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Systematic Literature Review of Spinal Cord Stimulation in Patients With Chronic Back Pain Without Prior Spine Surgery

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ABSTRACT

Objective: Low back pain is the leading cause of disability worldwide and one of the most common reasons for seeking health care. Despite numerous care strategies, patients with low back pain continue to exhibit poor outcomes. Spinal cord stimulation (SCS) is an evidence-based therapeutic modality for patients with failed back surgery syndrome. For patients without a surgical lesion or history, minimally invasive interventions that provide long-term reduction of chronic back pain are needed. Therefore, we conducted a systematic review of the evidence on SCS therapy in patients with chronic back pain who have not undergone spinal surgery.

Materials and Methods: A systematic literature search was performed to identify studies reporting outcomes for SCS in chronic back pain patients (with or without secondary radicular leg pain) without prior surgery using date limits from database inception to February 2021. Study results were analyzed and described qualitatively.

Results: A total of ten primary studies (16 publications) were included. The included studies consistently demonstrated favorable outcomes in terms of pain reduction and functional improvement following SCS therapy. Improvements also occurred in quality of life scores; however, not all studies reported statistically significant findings. Additionally, the studies reported that SCS resulted in high patient satisfaction, reductions in opioid use, and an acceptable safety profile, although these data were more limited.

Conclusion: Findings suggest that SCS is a promising, safe, minimally invasive, and reversible alternative option for managing chronic back pain in patients who have not undergone spinal surgery.

Keywords: Back pain, low back pain, spinal cord stimulation, surgery-naïve, systematic review

Conflict of Interest: Markus A. Bendel has contracted research with Nevro Corp., with all funds going to his institution. Jan M. Eckermann is a consultant to Nevro Corp., Medtronic Inc., and Boston Scientific and a shareholder in BeckerSmith Medical, Inc. Julie G. Pilitsis is a consultant for Boston Scientific, Nevro, TerSera, Medtronic, Saluda, and Abbott and receives grant support from Medtronic, Boston Scientific, Abbott, Nevro, TerSera, NIH 2R01CA166379-06, and NIH U44NS115111. She is a medical advisor and has stock equity in Aim Medical Robotics and Karuna. The remaininng authors have no conflicts of interest to disclose.

INTRODUCTION

Worldwide, low back pain is the leading cause of disability and the second most common reason patients seek health care for the relief of symptoms.[1–3] According to recent estimates, patients in the United States spent approximately $87.6 billion on health care services for low back and neck pain, and these costs are increasing rapidly.[2,4] When indirect costs, such as lost productivity, are considered, this cost estimate exceeds $100 billion per year.[2,5]

In this study, we focus on reviewing the use of spinal cord stimulation (SCS) as a treatment for relieving chronic back pain in patients who have not had prior back surgery. Many publications show that SCS provides pain relief for chronic back and leg pain in patients who have undergone surgery yet continue to experience chronic back pain. The diagnosis most frequently ascribed to such patients is failed back surgery syndrome (FBSS). Of note is that there is ongoing discussion about the utility of the term; however, due to a lack of consensus on alternative terms,[6,7] we use FBSS as it is commonly used in the literature.

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Many other patients diagnosed with chronic back pain have not had prior back surgery or are poor candidates for surgery, and conventional medical management (CMM) has provided them limited relief. We refer to these patients as having nonsurgical refractory back pain (NSRBP),[8] a condition that may be synonymous with a recently introduced term, persistent spinal pain syndrome type 1.[6]

Multiple conservative treatments exist for patients with back pain, including physical therapy, medication management, and percutaneous spine injections, but patients often become unresponsive to these treatments or experience side effects from medications over time and exhibit poor long-term outcomes.[2,9–11] These patients may then receive expensive health care services that provide minimal benefit or potentially cause harm, such as opioids and spinal fusion surgery.[2,10,12,13]

SCS therapy creates a neuromodulatory effect on the nervous system that can change the perception of pain by sending electrical impulses into the spinal cord.[14–18] It has become a popular treatment for many chronic pain conditions.[14,16,19,20] The SCS frequency and pulse width can be adjusted, and in this review, high-frequency SCS is defined as ≥10 kHz and low-frequency SCS as <10 kHz. FBSS is the most common indication for SCS and has the strongest evidence supporting its use.[11,16,21] In contrast, the use of SCS in surgery-naïve back pain patients currently has less evidence-based support, but much clinical interest. It must be noted that the evidence regarding long-term outcomes of decompression- or fusion-type spinal surgeries is also less than optimal.[2,13,22,23] In many patients undergoing spinal surgery, a specific, reliable source of pain is not identified.[24–27] An additional challenge occurs in the subset of patients for whom imaging reveals no clear surgical target and who, despite exhaustive conservative measures (e.g., epidural and facet injections), fail to receive sufficient pain relief. Given the concerns of invasiveness, cost, and efficacy surrounding spinal surgery and the challenges of treating patients with chronic pain in the absence of a clearly identified surgical lesion, there is a need for less invasive interventions that provide long-term pain reduction and functional restoration. Therefore, we sought to systematically review and analyze the clinical evidence on SCS therapy in patients with chronic back pain who have not previously undergone spinal surgery.

MATERIALS AND METHODS

The study was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[28,29]

Search Strategy

A literature search was developed to identify peer-reviewed clinical studies that evaluated SCS therapies in patients with chronic back pain without prior surgery (Supplementary Information: Search strategy). The following databases were searched from database inception to February 11, 2021: Medline (via OVID), PubMed, Embase (via OVID), and the Cochrane Library. Additional search restrictions were implemented to exclude non-English publications and review articles (ie, narrative, literature, and systematic reviews).

