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Systematic Review of Research Methods and Reporting Quality of Randomized Clinical Trials of Spinal Cord Stimulation for Pain

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Abstract: **This systematic review assessed design characteristics and reporting quality of published randomized clinical trials of spinal cord stimulation (SCS) for treatment of pain in adults and adolescents. The study protocol was registered with PROSPERO (CRD42018090412). Relevant articles were identified by searching the following databases through December 31, 2018: MEDLINE, Embase, WikiStim, The Cochrane Database of Systematic Reviews, and The Cochrane Central Register of Controlled Trials. Forty-six studies were included. Eighty-seven percent of articles identified a pain-related primary outcome. Secondary outcomes included physical functioning, health-related quality of life, and reductions in opioid use. Nineteen of the 46 studies prespecified adverse events as an outcome, with 4 assessing them as a primary outcome. Eleven studies stated that they blinded participants. Of these, only 5 were assessed as being adequately blinded. The number of participants enrolled was generally low (median 38) and study durations were short (median 12 weeks), particularly in studies of angina. Fifteen studies employed an intention-to-treat analysis, of which only seven specified a method to accommodate missing data. Review of these studies identified deficiencies in both reporting and methodology. The review's findings suggest areas for improving the design of future studies and increasing transparency of reporting.**

Perspective: ***This article presents a systematic review of research methods and reporting quality of randomized clinical trials of SCS for the treatment of various pain complaints. The review identifies deficiencies in both methodology and reporting, which may inform the design of future studies and improve reporting standards.***

Key words: *Neuromodulation, Clinical trials systematic review/meta analysis, Peripheral neuropathy, Pain, Disc disease.*

The use of spinal cord stimulation (SCS) for the treatment of chronic pain was first described in 1967.[67] Its development was based on the gate-control theory of pain, introduced a few years earlier by Melzack and Wall, who hypothesized that a "gate" in the dorsal horn of the spinal cord dictated transmission of nociception within the central nervous system.[49] The hypothetical gate could be closed when stimulation of large diameter myelinated fibers associated with touch, pressure, or vibration predominated over stimulation of thinner, unmyelinated pain fibers, in turn attenuating or eliminating noxious signaling to the brain. SCS was thought to represent a means of electrically closing the gate by stimulation of such large afferent fibers.

Small clinical trials assessing the efficacy of SCS in reducing pain in various chronic conditions, including low back pain, angina, peripheral vascular disease, peripheral neuropathy, complex regional pain syndrome, type I, and irritable bowel syndrome, were first published in the early 1970s. In 1984 the United States (US) Food and Drug Administration (FDA) approved SCS to treat chronic intractable pain in the trunk or legs, including pain associated with failed back surgery syndrome. The first randomized clinical trials (RCTs) of SCS were published in the mid-1990s,[57,73] and the first systematic review of efficacy of this approach shortly thereafter.[77]

Current applications of SCS can broadly be divided into conventional, high-frequency, and high-frequency burst stimulation.[50] In conventional SCS, the patient typically experiences paresthesias in the area of coverage. With high-frequency stimulation (HF-SCS), the stimulus is delivered at the dorsal columns at a higher frequency than conventional SCS. In burst stimulation, the stimulus is delivered at a low frequency with closely spaced high frequency pulses. As with HF-SCS, the patients are unlikely to experience paresthesias.

While systematic reviews have supported the efficacy of the various SCS modalities in terms of pain reduction, there are limitations of existing evidence and challenges in conducting research.[24,43] Limitations include the fact that many studies have small sample sizes, and have relatively short durations.[43] Challenges in designing SCS trials include the requirement for highly specialized care, the invasiveness of the procedure, and the costs of surgery and the devices.[20] The requirement for paresthesia with conventional SCS makes complete blinding with placebo or sham interventions a more complex undertaking.[60] Study duration may be an issue in that a device in the control arm may have been superseded by an updated device by the point at which a trial is completed, ie, the device field is currently evolving faster than the duration of many RCTs.[52] There may also be issues with patient selection; eg, clinical presentation or pain characteristics may influence the likelihood of a successful outcome.[43,54]

With these limitations and challenges in mind, the objectives of this review of RCTs of SCS for pain were to: 1) assess research methods employed, 2) document which outcomes were assessed and how they were reported, and 3) summarize patient characteristics. By

documenting current design and reporting, and by highlighting possible deficiencies in both, we hope to provide the foundation for recommendations for standardization and improvement in future trials.

Methods

The methods of this systematic review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (prisma-statement.org/) (Appendix e-1). The study protocol was registered with PROSPERO (CRD42018090412).[64] This protocol was also used as a framework for smaller, but related systematic reviews of placebo/sham-controlled trials and of cost-effectiveness studies.[10,11]

Search

MEDLINE, Embase, The Cochrane Database of Systematic Reviews, and The Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched to identify eligible studies up to February 7, 2018 (date of search) using appropriate search terminology (Appendix e-2). The same search terminology (restricted to publication year 2018) was repeated in January 2019 to identify eligible studies published as of December 31, 2018. WIKISTIM monthly newsletters were reviewed from February through November 2018 to identify new citations added to the topic of SCS.[59,83] The reference lists of all included studies were also reviewed for additional studies. The results of the search were used to inform 2 further analyses.[10,11]

