Vantaggi ed inconvenienti della neuromodulazione elettrica per il dolore cronico pelvico: una review sistematica

Contesto: Le pazienti che soffrono di dolore pelvico cronico(RPC) possono risentire un dolore refrattario alle strategie classiche di gestione del dolore. La neuromodulazione può attenuare il dolore.

Obiettivi: Valutare i vantaggi e gli inconvenienti della neuromodulazione per la RPC.

Acquisizione dei dati: Una ricerca comopleta di EMBASE, PUBMED e SCOPUS è stata effettuata per l' insieme della banca dati fino a gennaio 2018. Degli studi sono stati selezionati, dei dati sono stati estratti e la qualità è stata valutata da due esaminatori indipendenti. Una metaanalisi è stata utilizzata per combinare gli studi controllo randomizzati(ECR); altrimenti è stata utilizzata un'analisi narrativa.

Sintesi delle evidenze: Dopo aver esaminato 1311 abstract, 36 studi, dei quali 8 ECR, sono stati identificati, includendo 1099 pazienti. Gli studi hanno coperto un grande scala in termini di fenotipi di CPP e di metodi di neuromodulazione. Una metanalisi è stata possibile per la stimolazione percutanea del nervo tibiale e la stimolazione nervosa elettrica transcutanea, che hanno mostrato un miglioramento del dolore. Solo la sintesi narrativa è stata possibile per altre modalità(stimolazione del nervo sacrale, stimolazione del midollo spinale, stimolazione elettrica intravaginale e e stimolazione del nervo pudendo) che sembrano ridurre il dolore nelle pazienti che soffrono di CPP. I trattamenti hanno generalmente migliorato la qualità di vita ma con un tasso variabile di di eventi avversi.Numerosi studi hanno mostrato dei rischi elevati di bias e di confusione

Conclusioni: Nonostante la neuromodulazione possa migliorare i sintomi del RPC, dei lavori supplementari sono necessari con degli studi di alta qualità per confermarlo.

Sintesi del paziente: La neuromodulazione può essere utile per ridurre il dolore e migliorare la qualità dio vita nei pazienti che soffrono di dolore pelvico cronico, ma degli studi supplementari sono necessari

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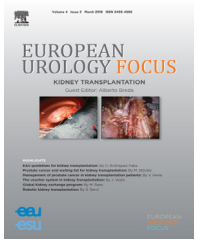

Review – Pelvic Pain

Benefits and Harms of Electrical Neuromodulation for Chronic Pelvic Pain: A Systematic Review

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Abstract

Context: Patients with chronic pelvic pain (CPP) may have pain refractory to conventional pain management strategies. Neuromodulation could provide relief of pain.
Objective: To evaluate the benefits and harms of neuromodulation for CPP.
Evidence acquisition: A comprehensive search of EMBASE, PUBMED, and SCOPUS was performed for the entire database to January 2018. Studies were selected, data were extracted, and quality was assessed by two independent reviewers. A meta-analysis was used to combine randomized controlled trials (RCTs); otherwise, a narrative analysis was used.
Evidence synthesis: After screening 1311 abstracts, 36 studies including eight RCTs were identified, enrolling 1099 patients. Studies covered a broad range in terms of phenotypes of CPP and methods of neuromodulation. A meta-analysis was possible for percutaneous tibial nerve stimulation and transcutaneous electrical nerve stimulation, which showed improvement in pain. Only narrative synthesis was possible for other modalities (sacral nerve stimulation, spinal cord stimulation, intravaginal electrical stimulation, and pudendal nerve stimulation) which appeared to reduce pain in patients with CPP. Treatments generally improved quality of life but with variable reporting of adverse events. Many studies showed high risks of bias and confounding.
Conclusions: While electrical neuromodulation may improve symptoms in CPP, further work is needed with high-quality studies to confirm it.
Patient summary: Neuromodulation may be useful in reducing pain and improving quality of life in patients with chronic pelvic pain, but more research is needed.

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1. Introduction

Chronic pelvic pain (CPP) is chronic or persistent pain perceived in structures related to the pelvis of men and women; pain must have been continuous or recurrent for at least 6 mo [1].

The cause of CPP may be unknown (CPP syndrome) or the pain may be due to identifiable disease. The prevalence of

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CPP has been reported as 5.7% in women and 2.7% in men [2]. A recent questionnaire study of adult women in the UK found a prevalence of CPP of 14.8% [3]. These individuals may suffer significant distress and detriment to their daily living and quality of life (QOL).

While there are various treatment options for individuals with CPP, the efficacy of single-modality treatment is limited [4]. Treatment options include physical treatment (eg, physiotherapy) pharmacological treatment (eg, analgesia, antibiotics, and antidepressants), intravesical treatments, surgical management, or psychological therapy. A combination of pharmacological treatment (such as alpha-blockers, anti-inflammatories, and antibiotics for prostate pain syndrome) may be considered and has been found to confer greater benefit than monotherapy in some conditions [5].

Importantly, there is marked heterogeneity among patients with CPP that complicates evaluation of treatments. A method of phenotyping patients with chronic prostate pain according to presentation as urinary, psychosocial, organ-specific, infection, neurological/systemic, and tenderness symptoms has been described [6]. Where management was tailored to the patient's phenotype, there was a significant improvement in QOL and symptoms. When these strategies fail, further therapeutic options can be limited.

Electrical nerve stimulation, in its many forms, has been used to treat pain conditions. The exact mechanism by which neuromodulation achieves pain control is unknown. The gate-control theory of pain proposes that stimulation of larger myelinated afferent nerve fibers can inhibit transmission in smaller nociceptive fibers [7]. Newer techniques of neurostimulation suggest that other mechanisms may be involved [8].

Electrical nerve stimulation has also been shown to be effective in the treatment of bladder dysfunction. Patients with refractory overactive bladder and pain were treated with percutaneous tibial nerve stimulation (PTNS), and in addition to an improvement in urinary symptoms, patients reported a significant improvement in pelvic pain [9,10].

There are many electrical nerve stimulation techniques and devices. These range from externally applied and non-invasive techniques used in an outpatient setting, such as transcutaneous electrical nerve stimulation (TENS), to implantable and invasive techniques that require sedation (local or general anesthesia), such as sacral nerve stimulation (SNS) or spinal cord stimulation (SCS). As techniques differ so widely, it is important to consider not only their efficacy, but also their safety and adverse effects.

