT	Botulinum toxin
GRA	Global response assessment
IC/BPS	Interstitial cystitis/bladder pain syndrome
ICPI	Interstitial Cystitis Problem Index
ICSI	Interstitial Cystitis Symptom Index
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
onaBoNT-A	OnabotulinumtoxinA
rimaBoNT-B	RimabotulinumtoxinB
VAS	Visual analog scores

Introduction

Botulinum toxin (BoNT) has demonstrated effectiveness in the treatment of several pain disorders, including focal dystonia, cervical dystonia/spastic torticollis, spasmodic dysphonia, oromandibular dystonia, temporomandibular

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disorder, refractory myofascial pain syndrome, and tension, and migraine-type headache [1]. These positive results of BoNT helping pain stimulated interest on the use of BoNT for a variety of genitourinary pain conditions. BoNT's mechanism of action for pain relief is thought to be primarily based on eliminating tonic muscle contraction and, subsequently, blunting nociceptive responses. In addition, BoNT has been shown to inhibit central glutamate release, thus diminishing excitatory amino acid receptors important to the central windup process and pain perception [1]. Central desensitization may be indirectly mediated via peripheral desensitization resulting from BoNT-induced inhibition of neurotransmitter release from primary sensory neurons (Fig. 23.1) [2, 3].

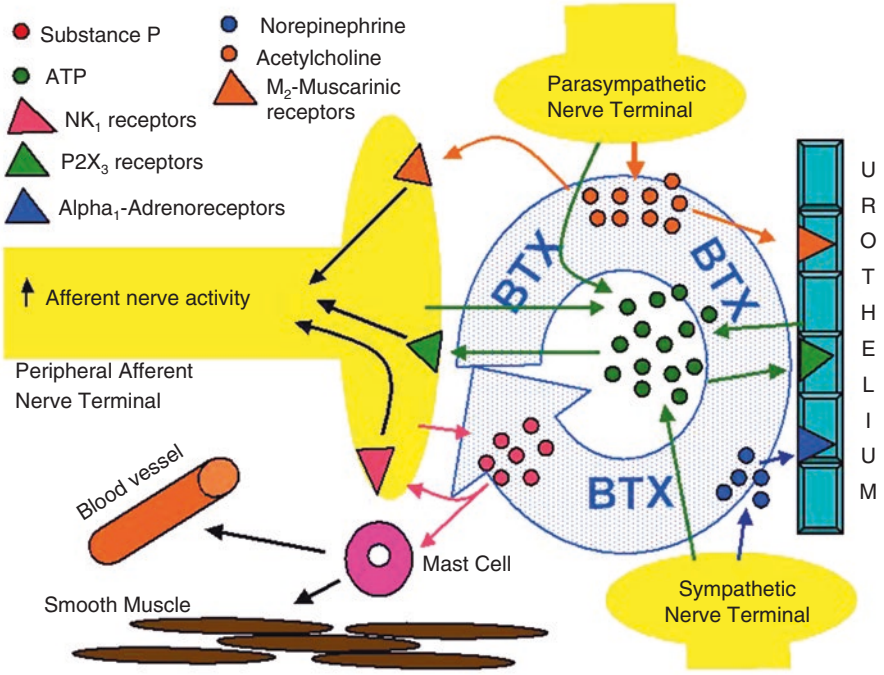

Fig. 23.1 Schematic diagram depicting neuronal (parasympathetic and sympathetic) and non-neuronal (e.g., urothelium) sources of various neurotransmitters (e.g., ATP, acetylcholine, norepinephrine, and substance P) that interact in a circuitous fashion to modulate bladder afferent nerve activity. *Circular arrow* depicts sites of action where botulinum toxin (BoNT) may inhibit neurotransmitter release and reduce sensory nerve excitability, thus decreasing clinical symptoms of urinary frequency, urgency, and pain (From Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. Urology. 2004;64(5):871–5; discussion 5. Reprinted with permission)

Considerations for Clinical Injection

Similar issues for injection for the treatment of pain exist as for neurogenic and idiopathic overactive bladder. Some key issues for pain indication to consider are listed below. Procedures, guidelines, and rules may differ among centers and countries.

- Urinalysis should be negative at the time of the procedure (if the patient has a history of chronic bacteriuria, appropriate preoperative antibiotic coverage is indicated).
- Since the incidence of pelvic pain is more common in younger women, attention for potential pregnancy and birth control is encouraged.
- Since the patient has bothersome pain and may be on significant analgesics already, a plan on peri- and post-procedure pain control should be discussed and agreed upon prior to BoNT injection.
- Risk of retention and potential for intermittent self-catheterization.
- Informed consent with notation of off-label use and black box drug warning.
- Sterile cystoscopic preparation with standard antibiotic coverage for a minor cystoscopic procedure.
- Usually, general anesthesia is required for interstitial cystitis/bladder pain syndrome (IC/BPS) patients as injection performed in conjunction with bladder hydrodistention.

The potential risk of incomplete emptying and retention is especially important in patients with pain. The clinician should utilize all measures available to prevent retention and worsening pain resulting from intermittent or indwelling catheterization . However, the patient should be aware, willing, and able to perform catheterization prior to injection.

Both rigid and flexible cystoscopic techniques work well in our hands and those of most experts without an apparent difference in clinical outcomes. Surgeon preference and institutional practice usually decide what technique is used. However, given the fact that most procedures in IC/BPS patients are performed under general anesthesia, a rigid cystoscope will allow more rapid and precise injections and does not require multiple operators.

Rigid scope: While any rigid cystoscope will work, one author (CPS) prefers using an ACMI® cystoscope with 12° lens, bridged with an Accessory Working Element loaded with a 25-G Cook® Williams needle. The rigid scope allows for easier orientation within the bladder compared to a flexible cystoscope, the working element facilitates rapid injection into the bladder, and the 25-G needle minimizes bleeding and potential backflow from the injection sites. Urethral and pelvic floor injections, if done concomitantly, can be accomplished easily with the use of a 25-G short spinal needle (i.e., urethral sphincter injections) and a disposable pudendal nerve block kit (i.e., levator muscle injections) (Fig. 23.2) [4].

We typically combine onabotulinumtoxinA injection with a hydrodistention and intravesical instillation. Literature demonstrates that hydrodistention can enhance the effect of bladder onabotulinumtoxinA injection [5]. The first observable change

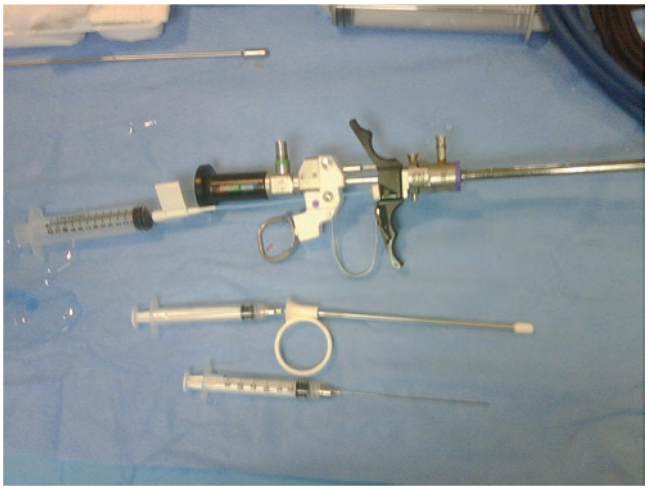

Fig. 23.2 Photograph depicting equipment used to inject BoNT-A in a female with IC and Chronic Pelvic Pain. *Top* of photograph shows ACMI® Cystoscope with 12° lens, bridged with an Accessory Working Element and loaded with a 25-G Cook® Williams Needle. This setup allows for easy orientation within the bladder, rapid injection requiring only one individual, and minimal bleeding or risk of backflow of toxin. The *middle* of photograph displays the 22-G short spinal needle used to target the external urethral sphincter and vulvar areas. The *bottom* of the photograph depicts the needle/trocar equipment from a disposable pudendal nerve block kit that is useful to localize and inject the levator muscles transvaginally (From Chancellor MB, Smith CP. *Botulinum Toxin in Urology*. 1st ed. Berlin Heidelberg: Springer-Verlag; 2011. Reprinted with permission)

noted by patients following BoNT injection is a reduction in urgency and frequency after 4–7 days. These variables continue to improve significantly by 4 weeks. Pelvic pain intimately associated with bladder filling or emptying should also improve with concomitant reductions in frequency and urgency.

Botulinum Toxin Reconstitution

Each vial of 100 U onabotulinumtoxinA (onaBoNT-A, Botox®, Allergan Inc., Irvine, CA) is usually reconstituted to 10 mL with injectable preservative-free saline, making the concentration equivalent to 10 U/mL. OnaBoNT-A is kept in the refrigerator according to instruction, and we usually do not reconstitute the onaBoNT-A until we know that infection has been ruled out or an appropriate antibiotic started to avoid wastage.

Dose

Each vial of abobotulinumtoxinA (aboBoNT-A, Dysport®, Ipsen Biopharm Ltd., Brisbane, CA) contains either 300 U (i.e., for glabellar lines) or 500 U (i.e., for

cervical dystonia). Studies have documented dilutions with preservative-free saline to a concentration of 25–100 U/mL.

Each vial of rimabotulinumtoxinB (rimaBoNT-B, Myobloc®, Solstice Neuroscience Inc., South San Francisco, CA) contains 5000 U/mL and, as opposed to onaBoNT-A (vacuum-dried) and aboBoNT-A (freeze-dried) preparations, is already reconstituted. Although few studies have used rimaBoNT-B to treat bladder overactivity, most have diluted to a concentration of 250 U/mL.

We routinely use 100 U of onaBoNT-A for first-time bladder injection in the majority of our IC/BPS patients. Based on the experience of others and ourselves, we generally have not found a benefit to increasing bladder injection dosage above 100 U in patients who do not respond at all to the initial treatment [5]. In particular, we are concerned that the higher dosage would cause urinary retention, an intolerable de novo complaint in this patient population. In a few select cases, we have reduced the dose below 100 U (i.e., 75 U) to minimize symptoms of incomplete emptying. Typical doses in adult patients treated with aboBoNT-A are 300–500 U, and for rimaBoNT-B doses range between 2500 and 5000 U, but neither one has been approved by regulatory agencies for any urologic indications.

The potency units of all commercially available BoNTs are specific to that particular preparation and assay method utilized. They are not interchangeable with other preparations of BoNT products and, therefore, units of biological activity of one toxin preparation cannot be compared or converted into units of any other botulinum toxins products assessed with any other specific assay method.

Injection Technique

We usually inject 1 mL per site (10 U onaBoNT-A/mL) so, for example, if we are using 100 U, there will be approximately ten injection sites (i.e., dissolving each bottle in 10 mL of preservative-free saline). Recent studies of BoNT injection for idiopathic overactive bladder have used suburothelial delivery to potentially target the suburothelial sensory pathway rather than paralysis of detrusor overactivity [6]. In our experience, the avoidance of retention is paramount in IC/BPS and therefore superficial suburothelial depth of injection is preferred in IC patients.

Successful outcomes have been reported with BoNT injection into only the trigone and bladder base (Fig. 23.3, see "Clinical Results" section) [7]. The rationale for trigone injection is that this portion of the urinary bladder contains a prominent parasympathetic plexus of BoNT receptor-positive nerves, although the role of this plexus on bladder urgency sensation and detrusor overactivity has not been fully explored [8]. This also does not take into account a possible therapeutic effect of BoNT on the abundant sensory nerves within the trigone. Although vesicoureteral reflux might be a potential complication after BoNT in these areas, studies have not supported this claim [9, 10]. In the present authors' personal experience over the past 15 years, submucosal trigone and bladder base injections of BoNT are associated with a low incidence of urinary retention and a similar efficacy to intradetrusor injection.

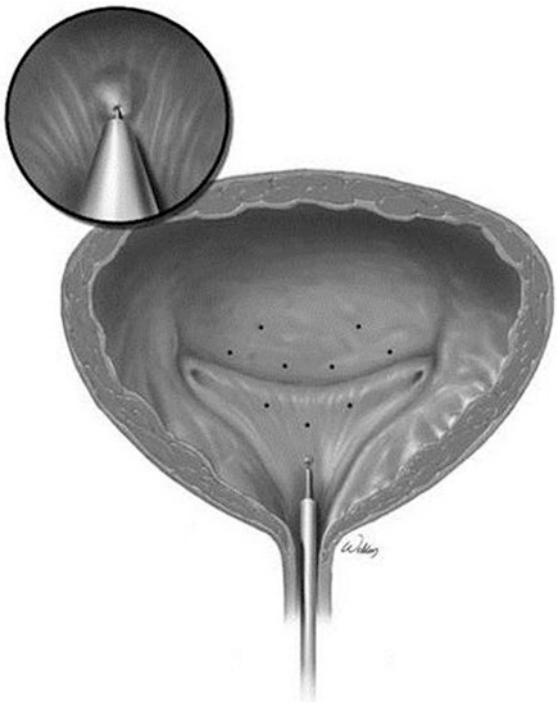

Fig. 23.3 Illustration depicting 10-point injection template of 100 U of onaBoNT into the trigone and bladder base to target the sensory rich nerve fibers in this location (From Chancellor MB, Smith CP. *Botulinum Toxin in Urology*. 1st ed. Berlin Heidelberg: Springer-Verlag; 2011. Reprinted with permission)

It should be emphasized that no standardized injection technique exists for BoNT injection in lower urinary tract tissues. Different bladder injection paradigms have been described (i.e., trigone vs. trigone-sparing) although none has been proven to be superior to the other.

Combined Bladder and Urethral/Prostate/Levator Injections

In our experience, many women with IC also have pelvic floor pain as well. Symptoms include pain in urethra, and dyspareunia. Treatment of these patients also includes injection of the urethral sphincter, levator muscles, and vulvar areas (Fig. 23.4; see Chapter 20: Trigger Point Injections). Thus, female patients may be injected with up to 400 U of onabotulinumtoxinA in one setting (i.e., 100 U in bladder, 50–66 U in urethral sphincter, 33–50 U in vulva or posterior fourchette), and 100–200 U in levator muscles.

In males, as in females, physical examination is useful to identify the trigger points of their pain symptoms. Targeting of the prostate or rhabdosphincter in males with bladder and pelvic floor symptoms is based on elicitation of pain with palpation of these areas on digital rectal examination. If combined with bladder injections, we typically inject 100 U in the bladder trigone and 100–200 U in the prostate or external urethral sphincter transurethrally using a 27-G Olympus endoscopic needle with sheath.

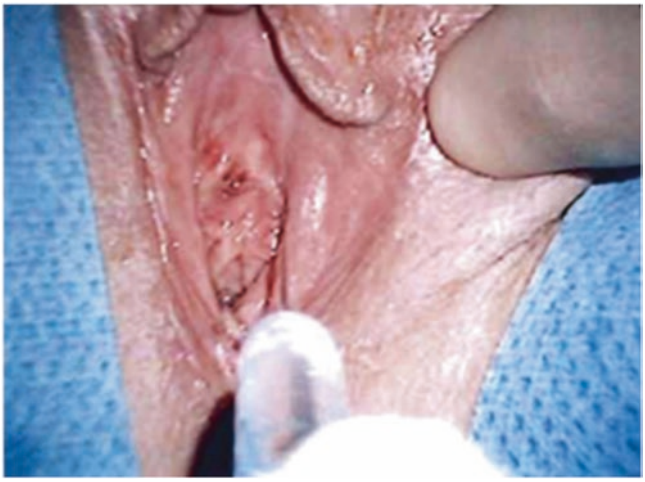

Fig. 23.4 Picture demonstrating peri-urethral injection in a female targeting the external striated sphincter. A 25-G spinal needle is inserted at the 3 and 9 o'clock positions in the periurethral folds for 1.5 cm and typically 33 U of onaBoNT-A are injected at each location (From Chancellor MB, Smith CP. *Botulinum Toxin in Urology*. 1st ed. Berlin Heidelberg: Springer-Verlag; 2011. Reprinted with permission)

Follow-Up

The response to BoNT injection and hydrodistention is often delayed and bladder and pelvic pain may acutely worsen following the procedure. We incorporate a four-pronged approach to prevent this from occurring:

1. Intravesical instillation including 40 mL of 1 % lidocaine, 10,000 units of heparin, and 600 mg of hydrocortisone.
2. Use of ketamine (25–30 mg I.V.) as bridging agent as patients are awoken from general anesthesia.
3. Belladonna and Opium suppository in the recovery room to minimize pelvic floor and bladder spasms.
4. Oral narcotic analgesics for home use. Ketamine has been shown to be effective in reducing postoperative pain in chronic opioid users [11].

We instruct our patients that they may notice some pain and blood-tinged urine, as well as possible difficulty urinating following treatment. These symptoms should resolve within 24 h, and they should call and contact us immediately if they have any questions or concerns. We discuss the appropriate antibiotic coverage and risk of infection in these patients who often have more bladder infections. For those who are not already on intermittent catheterization, we formulate a plan if urinary retention occurs.

It generally takes about 1 week for our patients to notice some relief of symptoms. If the injection helps, he or she will gain further improvement that usually reaches a maximal benefit at about 1 month. The beneficial effect is usually maintained for 6 months in IC/BPS and pelvic pain patients. Subsequently, urinary frequency/urgency and bladder/pelvic pain symptoms reoccur. These are signals we tell our patients to look for and to contact us to schedule a repeat injection.

Clinical Results

The first reported use of BoNT in IC/BPS was a case series of 13 women with National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-defined interstitial cystitis [12]. The patients underwent submucosal transurethral injections of 100–200 U of abobotulinumtoxinA (seven patients) or onabotulinumtoxinA (six patients) into 20–30 sites in the trigone and bladder base. Validated questionnaire (Interstitial Cystitis Symptom Index/ICSI, Interstitial Cystitis Problem Index/ICPI) or voiding charts and a visual analog pain scale were evaluated at baseline, at 1 month, and subsequently at 3-month intervals. Statistically significant improvements in ICSI, ICPI, frequency, nocturia, and pain were observed 1 month following treatment, in addition to improvements in first desire to void and cystometric capacity in those patients so evaluated (Fig. 23.5). Onset of symptom relief was 5–7 days following treatment, and mean duration of symptom relief was 3.7 months.

