Systematic Review

Effectiveness of Spinal Cord Stimulation in Chronic Spinal Pain: A Systematic Review

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Background: Chronic neuropathic pain has been recognized as contributing to a significant proportion of chronic pain globally. Among these, spinal pain is of significance with failed back surgery syndrome (FBSS), generating considerable expense for the health care systems with increasing prevalence and health impact.

Objective: To assess the role and effectiveness of spinal cord stimulation (SCS) in chronic spinal pain.

Study Design: A systematic review of randomized controlled trials (RCTs) of SCS in chronic spinal pain.

Methods: The available literature on SCS was reviewed. The quality assessment criteria utilized were Cochrane review criteria to assess sources of risk of bias and Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment (IPM – QRB) criteria for randomized trials.

The level of evidence was based on a best evidence synthesis with modified grading of qualitative evidence from Level I to Level V.

Data sources included relevant literature published from 1966 through March 2015 that were identified through searches of PubMed and EMBASE, manual searches of the bibliographies of known primary and review articles, and all other sources.

Outcome Measures: RCTs of efficacy with a minimum 12-month follow-up were considered for inclusion. For trials of adaptive stimulation, high frequency stimulation, and burst stimulation, shorter follow-up periods were considered.

Results: Results showed 6 RCTs with 3 efficacy trials and 3 stimulation trials. There were also 2 cost effectiveness studies available. Based on a best evidence synthesis with 3 high quality RCTs, the evidence of efficacy for SCS in lumbar FBSS is Level I to II. The evidence for high frequency stimulation based on one high quality RCT is Level II to III. Based on a lack of high quality studies demonstrating the efficacy of adaptive stimulation or burst stimulation, evidence is limited for these 2 modalities.

Limitations: The limitations of this systematic review continue to require future studies illustrating effectiveness and also the superiority of high frequency stimulation and potentially burst stimulation.

Conclusion: There is significant (Level I to II) evidence of the efficacy of spinal cord stimulation in lumbar FBSS; whereas, there is moderate (Level II to III) evidence for high frequency stimulation; there is limited evidence for adaptive stimulation and burst stimulation.

Key words: Neuropathic pain, chronic spinal pain, failed back surgery syndrome, spinal cord stimulation, high frequency stimulation, burst stimulation, adaptive stimulation

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Since its introduction in the late 1960s (1), epidural electrical stimulation of the dorsal columns of the spinal cord, commonly referred to as spinal cord stimulation (SCS), has been used frequently for the treatment of chronic pain (2-9). The first systematic review of the scientific evidence by Turner et al (10) in 1995 suggested a role for SCS in the treatment of neuropathic pain. However, this review was met with criticism because of the inclusion of, and heavy reliance upon, observational studies. A subsequent Cochrane Review in 2004 (11) likewise suggested that SCS showed promise in the treatment of neuropathic pain that had proven refractory to other treatment options. Taking into account criticism of previous systematic reviews on the subject of SCS effectiveness, Turner and colleagues (12) revisited the subject in 2004. This review was more widely accepted due to the use of evidence-based medicine criteria for grading the available studies. The only randomized controlled trial (RCT) (13) available at that time suggested patients received pain relief, while the functional improvement was harder to identify. The result of this review was a recommendation that more robust studies be performed to address deficiencies in the literature. These deficiencies included small sample sizes, short duration, as well as short follow-up, a lack of multicenter trials, and the retrospective nature of much of the compiled literature (14,15). Since then, multiple systematic reviews and effectiveness studies have been published (14-18).

Taylor et al (15), in a 2006 systematic review and meta-analysis, concluded that SCS improves analgesia, decreases analgesics consumption, improves quality of life, and has a favorable cost profile. The evidence was given a grade of B for failed back surgery syndrome (FBSS) and Complex Regional Pain Syndrome (CRPS). The cost effectiveness of SCS was subsequently confirmed by Bala et al (16) and others (14) with SCS given an evidence recommendation level of A for FBSS. This was based upon 3 studies that met the authors' inclusion criteria and demonstrated effectiveness in terms of pain reduction. Furthermore, the authors suggested that despite high initial costs, SCS resulted in a long-term cost reduction without defining the time period classified as long-term. In a systematic review of the literature with inclusion of 2 RCTs and 10 observational studies, Frey et al (4) indicated there is an evidence level of II-1 or II-2 for long-term relief in managing patients with FBSS, showing evidence obtained from multiple well-designed controlled trials without randomization or small RCTs.

With continued debate on efficacy, cost-utility, complications, and indications, SCS systems have become more complex with choices of multiple options based on available components and various levels of invasiveness, selectivity, longevity, and adjustability (2). Further, some clinical indications for SCS, even though considered to have remained relatively stable over the years, have faded away, such as cancer pain, pain associated with spasticity, post-herpetic neuralgia, brachial plexus avulsion, and phantom pain after amputation (2,19,20). Thus, the dominant indications continue to remain stable for neuropathic pain from FBSS and CRPS in the United States, and pain due to coronary or peripheral vascular ischemia in the extremities in other countries (2). Slavin (2) has described the growth of SCS innovations with developmental trends and new innovations, which are advancing at an exponential pace with more revolutionary developments expected. These advances are related to the changes during the past decade with rechargeable generators, multicolumn electrode leads, independent current delivery, percutaneously insertable paddle leads, long-range telemetry, self-adjustable stimulation, and the compatibility of magnetic resonance imaging (MRI), along with many other developments. Future developments include new stimulation paradigms, closed loop stimulation, new stimulation targets, the addition of neurochemicals, hardware improvement, and miniaturization. Even though the tone of applications and predictions has changed over the years , debate on efficacy continues. Eldabe et al (21) have described that through improved pain relief, SCS provides an important enhancement to the functionality and health-related quality of life for those with chronic low back pain. The National Institute for Health and Care Excellence (NICE) in the United Kingdom reviewed these trials and evidence of cost effectiveness (22-24). NICE recommends SCS as a treatment for patients suffering from refractory chronic neuropathic pain conditions, including chronic low back pain (25). Taylor et al (8), in a systematic review and meta-regression analysis, supported SCS as an effective pain relieving treatment for chronic low back pain with predominant leg pain with or without a prior history of back surgery. However, they cautioned that RCTs are needed to confirm the effectiveness of SCS in the chronic low back pain population with predominant low back pain.

This systematic review was undertaken to assess the role of SCS in chronic spinal pain with assessment of effectiveness.

1.0. Methods

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and meta-analysis of randomized trials, Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials, Cochrane guidelines, and quality of reporting of analysis (26-32).

