Neuromodulation in Chronic Pelvic Pain: A Narrative Review

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ABSTRACT

Chronic primary pelvic pain syndrome (CPPPS) is a heterogeneous disease with unknown pathogenesis and a lack of distinct pathological features, which complicates diagnosis and therapy and has a significant impact on patients' daily life. Because pharmacological management is ineffective and long-term use may result in additional system damage,

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developing a more effective treatment is critical. Neuromodulation has advanced rapidly over the last few decades, and various types of neuromodulations have demonstrated efficacy in the treatment of CPPPS. In this article we discuss the evolution of neuromodulation technology in the treatment of chronic pelvic pain, its application to various subtypes of chronic pelvic pain, and the comparison of relevant efficacy and parameter differences, as well as assess the relative advantages and disadvantages of sacral neuromodulation, percutaneous tibial nerve stimulation , transcutaneous electrical nerve stimulation, electroacupuncture, and pudendal neuromodulation. Furthermore, it was noted that chronic pelvic pain should be evaluated in terms of pain, associated symptoms, psychological problems, and quality of life. Although neuromodulation approaches have been shown to be effective in treating chronic pelvic pain, more extensive multicenter trials are required to confirm this.

Key Summary Points

Why carry out this study?

Chronic pelvic pain causes concomitant symptoms and psychological problems that seriously affect patients' quality of life.

Recently, neuromodulation has been developed as a therapeutic option for the treatment of chronic pelvic pain.

This paper investigates the effects and associated adverse events of neuromodulation in the treatment of various subtypes of chronic pelvic pain.

What was learned from the study?

Neuromodulation is effective in the treatment of chronic pelvic pain with few adverse events.

Chronic pelvic pain should be evaluated in terms of pain, associated symptoms, psychological problems, and quality of life.

INTRODUCTION

Chronic pelvic pain (CPP) is defined as chronic or persistent pain experienced by men or women in pelvic structures for a minimum of 6 months. It is frequently associated with negative cognitive, behavioral, sexual, and emotional consequences and is frequently accompanied by lower urinary tract symptoms, sexual, bowel, pelvic floor, or gynecological dysfunction [1].

CPP prevalence is significantly higher in women than in men, ranging from 5.7% to 26.6% in the former [2]. In contrast, CPP in men manifests primarily as prostatitis, with a prevalence ranging from 2.2% to 9.7% [3], and the risk increases with age [4]. A recent British study found that the prevalence rate of CPP in women aged > 25 years was 14.8%, while the incidence

rate was 20.5% in women of childbearing age and 9.6% in elderly females [5]. Recently, Balabuszek et al. [6] showed that pelvic venous disorders (PeVD) might be the cause of CPP in up to 30% of women with CPP. CPP causes not only pelvic floor pain but also causes psychological distress and simultaneous negative behavioral and sexual consequences, resulting in depression, anxiety, poor sleep quality, and marital tension accompanied by pain. Therefore, additional research on CPP is required [7, 8].

CPP can be further classified as specific disease-associated pelvic pain (chronic secondary pelvic pain) or chronic primary pelvic pain syndrome (CPPPS), depending on whether a classical pathology exists (such as infection or cancer). In this article, we place the emphasis on CPPPS and do not go into detail about cases with very obvious pathology. Formerly known as chronic pelvic pain syndrome (CPPS), it was renamed chronic primary pelvic pain syndrome (CPPPS) in the 2022 European Association of Urology (EAU) guidelines to align with the International Classification of Diseases 11th Revision (ICD-11) term for chronic primary pain. The pain of patients with CPPPS may be predominant in a single organ (e.g., a primary prostate pain syndrome [PPPS]) or in multiple pelvic organs when no specific organ is identified. At the same time, many people tend to use the term CPPPS and sub-divide it by psychological and functional symptoms [1]. This suggests that in the description of CPPPS, in addition to the location and nature of pain, we should also pay attention to its impact on the patient's psychological and functional symptoms, and ultimately on the quality of life (QoL). In this article, we analyze the classification of CPP according to terminal organs. In this system, CPPPS can be subdivided into Urological, Gynaecological, Gastrointestinal, Peripheral nerves, Sexological, Psychological, and Musculo-skeletal system. It can be further subdivided into syndromes based on terminal organs within each system, such as the urinary system, which includes PPPS, primary bladder pain syndrome, primary scrotal pain syndrome, and primary testicular pain syndrome, among others [1].

While the pathophysiology of CPPPS is unknown, Pontari and Ruggieri [9] believe that the symptoms of CPPPS are caused by a combination of psychological factors and immunological, neurological, and endocrine system malfunction. Initial variables (infection, trauma, psychology, among others) might result in self-perpetuating immunological, inflammatory, and/or neurogenic damage, which can progress to chronic pain. According to other studies, hyperalgesia, which is associated with the nervous system in particular, is thought to play a significant role in the development of chronic pain by causing changes in the peripheral and central nervous systems, resulting in a state of heightened sensitivity, in which normally unperceived stimuli are perceived, and sensations that would normally be perceived become pain [10, 11]. Yang et al. [12] used noxious heat stimuli to assess central sensitization in 36 patients with PPPS and 66 healthy men, employing a Computerized Visual Analog Scale (COVAS) to evaluate their feelings. After thermal stimulation, the average COVAS peak value of the perineum in the PPPS group was considerably higher than that in the control group ($p < 0.05$). Similarly, Lai et al. [13] investigated whether interstitial cystitis/bladder pain syndrome (IC/BPS) is hyperalgesia by applying fixed mechanical pressure (2 or 4 kg), and discovered that the VAS pain ratings in the IC/BPS group were significantly higher than those in the control group ($p = 0.028$), indicating segmental mechanical hyperalgesia in the suprapubic area (T10–T12). According to Lai et al., the process is due to the central sensitization of the visceral somatic convergent neurons in the T10–12 dorsal horn, which receives input from both the bladder and the T10–12 somatic structure. Chronic pain signals from the bladder to the central nervous system can enhance this neuron's excitability, which increases somatic signal transmission to the spinal cord, manifesting as segmental pain. Because the efficacy of pharmaceutical management is limited and long-term usage may cause additional system damage [14], we must consider a more comprehensive individualized management strategy that may include psychotherapy, physical therapy, biobehavioral therapy, medicines, and more invasive interventions. Neuromodulation, which does not have the systemic adverse effects associated with medication therapy, offers a promising alternative [15].

This article is based on previously conducted research, and none of the authors conducted any new human or animal studies. After a systematic search of the Medline, EMBASE, Cochrane Library, and the Health Technology Assessment databases for relevant articles, we extracted relevant peer-reviewed journal articles on neuromodulation therapy for CPP. We also discuss the history of neuromodulation techniques and their use in the treatment of chronic pelvic pain (Fig. 1).

NEUROMODULATION

Neuromodulation is the electrical stimulation of the nervous system to accomplish therapeutic effects [16]. It was developed on the basis of the gate control theory and achieving decreased pain by activating large-diameter Aβ fibers while inhibiting smaller Aδ and C fibers [17]. Other possible mechanisms include promoting the release of endogenous opioids, improving local circulation, and activating the descending inhibitory system [18–20]. This method of using nerve therapies to relieve patients' pain creates a new therapeutic option for pelvic pain. Its benefits include programmability, low risk, and specificity, which can help alleviate pain, enhance the functional status, improve QoL, and minimize the demand for medical resources [21]. "Natural electricity" has been used for pain treatment since ancient Egypt [22], and Scribonus Largus (46 AD) used a live black torpedo (40–100 V, 100 Hz) to cure headaches, establishing the first literature on local electric analgesia [23].