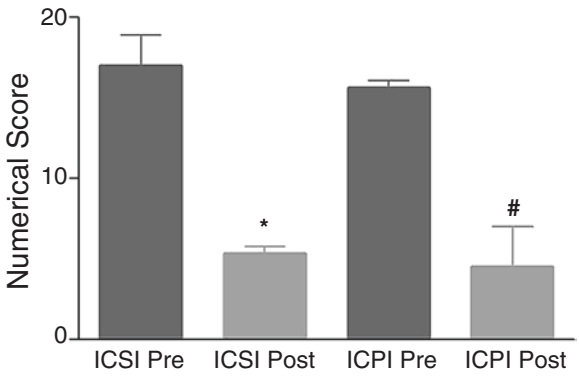

Fig. 23.5 Interstitial cystitis symptom index (ICSI) and interstitial cystitis problem index (ICPI) scores before and after onabotulinumtoxinA (i.e., onaBoNT-A, Botox®) treatment. Following onaBoNT-A treatment, mean ICSI scores decreased from 17.0 ± 1.9 to 5.3 ± 0.4 ($*p < 0.05$), and mean ICPI scores reduced from 15.7 ± 0.4 to 4.5 ± 2.5 ($^{\#}p < 0.05$) (From Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. Urology. 2004;64(5):871–5; discussion 5. Reprinted with permission)

Randomized Trials

Kuo and Chancellor compared the therapeutic results of intravesical onabotulinumtoxinA of 100 or 200 U plus hydrodistention with hydrodistention alone in a randomized clinical study [13]. Sixty-seven patients with IC/BPS who had failed conventional treatments were enrolled. Forty-four patients received suburothelial injection with 200 U ($n=15$) or 100 U ($n=29$) of onabotulinumtoxinA followed by cystoscopic hydrodistention 2 weeks later (BoNT-A group). The control group (23 patients) received the identical hydrodistention procedure without onabotulinumtoxinA injection. The symptom score decreased in all three groups, but pain scale reduction, functional bladder capacity, and cystometric bladder capacity increased only in the onabotulinumtoxinA groups at 3 months. Among 44 patients in the onabotulinumtoxinA group, 31 (70.5 %) had a successful result at 6 months, when compared to only eight (34.8 %) patients treated with hydrodistention alone ($p<0.001$).

This study demonstrated that intravesical injections of BoNT-A plus hydrodistention increased bladder capacity and provided long-term pain relief in patients with IC/BPS and that these effects were superior to those obtained with hydrodistention alone. Increasing the dose of BoNT-A from 100 to 200 U, however, did not provide an additive benefit in terms of pain relief or bladder capacity increase. By contrast, the higher dose of BoNT-A was associated with increased incidence of difficult urination and chronic urinary retention which might be intolerable de novo complaints after BoNT-A treatment.

The effects of aboBoNTA were evaluated in 50 IC/BPS patients who were randomized to hydrodistention and either aboBoNTA (500 U) or saline injection [14]. At 3 months follow-up, no difference in total O'Leary Sant questionnaire scores was observed, and aboBoNTA injected patients only showed greater improvement in O'Leary Sant Problem Index scores. Only 7 % of control and 19 % of aboBoNTA treated patients had a greater than or equal to 50 % reduction in their baseline symptoms. Unfortunately, the investigators injection protocol spared the trigone, so it remains to be seen whether their poor results were in part due to lack of targeting of bladder sensory nerves.

Most recently, Kuo and colleagues reported on a double-blinded placebo-controlled trial comparing the effects of onaBoNT-A (100 U) injection followed by a 15-min hydrodistention to placebo saline injection followed by hydrodistention [15]. Forty patients were injected with onaBoNT-A, and 20 patients were injected with saline. The bladder injections spared the trigone. At 8 weeks, a significantly greater reduction in pain visual analog scores (VAS) was observed in the onaBoNT-A group when compared to the saline control group (−2.6 vs. −0.9, respectively). Three-month success rates based on improvement in global response assessment (GRA) were 63 % in the onaBoNT-A group and only 15 % in the placebo group. However, dysuria was a much more common adverse event in the onaBoNT-A group compared to the placebo group (40 % vs. 5 % at 8 weeks, respectively).

Based on recent papers totally over 350 patients including one randomized trial, the latest American Urological Association (AUA) Guidelines on IC/BPS has elevated the use of BoNTA to a fourth-line treatment (AUA Clinical Guidelines, www.auanet.org).

Trigonal Injections

Smith and colleagues first reported on the successful use of BoNTA injections via a combination of trigonal and bladder base injections in 13 women with IC/BPS in 2004 [12]. Giannantoni and colleagues subsequently reported on the effects of onabotulinumtoxinA in 14 patients with IC/BPS [16]. Under short general anesthesia, patients were given injections of 200 U of commercially available onabotulinumtoxinA performed submucosally in the trigone and bladder floor under cystoscopic control. Overall, 12 patients (85.7 %) reported subjective improvement at 1 and 3 months' follow-ups. The mean VAS score was significantly reduced at 1 and 3 months after treatment, and daytime and nighttime urinary frequency decreased. Two patients reported incomplete bladder emptying.

Somewhat less encouraging was a case series report of eight women and two men with chronic IC/BPS unresponsive to other therapy [17]. Five patients were injected suburothelially with 100 U of BoNT-A (20 sites), while the other five patients had an additional 100 U of BoNT-A injected into the trigone. While functional and cystometric bladder capacity increased and frequency and pain scores improved mildly, significant improvements were noted in only two patients. No patient was symptom-free following treatment with BoNT-A. In addition, there were no therapeutic or adverse differences between the non-trigone and trigone injection groups.

In contrast, Pinto and colleagues reported the results of trigone-only injections with onaBoNT-A 100 U under sedation in 26 women with IC/BPS [18]. No concurrent hydrodistention was performed. At 3 months' follow-up, pain measured by VAS decreased by 71 % and marked improvements were also noted in O'Leary Sant Symptom Index and Problem Index scores (56 and 66 %, respectively). Sustained improvement was also noted upon reinjection.

Long-Term Results

Giannantoni and associates reported on the 2-year efficacy and tolerability of onabotulinumtoxinA injections in IC/BPS patients [19]. Thirteen women were prospectively included in the study. A total of 58 injections were administered in 13 women with IC/BPS with a mean of 4.8 injections per patient and a mean duration of 5.25 months between injections. Two hundred units of onabotulinumtoxinA were used in all patients. At 1 month and 4 months' follow-ups, ten patients reported a subjective improvement in their symptoms. Mean VAS scores, and mean daytime and nighttime urinary frequency decreased significantly. Nine patients at 1 month and seven patients at the 4-month checkup complained of dysuria. The three nonresponders to the first intravesical treatment session underwent another treatment 3 months later with satisfactory results. Beneficial effects persisted in all patients at 1 and 2 years' follow-ups.

Kuo described the beneficial effects of repeated onaBoNT-A injections (100 U) in 81 patients with IC/BPS, 30 who received four consecutive injections every 6

months [20]. Injections were performed under general anesthesia and were immediately followed by a hydrodistention for 15 min. ICSI and ICPI scores decreased by 33 and 44 %, respectively, and VAS were reduced by 48 % at 6 months following injection with onaBoNT-A. Better results were achieved in patients who received at least three consecutive onaBoNT-A injections. Dysuria was common, found in between 28.4 and 35.7 % of treated patients. Only one patient had to perform intermittent catheterization following injection.

Pinto and colleagues prospectively evaluated four consecutive trigonal injections of onaBoNT-A (100 U) in 16 women with IC/BPS [21]. Injections were performed without hydrodistention, and retreatment was allowed when requested upon reaching 3 months from the last injection. Over the course of four injection cycles, patients demonstrated consistent and sustained reductions in pain visual scale and O'Leary Sant Scores with a mean duration of response of approximately 10 months. No voiding dysfunction was observed from trigonal injections.

Ulcerative vs. Non-ulcerative IC/BPS

Investigators compared the effects of onaBoNT-A (100 U) injections into the posterior and lateral walls of 10 patients with ulcerative IC and 30 patients with non-ulcerative IC/BPS. Patients were reinjected every 6 months for a total of 2 years [22]. The primary endpoint was change in the GRA. They found that half of non-ulcerative IC/BPS patients responded successfully to onaBoNT-A injection, while no patients responded in the ulcerative IC group.

In contrast, a second study compared the effects of 100 U onaBoNT-A injected into the trigone in 10 ulcerative and 14 non-ulcerative IC/BPS patients [23]. Patients had similar baseline symptoms. At 1 month follow-up, both groups demonstrated similar improvements in pain (54 % ulcer vs. 57 % non-ulcer) and O'Leary Sant questionnaire scores.

Urethral Injections

One study compared the effects of periurethral onaBoNT-A (50 U) injections to saline injections in a randomized trial of 20 women with IC/BPS [24]. Nine patients were injected with onaBoNT-A. No difference was observed between groups and symptom visual scale did not improve following onaBoNTA injection.

We typically consider the following principles when treating an IC/BPS with onaBoNT-A injection:

1. Hydrodistend the bladder for 2–3 min at 80 cm while injecting 100 U into the trigone alone. Prior studies have shown that activating nerves during/following injection can increase BoNTA uptake [25]. Hydrodistention may be an excellent stimulus for sensory nerve activation.

2. We only hydrodistend for 2–3 min based on the latest AUA Clinical Guidelines on IC/BPS (www.auanet.org).
3. We also inject periurethrally with 33–50 U of onaBoNT-A to target the external urethral sphincter and reduce the incidence of stranguria and incomplete emptying.
4. We incorporate pelvic floor onaBoNT-A injections when the physical examination demonstrates levator pain.

Conclusion

Botulinum toxin appears to be a promising treatment option for chronic genitourinary pain syndromes. A direct anti-nociceptive effect may be the prominent mechanism of relief in IC/BPS. Acceptance of a descriptive taxonomy of pelvic pain syndromes should precede prospective randomized trials with standardized outcome measures to fully evaluate the clinical effectiveness of this treatment modality. Continuing research and efforts toward understanding the anti-nociceptive actions of botulinum toxin will more clearly define its role in specific pain syndromes.

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Neuromodulation

24

Priyanka Gupta, Chirag N. Dave, and Kenneth M. Peters

Introduction

Collectively, pelvic pain syndromes represent some of the most prevalent and challenging disease entities encountered in medicine today. Given the limited efficacy of available treatments and the often complex comorbid conditions that accompany these conditions, multimodal treatment is required. These difficulties have also propelled the development of new technology and research aimed at improving patient outcomes.

Although neuromodulation is not FDA approved for the treatment of pelvic pain syndromes, it is used regularly for accompanying urgency and frequency of urination; and studies suggest that pain symptoms may also improve. This chapter discusses the history, methodology, and outcomes associated with peripheral neurologic control of the bladder as well as the application of sacral, pudendal, and posterior tibial nerve stimulation for the treatment of pelvic pain.

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History

For nearly a century, the mainstay of treatment for overactive and painful bladder syndromes has consisted of noninvasive therapies such as behavioral modification, pelvic floor rehabilitation, and pharmacological therapy with a significant number of patients showing a poor response [1, 2]. Once these noninvasive therapies were exhausted, surgical procedures such as bladder augmentation, detrusor myomectomy, bladder denervation, and urinary diversion were employed, resulting in significant perioperative and long-term morbidity [2, 3]. As the understanding of bladder neurophysiology developed, novel therapies were hypothesized and tested. In 1989, Tanagho and his group pioneered the initial investigations into electrical stimulation for neuromodulation [4]. Neuromodulation is the electrical or chemical modulation of a nerve to influence the physiologic behavior of an organ and offers a minimally invasive, non-ablative, and reversible means to treat voiding dysfunction [2]. InterStim (Medtronic, Minneapolis, MN, USA) came to market in 1997, since then, hundreds of thousands of devices have been implanted for the treatment of urinary urgency, frequency, urge incontinence, urinary retention, and fecal incontinence. Continued research to improve technique and patient outcomes has been ongoing. The use of neuromodulation for other disorders such as complex regional pain syndromes and back pain with dorsal column nerve stimulators has been well documented, including the pelvic pain population.

Neuroanatomy

Voiding relies on proper structure and function of the central nervous system. During bladder filling, detrusor relaxation and heightened bladder neck and urethral smooth muscle tone is mediated through the sympathetic nervous system [1, 5]. The lumbar (hypogastric), pelvic, and pudendal nerves contain afferent and efferent axons. These are mixed nerves, which carry sympathetic, parasympathetic, and somatic fibers. The sensation of bladder fullness is sent via afferent axons through the sacral spinal cord to the pontine micturition center. The pelvic nerve afferents contain myelinated and unmyelinated C axons that sense bladder fullness. One theory regarding the origin of bladder pain is that in the setting of inflammatory or other inciting conditions there is a recruitment of C-fibers that creates a new afferent pathway that leads to pain. Once the signal is received, the efferent signal is sent via the parasympathetic pelvic nerves at the sacral spinal cord level S2-S4 prompting the bladder to contract while the urethra relaxes and voiding occurs. Also important for normal voiding is relaxation of the skeletal muscle of the external urethral sphincter via the somatic nervous system (pudendal nerve). Modulating afferent signals to the pontine micturition center is a proposed mechanism for neuromodulation [1, 6] (Fig. 24.1).

A number of reflex pathways, which bypass the pontine micturition center, have been described and are also potential targets for neuromodulation. In the vesicosympathetic reflex, bladder filling allows greater accommodation of filling by

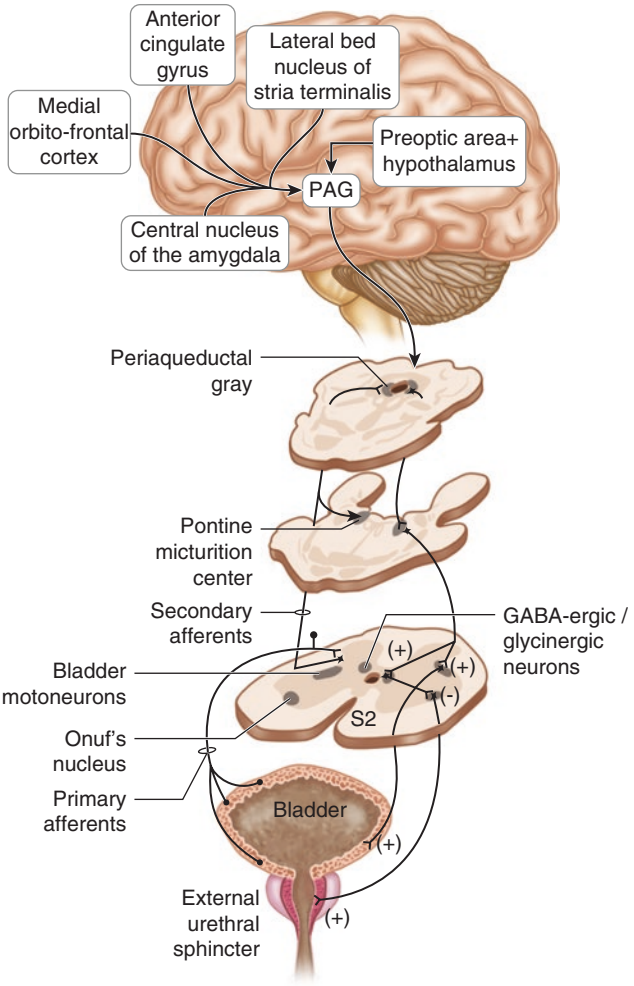

Fig. 24.1 Central nervous system and voiding reflex

stimulating lumbar sympathetics. The guarding reflex affects continence when sphincter tone increases with bladder filling mediated by sympathetic and pudendal efferents to the bladder neck and external urethral sphincter respectively [7] (Fig. 24.2). This is a normal reflex in the voiding pathway that is intended to prevent involuntary bladder emptying. As part of this reflex the pelvic floor muscles mediated by the somatic innervation of the pudendal nerve also contract to help prevent incontinence. In patients that have severe pelvic floor dysfunction this can lead to dysfunctional voiding due to the inability to relax and painful voiding symptoms. Disruption of any of these pathways can lead to problems with storage, such as urge or stress urinary incontinence, as well as problems with emptying such as urinary retention. As the sensation of bladder fullness is also mediated by sensory

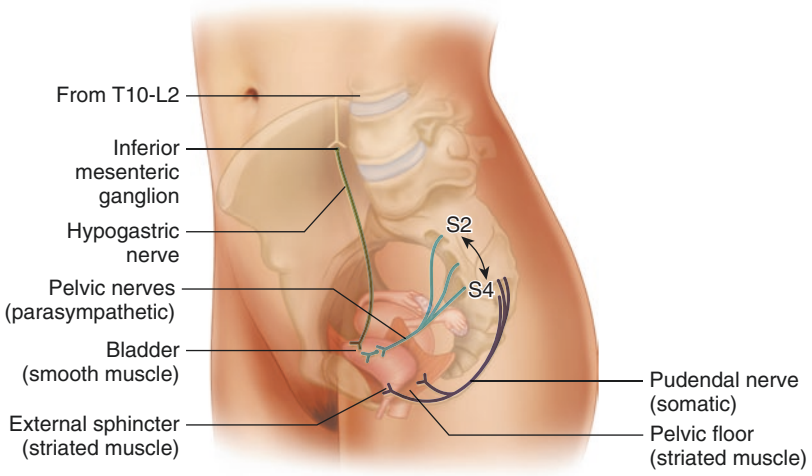

Fig. 24.2 Parasympathetic, sympathetic, and somatic nervous system control of lower urinary tract

nociceptive unmyelinated axons, it is possible that disruption of these pathways leads to increased recruitment of these fibers leading to the sensation of pain. Although the precise mechanism of neuromodulation is not understood, it appears to affect both the spinal and cortical centers for voiding control.

