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OTHER PAIN (N VADIVELU AND AD KAYE, SECTION EDITORS)

Clinical Effectiveness and Mechanism of Action of Spinal Cord Stimulation for Treating Chronic Low Back and Lower Extremity Pain: a Systematic Review

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Abstract

Purpose of Review The purpose of the present systematic review is to provide a current understanding of the mechanism of action and the evidence available to support clinical decision-making. The focus is to summarize randomized controlled trials (RCTs) and nonrandomized or observational studies of spinal cord stimulation in chronic pain to understand clinical effectiveness and the mechanism of action.

Recent Findings Several recent studies have demonstrated the benefit of spinal cord stimulation in managing chronic pain. Until recently, the mechanism of action was founded on a central paradigm derived from gate control theory, which is the need to stimulate the dorsal column of the spinal cord to generate paresthesia. The recent development of new therapies that do not rely on paresthesia has left the field without a clear mechanism of action that could serve as a strong foundation to further improve clinical outcomes. Consequently, multiple theories have emerged to explain how electrical pulse applied to the spinal cord could alleviate pain, including activation of specific supraspinal pathways, and segmental modulation of the neurological interaction. Recent systematic reviews also have shown the clinical effectiveness of spinal cord stimulation in managing chronic spinal pain, phantom limb pain, complex regional pain syndrome, and other chronic painful conditions.

Summary Spinal cord stimulation for the treatment of chronic pain is rapidly evolving with technology at its forefront. This comprehensive focused review evaluated 11 RCTs and 7 nonrandomized/observational studies which provided levels of evidence ranging from I to II.

Keywords Spinal cord stimulation · Neuromodulation · 10 kHz SCS · Burst stimulation · Dorsal root ganglion stimulation · Chronic pain · Neuropathic pain

This article is part of the Topical Collection on *Other Pain*

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Introduction

The field of electrical neuromodulation, conceived as an application of the gate control theory (GCT), was clinically introduced in the late 1960s when the first electrical spinal cord stimulation (SCS) system was used to relieve cancer pain [1, 2]. Multiple technological advances coupled with a need for interventions with nonopioid therapy due to the illicit opioid crisis [3–10] have resulted in significant increases of publications including randomized controlled trials (RCTs), systematic reviews and meta-analysis, cost utility analysis, and guidance defining indications and medical necessity [11•, 12, 13•, 14–18, 19•, 20–29, 30•, 31–34]. With advances in technology, effectiveness, and favorable cost utility, SCS appears to be a promising option for chronic pain patients with various chronic pain disorders. In addition, the mechanism of action was founded on a central paradigm derived from the GCT, which is the need to stimulate the dorsal column of the spinal cord to generate paresthesia [35]. However, the recent development of new modes of stimulation that do not rely on paresthesias has created a paradigm shift in understanding the mechanism of action, with the emergence of multiple theories [12, 13•, 16, 31].

Among the proposed theories, activation of specific supraspinal pathways [2] and segmental modulation of the neuroglial interaction [36] have gained attention as potential explanations for the clinically beneficial effects observed with recently introduced waveforms at sub-sensory amplitudes. The first of these, paresthesia-free SCS therapy, utilized stimulation with actively balanced rectangular pulses delivered at a high frequency (10 kHz), with a pulse width (PW) of 30 μs and current amplitudes set to levels significantly below the sensory perception threshold [37••]. Another waveform intended to reduce paresthesia is burst stimulation which operates by releasing trains of five rectangular charge-balanced cathodic pulses, similar in shape to tonic stimulation, with a PW of one millisecond, and an interpulse pause of one millisecond [38]. The result is a burst of pulses tightly grouped at a high pulse rate (500 Hz), delivered at a rate of 40 Hz [38]. In addition, the dorsal root ganglion stimulation (DRGS) added an additional dimension [39••].

Despite a multitude of publications, appropriately conducted large RCTs and systematic reviews with meta-analysis are scarce in assessing spinal cord stimulation for chronic pain. Consequently, this systematic review was undertaken to assess the mechanism of action and effectiveness of spinal cord stimulation for treating chronic low back and lower extremity pain utilizing RCTs, and moderate to high-quality nonrandomized studies.

Methods and Materials

This systematic review followed the review process established for evidence-based systematic reviews and meta-analysis [40].

