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REVIEW

# Neuromodulation for Management of Chronic Pelvic Pain: A Comprehensive Review

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## ABSTRACT

***Introduction***: Chronic pelvic pain (CPP) is a symptom that derives from a complex group of heterogeneous pathologies of the pelvic organs. The aim of this study was to review the available evidence on efficacy of neuromodulatory modalities including sacral neuromodulation, dorsal root ganglion stimulation, dorsal column neuromodulation, and pudendal nerve stimulation.

***Methods***: This narrative review focuses on updated information on neuromodulation for management of chronic pelvic pain. In 2022, we searched English-language studies on neuromodulation, pelvic pain, and chronic pain in a comprehensive search. We searched the fol-

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lowing databases: PubMed, Medline, SciHub, Cochrane Database of Systematic Reviews, and Google Scholar. We used the following combinations of keywords: neuromodulation, pelvic pain, chronic pain, chronic pelvic pain, pelvic pain treatment. We tried to include as many recent manuscripts as possible (within the last 3 years) but also included papers older than 3 years if they were particularly relevant to our topic. We also attempted to search for, use, and cite primary manuscripts whenever possible.

***Results***: CPP is a challenging entity to treat because of diagnostic inconsistencies and limited evidence for therapeutic modalities. Our review found evidence suggestive of benefit for all modalities reviewed but the data was of overall low quality with numerous limitations. The literature highlights a lack of randomized controlled trials for neuromodulatory therapies but suggests a growing role for such techniques in treating refractory chronic pelvic pain syndrome (CPPS).

***Conclusions***: This review explores the available evidence on efficacy of neuromodulatory modalities for CPPS and contextualizes the results with information about the type of neuromodulation, lead location and waveform, pain outcomes and assessment timepoints, and reported adverse effects.

**Keywords:** Neuromodulation; Chronic pain; Pelvic pain; Chronic pelvic pain; Pain treatment

**Key Summary Points**

Chronic pelvic pain (CPP) is a sign of various pelvic organ diseases. Chronic pelvic pain syndrome (CPPS) has several clinical manifestations, making a unified definition difficult

CPP is noncyclical pain with a 6-month duration that might affect physical performance and quality of life

This narrative review illustrates the variety of neuromodulatory methods that are available for the treatment of CPP, including sacral neuromodulation, conus medullaris stimulation, dorsal root ganglion (DRG) stimulation, dorsal column spinal cord stimulation (SCS), and pudendal nerve stimulation

All of the modalities we examined had evidence that appeared to be beneficial, but the data generally was of poor quality and had several flaws, such as varied research circumstances and small sample numbers

Our review draws attention to the dearth of randomized controlled studies for neuromodulatory treatments while also recognizing the expanding importance of these approaches for refractory CPPS

## INTRODUCTION

Chronic pelvic pain (CPP) is a symptom that represents a complex group of heterogeneous pathologies in specific pelvic organs. A consistent consensus definition continues to be elusive and perhaps appropriately so, considering the widely different clinical phenotypes that comprise chronic pelvic pain syndrome (CPPS). Broadly speaking, CPP is often defined as noncyclical pain that has a duration of at least 6 months with the potential to manifest with lower physical performance and quality of life [1].

CPPS has the potential to affect both men and women. A systematic review conducted in 2014 suggested that the lifetime prevalence of CPP ranged from 5.7% to 26.6%. The authors identified a scarcity of population-based prevalence studies and observed a number of obstacles to accurate estimation including lack of multidisciplinary studies, lack of statistical data and registration systems, lack of common definitions and consensus about CPP, inappropriate health system performance, and lack of education for both patients and clinicians [1]. An

accurate estimate of the incidence or prevalence of CPPS does not exist currently. Frustratingly, for patients in particular, inconsistent diagnosis and classification often manifest with self-management and inadequate referrals to specialists or multidisciplinary care teams [2].

Various groups and guidelines have advocated for individual treatment strategies aimed at identifying and targeting important characteristics of CPPS including predisposing factors and causes, chronic pain mechanisms for ongoing pain, associated visceral dysfunctions, associated musculoskeletal dysfunctions, emotional consequences, behavioral consequences, sexual consequences, and social consequences [3]. To support a multidimensional and multidisciplinary approach to management of CPPS, Shoskes et al. proposed a phenotype-based classification that comprised six domains including urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness (UPOINT) [4]. This approach has been supported by a systematic series of domains outlined by the International Continence Society Standardization for Terminology in CPP Syndromes. The domains detailed for CPPS include four domains involving the pelvic organs: lower urinary tract domain, female genital domain, male genital domain, and gastrointestinal domain. Two domains include sources that may be perceived in the pelvis: musculoskeletal domain and neurological domain. The final three domains detail factors that may influence the response to and impact of pain on the individual: psychological domain, sexual domain, and comorbidities [5]. Both classification structures are designed as clinical aids to ensure a logical and comprehensive mode of evaluation for a heterogenous syndrome.

In light of these expansive diagnostic challenges, interventional therapies including spinal cord stimulation have gained traction and popularity as a potential option for refractory CPPS. Novel targets for neuromodulation have continued to be identified under the original premise that the pathophysiology of CPPS may parallel some centralized, neuropathic and sympathetically driven pain models. In spite of the unique presentations and etiologies of CPPS, neuromodulation has demonstrated some efficacy with adequate and appropriate coverage to affected regions. Further research has continued to identify new targets and applications of neuromodulation in CPPS but identification and coverage of the pain transmission targets continue to be challenging [6].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## PELVIC PAIN MECHANISMS

Understanding the anatomy and neural pathways innervating the pelvic viscera is critical to identify appropriate neuromodulatory targets. The pelvis is an anatomic region located between the floor of the pelvic cavity and the pelvic brim. This area comprises both visceral and somatic structures with complex and varied innervations [7]. Visceral structures include the bladder, terminal ureters, urethra, ovaries, fallopian tubes, uterus, vagina, sigmoid colon, rectum, and associated vasculature and lymphatics. Somatic structures include the pelvic bones, ligaments, muscles, fascia, and body wall cutaneous dermatomes. Both somatic and visceral structures have the potential to cause CPP [8].

The somatic innervation of the pelvis derives from efferent motors fibers that originate from the spinal cord to innervate the skeletal muscle of the pelvic walls, pelvic floor, and perineum. Sensory afferent fibers transmit sensations from musculoskeletal organs and parietal peritoneum in addition to corresponding dermatomes and myotomes. The sacral plexus, formed by the lumbosacral trunk (L4 and L5 of lumbar plexus and anterior branches of S1–S4), provides somatic innervation of the pelvis including the levator ani, obturator internus, coccygeus, piriformis, gemellus, and quadratus femoris muscles. Innervation of the anterior and lateral abdominal wall originates from the intercostal nerves (T7–T11), subcostal nerve (T12), and iliohypogastric and ilioinguinal nerves (L1) [8].

The visceral innervation of the pelvis consists of efferent autonomic branches and

afferent branches [9]. The efferent autonomic system consists of sympathetic and parasympathetic fibers that supply the urethra, bladder, ureters, vagina, cervix, uterus, fallopian tubes, ovaries, sigmoid colon, rectum, anal canal, and visceral peritoneum in women. The afferent system transmits signals from abdominal wall, pelvic viscera, and visceral peritoneum [8, 10, 11]. A minimum of five pathways are believed to transmit nociceptive stimuli from the pelvis with three transmitting through the inferior hypogastric plexus [12]. The inferior hypogastric plexus is a major relay center and innervates the genital and reproductive tract, bladder, urethra, distal ureter, internal anal sphincter, and rectum. It also contributes to three other plexuses: rectal plexus, uterovaginal plexus, and vesical plexus. The superior hypogastric plexus supplies the ureteral, ovarian, common iliac, and inferior hypogastric plexuses [8]. Visceral afferents synapse to second-order neurons in the dorsal horn of the spinal cord with subsequent transmission to supraspinal regions for processing [11].

The efferent sympathetic neurons originate predominantly from the thoracolumbar spinal cord from T12 to L2 nerve roots and are transmitted via the superior hypogastric plexus. The efferent parasympathetic neurons originate from the S2 to S4 nerve roots and are transmitted in the splanchnic nerves [6, 10]. The phenomenon of vague or overlapping CPP symptoms is possibly explained by the idea that visceral nociceptors are through to be poorly myelinated or unmyelinated nerve endings that mediate both somatic and visceral stimuli. The input to the spinal cord is therefore influenced by somatic input and may participate in a "cross-talk" phenomenon in which afferent activation of a pelvic structure influences efferent output to another [8, 12].

