Neuromodulation for Chronic Pelvic Pain

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Overview

The goal of this chapter is to provide an in-depth overview of the pathophysiology of chronic pelvic pain (CPP), more specifically interstitial cystitis/painful bladder syndrome (IC/PBS) as well as review the AUA IC/PBS treatment guidelines with an emphasis on neuromodulation.

Pathophysiology of Chronic Pelvic Pain

The pelvic floor plays a critical role in supporting the pelvic viscera, as well as permitting the storage and evacuation of urine and feces, sexual function and, in women, parturition. Given these complex functions, it follows that the pelvic viscera and musculature would be at risk for chronic pain states. The nature of pelvic innervation further complicates the matter, as the sympathetic, parasympathetic, and somatic nervous systems all play a role, sometimes acting in consort and at other instances, singularly. The pelvic structural configuration and complex neuroanatomy make identifying noxious stimuli in this area troublesome. Indeed, delays in diagnosis can lead to a delayed treatment, which may risk conversion of an acute, unpleasant stimulus into a state of CPP [1].

CPP is a complex condition defined as "nonmalignant pain perceived in the pelvis in either men or women.In the case of documented nociceptive pain that becomes chronic, the pain must have been chronic or continuous for at least 6 months" [2]. This disease can be debilitating, with negative cognitive, behavioral, sexual, and emotional consequences that have a major impact on quality of life. CPP is seen more commonly in the female population, and was estimated in 2010 to affect over nine million American women [3]. The direct costs of CPP have been estimated at over $2.8 billion [4].

The etiology of CPP is likely multifactorial and variable between patients, but development of this pain syndrome is more common in women who have a history of endometriosis, sexual abuse [5, 6], vulvar vestibulitis, fibromyalgia [7], and irritable bowel syndrome [8]. In men, the most commonly suspected inciting factor is prostate pain, arising from either infectious or aseptic inflammatory etiologies [9, 10]. There is, however, no gold standard for diagnostic algorithm of chronic pelvic pain, and it remains a diagnosis of exclusion.

Although unclear, the pathophysiology of CPP seems to parallel many common centralized neuropathic and sympathetically driven pain models [1]. The prevailing hypothesis is

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that an insult or injury damages a specific structure or organ, leading to either: (1) somatic pain from skin, muscles, or soft tissues transmitted via sensory afferent nerves, or (2) visceral pain originating from a viscous structure transmitted through autonomic or sympathetic fibers (or both), which over time develops into neuropathic pain characterized by unpleasant paresthesias, allodynia, and hyperalgesia [11]. Just as patients with complex regional pain syndrome suffer hyperesthesia and allodynia in the affected extremity, patients with CPP often experience similar painful sensations with routine pelvic functions, such as urination, sexual intercourse, or ovulation. Indeed, in 2003, Janicki and colleagues postulated that CPP was a variant of complex regional pain syndrome, secondary to an inciting insult and subsequent "wind-up" phenomenon that subsequently hypersensitized local pelvic neurons, leading to the perception of pain with non-noxious stimuli [12].

In a pelvic medicine practice, one condition commonly associated with chronic pelvic pain is IC/BPS. IC/BPS is characterized by urinary frequency, urgency, dyspareunia, nocturia, and pelvic pain [13]. In 2009, the Rand Interstitial Cystitis Epidemiology study detailed a prevalence of 3–6% in the general population, affecting approximately 3.4 million US women [14].

The exact causal cascade of IC/BPS remains elusive though many experts agree that a defect in the urothelial glycosaminoglycan layer is the most likely primary underlying factor [3]. When the urothelium is exposed to urine due to inadequate GAG covering, mast cell activation occurs within the bladder wall, generating an influx of potassium ions that upregulates the afferent nerves, which in turn activate more mast cells, creating a positive feedback loop that leads to increased sensory nerve fiber activity in the bladder, chronic inflammation, and ultimately neuropathic pain, which can be manifested through visceral allodynia and hyperalgesia of the bladder and adjacent pelvic organs [15].

AUA Guidelines for Treatment of Interstitial Cystitis/Bladder Pain Syndrome

In an effort to clarify and standardize care for patients with IC/BPS, the American Urological Association published guidelines in 2014 [16]. With regard to diagnosis, the authors recommend that basic assessment should include "a careful history, physical examination, and laboratory examination to rule symptoms that characterize IC/BPS and rule out other confusable disorders." Moreover, they encourage that baseline voiding symptoms and pain scores be captured, in order to measure subsequent treatment effects. Per the diagnostic guidelines, cystoscopy and urodynamics are not necessary for the diagnosis of IC/BPS, but may be considered in complex presentations.