The gate control theory revived interest in electrical stimulation for pain relief in the twentieth century, and various forms of peripheral and central nervous system stimulation were studied in this context, especially transcutaneous electrical nerve stimulation (TENS), which developed rapidly during this period [24, 25]. Shealy et al. [26] developed the
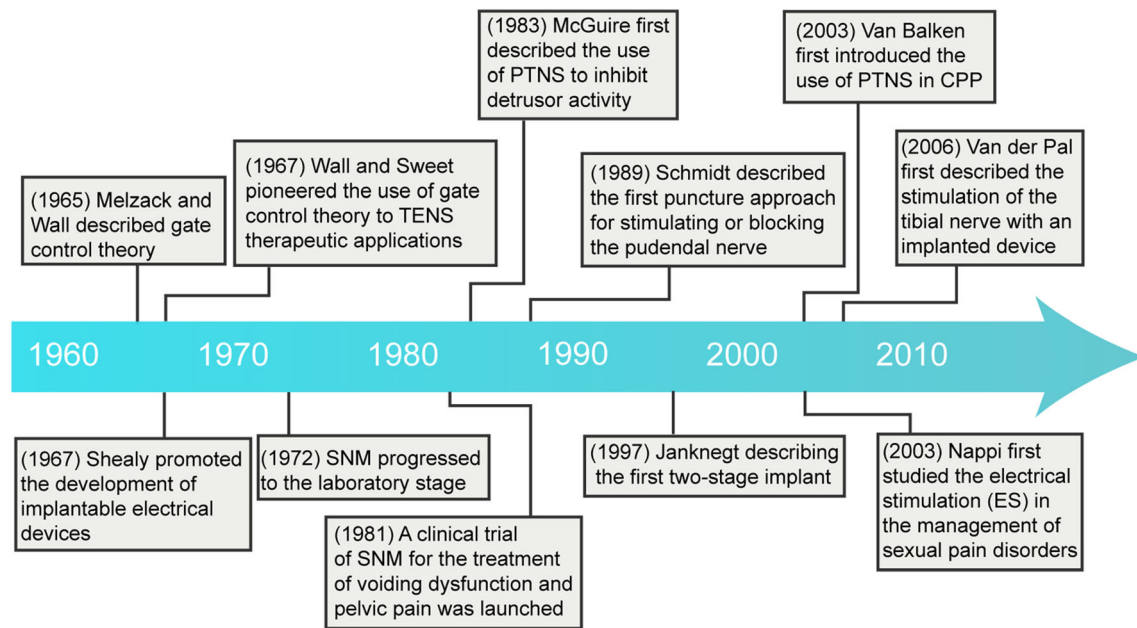
Fig. 1 Milestones in neuromodulation. Since the theory of gate control was put forward, various neuromodulation techniques have been developed and continuously improved. Neuromodulation has also expanded from its initial use in the treatment of lower urinary tract dysfunction to the treatment of chronic pelvic pain (CPP)

first implantable electrical device to treat chronic pain when they employed a neural augmentative device that stimulates the dorsal column to reduce intractable pain in patients with advanced cancer; this application promoted the development of implantable electrical devices. Based on this rationale, a variety of electrical nerve stimulation techniques and devices have evolved, ranging from non-invasive techniques like TENS to invasive treatments like sacral neuromodulation (SNM) that need anesthesia [27]. Currently, neuromodulation therapies primarily used to treat CPP include SNM, trigeminal nerve stimulation (TNS), TENS, electroacupuncture (EA), pudendal nerve stimulation (PNM), and others (Fig. 2).

Sacral Neuromodulation

Sacral neuromodulation primarily operates by continuously stimulating the S3 nerve roots with electrodes and generators. Schmidt et al. [28] discovered that sacral nerve roots control a wide range of complicated and integrated physiological activities in the pelvis. Following the development of pacemakers in the 1960s, there was a lot of optimism that electrical stimulation may help with other damaged physiological functions, such as pain management and bladder control. SNM progressed to the laboratory stage, and SNM was gradually investigated by directly stimulating the bladder wall, then the spinal cord, and lastly the sacral nerve roots [29]. Thuroff et al. [30] showed in animal tests the viability of stimulating the sacral nerve to modulate sphincter and bladder function. In 1981, a clinical trial of SNM was launched to treat voiding dysfunction and pelvic pain [31].

The staged test was a significant advancement in SNM technology, with Janknegt et al. [32] describing the first two-stage implant in 1997. Traditional SNM is separated into two parts: percutaneous nerve stimulation (PNE) and permanent electrode implantation attached to the subcutaneous stimulator, while the two-stage approach directly implants the permanent electrode during the test stimulation stage
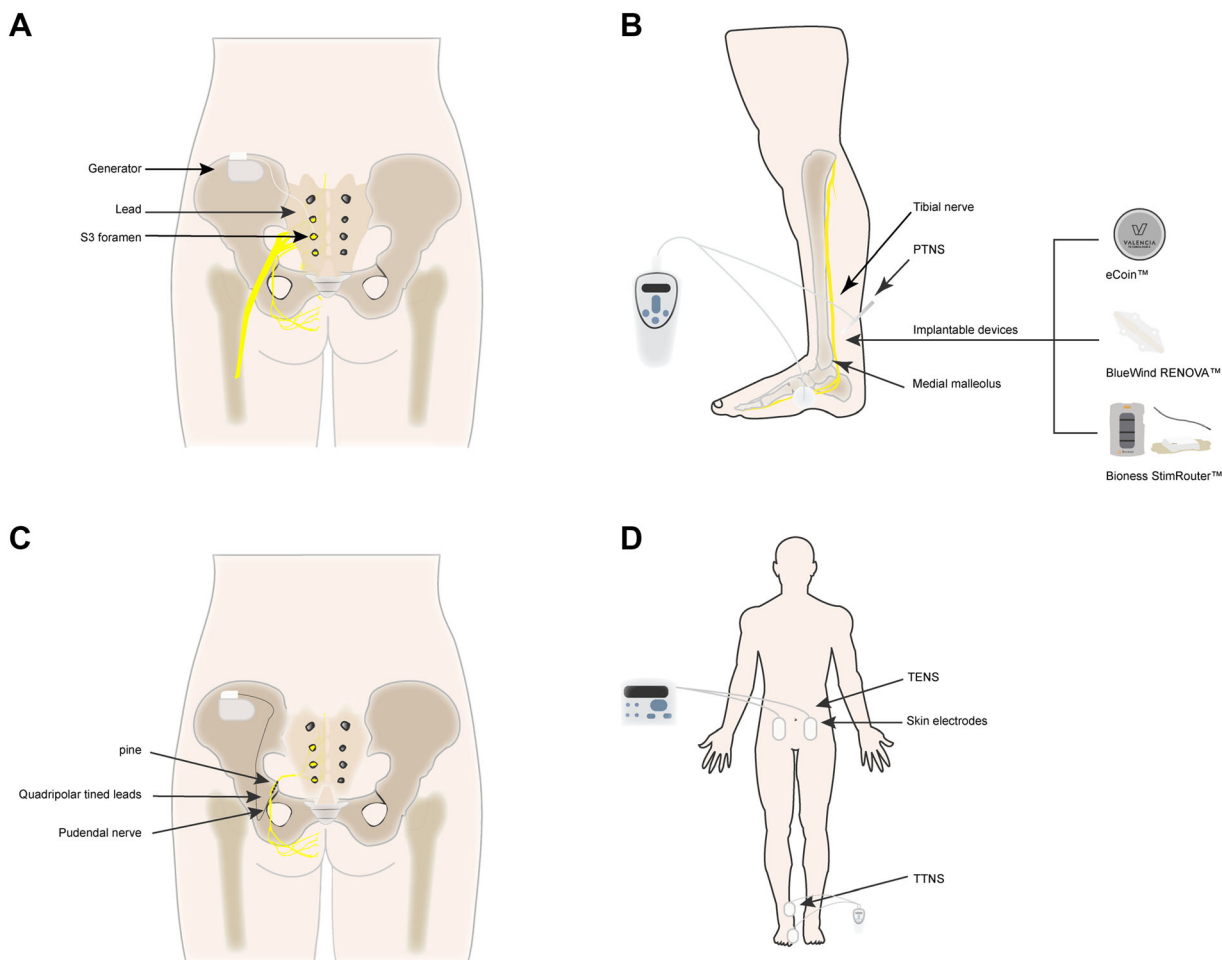
Fig. 2 Stimulation sites of various types of neuromodulations. **a** Sacral neuromodulation (*SNM*). Continuous stimulation of the S3 nerve roots with electrode and generator. The generator is placed in the subcutaneous tissues in the buttock region over the iliac crest. **b** Percutaneous tibial nerve stimulation (*PTNS*) and implantable devices (e.g., eCoin^(TM), BlueWind RENO-VA^(TM), Bioness StimRouter^(TM)). For PTNS, a needle is inserted into the posterior tibial edge of the 3 fingers cephalic of the medial malleolus, between the posterior tibial edge and the soleus tendon, and a glued neutral electrode is placed on the same leg near the arch of the foot. Implantable devices are secured near the tibial nerve while the patients are under local anesthetic. **c** Pudendal nerve stimulation (*PNM*). PNM is applied similarly to SNM. The pudendal nerve originates from S2-S4 of the sacral nerve with a greater range of stimulation of the sacral nerve root. **d** Transcutaneous electrical nerve stimulation (*TENS*) and transcutaneous tibial nerve stimulation (*TTNS*). In TENS, the skin electrodes are attached to the painful area. In TTNS, the tibial nerve is stimulated with transcutaneous surface electrodes instead of with percutaneous needle electrodes

(Table 1). In Janknegt et al.'s trial, ten patients with urinary dysfunction whose condition had not improved with PNE underwent a staged test; of these, eight patients improved by > 50% and underwent a second round of surgery [33, 34].