Study Selection

Following the database searches, duplicate studies were identified and removed from the list of references. Two reviewers (Christopher Vannaboutathong and Belinda J. Wagner) screened the remaining titles and abstracts according to the eligibility criteria (Supplementary Table S1). Studies were excluded if they were nonclinical, not peer-reviewed, or not reported with completeness (eg, conference abstracts or clinical trial registrations without detailed methods and results); involved patients with angina, peripheral nerve stimulation, peripheral vascular disease, peripheral artery disease, or spinal cord injury; used SCS for movement induction; or combined SCS with other treatments to address the same indication (eg, intrathecal drug pump).

Full-text articles of the studies deemed potentially eligible were subsequently retrieved after title and abstract screening and screened for a final assessment of eligibility. Any disagreements regarding study eligibility were resolved via discussion or, when necessary, a third reviewer. References identified from other sources (eg, industry or clinical experts, reference lists of included articles, coauthors) were also reviewed for inclusion.

Data Extraction

The primary outcome measures were the magnitude of change in pain from baseline to follow-up, the proportion of subjects achieving a 50% reduction in pain, and adverse events (AEs) related to the device or procedure. Outcome measures related to improvements in quality of life (QoL), disability, function, and changes in medication use were also extracted. Specifically, study, treatment, and population characteristics and data related to the outcomes of interest from each included study were extracted (Supplementary Table S2).

Data Analysis

The results of individual studies were analyzed qualitatively, including the similarity of subject populations, efficacy outcomes, and safety outcomes across studies. Continuous data were reported as mean or median values and categorical data as percentages. Due to the nature of the evidence on this topic, it was determined that a meta-analysis of study outcomes was not feasible.

Risk of Bias Assessment

The risk of bias (ROB) of eligible level I studies was evaluated using the Cochrane Collaboration ROB tool.[30] Studies were rated based on six specific domains: 1) sequence generation, 2) allocation concealment, 3) blinding, 4) incomplete outcome data, 5) selective outcome reporting, and 6) other miscellaneous sources of bias. Each domain was judged as having either a "low risk," "unclear risk," or "high risk" of bias. A low ROB means that bias, if present, is unlikely to seriously alter the results, an unclear ROB raises some doubt about the results, and a high ROB may seriously alter the results.

The ROB was assessed for each nonrandomized study using the Risk of Bias in Nonrandomized Studies of Interventions tool.[31] This tool assesses seven domains through which bias may be introduced into a nonrandomized clinical study: 1) bias due to confounding, 2) bias in the selection of participants, 3) bias in the classification of interventions, 4) bias due to deviations from

intended interventions, 5) bias due to missing data, 6) bias in the measurement of outcomes, and 7) bias in the selection of the reported results. Each domain was judged as having a "low," "moderate," "serious," or "critical" ROB, and the final assessments for each domain were used to grade the overall ROB of each study. When a study is judged to have a low ROB, it has low ROB assessments for all seven domains and is comparable to a well-performed randomized controlled trial (RCT). When a study is judged to have a moderate ROB, it has low or moderate ROB assessments for all seven domains and provides sound evidence for a nonrandomized study, but cannot be considered comparable to a well-performed RCT. When a study is judged to have a serious ROB, it has a serious ROB assessment in at least one domain, no critical ROB assessments in any of the six remaining domains, and its design or conduct has several problems. When a study is judged to have a critical ROB, it has a critical ROB assessment in at least one domain, and its design or conduct is too problematic to provide useful evidence and should be excluded from synthesis.

Quality of Evidence

The overall quality of evidence was rated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[32–34] Evidence was rated using criteria such as consistency, precision, indirectness, and study limitations, and graded the quality of evidence for each outcome as "very low," "low," "moderate," or "high." If the included evidence for an outcome originates only from randomized trials, its corresponding GRADE designation starts at high, whereas evidence originating from observational studies starts at low. Reasons for downgrading an initial GRADE designation include limitations in study quality (eg, ROB), important inconsistencies or heterogeneity between studies, uncertainty about the directness, imprecision or sparseness of the data, or a high probability of reporting or publication bias. Reasons for upgrading an initial GRADE designation include strong evidence of association based on consistent evidence from two or more studies, with no plausible confounders; evidence of a dose–response relationship; or a determination that all plausible confounders would have reduced the effect.

RESULTS

Search Results

A total of 1221 references were identified from the electronic database searches (Supplementary Fig. S1). Of these, 326 were conference abstracts, 212 were duplicate publications, 58 were commentaries, and 2 were short surveys; therefore, 623 citations were reviewed during title and abstract screening. The full texts of 109 articles were subsequently screened for eligibility, and 16 were included in this review, representing 10 primary studies and 6 secondary publications.[35–50] Reasons for exclusion of articles during abstract screening and full-text screening included not meeting the criteria for patient populations, study designs, follow-up periods, or interventions (ie, not SCS), irretrievable full texts, nonclinical studies, and conference presentations.

Characteristics of the Included Studies

The included studies were published between 2004 and 2021 (Supplementary Table S3). Among the ten primary studies, six were prospective cohort studies,[35,37,43,47,49,50] two were retrospective cohort studies,[44,48] one was a retrospective database study,[38] and one was subgroup data from a RCT.[45] Four of these studies were conducted in the United Kingdom (UK),[37,38,43,48] three were conducted in the United States (US),[44,45,49] two were conducted in Germany,[35,47] and the remaining study was a multinational study.[50] The sample sizes analyzed in the ten primary studies ranged from 8 to 1177 patients; the number of patients with back pain and no prior surgery ranged from 8 to 159 (total surgery-naïve patients = 357). An additional six articles were secondary publications of the aforementioned primary studies (Supplementary Table S4).[36,39–42,46] Final follow-up periods across all studies ranged from 12 to 36 months, and mean follow-ups, when reported, ranged from 10 months to 1.87 years. One retrospective database study followed patients for up to 11 years.