Treatments that may be offered are divided into first- through sixth-line groups based on the potential benefits to the patient, potential severity of the side effects, and reversibility of the treatment.

First-Line Treatments: Patient Education and Lifestyle Modification

First-line treatments should include patient education regarding normal bladder function and what is known and not known about IC/BPS. The multimodal approach to therapy should be explained to patients, as well as the rationale for a stepwise approach to therapy. Behavioral modification strategies include manipulating urine concentration and/or volume, application of local heat or cold to the suprapubic region, avoidance of foods known to irritate the bladder, meditation, guided imagery, pelvic floor muscle relaxation, and bladder training to suppress urinary urgency [17–20]. These interventions are recommended based on an NIDDK multicenter trial focused on treatment naïve IC/BPS patients. After undergoing a standardized education and behavioral modification program, including increased understanding of bladder and voiding physiology, stress management strategies, and avoidance of symptom triggers, 45% of patients

reported markedly or moderately improved symptoms on the Global Response Assessment [18]. In addition to global management of psychological stress, the guidelines also emphasize that clinicians may want to include multidisciplinary assistance when appropriate for management of factors that may exacerbate IC/BPS, such as irritable bowel syndrome symptoms, endometriosis, recurrent vaginitis/vestibulitis, menstrual pain, panic attacks, depressive episodes, and the like.

Second-Line Treatments: Physical Therapy, Pain Management, Medications, and Intravesical Instillations

Second-line treatments are numerous. They include manual physical therapy techniques, multimodal pain management, provision of certain medications (i.e., amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate), and instillation of intravesical therapies, such as DMSO, heparin, lidocaine, or a combination thereof.

Patients with IC/BPS often exhibit tenderness and/or banding of the pelvic floor musculature [21, 22]. It is unclear if these musculoskeletal findings represent primary pain generators or are themselves secondary phenomena elicited by the primary bladder pain of IC/BPS. Regardless of etiology, literature supports that manual physical therapy can provide symptom relief by treating these soft tissue abnormalities [23–25]. Preferred physical therapy techniques include myofascial and trigger point release. These targeted interventions fared better than global therapeutic massage in a 2012 randomized controlled trial, with 59% of patients undergoing myofascial release reporting moderate or marked improvement, versus only 26% of those receiving massage therapy [25]. Pelvic floor strengthening interventions, such as Kegel exercises, may exacerbate symptoms and should be avoided.

Multimodal pain management is encouraged in the AUA IC/BPS guideline. The goal of pharmacotherapy is to find a medication regimen that will provide significant pain relief with minimal side effects; tools include urinary analgesics, NSAIDs, narcotics, and a variety of non-opioid medications now being used for treatment of chronic pain, such as antidepressants, antiepileptics, and the like. The panel's clinical experience reflected diverse approaches to effective pain management, ranging from primary management by the urologist to use a multidisciplinary team incorporating an anesthesiologist or pain specialist provider. Complementary therapies, including physical therapy, psychological counseling, and stress management, are also recommended. Ultimately, the panel concluded that "the decision regarding how to approach [pain management] depends on the judgment and experience of the involved clinician, the severity of the patient's symptoms, and the availability of expertise and resources."

Also included in second-line therapies are a variety of oral medications directed specifically at the underlying mechanisms of IC/BPS, including (in alphabetical order) amitriptyline, cimetidine, hydroxyzine, and pentosan polysulfate. Amitriptyline has central and peripheral anticholinergic actions, it blocks the active transport system in the presynaptic nerve ending that is responsible for the reuptake of serotonin and noradrenaline, and it is a sedative with action that is presumably centrally based but is perhaps also related to antihistaminic properties [18]. This may explain the potential benefits in patients with IC/BPS. One randomized, controlled trial reported efficacy of oral amitriptyline (25 mg daily titrated over several weeks to 100 mg daily if tolerated) to be superior to placebo at 4 months, with 63% of the treatment group clinically improved compared to 4% of the placebo group [26]. However, side effects, including drowsiness, sedation, and nausea, were very common and were the major reason for withdrawal from the study.