Discomfort at the implantation site was the most common adverse event of SNM (ranging between 15 and 42%) [35], with additional adverse events including seroma at the implantation site, infection, wire migration, and device malfunction. However, the high surgical revision rate associated with SNM

Table 1 Traditional test and permanent implant versus staged test/implant

	Traditional test	**First stage: staged test**
S3 localization technique	Bony landmarks palpated	Fluoroscopic guidance and S2 ruled out
Lead type	Monopolar	Quadripolar
Placement method	Taped to the skin surface	Secured to the lumbosacral fascia with sutures
Voiding trial	5–7 days followed by removal of test lead and scheduling of traditional implant	2 weeks; with second stage scheduled at the time of first stage
	Traditional implant	**Second stage: staged implant**
Primary tasks performed	Place and test permanent lead Create generator pocket and connect generator	Responders have generator pocket extended and generator connected
Response assessed	Motor only	Motor and sensory

cannot be overlooked, although the incidence of adverse events and revision is significantly related to the learning curve for surgical methods, and competent mastery of surgical techniques drastically lowers their frequency [36].

Tibial Nerve Stimulation

The posterior tibial nerve is a mixed sensory-motor nerve containing fibers originating from spinal roots L4–S3 [37]. Acupuncture and moxibustion therapy in traditional Chinese medicine introduced the concept of stimulating the Sanyinjiao point (SP-6) to treat urinary symptoms over 2000 years ago, with the stimulating point most likely being the posterior tibial nerve [38]. TNS has been developed and can be roughly classified as percutaneous tibial nerve stimulation (PTNS), transcutaneous tibial nerve stimulation (TTNS), and implantable devices.

PTNS works by electrically stimulating the tibial nerve to alleviate pain and improve symptoms. McGuire et al. [39] was inspired by traditional Chinese medicine and discovered that an electric current could be applied percutaneously to the common peroneal nerve or posterior tibial nerve via a positive electrode, while the ground electrode was placed on the contralateral common peroneal nerve or posterior tibial nerve to achieve a similar effect to anal sphincter stimulation (detrusor contractile was effectively inhibited). PTNS was initially designed to treat lower urinary tract dysfunction; however, the associated pain feelings were significantly decreased after therapy, and Van Balken first introduced the use of PTNS in CPP in 2003 [14, 40–42].

PTNS mostly is used according to Stoller [43] and Govier et al. [40], in which the patient is supine or sitting, knees flexed (frog-leg position), and a 34-gauge needle is inserted into the posterior tibial edge of the 3 fingers cephalic of the medial malleolus, between the posterior tibial edge and the soleus tendon. A glued neutral electrode is placed on the same leg near the arch of the foot. The needle and electrode are connected to the stimulator and confirm proper needle placement by great toe flexion and/or fanning or plantar toe flexion of ipsilateral digits 2 through 5. Treatment parameters are: 0–10 mA; 200 µs; 20 Hz; 30 min. The frequency of treatment is usually once a week for 10–12 weeks [14, 44, 45]. Adverse events during PTNS procedures are rare, but can include slight bleeding or transient pain at the insertion site immediately after needle removal. Some patients reported experiencing mild tenderness at the insertion site at the next examination, but this did not preclude further treatment [46].

TTNS uses transcutaneous surface electrodes instead of percutaneous needle electrodes. TTNS is less invasive than the percutaneous technique and more easily accepted by patients [47]. The disadvantage of TTNS is that it may lose efficacy due to fixed-parameter settings, high skin

impedance, and the inaccurate position of the paste, resulting in patients experiencing a decreased therapeutic effect [38].

Van der Pal first described the stimulation of the tibial nerve with an implanted device in 2006 [48]. Implantation devices currently under development for feasibility tests are the RENOVA iStim™ implant (BlueWind Medical, Herzliya, Israel), the battery-powered eCoin™ (Valencia Technologies Corp., Valencia, CA, USA) implant and the StimRouter™ (Bioness, Santa Clarita, CA, USA) implant [37].

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation is a technique that generally includes the use of an electric current generated by a tiny portable device to stimulate nerves via the skin in order to relieve pain [49]. Wall and Sweet [50] pioneered the application of the gate control theory to TENS therapeutic applications. Eight patients with severe chronic cutaneous pain were stimulated by sensory nerves or nerve roots that supply the pain area, and four of them had pain relief. TENS has been routinely used to treat acute and chronic pain since the 1970s [51]. Clinically, TENS is used for stimulation at different frequencies, intensities, and durations of the pulse. According to the frequency, TENS can be divided into low frequency (< 10 Hz), high frequency (> 50 Hz) and burst (bursts of high-frequency stimulation applied at a much lower frequency). While low-frequency TENS provided at a higher intensity and causing muscle contractions is referred to as acupuncture-like TENS, high-frequency TENS supplied at low intensities without eliciting motor contractions is referred to as "conventional TENS" [18]. Gopalkrishnan and Sluka [52] compared different frequencies (high: 100 Hz; low: 4 Hz), strength (high: motor; low: sensory), and pulse duration (100 μs, 250 μs) on primary hyperalgesia in the rat inflammation model. The results showed that the effect of high-frequency stimulation was better than that of low-frequency stimulation, and that there was no statistical significance between different intensities and

pulse duration. In terms of adverse events, TENS is a non-invasive technology and is very safe, with few adverse events reported [53–55]

Electroacupuncture

Acupuncture is a critical component of traditional Chinese medicine and may be one of the earliest of the treatments that resemble neuromodulation [56]. EA is a branch of conventional acupuncture that includes inserting a needle and stimulating the area with electrical pulses rather than manual manipulation [57]. It is worth noting that some acupoints correspond to neuromodulation sites, such as the sacral nerve and tibial nerve, which may serve as mutual confirmation of neuromodulation and acupuncture. There have been limited reports of negative events associated with EA, with patients experiencing temporary low back discomfort at the needling site [58].

Pudendal Neuromodulation

The pudendal nerve, which originates from S2 to S4 of the sacral nerve, is also gaining interest due to its greater range of stimulation of the sacral nerve root than S3 alone [59]. In 1989, Schmidt [60] described the first puncture approach for stimulating or blocking the pudendal nerve. In 2015, Heinze et al. [61] introduced the "STAR" puncture technique, which they compared to the other three puncture procedures (Spinelli technique [62], Bock technique [63], Peters technique [64]). When the clinical outcomes of several procedures were compared in 20 patients with CPPPS, the STAR approach was shown to have the advantages of a shorter surgical time, fewer average puncture times, and improved treatment outcomes. PNM is applied similarly to SNM, and the pulse generator is implanted only after the test stimulation reaches the standard. Peters et al. [65] investigated the impact of PNM on pudendal neuralgia and observed remission in some patients who failed to respond to SNM. However, additional experimental research is required to determine whether PNM is superior to SNM.