In terms of the target patient populations, four studies limited enrollment to patients with chronic back pain (with or without secondary radicular leg pain) without prior spine surgery.[35,37,43,48] Surgery-naïve back pain patients represented a subgroup of the total enrollment in four studies.[38,44,45,50] One study evaluated scoliosis patients for whom surgical intervention was not suitable,[47] and the remaining study enrolled patients with intractable discogenic low back pain who did not have prior surgery (Supplementary Table S3).[49] With regard to the particular SCS devices, four studies evaluated high-frequency SCS (HF-SCS),[35,37,43,50] three studies evaluated traditional SCS,[47–49] two studies included a mix of SCS devices,[38,44] and the RCT compared HF-SCS to low-frequency SCS.[45] Thoracic (T) leads were placed in the T8–T11 region in three studies,[43,48,50] T8–T9 in two studies,[37,45] and T7–T8 in two studies.[45,49] One study stated that lead placement was done on a "case-by-case basis."[47] Lead placement details were not reported in three studies.[35,38,44]

The mean or median age across treatment groups ranged from 39 to 78 years, and the percentage of patients who were female ranged from 41.7% to 83.3% (Supplementary Table S5). The mean disease duration, when reported, ranged from 7.2 months to 13 years. The range of diagnoses for patients' chronic back pain was broad.

Efficacy Outcomes

Change in Pain Scores With SCS

To quantify pain, studies tended to use either the numeric rating scale or the visual analog scale. Across these pain measures and at varying time points, the studies consistently demonstrated reductions in pain scores with SCS (see Fig. 1 and Table 1 for summaries). In a majority of studies, reductions in pain were observed as early as 3 months after treatment,[37,40,47,49] with reductions in pain also evidenced at 6,[37,40,43,47,49,50] 9,[37] 12,[37,40,43,44,49] 24,[41] and 36 months postintervention.[36]

One study reported significant reductions in pain with traditional SCS at three and six months. However, in the 8 of 16 patients for whom 12-month data were available, the treatment effect did not reach significance.[47] In a comparison between traditional SCS and intrathecal drug delivery (ITDD), Raphael et al[48] reported that the two treatments provided similar pain reduction. Vallejo et al[49] found that SCS significantly reduced pain scores compared to controls at 12 months (62% vs 0%). Finally, Campwala et al[44] compared the degree of pain improvement from SCS between patients who had prior back surgeries and NSRBP patients and found similar levels of improvement at 12 months postimplantation.

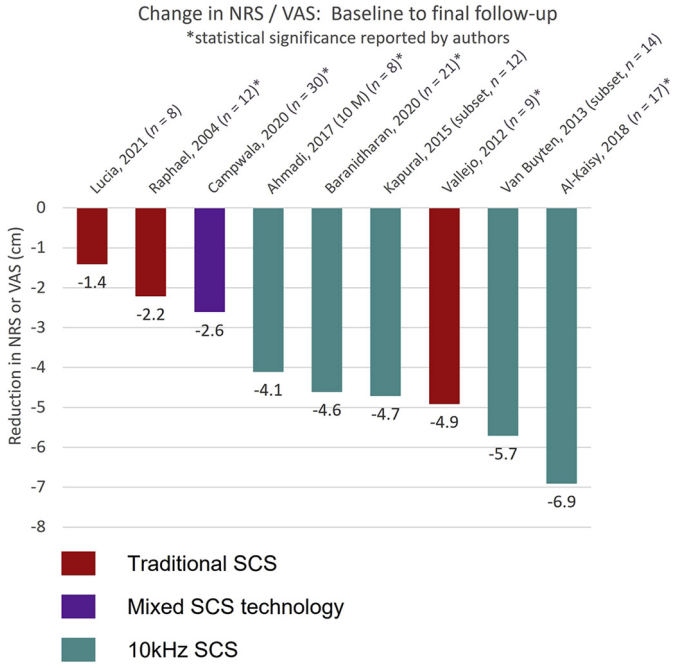

Figure 1. Reduction of pain by SCS in surgery-naïve patients from baseline to final follow-up.

Pain Relief With SCS

Pain relief is also measured as patient-reported percentage relief (range, 0%–100%). Response to therapy is defined as ≥50% pain relief, whereas ≥30% pain relief is considered as a clinically meaningful change.[51] The response to HF-SCS therapy at 12 months across three studies ranged from 52% to 90%.[37,40,43] Response rates at different time points were noted in three studies. Al-Kaisy et al[36,37] reported a response rate in 20 patients of 75% and 80% at 6 and 36 months, respectively, and Ahmadi et al[35] reported a response rate of 37.5% (3 of 8 patients) after a mean follow-up of 10 months.

Function and QoL With SCS

Improvements relative to baseline were seen in functional scores across five studies according to the Oswestry Disability Index (ODI) and in QoL scores across four studies according to the Short Form-36 (SF-36) and EuroQoL-5D (EQ-5D; see Table 2 for a summary).[37,40,43,44,47–49] However, in Vallejo et al,[49] the changes in ODI scores relative to baseline were not statistically significant, and in Lucia et al[47] and Raphael et al,[48] the changes in QoL relative to baseline in the SCS patients were not significant. In comparative studies, Raphael et al[48] reported that the degree of improvement in QoL at 12 months relative to baseline was significantly more favorable in the ITDD group ($n = 13$) relative to the SCS group ($n = 12$; $p < 0.05$).