1.1 Criteria for Considering Studies for This Review

1.1.1 Types of Studies

Randomized controlled trials

1.1.2 Types of Participants

Chronic spinal pain with or without surgery is included in this systematic review. CRPS of the extremities and SCS for other indications are not included.

1.1.3 Types of Interventions

Cervical, thoracic, and lumbar spinal cord stimulator lead placement (1, 2, and 3 leads) with implantable pulse generator.

1.1.4 Types of Outcome Measures

- The primary outcome parameter was pain relief.
- The secondary outcome measure was functional improvement.

1.2 Literature Search

All of the available trials in all languages from all countries providing appropriate management with outcome evaluations were considered for inclusion. Searches were performed from the following sources without language restrictions:

1. PubMed from 1966
   www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
2. Cochrane Library
   www.thecochranelibrary.com/view/0/index.html
3. U.S. National Guideline Clearinghouse (NGC)
   www.guideline.gov/
4. Previous systematic reviews and cross references
5. Clinical Trials
   clinicaltrials.gov/
6. All other sources including non-indexed journals and abstracts

The search period was from 1966 through March 2015.

1.3 Search Strategy

The search strategy emphasized chronic spinal pain with or without surgical interventions. The search terms included "spinal cord stimulation" or "dorsal column stimulation" or "low-frequency therapy" or "high-frequency therapy" in back pain or post surgery syndrome or neuropathic pain patients.

The search terminology was as follows :

((((Spinal Cord Stimulation) OR dorsal column stimulation) OR Low-frequency stimulation) OR high-frequency stimulation) AND (((((((chronic back pain) OR post laminectomy syndrome) OR post surgery syndrome) OR failed back surgery syndrome) OR Complex Regional Pain 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]))

1.4 Data Collection and Analysis

The review focused on randomized trials for efficacy, cost effectiveness, and other outcome measures. The population of interest was patients suffering with chronic spinal pain for at least 6 months. All of the studies providing appropriate management and with outcome evaluations and statistical evaluations were reviewed. Reports without appropriate diagnosis, non-systematic reviews, book chapters, and case reports were excluded. Ultimately, any study not following the patient population for at least one year was excluded regardless of the quality of the experimental design.

1.4.1 Inclusion and Exclusion Criteria

Effectiveness studies with at least 12 months of follow-up and randomized trials with at least 20 patients in each group, with appropriate sample size determination for specific pathology were included. All other trials comparing stimulation patterns were included irrespective of the duration of follow-up.

1.4.2 Methodological Quality or Validity Assessment

The quality of each individual article used in this analysis was assessed by Cochrane review criteria (Appendix 1) (30) and Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM – QRB) for randomized trials (Appendix 2) (31).

Utilizing Cochrane review criteria, studies meeting the inclusion criteria with a score of at least 8 of 12 were considered high quality and 4 to 7 were consid-

ered moderate quality; these were included in the review. Those with a score of less than 4 were considered low quality and were excluded.

Based on IPM-QRB criteria for randomized trials, the trials meeting the inclusion criteria that scored less than 16 were considered as low quality and were excluded. Those scoring 16 to 31 were considered moderate quality, and those scoring 32 to 48 were considered high quality; these were included in the review.

1.4.3 Data Extraction and Management

Working independently and in an unblinded, standardized way, 2 review authors established the search criteria, searched for relevant literature, selected the manuscripts, and extracted the data from the included studies. Any disagreement between the 2 reviewers were discussed and debated. If no compromise was reached, another author would review the disagreement and cast the deciding opinion.

Methodological quality assessment was performed by multiple review authors with groups of 2 authors reviewing 2 to 4 manuscripts. The assessment was carried out independently in an unblinded standardized manner to assess the methodological quality and internal validity of all the studies considered for inclusion. The methodological quality assessment was performed in such a way to prevent discrepancies from occurring; if they did occur, a third reviewer was called in and the discrepancy decided by consensus. Continued issues were discussed with the entire group and resolved.

If there was a conflict of interest with a reviewed manuscript (concerning authorship), or if the reviewer was also one of the authors or had any type of conflict, the involved reviewer did not review the manuscript for methodological quality assessment.

1.4.4 Measurement of Treatment Effect in Data Synthesis (Meta-Analysis)

If the literature search provided at least 3 randomized trials meeting the inclusion criteria and they were clinically homogenous for each modality and region evaluated, a meta-analysis was performed.

1.5 Outcome of the Studies

A trial was judged to be effective if the spinal cord stimulator implant was clinically relevant and effective, either with placebo or active controls. This indicates that the difference in effect for primary outcome measure was statistically significant on the conventional 5% level. In a study without effectiveness, no difference between the study treatments or no improvement from baseline would be identified. Further, the outcomes were judged at the reference point, with positive or negative results reported at one month, 3 months, 6 months, and one year or longer.

The outcomes assessment and parameters utilized are crucial in assessing surgical and intervention trials (33-39). In the past, a minimum 20% reduction in pain or change in pain scores of 2 has been considered as significant improvement by many authors, as well as the Food and Drug Administration (31,37). However, many of the reviewers, as well as policy makers, have considered these as clinically insignificant improvements. Consequently, for assessment of outcomes in SCS, as well as interventional techniques, clinically significant and robust measures have been incorporated with descriptions of at least 50% improvement as the criterion standard for clinically significant improvement (13,18,38-59). There also has been significant literature published describing the minimal clinically important difference using item response theory models (60) and also the importance of outcomes in health-related quality of life assessment (61). In addition, multiple approaches for estimating minimal clinically important differences have been described (62). Outcomes based on patient perspectives also have become important in recent years (63,64). The literature also emphasizes multiple facts of comparative analysis between 2 groups in active-control trials, instead of only comparing between both interventions, which may lead to inaccurate assessment leading to inappropriate conclusions of lack of efficacy (65-68).

The following outcomes were considered clinically meaningful or significant: a 3-point or greater change on an 11-point pain scale (0 - 10), or a 50% pain improvement from baseline and a 40% or greater improvement in functional status (13,18).

1.6 Summary Measures

Summary measures included 50% or more reduction of pain in at least 50% of the patients, or at least a 3-point decrease in pain scores and a relative risk of adverse events including side effects.

Improvement for less than 12 months is considered as short-term and longer than 12 months is considered as long-term.

1.7 Analysis of Evidence

The analysis of the evidence was performed based on the American Society of Interventional Pain Physicians' (ASIPP's) best evidence synthesis (32). This instru-

ment was developed utilizing and modifying extensive available criteria including the criteria of the United States Preventive Services Task Force (USPSTF) and Cochrane review criteria as illustrated in Table 1 (69-74).

The analysis was conducted using 5 levels of evidence ranging from Level I to V, or strong to opinion or consensus-based.