## NEUROMODULATION

### Summary

Electrotherapy neuromodulation (referred to as "neuromodulation" henceforth) has been used for pain management since ancient times. Scrobonus Largus, court physician to emperor Claudius, reported treatment of headaches with electric eels (4–100 V, 100 Hz) in 46–47 AD [13]. The era of modern neuromodulation is thought to have started in the 1960s with deep brain stimulation, followed by spinal cord stimulation, for intractable pain. Over the next 50 years, technological advances have significantly broadened the field of neuromodulation and impact on patient outcomes [6].

Current neuromodulation techniques for CPP target the sacral roots, pudendal nerve, mid-thoracic spinal cord, conus medullaris, and dorsal root ganglion (DRG) [6, 14, 15]. Unfortunately, given the complex nature of diagnosing CPP, it is increasingly common that patients are not evaluated by pain management specialists until unsuccessful treatment by two or more specialists from other fields (e.g., gynecology). By this point, CPP has often evolved into a chronic phase, rendering techniques including physical therapy, nerve blocks, radiofrequency lesions, and pharmacologic options increasingly ineffective. In such patients, neuromodulation may be the last bastion of potentially effective therapy. While the efficacy of neuromodulation for CPP often depends on adequate lead positioning, a lack of consensus exists with respect to the optimal target and location of leads [6].

### Sacral Neuromodulation

Sacral neuromodulation (SNM) is an emerging minimally invasive treatment option for refractory CPP. SNM was first described by Tanagho and Schmidt in 1982 [16] and applied to human patients in 1988 [17]. Originally approved in 1997 by the US Food and Drug Administration (FDA) for urinary urge incontinence, urinary urgency-frequency, and non-obstructive urinary retention, SNM was eventually adopted for off-label usage in recalcitrant CPP [18]. SNM is an attractive treatment target in CPP given the role of the sacral nerve roots in relaying sensory information from the pelvic floor [19–21]. These sensory fibers may theoretically be subject to neuromodulation at any portion of the anatomical trajectory. In reality,