Campwala et al[44] found a significant improvement in ODI at 12 months relative to baseline ($p < 0.001$). Moreover, the degree of improvement was similar between SCS patients who had prior surgery ($n = 82$) and those with NSRBP ($n = 52$; $p = 0.87$).

Patient Global Impression of Change and Patient Satisfaction With SCS

Patient outcomes using the Patient Global Impression of Change (PGIC) and patient satisfaction rates were reported in Al-Kaisy et al[37] At 12 months, 80% of patients were "much improved" or "very much improved" according to PGIC responses.[37] Additionally, 90% and 85% of patients responded "satisfied" and "very satisfied" with their treatment at 12 and 36 months, respectively, and all patients said that they would recommend the treatment to others.[36,37] In Raphael et al,[48] the authors only reported that there was no significant difference in patient satisfaction between SCS and ITDD.

Opioid Consumption With SCS

On average, opioid consumption declined following SCS (Table 3). When reported, the proportion of patients who had ceased opioid use at 12 months ranged from 16.7% to 66.7% (Fig. 2).[37,40,43,47,49]

Safety Outcomes

Adverse Events

Pain at the implantable pulse generator (IPG) was the most commonly reported AE, with incidence rates of 10% and 25% reported in two studies (Table 3).[35,37] Lead migration also occurred, with incidence rates of 8.3% and 15% reported in two studies.[37,48] Al-Kaisy et al[36,37] stated that no serious AEs occurred in their study, Raphael et al[48] reported that no patients experienced a neurological complication, and Vallejo et al[49] reported a 0% AE rate.

Surgical Revision and Explantation

Two studies reported surgical revision rates of 5% and 8.3%, which were due to pain at the IPG and lead migration, respectively, and two studies reported explantation rates of 5% and 16% (Table 3).[37,43,48] Additionally, in their multivariate regression analysis, Al-Kaisy et al[38] found that SCS patients with a "virgin back" were significantly less likely to have their device explanted relative to patients with FBSS ($p = 0.03$). It is important to note that not all explants occur for safety reasons; loss of efficacy, a need for magnetic resonance imaging, and remission of pain accounted for 78% of explantations.[38]

Risk of Bias and Quality of Evidence

The ROB assessment is summarized in Supplementary Tables S6 and S7. Of the eight non-RCTs reporting pain outcomes, six were deemed to have a moderate ROB and two to have a serious ROB. Of the six non-RCTs reporting functional outcomes, five were considered to have a moderate ROB and one to have a serious ROB. Of the four non-RCTs reporting QoL, three were deemed to have a moderate ROB and one to have a serious ROB. Of the two non-RCTs reporting patient satisfaction, both were deemed to have a moderate ROB. Of the five non-RCTs reporting medication use, all were considered to have a moderate ROB. Lastly, of the six non-RCTs reporting safety data, all were deemed to have a moderate ROB. Reasons for elevated ROB assessments were the variability in disease diagnosis, pain etiologies, and follow-up periods; potential recall bias in retrospective studies; incomplete data; and unblinded outcomes assessment. For the RCT by Kapural et al,[45] across the outcomes of pain, function, and medication use, all domains of the Cochrane ROB were deemed as having low risk, except for the blinding of patients/personnel and outcomes assessment, which were deemed high risk.

Based on the included evidence and associated ROB assessments, the overall quality of evidence was graded as "moderate" for pain according to the GRADE criteria. The baseline GRADE for observational studies was "low." Pain was upgraded to a

Table 1. Summary of Pain Outcomes for SCS Patients With Chronic Back Pain Without Prior Surgery.

Study	Follow-up (months)	Outcome and treatment group	Results	
			Baseline	Follow-up
Ahmadi (2017)	Mean: 10	NRS (0–10)*	8.9	4.8 (−4.1)‡
		HF-SCS (n = 8)		
		≥50% NRS reduction†		
		HF-SCS (n = 8)	-	37.5%
Campwala (2020)	12	NRS (0–10) for average pain*		
		Any SCS (n = 30)	7.4	4.8 (−37.3%)‡
Lucia (2021)	12	NRS (0–10) for pain during motion*		
		SCS (n = 8)	8.8	(−1.4)
Raphael (2004)	Mean: 22.4	NRS (0–10)* (p-value between groups >0.05)		
		SCS (n = 12)	9.0	6.5 (−2.0)‡
		ITDD (n = 13)	8.5	5.5 (−4.0)‡
Vallejo (2012)	12	NRS (0–10)* (p-value between groups = 0.004)		
		SCS (n = 9)	7.8	2.9 (−62%)‡
		Control (n = 4)	6.5	6.5 (0%)
Al-Kaisy (2018)	36	VAS (0–100)*		
		HF-SCS (n = 17)	79	10 (−69)‡
		≥50% VAS reduction†		
		HF-SCS (n = 20)	-	80.0%
Baranidharan (2020)	12	VAS (0–10)*		
		HF-SCS (n = 21)	8.0	(−4.6)‡
		≥50% VAS reduction†		
		HF-SCS (n = 25)	-	52.0%
Kapural (2015) (SENZA-RCT)	12	VAS (0–10)*		
		HF-SCS (n = 12)	7.2	2.5 (−4.7)
		≥50% VAS reduction†		
		HF-SCS (n = 12)	-	75%
Van Buyten (2013) (SENZA-EU)	12	VAS (0–10)*		
		HF-SCS (n = 14) at 12 m	8.1	2.4 (−5.7)
		≥50% VAS reduction†		
		HF-SCS (n = 14) at 12 m	-	71.4%

HF, high-frequency; ITDD, intrathecal drug delivery; m, months; n, number of patients analyzed; NR, not reported; NRS, numeric rating scale; SCS, spinal cord stimulation; VAS, visual analog scale; y, years.
*Mean or median value (change or % change from baseline).
†Proportion of patients.
‡Statistically significant ($p < 0.05$) versus baseline value.