The antihistamine cimetidine is proposed to benefit IC/BPS patients by competitive antagonism of the H_2 histamine receptor [27]. In their randomized controlled trial, Thilagarajah and colleagues reported efficacy of oral cimetidine (400 mg twice daily) to be statistically significantly superior to placebo in terms of total

symptoms, pain, and nocturia after 3 months of treatment [27]. Two observational studies reported that oral cimetidine (300 mg twice daily or 200 mg three times daily) resulted in 44–57% of patients reporting clinically significant improvement in symptoms at follow-up intervals of one and more than 2 years [28, 29]. No adverse events (AEs) were reported in these studies.

Hydroxyzine is a long-standing oral pharmacotherapeutic agent used for IC/BPS patients, on the principle that it prevents bladder mastocytosis via its antihistamine effects [30]. There is one randomized, controlled trial that, though underpowered, failed to show a statistically significant difference in symptom control relative to placebo with hydroxyzine therapy [31]. In contrast, an observational study reported 92% of patients experienced clinically significant improvement on hydroxyzine therapy, though this population all had systemic allergies, and may represent a subset of patients that is more likely to respond to hydroxyzine [32]. Adverse effects were common, but usually minor and self-limited, including short-lasting sedation and subjective weakness.

Pentosan polysulfate is hypothesized to improve IC symptoms by adhering to the bladder wall, buffering against cell permeability and penetration by irritating solutes. It is by far the most-studied oral medication for use in IC/BPS. Indeed, the AUA panel was able to consider seven randomized trials reporting on more than 500 patients including five trials that compared PPS to placebo, one trial that examined PPS dose–response effects, and one that compared PPS to cyclosporine A. Ultimately, after consideration of the data, the panel concluded that there was a statistically significant but clinically weak improvement in IC/BPS symptoms with use of pentosan polysulfate [16]. Adverse events were rare and generally not serious. The panel did specify that pentosan polysulfate appears to have lower efficacy in patients with Hunner's lesions.

Finally, intravesical therapies are also included in the second-line category, including (listed in alphabetical order) dimethyl sulfoxide (DMSO), heparin, and lidocaine instillations. DMSO is an organosulfur compound that is believed to reduce inflammation, relax the detrusor muscle, and act locally as an analgesic [33]. It may also cause temporary urothelial injury that allows for better penetration of other agents. If DMSO is to be used, the panel recommended limiting dwell time to 15–20 min, as DMSO is rapidly absorbed into the bladder wall and longer dwell periods are paradoxically associated with worsening pain. Additionally, the panel noted that if DMSO is administered in conjunction with other agents, such as heparin, sodium bicarbonate, steroid, or lidocaine, it potentially enhances absorption of these other substances, which could yield toxicity, particularly from local anesthetics such as lidocaine. No clinical studies have addressed the safety or potential for increased efficacy of these "cocktail" regimens relative to DMSO alone

Heparin is a highly sulfonated glycosaminoglycan (GAG) best known for its use in anticoagulation. However, when instilled intravesically, it can act as an exogenous GAG to decrease urothelial penetrability in IC patients [33]. Side effects with heparin instillation are infrequent and appear minor. Placebo-controlled trials are lacking.

Intravesical lidocaine functions as a topical anesthetic. Notably, alkalinization increases urothelial penetration of lidocaine and therefore is believed to increase efficacy; however, this can increase systemic absorption and potential toxicity. Relief is generally short term and limited to 2 weeks or less. Researchers are attempting to remedy this problem with an implantable lidocaine-eluting device, but this technology is not yet available to patients [34].

Third-Line Treatments: Hydrodistension and Fulguration of Hunner's Lesions

As third-line treatment, cystoscopy under anesthesia with hydrodistension can be performed. This intervention should be at low pressure (60–80 cm H2O) and for short duration (<10 min). This intervention is intended to serve three purposes: first, prior to distension, to inspect the bladder for other potential sources of symptoms

(bladder stones, tumors, etc.) and for Hunner's lesions; second, the distension itself may offer therapeutic benefit, and finally distension allows for disease "staging" by determining the anatomic as opposed to functional bladder capacity, thus identifying the subset of patients with substantially reduced capacity due to fibrosis. Three observational studies reported that one or two exposures to low-pressure, short-duration hydrodistention resulted in clinically significant relief of symptoms for a subset of patients. However, these benefits did decline over time: at 1-month efficacy ranged from 30 to 54%; at 2–3 months, from 18 to 56%; at 5–6 months, from 0 to 7% [35–37]. No adverse events were reported. The panel warns that potential benefits must be balanced against the possibility of a flare in symptoms following instrumentation.