Criteria for Considering Studies for This Review

Randomized trials and nonrandomized studies, in patients suffering with chronic low back and lower extremity pain, with thoracic and lumbar spinal cord stimulator lead placement with an implantable pulse generator were included.

The pain relief was the primary outcome while functional status improvement was the secondary outcome.

Literature Search

All the available literature of RCTs and nonrandomized studies published in English language from all countries with reporting of appropriate outcome evaluations were included. Searches were performed from PubMed from 1966 and Cochrane Library through December 2018.

Search Strategy

The focus of the search strategy was spinal cord stimulation in chronic low back and lower extremity pain.

The search terminology was as follows:

((((Spinal Cord Stimulation) OR dorsal column stimulation) OR Low-frequency stimulation) OR high-frequency stimulation) OR dorsal root ganglion stimulation AND (((((((chronic back pain) OR post laminectomy syndrome) OR post surgery syndrome) OR failed back surgery syndrome) OR neuropathic pain) OR Leg pain)) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Multicenter Study[ptyp] OR prospective study OR observational report or case series)).

Data Collection and Analysis

Data collection and subsequent analysis focused on RCTs and observational studies for clinical effectiveness. Only the patients with chronic spinal pain and lower extremity pain for at least 3 months were included with a minimum of 6-month follow-ups. All the studies with appropriate management, outcomes assessment, and statistical assessments were reviewed and included. However, case reports, book chapters, and studies without appropriate diagnosis were excluded.

Inclusion and Exclusion Criteria

All studies with appropriate outcome descriptions were included.

Methodological Quality Assessment

The quality of each individual manuscript used in this analysis was assessed by Interventional Pain Management

Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) for randomized trials [41] and Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) [42].

The studies scoring 32 to 48 were considered as high quality, 16 to 31 were considered as moderate quality, and those with less than 16 score were considered as low quality.

Data Extraction and Management

Two authors in an unblinded, standardized manner, established the search criteria, searched for relevant literature, selected the manuscripts, and extracted the data from the included studies. Any disagreements between the reviewers were discussed and debated, and final consensus and compromise was reached, with involvement of a third author.

Any conflict of interest with a reviewed manuscript in relation to authorship of the reviewers of this systematic review was eliminated by removing the manuscript from those reviewers and assigning it to one of the other authors.

Measurement of Treatment Effect in Data Synthesis (Meta-analysis)

If the literature provided at least 4 trials or studies meeting the inclusion criteria with clinical homogeneity for each modality, a meta-analysis was performed.

Outcome of the Studies

A study was judged to be effective if the spinal cord stimulator implant was clinically relevant at a clinically and statistically significant level.

Summary Measures

A 50% or more reduction of pain in at least 50% of the patients, or at least a 3-point decrease in pain scores, is considered as clinically significant. Improvement for less than 3 months is considered as short-term and 12 months or longer is considered as long-term.

Analysis of Evidence

Analysis and evidence synthesis were performed utilizing best evidence synthesis [43] developed and utilized by American Society of Interventional Pain Physicians (ASIPP). The analysis utilized a 5-level system of evidence ranging from level I to level V or strong to opinion or consensus-based (Table 1).

The evidence analysis was performed by at least 2 review authors independently, in an unblinded standardized manner. Any disagreements were resolved by consensus.

Results

Figure 1 shows the flow diagram. Our search strategy yielded 92 RCTs and 56 nonrandomized studies. Based on the criteria described in the methodology, a total of 11 RCTs [37••, 39••, 44••, 45••, 46–49, 50••, 51, 52•] and 9 nonrandomized studies [53–61] were considered for review and evaluation. Two studies were excluded from consideration due to the small number of patients included in the nonrandomized category without justification or sample size analysis [54, 57].

Due to lack of homogeneity, a meta-analysis was not feasible.

Methodologic Quality Assessment

The evaluation results for RCTs and nonrandomized/observational studies selected for review and evaluation are presented in Tables 2 and 3, respectively.

Only one RCT [52•] and one nonrandomized study [53] were considered to be of high quality, scoring 34 and 33 respectively. All other manuscripts were scored as moderate quality. The descriptive characteristics of the randomized trials and nonrandomized studies are described in Tables 4 and 5.