The objective of this review was to determine the efficacy and safety of electrical neuromodulation in the treatment of CPP. Primary outcomes are benefit (ie, improvement in pain and QOL) and harm (adverse events following treatment).

2. Evidence acquisition

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11]. The protocol for the review is available on PROSPERO (CRD42017054893; https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054893).

2.1. Data sources and searches

We systematically searched EMBASE, Medline, the Cochrane Central Register of Controlled Trials, and the Health Technology Assessment Database (from 1945 to January 2018). The search strategy is included in the Supplementary material. Titles and abstracts were retained for selection, after search results were combined and deduplicated.

2.2. Study selection

There was no restriction on primary study design (ie, to include randomized controlled trials [RCTs], nonrandomized comparative studies, single-arm case series, prospective and retrospective studies, and observational studies). Single-arm case-series were included if there were >10 participants and at least one baseline measurement. Case reports, editorial commentaries, and systematic or narrative reviews were excluded. There was no language restriction.

The inclusion criteria required the following: (1) trials with assessment before and after neurostimulation treatment; (2) adult participants with CPP (including all phenotypes of CPP), excluding those undergoing treatment for cancer but not excluding cancer survivors, and excluding pelvic organ prolapse (unless postoperative pain); (3) neuromodulation by any form of electrical neurostimulation; and (4) reporting outcomes included pain (as defined by the trialist).

Two review authors (A.C. and S.G.) independently screened titles and abstracts of identified records to identify potentially eligible trials, and then obtained full papers to determine the final set of studies. Where there was discrepancy between reviewers, a third reviewer was consulted (M.S.) and consensus was achieved.

2.3. Data extraction and risk of bias

Full text of potentially eligible studies was reviewed and data were extracted. Variables extracted were (wherever available) the following: year of publication, number and sex of participants, age of participants, type of pain syndrome, mean duration of symptoms, type of intervention, and specifics of stimulation (including protocol, frequency, pulse width, and amplitude). Outcomes were pain and adverse events (primary outcomes) and QOL (secondary outcomes). Data were extracted by two reviewers, and discrepancies were resolved as before. Where information was missing, authors were contacted.

For RCTs, the Cochrane Risk of Bias Assessment tool was used, including assessment of sequence generation (selection bias), allocation concealment (selection bias), blinding of participants, personnel and outcome assessors

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(performance bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias) [12]. For non-RCT studies, the Cochrane tool was used, and in addition, an a priori list of confounders was identified with clinical content experts (members of the European Association of Urology [EAU] Chronic Pelvic Pain Guidelines Panel). This enabled consideration of each confounder and determination of whether it was controlled for. These potential confounders were sex of patients, phenotype of CPP, presence of bowel or bladder dysfunction, distress or catastrophizing, and type of neurostimulation (including parameters and duration of treatment).

2.4. Data synthesis

For each of the included RCT studies using pain score (out of 10), we calculated the effect size (ES) and corresponding 95% confidence intervals (CIs). Since data were sparse, the meta-analysis addressed broad questions across study design. We calculated the overall standard mean difference between treatment and control groups using a random-effect model. Forest plots were generated in order to provide a visual representation of the results and to illustrate the direction and magnitude of effects.

No pooling was planned for non-RCTs due to different study designs and the expected clinical and methodological heterogeneity of included studies, but forest plots were generated to provide a visual representation of results to show the direction and magnitude of effects before and after treatment in studies reporting primary outcome of pain as a pain score.

Analyses were performed using the "metan" command of the Stata statistics software package (Stata 14.0 and 9.0 statistics software package, StataCorp 2009 Stata Statistical, SoftwardeRelease 14; StataCorp LP, College Station, TX, USA). Risk of bias summary and graph (Supplementary Fig. 1 and 2) were generated using Cochrane RevMan software v5.3 (Informatics and Knowledge Management Department, Cochrane, London, UK).

3. Evidence synthesis

3.1. Search results

The PRISMA diagram illustrates the literature search and results (Fig. 1). The final 36 studies consisted of eight RCTs, four randomized noncontrolled trials, one crossover trial, 18 prospective cohort studies, and five retrospective case series studies.

3.2. Study and patient characteristics

Table 1 describes the characteristics of included studies. Tables 2–4 describe outcomes of RCTs and non-RCTs.

3.3. Benefits and harms of electrical neuromodulation techniques

Fig. 2A shows the meta-analysis of the difference in pain scores between treatment groups and control in RCTs. An