During cystoscopy, if Hunner's lesions are visualized, the panel recommends fulguration with laser or electrocautery and/or injection of triamcinolone. Patients with Hunner's lesions who experience relief after fulguration or injection should be counseled that periodic retreatment is often required to maintain symptom control. Adverse events for these interventions are rare in the literature though the panel does recommend that patients undergoing laser fulguration be warned of the risk for forward energy scatter and resultant delayed bowel perforation.

Fourth-Line Treatments: Intradetrusor Botulinum Toxin and Trial of Sacral Nerve Stimulation (SNS)

Intradetrusor onabotulinum toxin-A (BTX-A) injection is a fourth-line off-label therapy for IC/BPS. It has more recently been combined with hydrodistension in the IC/BPS population, and clinicians are becoming more comfortable repeating dosing (typically 100 units, u) when symptoms return. A single RCT has been performed, by Kuo and Chancellor in 2009 [38]. Three groups were compared: Botox 200u with hydrodistension 2 weeks after injection, Botox 100u with hydrodistension at the time of initial injection, and Botox 100u with hydrodistension at the time of initial injection and 2 weeks afterward. Side effects, including elevated post-void residual and dysuria were markedly higher in the 200u group, such that randomization to this group was stopped prior to completion of the study. Patients were followed for 2 years, and success ranged from 80% at 3 months to 47% at 24 months in the BTX-A 200+ hydrodistension group, 72% at 3 months to 21% at 24 months in the BTX-A 100 + hydrodistension group, and 48% at 3 months to 17% at 24 months in the hydrodistension only group.

Pinto injected 100u into the trigone with retreatment at symptom return and followed patients for up to 3 years [39]. All patients reported subjective improvement at 1- and 3 months follow-up. Pain, daytime and nighttime voiding frequency and quality of life (QoL) improved significantly. Treatment remained effective in greater than 50% of the patients at 9-month follow-up. Retreatment was also effective in all patients with return of symptoms (62% of patients), with similar duration. Nearly one-third of patients had UTIs post-treatment 2 (but not after the other treatments); there was no urinary retention or clean intermittent catheterization required in this study. In the absence of placebo-controlled studies, the true effect of Botox injection for IC/BPS remains unclear. However, the existing studies suggest that a subset of patients will experience symptom relief for several months after treatment. Given the frequency and potential seriousness of side effects with the 200u dose, the AUA guideline panel recommends injection of the 100u dose as a fourth-line intervention for IC/BPS.

The guidelines also state that a trial of SNS may be offered to patients with refractory IC/BPS symptoms. Nonetheless, it is important to note that SNS is currently not FDA approved for the treatment of CPP or IC/BPS. However, many patients meet the urgency/frequency indication, for which SNS is FDA approved. While there are no prospective randomized trials a variety of observational studies were considered by the panel [40–43]. Follow-up ranged from 60 to 86 months across the studies, with success rates ranging from 72 to 80%. Significant improvements

in urgency, frequency, nocturia, voided volumes, and pain scores were noted amongst the studies. Device explantation for lack of efficacy or intractable side effects occurred in 0–28% of patients, and revision procedures for battery replacement, lead revision, or site change ranged from 21 to 50%. Mean battery life was approximately 93 months. Notably, Powell and Kreder note that patients are significantly less likely to proceed with stage 2 SNS implantation after PNE, relative to a stage 1 SNS trial [43]. Given the paucity of high-quality evidence and the moderately invasive nature of SNS, this remains a fourth-line treatment option per guidelines.

Fifth-Line Treatments: Cyclosporine A Therapy

Cyclosporine A (CyA) immunomodulatory therapy has been designated as a fifth-line intervention for refractory IC/BPS. One randomized trial compared CyA versus PPS, and demonstrated 75% improvement in the patients taking CyA versus only 19% in those on PPS after 6 months of treatment [44]. One recent retrospective study in the USA reported on 44 patients followed for a mean of 15 months, and reveals 59% reporting a meaningful clinical response with CyA therapy [45]. Notably, success rates were much higher in patients with Hunner's lesions (85% vs. 30% in those without). AE rates were high, with half of patients reporting at least one. These included rising serum creatinine, hypertension, alopecia, cutaneous lymphoma, mouth ulcers, and gout flares. Amongst the Hunner's lesion group, attrition due to AEs decreased the intention-to-treat effectiveness to 68%. Ultimately, these data suggest substantial efficacy of CyA, particularly in patients with Hunner's lesions; however, the lack of long-term data and the potential for serious adverse events is not trivial. The AUA guidelines panel encourages clinicians unfamiliar with CyA administration to seek guidance from experts regarding dosing and monitoring.