Level of Evidence

The level of evidence was graded based on a qualitative approach as described in Table 1 [43]. The level of evidence based on the results of the published studies of effectiveness of spinal cord stimulation in low back and lower extremity pain is shown in Tables 4 and 5.

The combined level of evidence for conventional SCS is level I to level II based on one relevant high-quality RCT [52•] and five moderate-quality RCTs [37••, 39••, 44••, 45••, 50••]. Five of the 6 studies provided data of long-term pain relief for 12 or 24 months.

When considering the different stimulation patterns of SCS independently, the evidence for high-frequency 10 kHz SCS is level II based on two relevant moderate-quality RCTs [37••, 49] and one high-quality relevant observational study [53] with long-term follow-ups (12 or 24 months).

The evidence for burst stimulation is level III to level IV based on one relevant moderate-quality RCT with a 12-month follow-up [50••].

The evidence for high-density stimulation is level III based on one relevant moderate-quality RCT [51].

The level of evidence for DRG stimulation for the treatment of CRPS I and causalgia is level III based on one relevant moderate-quality RCT [39••] and one relevant moderate-quality observational study [61].

Table 1 Qualitative modified approach to grading of evidence

Level I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials for effectiveness or Evidence obtained from multiple relevant high-quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures
Level II	Moderate	Evidence obtained from at least 1 relevant high-quality randomized controlled trial or multiple relevant moderate- or low-quality randomized controlled trials or Evidence obtained from at least 2 high-quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures
Level III	Fair	Evidence obtained from at least 1 relevant high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies or At least 1 high-quality relevant observational study or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures
Level IV	Limited	Evidence obtained from multiple moderate- or low-quality relevant observational studies or Evidence obtained from moderate-quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, and effectiveness of other measures

Modified from: Manchikanti et al. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 [43]

Discussion

The results of this review, while similar to previous manuscripts in many aspects, were also different in that multiple nonrandomized studies and more recent research have been utilized in this assessment, showing emerging evidence with multiple modes of stimulation. The evidence level was level I to level II for conventional spinal cord stimulation with inclusion of 6 moderate to high-quality randomized trials with 5 of 6 with 12- to 24-month follow-up, based on best evidence synthesis utilizing a qualitatively modified approach to the grading of evidence [37••, 39••, 44••, 45••, 50••, 52•]. However, the evidence for various types of new stimulation patterns was modest compared with conventional spinal cord stimulation. The evidence was level II for high frequency based on 3 RCTs with long-term follow-up [37••, 49, 53]. Similarly, the evidence for burst stimulation was level III to level IV based on one moderate-quality RCT [50••], however, with only 3-month follow-up. The evidence for high-density stimulation was level III based on a one-month moderate-quality RCT [51]. Finally, the level of evidence for DRG stimulation for the treatment of CRPS was level III based on one moderate-quality RCT [51].

The recent developments in evidence synthesis with the publication of numerous manuscripts and the value of multiple types of publications [2, 6•, 11•, 13•, 14, 16, 18, 19•, 22, 37••, 39••, 44••, 45••, 46, 47, 48, 49, 50••, 51, 52•, 53–61] have been discussed extensively [11•, 13•, 14, 16, 44••, 45••, 46, 47, 48, 49, 50••, 51, 52•, 53–61]. Consequently, advocates of real-world evidence feel that prospective or retrospective collection of large amounts of data, and subsequent analysis, gives a better understanding of the effectiveness and safety of any particular therapy [18, 19•, 23, 62, 63]. In addition, inappropriate conduct of systematic reviews, meta-analysis, and RCTs and conclusions reached in systematic reviews and guidelines have affected access to multiple interventions indicating reduced utilization patterns with a potential increase in morbidity and mortality [64–76]. However, appropriate randomized trials have been conducted for interventional techniques with properly designed and executed systematic reviews for interventional techniques including SCS [31, 33, 37••, 77–86]. In addition, enactment of the Affordable Care Act (ACA) also has played a role in increased levels of evidence synthesis with its focus on reducing health care expenditures, increasing affordable insurance coverage, and improving quality of care [87, 88]. However, the results of ACA in providing increased access to care with reduced cost and improved quality have been questioned, specifically based on multiple regulations with increasing costs for providers, in turn reducing access and also potentially the quality [87, 89]. Further, recent recommendations to reduce opioid utilizations and encouragement of nonopioid interventions provide an additional basis for neuromodulation [15, 87–92].

