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Neurostimulation for Chronic Pain: A Systematic Review of High-Quality Randomized Controlled Trials With Long-Term Follow-Up

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ABSTRACT

Objective: This study aimed to review the best evidence on the long-term efficacy of neurostimulation for chronic pain.

Materials and Methods: We systematically reviewed PubMed, CENTRAL, and WikiStim for studies published between the inception of the data bases and July 21, 2022. Randomized controlled trials (RCTs) with a minimum of one-year follow-up that were of high methodologic quality as ascertained using the Delphi list criteria were included in the evidence synthesis. The primary outcome was long-term reduction in pain intensity, and the secondary outcomes were all other reported outcomes. Level of recommendation was graded from I to III, with level I being the highest level of recommendation.

Results: Of the 7119 records screened, 24 RCTs were included in the evidence synthesis. Therapies with recommendations for their usage include pulsed radiofrequency (PRF) for postherpetic neuralgia, transcutaneous electrical nerve stimulation for trigeminal neuralgia, motor cortex stimulation for neuropathic pain and poststroke pain, deep brain stimulation for cluster headache, sphenopalatine ganglion stimulation for cluster headache, occipital nerve stimulation for migraine, peripheral nerve field stimulation for back pain, and spinal cord stimulation (SCS) for back and leg pain, nonsurgical back pain, persistent spinal pain syndrome, and painful diabetic neuropathy. Closed-loop SCS is recommended over open-loop SCS for back and leg pain. SCS is recommended over PRF for postherpetic neuralgia. Dorsal root ganglion stimulation is recommended over SCS for complex regional pain syndrome.

Conclusions: Neurostimulation is generally effective in the long term as an adjunctive treatment for chronic pain. Future studies should evaluate whether the multidisciplinary management of the physical perception of pain, affect, and social stressors is superior to their management alone.

Keywords: Drug-resistant pain, guideline, intractable pain, neuromodulation, refractory pain

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Chronic pain refers to pain that persists or recurs for more than three months,[1] and consistently ranks as the leading cause of disability worldwide,[2] with its high socioeconomic burden[3,4] and secondary downstream morbidities such as the concomitant psychiatric disorders.[5] The economic costs attributable to chronic pain have been estimated at $560 to $635 billion per year in the United States, which is strikingly 30% higher than the combined costs of cancer and diabetes.[4]

Patients with chronic pain are a unique challenge to multidisciplinary pain management strategies, including medical, rehabilitative, and behavioral therapy. Conventional management (pharmacotherapy and steroid injections) has several limitations,

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including limited clinical indications, suboptimal efficacy, and progressive reduction of treatment effects over time. Neurostimulation thus offers additional armamentarium in improving both short- and long-term cost-effective management of patients with chronic pain conditions.[6] In general, it is hypothesized that chronic pain is due to the dysfunction of neural structures and/or circuits that are involved in the perception of pain. Therefore, stimulation of these associated dysfunctional neural structures and/or circuitries that are putatively causing the experience of chronic pain would alleviate pain and/or the patient's perception of pain.[6] However, the specific mechanisms driving the efficacy of neurostimulation for chronic pain remain largely unclear. Neurostimulation therapies can broadly be categorized into invasive modalities such as motor cortex stimulation, minimally invasive modalities such as pulsed radiofrequency, and noninvasive modalities such as transcranial direct current stimulation.[6]

However, neurostimulation is associated with significant upfront financial costs, manpower requirements, and procedural risks.[7] Most neurostimulation therapies also commit the patient to a permanent implant and a lifetime of battery replacements.[7] Therefore, knowledge of the long-term benefit of neurostimulation is imperative so that the costs and benefits can be adequately weighed. Notwithstanding this, the long-term benefit of neurostimulation for chronic pain remains unclear, given existing reviews included 1) studies with any duration of follow-up and 2) lower-quality studies in the evidence synthesis.[6,8–10] Given this lack of clarity, we aimed to review the best available evidence on the long-term benefits of neurostimulation for chronic pain conditions.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

This systematic review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] We searched PubMed, the Cochrane Central Register of Controlled Trials, and WikiStim (https://www.wikistim.org/) for studies published between the inception of the data bases and July 21, 2022. The search strings used are reported in Supplementary Data Table S1.

We also hand-searched the references of relevant review articles.[6,8–10] The ClinicalTrials.gov data base also was queried for ongoing RCTs as of October 6, 2022. No language restrictions were imposed in our search. One author (YZ) screened the records for RCTs with a minimum of one-year follow-up (Fig. 1).

Assessment of Methodologic Quality

One author (YZ) graded the methodologic quality of RCTs with a minimum of one-year follow-up using the Delphi list criteria.[12] For every criterion fulfilled, one point was awarded. The total number of points awarded to each RCT was calculated to derive the Delphi list score, of a total of 9. An RCT with a Delphi list score of greater than the mean (ie, ≥5) was considered to be of high methodologic quality and therefore selected for evidence synthesis.

Level of Recommendation and Clinical Recommendation

For each of the treatment modalities described in the RCTs that were selected for evidence synthesis, the level of recommendation for the specific treatment indications was graded as I, II, or III by two authors (YZ and KRW) according to the American Association of Neurological Surgeons/Congress of Neurological Surgeons criteria, with level I being the highest level of recommendation.[13]

Data Collection

All data relevant to the evidence synthesis were extracted by one author (YZ).

Evidence Synthesis

The primary outcome for chronic cluster headache and migraine was the long-term reduction in weekly headache attack frequency, whereas the primary outcome for all other conditions was the long-term reduction in pain intensity as measured using the visual analog scale (VAS). The secondary outcomes were all other outcomes that were reported in the publications.

Owing to the small number of RCTs for each intervention and their treatment indications, evidence synthesis was done qualitatively. However, outcome data for the three RCTs that studied motor cortex stimulation (MCS) for chronic neuropathic pain were meta-analyzed because 1) there was more than one RCT for the same condition, and 2) the long-term outcomes were assessed at the same time point (one year postoperatively).[14–16] Individual participant data on one-year reduction in pain intensity were collected and pooled, and the number of patients who achieved the primary outcome was reported.[14–16] Subgroup analysis was performed by the etiology of pain.

RESULTS

A total of 41 studies with a minimum of one-year follow-up were identified, of which 26 articles reporting a total of 24 RCTs were considered high quality and therefore selected for evidence synthesis (Table 1).[14–39] Clinical recommendations regarding the use of neurostimulation for the long-term alleviation of chronic pain are presented in Table 2. Details of ongoing RCTs evaluating the use of neurostimulation for the treatment of chronic pain are presented in Table 3. Details of the 14 RCTs that reported outcomes at long-term follow-up (at least one year) but did not meet the cut-off Delphi list score for inclusion in the evidence synthesis are presented in Table 4. Illustrations of the neurostimulation therapies evaluated in the evidence synthesis and their specific treatment indications are summarized in Figure 2.

Motor Cortex Stimulation

MCS involves the delivery of electrical stimulation to the motor cortex contralateral to the painful side via an array of electrodes implanted in the overlying epidural space.[41] MCS has been postulated to relieve pain by 1) modulating the emotional aspect of pain through activation of the perigenual cingulate and orbitofrontal cortex and 2) inhibiting pain impulses at the spinal cord level via activation of the periaqueductal gray.[41]

We found four high-quality RCTs with one-year follow-up that investigated the efficacy of MCS for chronic pain, three of which included patients with neuropathic pain[14–16] and one of which included patients with poststroke pain.[17]

Across the four RCTs, 36 patients with baseline pain duration ranging from 1 to 25 years[14–17] were randomly assigned to receive either 1) active or sham stimulation for one month[14,17] or 2) two weeks[15]/one month[16] of active MCS, then two weeks[15]/one month[16] of sham MCS. After the randomization period, all patients in the sham MCS group crossed over to the active MCS group.[14–17]