Study Selection

Inclusion criteria were RCTs (of any design including parallel, cross-over, or cluster) evaluating SCS for any acute or chronic pain condition. Nonrandomized studies, abstracts, conference proceedings, and studies without a pain-related outcome were excluded. Studies of dorsal root ganglion stimulation were excluded (unless they also assessed SCS) as the anatomic target of dorsal root ganglion stimulation is more akin to peripheral nerve stimulation, and it is not clear to what extent the relevant mechanisms of pain relief might be the same for both. There were no exclusions based on lack of patient or clinician blinding, study duration, language, or sample size. Each stage of study selection was performed in duplicate and checked for agreement between reviewers (any combination of EM, MF, KB, or ER). Eligibility was determined by reading the abstract of each study identified by the search. Studies that clearly did not satisfy the inclusion criteria were eliminated, and full texts of the remaining studies were obtained. Two review authors read each of these full texts independently and reached agreement by discussion. Where agreement could not be reached, a third review author adjudicated. No attempts were made to anonymize studies before assessment.

Data Extraction

Four investigators (authors EM, MF, KB, ER) performed data extraction. A combination of 2 of the 4 investigators independently extracted information from each study and adjudicated discrepancies. A data extraction form was piloted prior to use (Appendix e-3). A coding manual was developed to clarify entry and promote consistency in the evaluation of study methodology (Appendix e-4). Risk of bias for methods related to randomization and adequacy of blinding (if applicable) was assessed as ''high risk,'' ''low risk,'' or ''unclear risk'' according to criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[26] Angina studies were assessed separately from other chronic pain syndromes because of assumed differences in inclusion criteria and other study design features.

Information related to population, funding source (s), inclusion criteria, interventions and controls, use of a trial/screening phase, duration, primary and secondary outcomes related to pain, collection of adverse events (AEs), methods of data analysis (eg, sample size calculations, clinical significance, handling of missing data), and baseline demographics (eg, number of participants, sex, and age) were collected. Descriptive statistics were used to provide the central tendency (mean or median), variability (expressed as ranges or standard deviations [SDs]), or percent of studies reporting a certain method. Descriptions were grouped into available data about the 1) population, 2) intervention, 3) comparator, 4) outcomes, and 5) study characteristics, with special attention to design and methodology.

Results

Search Results

Of the 1,227 de-duplicated records identified from the initial search of multiple databases, 1,108 were excluded, based on screening the title or abstract. An additional 68 were excluded after full text review: 15 were abstracts or protocols only, 16 were not randomized, 9 were studies of cost only, 13 were duplicate publications (ie, they reported data that had been reported in a previous manuscript), 13 had no pain outcome, and 2 were excluded for other reasons (Fig 1). The initial search was re-run through December 31st, 2018 and identified a further 2 studies, resulting in a total of 46 included studies,[1-9,13,14,16,25,27-29,31,35,36,38-42,44,46,48,53,55,56,58,61,65,66,68,70-75,79,81,82,84-86] 12 of which assessed outcomes in patients with angina.[3,4,9,13,16,25,27,40,41,44,46,86] In addition, seven extension studies were identified.[30,32-34,37,78,80]

No RCTs were found in acute pain or in cancer pain. The timeline of evidence reflects the evolution of SCS, from early studies comparing conventional (paresthesia-based) SCS to usual care, through studies where both groups received conventional SCS, but that compared different stimulation parameters, to the newest studies that compared burst- or HF-SCS with conventional SCS or other burst/HF settings.

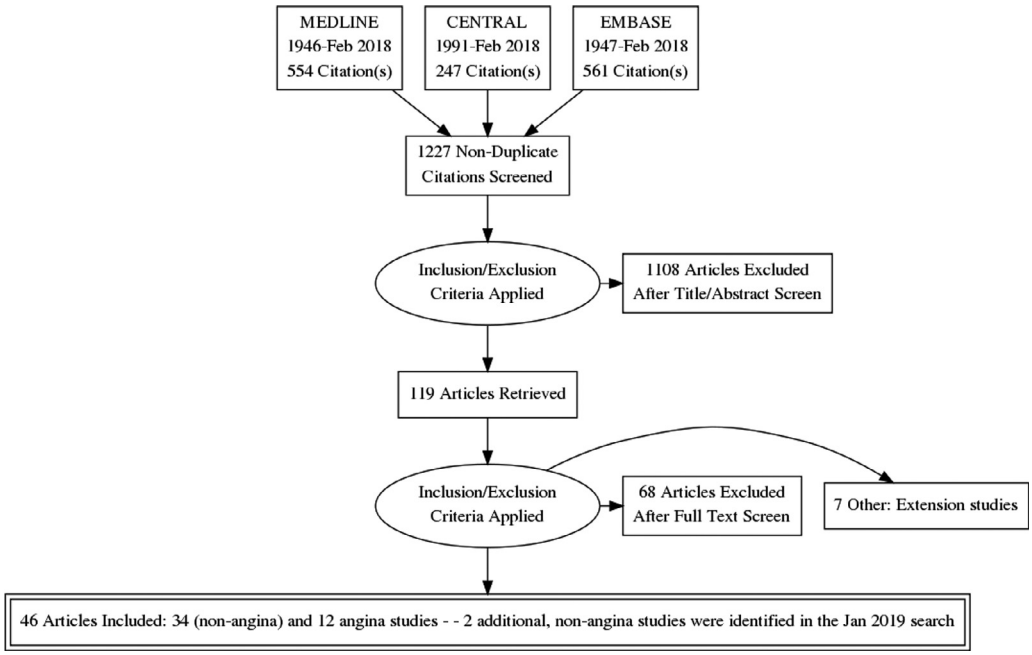

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram. Flow diagram which reflects the search and screening of articles to be included in the review.