Patient Selection and Preoperative Education for SNM

Patients with pelvic pain who choose to undergo neuromodulation should understand that treatment is primarily for the urgency/frequency component of their syndrome, but there is a possibility that it may also improve their pain. The procedure is performed in two stages so that improvement in symptoms can be observed prior to implanting a permanent device. Patients should be aware that symptom relief is not guaranteed and success is considered a 50 % improvement in overall symptoms, rather than complete resolution. The patients are informed that this is not a cure for their disease, rather a technique to manage their symptoms, and once the unit is turned off, their symptoms will return [8].

Other patient factors can affect neuromodulation outcomes. Sacral abnormalities can make identifying the location of the nerve technically challenging and possibly prohibitive for device placement. Patients with cognitive deficits may have trouble managing the device and this should be taken into consideration when choosing to trial SNM. Voiding dysfunction is more prevalent in the elderly and although some studies have shown that older patients might have less efficacy with neuromodulation [5, 9], others have shown age to have no impact on outcomes [10]. Therefore,

it is reasonable to trial SNM in the elderly with refractory voiding dysfunction. Neuromodulation is contraindicated in pregnancy due to the risk of fetal loss or preterm labor, and patients with an implanted device who become pregnant should have the device turned off for the duration of the pregnancy [5]. Patients should also be counseled that MRI of the abdomen or pelvis or diathermy is contraindicated due to concerns of heating the electrodes, dislocation of the device, or disruption of programming [11]. Patients should be screened separately at airports and be issued identification cards to inform others that the implant is in place.

Patients should know that neuromodulation is a two-stage procedure involving mild anesthesia and outpatient surgery. They should be screened for and counseled on anesthetic risk and usual complications of surgery. Patients should be informed that there is a 100 % reoperation rate due to depletion of the IPG in 4–6 years post-implant. Also, a 15–20 % reoperation rate is expected due to technical difficulties based on the implantable nature of the device [8]. Patients should be required to keep voiding diaries, which include pain scores, prior to lead implantation as well as during the test period. After first-stage lead placement, the patient will wear an external generator to adjust stimulation of the lead while they record the results. Second-stage permanent implantation should only take place if there is at least 50 % improvement in overall symptoms. Responding as moderately or markedly improved on a 7-point global response assessment (GRA) has been shown to correlate with significant improvements in voiding diaries and validated questionnaires [12]. The lead should be removed from patients who do not respond during the test phase.

Sacral Neuromodulation (SNM)

Sacral neuromodulation (SNM) is a technique by which the S3 nerve is targeted via a tined electrode inserted into the S3 foramen (Fig. 24.3). At this time only one device has been approved for treatment of overactive bladder and nonobstructive urinary retention (InterStim®, Medtronic Inc., Minneapolis, MN). The US Food and Drug Administration (FDA) approved it for these indications in 1997, and then in 2011 for fecal incontinence. SNM is not FDA approved for chronic pelvic pain; however, it has been shown to have some effect for chronic pelvic pain and is considered a fourth-line treatment for IC/BPS (interstitial cystitis/bladder pain syndrome) according to the 2014 American Urologic Association Guidelines [13].

SNM is a minimally invasive procedure that is performed through a two-stage process. The first-stage lead placement (FSLP) can be done under anesthesia in the operating room or as an office-based percutaneous nerve evaluation (PNE) in order to test the clinical effectiveness of the stimulation. There has been some debate regarding which method to use for stage one testing. PNE has been reported to have a 48-60 % positive clinical response rate in the literature [14, 15]. PNE has the advantage of being an outpatient procedure without anesthesia. However, it has the disadvantage in that it is a temporary single electrode that can easily migrate during the test period. In a comparative study of PNE versus FSLP, it was found that 69 % of patients that underwent FSLP had a positive response compared to 47 % with

Fig. 24.3 Tined lead

PNE ($p < 0.0001$) [14]. Other studies have found similar results; however, there is no consensus as to the preferred method for SNM screening, thus this is left to the surgeon's discretion and facility preferences. Specifically in the IC/BPS population, Peters et al. compared PNE to FSLP. They reported the test to implant ratio was 94 % in the FSLP group compared to 52 % in the PNE group. All patients choosing to undergo a PNE as their initial screen should have a scheduled surgery within 2 weeks. If the patient responds to the PNE they should have a permanent lead and IPG implanted. If they do not respond to a PNE, they should undergo an FSLP as this will result in clinical improvement in many patients who fail an initial PNE. The procedural steps for FSLP are described below.

FSLP Procedural Steps [5]:

1. The patient is positioned prone with pressure points padded in the operating room.
2. Intravenous sedation is administered and local anesthesia is administered at the proposed puncture site.
3. With the assistance of fluoroscopy, a directional guidewire is used to locate the midline which is marked with a vertical line. The intersection of the sacroiliac joint and the spinous process is then identified and marked with a transverse line. This defines the area of the S3 foramen (Fig. 24.4).

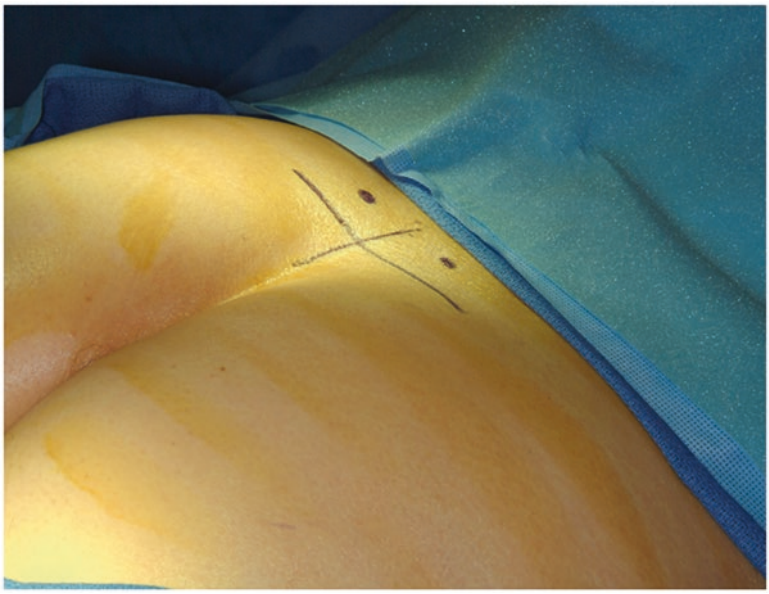

Fig. 24.4 FSLP landmark identified

4. If the S3 foramen is well seen on fluoroscopy in the anterior/posterior view, the upper medial aspect of the foramen is marked on the skin identifying the target area for the tined lead as this is the region where the nerve passes through the foramen (Fig. 24.5).
5. If the S3 foramen is not identified due to overlying bowel contents, a reasonable starting point is approximately 2 cm lateral and 3 cm superior to the point where the two lines cross (see step #3). This location is marked on both the right and left sides (Fig. 24.4).
6. A needle is then passed at a 60° angle into the entrance point to access the foramen and advanced to the edge of the inferior sacral bone plate (Fig. 24.6).
7. Electrical stimulation is then performed. The ideal response would be a bellow contraction of the pelvic floor followed by flexion of the great toe that occurs with less than 2 V of stimulation. A S4 stimulation would result in a bellows contraction alone and S2 stimulation would be suggested by plantar flexion of the entire foot with heel rotation.
8. Fluoroscopy along with the motor response can help confirm the appropriate foramen and an optimized S3 placement should be the goal. A clamp can be placed on the skin and positioned to help direct the correct location on the skin to target the area 1 cm above the hillock. In Fig. 24.6, imaging first shows the skin location to be too high, then too low, then just right. On the lateral view the target area should be about 1 cm above the S3 hillock. The hillock is the anterior protrusion of the bone from the anterior surface of the sacrum at the level of S3 as seen on the lateral x-ray (Fig. 24.7).

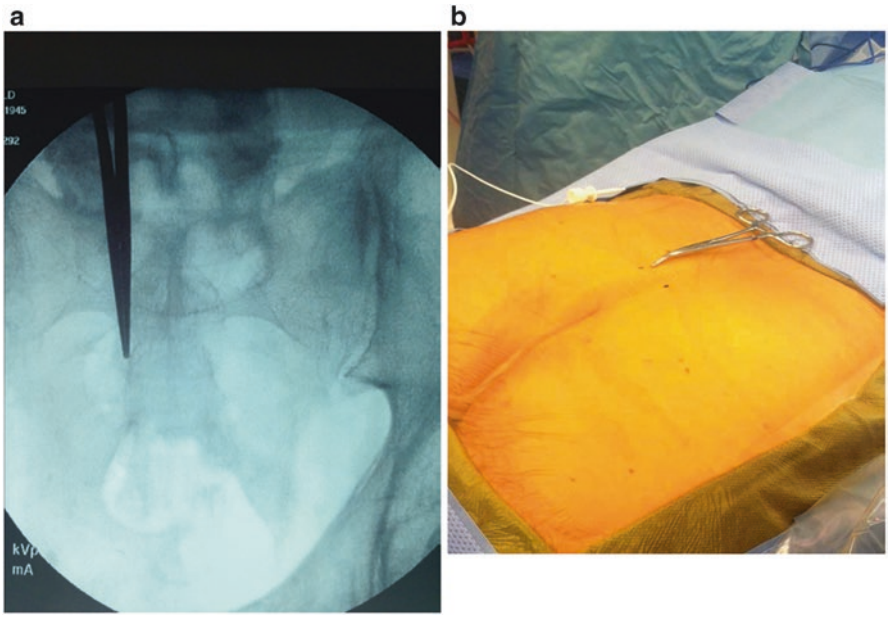

Fig. 24.5 Marking medial Edge of S3 foramen. Reprinted with permission from Medtronic

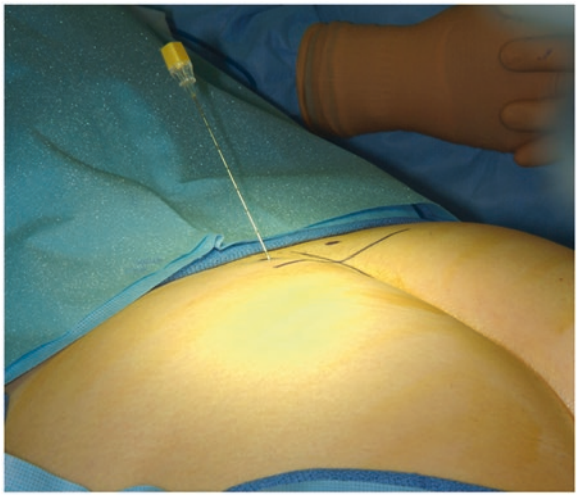

Fig. 24.6 Needle placement for SNM

9. The directional guide wire is then placed through the cannula and the tract is dilated using an introducer sheath, taking care not to advance the introducer beyond the inferior bone plate.
10. The tined lead with the curved stylet positioned inferior and lateral, is then deployed under fluoroscopic guidance. It has four cylindrical electrodes numbered

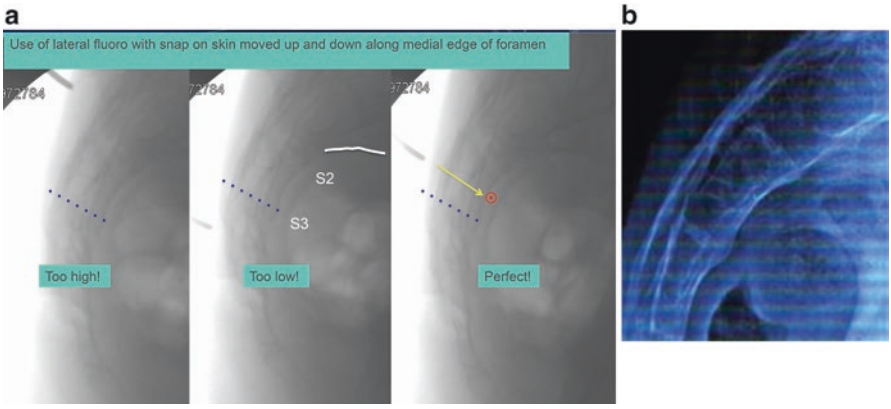

Fig. 24.7 (**a**, **b**) Determining ideal lateral location. Reprinted with permission from Medtronic

0–3. Leads 2 and 3 should straddle the bone edge. Each electrode is then stimulated individually. The motor responses are assessed with the goal to achieve response on all four electrodes under low voltage (ideally less than 2 V).

11. Lead position should be confirmed with fluoroscopy in the lateral and anterior–posterior positions (Figs. 24.8 and 24.9).
12. The potential site of the IPG is identified on the ipsilateral buttock and a 1 cm incision is made and a subcutaneous pocket created. The IPG will be placed here if the test stage is successful.
13. The percutaneous extension lead is connected to the tined lead, which is tunneled out of the contralateral buttock and connected to the external neuromodulation system (ENS) and programming parameters are set.
14. The incision is closed and the external portions of the leads are secured with sterile 4×4 dressings and a bandage.
15. Using the ENS, the patient trials various stimulation parameters during the 7–14-day test period and maintains voiding diaries and symptom scores.

PNE Procedural Steps [5]:

1. Position the patient in the prone position.
2. Locate the S3 foramen without radiographic assistance. Measure 10 cm from the coccyx along the midline of the spine and then measure 2 cm lateral and 3 cm superior to this point.
3. Inject a local anesthetic at the point that has been marked. Insert the needle at a 30–60° angle.
4. Confirm the lead placement by asking the patient to report the location of the sensation of stimulation. They should feel stimulation in the vaginal, scrotal, or rectal area and may exhibit flexion of the big toe.
5. A temporary electrode is passed through the needle and taped to the skin. This is then repeated on the opposite side.

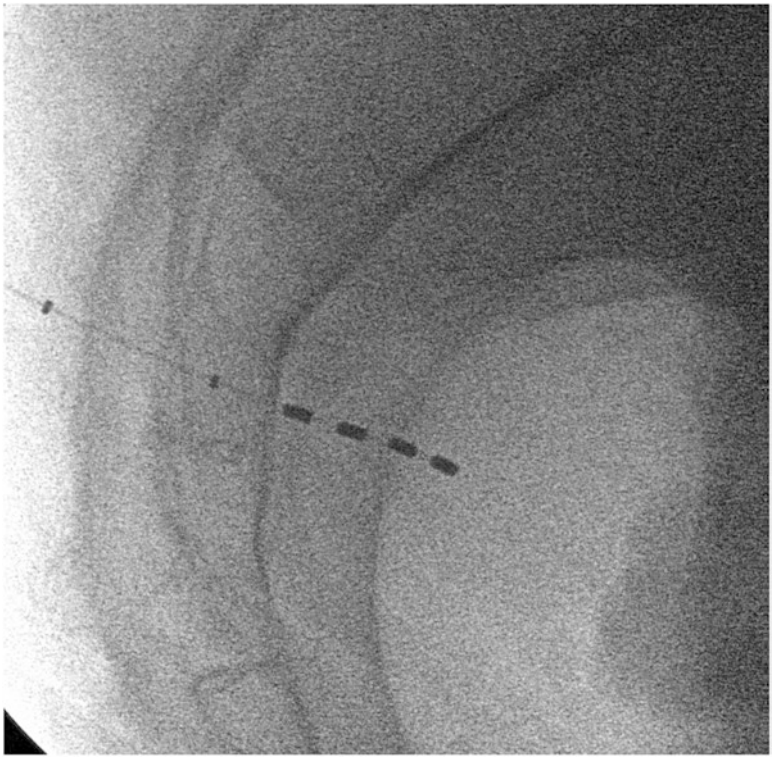

Fig. 24.8 Ideal lateral x-ray. Reprinted with permission from Medtronic

6. The lead is connected to an external temporary pulse generator which is worn by the patient for 3–7 days while completing voiding diaries and symptom scores.

Stage II Implantation Procedural Steps [5]:

1. Patients experiencing a greater than 50 % improvement in their symptoms are considered responders and should undergo a Stage II implant.
2. The previous pocket site is reopened and the incision is enlarged. The lead is then connected to a permanent IPG.
3. The device connections are tested and confirmed in the operating room. The pocket incision is closed with absorbable sutures.
4. Specific stimulation programs are tested and then programmed into the device postoperatively to achieve optimal device settings.