At least 2 of the review authors independently, in an unblinded standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus. If there were any conflicts of interest (e.g., authorship), those reviewers were recused from assessment and analysis for the study in question.

2.0 Results

Figure 1 shows a flow diagram of study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (27).

Our search strategy yielded 20 studies

Table 1. Qualitative modified approach to grading of evidence.

Level I	Evidence obtained from multiple relevant high quality randomized controlled trials
Level II	Evidence obtained from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials
Level III	Evidence obtained from at least one relevant moderate or low quality randomized controlled trial with multiple relevant observational studies or Evidence obtained from at least one relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies
Level IV	Evidence obtained from multiple moderate or low quality relevant observational studies
Level V	Opinion or consensus of large group of clinicians and/or scientists

Source: Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. Pain Physician 2014; 17:E319-E325 (32).

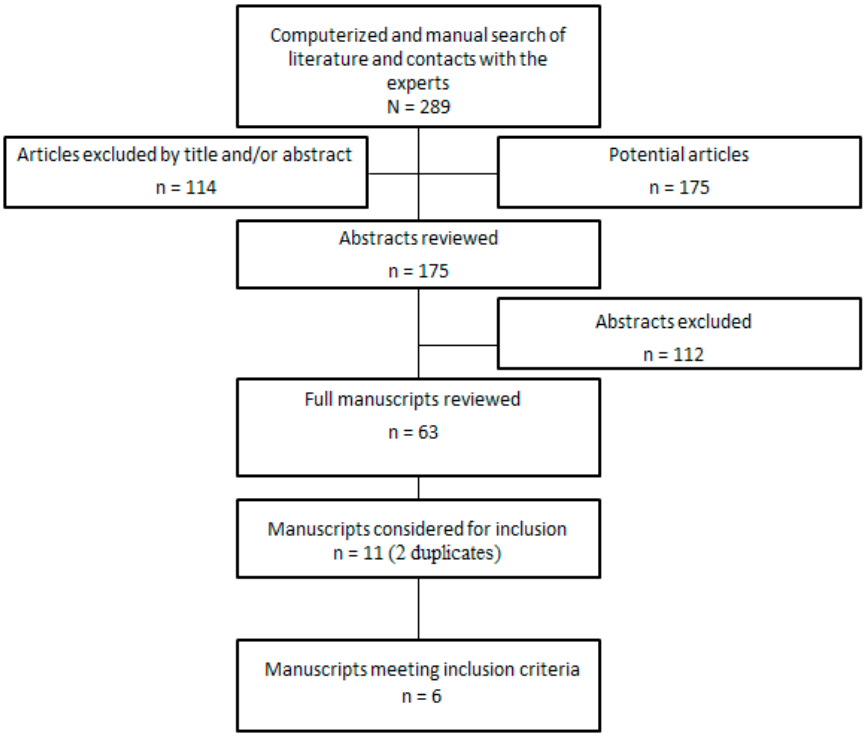

Fig. 1. *Flow diagram illustrating the literature used for evaluating spinal cord stimulation.*

Table 2. *Methodological assessment of randomized clinical trials evaluating spinal cord stimulation in chronic spinal pain.*

	Kapural et al (38,39)	North et al (13)	Kumar et al (18,86)	Schultz et al (77)	Perruchoud et al (78)	Schu et al (79)
Randomization adequate	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	U	Y	Y	N	N	Y
Patient blinded	Y	N	N	N	N	N
Care provider blinded	N	N	N	N	N	N
Outcome assessor blinded	N	N	N	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	N	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	N	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	U	Y	Y	Y	Y
Co-intervention avoided or similar in all groups	Y	Y	Y	Y	U	Y
Compliance acceptable in all groups	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y
SCORE	9/12	7/12	9/12	7/12	7/12	9/12

Y = yes; N = no; U = unclear

Source: Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941 (28).

(13,18,22,24,26,36,38,39,75-86). Of these, there were 9 RCTs managing chronic neuropathic spinal pain (13,18,22,38,75,77-79,81) after exclusion of the duplicates (39,86). Of these 9 RCTs, 3 trials of efficacy assessment (13,18,38) met the inclusion criteria for methodological quality assessment. Among the remaining trials, one assessed sensor-driven position-adaptive SCS (77), 2 assessed high-frequency SCS (38,78), and one assessed burst stimulation (79). One study by North et al was a cost effectiveness study (22) and a second one by North et al (75) was an electrode design. Consequently, 6 trials were considered for methodological quality assessment (13,18,38,77-79) after exclusion of duplicates (39,86). All of the trials were in the lumbar region and assessed efficacy in FBSS (13,18,38). There were no trials of SCS in thoracic or cervical spinal pain. Multiple studies and systematic reviews also conducted cost-utility and cost-effectiveness analysis (15,16,22,24,26,36,81,85).

2.1 Methodological Quality Assessment

A methodological quality assessment of the RCTs meeting inclusion criteria was carried out utilizing Cochrane review criteria and IPM-QRB criteria for randomized trials as shown in Tables 2 and 3.

2.2 Meta-Analysis

Even though there were 6 RCTs available, only 3 of them assessed efficacy (13,18,38), whereas other studies assessed adaptive stimulation (77), high-frequency stimulation (38,78), and burst stimulation (79). In addition, 3 trials of efficacy utilized vastly different inclusion criteria, which were not clinically homogenous. Thus, no meta-analysis was performed.

2.3 Study Characteristics

Appendix 3 shows the descriptive characteristics of the included RCTs.

2.4 Cost Effectiveness

An analysis was performed on 2 systematic reviews (16,24). The latest systematic review by Taylor et al (24) assessed cost effectiveness using a decision analytic model to examine the cost effectiveness of SCS versus conventional medical management (CMM) therapy versus re-operations in patients with FBSS. They assessed the cost effectiveness of SCS compared with CMM to be £5,624 ($8,765) for quality adjusted life year, with 89% probability that SCS is cost effective at a willingness to pay threshold of £20,000 ($31,170). Compared with re-operation, the incremental cost effectiveness of SCS was £6,392 ($9,962) for quality adjusted life year, with 82% probability of cost effectiveness at a £20,000 ($31,170) threshold. They also concluded that when the longevity of an implanted pulse generator (IPG) is 4 years or

Table 3. Methodological quality assessment of randomized trials of spinal cord stimulation utilizing IPM – QRB criteria.