NEUROMODULATION CLINICAL APPLICATIONS

Chronic Primary Pelvic Pain Syndrome

Chronic primary pelvic pain syndrome is a condition when the pain originates in numerous organs or when no single organ can be identified as the source of the pain. A variety of outcomes have been reported following the treatment of CPPPS with neuromodulation (Table 2). Everaert et al. [23] retrospectively studied 26 patients with CPPPS who failed to achieve pain relief with pelvic floor training and/or analgesic electrical stimulation and in whom 11 SNM were successfully implanted. After 32 ± 8 months of follow-up, nine of the 11 patients were satisfied with the treatment results according to VAS results. Siegel et al. [66] evaluated ten patients with chronic refractory pelvic pain, focusing on the concomitant psychological problems associated with CPPPS, as well as the effects of SNM on pain, depression, and QoL. At a median follow-up of 19 months, Beck Depression Inventory (BDI) scores had improved in six patients, facilitating overall patient recovery, and nine patients showed a decrease in the severity of their most severe pain compared to baseline, with pain hours decreasing from 13.1 to 6.9 h and transformed scores improving in seven of the eight conceptual areas measured by 36-Item Short-Form Health Survey (SF-36) [66]. On the contrary, Aboseif et al. [31] evaluated the pain intensity of 41 patients with CPPPS and noted that despite a drop in VAS from 5.8 to 3.7 in patients receiving SNM, there was no statistical significance ($p > 0.05$).

Van Balken et al. [14] first investigated the effect of PTNS on CPPPS; 12 weeks after treatment initiation, 14 of the 33 patients (42%) were considered to have subjective responses (patients requested continued treatment to maintain the achieved results), seven patients (21%) had objective responses (VAS reduction of $> 50\%$), and six patients (18%) had partial responses (a reduction of $> 25\%$). In another study, superior outcomes to those of Van Balken et al. were achieved, with 60% of patients improving their VAS score by $> 50\%$ and 30% improving their pain levels by 25–50% [67]. Gokyildiz et al. [45] conducted a randomized controlled trial (RCT) which used VAS, SF-36, McGill Pain Questionnaire (MPQ) and Female Sexual Function Index (FSFI) scores to examine the effect of PTNS treatment on QoL and sexual life in women with CPPPS. The results showed that women in the experimental group experienced significant improvements in emotional functioning, mental health, social functioning, and pain compared to the control group, as well as an increase in FSFI scores.

Schneider et al. [68] conducted prospective research of TENS for male CPPPS and found that after 12 weeks the treatment was considered to be effective in 29 of the 60 patients (48%), with the VAS score reduced from 6.6 (6.3–6.9) to 3.9. (3.2–4.6). The mean follow-up period among these 29 patients was 43.6 months, and the effect was sustained in 21 patients (72%), with significant increases in patients' QoL ($p < 0.001$). Heinze et al. [61] evaluated the efficacy of PNM in 20 patients with CPPPS and found that mean pain relief was statistically significant only when the STAR and Bock methods were used ($p = 0.018$); no statistical significance was demonstrated after a 4-week test period ($p = 0.15$) using unilateral PNM (Spinelli technique and Peters technique).

Primary Prostate Pain Syndrome

The term "primary prostate pain syndrome" refers to persistent or recurrent episodic pain (that may be clearly reproduced by palpating the prostate) in the absence of infection or other apparent local pathology [1]. Prostatitis is classified into four types by the National Institutes of Health (NIH), and PPPS is primarily type III prostatitis (chronic prostatitis/chronic pelvic pain syndrome) [69]. Some experts disagree with the term PPPS and recommend using CPPPS of the male instead of PPPS.

Kabay et al. [44] performed a RCT on PTNS treatment of patients with PPPS (Table 3), in which 89 individuals were randomly allocated to receive PTNS ($n = 45$) or sham treatment ($n = 44$). The PTNS group exhibited statistically

Table 2 Characteristics of studies included in the present review for efficacy of neuromodulation for the treatment of patients with chronic primary pelvic pain syndrome

First author (year)	Design	Patients (n)	Intervention	Comparison	Protocol
Everaert (2001) [23]	Retrospective	26	SNS (n = 26)	Comparison with baseline	NR
Gokyildiz (2012) [45]	RCT	26	PTNS (n = 12)	Routine intervention (n = 12)	12 weeks, 30 min
Schneider (2013) [68]	Prospective	60	TENS (n = 60)	Comparison with baseline	12 weeks, 30 min twice a day
Van Balken (2003) [14]	Prospective	33	PTNS (n = 33)	Comparison with baseline	12 weeks, 30 min
Siegel (2001) [66]	Prospective	10	SNS (n = 10)	Comparison with baseline	NR
Zabihi (2008) [36]	Prospective	30	SNS (n = 30)	Comparison with baseline	NR
Aboseif (2002) [31]	Prospective	64	SNS (n = 64, 41 with pain)	Comparison with baseline	NR
Kim (2006) [67]	Prospective	15	PTNS (n = 30)	Comparison with baseline	12 weeks, 30 min
Istek (2014) [20]	RCT	33	PTNS (n = 16)	Routine intervention (n = 17)	12 weeks, 30 min
Heinze (2015) [61]	Prospective	20	PNM (n = 20) (STAR technique Spinelli technique, Bock technique, Peters technique)	Mutual control	Percutaneous test stimulation (4 weeks)

Table 2 continued

First author (year)	Parameter			Outcome measure	Results	Follow-up (months)	Adverse event
	Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)				
Everaert (2001) [23]	14–21	210	NR	VAS, voiding dysfunction	Test stimulation effective: 16/26 Implant rate: 11/26	32 ± 12	NR
Gokyildiz (2012) [45]	20	200	0.5–10	VAS, SF-36, MPQ, FSFI	VAS: $p < 0.01$; SF-36: EG is better than before PTNS and also better than CG; MPQ: EG vs. CG (all aspects $p < 0.05$) FSFI: NSS	NR	5[b]
Schneider (2013) [68]	80	150	NR	VAS, QoL	VAS: 6.6–3.9 ($p < 0.001$); QoL: $p < 0.001$	43.6	0
Van Balken (2003) [14]	20	200	0–10	VAS, MPQ, SF-36	Subjective and objective responses[a]: subjective: 14 (42%) objective: 7 (21%) VAS: 6.5–5.4 ($p < 0.05$); MPQ: PRI ($p < 0.05$); SF-36: $p < 0.05$	NR	0
Siegel (2001) [66]	NR	NR	NR	VAS, BDI, SF-36	VAS: 9/10 had a decrease in the severity of the worst pain; BDI: 6 had an improved BDI score; SF-36: showed improvement in all 4 physical domains and 3 of the 4 mental domains	19	27[c]

Table 2 continued

First author (year)	Parameter Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)	Outcome measure	Results	Follow-up (months)	Adverse event
Zabihi (2008) [36]	NR	NR	NR	VAS, UDI-6, ICPI, ICSI, SF-36	Implant rate: 23/30 (77%) Improved: VAS: 40% ($p = 0.04$); UDI-6: 26% ($p = 0.05$); ICPI: 38% ($p = 0.007$); ICSI: 35% ($p = 0.005$); SF-36: NSS	15	5 explant, 4 infections[d]
Aboseif (2002) [31]	NR	NR	NR	VD, PS	PS: 5.8–3.7 ($p > 0.05$)	24	12 (18.7%)[e]
Kim (2006) [67]	20	NR	0–10	VAS, IPSS, 3-day frequency-volume charts	VAS: 8.1 ± 0.2 to 4.1 ± 0.6 ($p < 0.01$); VAS for urgency: 4.5 ± 1.0 to 2.7 ± 0.7 ($p < 0.05$); IPSS: NSS; The number of voids and bladder volumes: NSS	NR	Rare[f]
Istek (2014) [20]	20	200	0.5–10	VAS, SF-MPQ, SF-36	VAS: $p < 0.05$; SF-MPQ, SF-36: $p < 0.05$	6	9[g]

Table 2 continued

First author (year)	Parameter			Outcome measure	Results	Follow-up (months)	Adverse event
	Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)				
Heinze (2015) [61]	NR	NR	NR	PS	PS: Bock and STAR technique ($p = 0.018$), Spinelli and Peters technique ($p = 0.15$)	NR	NR