**Table 1** Summary of non-case reports for sacral neuromodulation in CPP

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Feler, 1999 [27] | Retrospective consecutive case series | 17 patients with IC | Sacral<br>10 (59%) | Unilateral and bilateral S2–S4<br>Retrograde<br>Waveform NS | None | VAS; narcotic use | Follow-up NS<br>Pre- and post-implant | Mean VAS decreased 5.1 (9.1 to 4)<br>6/10 "significantly" tapered narcotics | 1 CSF leak and reoperation<br>1 infection requiring removal<br>1 transient IPG site pain |
| Martellucci, 2012 [13] | Prospective multicenter consecutive case series | 27 patients with CPP w/prior pelvic surgery | Sacral<br>16 (59%) | 15 unilateral S3<br>1 bilateral S3<br>1 unilateral S4<br>Retrograde<br>Parameters: *F* 18–25 Hz, PW 210 μs | None | VAS | Mean follow-up: 37 months (range 12–71)<br>Pre-implant<br>Post-implant: 6 months, 12 months, 24 months, 36 months, 48 months, 60 months (for permanent) | Mean pre-op VAS of 8.1 improved to 2.1 at 6 months<br>VAS ranged from 1.9 to 2.3 for all follow-up timepoints (for permanent) | None |
| Sokal, 2015 [47] | Prospective case series | 9 patients<br>5 idiopathic CRPS<br>4 failed-back surgery syndrome | Sacral<br>9 (100%); not 2-stage protocol | Unilateral and bilateral<br>Anterograde<br>Waveform NS | None | VAS | Median follow-up: 1–48 months<br>Pre-implant<br>Post-implant: immediately, 6 months, 1 year | VAS improved from 9 to 2 immediately post; 3 at 6 months post, 6 at 1 year post<br>8/9 reduced analgesic meds | 3 infection<br>2 migration of electrodes |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Siegel, 2001 [41] | Prospective case series | 10 patients with CPP | Sacral<br>10 (100%) | Unilateral S3 (80%) or S4 (20%)<br>Transforaminal<br>Waveform NS | None | VAS; pain questionnaire | Median follow-up: 19 months (range 6–74)<br>Pre-implant and post-PNE<br>Post-implant: 1 month, 3 months, 6 months, median follow-up | VAS average improved 9.7 to 4.4 at median follow-up<br>90% with decrease in maximal pain severity; number of painful hours decreased 13.1 to 6.9 | 27 in total<br>6 wound complications<br>4 pain location changes<br>4 IPG site pain<br>3 return to baseline pain<br>2 UTIs<br>2 permanent explantation<br>2 revision of IPG or lead<br>2 electric shock sensations<br>1 increased pain<br>1 infection |
| Everaert, 2001 [42] | Retrospective series | 26 patients with CPP | Sacral<br>11 (42%) | Unilateral S3<br>Approach NS<br>Parameters: *F* 14–21 Hz, *A* 0.8–3.6 V, PW 210 μs | None | Patient satisfaction | Mean follow-up: 32 months<br>Timepoints NS | 9/11 patients reported satisfaction | 2 immediate failure<br>1 infection<br>1 electrode migration requiring revision |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Gajewski, 2011 [28] | Retrospective case series | 78 patients with IC | Sacral<br>46 (59%) | Open (cases pre-2005)<br>Transforaminal (cases post-2005)<br>Level or laterality and waveform NS | None | GRA | Mean follow-up: 61.5 months (range 12–132)<br>Pre-implant<br>Post-implant: 3 months, 6 months, 12 months, yearly thereafter | Average 80% improvement in GRA scale in 33/46 pts<br>70% scored GRA > 75% (i.e., "very good"); 30% scored GRA 50–75% (i.e., 'good") | Re-operation due to<br>21 poor outcome or worsened symptoms<br>6 painful stimulation<br>6 IPG pain<br>4 radiating leg pain |
| Ghazwani, 2011 [24] | Retrospective chart review | 21 patients with IC | Sacral<br>11 (52%) | Unilateral S3<br>Transforaminal<br>Parameters: *F* 14 Hz, PW 210 μs (for PNE) | None | Bladder pain score; UDI-6; number of pain meds used | Mean follow-up: 71.5 months<br>Pre-implant<br>Post-implant: 1-year and long-term follow-up | Bladder pain score improved 8 to 5 at 1 year and sustained at > 5 years (SS)<br>Decrease in number of meds at last visit 4.9 to 1.9<br>UDI-6 improved 8.9 to 4.6 | 3 implant site pain<br>2 battery deaths requiring IPG replacement |
| Chai, 2000 [29] | Prospective consecutive case series (PNE) | 6 patients with IC | Sacral | Laterality NS, S3<br>Transforaminal<br>Waveform NS: patient self-titration | None | VAS | Mean follow-up: 5 days<br>Pre-implant and post-PNE | Improved VAS 7.0 to 2.3 | None |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Aboseif, 2002 [40] | Prospective multicenter consecutive case series | 41 patients with CPP | Sacral<br>41 (100%) | Unilateral S3<br>Transforaminal<br>Waveform NS | None | VAS | Mean follow-up: 24 months (range 6–36)<br>Pre- and post-implant | Improved VAS 5.8 to 3.7 at follow-up | Complications in 12 (18.7%)<br>1 transient seroma formation at implant site<br>2 SWIs<br>1 DWI<br>2 wire migrations<br>2 device malfunctions<br>4 revisions |
| Comiter, 2003 [30] | Prospective case series | 25 patients with IC | Sacral<br>17 (68%) | Unilateral S3<br>Transforaminal<br>Parameters: *F* 16 Hz (initial), *A* 2.7 ± 1.7 V (final), PW 210 μs | None | VAS; ICSPI | Mean follow-up: 14 months (range 2–28)<br>Pre-implant<br>Post-implant: 2 months and every 3–6 months thereafter | Improved VAS 5.8 to 1.6 and improved ICSPI at 14 months | None |
| Peters, 2003 [31] | Prospective case series | 37 patients with IC | Sacral<br>26 (70%) | Unilateral S3<br>Transforaminal (15)<br>Open (11)<br>Waveform NS | None | 7-point pain survey ("markedly worse" to "markedly improved") | Mean follow-up: 5.6 months<br>Pre- and post-implant | "Significantly" (rating of "moderately" or "markedly" improved) improved pelvic pain (71%), quality of life (76%), vaginal pain (60%)<br>96% would undergo again and recommend to friend | 3 reoperations |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Whitmore, 2003 [32] | Prospective multicenter consecutive case series (PNE) | 22 patients with IC | Sacral | Bilateral S3 PNA<br>Transforaminal<br>Waveform NS | None | 4-point pain survey (range of 0 'none" to 3 'severe"); ICSPI | Mean follow-up NS<br>Pre- and PNE (7–14 days) | Improved pain 2.2 to 1.6<br>Improved ICSI 16.4 to 10.3<br>Improved ICPI 13.8 to 8.6 | 1 severe leg pain during PNE<br>1 paresthesia/skin tapping improved after turning off IPG |
| Kessler, 2007 [39] | Prospective consecutive case series | 17 patients with CPP | Sacral<br>7 (41%) | 5 unilateral S3<br>2 bilateral S3<br>Approach NS<br>Waveform NS | None | VAS; SSI | Mean follow-up 10 months (range 5–11)<br>Pre- and post- (1st & 2nd follow-ups NS) | Improved VAS 8 to 0 to 2<br>Improved SSI at both follow-ups (100%, 65% respectively) | 2 device failures |
| Lavano, 2006 [53] | Prospective case series | 7 persistent pelvic/ urogenital pain | Sacral<br>5 (71%) | Unilateral S3; bilateral S3; unilateral S4; bilateral S4<br>Transforaminal<br>Non-specific to pain population<br>Initial waveform: *A* 1.3–4.1 V, *F* 20–35 Hz, PW 210 μs | None | VAS; SF-36 | Mean follow-up: 8 months<br>Pre-implant<br>Post-implant: 1 month, 3 months, 6 months, 8 months, 10 months, 14 months | Improved VAS (at least 8 at pre-op to 4 or less by 1 month<br>Bilateral results > unilateral results<br>SF-36 improved at all follow-ups | 1 lead fracture<br>1 lead displacement<br>1 IPG site pain requiring revision |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Peters, 2007 [33] | Prospective, single-blind, randomized crossover | 17 patients with IC<br>4 SNM<br>13 PuNS | Sacral | Unilateral S3<br>Transforaminal<br>Parameters: *F* 16 Hz, PW 200 μs | PuNS | VAS; ICSPI; PUF | Mean follow-up: 6 months<br>Pre-implant<br>Post-implant: 6 months | 49% improved VAS (7.9 to 4.0)<br>Improvement in PUF total 24.2 to 18.6 in SNM<br>Improvement in ICSPI symptom only 14.3 to 10.7<br>No difference between SNS and PuNS for pelvic or vaginal pain | None |
| Falletto, 2009 [46] | Prospective multicenter consecutive case series | 27 chronic anal/perianal pain | Sacral<br>12 (44%) | Unilateral S3<br>Transforaminal<br>Parameters: *A* 1–3 V, *F* 18–21 Hz (50 Hz 1 × patient), PW 210 μs | None | VAS; SF-36 | Mean follow-up: 15 months (range 3–80)<br>Pre-implant<br>Post-implant: 3 months, 6 months, 12 months, annually thereafter | Improved VAS 8.2 to 2.2 at mean follow-up ($p < 0.001$)<br>Improved SF-36 physical component 26 to 39 and, specifically, bodily pain component<br>VAS 2 in 5 patients at 24 months | 1 surgical site infection<br>1 device failure at 24 months<br>1 implant pain requiring revision |
| Marinkovic, 2011 [25] | Retrospective, consecutive case-controlled review | 34 patients with IC | Sacral<br>30 (88%) | Unilateral S3<br>Transforaminal<br>Waveform NS | None | VAS; PUF | Mean follow-up: 86 months<br>Pre-implant<br>Post-implant: > 72 months | Improved VAS 6.5 to 2.4<br>Improved PUF 21.7 to 9.2 | 8 reoperations<br>5 lead migrations<br>3 IPG erosions |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Guardo, 2016 [48] | Prospective case series | 12 patients<br>5 coccydynia<br>3 IC<br>1 vulvodynia<br>1 postsurgical neuropathic pain<br>1 actinic proctitis | Sacral<br>8 (67%) | Unilateral S3<br>Anterograde<br>Waveform NS | None | VAS; SSI | Mean follow-up: 24 months<br>Pre-implant<br>Post-implant: 6 months, 12 months, 24 months | Follow-up VAS not reported<br>Mean SSI 67%, 63%, 62% at 6 months, 12 months, and 24 months follow-up (respectively) | 2 IPG site pain<br>1 IPG displacement requiring revision |
| Powell, 2010 [26] | Retrospective case series | 39 patients with IC/BPS | Sacral<br>22 (56%) | NS | None | Subjective pain; pain medication usage | Mean follow-up: 60 months<br>Pre-implant<br>Post-implant: immediate and at last follow-up | 11/17 (65%) with complete pain resolution<br>Pain medication usage decreased in 50–70%, with cessation in 20–60% of those dependent (depending on agent) | 11 explants<br>4 depleted battery<br>1 infection<br>2 malfunction<br>1 troublesome foot movements<br>3 insufficient symptomatic benefit |
| Maher, 2001 [34] | Prospective consecutive case series (PNE) | 15 patients with IC | Sacral<br>11 (73%) | Bilateral S3<br>Transforaminal<br>Parameters: *A* 0–10 V, *F* 15 Hz, PW 210 μs | None | VAS; SF-36 | Follow-up at 7–10 days<br>Pre-implant, post-PNE | VAS improved 8.9 to 2.4<br>SF-36 bodily pain score improved 19 to 46 | NS |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Marinkovic, 2019 [35] | Observational retrospective double cohort | 170 women with IC/BPS<br>Group A: 105 at low voltage (≤ 3 V)<br>Group B: 65 at standard voltage (≥ 4 V) | Group A: 100 (95%)<br>Group B: 48 (74%) | Transforaminal<br>S3<br>≤ 3 V (group A) versus ≥ 4 V (group B) | None | VAP; ICSPI; PUF | Mean follow-up: 120 months in group A; 116 months in group B | VAP improved 5 points in group A versus 2.6 points in group B<br>Group A superior with respect to ICSPI and PUF | Group A: 6.7% vs. group B: 9.2% (not SS) |
| Zabihi, 2008 [38] | Prospective consecutive case series | 30 patients with IC and CPP | Sacral<br>23 (77%) | Bilateral S2–S4<br>Anterograde<br>Waveform NS | None | VAS; ICSPI; SF-36 | Mean follow-up: 15 months (range 6–32)<br>Pre-implant<br>Post-implant: 6 months | 40% improvement in VAS<br>Pain component of ICSI and ICPI improved 44% and 33%, respectively<br>SF-36 bodily pain not significantly improved | 5 explantation<br>4 infections (3 revisions and 1 removal)<br>1 revision for device malfunction |
| Peters, 2003 [31] | Retrospective chart review (non-staged implantation) | 21 patients with IC | Sacral<br>21 (100%) | S3<br>Approach NS<br>Waveform NS | None | 7-point scale; intramuscular morphine dose equivalents; pain med usage | Mean follow-up: 15 months (range 7–23)<br>Pre-implant<br>Post-implant: 6 months | Mean narcotic use decreased by 36, (81.6 mg/day before versus 52.0 mg/day after implant)<br>18) discontinued narcotics/18) discontinued narcotics<br>95% of patients reported moderate or marked pain improvement | NS |

**Table 1** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation Number of permanent implant (percentage of patient population) | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Lavonius, 2017 [49] | Prospective case series | 4 patients with severe endometriosis who failed surgical treatment (one declined) | Sacral<br>3 (75%) | S3 or S4<br>Transforaminal<br>Waveform NS | None | 5-point pain scale; 10-point satisfaction scale | Mean follow-up: 2.5 years<br>Pre-implant<br>Post-implant: 6 months, 2.5 years | All 3 patients:<br>"Considerable" to "much improved" pain at 6 months<br>"Much improved" to "excellent improvement" at 2.5 years<br>"Considerable" or "excellent" improvement in QOL at 6 months and 2.5 years<br>Overall reduction in pain meds | NS |
| Elhilali, 2005 [56] | Retrospective case series | 4 pain patients<br>2 IC<br>2 CPP | NS | S3 (occasionally S2 or S4)<br>Transforaminal<br>Waveform NS | None | subjective pain | Mean follow-up: 6.5 years (range 1.3–13.3; NS to pain patients)<br>Pre-implant<br>Post-implant: every 6 months | Only 1 of 4 patients (25%) reported 'improvement" in pain | NS<br>Not specific to 4 pain patients |