"moderate" quality of evidence based on the magnitude and consistency of the treatment effects exhibited across trials. All other outcomes were graded as "low."

DISCUSSION

The purpose of this systematic review was to identify and evaluate the clinical evidence on the use of SCS in patients with chronic back pain (with or without secondary radicular leg pain) who have not previously undergone spinal surgery. The evidence derived from ten primary studies (including a total of 357 surgery-naïve back pain patients) consistently demonstrated favorable outcomes in terms of pain reduction and functional improvement. Improvements also occurred in QoL scores; however, not all studies demonstrated statistically significant findings. Additionally, the use of SCS was associated with promising findings in terms of patient satisfaction, reductions in opioid use, and an acceptable safety profile, although the data were limited. These results were seen across a range of different chronic back pain indications and over months to years of treatment. Future research on this topic should focus on its comparative effects and cost-effectiveness against other therapies indicated for this patient population, appropriate patient selection for SCS therapy, its effects within more specific patient populations and diagnoses, and whether lead placement level affects patient outcomes.

Efficacy of SCS in Patients With Chronic Back Pain Without Prior Surgery

SCS has been used in clinical practice for decades for the treatment of chronic back and leg pain, traditionally related to patients with FBSS.[11,16,21,52,53] The studies included in the current review showed that SCS was associated with pain relief, functional improvements, and decreases in the consumption of opioid medications in chronic back pain patients without prior surgery. In fact, based on the reported data, pain relief and functional improvements occur as early as three months and are sustained long term, even multiple years postimplantation. The evidence also demonstrated that SCS may improve patient satisfaction and QoL.

There are numerous high-quality studies supporting the use of SCS in patients with FBSS.[11,16,21,54–58] More specifically, in an RCT by North et al,[57] the authors compared SCS to repeated spine surgery in FBSS patients and found that, at a mean follow-up of three years,

Table 2. Summary of Studies Reporting Functional, Quality of Life, and Patient Satisfaction Outcomes for SCS Patients With Chronic Back Pain Without Prior Surgery.

Study	Function	QoL	Satisfaction
Al-Kaisy (2018)	- ODI scores significantly improved at 3, 6, 9, 12, and 36 months relative to baseline (all $p < 0.001$) - At 12 months, 80% of patients were "much improved" or "very much improved" on the PGIC relative to baseline	SF-36 PCS, SF-36 MCS, and EQ-5D scores all significantly improved at 3, 6, 9, 12, and 36 months relative to baseline (all $p < 0.05$)	- 90% and 85% of patients were "satisfied" or "very satisfied" at 12 and 36 months, respectively - 100% of patients said that they "would recommend the treatment to others" at 12 months
Baranidharan (2020)	ODI scores significantly improved at 6 and 12 months relative to baseline (all $p < 0.05$)	EQ-5D scores significantly improved at 6 and 12 months relative to baseline (all $p < 0.05$)	NR
Campwala (2020)	ODI scores significantly improved at 12 months relative to baseline ($p < 0.001$)	NR	NR
Lucia (2021)	ODI scores significantly improved at six months relative to baseline ($p = 0.018$)	SF-36 PCS and SF-36 MCS scores did not significantly improve at 3, 6, or 12 months relative to baseline (all $p > 0.05$)	NR
Raphael (2004)	NR	QoL scores on the NRS did not significantly improve relative to baseline ($p < 0.1$)	Only stated no significant difference between SCS and ITDD groups
Vallejo (2012)	ODI scores at 12 months improved, but were not significantly different relative to baseline ($p = 0.123$)	NR	NR
Kapural (2015) (SENZA-RCT); Van Buyten (2013) (SENZA-EU)	In the pooled analysis, ODI scores improved at 12 months relative to baseline	NR	NR

EQ-5D, EuroQoL-5D; ITDD, intrathecal drug delivery; NR, not reported; NRS, numeric rating scale; ODI, Oswestry Disability Index; PGIC, patient global impression of change; QoL, quality of life; SF-36: MCS, Short Form-36 Mental Component Summary; SF-36: PCS, Short Form-36 Physical Component Summary.

SCS patients were more successful in terms of pain relief (47% had ≥50% pain relief vs 12% in the reoperation group; $p < 0.01$) and the use of narcotics ($p < 0.025$) and were less likely to cross over to the other treatment group ($p = 0.02$). Another RCT by Kumar et al[56] compared SCS plus CMM to CMM alone in FBSS patients and determined that those treated with SCS had greater pain relief (48% had ≥50% pain relief vs 9% with CMM alone) at 6 months. They also demonstrated more favorable QoL, function, and treatment satisfaction.[56] Similar findings have been shown in more recent FBSS trials that compared SCS versus placebo.[54,55,58] In the current review, the included evidence showed that NSRBP patients treated with SCS experience similar results, demonstrating significant pain reductions and meaningful response rates. Of note, one of the included studies compared SCS patients without prior back surgery to those with prior surgery and found no statistically significant differences between the two groups across a range of clinical outcome measures.[44] Additionally, novel neuromodulation technologies are emerging that have demonstrated promising results in comparison to traditional SCS devices. Such efforts have multiple objectives: to develop more effective treatments for current SCS indications and treat a wider range of chronic pain conditions.[11,16,45]