		Kapural et al (38,39)	North et al (13)	Kumar et al (18,86)	Schultz et al (77)	Perruchoud et al (78)	Schu et al (79)
I.	TRIAL DESIGN AND GUIDANCE REPORTING						
1.	CONSORT or SPIRIT	2	2	2	2	2	2
II.	DESIGN FACTORS						
2.	Type and Design of Trial	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	2	2	2
4.	Imaging	3	3	3	0	0	0
5.	Sample Size	3	2	2	2	1	0
6.	Statistical Methodology	1	1	1	1	1	1
III.	PATIENT FACTORS						
7.	Inclusiveness of Population	2	2	2	2	2	2
8.	Duration of Pain	2	2	2	2	2	2
9.	Previous Treatments	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	1	2	2	0	0	0
IV.	OUTCOMES						
11.	Outcomes Assessment Criteria for Significant Improvement	4	2	2	0	0	0
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2
13.	Description of Drop Out Rate	1	1	2	1	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	2	2
15.	Role of Co-Interventions	1	1	1	0	0	0
V.	RANDOMIZATION						
16.	Method of Randomization	2	2	2	1	1	2
VI.	ALLOCATION CONCEALMENT						
17.	Concealed Treatment Allocation	2	2	2	0	0	1
VII.	BLINDING						
18.	Patient Blinding	0	0	0	0	0	0
19.	Care Provider Blinding	0	0	0	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST						
21.	Funding and Sponsorship	0	-3	-3	-3	0	0
22.	Conflicts of Interest	2	2	2	2	2	2
	TOTAL	36	31	32	20	23	24

Source: Manchikanti L, Hirsch JA, Cohen SP, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (31).

less, a rechargeable (which is initially more expensive) IPG is more cost effective than a non-rechargeable IPG. They utilized 2 RCTs (13,18) in this cost effectiveness analysis. This analysis was accepted by NICE (25). NICE recommended SCS approval in selected FBSS patients in October 2008 (25).

Three separate publications showing the cost effectiveness of SCS versus CMM (36,85) and repeat surgery (22) showed similar results. A prior systematic review performed in 2008 utilizing RCTs as well as controlled observational studies of FBSS concluded that SCS was more effective and less costly in the long-term.

2.5 Effectiveness

Of the 3 randomized trials evaluating SCS, all of

them reported effectiveness for short- and long-term relief (13,18,38) as shown in Table 4.

2.6 Level of Evidence

The indicated level of evidence for SCS is Level I to II based on 2 high-quality RCTs (18,38) and one moderate-quality RCT (13) for long-term relief of 18 to 24 months in managing patients with chronic spinal pain of FBSS in the lumbar spine.

The evidence is Level II to III for high frequency stimulation patterns based on one high-quality trial for high frequency stimulation (38,39), with Level IV evidence based on one moderate-quality RCT with a small sample size and inconclusive results for superiority of burst stimulation over traditional SCS (79). The evidence for adaptive stimulation is Level V based on one small, moderate-quality size trial (77).

3.0. Discussion

The current assessment of evidence suggests that SCS is a viable treatment option for patients with a diagnosis of FBSS, for whom conservative management has failed to provide adequate relief. This is based on 2 high-quality RCTs (18,38) and one moderate-quality RCT (13).

Overall, the evidence is Level I to II for the effectiveness of SCS based on 3 RCTs (13,18,38), with 2 high-quality trials (18,38) and one moderate-quality trial (13). The evidence for high frequency stimulation is Level II to III based on one high-quality RCT (38,39). The evidence for burst stimulation is Level IV with one small trial with inconclusive results (79). The evidence for adaptive stimulation is Level V based on one moderate-quality RCT (77). Further, cost effectiveness of SCS also has been demonstrated based on one systematic review (24), which was utilized in determination of coverage recommendations by NICE (25) and 2 studies (22,36) assessing cost effectiveness utilizing 2 prior RCTs (13,18). The results of this systematic review are up-to-date including a recently published RCT (38,39) with elevation of evidence for the efficacy of SCS and potential superiority of high frequency SCS compared to traditional SCS. Since the recent RCT was not available for utilization in previous systematic reviews, the present systematic review is more appropriate for clinical utilization. RCTs utilized in this systematic review are of either high-quality (18,38) or moderate-quality (13) based on Cochrane review criteria and IPM-QRB criteria.

The recent trial by Kapural et al (38,39) utilizing 10 kHz high-frequency stimulation, or HF10 therapy, provided better relief than low frequency or traditional SCS in the treatment of chronic back and leg pain in post lumbar surgery syndrome. These results (38,39) also confirm the efficacy of traditional SCS and add to the pre-existing evidence from North et al (13) and Kumar et al (18,86). Kapural et al (38,39) conducted a large multi-center RCT that utilized 198 patients with 97 patients assigned to traditional SCS therapy and 110

Table 4. Results of published studies of effectiveness of spinal cord stimulation in failed back surgery syndrome.

Study	Study Characteristics	Methodological Quality Scoring	Patients	Pain Relief		Results	
				≤ 12 mos.	> 12 mos.	Short-term ≤ 12 mos.	Long-term > 12 mos.
Kapural et al (38,39)	RA, AC	Cochrane:8/12 IPM-QRB: 34/48	SCS = 81 HF10 = 90	55% vs. 80%	55% vs. 80%	P	P
North et al (13)	RA, AC	Cochrane: 7/12 IPM-QRB: 31/48	SCS = 29 Reoperation = 31	52% vs. 10%	52% vs. 10%	P	P
Kumar et al (18,86)	RA, AC	Cochrane: 9/12 IPM-QRB: 32/48	Total = 100 CMM = 48 SCS = 52	18% vs. 48%	18% vs. 48%	P	P
Schultz et al (77)	RA, AC	Cochrane: 7/12 IPM-QRB: 20/48	Manual = 40 Adaptive = 36 Total = 76	U	NA	U	NA
Perruchoud et al (78)	RA, AC	Cochrane: 7/12 IPM-QRB: 23/48	Total = 33 Sham vs HFSCS = 20	N	NA	N	NA
Schu et al (79)	RA, AC	Cochrane: 9/12 IPM-QRB: 24/48	20	P (burst)	NA	U	NA

RA = randomized; AC = Active-control; SCS = spinal cord stimulation; CMM = conventional medical management; vs = versus; P = positive; N = negative; NA = Not applicable; U = undetermined; HF10 = 10 kHz high frequency therapy; HFSCS = high frequency spinal cord stimulation

patients assigned to HF10 therapy, with 92 and 97 trialed in each respective group with 81 and 90 successful trials receiving implantation, respectively. This trial included as a primary endpoint composite safety and efficacy, which included the percentage of patients responding to SCS therapy with at least a 50% reduction in visual analog scale scores without a stimulation-related neurological deficit. They also utilized multiple other parameters in reference to opioid analgesic usage, as well as remission with a decrease of pain to visual analog scale (VAS) of 2.5 with elimination of opioid use. They reported 79% of the patients responded to HF10 therapy who had back pain and leg pain, whereas the response rate was 51% with conventional SCS. In reference to the remitters with substantial improvement, for back pain, the proportion was 69% with HF10 therapy and 36% with traditional therapy, whereas for leg pain, the response rate was 67% with HF10 therapy and 43% with traditional SCS therapy. Thus, this study demonstrated that patients with leg pain respond better than those with back pain. Patient satisfaction rates were similar in both groups. Overall, the results in this trial were superior to 2 previously reported trials by North et al (13) and Kumar et al (18).