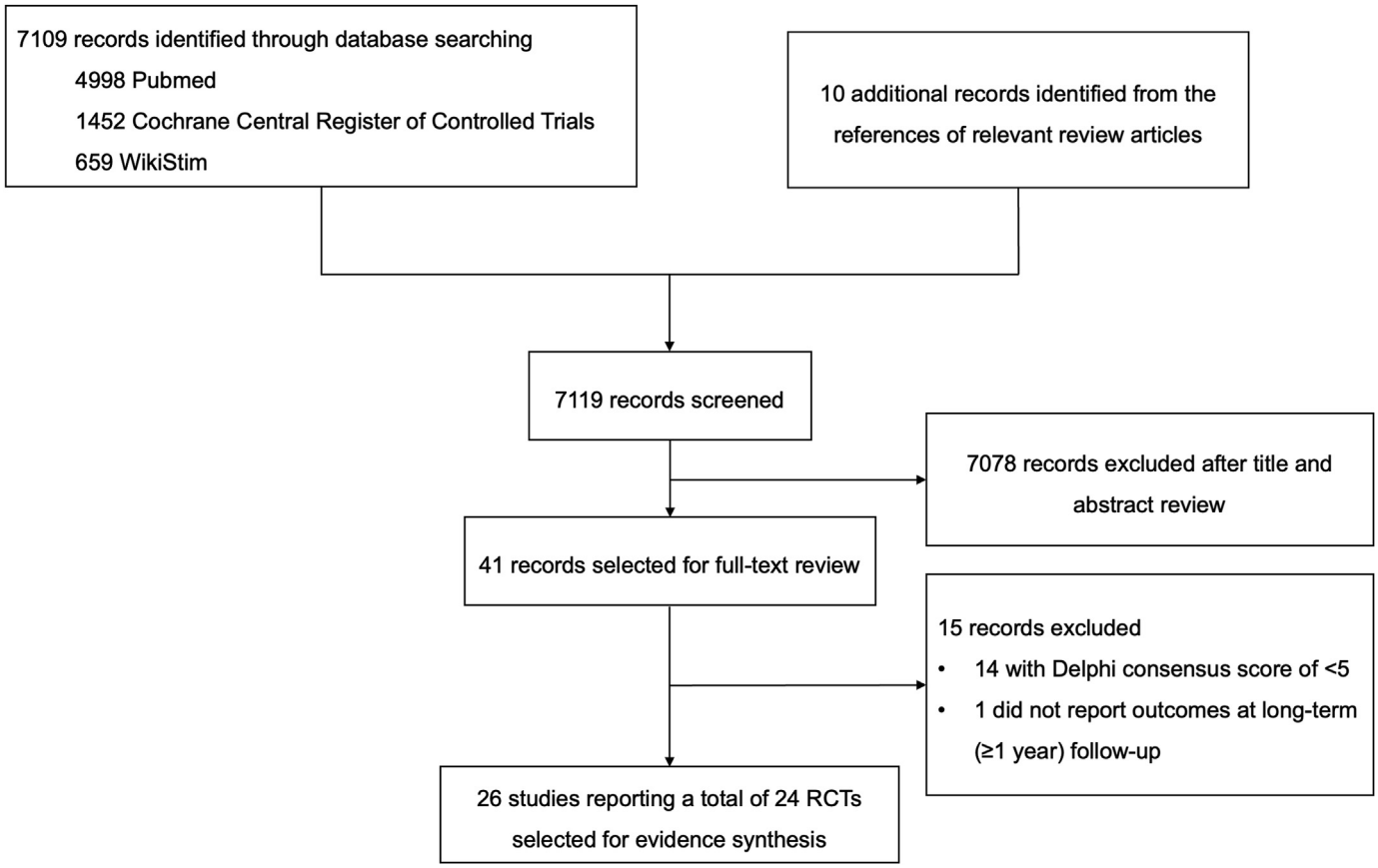

Figure 1. Study selection.

At one-year follow-up, the proportion of patients with ≥50% reduction in pain intensity for poststroke pain and neuropathic pain was 83.3% (five of six patients)[17] and 63.3% (19 of 30 patients), respectively.[14–16] Among patients with neuropathic pain,[14–16] patients with trigeminal neuralgia experienced the greatest one-year reduction in pain intensity (median 85%, range 0%–100%), followed by patients with postherpetic neuralgia (median 63%, range 0%–80%), and patients with pain secondary to brachial plexus trauma (median 40%, range 1%–95%).[14–16] MCS for neuropathic pain also was associated with a median (range) one-year improvement in health-related quality of life (HRQoL) of 43.5% (20%–80%) and a one-year reduction in the amount of analgesics taken of 42.5% (13%–100%).[15] No adverse events (AEs) were reported in the RCTs for chronic neuropathic pain.[14–17] Two implantable pulse generator (IPG) site infections occurred in the RCT for poststroke pain.[17]

Deep Brain Stimulation

Deep brain stimulation (DBS) involves the delivery of electrical stimulation via electrodes placed at specific brain targets or circuits to modulate their function.[7] The myriad proposed mechanisms of action for DBS largely converge on the stimulation-induced disruption of pathological brain circuitry at the ionic, protein, cellular, and network levels.[7,42–44] Despite being the first indication for its usage, DBS remains an off-label treatment for chronic pain, primarily owing to the stoppage of two large-scale studies in the 1980s and 1990s.[7,45,46]

We found two high-quality RCTs, one by Fontaine et al[18] for chronic cluster headache (CH) with one year of follow-up and another by Lempka et al[19] for patients with chronic poststroke pain with 18 months of follow-up.

In the RCT by Fontaine et al,[18] the ipsilateral posterior hypothalamus was targeted because previous studies implicated its role in the origin of CH attacks.[47] Eleven patients were implanted, with baseline disease durations ranging from three to 35 years and weekly attack frequencies ranging from seven to 53.[18] All 11 patients were then randomized to receive either active or sham DBS for one month, following which all patients in the sham DBS group crossed over to the active DBS group.[18]

At one-year follow-up, six of 11 patients (54.5%) experienced >50% reduction in weekly headache attacks.[18] Of these six patients, three no longer had any CH attacks.[18] There also were statistically significant improvements in anxiety (mean 6.3, 95% CI = 5.1–17.7, p = 0.008) and depressive symptoms (mean 4.1, 95% CI = 6.5–14.7, p = 0.052).[18] Three AEs were reported, including one IPG site infection, one loss of consciousness, and one recurrent syncope.[18]

In the RCT by Lempka et al,[19] the ventral striatum/anterior limb of the internal capsule (VS/ALIC) was targeted owing to its critical role in the regulation of affect. The authors hypothesized that improving pain-related affect may indirectly reduce pain intensity.[19] Nine patients with pain durations ranging from one to nine years were enrolled for bilateral implantation of DBS leads targeting the VS/ALIC.[19] All patients were then randomized to receive

Table 1. Summary of the Studies That Were Included in the Evidence Synthesis.

Source	Condition	Intervention	Treatment arms	Follow-up duration	No. of patients who completed long-term follow-up	Primary outcome at long-term follow-up	Number of study-related adverse events	Delphi list score
Velasco et al,[14] 2008	Neuropathic pain	MCS	MCS vs sham	1 y	8	7 of 8 (87.5%) had ≥50% reduction in pain intensity	None	7
Nguyen et al,[15] 2008					10	6 of 10 (60.0%) had ≥50% reduction in pain intensity	None	6
Lefaucheur et al,[16] 2009					12	6 of 12 (50.0%) had ≥50% reduction in pain intensity	None	6
Lefaucheur et al,[17] 2011	Poststroke pain				6	5 of 6 (83.3%) had ≥50% reduction in pain intensity	2 IPG site infections	7
Fontaine et al,[18] 2010	Cluster headache	DBS	DBS vs sham		11	6 of 11 (54.5%) had ≥50% reduction in weekly headache attack frequency	1 IPG site infection 1 loss of consciousness with hemiparesis shortly after test stimulation. Symptoms resolved spontaneously 2 h after the incident. 1 multiple severe syncope episodes associated with postural hypotension	9
Lempka et al,[19] 2017	Poststroke pain			18 mo	9	1 of 9 (11.1%) had ≥50% reduction in pain intensity	17 behavior changes 13 headache and worsened pain 8 sleep and alertness changes 7 abdominal and digestive disorders 6 balance difficulties and falls 5 surgical site infections 5 fatigue and weakness 2 seizures	7
Kapural et al,[20] 2022	Nonsurgical back pain	SCS	CMM vs CMM + 10,000 Hz SCS	1 y	64	50 of 64 (78.1%) had ≥50% reduction in pain intensity 31 of 64 (48.4%) had ≥80% reduction in pain intensity	2 implant site infection 1 poor wound healing 1 lethargy 1 osteomyelitis	5

(Continues)