SNM while not FDA approved for chronic pelvic pain has many publications in the literature supporting its use for pain. Patients with pelvic pain often suffer from pelvic floor muscle dysfunction that may contribute to lower urinary tract symptoms. In a study of 21 patients with refractory IC that were followed for 15 months,

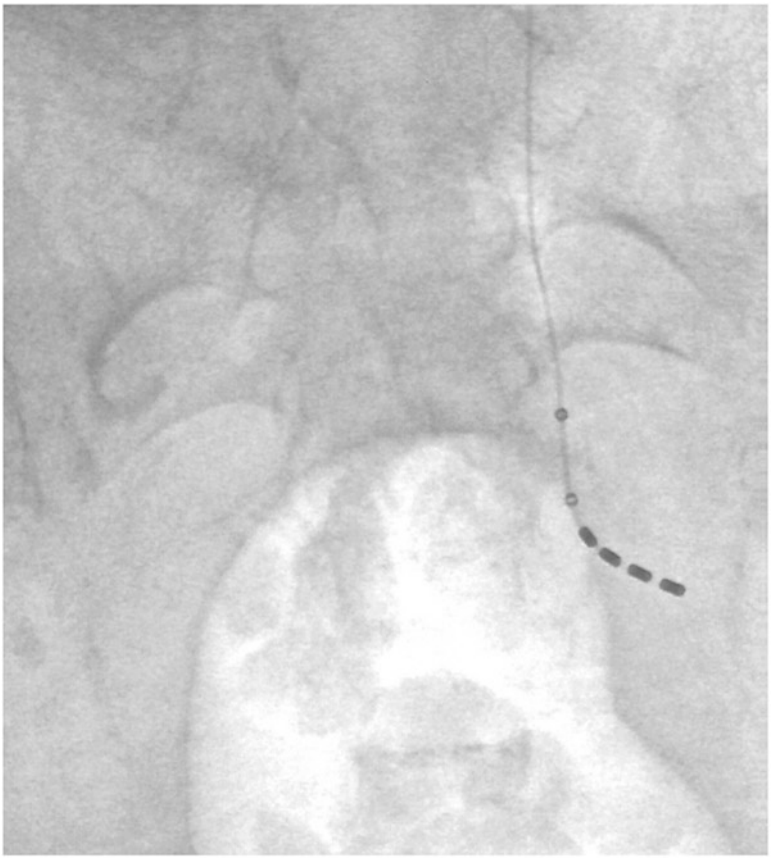

Fig. 24.9 Ideal A-P x-ray. Reprinted with permission from Medtronic

20 patients had moderate or marked improvement in pain and a statistically significant decrease in narcotic requirements was noted [16]. In a prospective study of 25 refractory IC/BPS patients by Comiter et al, 17 patients had SNM therapy and were followed for a mean of 14 months. They noted significant improvements in frequency, nocturia, and mean voided volume; however, most importantly the average Interstitial Cystitis Symptom and Problem Index (ICSI-PI) score decreased from 5.8 to 1.6 (scale 0–10) [17]. Gajewski et al. studied a cohort of 78 patients with IC/BPS that underwent SNM that were followed for 62 months postoperatively. They noted a success rate of 72 % [18]. In a recent study, patients that had SNM and pelvic pain reported a 35–72 % reduction in their visual analogue pain score [19]. A literature review of SNM in chronic pelvic pain patients revealed that the majority of published studies [18, 20] demonstrated decreased pain scores at long-term follow-up. Few adverse events were reported, the most common being explantation and lead revision [20]. SNM is a safe treatment to consider for patients with refractory IC/BPS and chronic pelvic pain.

Pudendal Neuromodulation (PNM)

The pudendal nerve is composed of fibers from S1-S3. The majority of the fibers are of the S2 and S3 nerve roots that play an important role in bladder function [2]. The pudendal nerve innervates the external urethral and anal sphincters, the pelvic organs, and the pelvic floor muscles making it an ideal target for neuromodulation and for treating symptoms of chronic pelvic pain. Schmidt first described the procedure for accessing the pudendal nerve for stimulation [21]. The method has since been modified and is considered an off-label therapy for patients with refractory IC/BPS symptoms. It is not FDA approved for lower urinary tract symptoms; however, several studies have shown it to be a safe treatment and useful for patients who have had an inadequate response to SNM [22, 23]. The optimal point to stimulate the pudendal nerve is at the level of the ischial spine. The steps of the procedure are described below.

PNM Procedural Steps [5]:

1. Place the patient in prone position with pressure points padded. Prep and drape the patient using sterile technique.
2. Place needle electrodes into the anal sphincter at the 3 o'clock and 9 o'clock positions. The electrodes will be used for intraoperative electromyography (EMG) monitoring (Fig. 24.10).
3. Access the pudendal nerve percutaneously through the ischiorectal space, by passing a foramen needle just medial to the ischial tuberosity in a medial-to-lateral

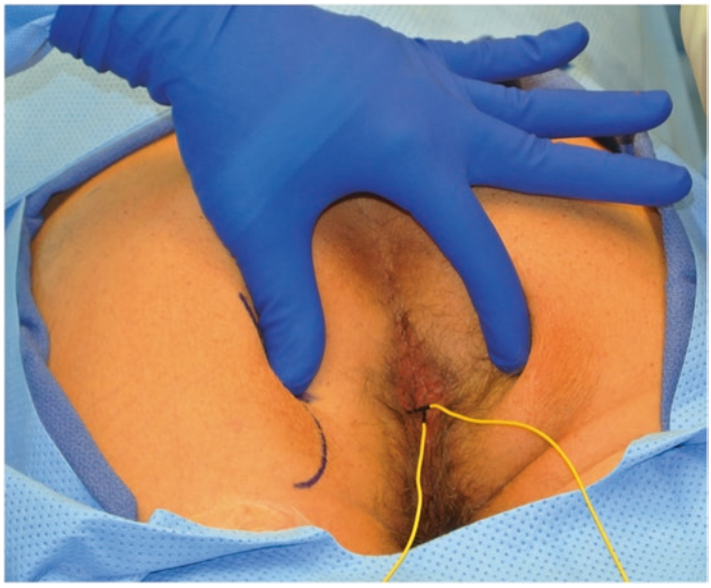

Fig. 24.10 Needle electrodes at the anal sphincter

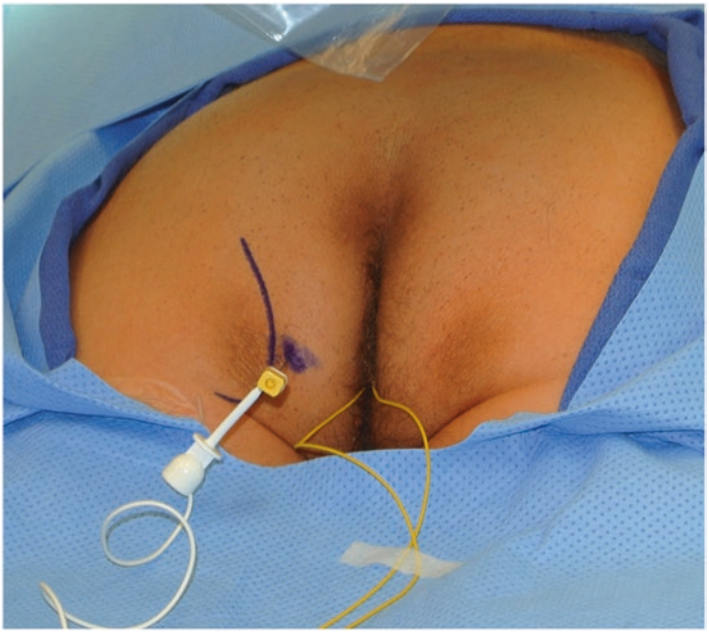

Fig. 24.11 Pudendal needle insertion

direction toward the ischial spine. As the needle is passed, stimulation is performed at 5Hz and 5 V to identify the nerve (Fig. 24.11). Seeing a compound muscle action potential (CMAP) on EMG and an anal wink on exam confirms pudendal nerve identification (Fig. 24.12).

4. The needle is advanced along the nerve while stimulating to confirm it is running parallel to the nerve. This allows multiple electrodes on the permanent lead to activate the nerve.
5. The position of the needle is verified under fluoroscopy and the image is saved (Fig. 24.13). A directional guide wire and lead introducer is placed, similar to the sacral neuromodulation procedure (Fig. 24.14).
6. A tined lead is advanced and positioned. Each electrode is stimulated and the voltage required to obtain a motor and EMG response is recorded. The tines are deployed and the lead is tunneled to the standard IPG site in the upper buttock. Due to the longer trajectory from the lead to the IPG site, a longer lead (41 cm) is used. The percutaneous extension lead is then connected and tunneled out of the contralateral buttock for temporary external stimulation. Fluoroscopy is used to confirm final positioning of the lead (Fig. 24.15).
7. Similar to SNM, pudendal nerve stimulation is performed as a staged procedure. The criteria for success ($\geq$50 % improvement in overall symptoms) should be met before permanent IPG implantation.

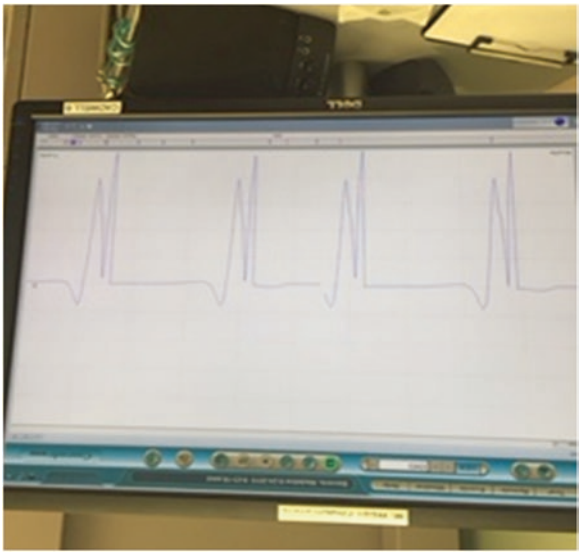

Fig. 24.12 CMAP tracing

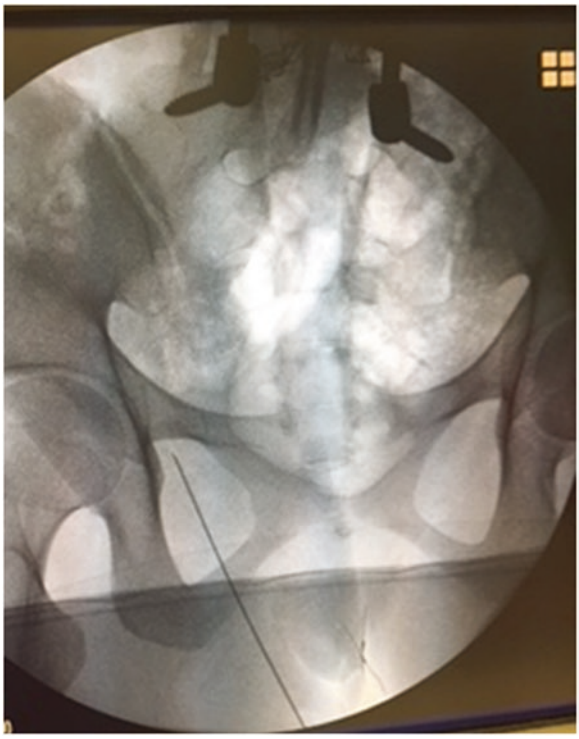

Fig. 24.13 X-ray imaging of needle placement

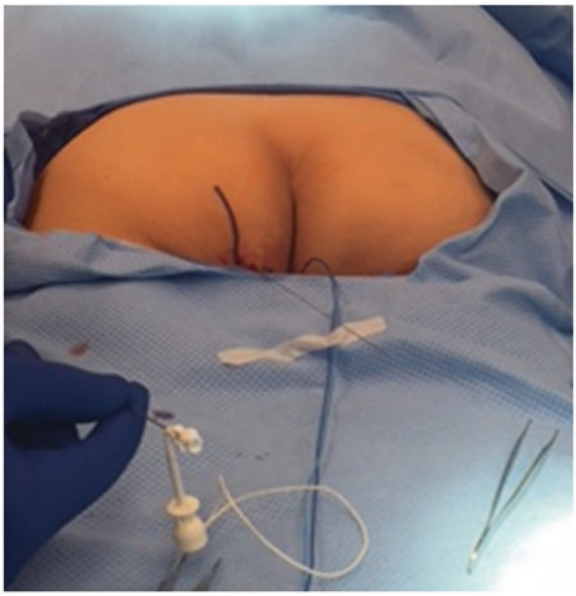

Fig. 24.14 Placement of bidirectional guidewire

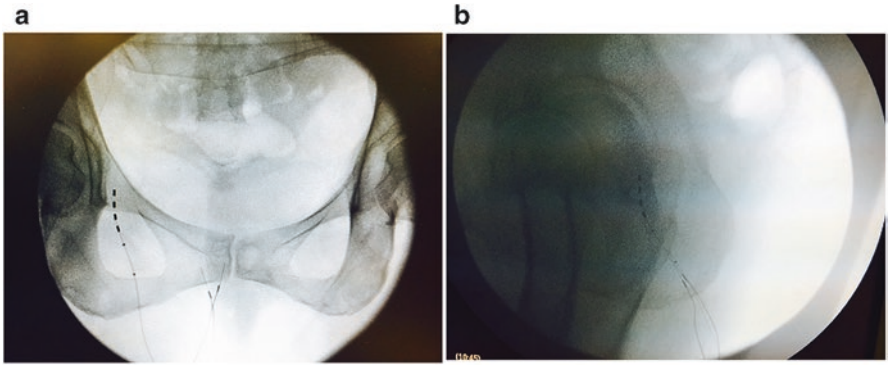

Fig. 24.15 (**a**, **b**) Fluoroscopic images of pudendal lead (**a**) AP and (**b**) lateral)

Key points with this procedure include positioning of the lead. When the nerve is identified, the foramen needle should be advanced and withdrawn to confirm the trajectory is parallel to the nerve. Ideally the lead should be positioned near the ischial spine on fluoroscopy. The positioning of the pudendal lead initially is more sensitive to movement. Therefore, the lead should be tested with the practitioner pressing down to simulate the patient lying on their back and then lifting up to stimulate sitting. Patients should be educated to sit down gently and avoid falls during the initial weeks after surgery to avoid displacing the lead before tissue ingrowth has occurred and the lead stabilized.

Data has shown that PNM is particularly effective for patients that have failed SNM for either refractory OAB and/or IC/PBS symptoms. A randomized, prospective, single-blinded crossover trial was performed in 2005 comparing SNM and PNM for voiding dysfunction. They noted a statistically significant reduction in symptoms, 63 % of PNM compared to 46 % of SNM patients. In an analysis of just the IC/BPS patients in this study 77 % of patients considered PNM to be a superior treatment [24]. In another study of 44 patients with refractory OAB and IC/BPS symptoms after SNM treatment, 93 % (41/44) responded to PNM. Less than 50 % of patients reported marked improvement in their symptoms at 1 year, but 83 % were still using the device and 74 % responded that they would have the procedure again [25]. In a recent pilot study by Peters et al. of 19 patients with pudendal neuralgia, after placement of PNM 3 had complete resolution of pain, three were almost complete, ten were significantly improved, and three had slight improvement. Of 10 patients that responded to a mailed survey 8/10 were satisfied with PNM [26]. PNM is an effective treatment for patients with refractory symptoms and should be considered a therapeutic option for patients with chronic pelvic pain and pudendal neuralgia.

The adverse events associated with PNM are similar to SNM, classifying it as a safe and minimally-invasive procedure. The technique for lead placement for PNM is more challenging. A recent study by Heinze et al. described using the landmarks of the ischial spine, ischial tuberosity, acetabulum, and anal rim to create a right-angled triangle and with a target point for needle insertion. In their pilot study of 20 patients they performed their technique in ten patients and noted decreased operative time, bilateral lead placement, and statistically significant decrease in mean pain intensity scores during the trial period. Their study was limited by the small number of patients and the need to verify reproducibility of their technique [27]. This highlights the importance of this procedure being performed by an experienced, high-volume surgeon [5].

Percutaneous Tibial Nerve Stimulation (PTNS)

The tibial nerve originates from the spinal segments that innervate the bladder and pelvic floor. Specifically it contains motor and sensory fibers from L4-S3 and can help modulate the micturition reflex [28]. Stimulation of the tibial nerve began with studies by McGuire and colleagues and 1983 and was modified to the modern technique when Stoller and colleagues described targeting the nerve above the medial malleolus [2, 29]. The exact mechanism of action for PTNS is unknown, but one hypothesis is that the stimulation of the afferent pathways to the sacral spinal cord leads to modulation of the efferent outflow to the pelvic organs and muscles [28]. In 2000 it was approved by the FDA for treating OAB symptoms but not for IC/BPS or pelvic pain. Studies have shown that it can be a therapeutic option for pelvic pain conditions and is a reasonable treatment option to consider. The procedural steps are described below.

PTNS Procedural Steps [5]:

1. The procedure is performed with the patient in the seated position.

2. Insert a 34-G needle 3 cm into the skin (three fingerbreadths above the medial malleolus).
3. Place a grounding pad on the arch of the ipsilateral foot.
4. Attach the system to the grounding pad and needle. Increase the amplitude of the stimulation until the large toe curls or the toes fan.
5. The stimulation session is typically performed for 30 min.

Stimulation is typically provided at 0.5 to 9 mA at 20 Hz depending on patient tolerance and response [28]. Typically patients receive 12 weekly sessions for 30 min each. This schedule was based on the results of the Study of Urgent® PC vs. Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUmiT Trial), which showed that bladder symptoms as noted on the GRA and QOL questionnaires improved at 12 but not 6 weeks [30]. A carry-over effect of continued symptom improvement is observed between treatments with PTNS, which is why continuous stimulation does not need to be provided. The STEP study examined a tapering protocol which consisted of two treatments every 14 days, then two treatments every 21 days, and then one treatment every 28 days. During the 36-month trial period patients had continued symptom improvement and required an average of 1.1 treatments per month [31]. Therefore, most PTNS regimens consist of once monthly 30 min sessions in responders after completing the initial 12 weekly sessions.

PTNS has shown to be an effective option for patients with chronic pelvic pain. In a study of PTNS for patient with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), a statistically significant improvement in the NIH Chronic Prostatitis Symptom Index and Visual Analogue Score was noted ($p < 0.001$) [32]. In a study of 33 patients with chronic pain that received 12 weekly sessions of PTNS, all demonstrated significant improvement in their quality of life and pain intensity. Twenty-one percentage of patients had greater than 50 % improvement in their mean VAS [33]. In another study of 13 patients with IC/BPS, 10 weekly treatments of PTNS were administered. Statistically significant improvement in pain scores was not realized; however, many patients reported improvement in their pain symptoms [34]. The experience with PTNS for chronic pelvic pain in the literature is still limited. The advantage of PTNS is that it is minimally-invasive with minimal side-effects. The disadvantage is that it requires significant time commitment from the patient and must be continued monthly to maintain a clinical response. Further study in the pelvic pain population is still needed but this is an additional therapeutic option to be considered in the treatment algorithm.