Safety of SCS in Patients With Chronic Back Pain Without Prior Surgery

The results of this review demonstrated that SCS is a relatively safe procedure given its low risk of serious AEs, surgical revision, and neurological complications.[37,48] The most common AEs are pain at the IPG site and lead migration; however, these events are not usually considered serious and can be resolved, if needed, with surgical revision or explantation.[11,52,59] Because SCS implantation is a minimally invasive procedure, it is feasible to safely reverse.[11,16,59] Notably, in the study by Al-Kaisy et al,[38] patients who had not previously undergone surgery and received HF-SCS were significantly less likely to undergo device explantation relative to FBSS patients ($p = 0.03$). Biological complications, such as infections, seromas, dural puncture headaches, abscesses or hematomas, or neurological problems, are uncommon following SCS.[11,59] The Neurostimulation Appropriateness Consensus Committee guidelines support the use of neurostimulation, in part due to its lack of

Table 3. Summary of Studies Reporting Medication Use and Safety Outcomes for SCS Patients With Chronic Back Pain Without Prior Surgery.

Study	Medication use	Safety
Ahmadi (2017)	NR	- Pain at IPG site: 25% - Explantation: NR
Al-Kaisy (2018)	- ME reduced by an average of 64% at 12 months relative to baseline - At 12 months, 16.7% of patients taking opioids at baseline ceased their use	- Lead migration: 15% - Pain at IPG site: 10% - Surgical revision: 5% (due to pain at IPG site) - Serious AE: 0% - Explantation: 5% at <24 months due to loss of efficacy (1/20)
Al-Kaisy (2020)	NR	- Explantation, OR for patients with "virgin back": 0.67 (95% CI 0.39 to 1.42; $p = 0.14$) (from the univariate analysis) relative to FBSS - Explantation, OR for patients with "virgin back": 0.48 (95% CI 0.25 to 0.92; $p = 0.03$) (from the multivariate analysis) relative to FBSS
Baranidharan (2020)	- ME reduced by an average of 18.9 mg at 12 months relative to baseline ($p = 0.018$) - At 12 months, 42.9% of patients taking opioids at baseline ceased their use, 7.1% reduced their use, and 50% maintained their use	- Explantation: 16% (4/20 required or requested)
Lucia (2021)	- At 12 months, 20.0% of patients taking opioids at baseline ceased their use	NR
Raphael (2004)	NR	- Lead migration: 8.3% - Surgical revision: 8.3% (due to lead migration) - Neurological complications: 0% - Explantation: NR
Vallejo (2012)	- ME reduced by an average of 69% at 12 months relative to baseline ($p = 0.036$) - At 12 months, 66.7% of patients taking opioids at baseline ceased their use	Any AE during implantation: 0% Explantation: NR
Kapural (2015) (SENZA-RCT); Van Buyten (2013) (SENZA-EU)	- In the pooled analysis, ME reduced by average of 45.5 mg at 12 months relative to baseline - In the pooled analysis, at 12 months, 28.6% of patients taking opioids at baseline ceased their use, 23.8% reduced their use, 33.3% maintained their use, and 14.3% increased their use	NR

AE, adverse event; CI, confidence interval; IPG, implantable pulse generator; ME, morphine equivalents; mg, milligrams; NR, not reported; OR, odds ratio.

side effects and the downward trend of device-related complications as the technology and surgical expertise for implanting the device improve.[52]

Study Limitations and Future Directions

To generate comprehensive insights into the efficacy and safety of SCS in chronic back pain patients without prior surgery, we performed a systematic review, narrative synthesis, and ROB assessment of the evidence; however, we acknowledge that this review was limited by the quality of the included studies. Indeed, they were predominantly observational with relatively small sample sizes, including patients with a range of diagnoses and pain etiologies. In addition, due to their observational design, many studies did not have a comparison or control group, meaning that the results should be carefully interpreted. Not all of the studies reported safety outcomes, and the retrospective studies included patients with a range of different follow-up periods and reported outcomes, making it difficult to generate a holistic account of the long-term effects of SCS in these patients. However, findings consistently suggested that SCS was effective and safe in this patient population.

To improve the evidence for SCS in chronic back pain without prior surgery, future research should consider quantifying patient-reported outcomes and systematically reporting AEs at specific time points. This would provide more valuable and interpretable results, especially when synthesizing the data and grading the quality of evidence.

CONCLUSION

Findings from this systematic review suggest SCS has an acceptable safety profile in patients with chronic back pain without prior surgery and is associated with improvements in pain, function, and opioid consumption. Neurological injury and serious AEs were not reported in any of the included studies; any reported AEs were considered minor and amenable to treatment. This review supports the notion of SCS as a first-line surgical therapy in patients whose chronic back pain has been difficult to manage by conservative treatment, particularly in the subgroup of patients whose source of pain cannot be clearly identified or is multifactorial. Overall, the current evidence suggests that SCS is a promising, suitable, and minimally invasive therapy for managing