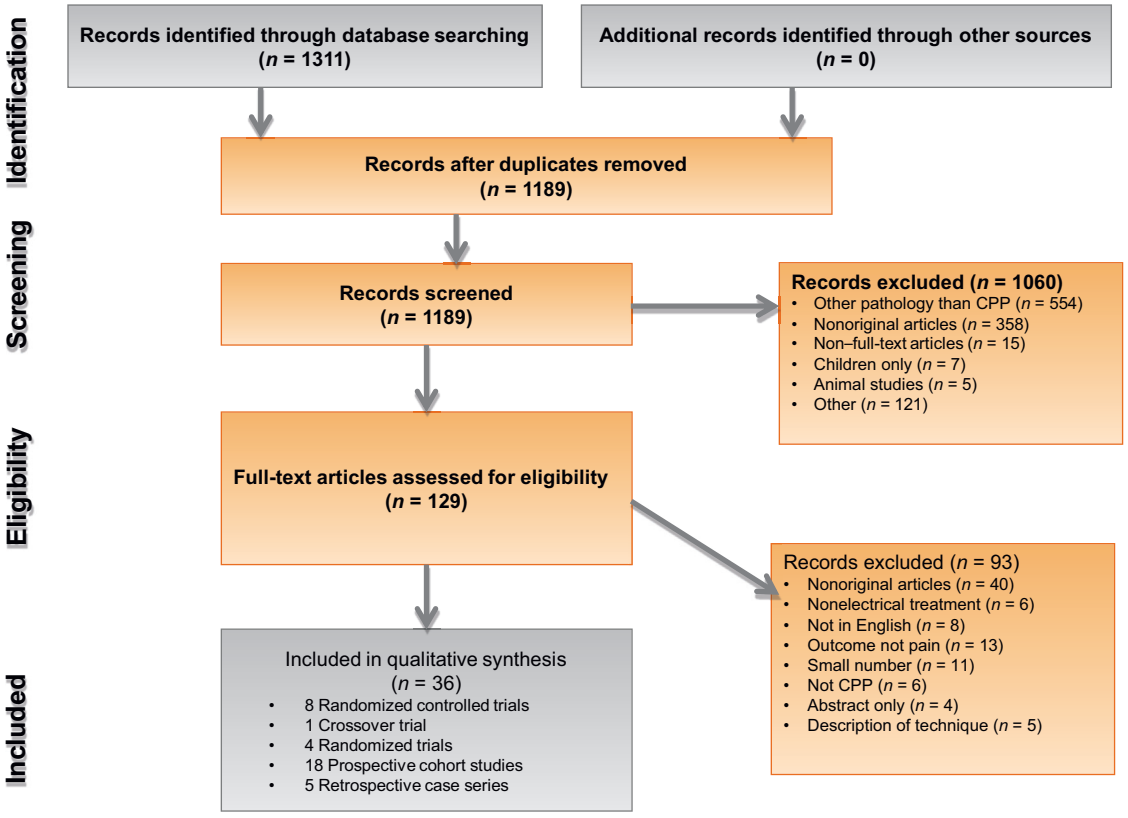

Fig. 1 – PRISMA flow diagram. CPP = chronic pelvic pain; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

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Table 1 – Characteristics of included studies.

Study	Total patients (female/male)	Mean age	Pain syndrome	Mean duration of symptoms (mo)	Intervention	Pulse frequency (Hz)	Pulse width (μs)	Amplitude (mA)	Protocol	Outcome measure	Time to follow-up (wk)	Adverse event/ reoperation rate (%)
Bai [29]	Cont 67 (67/0)	24.9	Dys	NR	Sham TENS	Nil	nil	Nil	30 min daily when in pain max. 8 d	PS, WHO-QOL BREF	12	0
	Exp 67 (67/0)	25.6	Dys	NR	TENS	2–100	NR	NR				0
Coban [46]	Cont 29 (24/5)	40.5	IBS	36	Sham TIES	Nil	Nil	Nil	Sham device	PS, IBS-GAI NRS, IBS-QOL	4	0
	Exp 29 (19/10)	43.1	IBS	36	TIES	80–150	NR	15–25	12 × 15 min			0
Gokyildiz [23]	Cont 13 (13/0)	NR	CPP	47	Routine	Nil	Nil	Nil	Nil	PS, SF-36 QOL, MPQ, FSFI	12	0
	Exp 13 (13/0)	NR	CPP	46	PTNS	20	200	0.5–10	12 × 30 min			8 [1]
Istek [24]	Cont 17 (17/0)	38.8	CPP	48	Control	20	200	0.5–10	12 × 30 min	PS, MPQ, SF-36	24	0
	Exp 16 (16/0)	44.4	CPP	47	PTNS	NR	Nil	Nil	Nil			0
Kabay [25]	Cont 44 (0/44)	38.5	CPP	46.5	Control	Nil	200	Nil	Nil	PS, VP, NIH-CPSI	12	NR
	Exp 45 (0/45)	37.9	CPP	54	PTNS	20	200	0.5–10	12 × 30 min			NR
Lauretti [30]	Cont 20 (20/0)	20	Dys	NR	Sham TENS	Nil	Nil	Nil	30 min at 8 h intervals when in pain; disposable device	PS, analgesia use, QOL	12	0
	Exp 20 (20/0)	20	Dys	NR	TENS	85	NR	Variable				0
Lee [31]	Cont 58 (58/0)	27.0	Dys	NR	Sham TENS	Nil	Nil	Nil	Sham disposable device	PS, analgesia use, WHO-QOL BREF	NR	0
	Exp 57 (57/0)	28.1	Dys	NR	TENS & thermotherapy	100–110	NR	NR	Stim/10 min then 20 min thermotherapy during 1 menstrual cycle max 8 d			0
Sikiru [32]	Exp 8 (0/8)	38.17	PPS	NR	TENS	100	100	25	20 min 5× wk for 4 wk	PS	4	NR
	Cont 8 (0/8)	46.83	PPS	NR	Control	Nil	Nil	Nil	Nil			NR
	Cont 8 (0/8)	45.38	PPS	NR	Analgesia	Nil	Nil	Nil	Nil			NR
Nonrandomized controlled trials												
Aboseif [13]	64 (54/10) 41 with pain	47	CPP [a]	69	SNS	NR	NR	NR	NR	PS	96	18.7 [2]
Armour [47]	Exp 19 (19/0)	31.1	Dys	NR	Low freq MA	Nil	Nil	Nil	3× every 7–10 d & days 1 & 2, & hand needle stimulation	PS, symptom diary, SF-36	52	7.4 [3]
	Exp 18 (18/0)	29.9	Dys	NR	High freq MA	Nil	Nil	Nil	3× during week before menses & days 1 & 2, & hand needle stimulation			
	Exp 18 (18/0)	29.3	Dys	NR	Low freq EA	2/100	NR	NR	3× every 7–10 d & days 1 & 2, & electrical stimulation			
	Exp 19 (19/0)	31.2	Dys	NR	High freq EA	2/100	NR	NR	3× during week before menses & days 1 & 2, & stimulation			
Buffenoir [45]	27; 20 implanted (NR)	NR	PN	NR	SCS	50–100	100–200	1.4–8.7	NR	PS	60	0
Comiter [14]	26; 17 (16/1) implanted	46	IC	NR	SNS	16	210	NR	NR	PS, ICSI, ICPI, VP	56	0
Feler [15]	11; 10 (NR) implanted	NR	IC	NR	SNS	NR	NR	NR	NR	PS	NR	33 [4]
Ghazwani [16]	21; 11 (11/0) implanted	44.3	BPS	36	SNS	14	210	NR	4–7 d	PS, VP, UD1-6	71.5	27 [5]
Heinze [43]	20 (NR)	NR	CPP	NR	PNS	NR	NR	NR	4 wk test period	PS	4	0
Kaplan [33]	62 (62/0)	NR	Dys	NR	TENS	100	95	50 Vmax	PRN	PS	Acute	NR
Kaplan [34]	102 (102/0)	18.2	Dys	NR	TENS	100	100	NR	PRN	PS	Acute	NR
Kim [26]	15 (10/5)	60	IC	68.4	PTNS	20	NR	0–10	12 × 30 min	PS, VP, SF-36, SUDI	12	"Rare"
Maher [17]	15 (15/0)	62	IC	62.4	SNS	15	210	NR	NR	PS, VP, SF-36	1	0
Marinkovic [18]	34; 30 (30/0) implanted	41	IC	93.72	SNS	NR	NR	NR	NR	PS, VP, PUF, satisfaction	86	27 [6]
Mira [35]	Exp 11 (11/0)	41	Endo	15	Acupuncture like TENS	8	NR	NR	Weekly/8 wk	PS, QOL	8	NR
	Exp 11(11/0)	30.9		20.4	TENS	85	NR	NR	Twice a day for 20 min		8	NR