Sixth-Line Treatments: Major Surgical Intervention

Per AUA guidelines, major surgical interventions, such as substitution cystoplasty and urinary diversion with or without cystectomy, may be undertaken in carefully selected patients for whom all other therapies have proven ineffective with regard to symptom control or quality of life. The panel cautions that "major surgery should be reserved for the small proportion of patients with severe, unresponsive disease, who are motivated to undergo the risks and lifelong changes associated with irreversible major surgery." The panel emphasizes that pain relief is not guaranteed, even with this aggressive intervention, as pain can persist even after cystectomy, especially in non-ulcer IC/BPS [46].

The AUA guidelines committee also comments on inappropriate therapies. Neither long-term oral antibiotic therapy nor long-term systemic steroid treatment should be offered. Similarly, intravesical Bacillus Calmette–Guérin (BCG) vaccine should not be administered. In terms of surgical interventions, the panel specifies that high-pressure, long-duration hydrodistension is potentially harmful and should not be offered. The panel concludes by emphasizing that the IC/BPS population constitutes an underserved group in need of adequate medical management, and encourages future efforts both at the basic science and clinical levels to develop better, safer treatment modalities for this complex condition. In particular, there is emerging interest in determination of an IC/BPS biomarker, both for diagnosis and outcomes measurement.

SNS for the Treatment of CPP and IC/PBS

An understanding of pelvic neuroanatomy is critical prior to consideration of sacral neuromodulation for CPP. The pelvic viscera are parasympathetically innervated by the S2–S4 nerve roots, and sympathetically innervated by the T12-L2 nerve roots. The parasympathetic outflow is transmitted via the pelvic splanchnic nerves (S2–S4), which converge into the

preganglionic pelvic splanchnic nerves. Sympathetic input to the pelvis arises from the thoracolumbar cord by way of the superior hypogastric plexus. The somatic afferents and efferents to the pelvis originate from the S2–S4 cord via the pudendal nerve, with S3 offering the primary supply to the anterior perineal musculature [1].

The first reported use of pelvic nerve electrostimulation occurred in 1878, when Saxtroph described his treatment of patients with urinary retention due to an a contractile bladder [47]. Over time, this modality evolved into modern day sacral neuromodulation when, in 1971, Nashold et al. described the first successful implantation of an SNS system to initiate voiding in a patient with spinal cord injury [48]. In 1981, Tanagho and Schmidt subsequently demonstrated that stimulation of the S3 nerve root could be applied to a variety of urologic pathologies, including incontinence and refractory urgency/frequency, by modulating detrusor and urinary sphincter function [49]. This research ultimately led to FDA approval of SNS for urinary urgency, frequency, and urgency incontinence in 1997. Later, in 1999, the SNS system was approved for idiopathic urinary retention and in 2011 for fecal incontinence. To date IC/PBS is not an FDA-approved indication for SNS.

The exact mechanism by which SNS modulates micturition remains unclear. It may activate or reset the somatic afferents involved with sensory processing and the micturition reflex pathways in the spinal cord [49]. Additional theories propose that SNS may interfere with the sympathetic signals to the bladder involved in the guarding and the vesicosympathetic reflexes, which control continence and filling, respectively [50]. On PET study, SNS has also been correlated with increased activity of the paraventricular gray area of the brain, which is involved in activation or inhibition of the micturition reflex [51].

Given that the etiology and pathophysiology of chronic pelvic pain can be hard to delineate and may vary between patients, if follows that the mechanism by which SNS may improve CPP symptoms is also unknown. However, most researchers agree that dysregulated central nervous system responses to non-noxious stimuli are the major underlying feature [52, 53]. Therefore, reason suggests that effective therapies work to modulate the nervous system. A possible mechanism for neuromodulation as therapy for CPP is based on the gate control theory, which states that pain perception depends on a pattern of peripheral nervous input. It is believed that a gate control mechanism is present at the spinal segment level that regulates the interaction between afferent nerve signals and pain sensation [54]. Interneurons of the spinal cord dorsal horn create gating components, and inhibition or facilitation of afferent fibers modulates pain signal input to the spinal transmission neurons. Impulses from the dorsal horn are controlled by a descending system containing fibers from the brainstem, thalamus, and limbic lobes [55]. Neuromodulation is believed to restore control at the spinal segmental gate as well as at the supraspinal sites such as the brainstem and limbic system nuclei, thereby "gating" peripheral stimuli and preventing the CNS signaling that leads to hyperalgesia. In essence, SNS restores the balance between excitatory and inhibitory impulses to and from the pelvic organs at the sacral and suprasacral levels.