Table 1. *Continued*

Source	Condition	Intervention	Treatment arms	Follow-up duration	No. of patients who completed long-term follow-up	Primary outcome at long-term follow-up	Number of study-related adverse events	Delphi list score
Petersen et al,[21] 2022	Painful diabetic neuropathy				142	121 of 142 (85.2%) patients had ≥50% reduction in pain intensity	8 procedure-related infections 2 IPG location revision 1 lead migration requiring revision	5
Kapural et al,[22] 2016	Back and leg pain		10,000 Hz vs traditional frequency (40–60 Hz) SCS	2 y	156	Significantly more patients in the 10,000 Hz SCS group had ≥50% reduction in intensity of back pain (76.5% vs 49.3%; $p < 0.001$) and leg pain (72.9% vs 49.3%; $p = 0.003$)	10,000 Hz SCS: 5 wound complications 1 paresis Traditional frequency SCS: 3 wound complications 1 arrhythmia 1 cardiac arrest 1 extradural abscess 1 intracranial hypotension 1 postlumbar puncture syndrome	5
Rigoard et al,[23] 2021	FBSS		Multicolumn vs monocolumn SCS programming	1 y	97	46 of 97 (47.4%) had ≥50% reduction in global pain intensity 58 of 97 (59.8%) had ≥50% reduction in leg pain intensity 45 of 97 (46.4%) had ≥50% reduction in back pain intensity	16 pain at lead implantation site 11 device-related infection 8 pain at IPG site 8 premature battery depletion 4 extension-related complication 2 wound inflammation 2 epidural hematoma 2 lead migration 2 lead malpositioning 1 adaptive stimulation dysfunction 1 dental avulsion during intubation 1 excessive sweating 1 vertigo 1 transient ischemic attack 1 nausea 1 diarrhea 1 perioperative high blood pressure 1 urinary incontinence 1 pain recurrence	9
Al-Kaisy et al,[24] 2022			Paresthesia mapping vs anatomy-based lead placement		39	Significant reduction in pain intensity between the baseline and 1-y follow-up visit ($p < 0.001$)	3 headache 2 pain at the IPG site 2 IPG unpairing, where the IPG was disconnected from the programmer 2 leakage at wound site/IPG scar 2 irritation around surgery site 2 pain due to falling 1 difficulty in urination and inability to bear weight on the right leg associated with preexisting cauda equina	7

(Continues)

Table 1. *Continued*

Source	Condition	Intervention	Treatment arms	Follow-up duration	No. of patients who completed long-term follow-up	Primary outcome at long-term follow-up	Number of study-related adverse events	Delphi list score
							1 worsening of right leg pain after implant 1 photophobia 1 explant due to suspicion of implant infection 1 right leg numbness 1 wound exploration due to weeping wound at the IPG site 1 swelling on the right side of the face, leg, and ankle 1 palpitation	
Breel et al,[25] 2021			1,000 Hz vs 30 Hz SCS		19	15 of 19 (78.9%) had >50% pain suppression	6 lead migrations 6 IPG pocket problems 1 increase in pain at 12 mo (resolved by reprogramming of the neurostimulator)	5
De Andres et al,[26] 2017			10,000 Hz vs traditional frequency (~40 Hz) SCS		55	Both groups experienced significant reduction in pain intensity ($p < 0.001$), but no statistically significant difference between the groups ($p = 0.560$)	10,000 Hz SCS: 4 lead migration from trial to permanent 3 unsuccessful trial 1 lead migration with replacement Traditional frequency SCS: 2 unsuccessful trial 2 lead migration with replacement	5
Rigoard et al,[27] 2019			CMM vs CMM + SCS	2 y	63	13 of 63 (20.6%) experienced ≥50% reduction in pain intensity	8 implant site infection 2 device stimulation issue 2 paresthesia 2 device deployment issue 1 device battery issue 1 back pain 1 implant-site cellulitis 1 implant-site pain 1 pelvic pain 1 pulmonary edema 1 urinary tract infection	5
Mekhail et al,[28] 2022	Back and leg pain		Closed-loop vs open-loop SCS		134	Significantly more patients in the closed-loop SCS group had ≥50% reduction in pain intensity (79.1% vs 53.7%; $p = 0.001$)	10 IPG pocket pain 10 lead migrations 3 muscle spasm or cramp 3 wound infections 2 dural puncture or tear 2 IPG malfunction due to electrocautery 2 unwanted stimulation location 1 back pain and bilateral radiation into legs	8

(Continues)

Table 1. *Continued*

Source	Condition	Intervention	Treatment arms	Follow-up duration	No. of patients who completed long-term follow-up	Primary outcome at long-term follow-up	Number of study-related adverse events	Delphi list score
							1 dysesthesia—lower extremity 1 epidural abscess 1 inadequate lead placement 1 lead fracture 1 low back pain 1 nausea and/or vomiting 1 pain at implant/incision site 1 skin irritation or redness 1 wound dehiscence No significant difference in procedure, device, and stimulation-related adverse events between closed- and open-loop SCS	
Deer et al,[29] 2017 Mekhail et al,[30] 2021 Levy et al,[31] 2020	Complex regional pain syndrome	SCS, DRGS	SCS vs DRGS	1 y	132	Significantly ($p < 0.001$) more patients in the DRGS arm (74.2% vs 53.0%) experienced ≥50% reduction in pain intensity	SCS: 29 procedure-related 5 pain at the incision sites 24 device-related 8 loss of stimulation due to lead migration 10 stimulation-related 5 overstimulation DRGS: 52 procedure-related 7 pain at the incision sites 39 device-related 10 IPG pocket pain 10 stimulation-related 3 overstimulation DRGS had significantly higher rate of procedure-related adverse events than SCS ($p = 0.018$). Only the most common adverse events were reported.	5
Sheng et al,[32] 2022	Postherpetic neuralgia	SCS, PRF	SCS vs PRF		67	SCS: 23 of 29 (79.3%) PRF: 16 of 38 (42.1%) had ≥50% reduction in pain intensity Reduction in pain intensity was significantly greater in the SCS group ($p < 0.001$)	SCS: None PRF: 2 surgical site hematomas	6

(Continues)

Table 1. *Continued*

Source	Condition	Intervention	Treatment arms	Follow-up duration	No. of patients who completed long-term follow-up	Primary outcome at long-term follow-up	Number of study-related adverse events	Delphi list score
Makharita et al,[33] 2018		PRF	PRF vs sham		50	Patients in the PRF group had significantly greater reduction in pain intensity ($p = 0.017$)	None	9
Dodick et al,[34] 2015	Migraine	PNS	PNS vs sham		133	47.8% of patients had ≥50% reduction in headache d and/or pain intensity	38 persistent pain and/or numbness at IPG/lead site 29 lead migrations 21 lack of efficacy or return of symptoms 17 undesirable changes in stimulation 11 expected postoperative pain or numbness at IPG/lead site 11 infections 8 skin erosions 8 battery failure 5 wound-site complications 5 allergic reactions to surgical materials	7
McRoberts et al,[35] 2013	FBSS	PNFS	Minimal vs subthreshold vs low-frequency vs standard PNFS		23	Significant reduction in pain intensity between the baseline and 1-yfollow-up visit ($p < 0.001$) 16 of 23 (69.7%) reported ≥50% reduction in pain intensity	10 decreased or loss of therapy 7 lead migration 6 surgical site complications 5 expected postoperative pain at IPG or lead site 5 unintended stimulation effect 4 bandage irritation 2 infection (subcutaneous) 2 persistent pain at IPG or lead site 1 local skin erosion 1 headache or increased headaches 1 fever and chills 1 nausea with stimulation	5
Oosterhof et al,[36] 2012	Non–cancer pain	TENS	TENS vs sham		165	No statistically significant difference in pain intensity between treatment arms ($p = 0.79$)	40 skin problems caused by the electrodes	9
Bisla et al,[37] 2021	Trigeminal neuralgia				52	No statistically significant difference in pain intensity between treatment arms ($p = 0.655$)	Not reported	7

(Continues)

Table 1. *Continued*

Source	Condition	Intervention	Treatment arms	Follow-up duration	No. of patients who completed long-term follow-up	Primary outcome at long-term follow-up	Number of study-related adverse events	Delphi list score
Barloese et al,[38] 2016	Cluster headache	SPGS	Full vs subperception vs sham SPGS	2 y	33	10 of 33 (30.3%) experienced ≥1 remissions (0 cluster attacks for >1 mo)	Not reported	6
Grazzi et al,[39] 2020	Migraine	tDCS	Anodal vs cathodal vs sham tDCS	1 y	135	Anodal: 29 of 44 (64.1%) Cathodal: 27 of 45 (60.0%) Sham: 21 of 46 (46.3%) had ≥50% reduction in weekly headache frequency No significant difference between groups (*p* value not reported)	None	9

Table 2. Clinical Recommendations Regarding the Use of Neurostimulation for the Alleviation of Chronic Pain in the Long Term.