Kumar et al published 2 manuscripts on their trial (18,86) with a 12-month follow-up and 18 month follow-up comparing SCS with CMM in patients with neuropathic pain secondary to FBSS with predominant leg pain. Medical management was similar in both groups and was actively managed. They randomized a total of 100 patients with 48 patients assigned to the CMM group and 52 patients assigned to the SCS group. At the 6-month analysis, there were 44 patients in the CMM group with 4 withdrawn to consent, and 50 patients in the SCS group with 2 withdrawn to consent. There were only 16 patients for the 12-month follow-up in the CMM group even though the intention to treat analysis utilized 41 patients. In the SCS group, 5 patients crossed to the CMM group, 2 were lost to follow-up, and one patient withdrew to consent. Primary outcomes at 12 months with at least 50% improvement in pain were achieved in 48% of the 71 patients implanted with a stimulator and 18% of the 17 patients receiving conventional medical therapy alone. A post-hoc analysis was performed to quantify the impact of crossovers: 34% of the SCS group and 7% of the CMM group achieved the primary outcome. Thirty-two percent of the patients experienced a total of 40 device-related complications with 20 patients (24%) requiring surgery to resolve the device-related events (86). At 24-month follow-up, of the 52 patients randomized to SCS, 42 patients, or 81%, were continuing SCS and reported significant improvement in leg pain, quality of life, and functional capacity. However, 46 of 52 patients randomized to SCS and 41 of 48 randomized to CMM who were available, the primary outcome was achieved in 37% of the patients randomized to SCS versus 2% to CMM, and by 47% of 72% of patients who received SCS as a final treatment versus 7% of 15 for CMM. Overall, this trial showed significant improvement, even though it was below the 50% for the primary outcome, when an intention to treat analysis was utilized. Overall, there was an 81% rate of improvement considering 52 randomized patients to SCS with a success rate in 42 patients.

North et al (13) randomized a total of 60 patients with complex interaction with crossover data and reporting. They reported that among 45 patients, with 90% available for follow-up, SCS was more successful than re-operation in 9 of 19 patients versus 3 of 26 patients. They also showed that patients who were initially randomized to SCS were significantly less likely to crossover than were those randomized to re-operation. Further, patients randomized to re-operation also had higher opioid requirements more often than those randomized to SCS. Even though the data are confusing and the study is of small size, it demonstrated the effectiveness of SCS and superiority over repeat surgical interventions.

Cost-effectiveness was evaluated in 2 systematic reviews (16,24) and 3 studies (22,36,85) yielding positive results.

Manca et al (36) conducted a prospective, randomized, controlled multi-center trial known as the PROCESS trial. Patients who had FBSS were evaluated for quality of life, resource consumption, and costs associated with both SCS and CMM. The SCS group had a 6-month mean total health care cost of CAN$19,486 ($14,908). This cost was significantly higher than the group who received CMM (CAN$3,994) ($3,506); the mean adjusted difference was CAN$15,395 ($11,778) ($P \leq 0.001$). Regarding health-related quality of life (HRQoL), the SCS group showed better improvement after adjusting for baseline variables, with a mean EuroQoL-5D (EQ-5D) score difference of 0.25 ($P \leq 0.001$) at 3 months and 0.21 ($P \leq 0.001$) at 6 months. Their conclusion was that while adding SCS treatment to patients on CMM who had neuropathic leg and back pain was more costly, these same patients had marked improvements in their health and functional status.

Kumar et al (85) measured the mean cost of 5 years of SCS treatment and CMM treatment. They found the cost to be CAN$29,123 ($24,799). CMM treatment for the same period was CAN$41,964 ($33,722). Their assessment showed that SCS costs were higher for the first 30 months, primarily due to initial implantation costs. After that, SCS costs were significantly lower than CMM costs. Further, QoL improved 27% in those receiving SCS compared to 12% in those receiving CMM. The SCS patients were overwhelmingly satisfied with their treatment: 88% reported being satisfied or very satisfied and 15% were even able to return to work, something none in the CMM group were able to do. Despite SCS's initial high cost, the authors assert that SCS can be a cost-effective strategy, in part due to the greater number of patients who receive SCS being able to return to work and to be productive.

North et al (22) performed a cost effectiveness and cost utility analysis based on an RCT (13). In the randomized, controlled, crossover trial, the data for the first 42 patients was collected by a neutral or unbiased third party. According to North et al (22), during a "3.1 year follow-up, 13 of 21 patients (62%) crossed to re-operation while 5 of 19 patients (26%) crossed to SCS ($P \leq 0.025$). The mean cost per success was $117,901 for crossover patients to SCS. No crossover patients to re-operation achieved success despite a mean per-patient expenditure of $260,584. The mean per-patient cost was $31,530 for SCS versus $38,160 for re-operation (intention to treat), $48,357 for SCS versus $105,928 for re-operation (treated as intended), and $34,371 for SCS versus $36,341 for re-operation (final treatment). SCS was dominant (more effective and less expensive) in the incremental cost-effectiveness ratios and incremental cost-utility ratios." They continued, "A bootstrapped simulation for incremental costs and quality-adjusted life years confirmed SCS's dominance, with approximately 72% of the cost results occurring below US policy makers' 'maximum willingness to pay' threshold." The authors concluded that SCS "was less expensive and more effective than re-operation in selected FBSS patients and should be the initial therapy of choice" compared to re-operation. Thus, "SCS is most cost-effective when patients forego repeat operation" and, if SCS should fail, "re-operation is unlikely to succeed."