Another possible mechanism of action lies in the treatment of underlying pelvic floor dysfunction. Hypertonia of the pelvic floor is commonly associated with CPP. SNS may inhibit inappropriate excitation of the pelvic floor musculature, thereby facilitating voiding and other pelvic floor functions [56].

SNS has shown consistent efficacy in the treatment of refractory overactive bladder, idiopathic urinary retention, and fecal incontinence. However, while studies suggest that SNS can relieve the concomitant voiding symptoms seen in IC/BPS, pain relief has proven more difficult to achieve [57]. One evolution of the therapy to address this deficit includes bilateral, rather than unilateral, lead placement, since pain is seldom unilateral [52]. Subsequent small-scale studies have suggested reductions in pain and narcotic use with this more aggressive approach to SNS. Indeed, Maher reported reduction in pain of

27% with SNS in a cohort of 15 patients [58], and Siegel described 60% improvement in pain with ten patients followed for a median of 19 months [59]. In addition to IC/BPS, SNS has proven effective for treatment of other pathologies, such as coccydynia, vulvodynia, anorectal pain, and pain from pelvic floor muscle dysfunction in small-scale studies [1]. Nonetheless, the extent of pain control varies greatly amongst patients and from one study to the next, and research has failed to consistently demonstrate an overall improvement in quality of life for CPP patients following SNS [60].

Everaert and colleagues performed one of the initial studies suggesting improvement in pelvic pain with SNS in a cohort of 26 patients with CPP refractory to conservative management [61]. S3 stimulation was effective in 16 of 26 patients, 11 of whom underwent implantation. At a mean follow-up of 36 months, all had improvement in pain, achieving pain scores <3/10 and reporting >50% pain relief relative to baseline.

Comiter prospectively studied a group of 25 patients with refractory IC/BPS undergoing trial of SNS [13]. Of these, 17 had at least 50% improvement in their voiding and pain symptoms and went on to permanent implantation. Average reported pain decreased from 5.8 to 1.6 on a 0–10 visual analog scale (VAS). Ultimately, 94% of patients who underwent implantation reported sustained improvement in all pain and voiding parameters at their last postoperative visits, with a mean follow-up of 14 months.

Whitmore et al. conducted a prospective multicenter clinical trial in 2003, for women with refractory IC/BPS [62]. They enrolled 33 patients with intractable IC/BPS who failed alternative therapies. Analysis of voiding diaries showed statistically significant decreases in urinary frequency, bladder pain, average volume voided, and maximum volume voided following SNS.

Siegel and colleagues used SNM to treat ten patients with refractory CPP, inserting leads into S3 for eight patients and S4 in two patients [59]. At follow-up of 19 months, 9 of the 10 patients reported decreased pain, with mean hours of pain per day decreasing from 13.1 to 6.9 following SNS implantation. The severity of pain decreased from 9.7 to 4.4 on a 0–10 pain scale.

Maher and colleagues prospectively evaluated 15 women undergoing SNS with IC/BPS using pain scores, voiding diaries, and validated quality of life surveys [58]. Mean bladder pain decreased from 8.9 to 2.4 points on a 0–10 pain scale. Quality of life parameters related to social functioning, bodily pain, and general health significantly improved during the stimulation period. Of the subjects, 73% requested to proceed to complete device implantation.

Peters and Konstandt retrospectively assessed the efficacy of long-term SNS in treating chronic pelvic pain associated with IC/BPS in a cohort of 21 patients [63]. Of these, 20 reported moderate or marked improvement in pain following SNS implantation. In those using chronic opioids, the mean dose decreased by 36% and 4 of 18 patients stopped all narcotics after SNS implantation.

Several studies have assessed the long-term efficacy of SNM for IC/BPS. Rackley and colleagues followed 22 patients with refractory IC/BPS who underwent implantation of SNS [64]. Over a 2-year period, five devices were explanted; two devices were removed because of infection and three because of failure to maintain efficacy. Amongst those whose devices remained in situ, 13 expressed continued benefit and 4 complained of loss of efficacy. The overall success rate at 2 years was 48%, suggesting that the device may lose some degree of success over time.