Source	Chronic pain condition		Clinical recommendation
Velasco et al,[14] 2008 Nguyen et al,[15] 2008 Lefaucheur et al,[16] 2009	Neuropathic pain		For patients with medically refractory chronic neuropathic pain, MCS may be considered as an adjunct to pharmacotherapy for the long-term improvement of pain intensity and quality of life (level II recommendation).
Lefaucheur et al,[17] 2011 Lempka et al,[19] 2017	Poststroke pain		For patients with medically refractory chronic poststroke pain, 1. MCS may be considered as an adjunct to pharmacotherapy for the long-term improvement of pain intensity (level II recommendation). 2. VS/ALIC DBS is not recommended as an adjunct to pharmacotherapy due to the high risk of adverse events and limited clinical benefit (level II recommendation).
Fontaine et al,[18] 2010 Barloese et al,[38] 2016	Cluster headache		For patients with medically refractory chronic cluster headache, 1. DBS targeting the posterior hypothalamus may be considered as an adjunct to pharmacotherapy for the long-term reduction of the frequency of headache attacks and improvement of affect (level II recommendation). 2. SPGS may be considered as an adjunct to pharmacotherapy for the long-term reduction of the frequency of headache attacks, headache-related disability, and analgesic consumption (level II recommendation).
Kapural et al,[22] 2016 Mekhail et al,[28] 2022	Back and leg pain		For patients with medically refractory chronic back and leg pain, 1. 10,000 Hz SCS is recommended over conventional frequency (40–60 Hz) SCS as an adjunct to pharmacotherapy for the long-term reduction of pain intensity and disability (level II recommendation). 2. Closed-loop SCS is recommended over open-loop SCS as an adjunct to pharmacotherapy because it offers superior long-term improvement in pain intensity, HRQoL, sleep, physical and emotional functioning, and reduction in voluntary opioid intake (level I recommendation).
Kapural et al,[20] 2022	Nonsurgical back pain		For patients with medically refractory chronic back pain and no history of spinal surgery, and who are ineligible for spinal surgery, 10,000 Hz SCS may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain intensity (level II recommendation).
De Andres et al,[26] 2017	FBSS	Trunk and/or limb pain	For patients with medically refractory chronic trunk and/or limb pain after back surgery, 1. 10,000 Hz SCS is not superior to conventional frequency (~40 Hz) SCS as an adjunct to pharmacotherapy for the long-term reduction of pain intensity, pain-related disability, anxiety and depressive symptoms, and improvement in quality of life (level I recommendation). 2. Both 10,000 Hz and conventional frequency (~40 Hz) SCS may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain intensity (level II recommendation).
Breel et al,[25] 2021		Unilateral neuropathic leg pain and minimal back pain	For patients with medically refractory chronic unilateral neuropathic leg pain and minimal back pain after back surgery, 30–1000 Hz SCS may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain intensity and improvement in quality of life and sleep quality (level II recommendation).
Rigoard et al,[27] 2019 Rigoard et al,[23] 2021		Predominant back pain	For patients with medically refractory and predominant chronic back pain after back surgery, 1. SCS may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain intensity and disability and improvement in quality of life (level II recommendation). 2. SCS delivered via multicolumn leads may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain intensity, disability, anxiety and depressive symptoms, pain medication intake, and improvement in quality of life (level II recommendation).
Al-Kaisy et al,[24] 2022 McRoberts et al,[35] 2013		Back pain	For patients with medically refractory chronic back pain after back surgery, 1. Both paresthesia mapping and anatomy-based placement of burst SCS leads may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain intensity and disability, and improvement in quality of life (level II recommendation). 2. Subthreshold, low-frequency, or standard PNFS may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain

(Continues)

Table 2. *Continued*

Source	Chronic pain condition	Clinical recommendation
		intensity and opiate medication intake, and improvement in quality of life (level II recommendation).
Petersen et al,[21] 2022	Painful diabetic neuropathy	For patients with medically refractory chronic painful diabetic neuropathy, 10,000 Hz SCS may be considered as an adjunct to pharmacotherapy for the long-term reduction of pain intensity (level II recommendation).
Deer et al,[29] 2017 Mekhail et al,[30] 2021 Levy et al,[31] 2020	Complex regional pain syndrome	For patients with complex regional pain syndrome, DRGS is recommended over SCS as an adjunct to pharmacotherapy for the long-term reduction of pain intensity and improvement in mood and quality of life (level II recommendation).
Sheng et al,[32] 2022 Makharita et al,[33] 2018	Postherpetic neuralgia	For patients with medically refractory chronic postherpetic neuralgia, 1. SCS is recommended over PRF as an adjunct to pharmacotherapy for the long-term reduction of pain intensity, bodily pain, physical role limitations, and pregabalin dose (level I recommendation). 2. PRF is recommended as an adjunct to pharmacotherapy for the long-term reduction of pain intensity and daily pregabalin dose and improvement in quality of life (level I recommendation).
Dodick et al,[34] 2015 Grazzi et al,[39] 2020	Migraine	For patients with medically refractory chronic migraine, 1. Occipital nerve stimulation may be considered as an adjunct to pharmacotherapy for the long-term reduction of headache frequency, intensity, pain-related disability, and improvement of affect (level II recommendation). 2. tDCS is not recommended as an adjunct to pharmacotherapy for the long-term reduction of headache frequency and analgesic intake (level I recommendation).
Bisla et al,[37] 2021	Trigeminal neuralgia	For patients with medically refractory chronic trigeminal neuralgia, TENS is recommended as an adjunct to pharmacotherapy for the long-term reduction of carbamazepine dose but not pain intensity and functional outcome (level I recommendation).
Oosterhof et al,[36] 2012	Non–cancer pain	For patients with medically refractory chronic non–cancer pain, TENS is not recommended as an adjunct to pharmacotherapy for the long-term improvement of pain intensity, perceived health status, and pain-related disability (level I recommendation).

either three months of active DBS, followed by three months of sham DBS, or vice versa.[19] At the end of the six-month randomization period, all patients in the sham DBS group crossed over to the active DBS group.[19]

At the 18-month follow-up, three of nine patients (33.3%) experienced ≥50% improvement in depressive symptoms.[19] However, only one patient (11.1%) experienced ≥50% improvement in pain intensity and pain-related disability.[19] A total of 63 study-related AEs were reported, the most common of which were behavioral changes (17 events, 27.0%).[19]

Spinal Cord Stimulation

Spinal cord stimulation (SCS) involves the delivery of electrical stimulation via electrodes placed in the epidural space overlying the dorsal columns of the spinal cord.[48] The mechanism of action of SCS purportedly differs depending on the pain profile.[9] In chronic ischemic pain, SCS was proposed to cause pain relief through vasodilation,[9,49] whereas in chronic neuropathic pain, SCS was proposed to cause pain relief via complex alterations to neural circuitry at both the spinal-segment and supraspinal levels.[9,50]

We found a total of 13 studies reporting 11 high-quality RCTs with long-term follow-up that evaluated the efficacy of SCS for the treatment of chronic pain.[20–32] Seven studies reporting a total of five RCTs compared SCS with other treatment options, specifically dorsal root ganglion stimulation (DRGS),[29–31] pulsed radiofrequency (PRF),[32] and conventional medical management (CMM).[20,21,27] The remaining six RCTs compared different SCS stimulation frequencies (10,000, 1,000, and 40–60 Hz)[22,25,26] and paradigms (monocolumn vs multicolumn,[23] paresthesia mapping vs anatomy-based lead placement,[24] and closed-loop vs open-loop[28]).

Back and Leg Pain

There were two RCTs that evaluated the use of SCS for the treatment of chronic back and leg pain, one of which compared 10,000 Hz with conventional frequency SCS, and another that compared closed- with open-loop SCS.[22,28]

In the RCT by Kapural et al, 198 patients with a mean (SD) pain duration of 13.6 years (11.3) were randomized to receive either 10,000 Hz SCS or conventional frequency (40–60 Hz) SCS.[22] Of the 198 patients randomized, 86.6% had a history of back surgery.[22] Blinding of the patients to treatment assignment was not possible because conventional frequency SCS produces paresthesia, whereas 10,000 Hz SCS does not.[22] The study investigators also could not be masked to treatment assignment owing to the differences in stimulator lead placement, intraoperative testing, and device programming between the treatment groups.[22]

A total of 156 patients completed two-year follow-up, during which significantly more patients in the 10,000 Hz SCS group had ≥50% reduction in the intensity of back pain (76.5% vs 49.3%; 27.2% difference; 95% CI = 10.1%–41.8%; $p < 0.001$) and leg pain (72.9% vs 49.3%; 23.6% difference; 95% CI = 5.9%–38.6%; $p = 0.003$) than patients in the conventional frequency SCS group.[22]

Table 3. Details of Ongoing RCTs Evaluating the Efficacy of Neurostimulation for Chronic Pain as of October 6, 2022. A Detailed Overview of Past and Current Ongoing Clinical Trials Also Was Reported by Yamamoto et al.[40]