Conclusions

Neuromodulation is an important treatment modality to consider when treating patients with pelvic pain syndromes. There are a variety of techniques for targeting the sacral, pudendal, and tibial nerves, which innervate the pelvic floor. All three techniques discussed in this chapter are important adjuncts to a multimodality approach to pelvic pain. They are primarily indicated for treating the bladder

symptoms associated with these syndromes; however, several studies have shown their efficacy for improving pain symptoms. As a provider of neuromodulation, it is imperative to counsel patients regarding expected outcomes, potential complications, and the need for future reoperation for device replacement.

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Cystectomy/Supravesical Diversion for Interstitial Cystitis

25

Jørgen Nordling

Introduction

Bladder Pain Syndrome (BPS) is one of most disabling of the pelvic pain syndromes because of the urinary symptoms of urgency and frequency accompanying the condition. Pain perceived to be of bladder origin is the key symptom for the diagnosis of BPS, but in many patients the urinary symptoms might have an equally or even higher influence on the quality of life of the patient. Some patients have to void up to 50 times per day and night up making patients' life anchored to the toilet, destroying ability to work, destroying social and family life and often with severe economical consequences [1].

As the etiology(ies) of the disease is unknown, treatment is empiric and symptomatic and in many cases insufficient. Reconstructive surgery in the form of bladder augmentation or even urinary diversion with or without cystectomy might be an option in these patients not responding satisfactory to conservative treatment.

It must however be remembered that urinary diversion and cystectomy includes extensive and, in principle, irreversible procedures for a disease that otherwise imply a modest risk of death or life-threatening complications, but carries of a number of severe consequences and up to 48 % of early complications like UTIs, pyelonephritis, ureteroileal leakage, and anastomotic/stomal stenosis [2].

In a questionnaire to urologists in USA in 2001 Gershbaum and Moldwin found urinary diversion to be the most common surgical treatment for BPS underscoring the severity of the disease for the patients quality of life and the limitations of conservative treatments [3].

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Patient Selection

About 25 % of patients with BPS do not become pain free after urinary diversion (Burkes D, 2013, personal communication). It is essential that a patient has been through an extensive workup and trials of conservative treatment before irreversible surgery is undertaken. In these cases, a decision to perform major reconstructive surgery is relevant. It is a decision made in close cooperation between the patient and the doctor. Many patients are very reluctant to accept such major surgery for a "not life-threatening disorder" because of the change of body image and the risk of short and long-term complications. If the patient for various reasons does not want major surgery, this of course settles the question. But also for the doctor, this is a difficult decision.

The first question that arises in patient selection is whether the pelvic pain really comes from the bladder. In the case of evident objective bladder pathology like Hunner lesions or a contracted bladder, this question is easily answered. The use of bladder-related symptoms, such as pain associated with bladder filling and relieved by bladder emptying, is more speculative. As with most other chronic pain syndromes, the decision to move forward with aggressive treatment is based upon small retrospective studies and expert opinion. In this context, it must however be remembered that in these patients two major symptoms are the underlying cause of the patients poor quality of life: PAIN and FREQENCY. At least it can be promised that a urinary diversion will solve the problem of frequency making daily life much easier to manage for some patients.

Choice of Procedure

It must be decided what sort of reconstructive surgery should be performed. Should the patient have a urinary diversion with or without a continent reservoir? Should the patient have a cystectomy? or a bladder augmentation? The literature seems to favor bladder augmentation to be reserved for patients with end stage Hunner lesion disease (classic IC or ESSIC type 3C) with a contracted bladder *and little or no pain* [4–7] although some report good results in other bladder pain groups including subtotal cystectomy in the procedure [8]. The relatively high percentage of patients needing to perform clean intermittent self-catheterization is also a limiting factor for choosing bladder augmentation, as many patients cannot tolerate the pain associated with urethral manipulation of any sort.

The amount of bowel surface to be incorporated into the urinary tract should be decided [9]. The risk of hyperchloremic metabolic acidosis must be considered making kidney function an important issue if a continent reservoir is considered. In this case a glomerular filtration rate in excess of 40 ml/min/1.73 m^2 body surface must be present. The use of a part of the ileum might compromise bile acid reabsorption leading to diarrhea and in patients with poor anal sphincter function to fecal incontinence. Also uptake of cobalamin/folic acid might be compromised.

Urinary Diversion

Urinary diversion in the form of a simple ileal conduit (Bricker procedure) or with a continent reservoir seems in most patients to be a reliable choice. A continent diversion requires a patient with an unspoiled cognitive ability and good manual dexterity. In a younger patient, meeting the above-mentioned prerequisites, a continent diversion might be preferable whereas an older patient probably is better served with a Bricker conduit due to risk of complications and difficulties handling self catheterization of a reservoir. However, it is important to note that it seems as patients with benign functional or inflammatory bladder diseases experience comparatively more problems with their reservoirs than patients with spinal cord injury or malignant bladder disease [10].

Recent reports seem to confirm the reasonably good clinical results after urinary diversion. In a Swedish study, 14 patients with Hunner lesions all became symptom free after diversion while only five of 13 BPS patients without Hunner lesion became symptom free after getting a continent reservoir [6]. In a study from Norway, 28 of 38 patients became pain free after either diversion (23 patients) or augmentation (15 patients). Two of the patients had Hunner lesions and became pain free [11]. Finally in a Danish report 19 of 23 patients became pain free after diversion with an ileal conduit. Also here two patients with Hunner lesions became pain free [12].

Braking down the literature on the outcome after urinary diversion based upon the different ESSIC types [13] is rather difficult. As mentioned above, outcome seems almost always very good in the Hunner lesion group (ESSIC type 3) (Fig. 25.1), while outcome in ESSIC groups 1 and 2 is more difficult to judge. In the

ESSIC Classification of bladder pain syndrome (BPS) types

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive[3]	XC	1C	2C	3C

[1] cystoscopy: glomerulations grade 2-3
[2] with or without glomerulations
[3] histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Fig. 25.1 ESSIC classification of cystoscopic and morphological findings

Danish study, 17 of 21 patients with ESSIC groups 1C and 2C became pain free (81 %) [12]. The bladder capacity during bladder hydrodistention in general anesthesia had no predictive value [12], and glomerulations during or after bladder distension had no pathophysiological meaning and no influence on disease progression or results of treatment [14].

Bladder Augmentation with Subtotal Cystectomy

Many patients are very reluctant to accept a urinary diversion with a stoma of any sort. Bladder augmentation with subtotal cystectomy has therefore been frequently used as an alternative. Due to our own poor results with this procedure we do not offer it to patients with BPS except for the rare patient with end stage contracted bladder and little or no pain. We inform the patient that we very rarely do this procedure due to the high risk of both persistent bladder pain and need for intermittent self-catheterization and reserve the procedure for patients with small contracted bladder with little or no pain. Almost all bowel segments have been tried including ileum, ileoceocum, coecum, right colon, sigmoid colon, and gastric segments. In the chapter on BPS from the 5th International Consultation on Incontinence it was concluded: *There is no significant difference between bowel segments with regard to outcome except for gastric tissue substitution that is associated with dysuria and persistent pain due to production of acids* [15].

Cystoplasty might be performed with an either subtrigonal or supratrigonal cystectomy. Subtrigonal cystectomy carries more complications with no better results and is therefore little used today. The results of supratrigonal approach reported by Nielsen et al. in 1990 were rather poor with two failures in eight patients. Van Ophoven reported 5-year results of orthotopic substitution enterocystoplasty in 18 patients with only two failures [8]. Rössberger reported excellent results in patients with Hunner lesion, but not so in patients with non Hunner BPS [6]. Finally, Kim had excellent results in 45 patients with Hunner lesions [7].

More favorable results have been reported in patients with small cystoscopic bladder capacity (<200 cc) [16, 17]. Cystoscopic low bladder capacity has in the literature been taken as a sign of end stage inflammatory fibrosis of the bladder. This is however not always the case. Sairanen et al. described the long-term effect of cyclosporine treatment in BPS patients [18], and in many of these patients functional bladder capacity after treatment far exceeded cystoscopic bladder capacity before treatment. Three patients with a cystoscopic bladder capacity of 200 cc, and an average functional bladder capacity of 70 cc, had a functional bladder capacity of 290, 220, and 350 cc after cyclosporine treatment. Two patients with a cystoscopic bladder capacity of 300 cc and a functional bladder capacity of 92 and 100 cc increased the functional bladder capacity to 490 and 350 cc.

Urinary Diversion with or Without Cystectomy?

Although supportive literature is scarce, it appears that pain relief after urinary diversion is comparable whether or not the bladder is also removed [19]. Andersen et al. [11] retrospectively evaluated 16 patients having subtotal cystectomy and bladder augmentation and 20 patients having diversion without cystectomy. Seven and eight patients respectively later had a cystectomy due to persistent pain, but it is unfortunately not reported if cystectomy relieved the pain. The final result was that there was no difference in pain improvement in patients with and without cystectomy. Sixteen of 20 non-cystectomized patients became pain free (80 %), while 12 of 18 cystectomized patients became pain free (66 %), ($p = 0.85$).

Secondary cystectomy rarely adds anything in the form of pain relief [6, 12], but should be performed if recurrent bacterial bladder infections are a part of the disease spectrum due to the risk of developing pyocystis [12].

Conclusion

In BPS patients, reconstructive surgery is the ultimate treatment choice after failure of conservative or less invasive surgical treatments have failed. Nevertheless, reconstructive surgery often ends up being the treatment of choice due to the lack of efficacy of less invasive treatments and the often severely disabling symptoms.

Urinary diversion is the most frequently chosen procedure. Although pain relief is "only" seen in about 80 % of the patients, the often equally disabling symptom of frequency is "cured" by this procedure. It is often clinically impossible to know if the pelvic pain is of bladder origin or not. More bladder-related symptoms like pain on bladder filling and relief by bladder emptying might help. Glomerulations at bladder distension and cystoscopic bladder capacity in general anesthesia are of no predictive value. Also objective findings of bladder pathology like Hunner lesion or increased mast cell count in the detrusor might be useful. The choice between a continent diversion and a conduit depends on patient preference, patient age, kidney function, and amount of intestine to be used.

Augmentation cystoplasty should be reserved for patients with contracted bladder and in the absence of pain, which in practice often is end stage Hunner lesion patients. It should be kept in mind that decreased bladder capacity during cystoscopy in general anesthesia might be due to inflammation and not fibrosis and thereby be reversible.

Primary cystectomy should be reserved for patients with a component of recurrent bacterial cystitis due to the risk of pyocystis. Secondary cystectomy has seemingly a limited symptomatic effect in patients having had a previous urinary diversion.

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Surgery for Vulvovaginal Pain Disorders and Dyspareunia

26

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Introduction

The International Society for the Study of Vulvovaginal Diseases (ISSVD) classifies vulvovaginal pain into two main categories: vulvar pain related to a specific disorder (e.g., dermatological, inflammatory, infection-related) and vulvodynia-idiopathic chronic vulvar pain. The most common subset of vulvodynia, vestibulodynia, is characterized by allodynia at the vulvar vestibule. The prevalence of vulvovaginal pain in women ranges from 14 to 34 % in younger women and from 6.5 to 45 % in older women [30]. In addition, a recently published study by Harlow and colleagues indicated that 8 % of women between the ages of 18 and 40 reported a history of vulvar burning or pain upon contact that, not only, persisted for more than 3 months and, but leads to dyspareunia that prevented or inhibited intercourse [18].

As the mechanism and etiology of vulvodynia and other causes of dyspareunia are further investigated in evidence-based research, standardized methods for diagnosis and treatment are being developed [10, 16]. While medical, cognitive behavioral, and physical/biofeedback therapy may be successful, some patients with dyspareunia and vulvodynia may turn to surgery as an option. The type of surgery caters to the etiology of pain and success rates vary with the type and technique of

Pictures: Transgluteal positioning: http://wiki.med.uottawa.ca/pages/viewpage.action?pageId=22151800.

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surgery performed. In general, surgery has been shown to offer relief of symptoms, return of sexual function, and a high degree of patient satisfaction [16].

The following chapter details the surgical procedures currently available and used to treat the more common etiologies of vulvovaginal pain and dyspareunia.

Anatomy

An understanding of the anatomy is necessary to evaluate and treat women with dyspareunia and/or vulvodynia. The components of the vulva include the perineum, labia majora, interlabial sulci, labia minora, prepuce of the clitoris, glans clitoris, and vulvar vestibule. The anatomical borders of the vulvar vestibule are Hart's line laterally and the hymen and urethral meatus medially. Hart's line demarcates non-keratinized squamous endothelium of the vestibule and keratinized epithelium of the labia minora [16]. The androgen-dependent, mucin secreting glands with ostia in the vestibule are the Skene's glands (paraurethral), minor vestibular glands, and Bartholin's glands.

The course of the pudendal nerve is also important to highlight, as much of the pathology is associated with this nerve. This is a mixed nerve that comprises of motor and sensory fibers derived from sacral roots S2, S3, and S4. There is a division of the roots past the sacral foramen into autonomic and somatic branches. The autonomic portion supplies the parasympathetic innervation to the pelvic organs while the somatic branches travel under the piriformis muscle. There is also a levator branch, which innervates the levator muscle. As we move caudally, the nerve passes through a narrow space between the sacrospinosus and sacrotuberous ligaments. Below the ischial spine the nerve has a terminal ending in the clitoris (the dorsal nerve of the clitoris). From here it enters what is known as "Alcock's canal" where it crosses the sacrotuberous ligament. The nerve then moves caudally to innervate the anal sphincter via the inferior rectal nerves and the skin of the posterior perineum. The final branches of the pudendal nerve are the bulbocavernosus branch that divides to innervate the urethra and the anterior perineum [5, 20, 26].

Diagnosis

Vulvovaginal disease is classified by the ISSVD as generalized (encompassing entire vulva), localized (focused area of the vulva such as clitoris or vestibule), or mixed type. Further subcategories are grouped by sensory responsiveness unprovoked (not requiring stimulus to illicit response), provoked (secondary to stimulus), or mixed [10]. A diagnostic algorithm shown below developed by the author (AG) (Fig 26.1) can aid health care providers to differentiate the causes of vulvar pain/provoked vestibulodynia. Utilization of this algorithm increases the chances of success of conservative treatment and also in selecting the most appropriate type of surgery if needed.

VESTIBULODYNIA
pain confined to the vestibule
TENDERNESS THROUGHOUT THE ENTIRE VESTIBULE
PAIN THROUGHT ENTIRE VESTIBULE
BUT GREATER AT 4, 6, 8 O'CLOCK
PAIN EXTENDS OUTSIDE THE VESTIBULE (physical exam only, not subjective)
PAIN CONFINED TO THE POSTERIOR VESTIBULE
PUDENDAL NEURALGIA
PE: severe tenderness when palpating the pudendal nerve at the ischial spine, most commonly unilateral or significantly greater on one side, tenderness and hypertonus of obturator internus muscle.
LABS: 3 Tesla MRI may show entrapment or scar tissue adjacent to the pudendal nerve in Alcock's canal.
CAUSES: pain of the anus, perineum, labia, and clitoris. Pain is exacerbated when sitting on hard surfaces and is improved when lying prone or standing. May have symptoms of persistent genial arousal disorder (PGAD). Pain improved temporarily with pudendal nerve block. History of coccyx trauma, hip pain, traumatic vaginal delivery, labral tear of hip.
TREATMENT: serial pudendal nerve blocks, oral gabapentin, oral pregabulin, pudendal nerve neuromodulation, pudendal nerve radio-frequency ablation, pudendal nerve neurolysis
OVERACTIVE (HYPERTONIC) PELVIC FLOOR MUSCLE DYSFUNCTION
PE: tenderness and erythema of the posterior vestibule only. Hypertonus of levator ani muscles, retracted perineum, tenderness to deep palpation of the perineum, post-coital fissure in posterior vestibule.
- Pain at 4, 8 o'clock if hypertonus of pubococcygeus muscle
- Pain at 6 o'clock if hypertonus of puborectalis muscle
- Urinary frequency, urgency, hesitancy, and sensation of incomplete emptying if hypertonus of the coccygeus muscles
- Constipation, rectal fissures, hemorrhoids if hypertonus of puborectalis muscle
LABS: elevated muscle tone measured with EMG
CAUSES: associated with anxiety, lower back pain, scoliosis, hip pain, 'holding urine', excessive core strengthening exercises
TREATMENT: pelvic floor physical therapy, diazepam 10 mg suppositories, vaginal dilators, home pelvic floor exercise, intramuscular botulinum toxin injections, cognitive behavior therapy, hypnosis, yoga (relaxation – not strengthening)
PERSISTENT GENITAL AROUSAL
PE: Allodynia of clitoris, sometimes tenderness of pudendal nerve
LABS: MRI of sacrum may reveal Tarlov cyst. MRI of lumbar spine may show disc herniation. Try ascending nerve blocks to find location of "lesion" - dorsal nerve of the clitoris → pudendal nerve block → epidural.
HISTORY: very disturbing sensation of arousal, can result suicidal ideation. Sometimes begins when starting or stopping psychotropic medications that increase dopamine or epinephrine
TREATMENT: Treat overactive pelvic floor muscle dysfunction (see left), treat pudendal neuralgia (see above). Chantix, Ambien, SSRI's, pericliteral Botulinum injections
INFLAMMATORY VESTIBULODYNIA
PE: erythema, induration and tenderness of vestibular and vaginal mucosa, leukorrhea, cervicitis/ectropion
HX: chronic infections, allergic reactions, copious yellowish discharge
LABS: wet mount with increased leukocytes, polymorphisms in IL1RA, MBL, IL1B
CAUSES: desquamative inflammatory vaginitis, chronic candidiasis, severe allergic reaction (Latex, semen, spermicide, vaginal creams)
TREATMENT: interferon 1.5 million units SQ TIW for 12 doses, montelukast, enoxaparin, cutaneous lysate
PERSISTENT
NEUROPROLIFERATION
ACQUIRED NEUROPROLIFERATIVE VESTIBULODYNIA
PE: Tenderness, erythema throughout the entire vestibule
LABS: Histology shows an increased density of c-afferent nociceptors (if using immunohistochemical stains S-100 or PGP 9) and increased number of mast cells. Polymorphisms in IL1RA, MBL, IL1B
HISTORY: persistent or chronic yeast infection, severe or recurrent allergic reaction. May be associated with urticarial, hives, and "sensitive skin"
TREATMENT: capsaicin 0.025% 20 minutes QHS for 12 weeks, topical gabapentin 4% cream, subcutaneous Botulinum toxin infections, if failed conservative treatments then vulvar vestibulectomy.
HORMONALLY ASSOCIATED VESTIBULODYNIA
PE: Gland ostia are erythematous, mucosal pallor with overlying erythema, decreased size of labia minor and clitoris.
LABS: High sex hormone binding globulin, low free testosterone, high number of CAG repeats in the Androgen Receptor
CAUSES: hormonal contraceptives, spironolactone, Tamoxifen, aromatase inhibitors, oophorectomy, amenorrhea, lactation.
TREATMENT: Stop offending medication, topical estradiol 0.01%/testosterone 0.1% in methylcellulose gel
CONGENITAL NEUROPROLIFERATIVE VESTIBULODYNIA
PE: tenderness of the entire vestibule (anterior and posterior) from Hart's line to the hymen, often with erythema that worsens after touch with cotton swab. Umbilical hypersensitivity in approximately 60% of women.
LABS: Histology shows an increased density of c-afferent nociceptors (if using immunohistochemical stains S-100 or PGP 9) and increased number of mast cells.
HISTORY: Pain since first tampon use, speculum insertion, and coitarche. No pain free sex. Often late coitarche > 25 years old
TREATMENT: Capsaicin 0.025% 20 minutes QHS for 12 weeks. Vulvar vestibulectomy.
Adapted from King, M., Rubin, R., Goldstein, A. Current Uses of Surgery for the Treatment of Genital Pain. *Current Sexual Health Reports*. 2014, Oct 3. Volume 6, Issue 4, pp 252-258.