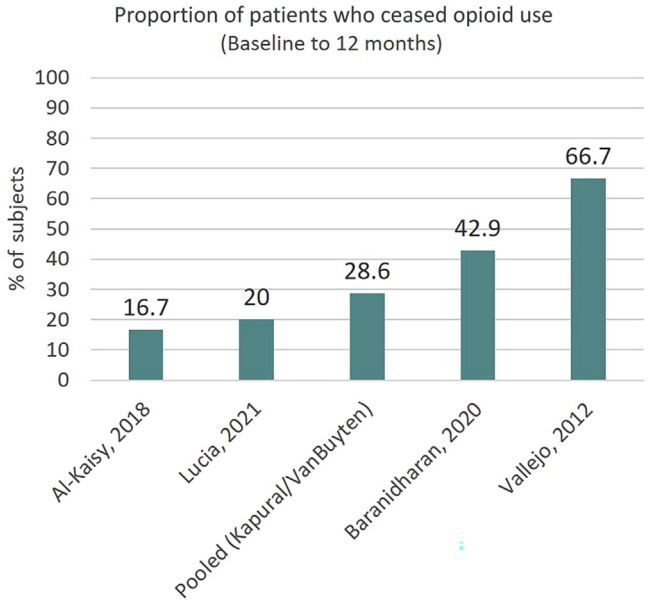

Figure 2. Cessation of opioid use in response to SCS treatment from baseline to 12 months.

chronic back pain patients who have not previously undergone spinal surgery. Additional clinical research in this area, such as comparing the effects and cost-effectiveness between SCS and other therapies, would be valuable when making treatment decisions.

Authorship Statements

All authors were involved in the critical review and manuscript preparation and approved the final published version. Christopher Vannaboutathong, Belinda J. Wagner, and Rose Province-Azalde contributed to the design of the study, while Christopher Vannaboutathong and Belinda J. Wagner performed the literature segmentation.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1111/ner.13519.

REFERENCES

1. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:743–800.
2. Traeger A, Buchbinder R, Harris I, Maher C. Diagnosis and management of low-back pain in primary care. *CMAJ*. 2017;189:E1386–E1395.
3. Deyo RA, Weinstein JN. Low back pain. *N Engl J Med*. 2001;344:363–370.
4. Dieleman JL, Baral R, Birger M, et al. US spending on personal health care and public health, 1996-2013. *JAMA*. 2016;316:2627–2646.
5. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J*. 2008;8:8–20.
6. Christelis N, Simpson B, Russo M, et al. Persistent spinal pain syndrome: a proposal for failed back surgery syndrome and ICD-11. *Pain Med*. 2021;22:807–818.
7. Ordia J, Vaisman J. Post-surgical spine syndrome. *Surg Neurol Int*. 2011;2:132.
8. Patel N, Calodney A, Kapural L, et al. High-frequency spinal cord stimulation at 10 kHz for the treatment of nonsurgical refractory back pain: design of a pragmatic, multicenter, randomized controlled trial. *Pain Pract*. 2021;21:171–183.
9. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: time to back off? *J Am Board Fam Med*. 2009;22:62–68.
10. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166:514–530.
11. Hong A, Varshney V, Hare GMT, Mazer CD. Spinal cord stimulation: a nonopioid alternative for chronic pain management. *CMAJ*. 2020;192:E1264–E1267.
12. Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. *JAMA Intern Med*. 2016;176:958–968.
13. Mannion AF, Brox JI, Fairbank JC. Consensus at last! Long-term results of all randomized controlled trials show that fusion is no better than non-operative care in improving pain and disability in chronic low back pain. *Spine J*. 2016;16:588–590.
14. Chivukula S, Tempel ZJ, Weiner GM, et al. Cervical and cervicomedullary spinal cord stimulation for chronic pain: efficacy and outcomes. *Clin Neurol Neurosurg*. 2014;127:33–41.
15. Deer TR, Skaribas IM, Haider N, et al. Effectiveness of cervical spinal cord stimulation for the management of chronic pain. *Neuromodulation*. 2014;17:265–271 [discussion: 71].
16. Song JJ, Popescu A, Bell RL. Present and potential use of spinal cord stimulation to control chronic pain. *Pain Physician*. 2014;17:235–246.
17. Chakravarthy K, Fishman MA, Zuidema X, Hunter CW, Levy R. Mechanism of action in burst spinal cord stimulation: review and recent advances. *Pain Med*. 2019;20:S13–S22.
18. Jensen MP, Brownstone RM. Mechanisms of spinal cord stimulation for the treatment of pain: still in the dark after 50 years. *Eur J Pain*. 2019;23:652–659.
19. Harmsen IE, Hasanova D, Elias GJB, et al. Trends in clinical trials for spinal cord stimulation. *Stereotact Funct Neurosurg*. 2021;99:123–134.
20. Grider JS, Manchikanti L, Carayannopoulos A, et al. Effectiveness of spinal cord stimulation in chronic spinal pain: a systematic review. *Pain Physician*. 2016;19:E33–E54.
21. Hofmeister M, Memedovich A, Brown S, et al. Effectiveness of neurostimulation technologies for the management of chronic pain: a systematic review. *Neuromodulation*. 2020;23:150–157.
22. Lafian AM, Torralba KD. Lumbar spinal stenosis in older adults. *Rheum Dis Clin North Am*. 2018;44:501–512.
23. Zaina F, Tomkins-Lane C, Carragee E, Negrini S. Surgical versus non-surgical treatment for lumbar spinal stenosis. *Cochrane Database Syst Rev*. 2016;2016:CD010264. https://doi.org/10.1002/14651858.CD010264.pub2.
24. Barrey CY, Le Huec JC, French Society for Spine Surgery. Chronic low back pain: relevance of a new classification based on the injury pattern. *Orthop Traumatol Surg Res*. 2019;105:339–346.
25. Ibrahimi-Kacuri D, Murtezani A, Rrecaj S, Martinaj M, Haxhiu B. Low back pain and obesity. *Med Arch*. 2015;69:114–116.
26. Kim B, Yim J. Core stability and hip exercises improve physical function and activity in patients with non-specific low back pain: a randomized controlled trial. *Tohoku J Exp Med*. 2020;251:193–206.
27. Sanzarello I, Merlini L, Rosa MA, et al. Central sensitization in chronic low back pain: a narrative review. *J Back Musculoskelet Rehabil*. 2016;29:625–633.
28. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
29. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
30. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
31. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
32. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490.