In the development of evidence with safety and cost utility, it is crucial to understand the mechanism of action of spinal cord stimulation in its various forms.

Historically, in 1965, Melzack and Wall [35] postulated the "Gate Control Theory" (GCT) of pain. This theory proposed that the activation of large, fast conducting myelinated A-beta fibers may reduce afferent nociceptive input, transmitted by small-diameter A-delta and C-fibers. Additionally, depolarization via electrical stimulation of mechanosensitive A-beta

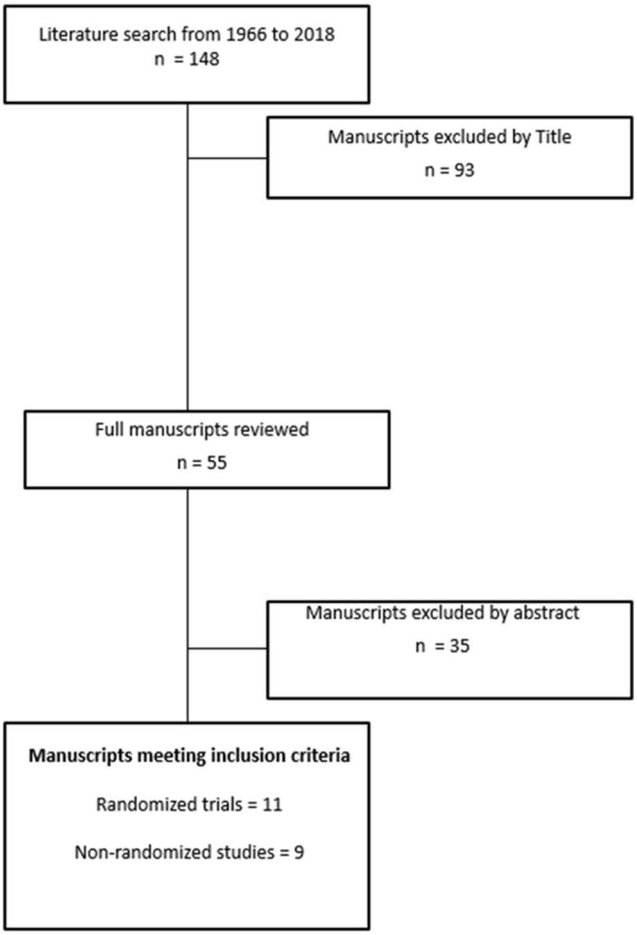

Fig. 1 Flow chart illustrating literature used for randomized controlled trials and nonrandomized studies for spinal cord stimulation

fibers was believed to lead to the generation of paresthesia in the body parts they innervate. Furthermore, the activation of intermediary inhibitory neurons in the dorsal column modulated the wide dynamic range (WDR) neurons via various neurotransmitters and neuromodulators (e.g., glutamate and gamma-amino-butyric acid (GABA)) [2]. In 1991, North et al. [93] suggested that this mechanism may have been accurate indicating that paresthesia overlapped painful areas and provided a statistically significant predictor of therapeutic outcome. Furthermore, clinical research reporting pain relief at high frequency in the absence of paresthesias has raised questions regarding the mechanisms underlying the observed effects. In addition, understanding of the anatomy and histology of the tissues exposed to the electrical signals as it relates to the SCS mechanism of action is crucial.