Study code	Interventions	Condition	Treatment arms
NCT04144972	DBS	Chronic pain	Closed-loop vs open-loop DBS
NCT05204472		Neuropathic pain	Burst vs tonic DBS
NCT05023460	PNS	Chronic cluster headache	Active vs sham PNS
NCT05516251		Migraine	PNS vs topiramate
NCT05287373		Neuropathic pain	PNS vs CMM
NCT04937010		Trigeminal–autonomic cephalgia	Active vs sham PNS
NCT03370107	rTMS	Central pain syndrome	Active vs sham rTMS
NCT04561401		Chronic pain	Pain rehabilitation with or without rTMS
NCT04182659		Gulf-war illness–associated migraine	Active vs sham rTMS
NCT04734847		Interstitial cystitis/bladder pain syndrome	
NCT05097729		Knee osteoarthritis–associated pain	
NCT03314584		Mild traumatic brain injury–associated headache	
NCT05176392			Headache education with active or sham rTMS
NCT02059096		Multiple sclerosis with central neuropathic pain	Active vs sham rTMS
NCT05488808		Neuropathic pain	
NCT04936646			
NCT04672044		Poststroke headache	Exercise with active or sham rTMS
NCT05226676		Posttraumatic neuropathic pain	Active vs sham rTMS
NCT04120129		Trigeminal neuralgia	
NCT03681262	SCS	Chronic back and/or leg pain	Burst vs high-frequency SCS
NCT04676022			SCS vs CMM
NCT04732325		Chronic trunk and/or limb pain	Burst vs tonic vs sham SCS
NCT04039633		Erythromelalgia	Burst vs sham SCS
NCT04244669		FBSS	Conventional vs differential target multiplexed SCS
NCT03957395		FBSS and CRPS	Burst vs tonic vs high-frequency vs sham SCS
NCT03733886		Neuropathic pain	Burst vs sham SCS
NCT03740763			SCS vs physiotherapy
NCT04852107	SCS, DRGS	Chronic back and/or leg pain	SCS vs DRS vs SCS + DRGS
NCT05370833	tDCS	Chronic pain	11 vs 5 sessions of tDCS
NCT03716830			Combinations of active and sham verum acupuncture and tDCS
NCT04332939			Exercise with active or sham tDCS
NCT04890964		Fibromyalgia	Active vs sham tDCS
NCT05066568			tDCS vs hypnosis
NCT05161871		Migraine	Active vs sham tDCS
NCT04578574		Neuropathic pain	
NCT04306289		Painful diabetic neuropathy	
NCT04250662		Pelvic pain	
NCT04579952		Posttotal knee arthroplasty pain	
NCT05099406	tDCS, tACS	Chronic pain	tDCS vs tACS vs sham
NCT04206215	tDCS, TUS	Carpal tunnel syndrome	Active vs sham tDCS and TUS
NCT03625752		Painful diabetic neuropathy	
NCT05138471	tDCS, TENS	Knee osteoarthritis-associated pain	Active tDCS with active or sham TENS
NCT02813629		Sickle-cell anemia-associated pain	Combinations of active and sham tDCS and TENS
NCT05152264	TENS	Endometriosis-associated pain	TENS vs CMM
NCT04683042		Fibromyalgia	Physiotherapy with or without TENS
NCT05155384		Interstitial cystitis/bladder pain syndrome	Biopsychosocial model-based therapy vs conventional physiotherapy + TENS
NCT05483816		Neuropathic pain	Virtual reality with active or sham TENS
NCT04169477			Conventional vs mixed-frequency TENS
NCT04795635	Transcutaneous magnetic stimulation	Posttraumatic neuropathic pain	CMM with or without transcutaneous magnetic stimulation
NCT03592329	tVNS	Migraine	Stress reduction training with active or sham tVNS
NCT02564172	Conus medullaris stimulation	Pudendal neuralgia	Conus medullaris stimulation vs CMM
NCT04148768	Interferential therapy, short wave diathermy	Chronic knee pain	Interferential therapy vs short wave diathermy

rTMS, repetitive transcranial magnetic stimulation; tACS, transcranial alternant current stimulation; TUS, transcranial ultrasound; tVNS, transcutaneous vagal nerve stimulation.

Table 4. Titles and Delphi List Scores of the Excluded Studies.

Title	Delphi list score
Effectiveness of cathodal tDCS of the primary motor or sensory cortex in migraine: a randomized controlled trial	4
Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischaemia: a prospective randomised controlled study	4
Long-term effect of peripheral nerve field stimulation peripheral nerve field stimulation as add-on therapy to spinal cord stimulation to treat low back pain in failed back surgery syndrome patients: a 12-month follow-up of a randomized controlled study	4
Outcomes of a multicenter, prospective, crossover, randomized controlled trial evaluating subperception spinal cord stimulation at ≤1.2 kHz in previously implanted subjects	4
The added value of subcutaneous peripheral nerve field stimulation combined with SCS, as salvage therapy, for refractory low back pain component in persistent spinal pain syndrome implanted patients: a randomized controlled study (CUMPNS study) based on 3D-mapping composite pain assessment	4
An analysis of the components of pain, function, and health-related quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management	3
Changes in pain, function and quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management	3
Spinal cord stimulation electrode design: a prospective, randomized, controlled trial comparing percutaneous with laminectomy electrodes: part II-clinical outcomes	3
Spinal cord stimulation versus conventional medical management for neuropathic pain: a multi-centre randomised controlled trial in patients with failed back surgery syndrome	3
Spinal cord stimulation versus reoperation for failed back surgery syndrome: a cost-effectiveness and cost utility analysis based on a randomized, controlled trial	3
Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial	3
Long-term outcomes using an SCS system capable of combination therapy: a randomized controlled trial (COMBO)	2
Occipital nerve stimulation for chronic migraine: a randomized trial	2
Randomized prospective study in patients with complex regional pain syndrome of the upper limb with high-frequency spinal cord stimulation (10-kHz) and low-frequency spinal cord stimulation	2

Patients in the 10,000 Hz SCS group also had a significantly lower degree of disability.[22] There were 14 serious study-related AEs, the most common of which were wound complications (eight cases), with no statistically significant difference between treatment groups.[22]

In the RCT that compared closed- and open-loop SCS, closed-loop SCS was hypothesized to be more effective than open-loop SCS because it can better maintain stimulation within the therapeutic range.[28] A total of 134 patients with pain durations of approximately 12 years and of which 59.7% (80 of 134 patients) had a history of back surgery were randomized to receive either open- or closed-loop SCS, with no crossover between treatment groups and unblinding to treatment assignment throughout the trial.[28]

The analysis of the two-year outcomes included all 134 patients who were randomized, although only 92 completed the two-year follow-up.[28] Patients in both groups experienced statistically significant improvements in pain intensity, HRQoL, sleep, physical and emotional functioning, and reduction in voluntary opioid intake.[28] However, the closed-loop group had a significantly greater proportion of patients with ≥50% reduction in pain intensity (closed-loop 79.1% vs open-loop 53.7%; difference = 25.4%; 95% CI = 10.0%–40.8%; $p = 0.001$),[28] in addition to greater improvements in HRQoL, sleep, physical and emotional functioning, and reduction in voluntary opioid intake.[28] A total of 42 AEs were reported, with the most common being IPG pocket pain and lead migration (ten events each, 23.8%).[28] There was no statistically significant difference in the incidence of AEs between both treatment arms.[28]

Nonsurgical Back Pain

Another RCT by Kapural et al compared the outcomes of CMM with a combination of 10,000 Hz SCS and CMM for nonsurgical back pain.[20] A total of 159 patients with a median pain duration of eight years who had chronic back pain that did not respond to CMM, had no history of spinal surgery, and were deemed ineligible for spinal surgery were randomly assigned to receive either CMM by itself or a combination of 10,000 Hz SCS and CMM.[20] At the six-month follow-up, 89.3% (67 of 75 patients) in the CMM group crossed over to the 10,000 Hz SCS group, whereas none of the patients in the 10,000 Hz SCS + CMM group crossed over to the CMM-only group.[20] The study only followed up with patients in the 10,000 Hz SCS + CMM group until one year postoperatively, whereas patients in the CMM group exited the study at the six-month follow-up.[20]

Of the 64 patients in the 10,000 Hz SCS + CMM group who completed the one-year follow-up, 78.1% (50 of 64) had ≥50% reduction in pain intensity, and 48.4% (31 of 64) had ≥80% reduction in pain intensity.[20] There were five study-related AEs, the most common of which was implant-site infection (two cases).[20]