33. Schunemann HJ, Cuello C, Akl EA, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol*. 2019;111:105–114.
34. Murad MH, Mustafa RA, Schunemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22:85–87.
35. Ahmadi SA, Vesper J, Schu S, Slotty PJ. High-frequency spinal cord stimulation in surgery-naive patients—a prospective single-center study. *Neuromodulation*. 2017;20:348–353.
36. Al-Kaisy A, Palmisani S, Smith TE, et al. Long-term improvements in chronic axial low back pain patients without previous spinal surgery: a cohort analysis of 10-kHz high-frequency spinal cord stimulation over 36 months. *Pain Med*. 2018;19:1219–1226.
37. Al-Kaisy A, Palmisani S, Smith TE, et al. 10 kHz high-frequency spinal cord stimulation for chronic axial low back pain in patients with no history of spinal surgery: a preliminary, prospective, open label and proof-of-concept study. *Neuromodulation*. 2017;20:63–70.
38. Al-Kaisy A, Royds J, Al-Kaisy O, et al. Explant rates of electrical neuromodulation devices in 1177 patients in a single center over an 11-year period. *Reg Anesth Pain Med*. 2020;45:883–890.
39. Al-Kaisy A, Van Buyten JP, Carganillo R, et al. 10 kHz SCS therapy for chronic pain, effects on opioid usage: post hoc analysis of data from two prospective studies. *Sci Rep*. 2019;9:11441.
40. Al-Kaisy A, Van Buyten JP, Kapural L, et al. 10 kHz spinal cord stimulation for the treatment of non-surgical refractory back pain: subanalysis of pooled data from two prospective studies. *Anaesthesia*. 2020;75:775–784.
41. Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. *Pain Med*. 2014;15:347–354.
42. Amirdelfan K, Yu C, Doust MW, et al. Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT. *Qual Life Res*. 2018;27:2035–2044.
43. Baranidharan G, Feltbower R, Bretherton B, et al. One-year results of prospective research study using 10 kHz spinal cord stimulation in persistent nonoperated low back pain of neuropathic origin: maiden back study. *Neuromodulation*. 2021;24:479–487.
44. Campwala Z, Datta P, DiMarzio M, Sukul V, Feustel PJ, Pilitsis JG. Spinal cord stimulation to treat low back pain in patients with and without previous spine surgery. *Neuromodulation*. 2021;24:1363-1369.
45. Kapural L, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. *Anesthesiology*. 2015;123:851–860.
46. Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. *Neurosurgery*. 2016;79:667–677.
47. Lucia K, Nulis S, Tkatschenko D, Kuckuck A, Vajkoczy P, Bayerl S. Spinal cord stimulation: a reasonable alternative treatment in patients with symptomatic adult scoliosis for whom surgical therapy is not suitable? A pilot study. *Neuromodulation*. 2021;24:1370-1376.
48. Raphael JH, Southall JL, Gnanadurai TV, Treharne GJ, Kitas GD. Multiple lead spinal cord stimulation for chronic mechanical low back pain: a comparative study with intrathecal opioid drug delivery. *Neuromodulation*. 2004;7:260–266.
49. Vallejo R, Zevallos LM, Lowe J, Benyamin R. Is spinal cord stimulation an effective treatment option for discogenic pain? *Pain Pract*. 2012;12:194–201.
50. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. *Neuromodulation*. 2013;16:59–65 [discussion: 6].
51. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009;146:238–244.
52. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. *Neuromodulation*. 2014;17:515–550 [discussion: 50].
53. Wolter T, Kieselbach K. Cervical spinal cord stimulation: an analysis of 23 patients with long-term follow-up. *Pain Physician*. 2012;15:203–212.
54. Al-Kaisy A, Palmisani S, Pang D, et al. Prospective, randomized, sham-control, double blind, crossover trial of subthreshold spinal cord stimulation at various kilohertz frequencies in subjects suffering from failed back surgery syndrome (SCS frequency study). *Neuromodulation*. 2018;21:457–465.
55. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. *World Neurosurg*. 2013;80:642–649. e1.
56. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain*. 2007;132:179–188.
57. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery*. 2005;56:98–106 [discussion: 7].
58. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. *Neuromodulation*. 2014;17:443–450.
59. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. Neuromodulation Appropriateness Consensus Committee. *Neuromodulation*. 2014;17:571–597 [discussion: 97–9].

COMMENTS

I wish to congratulate the authors for a well-conducted study, rigorous and robust statistical analysis, and a well-written paper.

The study reaffirms the effectiveness of SCS for back pain relief, functional improvement, and decrease in opioid use in patients who have not had prior back surgery. It is reassuring to patients with axial back pain who have failed extensive treatments and interventions that SCS is a realistic option. Some insurance companies consider peripheral nerve stimulation (PNS) for back pain as experimental but will approve SCS.

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I think this is a much-needed paper that demonstrates good overall outcomes of SCS on surgery-naïve patients with low back pain.

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