Coder Discrepancies

In total, 4,386 items were coded in our main analysis and 1,548 in our angina analysis. In the main analysis 591(14%) reviewer discrepancies occurred. A median of 10 reviewer discrepancies per study were noted in the extraction of angina studies for a rate of 9%. Disagreements were resolved by discussion between extracting reviewers/authors with consultation from a third reviewer/author if disagreement persisted. Disagreements most frequently occurred in assessments of the role of the sponsor, the type of analysis performed, and reporting of clinical significance.

Table 1. Summary Characteristics of Included RCTs

Characteristic	*Result*
Year published	
Median (range)	2014 (1994–2018)
Registered (%)	38.2
Included U.S. Sites (%)	32.4
Single center (%)	50
Multicenter (%)	50
Funding source* (%)	
Reported funding source	82.4
Industry	64.7
Government	17.7
Institutional	8.8
Professional society	2.9
Role of sponsor specified (%)	
Study design	11.8
Data collection	8.9
Data analysis	14.7
Manuscript preparation	8.9
Supplied devices	11.8
Role was NOT stated	58.8

Except where designated otherwise, denominator is 34 studies.
*Adds to more than 100% as some studies had multiple funding sources.

Non-angina Studies

Basic Characteristics

Study publication dates ranged from 1994 to 2018. Of the 34 non-angina studies, 38% were registered on a clinical trial website (Table 1). A minority of studies (32%) included US sites. A funding source was specified in 82% of studies, the majority being industry-sponsored. Most studies did not explicitly specify the role of the sponsor in the research.

Population

For the 34 trials, the median number of randomized participants was 38 (range 10–171; Table 2). Average age had less variability than the number of participants; mean average age in years was 54.7 (8.6). Sex was reported in all studies. The range of percentages of female participants across studies was 6 to 92%; the mean proportion of female participants was 50%.

The number of participants reported in each study as having completed the primary outcome assessment, and the number of participants analyzed, was similar to the number enrolled across the 34 trials; however, there was more variability amongst the completers in each study compared to the groups of those enrolled. In 6 studies, the number of participants completing the study was unclear.[5,28,58,70-72,81]

Some studies specified that participants meet a minimum pain intensity, pain duration, or both, in order to be included. Of the 41% of studies that required participants meet a minimum pain intensity score, the mean

Table 2. Summary of Participant Enrollment & Demographics

Characteristic	*Result*
Number of participants randomized after screen	
Median (range)	38 (10–171)
Number of participants completing (primary outcome)	
Median (range)	33 (9–171)
Unclear (%)	17.6
Age (median years; range)	53.5 (38.3–73)
Gender (% female)	
Mean % (SD)	50.1 (18.8)
INCLUSION CRITERIA	
One or more of the following required for inclusion (%)	
Minimum pain intensity score	41.2
Minimum pain duration	55.9
Minimum disability score	5.9
Failed other treatments	47.1
Willing to stop pain meds/keep stable dose	23.5
Pain Parameters for Study Entry	
For minimum pain intensity, mean score on 0–10 scale (SD)	5.2 (0.42)
For minimum pain duration, median (range) months	6 (0.5-–24)
Pain location identified for inclusion (%)	91.2
Pain location * (%)	
Leg pain	47.1
Failed back surgery	29.4
Back pain	23.5
CRPS-1	17.7
Peripheral vascular disease	14.7
Other unspecified neuropathic pain	14.7
Diabetic neuropathy	5.9
History of nerve-related injury	5.9
Irritable bowel syndrome	2.9
Heart failure	0
Other	14.7

Except where designated otherwise, denominator is 34 studies.
*Adds to more than 100% because some studies specified more than one location.

score was 5.2 (on a 0–10 visual analog or numeric scale). Of the 56% of studies that required a minimum duration of pain, the median number of months was 6, and the requirements ranged from 2 weeks to 24 months to qualify. Only two studies required that participants meet a pre-determined disability score for entry into their trials.[29,74] The proportion of studies requiring failure of other treatments was 47%, and 24% of studies required participant willingness to keep dosing stable or stop pain medication entirely.

Thirty-one of the 34 studies clearly identified one or more types or locations of pain as an inclusion criterion. Leg pain, failed back surgery syndrome, and back pain were identified in 16, 10, and 8 of the 34 studies, respectively.

Interventions and Comparators

With advances in SCS technology, devices now allow for variations of settings such as frequency, placement, amplitude, and pulse width, to an extent that earlier versions did not. The most commonly used intervention was what has come to be called ''conventional'' or ''paresthesia-based'' SCS (ie, permanently implanted percutaneous cylindrical leads or paddle electrodes placed in the midline epidural space); it was employed in 65% of the studies (Table 3). Other interventions included stimulation at high frequencies, and at burst intervals. The range of comparator or control interventions is also listed in Table 3.