Electrical stimulation is transmitted to the posterior aspect of the spinal cord via leads implanted in the epidural space [15]. The distance of cerebrospinal fluid (dCSF) between the stimulating electrode and the dorsal columns is variable, with the dCSF varying from 4 to 8 mm at the T6 level, and from 1.5 to 4 mm in the mid-cervical levels. Considering the conductivity of the CSF, the applied electric field spreads through the CSF volume which buffers the effects on the neural tissues of the dorsal columns. Therefore, power demands to generate paresthesia will depend on the variable dCSF along different spinal segments, and the effects of body position. It is pertinent to realize that the depolarization threshold for the dorsal column fibers is greater than the threshold to activate dorsal root fibers. These factors are particularly relevant in the mid-thoracic spine where the dCSF is larger, requiring higher stimulation current and/or pulse width to generate depolarization, potentially causing activation of the nerve roots creating unpleasant paresthesias in the chest wall. Midline lead placement and specific contact arrays to prevent lateral spread of the electrical field promote activation of the dorsal column fibers, instead of the more lateral dorsal root fibers. Another aspect of anatomy is that dorsal root ganglion stimulation (DRGS) targets DRG at the level of the intervertebral foramen, to modulate afferent signal from peripheral nerves. The DRG contains the cell bodies of pseudounipolar primary sensory afferent neurons that filter nonpainful and painful information transmitted from the periphery into the central nervous system. Because of the lack of CSF surrounding the DRG and the proximity of the electrical contacts, the amplitudes required to stimulate this structure are significantly lower than that required over the dorsal columns. Additionally, by focusing the electrical field to specific DRG, it is possible to selectively target limited distal areas and consequently reduce the energy consumption.

For the last 50 years since the inception of neuromodulation, the field has been developed upon the concept of neurons as electrical circuits conducting signals. It is prudent to understand though that neurons represent only 5–10% of the cells in the spinal cord. The other 90 to 95% of cells that are glia, which include ependymal cells, microglia, oligodendrocytes, and astrocytes, were previously considered as merely supporting elements of the neurons. However, glia have emerged as fundamental elements of the modulation, amplification, and, in the case of pain, distortion of sensory afferent information, as well as multiple biological processes, including cell to cell communication, homeostasis of neurotransmitters in the synaptic cleft, immune response, memory, and neuronal regeneration [94]. An illustration of the significance of glial cells relates to the key inhibitory and excitatory neurotransmitters, GABA and glutamate, respectively. Glia respond differently to specific frequencies, pulse widths, amplitudes, and pulse phases [95•, 96]. The glial response is observed by an increase and release of intracellular calcium concentrations which may be blocked by ziconotide, an N-type voltage calcium channel blocker. However, additional blockade of both ionotropic and metabotropic glutamate receptors is required to observe similar results, while 4-aminopyridine, a potassium antagonist, enhanced glutamate release, emphasizing the complex response of glial cells [97]. It is also interesting to note that in a neuromuscular

Table 2 Methodological quality assessment of randomized trials of SCS utilizing IPM-QRB criteria

		North et al. [44]	Kumar et al. [45]	Schultz et al. [46]	Perruchoud et al. [47]	Kapural et al. [37]	North et al. [48]	Deer et al. [39]	De Andres et al. [49]	Deer et al. [50]	Thomson et al. [51]	Al Kaisy et al. [52]
I	Trial design and guidance reporting											
1	CONSORT or SPIRIT	2	2	2	1	2	1	3	2	3	2	3
II	Design factors											
2	Type and design of trial	2	2	2	3	2	2	2	2	2	2	2
3	Setting/physician	1	1	2	2	2	2	2	2	2	2	2
4	Imaging	3	3	3	3	3	3	3	3	3	3	3
5	Sample size	2	2	2	0	3	0	3	2	2	1	1
6	Statistical methodology	1	1	1	1	1	1	1	1	1	1	1
III	Patient factors											
7	Inclusiveness of population	2	2	1	2	1	1	2	2	1	1	2
8	Duration of pain	1	2	1	1	1	2	2	2	2	1	2
9	Previous treatments	2	2	0	2	2	2	2	2	2	2	2
10	Duration of follow-up with appropriate interventions	2	2	0	0	2	0	1	1	1	0	1
IV	Outcomes											
11	Outcomes assessment criteria for significant improvement	2	4	2	0	4	2	4	4	4	2	3
12	Analysis of all randomized participants in the groups	1	1	2	1	2	2	2	2	2	1	1
13	Description of dropout rate	2	1	0	0	2	1	0	1	2	0	2
14	Similarity of groups at baseline for important prognostic indicators	2	2	2	2	2	1	2	2	2	2	2
15	Role of co-interventions	1	1	1	1	1	1	1	1	1	1	1
V	Randomization											
16	Method of randomization	2	1	2	2	2	1	2	2	1	0	2
VI	Allocation of concealment											
17	Concealed treatment allocation	0	0	0	2	0	0	0	1	0	0	2
VII	Blinding											
18	Patient blinding	0	0	0	1	0	0	0	0	0	1	1
19	Care provider blinding	0	0	0	0	0	0	0	0	0	1	1
20	Outcome assessor blinding	0	0	0	1	0	0	0	1	0	1	1
VIII	Conflicts of interest											
21	Funding and sponsorship	0	−3	−3	1	−3	−3	−3	−3	−3	−3	−3
22	Conflicts of interest	0	3	−3	2	2	2	2	0	2	2	2
	Total	28	29	17	28	31	21	31	30	30	23	34