Persistent Spinal Pain Syndrome

There were five RCTs in total that evaluated the efficacy of SCS for persistent spinal pain syndrome (PSPS).[23–27] Two of the RCTs compared the outcomes after various SCS frequencies for PSPS, with one comparing 10,000 Hz with traditional frequency (40–60 Hz)[26] and another comparing 1000 Hz with 30 Hz.[25] The remaining three RCTs compared CMM with CMM + SCS,[27] paresthesia mapping with anatomy-based placement of SCS leads,[24] and multicolumn with monocolumn SCS leads.[23]

In an RCT by De Andres et al, 60 patients with medically refractory pain of the trunk and/or limbs after back surgery were randomized to receive either 10,000 Hz or traditional frequency SCS.[26] There was some degree of blinding of treatment allocation to patients.[26] Specifically, the study was introduced to patients by informing them that there were two treatment groups, namely,

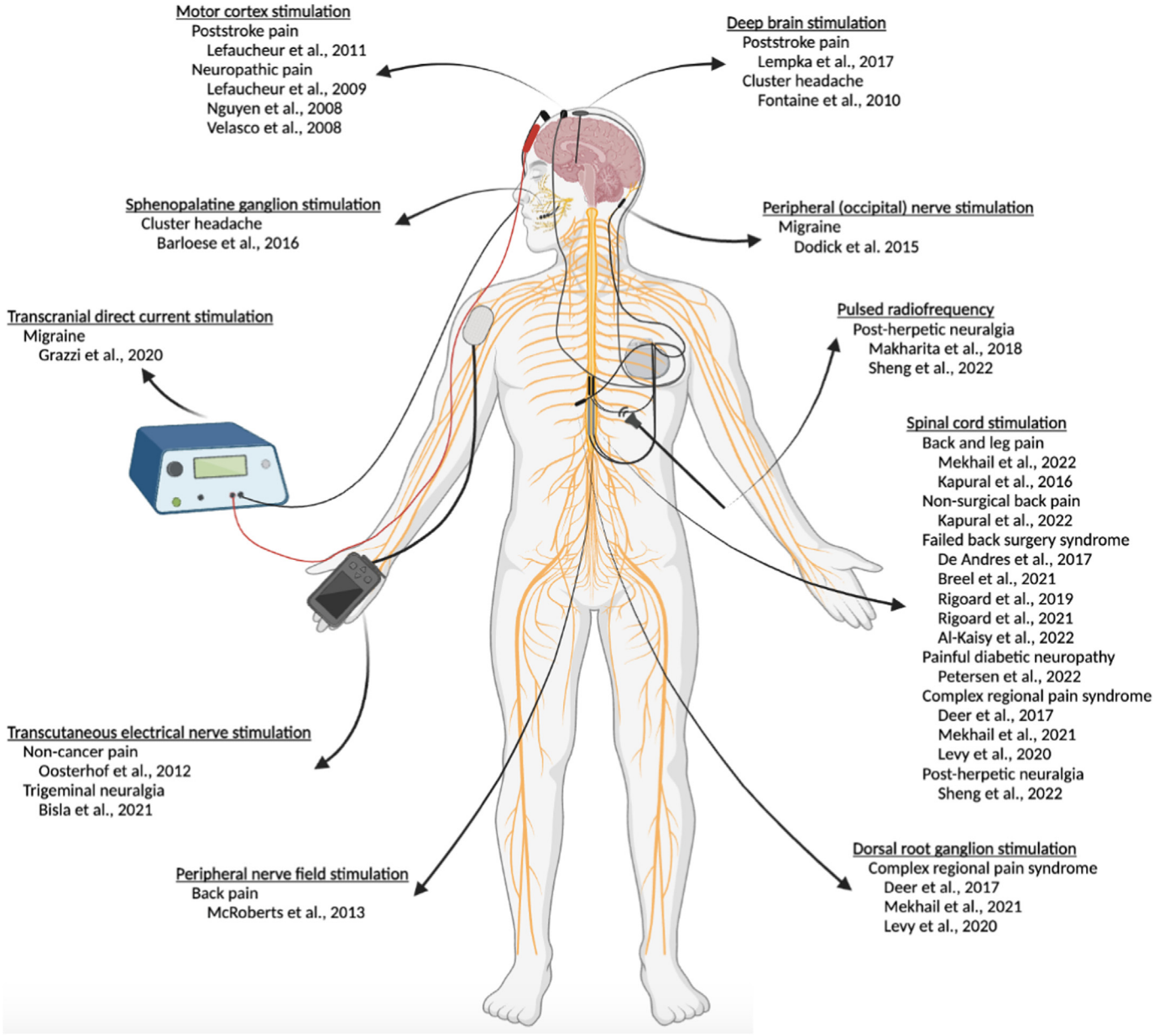

Figure 2. Illustration of the neurostimulation therapies evaluated in the evidence synthesis and their specific treatment indications. The figure was created on BioRender.com. [Color figure can be viewed at www.neuromodulationjournal.org]

10,000 Hz and traditional frequency SCS, and that treatment was equally effective in both.[26] It was explained that according to their random assignment, they might experience paresthesia as part of their treatment (which is expected for traditional frequency SCS but not 10,000 Hz SCS) but that this would not affect the final outcome of therapy.[26] The patients also received strict instructions not to discuss which of the different evaluations they were to undergo, the group in which they were included, and therefore whether they experienced paresthesia as part of their therapy.[26] There were no crossovers between treatment arms during the study.[26]

A total of 55 patients completed one-year follow-up, during which patients in the 10,000 Hz and conventional frequency treatment arms both experienced significant reduction in pain intensity ($p < 0.001$), though there were no statistically significant differences between the treatment arms ($p = 0.560$).[26] There also were no statistically significant differences in terms of pain-related disability, anxiety and depressive symptoms, and quality of life between the 10,000 Hz and traditional frequency SCS groups.[26] There were 12 AEs, the most common of which was an unsuccessful trial (five events).[26]

In the RCT by Breel et al, 32 patients with unilateral neuropathic leg pain and minimal back pain after back surgery were randomized to receive either 1000 Hz or 30 Hz SCS for 90 days, after which they underwent a five-day washout period with no stimulation and crossed over to the other treatment arm.[25] Patients who experienced ≥50% pain suppression in either trial period proceeded with permanent SCS implantation and were followed up in the open-label phase.[25] During the open-label phase, patients could adjust their stimulation strategies.[25]

A total of 19 patients completed one-year follow-up, during which 79% experienced >50% pain suppression and 47% experienced >80% pain suppression.[25] There also were statistically significant improvements in quality of life ($p < 0.01$).[25] Sleep quality also improved for 77% of patients.[25] There were a total of 13 AEs, the most common of which were lead migration and IPG pocket problems (six events each).[25]

In the RCT by Rigoard et al, 218 patients with predominant back pain after back surgery were randomized to receive either CMM only or CMM in addition to SCS.[27] After six months, patients could change their assigned treatment groups.[27] At six months, 2.4% of patients implanted with SCS (two of 83) opted to cease SCS therapy, whereas 72.6% of patients with CMM (77 of 106) requested to crossover to SCS.[27]

Of the 63 patients continuing SCS who completed two-year follow-up, 20.6% (13 of 63) achieved ≥50% reduction in lower back pain, with a mean (SD) improvement in VAS of 2.2 (2.0) points.[27] There also were statistically significant improvements in disability and quality of life ($p < 0.001$).[27] There were 21 AEs in total, the most common of which was implant-site infection (eight events).[27]

Al-Kaisy et al compared the outcomes after paresthesia mapping or anatomy-based placement of SCS leads for patients with chronic lower back pain after back surgery.[24] A total of 43 patients were implanted with two SCS leads.[24] The first lead was placed to cross the T8–T9 disk, and active contacts for this lead were chosen through paresthesia mapping.[24] The second lead was placed at the T9–T10 spinal anatomic landmark.[24] Patients then underwent a four-week, double-blind, crossover trial with a two-week testing period, with burst SCS delivered through each lead in random order.[24] At the end of the trial period, the patients expressed their preference for one of the two leads.[24] Subsequently, subjects received burst SCS with the preferred lead.[24] Twenty-one subjects (48.8%) expressed a preference for paresthesia mapping, and 21 (48.8%) preferred anatomic placement.[24] For the one subject who had no preference, the lead placed according to anatomical landmarks was used during the follow-up phase.[24]