CG Control group, *EG* experimental group, *FSFI* Female Sexual Function Index, *ICPI* Interstitial Cystitis Problem Index, *ICSI* Interstitial Cystitis Symptom Index, *IPSS* International Prostate Symptom Score, *MPQ* McGill Pain Questionnaire, *NR* not recorded, *NRS* Numeric Rating Scale, *NSS* no statistical significance, *PRI* pain rate intensity, *PS* pain scales, *PTNS* percutaneous tibial nerve stimulation, *QoL* quality of life, *RCT* randomized controlled trial, *SF-36* 36-Item Short Form, Health Survey, *SF-MPQ* short-form McGill Pain Questionnaire, *SNS* sacral nerve stimulation, *UDI-6* Urinary Distress Inventory Short Form, *VAS* visual analog scale (pain), *VD* voiding diary

[a]Subjective (patients' request to continue chronic treatment to keep the obtained success) and objective responses (decrease in mean VAS > 50% and VAS < 3 after treatment)

[b]Five patients: 2 patients had slight pain in the 3rd session, 1 patient had slight pain in the 8th and 10th sessions, 1 patient had hematoma in the 12th session, and 1 patient had slight pain
Subjective and objective responses

[c]Local wound complications developed in 6 cases, while new pain at the implanted neurostimulator site in 4 cases required noninvasive re-programming or surgical repositioning of the neurostimulator. In 4 patients the pain location changed and 1 patient reported worse pain relief. Three patients requested permanent explantation due to a return to baseline pain and 2 required revision for a reoperation rate of 50%

[d]Five explants, 4 infections. five (22%) devices were explanted, 4 for failure and 1 for infection. There were 4 (17%) infections, 3 of which underwent revisions, and 1 patient had the device removed

[e]Twelve patients (18.7%). The most common complication was seroma formation at the site of the IPG that resolved spontaneously

[f]There were rare complications with the procedure, including a temporary painful feeling at the insertion site

[g]Nine patients: 7 with slight pain and 2 with mild ecchymosis

Table 3 Characteristics of included studies for efficacy in patients with primary prostate pain syndrome treated with neuromodulation

First author (year)	Design	Patients (n)	Intervention	Comparison	Protocol	Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)	Outcome measure	Results	Follow-up	Adverse event
Sikiru (2008) [70]	RCT	24	TENS (n = 8) Analgesia (n = 8)	Control (n = 8)	20 min, 5 times a week, for 4 weeks	100	100	25	PS	PS: TENS vs. analgesia and control groups (p < 0.05); Analgesia vs. control group (p > 0.05)	NR	NR
Kabay (2009) [44]	RCT	89	PTNS (n = 45)	Sham PTNS (n = 44)	12 weeks, 30 min	20	200	1–10	VAS, NIH-CPSI	PTNS: p > 0.05 VAS: 7.6 ± 0.8 to 4.3 ± 0.6; VAS for urgency: 5.7 ± 0.8 to 3.4 ± 0.7; NIH-CPSI total score: 23.6 ± 6.3 to 10.2 ± 3.6; Sham PTNS: NSS	NR	NR
Seong (2017) [71]	Retrospective	63	HP (n = 32)	SP (n = 31)	15 min, twice a week, for 4 weeks	50	NR	NR	IPSS, NIH-CPSI	IPSS: both groups p < 0.05; NIH-CPSI: both groups p < 0.01	NR	0
Lee (2009) [58]	RCT	39	EA (n = 12)	Sham EA (n = 12), control (n = 12)	20 min, twice a week, for 6 weeks	4	NR	5–10	IPSS, NIH-CPSI	NIH-CPSI total score: EA vs. Sham EA and control: p < 0.001; pain-related symptoms: EA vs. Sham EA and control: p < 0.01	NR	1[a]
Yang (2017) [72]	Retrospective	45	EMS (n = 23), ESB (n = 22)	Mutual control	EMS: 30 min, twice a week, for 6 weeks ESB:45 min, twice a week for 2 weeks, then once a week for 4 weeks	EMS: 10/70; ESB: 10/70	NR	NR	VAS, IPSS, NIH-CPSI	NIH-CPSI: pain, QoL and total score in both groups (all p < 0.05); VAS, IPSS: in both groups (all p < 0.05); EMS vs. ESB: The mean pain score (p = 0.035), QoL (p = 0.012), and total score (p = 0.009) improved significantly in the ESB group compared with EMS group	12 weeks	0

EA Electroacupuncture, *EMS* electromagnetic stimulation, *ESB* electrical stimulation plus biofeedback, *HP* Hwanghyunhaedok pharmacopuncture, *NIH-CPSI* National Institute of Health Chronic Prostatitis Index, *SP* saline pharmacopuncture, *TENS* transcutaneous electrical nerve stimulation; for other abbreviations, see Table 1 footnote
[a]Only 1 Sham EA participant experienced lower back pain near the needling site, which resolved quickly

significant changes in the NIH Chronic Prostatitis Symptom Index (NIH-CPSI), pain, and urgency scale scores, whereas the sham group did not. Sikiru et al. [70] conducted a RCT of TENS in patients with PPPS, and statistical analysis revealed that TENS was much more effective than analgesics and placebo groups. Lee and Lee [58] explored the clinical efficacy of EA, which was performed twice a week for 20 min each time for 6 weeks. Their results showed that after 6 weeks, the EA group's pain and total NIH-CPSI score were significantly lower than those in the sham EA and control groups ($p < 0.001$).

Primary Bladder Pain Syndrome

Primary bladder pain syndrome (PBPS) refers to persistent or recurrent pain in the bladder region accompanied by at least one other symptom, such as increased pain with bladder filling or urinary frequency, without infection or other obvious local pathology [73]. Other terms for this disorder are "interstitial cystitis (IC)," "painful bladder syndrome (PBS)," "PBS/IC," or "BPS/IC", and the definition and diagnosis of this disorder vary from region to region.

The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) formulated criteria for a diagnosis of IC [74]. However, although the definition of IC is appropriate for scientific research, only about one-third of patients are thought to fulfill this diagnosis [75], which is detrimental to the clinical management of patients who have not been diagnosed with IC. The European Society for the Study of Interstitial Cystitis (ESSIC) recommends changing the nomenclature to bladder painful syndrome (BPS) to address this issue [73]. The 2022 EAU guidelines add the word "primary" to BPS, hence the name PBPS. Further classification of PBPS is based on cystoscopic findings with hydrodistention and morphologic findings in bladder biopsies.

TENS and intravaginal electrical stimulation were the first neuromodulation methods used for PBPS [76]. Maher et al. [77] performed a percutaneous sacral nerve root stimulation test on 15 women who had been diagnosed with PBPS (Table 4). As indicated by the Short Urinary Distress Inventory (SUDI) and SF-36, significant improvements in pelvic pain, voiding dysfunction, social functioning, and overall health-related QoL were observed and 73% of women requested to continue with the second phase of implantation. In a retrospective examination of 21 female patients with refractory PBPS treated with sacral neuromodulation, which was measured by VAS, voiding diary and the Urogenital Distress Inventory Short Form (UDI-6), 11 (52%) showed a 50% improvement in bladder pain and voiding symptoms after test stimulation and were considered for permanent implantation [78]. At the 1-year follow-up, significant improvements in bladder discomfort and voiding parameters were found, which were sustained at the 5-year follow-up. Marinkovic et al. [79] conducted a retrospective study of the treatment effect of SNM in 34 patients with refractory PBPS, with an average follow-up of 86 ± 9.8 months and at least a 6-year follow-up for each patient, and found that both the pelvic pain, Urgency/Frequency Patient Symptom (PUF) scale and the VAS score had improved significantly.

The introduction and implementation of the staged test has increased the effectiveness of SNM in patients. The staged test has a much greater success rate of test stimulation than the traditional test, increasing the rate of SNM implantation in the second stage. Comiter [33] examined 17 of 25 patients with PBPS who were eligible for stimulator implantation, including 4/10 (40%) of patients who received standard test stimulation and 13/15 who received the staged test (87%). Peters et al. [34] studied 37 patients with PBPS and discovered that the traditional test resulted in a 52% implantation rate compared to a 94% implantation rate with the staged test, while the traditional test resulted in a 27% reoperation rate compared to a 0% reoperation rate with the staged test.