Fig. 26.1

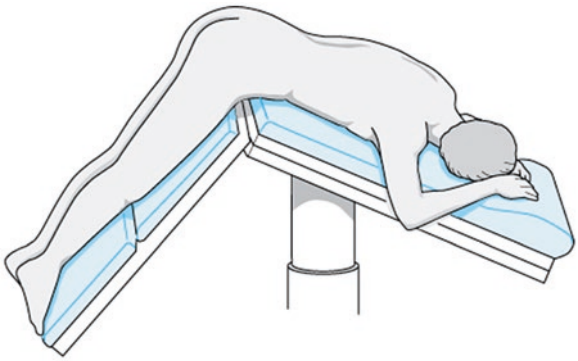
Surgical Management

Pudendal Neuralgia

Pudendal Neuralgia is a neuropathic pain that encompasses the anatomic area innervated by the S2-S4 sacral nerve roots. The path of the pudendal nerve is in a well-demarcated space between sacrospinous and sacrotuberous ligaments. This nerve exits the pelvis through the obturator internus muscle membrane known as Alcock's canal. The nerve terminates into three branches: dorsal nerve of clitoris, perineal nerve, and interior rectal nerve. With this neuropathy pain is exacerbated by sitting, alleviated by standing, supine position, and sitting on the toilet [2, 27]. The pain often originates from various causes such as trauma (e.g., routine cycling), perineal stretching during childbirth, orthopedic fractures, and after complicated hysterectomy.

Patients who fail medical therapy or physical therapy have options for surgical/procedural management when it comes to pudendal neuralgia. One option is a pudendal nerve block, which can be both diagnostic and therapeutic. These can be performed by transvaginal, transperineal, and transgluteal routes. There have been techniques that use CT-guided injections at regularly scheduled intervals into Alcock's canal with bupivicaine and triamcinolone [19].

If pain is not alleviated with serial pudendal nerve blocks then ***surgical nerve decompression*** can be performed. This can be done by one of four methods: transischiorectal, perianal, laparoscopic, and transgluteal [4, 21, 23, 25, 26]. The advantage of the transgluteal method is good visualization of pudendal nerve. This procedure involves the patient to be placed in a jack-knife prone position with an incision made over the sacrotuberous ligament. When this ligament is divided at the narrowest point the nerve can be visually identified or with the help of NIMS monitor (Nerve Integrity Monitoring system; Medtronic, Minneapolis, MN). The pudendal nerve is decompressed from piriformis muscle to Alcock's canal.



The last potential effort to treat pudendal neuralgia is with ***Neuromodulation***. Goldstein et al state that this works by altering patient's perception of pain by

applying an external source of electrical current to the affected region. This electric current is delivered by a standard quadripolar times lead device that is implanted next to the pudendal nerve. This is placed under fluoroscopic guidance while simultaneously using a needle electromyography at external anal sphincter to monitor activity of pudendal nerve [17]. Eventually, this device is programmed for the specific patient and connected to an external stimulator. The initial device is temporary and if pain is reduced on subsequent visits a permanent pulse generator will take the place of the temporary implant. More randomized control trials are needed to test the efficacy of treatment of pudendal neuropathy and other chronic pelvic pain conditions, but the initial conclusions provide a promising start.

Surgery for Vulvar Vestibulitis/Neuroproliferative Vestibulodynia

In patients with pain secondary to vestibulitis immunohistochemistry has also shown increased density of nociceptors in the vestibular endothelium. Due to the increased density of nerve fibers these patients experience symptoms described as "cutting, rawness, or burning." This diagnosis is confirmed by three findings as described by Friedrich: extreme tenderness upon palpation of vestibule with cotton swab, vestibular erythema, and severe pain upon vaginal entry with speculum, tampon, penis, etc [11].

In 1981, [32] were the first to describe vulvar vestibulectomy. The original perineoplasty involved excision of a triangular area of skin with base at vaginal outlet and apex near the anal opening without any vaginal mucosa in the specimen. Then ~3–4 cm of vaginal mucosa was undermined and underlying scarred tissue was removed. The remaining vaginal mucosa was reapproximated to the perineum.

Over time several variations and modification of this technique have evolved. Vestibulectomy may be complete (excision of the mucosa of the entire vulvar vestibule and mucosa near the urethra) or modified (excision is limited to the mucosa of the posterior vestibule) [10]. The procedure of complete vestibulectomy with vaginal advancement is outlined by Goldstein. First, labia minora are grasped with Allis clamps and when spread laterally the entire vulvar vestibule is exposed. A marking pen is used to demarcate the vulvar vestibule by creating parallel lines on both sides of the urethra (medial to the Skene's gland ostia) and by extending these lines superiorly to Hart's line and then inferiorly following the same line then joining the parallel lines 0.7 cm below the introitus on the perineum. Local injection of Marcaine 0.5 % with epinephrine is injected submucosally to the area prior to any incision. The entire vulvar vestibular mucosa is excised using a scalpel to a depth of 3 mm and extending 5 mm past the hymenal ring, thereby removing all of the vestibular endoderm and the complete hymen. The next step is the creation of the vaginal advancement flap. This is achieved by grasping the vaginal mucosa with two Allis clamps and 2 cm of vaginal mucosa is carefully dissected off the recto-vaginal fascia. The flap will eventually cover the defect in the posterior vestibule. After the defects in the anterior vestibule are closed, two

rows of mattress stitches of 2–0 Vicryl are used to attach the flap in an advanced position. The mattress stitches should penetrate the vaginal mucosa and then should be "back-handed" through the recto-vaginal fascia and then go back through the vaginal mucosa. By placing these mattress sutures in the anterior-posterior direction the chance of narrowing the diameter of the introitus is decreased. It is important that an assistant applies gentle downward traction on the advancement flap to ensure the placement of the mucosa. Mattress sutures decrease tension when the suture line is brought to the perineum thereby decreasing the risk of dehiscence. These sutures also help prevent hematoma formation. Finally, the advancement flap is approximated to the medial aspect of the labia minora and to the perineum with 4–0 vicryl suture (~20 interrupted stitches are needed) to complete the procedure. While performing this procedure it is essential to pay close attention to the urethral meatus. Poor closure of the anterior defects could lead to postoperative hematoma and urinary retention. After completion of the procedure, a Foley catheter should be inserted into the urethra to confirm urethral patency and rectal exam should be performed to confirm that the mattress stitches did not go through the rectum and that there is not a hematoma under the advancement flap (Photo 26.1) [13].

A posterior vestibulectomy is a somewhat abridged version of the total vestibulectomy. There is only a partial excision of the vestibule from the 10 o'clock to 2

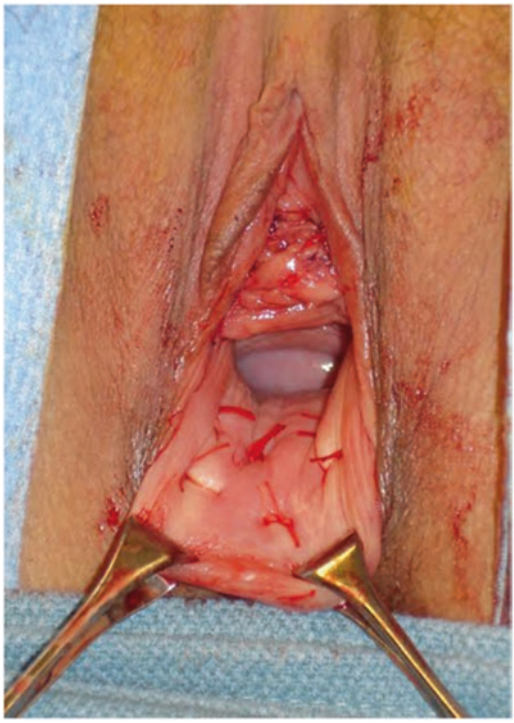


Photo 26.1 Mattress stitches are used to anchor the vaginal advancement flap in an advanced position

o'clock positions within Hart's line. Some women may prefer this option since there may only be symptoms that arise from the posterior vestibule [30]. The authors of this chapter, however, have found that leaving the anterior vestibule increases the risk of residual allodynia and dyspareunia postoperatively.

Another modification identified by Goetsch involves minimal tissue removal. The skinning technique is used to remove "defined tender parts" of the vestibule. The major part of the hymen is left intact since it is needed for closure of the denuded area. Therefore, no vaginal advancement is needed. The risk of intraoperative bleeding and postoperative infections may be decreased by this method. Another benefit is that general anesthesia is not needed and postoperative pain is better managed [12]. Again, the authors of this chapter, however, have found that leaving the residual vestibule increases the risk of residual allodynia and dyspareunia postoperatively.

Prior to surgery, potential complications should be discussed with the patient. The risks can include bleeding, infection, increased pain, hematoma, wound dehiscence, scar tissue formation, cosmetic changes, and Bartholin's cyst formation. However, the risk of these complications is small and these complications are usually easily managed [14]. Therefore, it is essential to not over-emphasize the risks of the procedure. Forty-one of 44 published peer-reviewed studies have shown a success rate of 80 % or greater with vulvar vestibulectomy and several studies show patient satisfaction rates greater than 90 %. Additionally, many studies show an improvement in sexual function when this was measured as an outcome [6, 7, 29]. Given these positive results, it has been suggested that vulvar vestibulectomy may, in some cases, be an appropriate first-line treatment vs. some of the more conservative options [28].

Surgery for Dyspareunia Secondary to Vulvar Lichen Sclerosus

Lichen Sclerosus (LS) is the most common vulvar inflammatory dermatosis secondary only to contact dermatitis. This is a chronic inflammatory process that is defined by lymphocyte-mediated changes that affects genital skin and mucosa. Clinical presentation aside from itching may include pain, dysuria, urinary retention, and dyspareunia. LS may also result in painful defecation if there is perianal involvement and may result in constipation [22].

The structures most commonly affected by vulvar LS are the medial labia majora, inter-labial sulci, labia minora, clitoral hood, clitoris, and posterior fourchette. For this reason, when it is left untreated, vulvar LS can cause vulvar scarring leading to labial resorption, clitoral phimosis, introital stenosis, and recurrent fissures/erosions of the anterior and posterior vestibule. As a result, surgical intervention is sometimes needed [24].

Patients may present with clitoral phimosis as a result of vulvar LS. Goldstein and Burrows highlight one method of clitoral phimosis repair that involves insertion of a lacrimal duct probe between the clitoris and prepuce to lyse any adhesions. Then, Iris scissors are used to create a small dorsal incision in the prepuce.

Trimming of the prepuce edges may prevent recurrent adhesions and silver nitrate or Monsel's solutions may be used to obtain hemostasis. Another option is oversewing the prepuce for hemostasis and adhesion prevention. Postoperative application of clobetasol 0.05 % ointment daily to surgical site may prevent Koebernization (reactivation of active lichen sclerosus caused by trauma) and recurrent adhesions. Goldstein and Burrows described a small case series in which there was 100 % satisfaction with this procedure. All patients reported increased clitoral sensitivity and improved orgasm after undergoing this procedure (Photo 26.2) [15].

Another potential complication of vulvar LS is introital stenosis which can lead to recurrent tearing during penetration (vulvar granuloma fissuratum). This may obviously cause significant dyspareunia and sexual dysfunction. These women are initially treated with high dose topical corticosteroids and use of graduated vaginal dilators. If these interventions fail a ***perineoplasty*** may be needed to widen the introitus. In this surgical procedure the scarred endothelium of the posterior fourchette and of the perineum are excised and a vaginal advancement flap is used to close the defect (Photo 26.3).

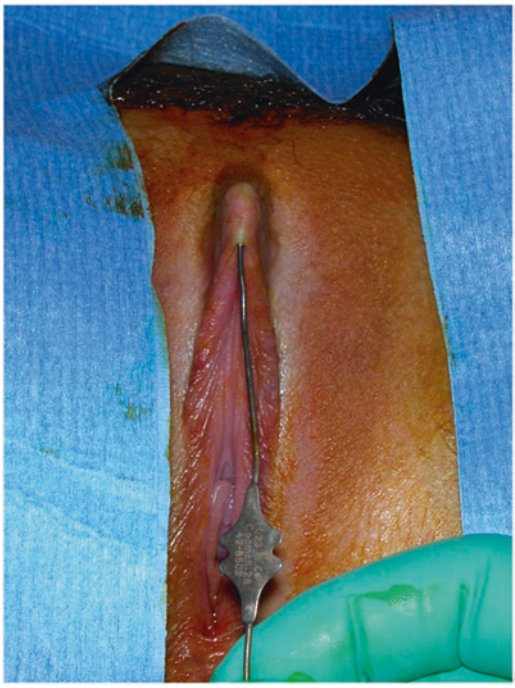


Photo 26.2 A lacrimal probe is used to lyse adhesions between the prepuce and glans clitoris

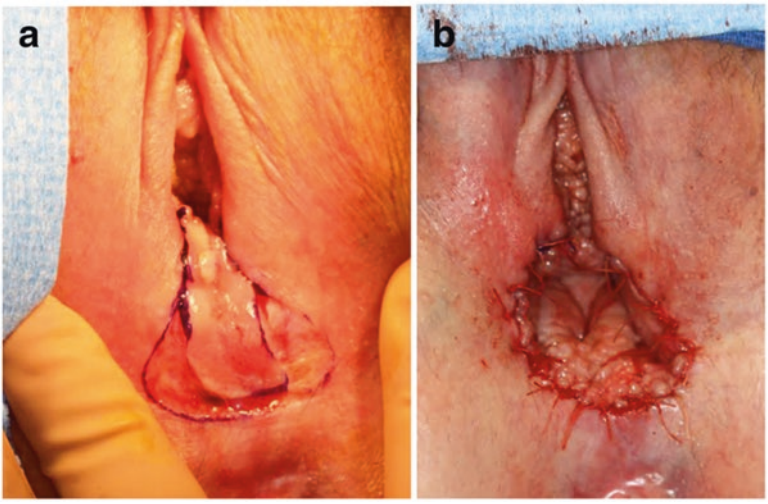


Photo 26.3 (**a**) Outline of vulvar vestibule. (**b**) After advancement flap used to cover posterior vestibule

Surgery for Pain Secondary to Severe Hiradenitis Suppurativa

Hiradenitis suppurative (HS), like LS, is a chronic inflammatory skin disease. The disease is clinically classified using the Hurley stages (Table 26.1).

While effective topical treatment with resorcinol 15 % is available there are severe cases that may require systemic and surgical treatment. Systemic treatment includes acitretin, antibiotics, and tumor necrosis factor α (TNF-α). Surgical intervention options available include deroofing, CO2 laser treatment or excision, excision of the entire area containing the lesions using the "skin-tissue-saving excision with electrosurgical peeling" (STEEP technique), and radical excision of the affected area with wide margins [8, 9, 31].

In this chapter, we will focus on intervention for severe HS which include STEEP technique and wide local excision. Both may be done with local or general anesthesia and is often determined by the extent of disease and anticipated level of complication of the procedure [3]. The STEEP technique is a procedure devised by the Department of Dermatology at the University of Groningen, University Medical Center Groningen in The Netherlands. This involves sequential tangential transections in attempts to remove all lesional tissue.