**Table 1** continued

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|---|---|---|---|---|---|---|---|---|---|
| Vancaillie, 2018 [45] | Retrospective case series | 64 patients with perineal pain | Sacral<br>36 (56%)<br>Pain data from 43 patients used | Bilateral S3–S4<br>Majority extending to L5 or S1 ± pudendal nerve, hypogastric leads<br>Anterograde<br>Waveform NS | None | VAS | Mean follow-up: 24.7 months (range 3–72)<br>Pre-implant<br>Post-implant: follow-up | VAS improved 8.3 to 4.9<br>74% improved pain, 21% no change, 5% worsened pain | 10 explants due to infection, ineffectiveness, excess granulation, tissue, need for MRI, allergy, worsening pain |
| Govaert, 2010 [78] | Retrospective case series of prospective data | 9 patients with anorectal pain | Sacral<br>4 (44%) permanent | S3<br>Approach NS<br>Parameters: *A* 0–10 V (PNE),<br>*F* 16 Hz, PW 210 μs for PNE and permanent | None | VAS; Global perceived effect (7-point Likert scale) | NS<br>Pre-implant<br>Post-implant: 1 month, 3 months, 6 months, 12 months, and yearly thereafter | VAS improved median 8 to 2 at 6 months<br>1 patient (25%) "completely recovered" and three (75%) "much improved"<br>Unclear timepoints | 3 explants and replacements<br>1 infection<br>2 implant pain |

*A* amplitude (volts), *bilat* bilateral, *CRPS* complex regional pain syndrome, *CSF* cerebrospinal fluid, *DWI* deep wound infection, *F* frequency (hertz, Hz), *GRA* Global Response Assessment, *IC/BPS* interstitial cystitis/bladder pain syndrome, *IPG* implantable pulse generator, *NS* not specified, *PNE* percutaneous nerve evaluation, *PuNS* pudendal nerve stimulation, *PW* pulse width (microseconds, μs), *SF-36* 36-Item Short Form Health Survey, *SIJ* sacroiliac joint dysfunction, *SNM* sacral neuromodulation, *SS* statistical significance, *SSI* subjective symptom improvement, *SWI* superficial wound infection, *PDI* pain disability index, *QOL* quality of life, *VAS* visual analog scale, *VD* vulvodynia

caudal neuroanatomy is less mobile, less packed, and has a thinner insulating dorsal cerebrospinal fluid (CSF) layer relative to the conus medullaris and cauda equina. In addition, spatial representation of the distal sacral fibers diminishes in the cephalad direction; a stimulus may therefore preferentially recruit cephalad fibers. At the level of the thoracic spinal cord, sacral fibers are also smaller than lumbar fibers entering the dorsal column. The size discrepancy necessitates more energy to stimulate sacral fibers at the cost of indiscriminately stimulating thoracic fibers and inducing extraneous paresthesias. Thus, sacral nerve root stimulation may provide more selective pain modulation and stable delivery of electric pulses relative to cephalad structures [6, 19].

In 1997, a staged protocol involving a peripheral nerve evaluation (PNE) trial prior to permanent device placement was developed to identify favorable responders [22, 23]. Leads are typically inserted with local anesthesia and connected to an external temporary stimulator to allow for patient sensory responses. Trial duration generally lasts between 1 and 4 weeks and necessitates at least 50% symptomatic improvement to justify permanent SNM implant; a minimum 2-week trial period is recommended [22, 24, 25]. Success rates of PNE trials are typically around 50% with a reported range of 40–100% [24, 26]. Our review suggests a PNE success rate of 41–100% (Table 1). In studies that described lead arrangements, quadripolar leads were more utilized than octopolar leads and unilateral nerve roots were targeted more than bilateral nerve roots. Any roots from S1 to S4 were subject to neuromodulation with the most common target being unilateral S3 (Table 1).

Of the multitude of etiologies that underlie CPP, interstitial cystitis/bladder pain syndrome (IC/BPS) is the most well-documented indication for SNM (Table 1). In sum, 15 of 35 studies exclusively treated for this indication [21, 24–37]. Several studies did not characterize CPP by diagnosed etiology [13, 38–42]. Perineal or anorectal pain was reported in four studies [43–46].

Martellucci et al. reported pain outcomes in a population of patients with CPP and prior pelvic surgeries [13]. Falletto et al. documented outcomes of SNM in patients with chronic anal and perianal pain [46] Sokal et al. applied SNM to patients with idiopathic CRPS and failed-back surgery syndrome [47]. Less common indications included vulvodynia [20, 48], coccydynia [48], severe endometriosis [49], postsurgical neuropathic pain [48], actinic proctitis [48], sacroiliac joint dysfunction [50], dyspareunia [50, 51], clitoral pain after abdominal surgery [52], and cauda equina syndrome [51] (Table 1).

Lead placement strategies are broadly stratified into percutaneous (retrograde, anterograde, and transforaminal) and open approaches. The retrograde, also known as cephalocaudal, approach has been described as the standard technique for SNM implantation [6, 19] and entails lumbar epidural puncture with caudal advancement of electrodes. Unfortunately, this approach has a relatively high technical failure rate as advancement in the sacral promontory is frequently impossible [48]. Additionally, the retrograde approach lends itself to an increased risk of dural puncture, intrathecal lead placement, and cerebrospinal fluid leak. Reported stimulation parameter ranges include amplitude of 0.8–1.6 V, frequency of 30–50 Hz, and pulse width of 350–450 μs [53]. In our review, five studies described the retrograde approach [13, 20, 21, 27, 51]. Stimulation parameters were described in three of these studies and were variable (Table 1) [13, 20, 51].

In contrast, the anterograde, also known as the caudal or trans-hiatal, approach is technically easier and entails needle advancement under fluoroscopic guidance through the sacral hiatus. The risk of dural puncture is decreased compared to the retrograde approach. Leads emerging from the needle often need to be advanced a short distance to the nerve roots. However, the thin subcutaneous layer overlying the sacral hiatus often makes lead anchoring difficult and increases the risk of skin erosion. The anterograde approach has raised concerns regarding implant sterility and risk of infection [6, 48, 53]. In total, six studies described the anterograde approach [20, 38, 45, 47, 48, 50]. Stimulation parameters were described in two cases reports, of which only one mentioned voltage (Table 2). Parameters included

**Table 2** Characteristics of selected case reports on sacral neuromodulation

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Alo, 1999 [20] | Case series | 1 patient with VD; 1 patient with IC | Sacral (2 permanent implant) | Bilateral S2–S3 and S2–S5<br>Anterograde<br>Parameters: frequency 200–1200 Hz, pulse width 20 μs<br>Retrograde<br>Parameters: frequency 75–300 Hz, pulse width 250 μs | None | VAS | Pre- and post-PNE (7-day mean) | VAS improved 9.5 points to 0.5<br>2 of 2 proceeded to permanent implant | NS |
| Zermann, 2000 [37] | Case report | 1 woman with IC | Sacral (1 permanent implant) | Unilateral S3<br>Approach and waveform NS | None | VAS<br>Pain medication usage | Pre- and post-PNE (6 months mean) | VAS improved from 6.7 (pre) to 1.3 (PNE) to 0 (post)<br>Discontinued all pain medications and antidepressants | NS |

**Table 2** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Alo, 2001 [21] | Case report | 1 patient with IC | Sacral (1 permanent implant) | Unilateral S1<br>Retrograde<br>Parameters: amplitude NS, frequency 30 Hz, pulse width 160 μs | None | VAS, SF-36 | Pre- and post-implant (1-year mean follow-up) | VAS improved from 10 to 0–1 | NS |
| Kim, 2010 [51] | Case report | 1 patient with SIJ dysfunction and dyspareunia | Sacral (1 permanent implant) | Unilateral S1<br>Retrograde<br>Parameters: amplitude NS, frequency 30 Hz, pulse width 160 μs | None | VAS; SF-36 | Pre- and post-implant;<br>10 days (VAS); 3 months (SF-36); 16 months subjective report | VAS improved from 9 to 2–3<br>SF-36 bodily pain improved from 20 to 50<br>Decreased analgesics to intermittent usage at 16 months | NS |

**Table 2** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Kim, 2010 [79] | Case report | 2 women with cauda equina syndrome | Sacral (2 permanent implant) | Unilateral S3<br>Transforaminal<br>Patient 1<br>Parameters: 2(−) 1(+)<br>Amplitude 3.8 V, frequency 54 Hz, pulse width 300 μs<br>Patient 2<br>Parameters: 1( ) 2(−)<br>Amplitude 3.6 V, frequency 50 Hz, pulse width 330 μs | None | VAS<br>Pain medication usage | Pre- and post-implant<br>(19 months mean follow-up) | Average VAS improved from 9.5 to 4.5<br>Pain medication usage decreased | NS |