This systematic review shows the continued need for future studies illustrating effectiveness and superiority of high frequency stimulation and potentially burst stimulation. None of the effectiveness trials were performed with placebo control, as it is not feasible. Future directions including new programing platforms using burst stimulation and high frequency stimulation could potentially hold great promise with regard to extending the benefits of SCS to a greater range of patients suffering from axial low back pain with or without radicular symptoms. Burst stimulation, utilizes complex programming to deliver high-frequency stimuli of a 40 Hz burst mode with 5 spikes at 500 Hz per spike delivered in a constant current mode. Using this methodology, DeRidder et al (87) suggested that this programming mode may provide paresthesia-free stimulation resulting in better pain relief of low back and leg pain when compared to traditional tonic stimulation. This programming mode also allows comparison with placebo control since the stimulation is often undetected by the patient. This is an important point of criticism of the stimulation literature, since placebo-controlled studies are impossible to perform due to the nature of the interventions. The second stimulation mode that may hold promise for future application is 10 Kilohertz-frequency stimulation (10 kHz). Similar to burst stimulation, pain relief is achieved without the sensation of paresthesia by the patient. Additionally the data recently published in a small case series by Tiede and colleagues (88), and subsequently in a larger scale 2-center case series by Van Buyten et al (80), suggest that this stimulation rate may also improve pain relief not only from radicular lower extremity pain but also of low back pain. The ability to consistently provide pain relief from both low back and leg pain, often a variable and inconsistently covered symptom constellation by traditional tonic, paresthesia-based SCS, represents the potential for neuromodulation to improve outcomes in a greater number of patients (80).

Given the rapid pace of development of new stimulation platforms, systems designed to deliver paresthesia-free pain relief, and new technology to target isolated dermatomes or nerve fields, the science of neuromodulation is rapidly evolving beyond the traditional SCS tonic paresthesia approach. While the current review suggests efficacy and cost effectiveness for FBSS and CRPS with currently available technology, it is likely that future reviews will not center on establishing SCS or neuromodulation in general as effective but will evaluate the rapidly growing data on new applications of stimulation parameters and technology to identify which patient subsets are likely to benefit most from more finely targeted therapies.

4.0 Conclusion

The evidence for SCS in the treatment of neuropathic pain is continuing to grow as more prospective and randomized trials are being performed. Based on the available evidence, we conclude that SCS for FBSS meets best evidence synthesis criteria for Level I to II evidence based upon clinical efficacy and demonstrated cost effectiveness. Future directions will center around the ability to better identify patient subsets who are likely to benefit most from neuromodulation as well as evaluation of the rapidly emerging technologies that are coming into the clinical arena.

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Conflicts Of Interest:

Dr. Grider is a non-paid consultant to Medtronic and on the scientific advisory board of Intralink Spinal (also non-paid).

Dr. Manchikanti has provided limited consulting services to Semnur Pharmaceuticals, Incorporated, which is developing nonparticulate steroids.

Dr. Justiz is a consultant for St. Jude Neurmodulation and Epimed International.

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Appendix 1. *Sources of risk of bias and Cochrane Review rating system.*

A	1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments. Examples of inadequate methods are alternation, birth date, social insurance/ security number, date in which they are invited to participate in the study, and hospital registration number.	Yes/No/Unsure
B	2. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?		
	3. Was the patient blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/Unsure
	4. Was the care provider blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/Unsure
	5. Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: –for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" –for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination –for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome –for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., co-interventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes" –for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data.	Yes/No/Unsure
D	Were incomplete outcome data adequately addressed?		
	6. Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored.	Yes/No/Unsure
	7. Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.	Yes/No/Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	In order to receive a "yes," the review author determines if all the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/Unsure
F	Other sources of potential bias:		

Appendix 1 (cont.). *Sources of risk of bias and Cochrane Review rating system.*

	9. Were the groups similar at baseline regarding the most important prognostic indicators?	In order to receive a "yes," groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/Unsure
	10. Were co-interventions avoided or similar?	This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.	Yes/No/Unsure
	11. Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number, and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore, it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/Unsure
	12. Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/Unsure

Source: Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941 (28).

Appendix 2. *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB*

		Scoring
I.	**TRIAL DESIGN AND GUIDANCE REPORTING**	
1.	**CONSORT or SPIRIT**	
	Trial designed and reported without any guidance	0
	Trial designed and reported utilizing minimum criteria other than CONSORT or SPIRIT criteria or trial was conducted prior to 2005	1
	Trial implies it was based on CONSORT or SPIRIT without clear description with moderately significant criteria for randomized trials or the trial was conducted before 2005	2
	Explicit use of CONSORT or SPIRIT with identification of criteria or trial conducted with high level reporting and criteria or conducted before 2005	3
II.	**DESIGN FACTORS**	
2.	**Type and Design of Trial**	
	Poorly designed control group (quasi selection, convenient sampling)	0
	Proper active-control or sham procedure with injection of active agent	2
	Proper placebo control (no active solutions into active structures)	3
3.	**Setting/Physician**	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology/radiology/ortho, etc.	1
	Interventional pain management with interventional pain management physician and neuro or spine surgeons for SCS	2
4.	**Imaging**	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	**Sample Size**	
	Less than 50 participants in the study without appropriate sample size determination	0
	Sample size calculation with less than 25 patients in each group	1
	Appropriate sample size calculation with at least 25 patients in each group	2
	Appropriate sample size calculation with 50 patients in each group	3
6.	**Statistical Methodology**	
	None or inappropriate	0

Appendix 2 (cont.). *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB*

		Scoring
	Appropriate	1
III.	**PATIENT FACTORS**	
7.	**Inclusiveness of Population**	
7a.	**For spinal cord stimulation procedures:**	
	Poorly identified mixed population	0
	Clearly identified mixed population	1
	Disorders specific trials (i.e., well defined disc herniation or spinal stenosis or post surgery syndrome)	2
8.	**Duration of Pain**	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9.	**Previous Treatments**	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	**Duration of Follow-up with Appropriate Interventions**	
	Less than 3 months or 12 weeks for epidural and facet joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for epidural and facet joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 17 months for epidural and facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	2
	18 months or longer for epidural and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	3
IV.	**OUTCOMES**	
11.	**Outcomes Assessment Criteria for Significant Improvement**	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	2
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	**Analysis of all Randomized Participants in the Groups**	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13.	**Description of Drop Out Rate**	
	No description of dropouts, despite reporting of incomplete data or ≥ 20% withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14.	**Similarity of Groups at Baseline for Important Prognostic Indicators**	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1