STEEP, unlike wide excision, saves the maximal amount of healthy tissue. This was done at the specialized center in the Netherlands under general anesthesia for patients (men and women) who have extensive stage II or III disease. In this specific study primary operations were performed not only on the vulvar area, but also in groins, armpits, and buttocks where HS is common. In this procedure wound healing was left to secondary intention. While further studies for use of STEEP on just

Table 26.1 The Hurley stages of huradenitis suppurativa

Stage	Characteristics
I	Presence of abscesses and nodules
II	Stage I plus formation of sinus tracts Presence of healthy skin between lesions
III	Stage I plus formation of sinus tracts No healthy skin identified between lesions

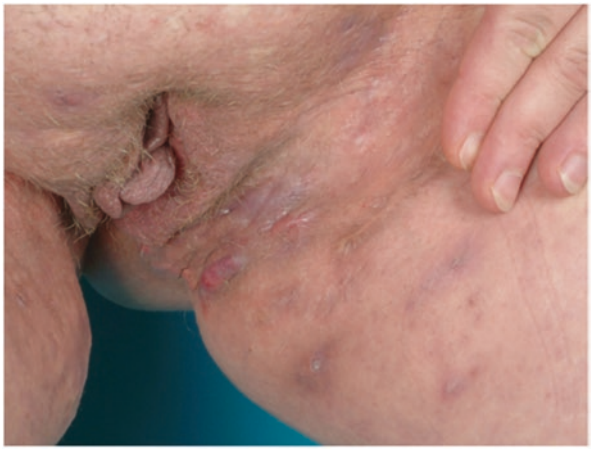


Photo 26.4 Bilateral hidradenitis suppurativa (Hurley's Staging III) in the perianal, perineal, and mons pubis

women and vulvar HS are needed this offers a viable, minimally invasive, option instead of wide excision for more severe cases.

Wide surgical excisions for all areas affected by hiradenitis involve wide margins of 1 cm and deep margin, which includes skin, subcutaneous tissue to the underlying fascia. Reconstruction techniques of the perianal and perineal regions described by Alharbi included use of transposition of fasciocutaneous flap in six sites and gracilis musculocutaneous flap in two patients. Essential to both techniques are preservation of the vulva and anal sphincter (Photo 26.4) [1].

Again, this mode of surgical treatment is not specifically studied in the subpopulation of women with hiradenitis suppurative but shows promising results and can be offered in cases of Hurley stages II and III HS. Further studies will be needed to investigate the efficacy of wide excision alone or the use of more minimally invasive surgical techniques such as the STEEP procedure with peri-operative Immunosuppression in women with specifically vulvar HS.

Conclusion

Overall, vulvar pain of any etiology presents a challenge when it comes to treatment. This chapter aims to show available surgical techniques for treating more difficult cases that are unresponsive to more conservative treatment. Surgical treatment, in some cases, may also be considered a first-line therapy depending on the clinical situation.

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The Surgical Management of Scrotal Pain

27

Michael P. Hoeh and Laurence A. Levine

Abbreviations and Acronyms

CSCP	Chronic scrotal content pain
MDSC	Microdenervation of spermatic cord
NSAIDS	Nonsteroidal anti-inflammatory drugs
TENS	Transcutaneous electrical nerve stimulation
VTI	Vascular Technology Inc.

Introduction

Chronic orchialgia is defined as intermittent or constant testicular pain 3 months or longer in duration that significantly interferes with the daily activities of the patient so as to prompt him to seek medical attention [1, 2]. It should be noted that frequently the patient will not only have testicular pain, but also pain involving the epididymis, vas deferens, or adjacent paratesticular structures. Therefore, a more appropriate term would be chronic scrotal content pain (CSCP). It is estimated that about 3 % of all urology visits are attributable to CSCP [3, 4]. Despite this relatively common complaint, the diagnosis and treatment of CSCP can be a frustrating process for both the patient and the physician as there is no recognized or accepted

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standard protocol for evaluation, nor is there a clearly established effective treatment regimen.

Although CSCP may occur at any age, the majority of patients present in their mid to late thirties [5]. Pain may be unilateral or bilateral, constant or intermittent, spontaneous or exacerbated by physical activities and pressure. It can remain localized in the scrotum or radiate to the groin, lower abdomen, perineum, or back of the legs. Clinical examination usually demonstrates a tender testicle, epididymis, and/or cord structures but in most men there is no obvious structural abnormality and there may not be any identifiable pain on palpation. The impact of CSCP on quality of life can be significant, causing limitations to work, social, and sexual interactions. Depression is frequently seen in these patients [6].

The ultimate goal of CSCP treatment is to identify and treat identifiable causes of pain and to return the patient to normal daily activities without the use of analgesics. A variety of treatments are available, including medical and surgical options with variable results as reported typically in small, noncontrolled trials.

Etiology

Up to 50 % of patients will present with no identifiable etiology [1, 3, 7]. Pain in the scrotal contents can be due to direct sources, including varicocele, spermatocele, hydrocele, tumor, torsion, infection and can follow direct trauma as well as iatrogenic injury following vasectomy or inguinal hernia repair. Multiple studies have reported that when an identifiable and surgically correctable etiology is found, surgery should be the therapy of first choice which has been shown to be highly effective, with most studies noting over 75 % pain relief [8–11].

Referred pain can occur as a result of ureteral stone disease, inguinal hernia, pelvic floor myalgia or spasm, intervertebral disc pathology, and rarely retroperitoneal tumors [12], polyarteritis nodosa [13], and an aneurysm of the abdominal aorta [14]. Psychiatric issues including malingering behavior should also be considered. Importantly, it has been recognized that chronic genital pain may be associated with a history of sexual abuse [6].

Urologists are most likely to see postvasectomy pain syndrome, with a reported incidence of 0.9–54 %, but fewer than 10 % of patients are bothered enough to seek treatment [9, 15, 16]. While pain may develop immediately after vasectomy, the mean time to chronic pain onset has been reported to be 2 years with some patients presenting up to 7 years following vasectomy [17, 18]. The pathogenesis for postvasectomy is unclear, but may include congestive epididymitis, sperm granuloma, or nerve entrapment. All men seeking vasectomy should be counseled on the possibility of this morbidity.

The etiology of chronic epididymitis is unclear but may include previous bacterial infections including prostatitis, sexually transmitted infection, trauma, catheterization, or retrograde urination. It has recently been reported that mild epididymitis may be an under-recognized cause of CSCP. Studies have shown that when pain is isolated to the epididymis, even in the presence of a negative urine culture, a four to

six week trial of NSAIDS and empiric antibiotics may improve pain in a substantial number of patients [19].

It is important to note that CSCP may be part of chronic prostatitis/chronic pelvic pain syndrome, for which up to 50 % of men are reported to also have pain in the testes [20]. Pelvic floor dysfunction is characterized by pelvic floor muscle dyssynergia, overactivity, and/or hypertonicity, which may lead to perineal and scrotal content pain. Patients suffering from this process may also complain of constipation or pain with defecation, urinary frequency or dysuria, painful ejaculation, or pain with intercourse [21].

Evaluation

Evaluation should include ruling out medically important and reversible causes such as those previously listed. History should focus on onset, duration, nature (sharp, dull, burning, pressure, etc.) severity (graded on a 0–10 scale), location, and referral of pain. The physician should ascertain whether certain activities exacerbate or ameliorate the pain, including voiding, bowel movements, sexual or physical activity, and prolonged sitting, which the authors have found to be one of the most common complaints in this population. Past surgeries are important, which may involve the spine, inguinal, scrotal, pelvic, or retroperitoneal areas. Psychosocial questions are in order to determine whether there is a disability associated with pain, if there is potential secondary gain, and if there are signs or symptoms of depression or history of sexual abuse.

Physical examination should focus on the genitalia. The patient should be examined while standing and supine, starting the genital exam on the non-painful or less painful side if bilateral. A detailed examination of the testes, epididymes, and vasa is indicated, and a 360° rectal exam is also recommended to evaluate for prostate abnormalities and tenderness and/or hypertonicity of the pelvic floor musculature. Sinaki and colleagues describe a condition known as pelvic floor tension myalgia, which is characterized by continuous habitual contraction of muscles in the pelvic floor. These patients are usually noted to have point tenderness in the pelvic floor muscles or areas of attachment and pelvic floor physical therapy appears to have an important role in the management of these patients in particular [22]. Further examination includes a urinalysis, urine and semen culture if indicated. All patients should undergo a duplex scrotal ultrasound, which is a crucial study for the evaluation of scrotal content pain [23]. MRI or CT scan of the spine is indicated in those with a history of back or hip pain.

A critical diagnostic tool is the spermatic cord block, which is performed by injecting 20 mL of 0.25 % bupivacaine without epinephrine into the spermatic cord at the pubic tubercle level [24]. If pain is truly from the scrotal contents and not referred, spermatic cord block or division of the scrotal and spermatic branches of the genitofemoral and ilioinguinal nerves should relieve the pain [6, 25]. Consideration of a series of blocks including a saline control for diagnosis is reasonable but remains controversial for ethical reasons and may not delineate

malingering. In addition, it may prove to be a burden to patients who come from a distance for treatment.

Nonsurgical Treatment

Many authors suggest a multidisciplinary team approach involving a urologist and a pain clinic specialist after conservative measures fail [2]. In patients with signs of pelvic floor dysfunction we highly recommend offering referral to a specialized pelvic floor physical therapist. Pelvic floor physical therapy includes biofeedback, manual muscle testing, pelvic floor massage, medical management of constipation, relaxation techniques, and/or development of an individualized home exercise program.

Figure 27.1 summarizes our suggested treatment algorithm for the patient with chronic scrotal pain. Treatment should start with simple noninvasive and nontoxic approaches including nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics when there is evidence of infection. Quinolone antibiotics are typically preferred, as they appear to have the highest penetration into these structures and may be given up to 4 weeks or longer if indicated. Other oral agents include antidepressants such as amitriptyline 10–25 mg qhs or nortriptyline 10–150 mg daily, which inhibit norepinephrine release at first- and second-order neurons, or anticonvulsants such as gabapentin and pregabalin which are calcium channel modulators affecting afferent pain fibers.

Acupuncture, pelvic floor physical therapy, as well as psychological evaluation and support are other treatment modalities that may be beneficial [6, 26]. The authors have found pelvic floor therapy in particular has provided significant improvement or resolution in symptoms for men with signs and symptoms of pelvic floor dysfunction and we now routinely recommend specialized pelvic floor physical therapy to these patients.

Nerve blocks as a single injection or series have also been used as a form of treatment with or without steroids in an effort to break the pain cycle. Studies have demonstrated that spermatic cord blocks with a local anesthetic and steroid may provide short-term and occasionally long-term relief, which may be repeated at varying intervals [27]. In our experience this approach is not successful when the duration of chronic pain exceeds 6 months.

Long-term treatment with analgesics (i.e., narcotics) focuses mainly on symptom reduction and not on treating the underlying pathological condition, and therefore should be considered only when all other treatments fail. Chronic opioid use has also been frequently associated with hypogonadism [28].

Pulsed radiofrequency of the spermatic cord and genital branch of the genitofemoral nerve have recently been reported for the treatment of chronic testicular pain in small noncontrolled trials [29, 30]. This approach seems particularly effective when a cord block results in local temporary relief.

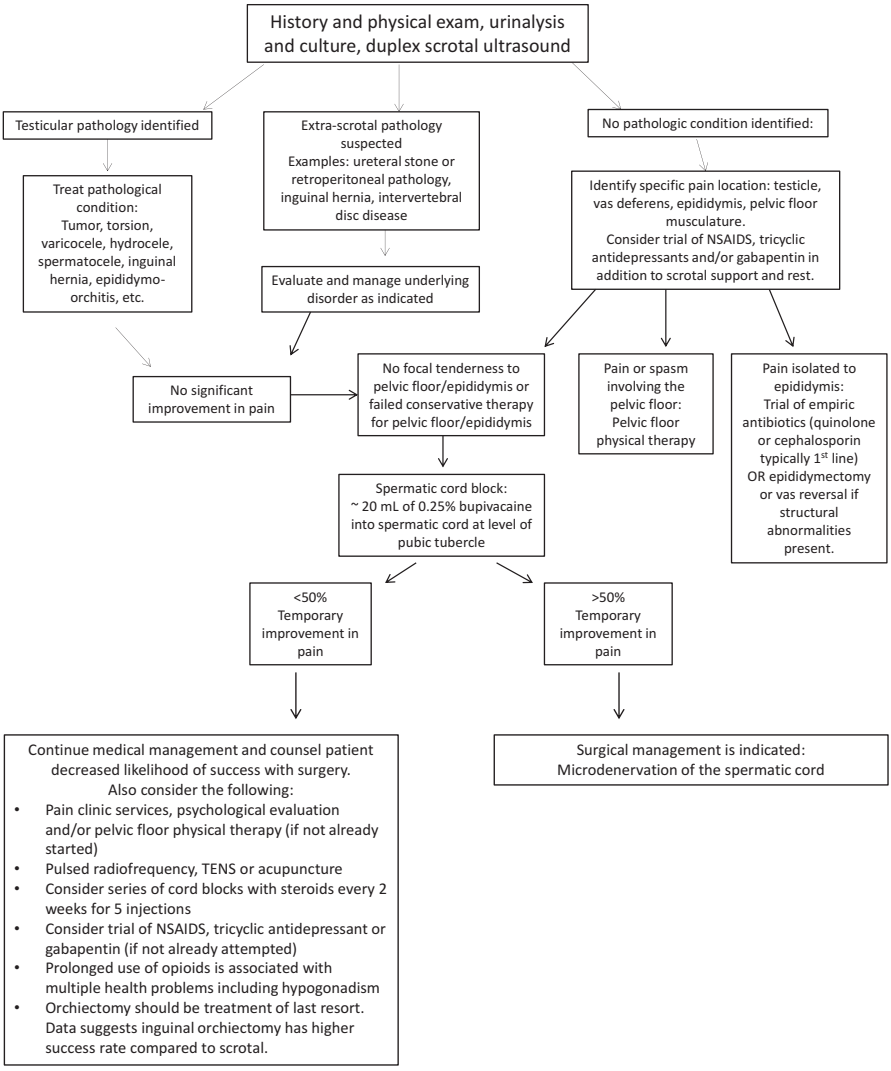

Fig. 27.1

Surgical Treatment

Microdernervation of the Spermatic Cord (MDSC)

MDSC is an attractive surgical option that has emerged over the past two decades. The absolute predictor to a successful MDSC has yet to be defined, but it appears that near complete to complete temporary relief of pain after spermatic cord block is our best guide [31]. Sparing the testicle is advantageous for both psychological

and physiological reasons. The goal of the operation is to divide all structures that may be carrying neural fibers. It is important to attempt preservation of all three arteries supplying blood flow to the testicle (testicular, cremasteric, deferential), along with several lymphatics to reduce the likelihood of hydrocele and preservation of the vas if it has not already been taken. Preoperative counseling is critical, as the pain may be persistent and can rarely worsen. MDSC also carries the real, but low, risk of testicular atrophy, hypogonadism, hematoma, hydrocele, and infertility. MDSC may also be successfully performed after prior surgical correction for pain has failed, including prior varicocelectomy, hernia repair, vasectomy reversal, and epididymectomy [32].

Technique

The surgical procedure is usually performed in an outpatient setting under general anesthesia with the aid of an operating microscope at 4–8× power. The patient remains in supine position and the ipsilateral inguinal area and genitals are prepped and draped. The external inguinal ring is palpated and a 3–4 cm inguinal incision is made directly over the spermatic cord to expose the external inguinal ring.

The cord is isolated circumferentially. The ilioinguinal nerve is identified typically emerging laterally from the external inguinal ring and a 2–3 cm segment is excised and ligated (Fig. 27.2). The proximal end is buried under the external inguinal ring to decrease the risk of neuroma formation. The spermatic cord is elevated and brought to rest on a 5/8-in. penrose drain.

The operating microscope is brought to the field and the anterior spermatic cord fascia is opened for 3–4 cm to expose the cord contents (Fig. 27.3). A 20 MHz Microvascular Doppler System ultrasound (Vascular Technology, Inc. [VTI] Nashua, NH) is used to identify the location of the testicular, cremasteric, and deferential arteries and branches are secured with micro-vessel loops. Several lymphatics are spared to prevent hydrocele formation (Fig. 27.4). The internal spermatic veins are ligated and divided. Electrocautery is used to divide all of the cremasteric musculature and spermatic cord fascia (Fig. 27.5).