Table 1 (*Continued*)

Nonrandomized controlled trials												
De Oliveira [41]	24 (24/0)	35.8	CPP	NR	IES	8	1	NR	10 sessions	PS	28	NR
De Olviera [42]	Cont/Exp 15 (15/0)	40	CPP	NR	IES/placebo	8	NR	NR	10 × 30 min twice/wk	PS	Acute	NR
	Exp/Cont 11 (11/0)				Placebo/IES	8	NR	NR				
Peters [19]	37; 26 (20/6) implanted	45	IC	NR	SNS	NR	NR	NR	NR	CSR	22.4	11.5 [7]
Peters [44]	19 (12/7)	54.8	PN	NR	PNS	NR	NR	NR	NR	GRA	2	NR
Powell [20]	39 (32/7) 22/39 implanted; 17/22 with pain	54.4	BPS	NR	SNS	NR	NR	NR	NR	% without pain; success [b]	239.6	50 [8]
Ragab [27]	20 (20/0)	40.8	BPS	54	PTNS	NR	NR	NR	12 × 30 min	PS, VP, ICSI, ICPI, GRA	12	NR
Schneider [36]	60 (60/0)	46.9	CPP	NR	TENS	80	150	NR	30 min twice a day for 12 wk	PS, QOL	12	0
Schiotz [37]	21 (21/0)	24	Dys	NR	TENS	Variable	Variable	NR	PRN	PS	Acute	NR
Siegel [21]	10 (9/1)	48	CPP	36	SNS	NR	NR	NR	NR	PS, SF-36	19 (median)	27 (total) [9]
Thomas [38]	12 (12/0)	32.2	Dys	NR	TENS	low 2; high 100	NR	NR	2 treatments/mo, 3 modes, 3 mo; patient choice in final month	PS	12	NR
	19 (19/0)	32.2	Dys	NR	EA	low 2; high 100	NR	NR			12	NR
Tugay [39]	Exp 17 (17/0)	21.29	Dys	NR	TENS	120	100	NR	20 min	PS	24 h	0
	Exp 15 (15/0)	21.4	Dys	NR	TIES	0–100	NR					
Vallinga [40]	Cont 17 (17/0)	26.7	PV	NR	TENS	80	50–180	NR	90 min/d for 12–16 wk	PS, FSFI, FSDS, MPQ	40.4	NR
Van Balken [28]	33 (33/11)	51.6	CPP	60	PTNS	20	200	0–10	12 × 30 minute	PS, GR	12	NR
Yang [48]	Exp 23 (0/23)	45.6	CPP	20.4	EMS	NR	NR	NR	Twice weekly for 6 wk	PS	12	NR
	Exp 22 (0/22)	43.4		30.4	ES plus biofeedback	NR	NR	NR	Twice weekly for 2 wk, then once weekly for 4 wk			
Zabihi [22]	30 (21/9); 23/30 implanted	46.3	CPP	NR	SNS	NR	NR	NR	NR	PS, ICSI, ICPI, UD1-6, SF-36, % improvement in symptoms, GR	26	22 (explantation); 17 (infection)

AE = adverse events; BPS = bladder pain syndrome; Cont = control; CPP = chronic pelvic pain; CSR = Dys = dysmenorrhea; EA = electrical acupuncture; EMS = electromagnetic stimulation; Endo = endometriosis-related pain; ES = electrical stimulation; Exp = experimental; IBS = irritable bowel syndrome; FSDS = Female Sexual Distress Scale; FSFI = female sexual function index; GRA = global response assessment; IBS-GAI NRS = IBS global assessment index numerical rating score; IBS-QOL = IBS quality of life score; ICPI = interstitial cystitis problem index; ICSI = interstitial cystitis symptom index; IES = intravaginal electrical stimulation; High freq EA = high-frequency electrical acupuncture; High freq MA = high-frequency manual acupuncture; IC = interstitial cystitis; Low freq EA = low-frequency electrical acupuncture; Low freq MA = low-frequency manual acupuncture; MPQ = McGill Pain Questionnaire; NIH-CPSI = National Institute of Health Chronic Prostatitis Index; NR = not recorded; PN = pudendal neuralgia; PNS = pudendal nerve stimulation; PPS = prostate pain syndrome; PS = pain score; PTNS = percutaneous tibial nerve stimulation; PUF = pelvic pain and urinary urgency frequency patient index; PV = provoked vestibulodynia; QOL = quality of life; SCS = spinal cord stimulation; SF-36 = Short Form (36) Health Survey; SNS = sacral nerve stimulation; SUDI = Standard Urogenital Distress Inventory; TENS = transcutaneous electrical nerve stimulation; TIES = transcutaneous interferential electrical stimulation; UD1-6 = urogenital distress inventory short form; WHO = World Health Organization; 1 = hematoma; 2 = seroma, superficial wound infection, mechanical failures, and reimplantation; 3 = bruising, soreness, and fatigue; 4 = intrathecal implant, systemic infection and explantation, and allodynia; 5 = pain leading to change of implantation site and change in stimulation parameters; 6 = reoperation rate; 7 = reoperation rate; 8 = explantation; 9 = complications in total (wound problem, pain, urinary tract infection, implant infection, electric shock, explantation, and revision).

[a]CPP as a subgroup of voiding dysfunction.

[b]Success = >50% improvement of pain/urgency/frequency/urge urinary incontinence.

Table 2 – Treatment outcomes of randomized controlled studies.