**Table 2** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Marcelissen, 2010 [52] | Case report | 1 patient with clitoral pain post-abdominal hysterectomy | Sacral (1 permanent implant) | Unilateral S3<br>Approach and waveform NS | None | VAS | Pre-, PNE, and post-implant (6 months mean follow-up) | VAS decreased from 7.5 pre- to 1.5 PNE to 0 post-implant<br>VAS max decreased from 8.5 pre- to 3.5 PNE to 1 post-implant | NS |
| Yang, 2010 [43] | Case report | 1 woman with anorectal pain | Sacral (1 permanent implant) | Bilateral S2<br>Retrograde<br>Parameters: amplitude 0.8–20 V, frequency 30 Hz, pulse width 210 μs | None | VAS<br>Pain medication usage | Pre- and post-implant (6 months mean follow-up) | VAS decreased from 8 pre- to 1–2 post-implant<br>Decreased usage of all pain medications with discontinuation of all opioids except tramadol | NS |

**Table 2** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Yakovlev, 2014 [50] | Case report | 1 woman with bilateral sacroiliitis | Sacral (1 permanent implant) | Bilateral S1–S4<br>Anterograde<br>Lead 1: electrode 2(+) 3(−) 4(+)<br>Lead 2: electrode 10(−) 11(+) 12(−)<br>Parameters: amplitude 1–10.5 V, frequency 60 Hz, pulse width 300 μs | None | VAS<br>Opioid usage | Pre- and post-implant (6 months and 12 months) | > 90% decreased in VAS score at 6 months<br>VAS decreased from 6.5 to 2 at 12 months<br>Decreased opioid usage | NS |

*IC* interstitial cystitis/bladder pain syndrome, *ICSPI* O'Leary/Sant IC Symptom Problem Index, *NS* not specified, *PNE* percutaneous nerve evaluation, *post* post permanent SNM implant, *pre* pre-SNM, *PW* pulse width (microseconds, μs), *SF-36* 36-Item Short Form Health Survey, *SIJ* sacroiliac joint dysfunction, *PDI* pain disability index, *VAS* visual analog scale, *VD* vulvodynia

amplitude of 1–10.5 V, frequency of 60–1200 Hz, and pulse width of 20–300 μs [20, 50].

The third method is the transforaminal approach, usually targeting the S3 nerve root, which is technically easier and has been widely adopted in staged SNM. The approach has a reduced risk of dural puncture and skin erosion but at the cost of a higher incidence of reprogramming and lead migration due to challenges with anchoring. Anterior lead positions also tend to stimulate motor fibers and may generate uncomfortable paresthesias. Tined leads have improved fixation success [54, 55]. Previously reported stimulation parameters include amplitudes of 0.8–1.0 V, frequencies of 25–30 Hz, and pulse width of 180–210 μs [53, p. 200]. In total, 17 studies employed the transforaminal approach [24, p. 2; 25, 28–35, 40, 41, 46, 49, 51, 53, 56]. Stimulation parameters were described in eight studies (Table 1) with amplitude of 1–9 V, frequency of 14–54 Hz, and pulse width of 200–300 μs. Notably, Marinkovic et al. compared long-term pain outcomes in patients who underwent neuromodulation with low voltage (less than or equal to 3 V) to high voltage (at least 4 V) [35].

The final approach is open surgery, which is often a last resort and has been largely replaced by the aforementioned minimally invasive alternatives. Open surgery has previously been described as placing paddle leads unilaterally or bilaterally following a partial L5–S1 laminectomy. Leads are advanced caudally beneath the dorsal sacrum to overlay the S2–S4 roots. Paddle leads may provide broader paresthesia coverage. Stimulation parameters are typically set to lower amplitudes and higher frequencies [28, 31]. Overall complication rates have previously been reported as 5% and consist primarily of infection, subdural implantation, and CSF leak [53]. Our review identified two studies describing open surgery in patients with CPP though stimulation parameters were not included [28, 31].

Our literature review of SNM for the treatment of CPP identified 35 manuscripts published from 1999 to 2018, of which eight were case reports. A total of 786 patients with CPP were SNM candidates, 542 of whom had documented long-term pain outcomes after permanent implantation [20, 29, 32, 34] (Tables 1, 2). Long-term pain outcomes were most commonly quantified with the visual analogue scale (VAS) and occasionally with 4- to 7-point ordinal pain scales. Other metrics related to pain included pain medication usage, 36-Item Short Form Health Survey (SF-36) scores, subjective symptom improvement, Pain Urgency and Frequency questionnaire (PUF), O'Leary/Sant IC Symptom Problem Index (ICSPI), and Global Response Assessment (GRA).

All but one study reported improvement in long-term pain outcomes in the majority of patients who had at least one follow-up based on aforementioned metrics. Of the four patients who underwent permanent SNM in a study by Elhilali et al., only one (25%) experienced subjective mean pain improvement on follow-up at 6.5 years [56]. Analysis for statistical significance was included in 15 studies [13, 24, 25, 29, 30, 32, 34–36, 38–40, 45–47], though only 12 studies provided analysis for the permanent implantation stage [13, 24, 25, 30, 35, 36, 38, 39, 45–47]. Of the 12 studies, six of which were prospective, recalcitrant chronic pelvic pain and interstitial cystitis/painful bladder syndrome were the most common indications for SNM (Table 1). Four studies were conducted in specific populations including CPP with prior pelvic surgery [13], idiopathic CRPS and failed-back surgery syndrome [47], and chronic anal and/or perineal pain [45, 46]. Mean and median duration of CPP, if specified, spanned between 3 and 6 years. Approaches were not described consistently but the most common target of neuromodulation was the S3 root unilaterally (Table 1). Progression to permanent implant ranged from 44% to 100%. VAS was observed to improve by at least 2.6 points minimum but by at least 3 points on follow-up of at least 6 months [13, 24, 25, 35, 36, 38, 39, 45–47] (Table 1).

Marinkovic et al. retrospectively studied the largest CPP population with the longest follow-up to date [35]. Long-term pain outcomes in 100 patients with IC/BPS with low voltage (less than or equal to 3 V) were compared to 48 patients with IC/BPS with high voltage (at least

4 V) S3 root stimulation. Conversation rates to permanent implant were superior in the low voltage group (95.4% vs. 73.8%; $p < 0.001$) with a higher subsequent success rate (87.6% vs. 66.2%, $p < 0.002$). On 10-year follow-up, the low voltage group (mean voltage 3.35 V) reported a VAS improvement of 5 points versus 2.6 points in the high voltage group (mean voltage 6.06 V). Furthermore, the low voltage group demonstrated superior ICSPI and PUF scores. Complication rates were similar (6.7% vs. 9.2%, $p > 0.18$). Two other studies demonstrated statistically significant decreases in use of pain medications. Peters et al. observed a decrease in narcotic usage by 36% following permanent implant, from 81.6 mg per day before implantation to 52.0 mg per day after implantation. Notably, 22% of patients (4 of 18) discontinued narcotics altogether and 95% of patients reported moderate to marked improvement in pain at 15 months mean follow-up [36]. Ghazwani et al. also observed a decrease from 4.9 to 1.9 ($p \leq 0.001$) in the number of unique pain medications used at a mean follow-up of 71.5 months in 11 patients who underwent permanent implant [24] (Table 1).

Of particular interest, 4 of 12 studies reported non-sustained pain control or conflicting improvement in pain during follow-up [13, 38, 40, 47]. Martellucci et al. prospectively studied 16 patients with CPP and prior pelvic surgery who underwent implantation with a retrograde and primarily unilateral S3 approach. Reported VAS improved from 8.1 to 2.1 at 6 months but the improvement was not sustained at 12–60 months as a result in part of patients lost to follow-up [13]. Sokal et al. prospectively studied nine patients with idiopathic CRPS/failed back surgery syndrome who were implanted with an anterograde mixed laterality approach, spanning S2–S4. VAS improved from 9 pre-operatively to 3 postoperatively at 6 months ($p = 0.043$) but again, statistical significance was not sustained at 12 months [47]. In 2001, Aboseif et al. conducted a prospective study of 41 patients with CPP who underwent implantation with an anterograde, unilateral S3 approach. Reported VAS was not significantly improved at mean follow-up of 24 months [40]. Separately, Zahibi et al. retrospectively studied 23 patients with bilateral S2–S4 permanent implants inserted via anterograde approaches. In spite of a 40% overall improvement in VAS ($p = 0.04$) and the pain components of the ICSI (44%, $p < 0.05$) and ICPI (33%, $p < 0.05$), SF-36 bodily pain score was not significantly improved on follow-up at 6 months.

Complications with SNM implant included explant from infection, pain at implantation site, poor analgesic efficacy, intolerable paresthesias, lead migration or displacement, lead breakage, or device failure (Tables 1, 2). Device failures generally consisted of malfunction or battery failure. CSF leak was reported in one study and was unique to the retrograde approach [27]. Overall, adverse effects were inconsistently reported.