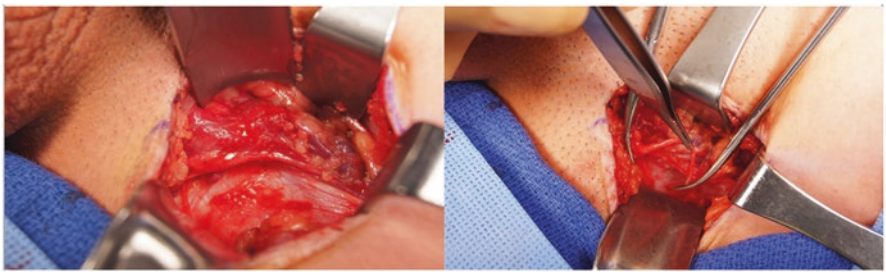

Fig. 27.2 *Left*: The ilioinguinal nerve is identified typically emerging laterally from the external inguinal ring. *Right*: A 2–3 cm segment is excised and ligated

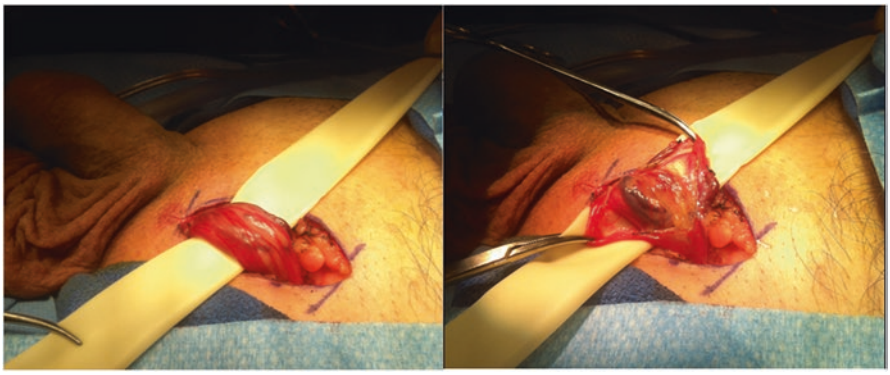

Fig. 27.3 Spermatic cord supported by a Penrose drain. Penrose drain with cord fascia opened

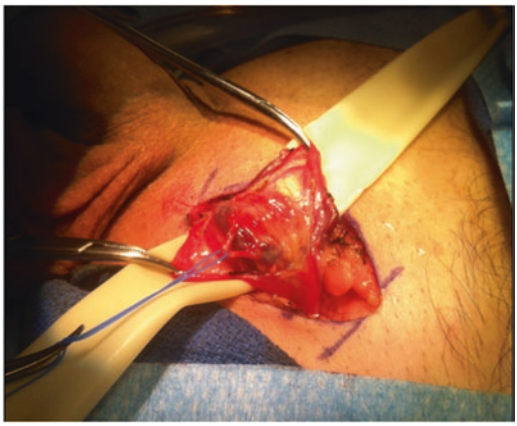

Fig. 27.4 Lymphatics are spared and secured with vessel loops to prevent hydrocele formation

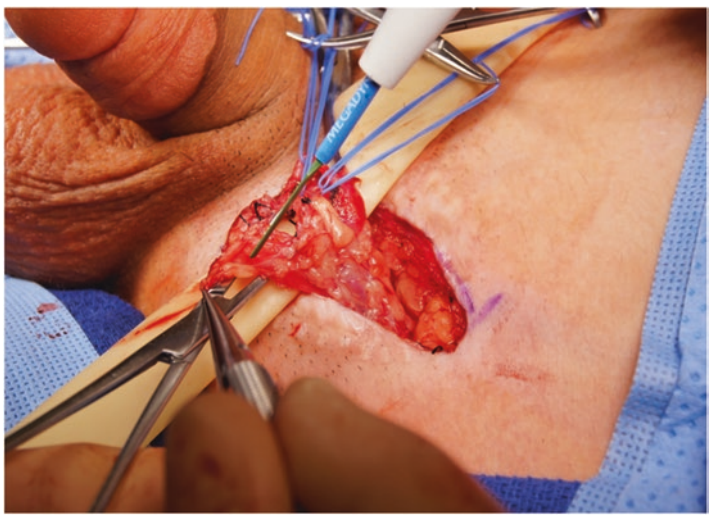

Fig. 27.5 Electrocautery is used to divide all of the cremasteric musculature and spermatic cord fascia

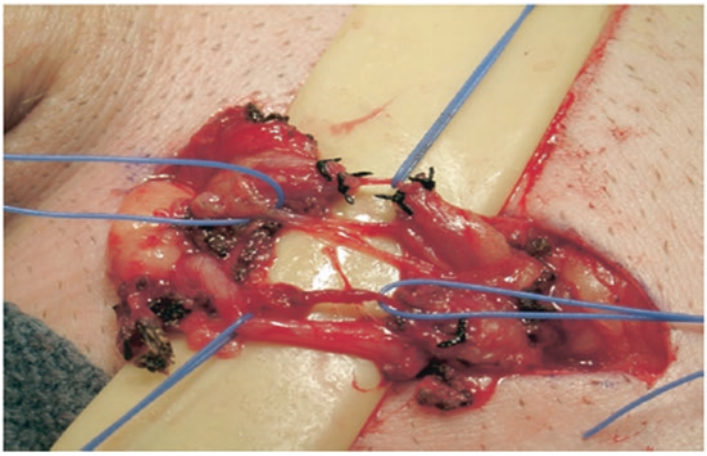

Fig. 27.6 After completion of dissection, only the cremasteric artery, lymphatics, internal spermatic artery, and vas deferens remain (top to bottom)

In men who have not undergone vasectomy, the vas deferens is preserved to prevent epididymal congestion, which may contribute to post-vasectomy pain syndrome. In this situation, the vas is stripped of the fascial outer layer to ablate afferent nerve pathways carrying potentially noxious stimuli. In those who underwent prior vasectomy the vas is divided again to ensure that any neural fibers within and on the vas are severed.

Prior to closure, pulsatile flow within the preserved arteries is checked with the micro-Doppler. If poor flow due to spasm is noted then topical papaverine is applied to the vessel surface to encourage vasodilation. After completion of dissection, only the vas deferens, several lymphatics, and the testicular, cremasteric, and deferential arteries should remain (Fig. 27.6). The cord is then placed back into its original position and 10 cc 0.5 % bupivacaine without epinephrine is injected into the wound, which is closed in layers.

MDSC after successful spermatic cord block has been shown to provide complete relief of pain in 71–100 % of patients, with an average pain-free rate experienced by 83 % of patients, 12 % with improved symptoms, and 5 % demonstrating no change.[34–45] Informed consent is critical, as the pain may persist but rarely worsens. Pain relief may be immediate but has been reported to take up to 3–6 months. Recurrent pain after complete relief rarely occurs and in those with bilateral pain it is recommended to address the more painful side first as the pain on the contralateral side may resolve by taking away the primary noxious stimulus.

Epididymectomy

A review of the literature would suggest that epididymectomy is an option when the pain is localized to the epididymis only and appears to have its best outcomes following vasectomy [33, 34]. Overall reported success with epididymectomy ranges from 10 to 92 %[35–37]. Predictors of successful epididymectomy include a palpable painful epididymis and tender cystic lesions isolated to the epididymis.

Predictors of poor outcome include presence of chronic inflammation of the epididymis without structural findings on examination or ultrasound imaging, and pain in adjacent structures including the testicle or cord [45].

Technique

Local or general anesthesia may be used and intravenous antibiotics should be considered, particularly if the patient has a history of genitourinary infections. The testis is delivered through an anterior ipsilateral scrotal incision. The tunica vaginalis is opened to allow access to the vas deferens and epididymis. The head of the epididymis is identified. A stitch may be placed through the head to allow for gentle retraction during surgery (Fig. 27.7). The straight portion of the vas deferens is

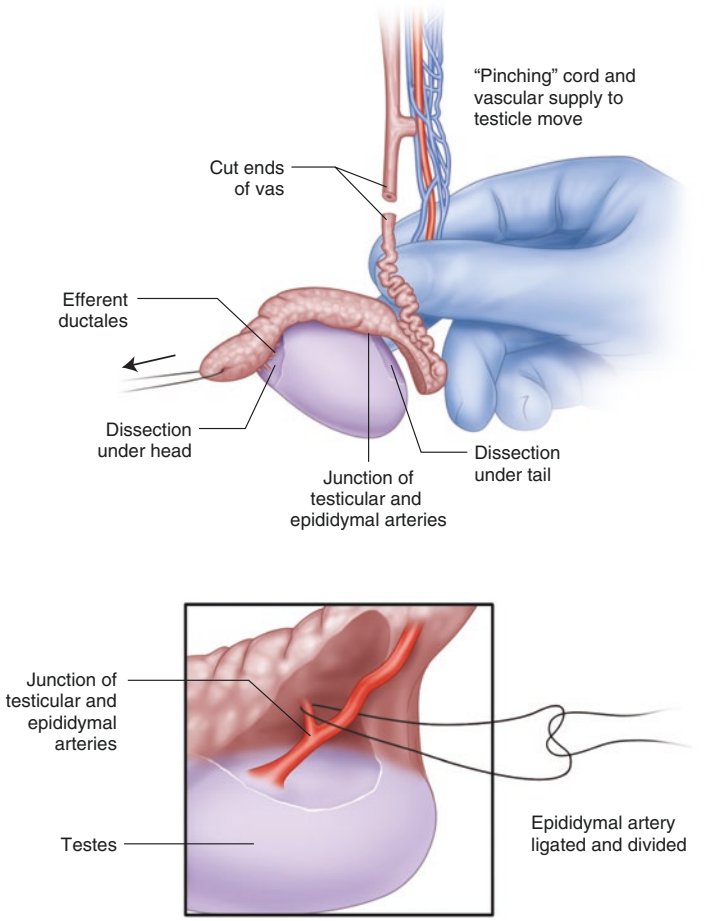

Fig. 27.7 Dissection under the head of the epididymis is carried distally to the end of the convoluted vas. A stay stitch may be placed in the head to allow gentle retraction. Likewise the thumb and forefinger may be used to isolate the epididymis from the testis and spermatic cord during dissection

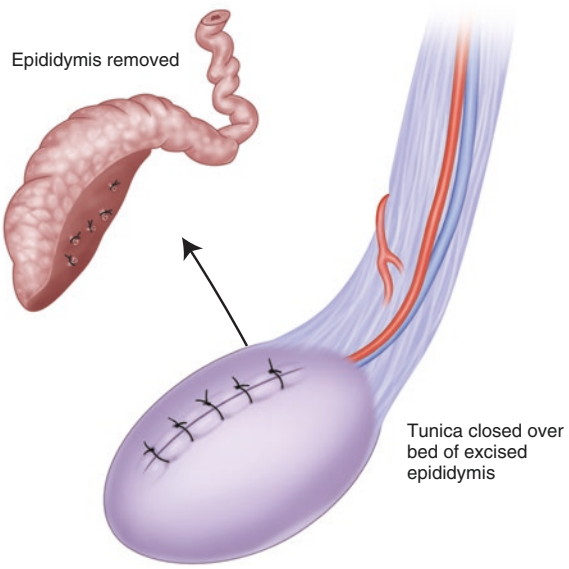

Fig. 27.8 The epididymis is removed, preserving the blood supply to the testis. The remaining tunica is then closed using absorbable 4–0 suture

identified, isolated, and divided just distal to the convoluted vas. The lumen of the distal vas is ligated or fulgurated. The convoluted vas is then carefully dissected from the spermatic cord and testis with blunt and sharp dissection. The testicular and epididymal arteries are typically encountered at the middle and distal third of the epididymis. Care should be taken to only divide the epididymal arteries, preserving the testicular blood supply. Once the epididymis is removed, meticulous hemostasis should be achieved prior to closing the remaining tunical defect, which is closed using absorbable 4–0 sutures (Fig. 27.8). The dartos is closed in at least one layer of absorbable 3–0 suture and skin is closed using interrupted or subcuticular suture. A penrose drain may also be placed prior to closure if necessary.

Vasectomy Reversal

For men with post-vasectomy pain syndrome, vasectomy reversal has been offered as an open-ended procedure or with vasovasotomy. Vasectomy reversal for post-vasectomy pain syndrome has been associated with 50–69 % complete pain relief and up to 100 % having improvement of pain [38–41]. However, at this time only a few studies have been published supporting this approach. The advantages to this approach are potential resolution of pain and preservation of all intrascrotal structures. However, it clearly reverses the purpose of the vasectomy, is costly, and may not be covered by insurance. In addition, MDSC is an option for men with post-vasectomy pain syndrome with reportedly higher success rates without affecting the patient's infertility status.

General anesthesia is recommended and intraoperative antibiotics should be considered. The initial surgical incision may be through a small 3–4 cm midline raphe incision (if bilateral reversal is desired) or through a transverse or vertical ipsilateral hemiscrotal incision (for unilateral reversal). A healthy portion of the vas is isolated both proximally and distally to the prior vasectomy site and secured with Babcock clamps. It is usually preferred to avoid violating the tunica vaginalis of the testis and care should be taken to preserve the periadventitial sheath of the vas to preserve its blood supply.

A 90° transection of the vas is performed at both ends, preferably using a slotted nerve-holding clamp (Accurate Surgical and Scientific Instrument Corp., Westbury, NY). The obstructed segment, along with any prior surgical clips or sperm granuloma, is excised. Fluid is coaxed from the testicular side of the vas and examined under the microscope for spermatozoa. The abdominal portion is cannnulated with a 24-G angiocatheter and 5–10 mL of saline or dilute methylene blue solution is slowly injected to confirm patency.

We recommend utilizing a Microspike Approximator clamp (ASSI Corp., Westbury, NY) to stabilize both ends of the vas during the anastomosis (Fig. 27.9). Anastomotic techniques vary, for the modified 2-layer technique at least four full-thickness interrupted 9–0 double-armed nylon sutures are placed at the 12, 3, 6, and 9 o'clock positions, followed by an additional four or more partial-thickness sutures. We recommend using double-armed 9–0 or 10–0 ethicon or Sharpoint nylon (Surgical Specialties Corp., PA) sutures for the anastomosis. The mucosal lumen can be gently dilated with the microvessel dilator as needed to facilitate suture placement. After the three anterior full-thickness sutures are tied, two partial-thickness sutures are placed.

The vas deferens is rotated 180° by flipping the approximating clamp. The lumen is irrigated with heparinized lactated Ringer's prior to placing the final full-thickness suture to prevent clot formation. The remaining full-thickness suture is placed followed by interrupted partial-thickness sutures, which are then tied.

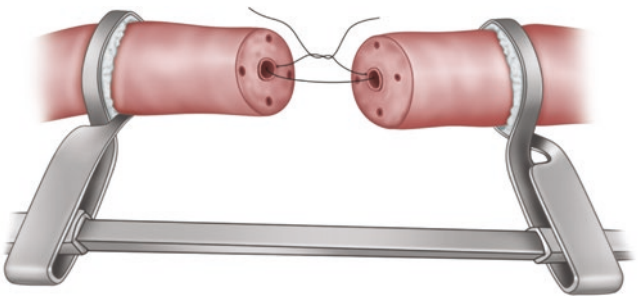

Fig. 27.9 A microspike approximating clamp is used to stabilize the proximal and distal ends of the vas during anastomosis

Orchiectomy

Orchiectomy has been shown to significantly decrease pain in 40–75 % of patients [42]. Small studies suggest that inguinal orchiectomy is associated with improved pain relief rates when compared to a scrotal approach [43]. Advantages to this approach include technical ease and ability to easily perform under sedation if necessary. However, most contemporary authors agree that orchiectomy is a treatment of last resort given its somewhat modest success rate.

To perform an inguinal orchiectomy, the initial incision is similar to that performed for MDSC. The spermatic cord is isolated and secured with a penrose drain. The surgeon uses blunt dissection around the spermatic cord down to the level of the pubic tubercle. The surgeon's finger should easily pass posterior to the cord along the floor of the inguinal canal. The surgeon should then push the testis from the base of the hemiscrotum into the incision to facilitate delivery of the testis. Blunt dissection and electrocautery may also be employed to free the testis from any further fascial attachments (Fig. 27.10). Care should be taken while dividing the gubernacular attachments of the testis, to avoid button-holing of the skin. The gubernacular attachments are often quite vascular, and may require 3–0 chromic ties for hemostasis.

The spermatic cord is divided, using several 2–0 permanent ties. We typically isolate and tie the vas deferens separately from the remaining cord. The specimen is

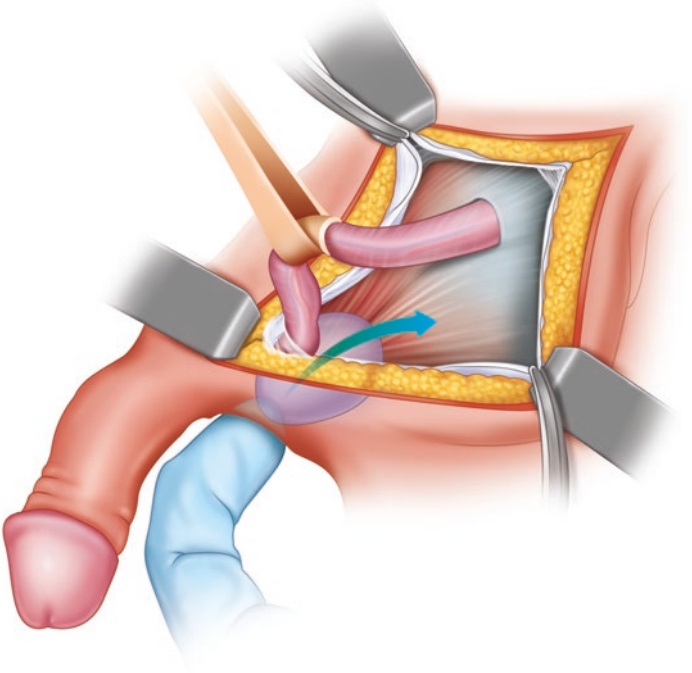

Fig. 27.10 With gentle traction on the spermatic cord, which is secured via a penrose drain, the surgeon gently pushes the testis from the base of the hemiscrotum toward the incision to facilitate testis delivery

removed and the wound is irrigated. Meticulous hemostasis is achieved prior to closure and if necessary a small ¼-inch Penrose drain may be placed in the scrotum prior to closure. A 3–0 absorbable suture is used to re-approximate the external oblique aponeurosis and 4–0 absorbable subcuticular suture for skin.

Conclusion

CSCP may occur due to a number of underlying conditions. A thorough history and physical examination is critical to the evaluation and management of this disease process and the steps are outlined in Fig. 27.1. Readily reversible causes such as those listed above should be identified and treated. Pelvic floor physiotherapy should be offered to patients with signs and symptoms of pelvic floor dysfunction. Medical management options for idiopathic CSCP may include NSAIDs, empiric antibiotics, tricyclic antidepressants, and calcium-channel modulators, all of which have had variable reported success rates. A critical diagnostic tool is the spermatic cord block. If the patient experiences a 50 % or greater temporary improvement in pain, surgical management is offered. MDSC has the highest reported success rates and is advantageous in that the testis is spared. Epididymectomy may be indicated for pain localized to the epididymis. Vasectomy reversal may be an option for post-vasectomy pain syndrome, though MDSC should be considered first-line for most patients as it currently has higher reported success rates without affecting the patient's sterility status. Orchiectomy should be considered a treatment of last resort given its associated morbidity with modest success rates.

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