A total of 39 patients completed one-year follow-up, during which there was a significant improvement in the back and leg pain intensity ($p < 0.001$) for both paresthesia mapping and anatomic placement groups.[24] There also was a statistically significant improvement in disability and quality of life ($p < 0.001$) in both the paresthesia mapping and anatomic placement lead groups.[24] With regard to patient satisfaction, 94% of the subjects who used anatomic placement lead and 85% of the subjects who used paresthesia mapping lead were reported to either be satisfied or very satisfied.[24] There were 58 AEs, the most common of which was headache (three cases).[24]

Rigoard et al compared the efficacy of multicolumn with monocolumn SCS leads for the treatment of predominant back pain after back surgery.[23] A total of 109 patients with baseline mean (SD) pain duration of 5.1 (5.7) years were implanted with a multicolumn SCS lead.[23] Patients were then randomized to receive either multicolumn or monocolumn SCS, via the implanted multicolumn SCS lead.[23] At the six-month follow-up, patients in the monocolumn SCS group could cross over to the multicolumn group.[23] Patients in the multicolumn group could not cross over to the monocolumn group.[23] At the six-month follow-up, all patients in the monocolumn SCS group crossed over to the multicolumn SCS group.[23]

A total of 97 patients completed one-year follow-up, all of whom were using multicolumn SCS.[23] Of these 97 patients, 47.4%, 59.8%, and 46.4% experienced ≥50% reduction in global pain, leg pain, and back pain, respectively, from baseline, and this difference was statistically significant ($p < 0.0001$).[23] There also was a statistically significant improvement in disability and quality of life and a reduction in anxiety and depressive symptoms and pain medication intake ($p < 0.0001$).[23] There were 65 AEs, the most common of which was pain at the lead implantation site (16 cases).[23]

Painful Diabetic Neuropathy

Petersen et al evaluated the efficacy of 10,000 Hz SCS for the treatment of painful diabetic neuropathy.[21] A total of 216 patients with baseline median [interquartile range] duration of peripheral neuropathy of 5.6 [3.0–10.1] years[51] were randomized to receive either CMM alone or 10,000 Hz SCS in addition to CMM.[21] At the six-month follow-up, patients who had <50% pain relief, were unsatisfied with the treatment and who were deemed medically appropriate by the investigator were given the option to switch to the other treatment arm. Among those in the CMM-alone group, 81.1% crossed over to the 10,000 Hz SCS + CMM group, whereas none from the 10,000 Hz SCS + CMM group crossed over to the CMM-alone group.[21]

At one-year follow-up, 121 of 142 patients (85.2%) in the 10,000 Hz SCS + CMM group experienced ≥50% reduction in pain intensity.[21] There were 11 procedure-related AEs, of which eight were infections.[21]

Dorsal Root Ganglion Stimulation

Although SCS is generally effective for the treatment of central neuropathic pain, its efficacy falters for focal and peripheral neuropathic pain.[29,52] The inefficacy of SCS has been attributed to its lack of precision caused by various factors such as shunting of energy by the cerebrospinal fluid, positional variations in stimulation, segmentation of spinal sensory input, and lead migrations.[29,53] DRGS was postulated to be more efficacious than SCS for the treatment of peripheral neuropathic pain because DRGS provides more precise targeting of the affected area.[29] There was one RCT that compared the efficacy of SCS with that of DRGS for the treatment of complex regional pain syndrome (CRPS), the outcomes for which were reported in three separate studies.[29–31]

A total of 152 patients with chronic lower extremity pain secondary to CRPS types I or II of baseline mean (SD) pain duration of approximately seven years were randomized to receive either SCS or DRGS.[29] Owing to the differences in the nature of the procedure and programming, blinding to treatment allocation was not possible.[29]

At one-year follow-up, significantly ($p < 0.001$) more patients in the DRGS arm (74.2%, 49 of 66) than in the SCS arm (53.0%, 35 of 66) experienced ≥50% reduction in pain intensity.[29] Patients in the DRGS arm also experienced significantly greater improvement in quality of life and mood than the SCS arm.[29] Regarding cost-effectiveness, DRGS was more costly than SCS owing to higher conversion from trial to permanent implant and shorter battery life, but DRGS was the most beneficial therapy owing to more patients receiving permanent implants and experiencing a higher quality of life than with SCS.[30] Interestingly, DRGS also was noted to provide more stable pain relief through the 12 months of follow-up, but the efficacy of SCS appeared to decrease over the 12 months of follow-up.[31] With regard to AEs, DRGS had a significantly higher rate of procedure-related AEs than did SCS ($p = 0.018$), with the most common being pain at the incision sites.[29]

Pulsed Radiofrequency

PRF involves the transmission of radiofrequency waves to a target nerve via a radiofrequency needle[54] and has been postulated to work by downregulating calcitonin gene-related peptide levels.[55]

We found two high-quality RCTs with one-year follow-up that studied the efficacy of PRF for chronic postherpetic neuralgia. Sheng et al compared PRF with SCS,[32] whereas Makharita et al compared active with sham PRF.[33]

Sheng et al randomized 70 patients with baseline pain durations of approximately three years to receive either PRF or SCS with no crossover between treatment groups and unblinding to treatment assignment throughout the trial.[32] At one-year follow-up, patients in both treatment groups experienced statistically significant reductions in pain intensity ($p < 0.001$), bodily pain ($p < 0.001$), physical role limitations ($p < 0.001$), and pregabalin dose ($p < 0.001$).[32] Patients in the SCS group experienced significantly greater reductions in all the above outcomes than did those in the PRF group ($p < 0.001$).[32] Two surgical site hematomas were reported in the PRF group.[32]

Makharita et al randomized 50 patients with baseline pain durations of approximately 14 months to receive two cycles of either active or sham PRF, with no crossover between treatment groups, and unblinding to treatment assignment throughout the trial.[33] At one-year follow-up, patients in the active PRF group experienced a significantly greater reduction in pain intensity ($p = 0.017$) and improvement in HRQoL ($p < 0.050$) than did patients in the sham PRF group.[33] Patients in the active PRF group also had a greater reduction in daily pregabalin dose, though this was only statistically significant up to the nine-month follow-up ($p = 0.015$) and not at one-year follow-up ($p = 0.140$).[33] There were no AEs in either treatment arm.[33]

Peripheral Nerve Stimulation

Peripheral nerve stimulation (PNS) involves the implantation of an electrode targeted at a peripheral nerve for the delivery of electrical stimulation.[56] PNS has been proposed to work by modulating the inflammatory pathways, autonomic nervous system, and endogenous pain inhibition pathways.[57]

We found one high-quality RCT with one-year follow-up that evaluated the efficacy of PNS for chronic migraine.[34] In the study by Dodick et al, 157 patients with baseline mean (±SD) pain duration of 23.3 (±14.4) years were randomized to receive either active or sham PNS (occipital nerve) for 12 weeks.[34] After the randomization period, all patients in the sham PNS group crossed over to the active PNS group.[34]

At one-year follow-up, 47.8% of randomized patients (75 of 157) experienced ≥50% reduction in headache days and/or pain intensity.[34] There also was a significant reduction in migraine-related disability ($p < 0.001$) and an improvement in affect ($p < 0.001$).[34] There were 153 AEs, the most common of which was persistent pain and/or numbness at IPG/lead site (38 cases).[34]

Peripheral Nerve Field Stimulation

Peripheral nerve field stimulation (PNFS) is a procedure in which percutaneous electrode leads are implanted to stimulate a painful area.[35] According to the gate-control theory, the activation of large, thickly myelinated Aβ fibers through PNFS can inhibit the transmission of painful signals carried by small myelinated Aδ and unmyelinated C fibers in the same region.[35,58]

We found one high-quality RCT with one-year follow-up that studied the efficacy of PNFS for chronic back pain after back surgery.[35] In their RCT, McRoberts et al implanted patients with trial leads and thereafter randomized them to receive one of four stimulation paradigms (minimal, subthreshold, low-frequency, or standard stimulation).[35] The patients were rotated among these paradigms in intervals lasting from four to eight days.[35] If the patient reported ≥50% reduction in pain intensity during any of the three active stimulation paradigms (subthreshold, low-frequency, standard stimulation), a permanent stimulation system was implanted.[35] During the follow-up period, programming parameters were optimized and adjusted as needed, and patients were able to switch between the various stimulation paradigms.[35]

A total of 23 patients completed one-year follow-up.[35] There was a significant reduction in pain intensity between the baseline and one-year follow-up visit ($p < 0.001$), with 69.7% (16 of 23) reporting ≥50% reduction in pain intensity.[35] There also was a significant improvement in quality of life ($p < 0.001$), and almost all patients indicated they would undergo the procedure again.[35] As for opiate medication intake, 43.5% (ten patients) reported an overall decrease.[35] A total of 45 AEs were reported, with the most common being decreased or loss of efficacy (ten cases).[35]