## Conus Medullaris Stimulation

Conus medullaris stimulation (CMS) was first described in 1970 to improve the function of a paralyzed bladder in a paraplegic patient [57]. To our knowledge, isolated CMS for CPP has only been described in one study. The conus medullaris is the tapered distal end of the spinal cord and transitions into the cauda equina, a bundle of lumbar and sacral nerve roots that innervates the pelvic anatomy. It typically aligns with the lower third of the L1 vertebral body but may span anywhere between the middle of T12 to the upper third of L3. As a result of anatomic variation, definitive localization of the conus medullaris with imaging is essential. Similar to the PNE trial described for SNM, a trial period lasting 1–3 weeks is generally conducted prior to permanent CMS [58].

CMS for management of CPP has only been described in a prospective multicenter case series of 27 patients with refractory unilateral or bilateral pudendal neuralgia (PN). Refractory PN was diagnosed by the Nantes criteria. Patients had to meet multiple requirements including failed response to standard pain management, failed pudendal nerve decompression surgery via Robert's technique using a transgluteal approach, chronic neuropathic pain per the

Neuropathic Pain Diagnostic Questionnaire, and maximum pain VAS of at least 50/100. A 50% reduction in maximum pain and/or average pain and/or greater than 50% increase in sitting constituted a successful trial [58].

Specific technical approaches were guided by patient anatomy. In the trial phase, a stimulating electrode was implanted under fluoroscopic visualization. The preferred approach was the transcutaneous technique with a Lamitrode S8 electrode. In cases of complex spinal anatomy including spinal deformity and prior lumbar surgery, a direct surgical approach with two- or three-column electrodes was used. Intraoperative stimulation tests were performed under local anesthesia and electrode placement was confirmed with fluoroscopy prior to discharge regardless of technique. Permanent CMS candidates underwent subsequent implantation of a subcutaneous generator. Reported CMS settings included intensity of 1.4–8.7 mA, pulse width of 60–325 ms, and frequency of 50–200 Hz [58].

Twenty of 27 patients (74%) progressed to permanent CMS implantation with a mean follow-up of 15 months. In this cohort, mean age was 60 years with pain characteristics that included bilateral pain in 90%, mean pain duration of 72 months, and mean follow-up after pudendal nerve decompression surgery of 29 months; 75% of the cohort preferred an intensity between 1.5 and 3 mA with roughly 50% needing a pulse width of less than 100 ms. A frequency greater than 100 Hz was necessary in 85% and 40% needed 200 Hz. Stimulation parameters did not require significant adjustments. On follow-up, maximum VAS was reduced by 53.5% with a concomitant reduction in average VAS of 51.4% and tripling of sitting time. In addition, the estimated percentage of improvement was 55.5%. All patients reported a preference for undergoing the procedure again. Complications were isolated to one electrode displacement and one superficial surgical site infection [58].

## Dorsal Root Ganglion Stimulation

Dorsal root ganglion (DRG) stimulation has emerged in a handful of small studies as a potentially promising target for chronic pelvic pain. The DRG is a bilateral structure at each vertebral level that houses the cell bodies of primary sensory neurons and is intimately involved in the transmission of noxious stimuli including pain. Studies conducted in rats demonstrated reduced neuronal excitability and action potential propagation with electrode-mediated stimulation of the DRG, thus suggesting that artificial stimulation of the DRG may modulate the transmission of pain signals in chronic pain syndrome. The DRG is accessible via fluoroscopically guided electrode placement into the epidural space. A trial of stimulation is typically performed prior to permanent implantation of an implantable pulse generator (IPG). Up to four DRGs may be stimulated with conventional DRG devices. Purported advantages of DRG stimulation include the precise ability to target subdermatomal pain and insensitivity of lead placement to posture and patient movement.

In our review, we identified four studies evaluating DRG stimulation for treatment of chronic pelvic pain (Table 3). The studies ranged in design from case reports to prospective randomized controlled trials. Of particular interest to our discussion, patients in the studies presented with chronic groin and/or buttock pain related to multiple etiologies including complex regional pain syndrome (CRPS), causalgia/neuropathy, and/or pelvic girdle pain. For the majority of the cases, DRG stimulation was pursued as an interventional option for refractory pain syndromes often in the context of failed medical management with chronic oral analgesics. Due in part to the heterogeneous indications for DRG stimulation, technical parameters varied considerably. Leads were inserted at levels ranging from lower thoracic to sacral vertebrae [59]. Only two of the four studies included waveform parameters for stimulation; parameters included frequencies ranging from 20 to 40 Hz with pulse width between 200 and 500 μs [60, 61].

**Table 3** Characteristics of selected studies on dorsal root ganglion stimulation

| First author, year | Study design | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Deer, 2017 [60] | Prospective randomized comparative trial | 152 adult patients with chronic, intractable neuropathic pain of lower limbs associated with diagnosis of CRPS I or causalgia | Axium™ DRG stimulation | Leads in lateral epidural space from T10 to S2<br>For patients still enrolled at 12 months:<br>Waveform mean frequency 19 Hz<br>Mean width 289.8 μs<br>Mean amplitude 827.4 μA | SCS | Treatment success rates as measured by<br>(1) Successful trial reporting ≥ 50% reduction in VAS<br>(2) Reported ≥ 50% reduction in VAS at 3 months<br>(3) No stimulation-related neurological deficit<br>Secondary pain outcomes<br>Paresthesia intensity<br>Short-Form-36<br>POMS<br>BPI<br>Subject satisfaction<br>Stimulation specificity | 3, 6, 9, and 12 months post-implant | Proportion of subjects with treatment success at 3 months in the DRG arm statistically greater than SCS arm<br>Significantly less postural variation in perceived paresthesia intensity in DRG group<br>Patients in DRG group experienced improvements in SF-36, POMS, and BPI<br>High degrees of patient satisfaction in both groups (no statistically significant between groups) | No stimulation-related neurological deficits noted<br>No significant difference in device-related or serious AEs between groups |

**Table 3** continued

| First author, year | Study design | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Hunter, 2019 [59] | Retrospective registry questionnaire | 217 patients with pain-related diagnoses (6 pelvic pain) | Axium™ DRG stimulation | T12 to S3 for pelvic pain<br>Stimulation waveform parameters not specified | None | NRS reduction<br>% of patients achieving trial success (≥ 50% reduction in NRS)<br>Mean relief % | Not specified | Pelvic pain<br>Mean NRS reduction 76.8%<br>Trial success 83.3%<br>Mean relief 76.67% | Not specified |
| Rowland, 2016 [61] | Case report | 37-year-old woman with 9-year history of chronic pelvic girdle pain | DRG stimulation | Left-sided L1 and L2<br>Lead A at L1:<br>Voltage 575–650 μA<br>Pulse width 200–530 μs<br>Frequency 20–40 Hz,<br>Impedance 911–1016 Ω<br>Lead B at L2:<br>Voltage 750 mV<br>Pulse width 300 ms<br>Frequency 20–40 Hz<br>Impedance 895 Ω | None | MPQ score<br>Patient self-reported quality of life | 6 months | 29% reduction in MPQ score<br>Patient reported significant increase in quality of life and mobility | Not specified |

**Table 3** continued

| First author, year | Study design | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Schu, 2016 [62] | Retrospective review | 29 patients with chronic, intractable neuropathic groin pain | Axium™ DRG stimulation | T11 to L3<br>Stimulation waveforms parameters not specified | None | VAS score | Average follow-up 27.8 weeks | 86.2% (25/29) positive trial (> 50% pain reduction)<br>82.6% (19/23) with > 50% reduction in pain at latest follow-up<br>Demonstrated specificity with avoidance extraneous coverage, minimal change in position, and temporal stability | Not specified |

*AE* adverse events, *BPI* brief pain inventory, *CRPS* complex regional pain syndrome, *DRG* dorsal root ganglion, *MPQ* McGill Pain Questionnaire, *NRS* numeric rating scale, *POMS* profile of mood states, *SCS* spinal cord stimulation, *SF-36* 36-Item Short Form Health Survey, *VAS* visual analog scale

Overall, DRG stimulation was observed to provide significant pain relief for the study participants. Average decrease in VAS and numerical rating scale (NRS) scores exceeded 50% in all multipatient studies [59, 60, 62]. Patients reported increased quality of life in addition to improved function and mobility [60, 61]. The most longitudinal study followed patients for at least 12 months post-implantation and observed sustained pain relief [60]. Compared to traditional spinal cord stimulation (SCS), one randomized controlled trial noted significantly improved reduction in pain scores with DRG stimulation [60]. Of note, the DRG implants were also observed to be more resistant to postural variation with respect to adequacy of pain coverage [60, 62]. Unfortunately, the remaining studies examining DRG stimulation were not designed with a control group. Across all studies, DRG stimulation was observed to have no difference in adverse event rates compared to traditional SCS therapy. The most common adverse events reported included incisional site pain, IPG pocket pain, and overstimulation [60].