Author			Pain scores									
	Total patients	Group	NRS before	SD	NRS after	SD	*p* value	NIH-CPI pain index before	SD	NIH-CPI pain index after	SD	*p* value
Bai [29]	67	Cont	7.2/10	1.4	6.7/10	NR	<0.01	NR	NR	NR	NR	NR
	67	Exp	7.3/10	1.4	5.4/10	NR	<0.01	NR	NR	NR	NR	NR
Coban [46]	29	Cont	66.6/100	23.4	28.1/100	26.5	<0.001	NR	NR	NR	NR	NR
	29	Exp	56/100	20	21.3/100	20.9	<0.001	NR	NR	NR	NR	NR
Gokyildiz [23]	13	Cont	7.95/10	1.03	7.87/10	0.88	NR	NR	NR	NR	NR	NR
	13	Exp	8.08/10	1.72	2.62/10	2.7	NR	NR	NR	NR	NR	NR
Istek [24]	17	Cont	6.5/10	1.1	6/10	1.5	0.213	NR	NR	NR	NR	NR
	16	Exp	8.4/10	1.1	3.8/10	3.5	0.001	NR	NR	NR	NR	NR
Kabay [25]	44	Cont	7.4/10	0.9	7.2/10	0.4	>0.05	NR	NR	NR	NR	NR
	45	Exp	7.6/10	0.8	4.3/10	0.6	<0.001	NR	NR	NR	NR	NR
Lauretti [30]	20	Cont	8/10	NR	7/10	NR	NR	NR	NR	NR	NR	NR
	20	Exp	8/10	NR	2/10	NR	<0.001	NR	NR	NR	NR	NR
Lee [31]	58	Cont	5.98/10	1.36	5.64/10	1.58	NR	NR	NR	NR	NR	NR
	57	Exp	6.01/10	1.03	4.23/10	1.5	<0.001	NR	NR	NR	NR	NR
Sikiru [32]	8	Cont	NR	NR	NR	NR	NR	20.25	3.73	15.88	1.55	NS
	8	Exp	NR	NR	NR	NR	NR	16.38	2.88	9	0.93	<0.05
	8	Analgesic	NR	NR	NR	NR	NR	17.13	4.91	13.38	1.5	NS

Exp = experimental; NIH-CPI = National Institute of Health Chronic Prostatitis Symptom Index; NR = not recorded; NRS = Numeric Rating Scale; Cont = control; NS = not significant; SD = standard deviation.

Table 3 – Pain outcomes of non-RCT.

Author	No. of patients/therapy	NRS before	NRS after	*p* value
Aboseif [13]	41/SNS	5.8/10	3.7/10	>0.05
Armour [47]	19/low freq MA	5.5/10	4/10	<0.001
	18/high freq MA	4.4/10	2.9/10	<0.001
	18/low freq EA	5.5/10	4.2/10	<0.001
	19/high freq EA	5.7/10	4.2/10	<0.001
Buffenoir [45]	20/SCS	55.0/100	26.2/100	<0.001
Comiter [14]	25/SNS	5.8/10	1.6/10	<0.01
Feler [15]	10/SNS	9.1/10	4/10	NR
Ghazwani [16]	11/SNS	8.09/10	5/10	<0.001
Heinze [43]	20/PNM	85 mm	40 mm	0.018
Kim [26]	15/PNS	8.1/10	4.1/10	<0.01
Maher [17]	15/SNS	8.9/10	2.4/10	<0.001
Marinkovic [18]	30/SNS	6.51/10	2.43/10	
Mira [35]	11/acupuncture-like TENS	5.73/10	2.55/10	0.002
	11/TENS	5.95/10	2.48/10	<0.001
De Oliveira [41]	24/IES	8.3/10	2.1/10	<0.05
Ragab [27]	20/PNS	5.65/10	5.25/10	NS
Schneider [36]	60/TENS	6.6/10	3.9/10	<0.001
Schiotz [37]	21/TENS	6.73/10	5.18/10	0.0009
Siegel [21]	10/SNS	4.7/5	2.2/5	NR
Thomas [38]	12/TENS	375/900	245/353 [a]	<0.05/NS
Tugay [39]	15/EA	72.2/100	17.5/100	<0.05
	17/TENS	79.4/100	21.2/100	<0.05
Thomas [38]	12/TENS	375/900	245/353 [a]	<0.05/NS
	19/acupuncture [26]	412/900	280/210 [a]	<0.05/<0.01
Vallinga [40]	39/TENS	8	3.2	<0.01
Van Balken [28]	33/PNS	6.5	5.4	<0.05
Yang [48]	23/EMS	5.5	3	<0.001
	22/ES plus biofeedback	5.9	2.4	<0.01

EA = electrical acupuncture; EMS = electromagnetic stimulation; ES = electrical stimulation; IES = intravaginal electrical stimulation; SNS = sacral nerve stimulation; SCS = spinal cord stimulation; high freq EA = high-frequency electrical acupuncture; high freq MA = high-frequency manual acupuncture; low freq EA = low-frequency electrical acupuncture; low freq MA = low-frequency manual acupuncture; NR = not recorded; NRS = Numeric Rating Scale; NS = not significant; PNM = pudendal neuromodulation; PNS = percutaneous tibial nerve stimulation; RCT = randomized controlled trial; TENS = transcutaneous electrical nerve stimulation.

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Table 4 – Treatment outcomes of non-RCT: change in pain trialist–defined outcomes.

Author	No. of patients/ therapy	Trialist-defined outcomes (decrease in pain)				GRA: improvement in pain in % patients			Trialist-defined outcome		
		Marked response (%) *	Moderate response (%) **	Mild/no response (%) ***	Mod-marked improvement (%)	Small/ slight	Significant/ remarkable	Almost/ complete	Complete	% Cured	Improvement in NRS (%)	% Reduction in max NRS	% Reduction in average NRS
Buffenoir [45]	20/SCS											53.5	51.4
Kaplan [33]	62/TENS	31.2	59	9.8									
Kaplan [34]	102/TENS	56.9	30.4	12.7									
Peters [19]	26/SNS				71								
Peters [44]	19/PNM					16	52	16	16				
Powell [20]	39/SNS									77			
Zabihi [22]	23/SNS										40		

GRA = global response assessment; NRS = Numeric Rating Scale; PNM = pudendal neuromodulation; RCT = randomized controlled trial; SCS = spinal cord stimulation; SNS = sacral nerve stimulation; TENS = transcutaneous electrical nerve stimulation.

overall ES of −2.41 (95% CI −2.87, −1.95) was found, representing statistically significant benefit of treatment over control and translating to an improvement in pain score of 2.4/10, a clinically meaningful amount.

For non-RCTs, Fig. 2B and C show forest plots of change in pain scores before and after the procedure by condition and treatment, respectively.

3.3.1. *Benefits and harms of SNS*

A total of 10 studies evaluating the efficacy of SNS were identified [13–22], comprising six prospective cohort studies [13–15,17,19,22] and four retrospective case series [16,18,20,21]. No RCTs were identified. Follow-up ranged from 4 to 239 mo. Pain conditions as defined by authors included CPP, bladder pain syndrome (BPS), and interstitial cystitis (IC; Table 1). Where reported, a mean of 69% of patients undergoing test stimulation proceeded to formal implantation (range 52–91%).