Researchers reported permitting supplementation of the treatment intervention by co-administration of noninvasive therapy (such as physical therapy, medication) in 65% of studies. Similarly, study methods in 59% of publications noted that adjustments (eg, in programming of SCS) were allowed to the assigned intervention. The greatest proportion of studies (32%) allowed adjustments in both intervention and control arms; 24% were permitted in the intervention alone; only 1 study reported allowing adjustments to only the control group.[29]

In 2 of the 14 parallel group studies, participants who failed to achieve adequate pain management with an assigned intervention were allowed to switch to the alternative treatment.[38,56]

Outcomes

The vast majority of studies (94%) clearly identified a single primary outcome measure or multiple primary outcome measures (Table 4). Researchers reported 1

Table 3. Summaries of the Interventions and Comparators

Characteristic	*Result*
Intervention	
Type of SCS* (%)	
Conventional paresthesia-based	64.7
High-frequency	23.5
High-frequency burst	17.7
Other settings (eg, "shuffle" between conventional and high-frequency)	20.6
Control (comparator)* (%)	
Conventional paresthesia-based SCS	38.2
High-frequency or high-frequency burst	8.8
Dorsal root ganglion stimulation	5.9
Placebo†	29.4
Usual care (clinician decides)	20.6
Physical therapy	5.9
Surgery	2.9
Usual care (defined by protocol)	2.9
Co-administration of other noninvasive treatments allowed for all arms of the study (%)	
Yes	64.7
Not specified	32.4
Methods allowed for SCS adjustments (%)	
Yes	58.8
Intervention only	23.5
Control only	2.9
All arms allowed adjustments	32.4
SCS adjustments* (%)	
>1 adjustment allowed	35.2
Amplitude (voltage)	52.9
Electrode location/placement	14.7
Frequency/kHz	14.7
Pulse width (microsecond)	14.7
On/off	8.8
Not specified	5.9
Stimulation waveform	0

Except where designated otherwise, denominator is 34 studies.
*Adds to more than 100% because some studies permitted more than 1.
†SCS unit switched off or programmed to produce subthreshold stimulation.

primary outcome in 59% of the studies; accordingly, 35% of the studies reported multiple primary outcomes. The breakdown of the different outcomes can be seen in Table 4. Pain intensity was the most frequent outcome in both those studies that assessed 1 and those that assessed more than 1 primary outcome.

Secondary outcomes were also collected at high rates in most of the studies, given the effect of pain on other domains. The list of other outcomes includes physical functioning, health-related quality of life, emotional distress, and opioid use.

Safety was represented by the authors' reporting of AEs or side effects. Adverse events were reported as a primary outcome in three studies (Table 4).[1,29,81] The list of reported AEs is in Table 4. Many trials did not prespecify assessment of SCS-related AEs. Adverse events of note were incidences of lead migration, inadequate paresthesia coverage, or both; 41% of studies reported these findings. Infection and pulse generator discomfort had the next highest rates of reporting. Most studies either did not report SCS-related AEs, or reported that AEs did not occur.

Methods of Outcome Reporting

The efficacy and safety results from the studies were reported in different units. The most frequent method of reporting was the mean score of outcomes at a specified time; 41% of studies reported using these units. The remaining units in which primary outcomes were reported are shown in Table 5.

In the secondary outcomes, responder rates (proportion of participants who met a cut point for improvement) were reported in 68% of the studies.

Clinical significance of the reported outcome was not discussed in 38% of the studies. When clinical significance was addressed, it was reported as a percent change in 38% of the studies, leaving a reporting of absolute change as the method in 24% of the studies.

When the primary outcome measure was assessed at multiple timepoints, the intervals between assessments ranged from less than one day to more than one month, with the latter occurring in 38% of studies. The primary outcome endpoints were generally assessed at 12 weeks (median) but ranged from 0 (less than a day) to 208 weeks.

Table 4. Summary of Study Outcomes

EFFICACY		*Result*	
Primary outcome(s) specified (%)		94.1	
Primary outcome pain-related (%)		52.9	
Single primary outcome reported (%)		58.8	
Pain intensity		32.4	
Quantitative sensory testing		5.9	
Patient preference		5.9	
Pain relief		2.9	
PGIC		2.9	
Other		8.8	
Multiple primary outcomes reported* **(%)**		35.3	
Pain intensity		26.5	
Pain relief		5.9	
Patient satisfaction		5.9	
No neurological deficit		5.9	
Multidimensional pain questionnaire		2.9	
Health related quality of life		2.9	
PGIC		2.9	
Responder analysis		2.9	
Other		11.8	
Secondary outcomes reported* **(%)**			
Pain intensity		52.9	
Function/disability		44.1	
Health-related Quality of Life		41.2	
Multidimensional pain questionnaire		38.2	
Patient satisfaction		38.2	
Patient preference		29.4	
Depression		26.5	
Reduction in opioid use		26.5	
PGIC		23.5	
Sleep		20.6	
Pain relief		17.7	
Mood		14.7	
Pain catastrophizing		14.7	
No neurological deficit		11.8	
Quantitative sensory testing		5.9	
SAFETY		Result	
Adverse event prespecified as an outcome (%)		47.1	
Adverse event was primary outcome (%)		8.8	
Serious adverse events reported (%)		47.1	
Adverse event caused adjustment in regimen			
Unclear (%)		64.7	
Reported Adverse Events (%)	YES Reported but NOT Prespecified (%)	YES Prespecified in Methods (%)	NO (%)
Neurologic injury	11.8	5.9	82.4
Localized pain	20.6	0	79.4
Lead migration/inadequate coverage	41.2	8.8	50.0
Pulse generator discomfort	32.4	0	67.7
Infection	38.2	2.9	58.8
Fractured electrode	14.7	0	85.3
Hardware malfunction	20.6	5.9	73.5
Other	44.1	0	55.9