ex vivo model, perisynaptic Schwann cells (a type of peripheral glia) respond differently to burst or tetanic stimuli [98]. Further, electrical stimulation of oligodendrocytes, another type of glia involved in myelination, generates spontaneous action potentials and influences the conduction velocities of action potentials transmitted by the neurons they surround [99]. In addition, glial cells can have either a neuroprotective or neurotoxic influence, by promoting anti-inflammatory or pro-inflammatory states, respectively, on the neurons they surround [100•].

Additional mechanisms also surround the evidence for a segmental mechanism with intensity-dependent antidromic activation of small-diameter afferent fibers that trigger dorsal horn intermediary neurons to release extracellular protein kinase B and GABA, activating unmyelinated neurons that in turn will lead to peripheral release of the potent vasodilator, calcitonin gene–related peptide [101]. There is also evidence pointing to supraspinal effects of SCS. Pain stimulation is processed biologically in parallel by two supraspinal pathways: a

Table 3 Methodological quality assessment of nonrandomized or observational studies of SCS utilizing IPM-QRBNR criteria

		Al Kaisy et al. [53]	Russo et al. [55]	Rosenberg et al. [56]	Gatzinsky et al. [58]	Veizi et al. [59]	Russo et al. [60]	Huygen et al. [61]
I	Trial design and guidance reporting							
1	STROBE or TREND	3	2	2	2	2	3	2
II	Design factors							
2	Type and design of trial	2	1	2	2	1	4	2
3	Setting/physician	2	2	2	2	2	2	2
4	Imaging	3	3	3	3	3	3	3
5	Sample size	3	1	1	0	3	0	0
6	Statistical methodology	1	1	2	2	2	1	1
III	Patient factors							
7	Inclusiveness of population	3	2	3	4	3	3	3
8	Duration of pain	2	1	1	2	1	2	2
9	Previous treatments	2	0	2	2	1	1	2
10	Duration of follow-up with appropriate interventions	3	2	2	2	3	2	2
IV	Outcomes							
11	Outcomes assessment criteria for significant improvement	4	4	3	4	2	2	2
12	Description of dropout rate	2	0	0	1	2	0	1
13	Similarity of groups at baseline for important prognostic indicators	2	0	0	0	2	0	0
14	Role of co-interventions	2	1	1	1	1	1	2
V	Assignment							
15	Method of assignment of participants	2	1	4	4	1	4	4
VI	Conflicts of interest							
16	Funding and sponsorship	− 3	2	− 3	− 3	− 3	− 3	− 3
	Total	33	23	25	28	26	25	25

medial pathway involved in attention and affection, and a lateral pathway involved with discrimination [102].

The first RCT by North et al. [44••] showed that SCS was more efficacious than reoperation in patients with chronic pain and previous failed back surgery syndrome. The second RCT by Kumar et al. [45••] demonstrated that SCS plus conventional medical management (CMM) provided sustained pain relief for at least two years resulting in statistically better outcomes compared with CMM alone. The concept of 10 kHz SCS which does not require paresthesia for pain treatment prompted the first large-scale pivotal trial (SENZA-RCT) [37••] comparing two active SCS treatments in the USA. The SENZA-RCT enrolled 198 subjects and found that 10 kHz SCS had a responder rate (> 50% reduction in pain) of 76.5% for back pain and 72.9% for leg pain at 2-year follow-up. This was superior in comparison with 50.7% for both back and leg pain in patients randomized to traditional SCS. The results of the SENZA-RCT study validated the outcomes from a previous observational study published by Al Kaisy et al. [53].