All studies reported a decrease in pain score following SNS. In some studies, the primary outcome was reported as a pain score (out of 10), which is illustrated in Fig. 2C; this was statistically significant in five studies [14,16–18,22] although not significant in one [13]. A decrease in score following treatment ranged from 3.1 to 6.5/10 [13–17], with a mean reduction of 4.4/10. One study reported a marked improvement in pelvic pain in 71% of participants [19]; another long-term study found that 64% of patients reported no pelvic pain at the last clinic visit with average follow-up of approximately 5 yr [20].

QOL parameters were measured in three studies [17,21,22]. There was some statistically significant improvement in QOL, as measured by the Short Form (36) Health Survey (SF-36) questionnaire in two studies, including general health, bodily pain and social functioning, and physical domains, social functioning, and mental health [17,21], but another study reported no statistically significant improvement in QOL following SNS.

Safety of SNS was reported in all 10 studies. No adverse events were described in two studies [14,17]. There was a large variation in adverse events and in details reported. The reported rates of adverse events ranged from 0% to 50%. Events not requiring reoperation included pain, failure of function of device, wound infection, and seroma. Where reported, reoperation rate ranged from 11% to 50% [18–20,22]. Indication for reoperation included lead migration, malfunction, systemic infection, intrathecal implantation, erosion, and loss of efficacy (Table 1).

3.3.2. *Benefits and harms of PTNS*

Six studies, three RCTs, and three non-RCTs evaluated the efficacy of PTNS in CPP [23–28]. Follow-up ranged from 12 to 24 wk. Pain conditions were CPP, IC, and BPS.

All three RCTs demonstrated a statistically significant reduction in pain scores, with the mean reduction of score ranging from 3.3 to 5.3/10; no significant reduction was seen in control groups (no treatment or sham PTNS) [23–25]. In two of three non-RCTs, there was a significant reduction in pain score following treatment for CPP and IC [26,28], but the third study demonstrated no significant

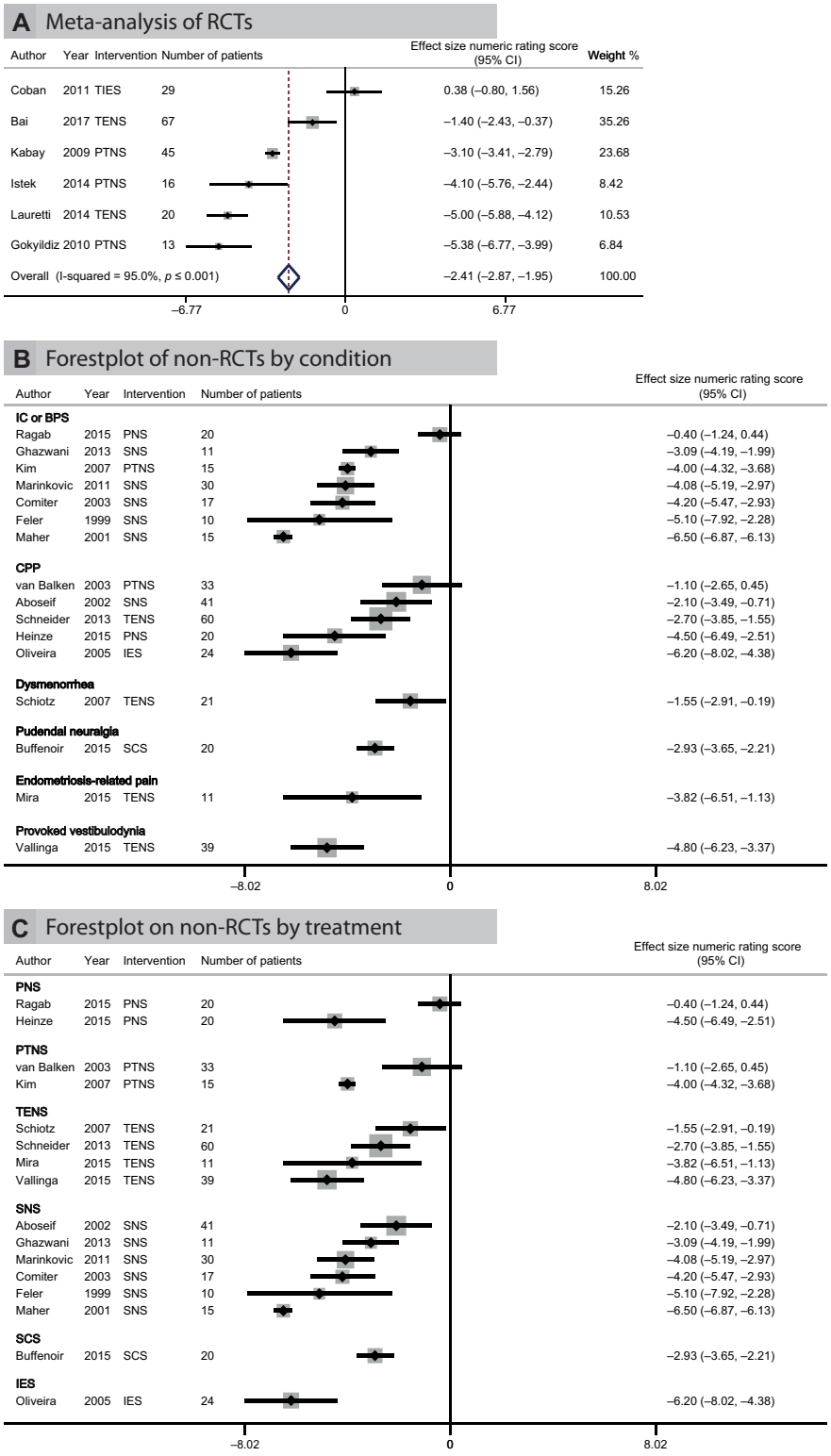

Fig. 2 – Pain scores in RCTs and non-RCTs. (A) Meta-analysis of the difference in pain scores between treatment groups and control in RCTs. For non-RCTs, forest plots of change in pain scores before and after the procedure by (B) condition and (C) treatment. BPS = bladder pain syndrome; CI = confidence interval; CPP = chronic pelvic pain; IC = interstitial cystitis; IES = intravaginal electrical stimulation; PNS = pudendal nerve stimulation; PTNS = percutaneous tibial nerve stimulation; RCT = randomized controlled trial; SCS = spinal cord stimulation; SNS = sacral nerve stimulation; TENS = transcutaneous electrical nerve stimulation; TIES = transcutaneous interferential electrical stimulation.

improvement in pain for BPS (Table 3) [27]. One RCT evaluating long-term effect of PTNS found that the improvement in pain score in PTNS group was maintained at 6-mo follow-up [24].