PGIC, patient global impression of change.
Except where designated otherwise, denominator is 34 studies.
*Some studies had more than one type of outcome.

Study Characteristics and Analysis

The majority of studies used a cross-over design (59%); the remaining studies used a parallel-group design (Table 6). Open-label (no blinding) was reported in 68% of studies. Where studies were defined as blinded, they were most frequently reported as double blind. In 3 studies, the participant, the interventionist, and the outcome assessor were all blinded.[1,74,75] Of the

Table 5. Summary of Outcome Reporting

Method of Reporting Primary Outcomes (%)	*Result*
Mean score of outcomes at a specified time	41.2
Pain intensity: patients with a specified level at a specified time (responders)	17.7
Mean change in score of outcomes at a specified time	17.7
Pain intensity: difference at a specified time	11.8
Pain relief: patients with a specified level at a specified time (responders)	11.8
Time-to-event designated by the study	5.9
No stated primary outcome measure	5.9
Other	11.8
Method of Reporting Secondary Outcomes (%)	
Pain relief: patients with a specified level at a specified time (responders)	67.7
Time-to-event designated by the study	32.4
Pain intensity: difference at a specified time	14.7
Pain intensity: patients with a specified level at a specified time (responders)	11.8
Mean score of outcomes at a specified time	2.9
Mean change in score of outcomes at a specified time	8.8
No stated primary outcome measure	5.9
Other	58.8
Clinical significance of outcome reported (%)	
Percent change (eg, 30% or 50%)	38.2
Absolute change (eg, point reduction)	23.5
Not defined	38.2
If assessed at multiple timepoints, interval between primary outcome assessments (%)	
Less than 1 day	20.6
1 day up to 1 week	11.8
More than 7 days up to 1 month	8.8
More than 1 Month	38.2
Variable	11.7
Not specified	8.8
Timing of primary outcome endpoint (weeks)	
Median (range)	12 (0–208)

Except where designated otherwise, denominator is 34 studies.

11 studies that attempted blinding, 2 were assessed as having a high risk of bias, 6 a low risk, and 3 were assessed as having an unclear risk of bias. None of the studies were assessed as having a high risk of randomization bias, and the majority (74%) was assessed as having a low risk of randomization bias.

An initial trial of SCS, after which patients were enrolled and randomized, occurred in 56% of the studies.

The washout periods reported in the cross-over studies were very short or nonexistent. The range of days for washout was 0 to 14 days, with a median of 0 days.

For their primary analysis, more than half of the studies employed a superiority analysis. In 32% of the studies, the analytic approach was unclear or not specified. A noninferiority analysis was reported as being used for the primary analysis in 12% of the studies, and only 1 study was reported to be an equivalence study.[74]

Researchers reported a sample size calculation in 62% of the studies. Of the elements required to calculate a sample size (ie, power, difference to detect, and alpha), 59% reported the percent power the study aimed to achieve, 56% reported the degree of change in outcome that the trial was designed to detect, and 74% reported the assumed alpha (eg, .05). Sixteen studies (47%) reported a sample size calculation along with all of the required elements for its calculation.

While approximately one-third of the sample reported assessing multiple primary outcomes, only 12% of all studies (four of the 12 with multiple outcomes) reported use of a statistical adjustment for multiple outcomes. The majority of studies (59%) reported that they employed a per-protocol (completer) analysis only. Eleven studies (32%) employed an intention-to-treat (ITT) or modified ITT analysis, and 2 studies reported both a per-protocol and an ITT analysis. Of those that employed an ITT or modified ITT analysis, 5 of 13 reported using a method to accommodate missing data, most commonly last observation carried forward (LOCF).

Angina Studies

Twelve studies (26% of 46) assessed the use of SCS in patients with angina.[3,4,9,13,16,25,27,40,41,44,46,86] The majority of these studies were single site (75%), and only 1 study included US sites.[86] Three studies indicated no funding source, but others were industry or government sponsored research, or both. Three studies were publicly registered.[16,40,86] All studies were in severe angina or angina refractory to other treatments, or both. Three studies (25%) used cross-over designs with no washout phase;[9,13,41] all other studies were parallel group designs. Half of studies had some degree of