The therapeutic effect of PTNS on PBPS is controversial. Zhao and Nordling [46] performed weekly PTNS for 10 weeks in 14 patients and found no statistically significant changes in the final pain score, voiding function, Interstitial Cystitis Problem Index (ICPI), Interstitial Cystitis Symptom Index (ICSI), or health status

Table 4 Characteristics of included studies for efficacy in patients with primary bladder pain syndrome treated with neuromodulation

First author (year)	Design	Patients (n)	Intervention	Comparison	Protocol	Parameter			Outcome measure	Results	Follow-up	Adverse event
						Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)				
Sudol (2020) [80]	Prospective	16	PTNS (n = 10)	Comparison with baseline	12 weeks, 30 min	20	200	0–10	VAS, PUF, GRA, ICPI, ICSI	GRA response rate: 40% at week 6 and 30% at week 12; 70% of the cohort had some degree of improvement	NR	0
Zhao (2004) [46]	Prospective	14	PTNS (n = 13)	Comparison with baseline	10 weeks, 30 min	20	NR	0–10	VAS, VD, ICPI, ICSI, SF-36	VAS: NSS; VD: NSS; ICPI, ICSI, SF-36: NSS	NR	Rare[b]
Zhao (2008) [81]	Prospective	18	PTNS (n = 18)	Comparison with baseline	30 min, twice a week, for 5 weeks	20	NR	0–10	VAS, VD, ICPI, ICSI, SF-36	VAS: NSS; VD: nighttime bladder volume: $p < 0.05$; ICPI, ICSI: $p < 0.05$; SF-36: health status scales scores: $p < 0.05$	NR	Rare[b]
Maher (2001) [77]	Prospective	15	SNS (n = 15)	Comparison with baseline	Percutaneous test stimulation	15	210	NR	PS, VD, SF-36, SUDI	PS: 8.9–2.4 ($p < 0.001$); VD: mean voided volume ($p < 0.001$); Mean daytime frequency and nocturia ($p < 0.012$ and 0.007 respectively); SF-36 and SUDI: the quality-of-life parameters of social functioning, bodily pain and general health: $p < 0.05$;	1 week	0
Comiter (2003) [33]	Prospective	25	SNS (n = 25)	Comparison with baseline	NR	16	210	NR	VD, PS, ICSI, ICPI	17/25 qualified for permanent stimulator implantation; VD: mean daytime frequency and nocturia ($p < 0.01$); mean voided volume ($p < 0.01$); PS: 5.8–1.6 ($p < 0.01$); ICSI, ICPI: $p < 0.01$	14 months	0
Peters (2003) [34]	Prospective	37	SNS (n = 37)	Comparison with baseline	Traditional test (n = 21) vs. staged test (n = 16)	NR	NR	NR	VD, Symptoms	Implant rate: Traditional test: 52%; staged test: 94%; Implant patients: 24-h voids reduced 51%; more than 2/3 of patients reported a moderate or marked improvement in symptoms	5.6 months	Eeoperation rate:3/26 (11.5%)

Table 4 continued

First author (year)	Design	Patients (n)	Intervention	Comparison	Protocol	Parameter			Outcome measure	Results	Follow-up	Adverse event
						Pulse frequency (Hz)	Pulse width (µs)	Amplitude (mA)				
Marinkovic 2011 [79]	Retrospective	34	SNS (n = 34)	Comparison with baseline	NR	NR	NR	NR	VAS, PUF	Implant rate: 30/34; VAS: 6.5 ± 2.9 to 2.4 ± 1.1 ($p < 0.01$); PUF: 21.6 ± 8.6 to 9.2 ± 6.6 ($p < 0.01$)	86 ± 9.8 months	Reoperation rate: 8/30 (27%)[c]
Powell (2010) [82]	Retrospective	39	SNS (n = 39)	Comparison with baseline	Traditional test (n = 33) vs. Staged test (n = 11)	NR	NR	NR	Success[a]	Implant rate: 22/39 Traditional test: 13/33 (39.4%) vs. staged test: 9/11 (81.8%) ($p = 0.015$); long-term success: traditional test: 12/13 (92.3%) vs. staged test: 7/9 (77.8%) ($p = 0.329$)	59.9 months	11 (50.0%) devices required explantation[d]
Ghazwani (2011) [78]	Retrospective	21	SNS (n = 21)	Comparison with baseline	NR	14	210	NR	VAS, VD, UDI-6	Implant rate: 11/21 (52%); VAS, VD and UDI-6: significant improvement at 1-year follow-up and maintained at 5-year follow-up	71.5 ± 9.3 months	No extraction[d]
Ragab (2015) [83]	Prospective	20	PTNS (n = 20)	Comparison with baseline	12 weeks, 30 min	NR	NR	NR	VD, VAS, ICPI, ICSI, GRA	VD, VAS, ICPI, ICSI, GRA: NSS	NR	NR

GRA Global response assessment, *ICPI* Interstitial Cystitis Problem Index, *ICSI* Interstitial Cystitis Symptom Index, *PUF* Pelvic Pain and Urgency/Frequency Patient Symptom Scale, *SUDI* Short Urinary Distress Inventory, *UDI-6* Urogenital Distress Inventory Short Form; for other abbreviations, see Table 1 footnote

[a]Success: > 50% improvement of pain/urgency/frequency/urge urinary incontinence

[b]Rare: Minor bleeding immediately after removing the needle or a temporary painful feeling at the insertion site. Some patients had slight tenderness at the insertion site at the next examination

[c]Reoperation rate: 8/30 (27%), five cases of lead migration (secondary to falls and automobile trauma) and three implantable pulse generator erosions (secondary to trauma) without infection

[d]No extraction: Two patients underwent changing of their IPGs due to ended battery life, 3 patients had experienced pain at the site of implantation, of whom 2 of were managed by changing the site of implantation to the other side, and the third patient was managed by adjustment of stimulation parameters (pulse width and amplitudes)

scale scores on the SF-36. They subsequently increased the frequency of stimulation from weekly to twice weekly (for a total of 10 weeks), which resulted in statistically significant changes in nighttime bladder volume, ICPI, ICSI, and SF-36 scores [81]. Ragab et al. [83] offered PTNS to 20 female patients for 12 weeks at a rate of 30 min per week and observed no significant improvements in VAS, ICSI, ICPI, global response assessment (GRA), or voiding diary.

Primary Dysmenorrhea

Menstrual pain without organic pathology is referred to be primary dysmenorrhea (PD) [84]. During the menstrual cycle, pain typically lasts between 8 and 72 h. It is typically characterized by cramps or a dull persistent aching in the lower abdomen that may radiate to the lower back or legs [85]. The main mechanism of PD is believed to be increased prostaglandin release in the endometrium, which results in irregular uterine contractions, decreased uterine blood flow, and ischemia discomfort [86]. Bendek et al. [87] have shown that while pain generally worsens throughout the day and also before and during the first days of menstruation, and symptoms are usually reduced by lying down, this could be due to PeVD.

Nnon-steroidal anti-inflammatory medications (NSAIDs) and oral contraceptives are frequently used to treat PD. These medications, however, are associated with a number of side effects, including nausea, intermenstrual bleeding, and breast soreness [88]. Non-pharmacological therapies have also been indicated, such as acupuncture, physical therapy, exercise, hyperthermia, and TENS [89].

Bai et al. [54] conducted a RCT on TENS for the treatment of PD (Table 5) and found that, compared to the control group, those in the TENS group achieved had a greater analgesic effect in terms of numeric rating scale (NRS), duration of dysmenorrhea pain relief, and quantity of ibuprofen tablets, but no significant difference in QoL. Tugay et al. [85] compared TENS to interfering current (IFC) for PD and discovered that both TENS and IFC were effective for PD, but that TENS was less expensive, more portable, and easier to use.

Combining TENS with hyperthermia is also an effective way to treat PD. Lee et al. [88] used high-frequency TENS in combination with hyperthermia for the treatment of pain in women with PD and showed a significant reduction in pain scores in the study group using an integrated high-frequency-TENS/hyperthermia device, with a statistically significant difference compared to the control group using sham devices. In contrast, Machado et al. [89] divided subjects into the hyperthermia + TENS group, the hyperthermia group, the TENS group, and the placebo group, with all patients receiving either the hyperthermia or the placebo, followed by TENS or the placebo. Only the hyperthermia + TENS group and the hyperthermia group were found to have a better treatment effect, and there was no statistical difference between the TENS group and the placebo group.