Appendix 2 (cont.). Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB

		Scoring
	Groups similar with appropriate randomization and allocation	2
15.	**Role of Co-Interventions**	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	**RANDOMIZATION**	
16.	**Method of Randomization**	
	Quasi randomized or poorly randomized or not described	0
	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High quality randomization (Computer generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call, pre-ordered list of treatment assignments, etc.)	2
VI.	**ALLOCATION CONCEALMENT**	
17.	**Concealed Treatment Allocation**	
	Poor concealment of allocation (open enrollment) or inadequate description of concealment	0
	Concealment of allocation with borderline or good description of the process with probability of failure of concealment	1
	High quality concealment with strict controls (independent assignment without influence on the assignment sequence)	2
VII.	**BLINDING**	
18.	**Patient Blinding**	
	Patients not blinded	0
	Patients blinded adequately	1
19.	**Care Provider Blinding**	
	Care provider not blinded	0
	Care provider blinded adequately	1
20.	**Outcome Assessor Blinding**	
	Outcome assessor not blinded or was able to identify the groups	0
	Performed by a blinded independent assessor with inability to identify the assignment-based provider intervention (i.e., subcutaneous injection, intramuscular distant injection, difference in preparation or equipment use, numbness and weakness, etc.)	1
VIII.	**CONFLICTS OF INTEREST**	
21.	**Funding and Sponsorship**	
	Trial included industry employees	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only with supporting entity unrelated to industry	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
22.	**Conflicts of Interest**	
	None disclosed with potential implied conflict	0
	Marginally disclosed with potential conflict	1
	Well disclosed with minor conflicts	2
	Well disclosed with no conflicts	3
	Hidden conflicts with poor disclosure	–1
	Misleading disclosure with conflicts	–2
	Major impact related to conflicts	–3
TOTAL MAXIMUM		48

Source: Manchikanti L, Hirsch JA, Cohen SP, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of interventional pain management specific instrument. Pain Physician 2014; 17:E263-E290 (31).

Appendix 3. *Description of the characteristics of included randomized controlled trials of spinal cord stimulation.*

Study Study Characteristic Methodological Quality Scoring Country	Number of Patients & Selection Criteria	Control	Interventions	Outcome Measures	Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Kapural et al (38,39) Randomized control trial, active-control Cochrane: 8/12 IPM-QRB: 34/48 United States	• 198 patients were randomized with 101 assigned to high-frequency (HF10 therapy) whereas 97 assigned to traditional SCS. • In traditional SCS group, 92 were trialed with 81 successful SCS trials. • 97 patients were trialed in the high frequency group with 90 patients successful in SCS trial.	• SCS with traditional stimulation with adjustment of optimal overlap of paresthesia in the region of the back and leg pain. • 97 patients were randomized to control or conventional group. • 92 patients were trialed with 81 successful SCS trials receiving implants.	• Patients in high-frequency (HF10 therapy) group received SCS implant delivering 10,000 Hz with amplitude adjusted to optimal analgesic response.	• VAS for back and leg pain, ODI, global assessment of functioning • The primary endpoint of the study was a composite of safety and efficacy: the percentage of patients responding to SCS therapy for back pain (> 50% reduction in VAS score) without a stimulation-related neurological deficit.	Follow-ups 1, 3, 6, 9, 12, 18, and 24 months	• At 12 month follow-up, responder rates were significantly higher for HF10 therapy at all endpoints. • Back pain responder rate was 80% for HF10 therapy compared to 50% for traditional SCS. • Leg pain responder rate was 80% for HF10 therapy and 55% for traditional SCS. • A significant proportion of patients in HF10 group (67%) were considered in remission compared to 35% to 40% with traditional SCS for back and leg pain, with reduction of pain to 2.5 or less on a scale of 0 to 10. • Pain remission of NRS to less than 2.5 as remitters • Results were sustained at 18-month follow-up	• Randomized, double-blind active-control trial • Large sample size • Robust outcomes in both SCS groups, more so in high frequency stimulation therapy group	• Active-control trial with no placebo • Investigators were allowed to adjust patients' pain medication usage after device activation which may potentially confound the effects of SCS with opioid therapy.	Positive randomized active-control trial showing efficacy of traditional and high frequency SCS. This study with a large sample size with long-term follow-up showed positive results for traditional SCS with paresthesia, and high frequency stimulation without paresthesia at one year and 18-month follow-up.
North et al (13) Randomized controlled, active-control Cochrane: 7/12 IPM-QRB: 31/48 United States	• 60 patients with surgically remediable nerve root compression were assigned with 30 patients randomized to SCS trial and 30 patients randomized to reoperation with failed back surgery syndrome • Patients were randomized to 3 groups: 1. SCS trial and implant 2. Reoperation group and reoperation 3. Crossover group to reoperation from SCS trial and SCS trial and implant from reoperation group prior to intervention	• Repeat surgery with laminectomy and/or foraminotomy and/or discectomy with or without fusion with or without instrumentation • Total number of patients randomized = 26 with 14 crossing over to SCS trial from reoperation group • 5 patients from SCS group crossed over to reoperation prior to intervention. Total: 31 patients	• Permanent implantation with resume electrode, X-trel or Itrel pulsed generator; Medtronic, Inc. if they reported at least 50% estimated relief of pain with improved physical activity • Total number of patients randomized and obtained SCS insurance authorization = 24 with crossover to reoperation = 5 • Crossover from reoperation group to SCS trial = 14 Total: 29 patients	• Pain relief and patient satisfaction • Significant improvement • Definition of success: At least 50% pain relief and patient satisfaction with treatment	• Follow-up = mean 2.9 ± 1.1 year, ranging from 1.8 to 5.7 years, after 6 month crossover	• Outcome based on last treatment including crossover, 52% of patients receiving SCS followed for long-term were success (15 of 29), whereas for reoperation, it was 3 of 31 with a 19% success rate. • SCS was more successful even with intent to treat analysis utilizing patients who were not available for follow-up with 9 out of 23 instead of 9 of 15 with a success rate of 39% instead of 47%.	• Randomized active-control trial with long-term follow-up • Positive results with 52% success rate in SCS compared to 10% in reoperation group • 90% of the patients were available for follow-up around 3 years.	Active-control trial, small sample size, confusing reports of results. Overall success rate of 39% with intent to treat analysis in the SCS group compared to 12% in the reoperation group. • Of the 99 patients invited to participate, only 60 patients consented for randomization. • Even though workers' compensation patients were equally randomized, they were treated less often.	A positive study of moderate quality with relatively small sample size even though of long-term follow-up.