Table 6. Summary of Study Design, Methods, and Analytic Techniques

Study Design and Methods Summary	*Result*
Design (%)	
Cross-over	58.8
Parallel	41.2
Blinding (%)	
No blinding (open label)	67.6
Single-blind	3.0
Double-blind	20.6
Triple-blind	8.8
Participants blinded	26.5
Investigator	23.5
Outcome assessors	20.6
Adequacy of blinding (%)	
No blinding	67.6
High risk of bias	5.9
Low risk of bias	17.7
Unclear	8.9
Randomization integrity (%)	
High risk of bias	0
Low risk of bias	73.5
Unclear	26.5
Adverse events collection method (%)	
Actively	0
Passively	0
Both actively and passively	8.8
Unclear	91.2
Studies with SCS trial/screening phase (prerandomization) (%)	55.9
Cross-over studies: washout duration (days)	
Mean (SD)	1.8 (3.8)
Median (Range)	0 (0–14)
Study duration in weeks	
Median (Range)	12 (0–298)
Mean (SD)	34.7 (49.8)
Comparison of randomized groups (%)	
Stated/shown to be equal in all arms	38.2
Stated as not equal with explanation or accommodation	2.9
Stated as not equal with no explanation or accommodation	0
Nothing stated about comparability of groups or unclear	58.8
Summary of Analytic Procedures	
Type of analysis (%)	
Superiority	52.9
Noninferiority	11.8
Equivalence	2.9
Not specified	32.4
Required sample size reported (%)	61.8
Required elements for sample size estimation reported (%)	
1. Significance level	73.5
2. Power calculation	58.8
3. Treatment effect size to be detected	55.9
Reported statistical adjustment for multiple outcomes (%)	11.8*
Type of analysis† (%)	
Intention-to-treat	35.3
Modified intention-to-treat	2.9
Per-protocol (completer analysis)	64.7
Not reported	2.9
For Intention-to-Treat and Modified Intention-to-Treat Analyses, Plan for Accommodation of Missing Data (N = 13) (%)	
Last observation carried forward	23.1
Other	15.4
Not reported	61.5

Except where designated otherwise, denominator is 34 studies.
*4 out of 34 studies reported adjustment (4 of 12 with multiple outcomes).
†Adds to more than 100% as some studies performed more than one analysis.

blinding (mostly of outcome assessors) with insufficient detail to assess risk of bias. Bias assessment of randomization procedures was rated as unclear due to insufficient detail in 10 studies; 2 studies were rated as low risk for bias due to randomization.[16,46]

Conventional (paresthesia-based) use of SCS was assessed in all studies; most studies specified that SCS was utilized in addition to other treatments such as nitroglycerin. Half of the trials allowed for adjustments to interventional SCS settings. Two studies compared SCS against surgery (eg, revascularization), 1 against usual care, and 6 against implant without activation or with subthreshold stimulation. Duration of the intervention varied from less than 1 week[9] to up to 52 weeks;[46,86] most studies evaluated the intervention for durations of 4 to 8 weeks. Outcomes varied amongst studies but commonly included number of angina attacks and nitroglycerin consumption. Seven studies (58%) assessed health-related quality of life and 7 (58.3%) also assessed physical function/disability.

Of the 12 studies, 3 prespecified AEs as an outcome,[16,46,86] and 6 (50%) reported serious AEs.[3,4,16,40,46,86] Specific AEs reported in studies were lead migration (42%), localized pain (25%), infection (25%), pulse generator discomfort (17%), hospitalization (8%), death (8%), battery life (8%), and other cardiac complications.

Only 3 of the angina studies reported superiority analyses, all of which described sample size calculation and the elements required to calculate sample size.[40,46,86] Per-protocol analysis was conducted in 50% of studies, 17% utilized ITT, and 25% utilized both methods of analysis. Two of the studies that reported both types of analyses accommodated missing data with LOCF.[46,86] No other studies described methods for missing data. The median number of patients randomized was 25 (range 10−104), and the mean age was 64.4 (5.0).

Extension Studies

Seven extension studies were identified from the search, four of which were extensions of a study included in our main analysis.[31] Most extension studies reported follow-up data from 24 months.[30,32,37,78] Additionally, most extension studies reported follow-up data for the same efficacy and safety outcomes originally described. One study reported efficacy and safety outcomes only from the SCS arm of the original study and identified additional AEs (ie, new pulse generator implantation, lead replacement) with 24-month data.[78]

Of the 4 extension studies from the research conducted by Kemler et al, 1 reported 12-month data for outcomes related to pressure sensibility, warmth and cold sensibility, and mechanical hyperalgesia.[34] Efficacy data were also presented for 2-year follow-up with added reporting of AEs, such as revision of pulse generator pocket, lead replacement, reimplantation, disturbed urination, cramping, and explantation.[32] Another extension presented 5-year data for pain intensity.[33] Lastly, an analysis of prognostic factors for successful SCS-related outcomes in an extension study was presented.[80]

Discussion

Where design and methodology from angina studies were similar to non-angina studies, data are summarized for all; where differences exist, findings from angina studies are separated.

Study Features and Designs

In studies that reported funding, the majority were supported financially by device manufacturers. However, the sponsor's role in the trial was less clear. Given the expense, it is perhaps not surprising that devices were supplied without cost by the manufacturer in many studies. Industry-sponsored studies have been associated with a higher likelihood of positive outcomes.[60]

Most angina studies were conducted at a single site. Multicenter studies are thought to have greater external validity, but they may have less internal validity, and more measurement error.[60] Sixteen of the 46 studies were registered on a clinical trial website, typically the National Institute of Health site. Given that this was not established for sponsors and principal investigators to submit protocols or results of clinical studies until 2008, the majority of registered studies are recent. However, many studies published after 2010 did not post a protocol or results, and this did not appear to be associated with whether or not they were conducted in US sites.