In 30 patients who underwent SNS, Marinkovic et al. report a 64% reduction in pain at an average of 86 months follow-up [42]. Similarly, Powell and Kreder report 78% ongoing efficacy in their cohort of nine patients followed for 5 years [43]. In their retrospective review, Gajewksi and Al-Zahrani reported on their cohort of 46 patients who underwent SNS implantation for CPP; these patients were then followed for an average of 62 months, and 13 of the 46 (28%) underwent removal, most commonly for poor outcome or painful stimulation [40]. In a follow-up study of 21 female patients with SNS for bladder pain syndrome, they had an implant rate of 52% after

PNE, with durable long-term improvements in reported visual analog pain scale scores at 5 years of follow-up [41].

Given the inconclusive data regarding long-term efficacy of SNS, management of patient expectations at the time of trial stimulation and device implantation is essential. Patients must be told that SNS is not FDA approved for the treatment of chronic pelvic pain and counseled that the long-term durability of SNS for management of chronic pelvic pain remains unclear.

Technical Considerations and Lead Placement

Despite interest in SNS for treatment of chronic pelvic pain, conflict remains regarding the correct lead position for optimal benefit. Targeting of non S3 nerve roots or multiple unilateral nerve roots, as well as bilateral stimulation, has been proposed. Indeed, some authors even postulate that a spinal cord stimulator, rather than a sacral nerve stimulator, offers the greatest potential for benefit [1]. With neuropathic pelvic pain, the sacral portion of the cord theoretically appears to be the most ideal target for neuromodulation. However, even though the pelvis receives both somatic and visceral innervation from the sacral cord, the unpredictable course of the sympathetic nervous system fibers means that some innervation could escape neuromodulation directed at the sacral cord, diminishing pain relief. Thus, coming to consensus regarding optimal lead placement proves difficult.

For FDA-approved indications, SNS targets the S3 nerve root. However, some authors have inquired as to whether targeting other nerve roots may offer greater benefit for CPP patients. In their 2008 study, Zabihi and colleagues evaluated the efficacy of bilateral caudal epidural sacral neuromodulation for the treatment of refractory pelvic pain in the setting of IC/BPS [52]. This was accomplished by deploying a quadripolar lead in a retrograde fashion under fluoroscopy over the S2–S4 nerve roots. In their study, 30 consecutive female patients underwent bilateral S2–S4 sacral neuromodulation via the retrograde approach. Of these patients, 77% had good responses and underwent permanent implantation. At last follow-up (mean 15 months, minimum 6 months), quality of life measures were significantly improved relative to pre-implantation, with mean 40% improvement in pain scores by VAS. Thus, the authors conclude that in patients with refractory CPP, bilateral caudal epidural sacral neuromodulation is another possible mode of treatment.

Since CPP is likely mediated by more than one sacral root, either unilaterally or bilaterally, the stimulation of only one nerve root may not be sufficient for symptom control. To date, no trial has compared unilateral versus bilateral stimulation although several studies suggest efficacy of the bilateral approach. Steinberg and colleagues retrospectively reviewed 15 patients who underwent bilateral S3 stimulators for refractory IC/BPS symptoms, including pain [65]. At a mean follow-up of 14 months, the mean decrease in frequency and nocturia was 10.4 voids and 2.6 voids, respectively. Pain scores were not captured independently, but patient satisfaction did improve as measured by the urinary distress inventory short form, which queries pain levels.

Future Directions for Treatment of CPP Using Neuromodulation

In addition to SNS, other neuromodulatory approaches have been suggested for the treatment of CPP, including posterior tibial nerve stimulation (PTNS), pudendal nerve stimulation (PNS), and caudal epidural S2–S4 SNS placement. Kim et al. evaluated the effect of PTNS in 15 patients (10 women and 5 men) with CPP in an open prospective clinical trial [66]. After 12 weeks of PTNS, 60% of patients had an improvement of more than 50% on a visual analog pain scale, and 40% achieved a mean VAS less than 3. Van Balken et al. evaluated PTNS in 33 patients with CPP as their primary complaint in a prospective multicenter trial [67]. In 21% of patients, mean VAS decreased more than 50%, and after 12 weeks of treatment, 7 patients (21%) had a mean VAS less than 3. In aggregate, PTNS boasts modest overall success rates for chronic

pelvic pain, and randomized, placebo-controlled trials with longer term follow-up are warranted.