Sphenopalatine Ganglion Stimulation

Sphenopalatine ganglion stimulation (SPGS) involves the implantation of an electrode targeted at the SPG, through which electricity can be delivered for the treatment of chronic head and facial pain.[59]

We found one high-quality RCT by Barloese et al with two-year follow-up that evaluated the efficacy of SPGS for chronic CH.[38] The principle underlying SPGS was to prevent CH attacks by interrupting the trigeminal-autonomic reflex.[38] The baseline mean (±SD) disease duration was 10.5 (±8.3) years (range one–36), and the mean (±SD) weekly attack frequency was 16.8 (±13.7) (range five–70). Thirty-three patients underwent transoral insertion of a microstimulator targeting the sphenopalatine ganglion ipsilateral to the side of the CH attacks, before proceeding to the randomization phase for eight weeks.[38] During the randomization phase, patients were asked to activate the stimulator during their CH attacks, after which the stimulator would deliver full-perception, subperception, and sham stimulation in random order.[38] After the randomization period, all patients had their stimulators programmed to full-perception mode.[38]

At two-year follow-up, ten of 33 patients (30.3%) experienced one or more remissions (zero cluster attacks for longer than one month).[38] These ten patients who experienced remission also experienced significant improvement in headache-related disability (p=0.012) and reduction in preventive medication use, with six not using triptans and three not using short-term treatments at all.[38] AEs were not reported.[38]

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) involves the delivery of pulsed electrical currents across the intact skin surface to stimulate the underlying nerves[9,60] and broadly shares similar mechanisms of action to PNS for the relief of chronic pain.[57]

We found two high-quality RCTs that examined the efficacy of TENS for chronic pain, one of which included patients with non–cancer pain[36] and another that included patients with trigeminal neuralgia.[37]

Oosterhof et al randomized 165 patients with baseline non–cancer pain durations of approximately four years to receive either active or sham TENS for one year, with no crossover between treatment groups and unblinding to treatment assignment throughout the trial.[36] At one-year follow-up, there were no statistically significant differences in pain intensity ($p = 0.79$), patient satisfaction ($p = 0.74$), perceived health status ($p = 0.57$), and pain-related disability ($p = 0.89$) between the treatment groups.[36] There were 40 cases of skin problems caused by the electrodes.[36]

Bisla et al randomized 52 patients with trigeminal neuralgia of at least six months to receive either active or sham TENS for six weeks, with no crossover between treatment arms and unblinding to treatment assignment throughout the trial.[37] At one-year follow-up, there were no statistically significant differences in pain intensity ($p = 0.655$) and functional outcomes ($p = 0.968$) between active and sham TENS.[37] However, the mean dose of carbamazepine was significantly lower in the active TENS group ($p = 0.009$).[37] AEs were not reported.[37]

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) involves the noninvasive delivery of electrical currents to specific brain regions, causing polarity-dependent shifts of resting membrane potential, thereby modulating neuronal activity at the site of stimulation and its associated structures.[61,62]

We found one high-quality RCT with one-year follow-up that examined the efficacy of tDCS for chronic migraine.[39] A total of 135 patients with approximately 20 days of migraines per month at baseline were randomized to receive either anodal, cathodal, or sham tDCS targeted at the right primary motor cortex for five sessions over five days, with no crossover between treatment arms and unblinding to treatment assignment throughout the trial.[39] The primary motor cortex was targeted for the same reasons as MCS was proposed for chronic pain,[14–17] and hence, this RCT was essentially an evaluation of tDCS as a noninvasive alternative to MCS.[39] The decision was made to compare anodal with cathodal tDCS because they differ in terms of their effect on neuronal excitability, with anodal tDCS increasing and cathodal tDCS decreasing excitability.[39,61]

At one-year follow-up, there were no statistically significant differences in the number of patients with ≥50% reduction in weekly headache attack frequency (anodal 64.1%, cathodal 60.0%, sham 46.3%; p value not reported) and the number of analgesics taken per month (anodal 10.6 ± 8.4, cathodal 10.4 ± 10.4, sham 12.6 ± 8.9; p value not reported) between the treatment arms.[39] There were no reported AEs.[39]

DISCUSSION

The evidence synthesis suggests that neurostimulation is generally effective in the long term as an adjunctive treatment for chronic pain (Table 2). However, across most of the treatment modalities, there was significant variability in long-term efficacy. For example, MCS was associated with a long-term reduction in pain intensity ranging from 0% to 100%.[14–17] This variability could be a consequence of inadequate attention paid to the psychologic and social factors contributing to the perception of pain.[63]

The intimate bidirectional relationship between chronic pain and affect has been clear since the time of Plato.[64] Not only does chronic pain profoundly increase the risk of developing affective disorders,[63] but underlying affective disorders also exacerbate pain intensity,[63] presumably owing to overlaps in the neural circuitry controlling pain perception and affect.[65] This relationship creates a positive feedback loop wherein pain worsens affect, and affect in turn also worsens pain. The high cost of treatment for chronic pain also may cause psychologic stress and treatment default, thereby worsening affect and pain intensity.[4,66]

Given these complexities, in which biological, psychologic, and social factors mutually coexist and exacerbate one another, a holistic biopsychosocial approach to managing chronic pain is theoretically the optimal management strategy. However, the studies included in this evidence synthesis targeted either the physical perception of pain or affect in isolation. Future studies should therefore also evaluate whether the combined management of the physical perception of pain, affect, and social stressors is superior to managing them separately. Details of ongoing RCTs evaluating the efficacy of neurostimulation for chronic pain are summarized in Table 3.

Another important limitation is that in most of the RCTs included, patients were already unblinded to their treatment allocations before long-term outcome assessment. For these RCTs, the therapy being assessed cannot be considered as causally associated with the outcome, given contributions to the long-term outcome by the placebo or nocebo effect due to unblinding to treatment allocation cannot be ruled out.[67] In addition, patients in the sham stimulation treatment arm were crossed over to the active stimulation treatment arm before outcome assessment at long-term follow-up. Therefore, in terms of the long-term outcomes, these RCTs are essentially a comparison of active stimulation alone with active and sham stimulation, which does not directly provide information on whether the therapy is causally associated with the long-term outcome. For these reasons, even though the RCTs supporting the use of the therapy were of high methodologic quality, a level II instead of a level I recommendation was given.

Nevertheless, neurostimulation has an important adjunctive role in managing chronic pain and complements currently available pharmacologic and psychobehavioral therapeutic options.

CONCLUSIONS

Neurostimulation is generally effective in the long term as an adjunctive treatment for chronic pain. Future studies should evaluate whether the multidisciplinary management of the physical perception of pain, affect, and social stressors is superior to their management alone.

Authorship Statements

Yilong Zheng and Kai Rui Wan conceptualized and designed the study, designed the search strategy, and interpreted the data. Kai Rui Wan and Justin Rui Xin Ker critically revised the manuscript for important intellectual content and supervised the study. Yilong Zheng screened the articles, collected the data, performed the data analysis, and drafted and critically revised the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2023.05.003.

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COMMENTS

Zheng et al have done a very timely review of the extant literature on neuromodulation for chronic pain. At a time when a few individual studies with the most vexed and perplexingly impaired methods are published and their negative findings are trumpeted from the social media rooftops as full and complete prima facie evidence that all studies must therefore be placebo, it is reassuring to see high-quality science performed that looks at the broad aspect of the field. The findings are that multiple neuromodulation therapies are effective across a range of chronic pain conditions, based on high-quality RCT evidence. This finding is neither shocking or controversial, and as such, I suspect it will not be granted the same social media messaging time as certain other studies, but nevertheless, it grounds these therapies to a firm foundation of efficacy, and subsequent analyses of the data, more granular in nature, should allow clinicians to extract detailed treatment approaches that can be compared with the recommendations of best practice guidelines. I applaud the authors for the extensive work they have undertaken with this review. In particular, the focus on studies with one year or more of follow-up, as the authors have done here, is critical in establishing the real-world benefit of these therapies. The field of neuromodulation should now task itself with seeing a doubling of these studies to 48 by the year 2030, a difficult but not impossible task.

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Neuromodulation is used to treat a variety of conditions in several anatomic regions. The authors have provided a good summary of each of the major types of neuromodulation therapies and summarized those studies that provide some of the strongest evidence of its success. Although the evidence is positive for neuromodulation as a therapy, this review also has identified a lack of strong randomized controlled trial evidence in this area.

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The use of neuromodulation for control of pain is not new and has been utilized for decades with effective control of some very complex pain syndromes. This modality has a high level of evidence in medical literature for its efficacy and safety. One of the main concerns is that it needs a high level of training and experience which may not be always available in certain parts of the country.

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