We analyzed pain location based on inclusion criteria. Such criteria were often broad and resulted in potentially heterogeneous patient populations that may have different prognostic factors. The requirement for a minimum duration or severity of disability was uncommon. A requirement for a minimum pain intensity or duration was considerably more common, with cut-offs of at least moderate severity and minimum durations ranging from 2 weeks to 2 years. Chronic pain is routinely defined as pain of 3 months or greater duration; therefore, inclusion of subjects with shorter durations of pain means that many did not meet this criterion. Studies with minimum pain or disability criteria, or that only included patients resistant to other treatments, may more closely reflect candidates for SCS, in that SCS can be seen as a treatment of last resort.[18] Most studies did not stipulate that patients had to discontinue their current analgesic regimen or keep dosing stable. While this may affect the internal validity, it likely better reflects clinical practice, and may also avoid missing data.[12]

Overall, study designs were evenly split between parallel group and cross-over design. Cross-over trials generally have smaller sample sizes, are less expensive to conduct, and may increase enrollment.[62] On the other hand, they may take longer to complete. Included cross-over studies frequently had no washout. While the duration, if any, of carryover effect of a previous SCS intervention is unclear, the possibility that this may have an effect on outcomes cannot be ruled out. While not noted, the lack of washout may have been due to concerns about return of pain during this period. To mitigate for this, 1 study offered participants opioid prescriptions for the 1-week washout period.[53] Another study waited for pain to return to 80% of baseline

before initiating the alternate intervention.[74] Other studies only collected outcomes in the last few days of a cross-over period to minimize carryover.

As mentioned, conventional SCS is associated with paresthesia, which may preclude complete patient blinding using a comparator of sham or placebo therapy. It is, therefore, not clear whether investigators or even outcome assessors can be blinded in studies of conventional SCS. Patient blinding with placebo or sham treatment can potentially be achieved in studies where participants receive either HF or burst SCS, as both are reported to not cause paresthesia.[10] Risks of unblinding through rapid draining of the battery in the intervention phase can be attenuated by programming a current leak during the placebo periods. Six studies compared HF or burst SCS with placebo or sham. Of the 17 studies that attempted any type of blinding, 11 blinded participants. Of these, only 5 were assessed as being adequately blinded. Lack of blinding or inadequate blinding is associated with a high risk of study bias. Encouragingly, many newer studies incorporated sham/placebo into their design.

We assessed 27 studies (59%) as having a low risk of bias related to randomization. This is similar to findings from assessments of randomization in studies of pharmacological interventions.[17]

Twenty-two studies (48% of 46) incorporated a trial or screening phase, such as testing SCS with a temporary electrode, and assigning participants as having a successful trial if their pain was reduced. The use of a short-term endpoint to determine which participants should continue to the main study phase, a type of enrichment of the study population, has been recommended.[15,60]

The majority of studies allowed for SCS adjustments during the intervention, most often in signal amplitude. The ability to tailor settings to individual patients has increased, which potentially optimizes the chances for a positive outcome, but also adds to the complexity of conducting a trial, of providing SCS in clinical practice, and to the expertise required for administration.[21]

The median duration of intervention and time to assessment of the primary outcome was 12 weeks (angina studies were mostly less than 8 weeks). This is similar to studies of pharmacological interventions for chronic pain.[17] This duration may not adequately predict success, in that analgesic efficacy of both pharmacological and nonpharmacological treatments may change in patients with chronic pain. A prospective study of SCS with a 12-year follow-up demonstrated that after three years of treatment, 40% of initially successfully treated (defined as at least 30% pain relief) cases were reassigned as failures, and that this increased to 60% by 12 years.[21] Clearly, there are major challenges to retaining participants in RCTs for prolonged periods. Many studies have tried to offset this by having open-label extension periods.

Statistical Analysis

The vast majority of studies (87%) specified a primary outcome(s), most of which were pain-related. This is superior to a review of noninvasive nonpharmacological studies, where only 62% identified a primary outcome.[12] Consensus guidelines have recommended 4 chronic pain outcome domains: pain intensity; physical functioning; emotional functioning; and patient ratings of improvement.[76] Pain is by its nature subjective but clinically important to patients. Objective endpoints, such as limb survival in patients with peripheral vascular disease, or reductions in opioid use, were less frequent. Surrogate endpoints, such as sensation and coverage of paresthesia, were common, but do not necessarily translate to pain relief.[60] Given current concerns with opioids, one might have expected to see more of the recent studies compare opioid use among groups.