DRG stimulation therapy appears to be a promising treatment modality for chronic pelvic pain, albeit with a limited and heterogeneous evidence base. Patient outcomes with respect to pain relief and improvement of function in the single randomized control trial to date observed superiority compared to traditional SCS therapy. Additional high-quality research with standardized patient populations is needed to understand the long-term efficacy and potential role of DRG stimulation for chronic pelvic pain.

### Dorsal Column Stimulation

Dorsal column SCS is a mainstay of interventional treatment for chronic pain syndromes and has been posited as a potential option for chronic pelvic pain syndromes. Dorsal column (DC) lesions in particular have been shown to attenuate the pain associated with pelvic cancer, thus implying a potential role for spinal cord neuromodulation in managing non-malignant etiologies of pelvic pain [63]. Interestingly, significant overlap has been observed between chronic pelvic pain syndromes and CRPS, especially with respect to hypersensitization of pain-sensing neurons in response to non-painful stimuli. For chronic pelvic pain, this allodynia-like phenomenon often manifests with urination, bladder distension, sexual activity, ovulation, or even prolonged sitting [6, 64]. The overlap of potential pain pathways and clinical presentation has raised the profile of SCS as a potential management option for chronic pelvic pain [65]. Similar to DRG stimulation, SCS is initiated with placement of electrodes in the epidural space with permanent implantation considered after a successful trial period. Notably, SCS stimulation is focused on ascending nerve tracts in the spinal cord and has been demonstrated to offer a less targeted region of analgesia compared to DRG stimulation.

In our review, we identified ten studies evaluating SCS for management of chronic pelvic pain. Nine studies were either case reports or case series for a cumulative of 56 patients (Table 4) and one study was a randomized controlled trial comparing SCS to DRG stimulation [60]. The designated etiology of patient's chronic pelvic pain was heterogeneous and included irritable bowel syndrome (IBS), pudendal neuralgia, post-herniorrhaphy pain, Bannayan-Riley-Ruvacalba syndrome, and nonspecific pelvic pain. As with patients undergoing DRG stimulation, patients had generally failed conservative management prior to being offered SCS therapy.

One case series of three patients involved high-frequency SCS whereas the others involved conventional SCS therapy [66]. The studies displayed heterogeneity with respect to description of SCS implantation technique. In general, lead implantation was in the mid- to lower-thoracic spine with the highest reported lead at T5 and lowest at L2. Only two studies reported on specifics of the waveform parameters used; amplitude ranged from 1.8 to 3.8 V with a pulse width range from 300 to 450 μs. Frequency ranged from 40 to 65 Hz with the exception of the high-frequency stimulation patients who were stimulated at 10 kHz [66–68].

**Table 4** Characteristics of selected studies on dorsal column stimulation

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Hunter, 2013 [6] | Case series | 5 patients with chronic pelvic pain who failed treatment with conventional medications and interventional techniques | SCS | 2 at T6; 2 at T7; 1 at T12–L1<br>Waveform not specified | None | Progression to permanent SCS implant following trial period<br>Patient self-reported pain relief | 1-week trial period<br>Follow-up between 1 and 10 months post-permanent implant | 4 out of 5 patients proceeded to permanent implant<br>Patients with permanent implant reported > 50% pain relief and decreased opioid requirements | 1 revision for lead migration |
| Kapural, 2006 [69] | Case series | 6 female patients with severe visceral pelvic pain | SCS | 4 at T11, 1 at T11–12, 1 at L1<br>Waveform not specified | None | VAS score<br>PDI questionnaire<br>Opioid consumption converted to morphine milligram equivalents | 1–2-week trial period<br>Mean follow-up time 30.6 months | All patients experienced > 50% decrease in pain<br>Significant decrease in median VAS (9 ± 0.89 to 2.3 ± 1.6) and PDI scores (58 to 19.7)<br>Opiate use decreased from average 22.5 mg to 6.6 mg of morphine sulfate equivalents per day | 2 revisions for lead migration |

**Table 4** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Krames, 2004 [67] | Case report | 50-year-old woman with IBS and chronic abdominal pain | SCS | T8<br>Trial waveform parameters<br>Amplitude 3.2 V<br>Pulse width 300 μs Frequency 40 Hz<br>Permanent waveform parameters<br>Amplitude 3.8 V<br>Pulse width 450 μs Frequency 65 Hz | None | Patient self-reported pain relief<br>Opioid use | 10 months | Initial reduction in self-reported pain from 9–10/10 to 2–3/10<br>Return of pain 6 months post-implant with increase in opioid requirement to approximately pre-implant levels<br>Patient self-reported increased quality of life | Not specified |

**Table 4** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Khan, 2005 [70] | Case series | 9 patients with abdominal visceral pain | SCS | 5 non-alcohol pancreatitis: T5–T6<br>3 generalized abdominal pain and wall neuroma: T5–7<br>1 post-traumatic splenectomy: T6–7<br>Waveform not specified | None | VAS scores<br>Analgesic use | 3 months–7 years | All patients reported marked pain relief (approximately 5 points on VAS)<br>All patients reported > 40% decrease in analgesic requirement | 1 revision for lead migration |
| Tiede, 2006 [71] | Case reports | 2 patients with refractory abdominal visceral pain | SCS | T2<br>Waveform not specified | None | Patient self-reported pain relief<br>Analgesic use | 3–4 months | Patient 1:<br>Decrease in pain from 10/10 to 2/10<br>Discontinuation of opioid use<br>Resumed opioids after lead migration and revision<br>Patient 2:<br>Decrease in pain from 8/10 to 2–3/10<br>Discontinued breakthrough and decreased baseline dose by 33% | 1 revision for lead migration after fall |

**Table 4** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Buffenoir, 2015 [58] | Prospective case series | 27 patients with pudendal neuralgia (Nantes criteria); chronic neuropathic pain (DN4); failure of pain management; failure of decompression surgery; VAS $\geq$ 50/100 | SCS | Waveform parameters<br>Stimulation intensity 1.4 to 8.7 mA<br>Pulse width 60 to 325 µs<br>Frequency 50 to 200 Hz | None | Average ($VAS_{average}$) and maximum ($VAS_{max}$) VAS scores<br>Maximum tolerated sitting time<br>Estimated percentage improvement of pain<br>Proportion of patients who would undergo procedure again | 10–24 months | 20 of 27 patients with successful implantation trial (greater than 50% reduction of maximum pain and/or average pain and/or greater than 50% increase of sitting time before onset of pain)<br>Mean reduction in $VAS_{max}$ of 53.5% and $VAS_{average}$ of 51.4% in permanent implant patients<br>Mean sitting time tripled compared to baseline<br>Mean estimated percentage improvement 55.5% (range 40–80%)<br>100% patient satisfaction | 1 electrode displacement (test phase)<br>1 superficial infection of skin exit site (test phase) |
| Simopoulos, 2018 [66] | Retrospective case series | 3 patients with chronic refractory neuropathic pelvic pain | High frequency (10 kHz) SCS | T8 and T9<br>High-frequency (10 kHz) stimulation | None | VAS scores<br>Patient self-reported quality of life | 9–12 months | All patients experienced decrease in VAS score<br>Patient 1: 8.2 to 4.0 (improved sitting tolerance)<br>Patient 2: 8.3 to 3.3 (75% reduction in opioids)<br>Patient 3: 7.5 to 4.1 (improved sitting tolerance) | Not specified |

**Table 4** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief result | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Elias, 2000 [72] | Case reports | 2 patients with post-herniorrhaphy pain syndrome | SCS | T7 and T8 | None | Patient self-reported pain relief<br>Opioid use | 4–6 months | Both patients underwent successful SCS trials (> 50% on VAS scale)<br>Reduction in opioid requirements in both patients<br>One patient reported > 50% reduction in pain on follow-up (other patient's pain relief not reported) | 1 patient reported muscle cramps with continuous use: resolved with cyclic stimulation |
| Yakovlev, 2009 [68] | Case report | 18-year-old woman with intractable abdominal pain Bannayan-Riley-Ruvacalba syndrome | SCS | T6–T7<br>Amplitude 1.8–2.3 V<br>Pulse width 450 μs<br>Frequency 40 Hz | None | Patient self-reported pain relief | 6 months | Patient reported "excellent" pain relief<br>Improved bowel function and ability to perform daily activities of life | Reprogramming at 1 month |

*IBS* irritable bowel syndrome, *PDI* pain disability index, *SCS* spinal cord stimulator, *VAS* visual analog scale, *DN4* Neuropathic Pain Diagnostic Questionnaire