All three RCTs examined QOL following PTNS for CPP. All demonstrated a statistically significant improvement in QOL as measured by the SF36 [23,24] and National Institute of Health Chronic Prostatitis Index (NIH-CPSI)/QOL domain [25]. At 6 mo after the procedure, a continued significant improvement in the social functioning score was observed [24]. QOL was measured in two non-RCTs, demonstrating a significant improvement in QOL measured by SF-36 in one study [28], but no improvement in QOL as measured using the International Prostate Symptom Score QOL domain in another [26].

Adverse events were rare following PTNS and reported in three of six studies [23,24,26]. Temporary slight pain at the surgical site was described in all studies where adverse events were reported and hematoma in one patient [23].

3.3.3. *Benefits and harms of TENS*

Twelve studies, including four RCTs, evaluated the efficacy of TENS for CPP [29–40]. One RCT combined TENS and thermotherapy [31]. Follow-up of RCTs ranged from 4 to 12 wk (not recorded in one study). Follow-up of non-RCTs ranged from immediately following treatment to 40 wk. Pain conditions were dysmenorrhea, endometriosis-related pain, CPP, provoked vestibulodynia (PV), and prostate pain syndrome.

Three RCTs found a statistically significant reduction in pain following TENS therapy (mean reduction of 1.9 and 4/10) or NIH-CPSI pain domain, compared with either sham or placebo [29,30,32]. When TENS was combined with thermotherapy and compared with sham, a significant reduction of 1.8/10 was reported [31].

Regarding non-RCTs, a statistically significant reduction in pain score was reported in three studies [38–40]. Two studies of TENS for dysmenorrhea reported a moderate or marked improvement in pain in 91.2% and 87.3% of patients, although 9.8% and 12.7%, respectively, reported no or mild improvement [33,34]. One study compared two methods of TENS (self-applied and acupuncture-like TENS) in women with endometriosis and demonstrated a statistically significant improvement in pain in both treatment modalities with a mean overall improvement of 3.5/10 [35].

QOL outcomes were measured in five studies [29–31,35,36]. Two RCTs comparing TENS and TENS plus thermotherapy with sham for dysmenorrhea found no significant improvement in QOL as measured by the WHO QOL-BREF questionnaire [29,31]. Another RCT evaluated QOL following TENS for dysmenorrhea versus sham, and demonstrated a statistically significant improvement in trialist-defined QOL outcomes including capacity to get out of bed, food/drink intake, and quality of sleep, but no significant improvement in daily activities [30]. A randomized study comparing modes of TENS (self-applied and acupuncture-like TENS) reported whole-group results for QOL and found a statistically significant improvement in the endometriosis QOL score [35]. Another study reported a statistically significant improvement in QOL following TENS in men with CPP. Trialist-defined improvement in QOL by patient satisfaction was described as follows: prior to treatment, all patients felt dissatisfied, unhappy, or terrible, and after treatment, 48% were mostly satisfied, pleased, or delighted.

Two studies reported longer-term outcomes of patients after TENS treatment had been withdrawn [36]. One study reported a successful outcome in 45% of men treated with a 12-wk course of TENS for CPP; at a mean follow-up of 43.6 mo, the effect was retained in 72% of these men [36]. Another study of women with PV reported a statistically significant improvement in pain at a mean duration of use of 6.2 mo. At a mean follow-up of 10.1 mo (after 12–16 wk of treatment), it was found that this effect was maintained [35].

3.3.4. *Efficacy of other methods of neuromodulation*

Two studies evaluated intravaginal electrical stimulation (IES) in women with CPP [41,42]. One randomized crossover trial compared active with placebo IES. While pain was measured, results were reported as a proportion of women with a pain score of $\leq$3/10 after treatments. At baseline, 27.3% of those receiving placebo followed by active treatment, and 20% of those receiving active treatment followed by placebo reported pain scores of $<$3.10. Following treatment, there was a statistically significant reduction in pain for both placebo and treatment groups, but the effect was more noticeable for active treatment [42]. Those undergoing active followed by placebo treatment (86.7% and 78.6%, respectively) reported a pain score of $<$3. The group undergoing placebo followed by active treatment (54.5% and 90.9%, respectively) reported a pain score of $<$3. There were no adverse events, and QOL outcomes were not assessed. A prospective series of women with CPP by the same authors reported a significant reduction in pain, with a mean reduction of 6.2/10 continuing 7 mo after treatment [41]. QOL outcomes were not assessed and adverse events were not reported.

Pudendal nerve stimulation (PNS) was examined in two studies. In a prospective pilot study evaluating PNS for CPP, there was a statistically significant reduction in the pain score measured at 4-wk follow-up [43]. No QOL measures were assessed, nor were any adverse events reported. Another prospective pilot study of patients with pudendal neuralgia reported subjective response rates of patients at 2 wk, and demonstrated a 36% rate of complete or almost complete pain relief, 52% rate of significant/remarkable pain relief, and 16% rate of slight/small pain relief compared with nerve block. Of the patients, 26% underwent explantation of the device. Adverse events and QOL outcomes were not measured [44].

One prospective cohort study evaluated SCS for pudendal neuralgia. In those patients who responded to test stimulation, there was a significant reduction in pain with a mean reduction in of 2.9/10 [45]. QOL outcomes were not measured, and no adverse events reported.

Transcutaneous interferential electrical stimulation (TIES) was evaluated by one RCT, comparing it with sham

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TIES in patients with irritable bowel syndrome (IBS), demonstrating a significant reduction in pain for both the treatment and the placebo group. The decrease in pain score continued, and was statistically significant in both the treatment and the placebo group at follow-up in the 1 st month of treatment. In the treatment group, there was a statistically significant improvement only in QOL, as measured by total IBS-QOL score. No group comparisons and adverse events were reported [46]. Another study randomized women with dysmenorrhea to either TENS or TIES [39]. There was a significant reduction in pain for both groups with no adverse events; QOL outcomes were not evaluated.