The SENZA-RCT opened the way for additional large-scale RCTs, two of them published recently by Deer et al. [39••, 50••]. The first of these RCTs was the ACCURATE study [39••] evaluating DRG stimulation in comparison with traditional SCS for the treatment of chronic intractable pain the lower limbs attributed to complex regional pain syndrome (CRPS). Responder rate (> 50% pain relief) for DRGS was found to be significantly superior to that for conventional SCS, with DRGS having a responder rate of 74% compared with traditional SCS's rate of 53% at 12 months, with inclusion of 105 patients. Deer et al. [50••] also published the results of another pivotal RCT (SUNBURST study), which evaluated the effectiveness of burst SCS in comparison with traditional tonic SCS in patients with chronic pain of the trunk and/or limbs. The study included 100 subjects that evaluated either tonic or burst SCS for 12 weeks and then crossed over to the other type of stimulation for an additional 12 weeks before letting the patient choose their therapy and continue until the 24-month follow-up visit. The study set their percentage of pain relief for responders at 30% as opposed to 50% used in

Table 4 Results of published randomized trials of effectiveness of spinal cord stimulation in low back and lower extremity pain

Study	Study characteristics	Methodological quality scoring	Patients	Pain relief		Results	
				≤ 12 months	≥ 12 months	Short-term ≤ 12 months	Long-term ≥ 12 months
Kapural et al. [37]	RA, AC	IPM-QRB: 31/48	SCS = 81 HF10 = 90	55% vs. 80%	55% vs. 80%	P	P
Deer et al. [39]	RA, AC	IPM-QRB: 31/48	SCS = 54 DRG = 59	56% vs. 81%	53% vs. 74%	P	P
North et al. [44]	RA, AC	IPM-QRB: 28/48	SCS = 29 Reoperation = 31	52% vs. 10%	52% vs. 10%	P	P
Kumar et al. [45]	RA, AC	IPM-QRB: 29/48	Total = 100 CMM = 48 SCS = 52	18% vs. 48%	18% vs. 48%	P	P
Schultz et al. [46]	RA, AC	IPM-QRB: 17/48	Manual = 40 Adaptive = 36 Total = 76	U	NA	U	NA
Perruchoud et al. [47]	RA, AC	IPM-QRB: 28/48	Total = 33 Sham vs. HFSCS = 20	30% vs. 42%	NA	N	NA
North et al. [48]	RA, AC	IPM-QRB: 21/48	Total = 22 Paresthesia-based stimulation vs. subperception stimulation = 22	41% vs. 95%	NA	NA	NA
De Andres et al. [49]	RA, AC	IPM-QRB: 30/48	Total = 55 Conventional = 29 HF = 26	Similar	Similar	U	U
Deer et al. [50]	RA, AC	IPM-QRB: 30/48	Total = 100 Tonic and burst alternate = 45 vs. 55	51% vs. 60%	51% vs. 60%	P	P
Thomson et al. [51]	RA, AC	IPM-QRB: 23/48	Total = 20	Similar	Similar	P	P
Al Kaisy et al. [52]	RA, DB	IPM-QRB: 34/48	Total = 24 Crossover with sham low frequency and HF	HF superior at 3-month FU	NA	P	NA

RA, randomized; *AC*, active control; *DB*, double blind; *IPM-QRB*, Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment; *SCS*, spinal cord stimulation; *HF*, high frequency; *DRG*, dorsal root ganglion; *CMM*, conventional medical management; *U*, unclear; *NA*, not applicable; *N*, negative; *P*, positive

Table 5 Results of published nonrandomized studies of effectiveness of spinal cord stimulation in low back and lower extremity pain

Study	Study characteristics	Methodological quality scoring	Patients	Pain relief		Results	
				≤ 12 months	≥ 12 months	Short-term ≤ 12 months	Long-term ≥ 12 months
Al Kaisy et al. [53]	Prospective	IPM-QRBNR: 33/48	HFSCS = 68	88%	88%	P	P
Russo et al. [55]	Retrospective	IPM-QRBNR: 23/48	HFSCS = 155	81%	81%	P	P
Rosenberg et al. [56]	Prospective	IPM-QRBNR: 25/48	401 implanted 252 followed	59%	58%	P	P
Gatzinsky et al. [58]	Prospective	IPM-QRBNR: 28/48	81	—	63%	P	P
Veizi et al. [59]	Prospective/ Retrospective	IPM-QRBNR: 26/48	Total = 213	74%	74%	P	P
Russo et al. [60]	Prospective/ Preliminary	IPM-QRBNR: 25/48	Closed loop 36	83%	NA	P	NA
Huygen et al. [61]	Prospective	IPM-QRBNR: 25/48	56	58%	49%	P	P

IPM-QRBNR, Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies; *HFSCS*, high-frequency spinal cord stimulation; *P*, positive; *NA*, not applicable

other studies. With this lowered margin of relief, the study found burst SCS had a 60% responder rate while traditional tonic SCS has a 51% rate.