**Table 5** Characteristics of selected studies on pudendal nerve stimulation

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Pain outcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Carmel, 2010 [75] | Retrospective case series | 3 female patients with refractory chronic pelvi-perineal pain by Nantes criteria | Pudendal nerve stimulation with IPG | Electrodes placed on external anal sphincter, gluteus medius and maximus, adductor longus, tibialis, and gastrocnemius<br>Waveform parameters patient 2: pulse width 450 μs | None | Patient self-reported pain on scale 0 to 10 and improvement from 0 to 100% | 24 months | > 80% pain relief in all 3 patients | No major complications |
| Peters, 2015 [74] | Retrospective chart review and patient survey | 19 patients with clinically diagnosed pudendal neuralgia | Pudendal nerve stimulation with IPG | Quadripolar lead placed on pudendal nerve via ischial-rectal approach<br>Waveform not specified | None | Patient self-reported pain relief<br>7-point scaled global response assessment | 0–6 years | All patients self-reported improvement in pain 2 weeks after lead placement (by at least 50%) and just prior to IPG implant<br>5 patients explanted (1 total symptom resolution; 1 no longer using device; 3 lost efficacy)<br>Neuromodulation rated second most effective treatment option after medications<br>80% of respondents satisfied with neuromodulation; 20% neutral | Not specified |

**Table 5** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Painoutcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Peters, 2010 [33] | Retrospective chart review and patient survey | 84 patients with urologic symptoms secondary to interstitial cystitis, urge incontinence, and/or urinary retention | Pudendal nerve stimulation with IPG | Quadripolar tined electrodes placed at pudendal nerve via ischial-rectal approach<br>Waveform not specified | None | Patient self-reported pain relief on voiding diaries<br>Interstitial Cystitis Symptom Index and Problem Index (ICSI-PI)<br>Global response assessment (GRA) questionnaire survey | 2 weeks, 3 months, 6 months, 12 months<br>Mailed survey at median 24 months | Positive pudendal response (50% improvement) in 60/84 (71.4%)<br>No significant change in patient self-reported pain on voiding diaries<br>Improved ICSI-PI scores at 12-month follow-up<br>> 50% reported slightly, moderately, or markedly improved pain on GRA survey | 3 patients required restaging (revision) for lead migration<br>2 patients required replacement with sacral lead for pain and/or uncomfortable stimulation<br>1 local wound infection<br>5 patients explanted (reasons not specified) |

**Table 5** continued

| First author, year | Study design and setting | Patient population | Type of neuromodulation | Lead location and type of waveform | Control group | Painoutcomes assessed | Pain assessment timepoints | Pain relief results | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Peters, 2007 [77] | Prospective, single-blind, randomized crossover trial | 22 patients with refractory interstitial cystitis receiving sacral nerve stimulation for voiding dysfunction | Pudendal nerve stimulation with external stimulator box | Quadripolar tined electrodes placed at S3 nerve root and pudendal nerve via posterior approach<br>Waveform parameters: pulse width 200 μs, rate 16 Hz | None | VAS, ICSPI, and PUF questionnaires<br>Proportion of patients choosing pudendal or sacral stimulation | 1 month, 3 months, and 6 months | 17/22 patients responded positively (> 50% improvement in symptoms) to neuromodulation<br>No significant short-term difference between pudendal and sacral stimulation for pelvic or vaginal pain<br>13/17 responders chose pudendal stimulation for permanent implant<br>At 6-month follow-up, 49% reduction in VAS score in pudendal vs. 29% in sacral ($p$ not reported) | 2 patients (one sacral, one pudendal) required drainage of sterile seroma around IPG |
| Armstrong, 2016 [76] | Case report | 35-year-old woman with complex pelvic neuropathy and established diagnosis of interstitial cystitis | Combined sacral and pudendal nerve stimulation with IPG and simultaneous pudendal nerve decompression | Four-lead stimulator (two leads at sacral hiatus and two leads adjacent to pudendal nerves)<br>Waveform not specified | None | Patient self-reported pain relief | 3 months, 6 months | Resolution of all pelvic pain at 6 months (except after strenuous activity)<br>Resumption of ADLs at 6 months | None |

*ADL* activities of daily living, *IPG* internal permanent generator, *VAS* visual analog scale, *ICSPI* O'Leary/Sant IC Symptom Problem Index, *PUF* Pain Urgency and Frequency (questionnaire)

Heterogeneity in reporting of patient outcomes was also evident with only a fraction of the studies reporting quantitative VAS scores. Follow-up times varied from 3 months to upwards of 3 years. With these limitations in mind, outcomes appeared to be positive with reported VAS scores decreasing by more than 50% across multiple case reports [6, 58, 66, 67, 69–71; 72, p. 20]. Notably, analgesic requirements were also markedly reduced following SCS implantation though one case series of six patients observed no significant reduction in opioid use [6, 67, 69–72]. Quality of life, including patient mobility and sitting tolerance, was also noted to be improved [58, 66; 67, p. 200; 68, 69]. Two case studies, however, reported on the eventual return of pain and opioid requirements [67, 71]. A total of five revisions were reported, all for lead migration, which represented slightly less than 10% of all patients studied.

Spinal cord stimulation therapy appears to be a viable option for chronic pelvic pain as reported through case reports and case series. To our knowledge, no randomized controlled trials are available comparing SCS to placebo in this population. The purported efficacy should be tempered with an appreciation of the limitations of case reports and series and potential for significant bias. Nevertheless, given the difficult-to-treat and refractory nature of chronic pelvic pain, SCS holds promise as a potential strategy for pain relief.

### Pudendal Nerve Stimulation

Targeted neuromodulation of the peripheral nervous system via pudendal nerve stimulation has also been investigated as a treatment modality for chronic pelvic pain. Interestingly, relief of pain with a pudendal nerve block is often used as diagnostic criterion for pudendal neuralgia [73]. Perhaps it is unsurprising that a natural corollary has been targeting of the pudendal nerve with permanent implantation of electrodes for refractory chronic pain. Prior research has demonstrated that pudendal nerve stimulation may be effective for treatment of neurogenic bladder [22]. Electrode implantation has been demonstrated with minimally invasive needle techniques and neurophysiologic guidance under local anesthesia [33, 74]. As with dorsal column and dorsal root ganglion stimulation, a successful trial generally precedes permanent generator implantation.

In our review, we identified five studies comprising a total of 129 patients who underwent pudendal nerve stimulation for chronic pelvic pain (Table 5). The study designs included two retrospective studies, a case series, a case report, and a prospective double-blind crossover trial comparing pudendal nerve stimulation to sacral stimulation. The most common identified etiologies of pain were interstitial cystitis and pudendal neuralgia. All patients underwent pudendal nerve stimulation therapy with electrode placement along the course of the pudendal nerve; one case report discussed a patient who underwent concomitant pudendal nerve decompression. The majority of procedures involved a posterior ischial-rectal approach. Only one study discussed waveform parameters: pulse width of 200 μs and frequency of 16 Hz [33].

Patients were followed longitudinally from 6 months to 6 years with evaluation of mixed pain outcomes. Three studies reported promising results with greater than 80% pain relief and overall high patient satisfaction [74–76]. The largest study, however, comprising an 84-patient case series, did not identify a statistically significant change in self-reported pain scores at the 12-month follow-up, though more than half of the patients reported improvement in pain [74]. When compared with sacral neuromodulation, pudendal nerve stimulation appeared to offer no significant short-term advantage. However, a majority of blinded patients in the crossover trial elected for pudendal nerve stimulation over sacral stimulation and long-term VAS score reduction was greater in the pudendal nerve stimulation group [33]. Reported complications of implantation included lead migration, paresthesias, infection, and seroma formation [33, 77].

Of the limited data available, pudendal nerve stimulation appears to have a positive impact on pelvic pain outcomes. Notably, the spectrum of pathologies investigated was smaller in scale

than for either DRG or SCS therapy. The peripheral nature of the technique may ultimately limit the indications of the therapy in comparison to a more centrally acting therapy. Conversely, in an appropriately selected subset of patients, pudendal nerve stimulation may offer selectively targeted analgesia.

## CONCLUSION

This narrative review highlights the array of neuromodulatory modalities such as sacral neuromodulation, conus medullaris stimulation, DRG stimulation, dorsal column SCS, and pudendal nerve stimulation available for the treatment of CPP. We found evidence suggestive of benefit for all modalities reviewed but the data was of overall low quality with numerous limitations including heterogeneous study conditions and sample sizes. Our review highlights the lack of randomized controlled trials for neuromodulatory therapies but acknowledges the growing role of such techniques for refractory CPPS.

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