Kaplan et al. [53] evaluated the efficacy of a portable TENS device in 102 patients with PD. The results showed marked pain relief in 58 patients (56.9%) and moderate pain relief in 31 patients (30.4%), and the same number of patients stopped or reduced the use of analgesics during the trial. Lauretti et al. [55] also evaluated the safety and effectiveness of a portable TENS device. The average VAS in the TENS group decreased from 8 ± 1 to 2 ± 1 ($p < 0.001$), and the use of analgesics stopped or decreased, while there were no significant changes in pain scores and drug use in the control group, and the QoL in the TENS group was significantly improved ($p < 0.05$).

Another neuromodulation technique that is more common in PD is EA. Armour et al. [90] investigated the effect of varying the frequency of treatment and the use of manual acupuncture or EA on PD symptoms. All groups showed a statistically significant reduction in pain compared to baseline, but there was no difference between groups ($p < 0.05$).

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a chronic or recurrent episodic pain in the bowel associated with a disorder of bowel habits (such as

Table 5 Characteristics of included studies for efficacy in treating patients with primary dysmenorrhea with neuromodulation

First author (year)	Design	Patients (n)	Intervention	Comparison	Protocol	Parameter			Outcome measure	Results	Follow-up	Adverse event
						Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)				
Bai (2017) [54]	RCT	134	TENS (n = 67)	Sham TENS (n = 67)	30 min daily when in pain, for a maximum of 8 days	2–100	NR	NR	NRS, Pain[a], Number[b], WHO-QOL-BREF	NRS: $p < 0.01$; Pain[a]: $p < 0.01$; Number[b]: $p < 0.01$; WHO-QOL BREF: NSS	12 weeks	0
Wu (2012) [91]	RCT	66	AL-TENS (n = 34)	stimulate pseudopoints (n = 32)	20 min, twice a week, for 8 weeks	120	NR	NR	NRS, SF-MPQ	NRS: $p < 0.001$; Total pain score: $p < 0.001$; Change in total pain score: $p < 0.001$	NR	NR
Machado (2019) [89]	RCT	88	Thermotherapy + TENS (n = 22), Thermotherapy (n = 22), TENS (n = 22)	Placebo (n = 22)	Thermotherapy: 20 min, TENS:30 min during 1 menstrual cycle	100	200	NR	NRS, MPQ, PPT, CPM	NRS: $p \leq 0.05$ after 20 min: T[c] + TENS vs. TENS, T vs. TENS and Placebo after 110 min and 24 h: T vs. TENS and Placebo. Abdomen PPT: $p \leq 0.05$ after 50 min: T + TENS vs. TENS and Placebo after 110 min: T + TENS vs. Placebo; T vs. Placebo. Lumbar PPT and CPM: NSS	24 hours	NR

Table 5 continued

First author (year)	Design	Patients (n)	Intervention	Comparison	Protocol	Pulse frequency (Hz)	Pulse width (µs)	Amplitude (mA)	Outcome measure	Results	Follow-up	Adverse event
Lee (2015) [88]	RCT	115	TENS & thermotherapy (n = 57)	Sham TENS (n = 58)	Stimulation 10 min, then thermotherapy during 1 menstrual cycle	100–110	NR	NR	VAS, Pain[a], Number[b], BPI, WHO-QOL BREF	VAS: $p < 0.001$; Change in pain score: $p < 0.001$; Pain[a]: $p < 0.001$; Number[b], BPI and WHO-QOL BREF: NSS	NR	0
Lauretti (2015) [55]	RCT	40	TENS group (TG) (n = 20)	placebo group (PG):(n = 20)	30 min at 8 h intervals when in pain, for up to 7 days	85	NR	L:10 M:20 H: 30	VAS, Number[b], QOL	VAS: TG:8.0 ± 1.0 to 2.0 ± 1.0; PG:8.0 ± 1.0 to 7.0 ± 2.0; TG vs. PG ($p < 0.01$); Number[b]: TG ($p < 0.05$); PG ($p > 0.05$); QOL:TG($p < 0.05$)	3 months	0
Kaplan (1997) [53]	Prospective	102	TENS (n = 102)	Comparison with baseline	Adjust themselves during 2 menstrual cycles	100	100	0–50	PS, Number[b]	Degree of pain relief: Marked:56.9%; Moderate:30.4%; Drug intake during TENS use: Stopped medication:56.9%; Reduced dosage:30.4%	NR	0
Schiotz (2007) [19]	Prospective	21	new TENS device (OVA) (n = 21)	Comparison with baseline	Used the OVA device during every other cycle during 4 menstrual cycles	A:110 B:110 C:100	A: 110 B: 50 C: 2 (brusts)	0–60	VAS, Number[b]	VAS:6.7 ± 2.3 to 5.2 ± 2.2 ($p = 0.0009$); Number[b]: $p = 0.003$	6-8 months	0
Tugay (2007) [85]	Prospective	32	TENS (n = 17)	IFC (n = 15)	20 min	TENS: 120 IFC: 0–100/ 90–100	TENS: 100 IFC:NR	NR	VAS	VAS: TENS: $p < 0.05$; IFC: $p < 0.05$; TENS vs. IFC: $p > 0.05$	24 hours	0

Table 5 continued

First author (year)	Design	Patients (n)	Intervention	Comparison	Protocol	Parameter			Outcome measure	Results	Follow-up	Adverse event
						Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)				
Armour (2017) [90]	Prospective	74	LF-MA ($n = 19$); HF-MA ($n = 18$); LF-EA ($n = 18$); HF-EA ($n = 19$)	Mutual control	HF:3 times during week before menstruation LF: once a week Both start treatment within 48 h after menstruation during 3 menstrual cycles	2/100	NR	NR	NRS, MPD, SF-36	NRS: all groups ($p < 0.001$) between groups ($p > 0.05$); MA vs. EA: less analgesic medication ($p = 0.02$); SF-36: HF vs. LF ($p < 0.05$)	12 months	52/702 $(7.4\%)^d$

BPI Brief Pain Inventory, *CPM* conditioned pain modulation, *HF-EA* high-frequency electrical acupuncture, *HF-MA* high-frequency manual acupuncture, *LF-EA* low-frequency electrical acupuncture, *LF-MA* low-frequency manual acupuncture, *MPD* menstrual pain diary, *PPT* pressure pain threshold, *TENS* transcutaneous electrical nerve stimulation, *WHO-QoL BREF* World Health Organization quality of life (WHO-QoL)-BREF; for other abbreviations, see Table 1 footnote

[a]Pain: The duration of relief from dysmenorrheal pain

[b]Number: The reduced number of analgesics taken

[c]Thermotherapy

[d]52/702 (7.4%): Bruising (3.7%), post-treatment soreness (1.4%), fatigue (1.1%)

constipation, diarrhea, or a combination of constipation and diarrhea) in the absence of confirmed infection or other obvious pathology. Symptoms should appear at least 6 months before diagnosis and within the last 3 months [92].

Patients with IBS pay more attention to the model of complementary and alternative medicine (CAM) due to the unsatisfactory effect of conventional drug treatment [57]. Coban et al. [93] conducted a RCT on the effectiveness of transcutaneous interferential electrical stimulation therapy for patients with IBS; after 4 weeks and 12 sessions of treatment, the severity of symptoms in the interferential current (IFC) group and placebo group was significantly improved. However, the severity of symptoms in the IFC group continued to decrease significantly at 1 month after treatment, while in the placebo group, there was no significant change at 1 month from the end of treatment. In addition, the VAS of the IFC group continued to decrease significantly in the first month after treatment, and the QoL was significantly improved compared with that at the end of treatment. Fassov et al. [94] evaluated the efficacy of SNM in 21 patients with IBS. The results showed that IBS-specific symptom scores decreased with borderline significance during stimulation ($p = 0.0572$), and that pain and the number of daily bowel movements improved significantly during stimulation ($p = 0.0188$; $p = 0.0373$).

Sexual Pain Syndrome

Chronic primary pelvic pain syndrome in this respect mainly involves dyspareunia and pelvic pain with sexual dysfunction. Dyspareunia is pain perceived within the pelvis during intercourse, which applies to both women and men. These patients' sexual dysfunction is caused by chronic pain, urinary symptoms, or psychological problems brought by CPPPS; as a result, their sexual function has improved with CPPPS treatment [95].