The pudendal nerve originates from the S2, S3, and S4 nerve roots, such that PNS provides broader stimulation compared to targeting S3 alone. In a retrospective study by Peters et al., 84 patients underwent PNS for IC/BPS and overactive bladder [68]. A positive pudendal response, defined as greater than 50% improvement in symptoms following pudendal lead placement, was achieved in 71% of subjects. Notably, almost all (93%) with a history of failed sacral neuromodulation responded to the pudendal lead. This may be due to the unique ability of the pudendal approach to offer increased afferent stimulation through the S2–S4 nerve roots. However, accurate placement of the tined lead in the pudendal location can prove challenging and time consuming for the surgeon. To combat this pitfall, Heinze and colleagues devised the STAR (ischial Spine, ischial Tuberosity, acetabulum, and anal Rim) technique using fixed anatomic landmarks to improve PNS placement in their 2014 pilot study using this technique in 20 patients with refractory chronic pelvic pain [69]. In the ten patients who underwent placement by the STAR technique, they noted a mean operative time of 85 min for bilateral PNS lead placement, versus a mean of 105 min for unilateral PNM lead placement using techniques previously described in the literature. In the patients who underwent STAR PNS placement, there was a statistically significant decrease in pain at the conclusion of the 4-week trial, with 90% proceeding to generator implantation.

In a follow-up study in 2007, Peters and colleagues compared sacral neuromodulation versus PNS for refractory IC/BPS symptoms [70]. In their study, 22 patients with refractory IC/BPS underwent placement of a tined lead at S3 and another lead at the pudendal nerve. Each was tested in a blinded manner for 7 days. The authors found that the time required to place a pudendal lead was about 30% less than that required for a sacral lead. Of the 22 patients, 77% responded and had a permanent implant placed. PNS was chosen as the better lead in 77% and SNS in 24%. The order in which the lead was stimulated had no effect on the final lead implanted, and there was no measurable "carry-over" effect. The overall reduction in symptoms was 59% for PNS and 44% for SNS, leading the authors to conclude that PNS may offer advantages beyond traditional SNS in some patients with refractory IC/BPS.

Caudal epidural SNS also provides stimulation of the S2–S4 nerve roots. This procedure involves deploying a quadripolar lead over the S2–S4 sacral nerve roots. While literature regarding this technique is scarce, Zabihi et al. did evaluate the efficacy of bilateral caudal epidural SNS for the treatment of refractory chronic pelvic pain and IC/BPS in a 2008 study [52]. In his trial of 30 patients, 77% had a successful trial stimulation and underwent permanent implantation. At mean follow-up of 15 months, median pain scores were improved by 40% relative to baseline. Similar improvements were seen on validated patient symptom questionnaires. On average, patients reported a 42% improvement in symptoms. However, four patients eventually underwent explantation due to treatment failure. Subsequent studies are still needed.

Before SNS is widely adopted for the treatment of chronic pelvic pain, further investigation is warranted. Indeed, large-scale, multicenter randomized controlled trials with long-term follow-up data, comparing SNS with other non-neuromodulatory modalities, as well as non-sacral neuromodulation, for treating CPP would help clinicians counsel patients and offer appropriate interventions. Moreover, such studies could offer insight into predictors of SNS treatment response. Given that this intervention is moderately invasive, it is important to avoid it in patients who are unlikely to benefit and rather target it toward likely responders, and we currently do not have high-quality evidence regarding how to make this distinction.

Summary

SNS has been shown to be an effective treatment for refractory non-obstructive urinary retention, urgency/frequency, urgency urinary incontinence, and fecal incontinence. However, SNS currently has no FDA approval for the treatment

of chronic pelvic pain. Since many patients with CPP experience insufficient results with conservative treatment, minimally invasive intervention such as SNS could offer a promising middle ground that avoids a major surgery, such as bladder augmentation or urinary diversion. The currently published results suggest that SNS may be a valuable alternative treatment option for CPP patients. However, the majority of published studies were small, retrospective, and lacking in long-term follow-up. Inclusion and exclusion criteria varied between studies and outcomes were not uniform. In particular, not all studies clarified improvements in voiding outcomes versus pain outcomes. These features make the current body of literature regarding SNS for CPP difficult to generalize. Large-scale randomized trials with long-term follow-up and clearly stated, strict inclusion criteria are needed in order to more thoroughly evaluate SNS as a treatment for CPP.

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