Electrical acupuncture (high- and low-frequency modes) was compared with manual acupuncture in a trial of women with dysmenorrhea [47]. Primary outcome was pain at 12 mo, but only 38% of women completed treatment and 12-mo data were available for 28% of women. While there was a significant improvement in pain scores in all groups, there was no difference in the mode of stimulation or frequency. At 1-mo follow-up, there was a significant improvement in QOL, as measured by the SF-36 questionnaire in the total physical component for electrical compared with manual acupuncture. Adverse events were reported in 7.4% including hematoma, soreness, and fatigue. Another study compared TENS with different methods of acupuncture, including manual, low-, and high-frequency electrical acupuncture, in women with dysmenorrhea and found a statistically significant improvement in pain score in all modes of acupuncture treatment [38]. QOL and adverse events were not reported.

One retrospective study compared electrical stimulation plus biofeedback with electromagnetic stimulation in men with CPP. Both treatment modalities reported a statistically significant improvement in visual analog scale, with a mean pain reduction of 2.5/10 in the ES group. A statistically significant improvement in QOL as measured by the QOL domain of the NIH-CPSI was demonstrated. Adverse events were not reported [48].

3.4. Risk of bias and confounding

There was a notable risk of bias in both RCTs and non-RCTs, as shown by Supplementary Figs. 1 and 2. In RCTs, this was most commonly blinding, selection, and performance bias. In non-RCTs, selective outcome reporting and attrition bias was found in the majority of studies, which could lead to inflation of treatment benefits.

Across the entire study set, power calculations were performed in nine studies in total, of which only six were adequately powered.

3.5. Discussion

3.5.1. Principal findings

This study systematically reviewed the efficacy and safety of neuromodulation in patients with CPP. There was a wide range of pain conditions and treatment modalities, but overall neuromodulation produced a reduction in pain and, in the trials that assessed it, in QOL scores, with no major safety problems. The risk of bias and confounding was high, particularly for the nonrandomized studies, and hence results should be interpreted with caution.

3.5.2. Findings in the context of existing evidence

Neuromodulation may be an effective treatment in patients with idiopathic overactive bladder. A recent systematic review of SNS and PTNS found that while both modalities gave promising results in terms of improvements in overactive bladder symptoms, studies were limited by poor quality [49]. Therefore, in patients with voiding dysfunction and pain, refractory to standard treatment, neuromodulation techniques could offer treatment improving both pain and urinary symptoms.

3.5.3. Implications for research

The highest quality of evidence for systematic reviews is from appropriately powered RCTs. Ideally, further large-scale RCTs are needed in all neuromodulation modalities. Long-term outcome data are scarce; therefore, future research should include evaluation of lasting effects of treatment. A precise definition of participants and CPP subgroup or phenotype should be used. Primary endpoints should be standardized and established QOL measures should be applied. QOL outcomes should be measured in addition to pain as significant QOL improvements may be noted without discernible change in pain. Adverse events should be reported, including the time when they occur in a standardized form. All parameters for stimulation need to be clearly stated and recorded (eg, pulse width, frequency of stimulation and amplitude, perceived intensity, and technique of establishing the end point for electrode insertion).

3.5.4. Implications for practice

CPP can prove difficult to treat satisfactorily, and a holistic approach tailored to an individual patient is recommended using clinical experience [1]. The neurostimulation techniques described in this review are varied and differ in invasiveness and side-effect profiles, so each patient should be provided with sufficient information about the alternatives proposed to make an informed decision on which treatment to consider. TENS has been shown to be an effective treatment for women with CPP secondary to dysmenorrhea and is free from adverse events, with the advantage that it can be self-applied and cost effective. Similarly, PTNS has been shown to be effective in a variety of pain conditions with minimal complications; however, it is time consuming with current routinely available approaches. More invasive techniques, such as SNS, require a trial period of stimulation (after which a number of patients will not continue). While patients may achieve symptomatic relief, this should be weighed up against a higher complication rate. Similarly with non-neuromodulation techniques, the aim is not only pain relief but also improved function, although this may not be achievable [50]. It is important to bear in mind that QOL may be affected directly by both functional improvement and pain reduction.

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Neuromodulation techniques may not be available to all patients due to geographical or financial constraints. As robust evidence is not currently available, patients should ideally undergo treatment at tertiary centers under expert practitioners and preferably as part of a trial.

3.5.5. Limitations of this study

Studies identified in the review were largely of poor quality with a significant risk of bias. Only eight RCTs were identified, and there is a risk of publication bias, whereby studies with negative findings are not published but could affect the overall effects of treatment estimated in this paper. Several studies were very likely underpowered, and where power calculations were performed, only a third were adequately powered.

Patients with CPP are a heterogeneous group with multiple definitions, and there were not sufficient data to estimate the therapeutic benefit for subgroups included in the review, particularly given the large variety of treatment protocols. Further, follow-up is insufficient to show treatment gains over a realistic time frame for a chronic problem, limiting clinical generalizability.

While the primary outcome of pain reduction was described in all studies, the method of reporting this outcome differed. QOL outcomes were reported in less than half the studies, and well-established QOL scales were not always used. Adverse events were reported in just over half of studies examined, but should be recorded in all trials.

The strength of this review is that it adhered to the published protocol and followed search criteria devised by members of the EAU CPP Guideline Panel. Practitioners were involved at all stages to ensure that results were clinically useful. A sufficient number of RCTs were identified to perform an overall meta-analysis. The weaknesses of this review were possible publication bias, and the lack of data from original studies to allow more specific conclusions about subgroups or methods of neuromodulation. No response was received when authors were contacted for further information.

4. Conclusions

Neuromodulation may provide an effective treatment option in patients with CPP refractory to standard treatment, reducing pain and improving QOL with an acceptable rate of complications, but study quality is insufficient for a more certain conclusion. Quality of studies was generally poor, and therefore larger-scale, well-designed, and powered RCTs with long-term outcomes are needed.

Author contributions: Angela M. Cottrell had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cottrell, Schneider, Goonewardene, Baranowski, Engeler, Borovicka, Dinis-Oliveira, Elneil, Hughes, Messelink, de C Williams.

Acquisition of data: Cottrell, Schneider, Yuan.

Analysis and interpretation of data: Cottrell, Schneider, de C Williams.

Drafting of the manuscript: Cottrell, de C Williams.

Critical revision of the manuscript for important intellectual content: Goonewardene, Baranowski, Engeler, Borovicka, Dinis-Oliveira, Elneil, Hughes, Messelink, de C Williams.

Statistical analysis: Schneider.

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Supervision: de C Williams, Baranowski, Engeler.

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Appendix A. Supplementary data

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