Nappi et al. [96] conducted the first study on the therapeutic effect of electrical stimulation (ES) in sexual pain disorders and concluded that

ES may be beneficial in the management of sexual pain disorders. Dionisi and Senatori [97] investigated the safety and efficacy of TENS in the treatment of 45 women with postpartum vulva pain and dyspareunia, with 84.5% of the women reporting pain relief after only five TENS session and 95% of the women achieving complete remission of symptoms at the end of the treatment period (a total of 10 sessions). At the 8-month follow-up, all women were pain free and had fully recovered sexual behavior, with dyspareunia dropping from 2–3 to 0 on the Marinoff Dyspareunia scale ($p < 0.05$). Vallinga et al. [98] evaluated the feasibility of TENS for the treatment of therapy-resistant provoked Vestibulodynia (PVD) in women. VAS scores for vulvar pain were significantly lower after TENS and at follow-up (mean time 10.1 ± 10.7 months) than at baseline, and sexual function scores on the FSFI were significantly higher, and decreased from 23 to 4% of patients undergoing vestibulectomy. Van Balken et al. [95] evaluated the effect of PTNS therapy on patients' sexual dysfunction, in which only 39.1% (9/23) of patients in the subgroup of CPP were subjective respondents (requesting continued treatment), and their sexual satisfaction was not significantly improved.

DISCUSSION

Chronic pelvic pain, especially CPPPS, is difficult to treat because its pathogenesis is not well understood. The effectiveness of pharmacological management is limited, and long-term use may bring other system damage, so it is particularly important to find a more effective treatment. Neuromodulation is a relatively benign therapeutic technique, which bridges the gap between conservative pharmacological management and highly invasive surgical procedures [31].

Each neuromodulation technique has its own advantages and disadvantages. As an invasive technology, SNM requires more specialized skills and equipment, and complications and high costs also need to be considered, especially with the associated high revision rates. However, in recent years, with the advancement of technology and the improvement of operators' ability, the success rate of the treatment of CPP has been increasing [35, 99]. Compared with SNM, PTNS is less invasive, with fewer complications, and has a lower cost. However, PTNS requires outpatient treatment once a week or more, and patients may give up on PTNS treatment for personal reasons, such as scheduling problems [100]. As well, the lack of long-term follow-up studies makes it impossible to judge its long-term effects [101]. TENS has the advantage of being simple and safe to use, patients can even be trained to deliver TENS themselves. In particular, the invention of small portable TENS devices allows patients to hide them under clothing without affecting daily activities [19, 53, 55]. For patients with PD, this can effectively reduce their absenteeism and improve their QoL.

Additionally, EA is less invasive and associated with fewer adverse outcomes. While EA reduces the difficulty of operation in comparison to manual acupuncture, it requires specific acupoint selection, which demands extensive theoretical understanding of traditional Chinese medicine and extensive clinical experience [90]. PNM, compared with S3 stimulation alone, PNS originating from S2, S3, and S4 stimulates the sacral nerve roots more widely and may have a greater effect.

RESEARCH LIMITATIONS AND FUTURE DIRECTION

The main limitation of this paper is that most of the included studies were single-center studies with small sample sizes. We evaluated the quality of the included studies. The included RCTs were evaluated by the Cochrane risk bias assessment tool, and the non-RCTs were evaluated by MINORS criteria. (See Electronic Supplementary Material file 1 for the assessment results). It can be seen that most of the non-RCTs included in the MINORS criteria belong to medium–high quality studies. The bias mainly comes from "Unbiased assessment of the study endpoint" and "Prospective sample size calculation". This is due to the small sample size

included in many studies. As a small sample, single-center study, it is difficult to implement a blind method and set up the control group. But in looking at the whole picture, we included most of the studies belonging to the medium–high quality. Of the included studies, six had a sample size of < 20 persons and all were non-RCT studies. These studies used a number of methods to control bias. For example, Kim et al. [67] kept all patients who underwent history, physical, and urological examination, and the inclusion and exclusion criteria were strictly controlled to avoid secondary pain and other possible confounders. Sudol et al. [80] used more high-quality questionnaires to evaluate the therapeutic effect of PTNS (VAS, PUF, GRA, ICPI, ICSI).

There are still several areas for improvement in the application of neuromodulation technologies in CPP at the present time. To begin with, it is difficult to compare the exact effects of neuromodulation techniques across studies for a variety of reasons, including the following: (1) patients with CPP are a heterogeneous group with multiple definitions, resulting in different patient populations included within different studies at the beginning of the study [27]; (2) stimulus parameters, such as frequency, intensity, and pulse duration, are typically not specified or maintained constant when studies are conducted [18]; (3) the questionnaire used to measure outcomes varied between studies, making direct comparison of treatment outcomes difficult. Due to a lack of data, it is impossible to determine the most appropriate treatment parameters for a variety of patient types, which impedes the customization of a patient's overall treatment plan and has an effect on the final treatment effect. As a result, researchers should make every effort to be consistent, including properly describing and recording the stimulus parameters and evaluating the results using internationally established rating scales.

Second, as a treatment for chronic pain, the long-term therapeutic effect of neuromodulation should be considered, but many studies lack data in this area for a multitude of reasons, most notably for PTNS, where it is difficult to determine the long-term therapeutic effect due

to a lack of long-term follow-up [35]. Another concern is that the QoL should not be neglected. Additionally, the QoL should not be overlooked because CPP has a similar effect on QoL as other chronic illnesses such as diabetes, Crohn's disease, and congestive heart failure [102]. Finally, as a critical component of multimodal treatment, it is crucial to address the psychological issues of patients with CPP [103]. According to a study of 500 patients, 80% of these patients experienced psychological problems, primarily pain-induced depression [104]. The contemporary understanding of pain stresses that psychological variables can significantly influence how noxious inputs are perceived as pain, and that negative emotions can increase sensitivity to pain [105]. Van Balken et al. [95] discovered that patients with poor mental health had a much worse prognosis than those with normal mental health, even when the severity of symptoms was the same. Thus, ignoring psychological problems, simple pain treatment is insufficient, potentially reducing the actual benefit of pain treatment and affecting prognosis. The authors advise that patients' assessments should incorporate pain, comorbid symptoms, psychosocial problems, and QoL, with pain serving as the primary measure and the others as secondary outcomes [101].

There are numerous aspects that could serve as avenues for future studies on the neuromodulation application in CPP: The first aspect is treatment frequency: The optimal frequency of treatment for patients with CPP is unclear, and whether treatment frequency influences treatment outcome is still disputed. Zhao et al. [81] changed the frequency of PTNS treatment and discovered that the effect was better in various symptoms and QoL when compared to previous trials. Finazzi Agro et al. [106] compared the effects of weekly PTNS with 3 weekly PTNS on individuals with overactive bladder syndrome and observed that the frequency change of PTNS treatment had no effect. The second aspect is placebo: a more effective sham treatment group is required because, despite the RCTs, many studies have employed sham stimulation in the placebo group to simply not activate the device, implying that patients in the control group are likely to be aware that

they are not being treated [42, 50]. The third aspect is new devices: the development of new devices may potentially improve therapeutic efficacy [107]. SNM, for example, will lower reoperation rates by developing novel magnetic resonance imaging-safe or rechargeable devices that do not require surgical replacement of the generator [35].

CONCLUSION

Chronic pelvic pain is a highly heterogeneous syndrome, and its pain and various accompanying symptoms significantly impair patients' daily life. Although the precise mechanism of CPP is unknown, central sensitization appears to play a significant role. Pharmacological therapy of CPP is ineffective and is associated with a high number of adverse consequences. As a result, it is crucial to seek individual and diversified treatment. The emergence of neuromodulation has opened a new therapy option for pelvic floor pain. This review demonstrates that neuromodulation can effectively treat pain and symptoms, thereby enhancing patients' QoL, with fewer adverse events, particularly with non-invasive transcutaneous electrical nerve stimulation, which has been associated with few reported adverse effects. However, existing studies lack effective placebo controls and long-term follow-up; therefore, additional research is required to demonstrate efficacy and safety.

ACKNOWLEDGEMENTS

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