No other pivotal studies had been published to the date of the analysis, although multiple studies had evaluated variations in SCS therapy [46, 47, 49, 53–59]. Of importance, in the tradition of real-world evidence [62–64, 66, 67, 71], was the multicenter prospective study in the USA by Rosenberg et al. [56] of conventional SCS safety and efficacy, along with the associated changes in psychological and functional outcomes under the standard of care conditions of the therapy. The study enrolled 640 subjects, 401 subjects were implanted and 321 of these completed the 6-month follow-up visit, and only 252 completed the 12-month follow-up visit. The study confirmed that SCS was effective in providing pain relief and significant improvement of subjects' psychological and functional outcomes measures in this large population of subjects. The mean patient reported percentage pain relief was 58% at 12 months, with a responder rate of 70% for patients still enrolled at the end of study (40% in the intention to treat (ITT) population).

Another prospective multicenter study in Europe by Gatzinsky et al. [58] evaluated conventional SCS in 81 subjects with chronic pain in one or both legs with or without back pain implanted with percutaneous octapolar leads. They found that conventional SCS was effective at reducing leg pain by 41 mm (VAS) relative to baseline after 6 months, which was sustained at the 12 months visit.

Two observational studies evaluated technical improvements geared to improve outcomes of paresthesia-based SCS [59, 60]. Russo et al. [60] reported on the utilization of evoked action potentials in a closed-loop feedback adjustment of the stimulation amplitude to deliver efficient stimulation and reducing uncomfortable sensations upon positional changes. The study included only 36 subjects implanted (out of 51 who underwent a trial procedure) with the novel SCS system, with 30 completing the 6-month follow-up visit. The results imply an additional benefit by using the closed-loop feature of the system. Veizi et al. [59] reported the evaluation of a model-based algorithm designed to guide electrode selection for optimal targeting of neural structures to cover pain dermatomes with paresthesia more efficiently in 213 patients, followed for 24 months. The study revealed that utilizing the novel algorithm significantly reduces the overall pain mean NPRS score (169 subjects) by 4.23 points, with a 74% responder rate (subjects with > 50% pain relief) at 24 months.

The limitations of this systematic review include paucity of RCTs despite increases in publications, and heterogeneity among the studies, precluding quantitative analysis. Further, the studies thus far conducted are smaller indicating the need for larger studies. In summary, from the evidence shown by these studies and our evaluation that SCS and DRGS could be beneficial interventions for patients with low back and leg chronic pain and CRPS of the lower extremities and may be considered if clinically indicated.

Conclusion

This systematic review presents an evaluation and discussion of multiple relevant clinical trials that evaluated the efficacy of both SCS (conventional, subthreshold, and burst) and DRGS. Eleven RCTs and 7 nonrandomized/observational studies provided a current level of evidence for these therapies and the variations that have resulted since the inception of paresthesia-free SCS. Moderately high- to high-quality evidence favors the utilization of high-frequency (> 5 kHz) SCS, burst SCS, and even DRGS over traditional SCS for specific conditions.

Compliance with Ethical Standards

Conflict of Interest Dr. Ricardo Vallejo is a paid consultant and advisory board member for Medtronic Inc.

Dr. Ashim Gupta declares no conflict of interest.

Dr. David L. Cedeño is a paid consultant and advisory board member for Medtronic Inc.

Mr. Alejandro Vallejo declares no conflict of interest.

Mr. William J. Smith declares no conflict of interest.

Mr. Samuel M. Thomas declares no conflict of interest.

Dr. Ramsin Benyamin is a paid consultant for Medtronic Inc.

Dr. Alan D. Kaye is a speaker for Merck and a Section Editor for Current Headache and Pain Reports. He has not been involved in the editorial handling of this manuscript.

Dr. Laxmaiah Manchikanti declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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