Appendix 3. *Description of the characteristics of included randomized controlled trials of spinal cord stimulation.*

Study Study Characteristic Methodological Quality Scoring Country	Number of Patients & Selection Criteria	Control	Interventions	Outcome Measures	Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Kumar et al (18,86) Randomized controlled, active-control Cochrane: 9/12 IPM-QRB: 32/48 Australia and 7 European countries	• 100 patients randomized to 2 groups of spinal cord stimulation (n = 52) versus conventional medical management (n = 48) for neuropathic pain of radicular origin of lower extremity • 48 were randomized to medical management group • Only failed back surgery syndrome patients were selected	• Medical management with 48 patients randomized versus 52 in the spinal cord stimulation group. • 44 patients were analyzed	• Conventional SCS • 52 patients underwent trial stimulation and 48 were permanently implanted with Medtronic Itrel 3 system	• VAS and percent of improvement in pain, ODI, opioid intake, SF-36 • The primary outcome was the proportion of patients achieving 50% or more pain relief in legs. • Secondary outcomes were health-related quality of life, functional capacity, use of pain medication, and non-drug pain treatments.	1, 3, 6, 9, 12, and 24 months	• At 12 months, the primary outcome was achieved in 48% of the 71 implanted with a stimulator and 18% of the 17 patients receiving conventional medical therapy alone. • The results showed successful outcomes in 81% of the patients (42 of 52) randomized to spinal cord stimulation with pain relief, quality of life, and functional capacity at 2-year follow-up. • However, at 24 months, of 46 of 52 patients randomized to SCS and 41 of the 48 randomized to CMM who were available, the primary outcome was achieved by 17 (37%) randomized to SCS versus one (2%) to CMM and by 34 (47%) of 72 patients who received SCS as final treatment versus one (7%) of 15 for CMM.	• This is an RCT with appropriate sample size, with multiple outcome parameters and long-term follow-up. • 81% or 42 of 52 patients randomized showed significant improvement considering only pain relief; however, only 47% or 34 of 72 patients who received SCS had final treatment and only 17 or 37% of the patients who received randomization originally showed significant improvement while considering primary outcome.	• Based on the study design, active-control, blinding was not possible. • The primary outcome was achieved in only 17 or 37% randomized to SCS versus one (2%) to CMM. • A disadvantage in patients with SCS was that 13 or 31% of the patients required a device-related surgical revision.	This study shows effectiveness of SCS in patients with failed back surgery syndrome.
Schultz et al (77) Randomized controlled trial, active-control, crossover with open label Cochrane: 7/12 IPM-QRB: 20/48 United States	• 79 patients randomized • Patients were implanted with RestoreSensor neurostimulation device (Medtronic, Inc., Minneapolis, MN) that could be programmed to either automatic position, adaptive stimulation, or manual adjustment stimulation parameters	Manual adjustment stimulation parameters after successful implantation of restore sensor	Automatic position-adaptive stimulation (AdaptiveStim) after implantation of RestoreSensor neurostimulation device	Pain relief • Improved comfort, improved activity, improved sleep • Primary outcome = proportion of patients with improved pain relief	1 to 12 weeks on a weekly basis	• With intent to treat analysis, 86.5% of patients achieved the primary objective of improved pain relief • Functional improvement reported with position adaptive stimulation including improved comfort during position change (80.3%), improved activity (69%), and improved sleep (47.9%). • The incidence of device-related serious adverse events was 3.9%.	• Randomized controlled trial, crossover, with open label • Reasonably large sample • Significant success rate reported in 86.5% of the patients with low complication rate and improvement with comfort levels, activity, and sleep	• Randomized controlled trial which was open-label and crossover • The results were reported only for adaptive SCS; comparisons were not available for readers • Significant improvement was considered with a predefined minimum success rate of 25% with an adverse event rate of 3.9%	A moderate quality study with an appropriate sample size but reporting the results of only adaptive SCS showing borderline improvement with a predefined success rate of 25%.

Appendix 3. *Description of the characteristics of included randomized controlled trials of spinal cord stimulation.*

Study Study Characteristic Methodological Quality Scoring Country	Number of Patients & Selection Criteria	Control	Interventions	Outcome Measures	Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Perruchoud et al (78) Randomized, double-blind, placebo controlled trial Cochrane: 7/12 IMP-QRB: 23/48 Switzerland and United Kingdom	40 patients already treated with SCS were recruited. The study was performed to assess analgesic efficacy of high-frequency SCS	Sham stimulation (no stimulation) in patients with implanted SCS with impulse generator, either rechargeable or battery powered	HFSCS at 5kHz in implanted SCS with impulse generator, either rechargeable or battery powered	Global impression of change, VAS, EuroQol	2 and 4 weeks	• The primary endpoint with proportion of patients was seen in 42.4% of the patients in the high frequency stimulation group compared to 30.3% in the sham group with no stimulation. • At visit 3, a similar proportion of patients responded to both treatments with 52.9% in the high frequency SCS group (9 of 17), and 50% with the sham or no stimulation group (8 of 16). • At follow-up visit 5, 31.3% of the patients responded to HFSCS versus only 11.8% of the patients in the no stimulation group with no statistically significant difference in the interaction term • The mean VAS on sham was 4.6 versus 4.35 on HFSCS. • The mean EuroQol 5 dimensional index with HFSCS was 0.48 versus 0.46 with sham	• First randomized double-blind placebo controlled trial assessing the analgesic efficacy of high frequency SCS.	• Small sample size with only 33 of the 40 patients with available data • No significant difference between no stimulation and HFSCS • It raises numerous questions about SCS itself instead of HFSCS as sham patients also responded with placebo effect	Very small randomized placebo-controlled trial showing negative results of high frequency stimulation, which was equivalent to no stimulation.
Schu et al (79) Randomized, double-blind, placebo controlled Cochrane: 9/12 IPM-QRB: 24/48 Germany and United Kingdom	• 20 patients randomized to 6 sequences with tonic, burst, and placebo stimulations with crossovers at 2 week and 3 week follow-up to assess effectiveness of burst SCS patterns for the treatment of failed back surgery syndrome with 3 randomized groups. • All patients were implanted with SCS	• Third randomized group was placebo • Placebo group with no stimulation with device being switched off.	• The first randomized group received HFSCS at a frequency of 500 Hz • The second randomized treatment group received burst stimulation – packets of 5 pulses (pulse with 1 mm per second) at 500 Hz, delivered 40 times per second at subsensory amplitude	NRS scores, pain quality, pain-related disability	1-3 weeks	• For the burst stimulation treatment group, mean NRS and SFMPQ scores were significantly decreased compared with the other treatment groups. • Mean NRS and SFMPQ scores were not significantly different between 500 Hz tonic stimulation and placebo stimulation • Lowest mean ODI scores were observed under burst stimulation, with no significant differences between the categories • Burst stimulation was significantly preferred by 80% of the patients	• Randomized, double-blind placebo controlled trial • Showed positive results for burst stimulation and tonic stimulation with lack of response to placebo or no stimulation	• Very small sample size with same patients undergoing different stimulations or no stimulation and also have been receiving conventional stimulation for one to 1.5 years which may cause substantial issues with modulation of pain, specifically since the treatments are changed each week in the same patient.	Positive results of burst stimulation in an extremely small study with multiple confounding issues.

VAS = Visual Analog Scale; ODI = Oswestry Disability Index; SF-36 = Short-form 36; CMM = Conventional medical management; SCS = spinal cord stimulation; HFSCS = high-frequency spinal cord stimulation; NRS = Numeric Rating Scores; SFMPQ = Short-form McGill Pain Questionnaire; PCS = pain catastrophizing scale

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