Adverse events were assessed as a primary outcome in 4 studies. Most studies did not specify whether AEs were collected actively (eg, a checklist), passively (eg, open-ended questions), or both. Reporting of paresthesias is of interest, in that studies have assessed them either as an indicator of efficacy or as an AE or side effect, or as both. With the advent of SCS parameters that reduce or eliminate paresthesia, it may be considered as a risk of unblinding. Finally, the majority of studies did not report the number of participants that required SCS adjustments because of AEs. Given recent reports of serious AEs in patients implanted with SCS, and differences in FDA criteria for device approval, more rigorous assessment of such events along with complete and transparent reporting are needed.[69] A single noninferiority study has led to FDA approval of at least 2 SCS devices after 2015, according to the premarket approval database. For older SCS devices, additional data were often provided; however, most of these data were not based on RCTs.[7,8,29,63]

Almost half of studies did not specify the type of analysis performed. Where specified (or inferred), 21 were superiority studies, 4 were noninferiority, and 1 was an equivalence analysis. It has been suggested that noninferiority analyses may be appropriate for SCS studies, in that new devices may offer more stimulation parameters without necessarily being superior to an existing product;[60] however, such studies have been criticized for not paying sufficient regard to patients' interests.[19]

In studies that reported analysis of multiple primary outcomes, 5/15 performed multiplicity adjustments to prevent an increase in the probability of type I error (ie, a false positive result). Systematic reviews of pharmacological, interventional, and noninterventional nonpharmacologic treatments identified deficiencies in reporting and, potentially in turn, the execution of multiplicity adjustment.[12,23] Our finding of only 33%, while based on a small number of studies, is broadly in agreement with both reviews.

In 46% of studies, authors presented sample size, along with all required elements for its calculation, for the primary outcome. By comparison, a 2015 review of both noninvasive pharmacologic and interventional pain treatments, noted that 65% of studies reported at least 1 element of a sample size calculation.[45] The

Consolidated Standards of Reporting Trials (CONSORT) organization recommends reporting of all elements; the lack of such has been associated with additional methodological deficiencies.

Twenty-six studies (56%) analyzed only participants who completed the study and contributed data at all time points. These are similar to those from reviews of pharmacologic and other nonpharmacologic treatments.[12,22] It has been suggested that per-protocol analyses may artificially inflate efficacy of a test intervention.[16] Eighteen studies employed an ITT analysis. Of these, only seven specified a method to accommodate missing data. This was typically achieved by imputation, using LOCF. LOCF analyses are thought to have a relatively high risk of bias, in that they can attribute pain relief to participants who have withdrawn.[26]

Reporting of Results

Average enrollment and demographics were similar to studies of pharmacologic treatments for chronic pain.[47] It has been suggested that studies enrolling at least 200 participants per arm are required to overcome random effects in estimating treatment effects.[51] None of the trials in this review met this criterion.

Similarity of comparator groups at baseline is essential to prevent confounding. Half of included studies either did not report similarity or did not present sufficient data for comparison. Twenty studies described groups as being comparable at baseline, although they may not have been adequately powered. In 3 studies having groups that were not similar at baseline, 2 provided explanation or methods to accommodate differences.

This systematic review provides the first overview, to our knowledge, of research methodology and reporting quality of published RCTs of SCS for pain. Grider et al performed a systematic review of effectiveness of SCS in chronic spinal pain, with a quality assessment, but did not review methodology.[24] North et al provided a narrative review of methodology.[60] We assessed all methods of SCS for any painful conditions. We searched multiple databases and accepted manuscripts published in any language (although no foreign language studies met criteria). Our review also has limitations. We were constrained by what was reported. We attempted to verify data posted on clinical trials websites; however, information from these is not always complete or accurate.[60] Therefore, for some aspects of study methodology we inferred entries based on what was (or was not) reported. Complete data submitted as part of FDA premarket approval was not reviewed.

Many of the methodological and reporting deficiencies highlighted in this review are similar to those in

Table 7. Reporting Recommendations for RCTs of SCS for Pain

Reporting recommendations for randomized clinical trials of spinal cord stimulation for treatment of pain

The following information should be clearly reported

Reporting
- Source of funding and specific role of funder in compensation, study design and analysis

Study design
- Parallel group, cross-over, other
- Posting of a protocol detailing a priori inclusion criteria, outcomes assessed (with clear delineation of primary and secondary endpoints, and if multiple endpoints are primary, methods for multiplicity adjustment) and statistical methods employed on a website such as www.clinicaltrials.gov.

Study methodology
- Clinical eligibility criteria
- Duration of washout in cross-over trials
- Extent and methodology of blinding
- Methods of randomization and its concealment
- Role of screening phase in enrollment of participants
- Initial settings and adjustment parameters for SCS units
- Allowance of concurrent treatments
- Methods to ensure balanced expectation of benefit of both researchers and patients (equipoise) between groups, and also balance of non-intervention treatment between groups (eg, programming time, psychological support, physical activity, rescue meds, etc.)

Outcomes
- Primary and secondary outcomes
- Assessment of adverse events, including what and how these were assessed

Statistical analysis
- Number of participants and reasons for withdrawing
- Similarity of groups at baseline and methods for accommodating differences
- Type of analysis (superiority, noninferiority, etc.)
- Sample size calculations, power analyses, and assumed effect size
- Methods for dealing with missing data

Interpretation
- Clinical significance of any statistically significant difference

studies of other interventions used in the treatment of pain. Among those that are unique to the field of SCS, is the difficulty with performing completely blinded, placebo-controlled studies involving paresthesia-based (conventional) SCS. Although most studies included conventional SCS arms, such interventions are not necessarily homogeneous and have evolved over time, which may be problematic for interpretation of findings both within and between studies. Reporting recommendations are presented to increase transparency and, in turn, shape the design of future clinical trials (Table 7). Improved methodology will increase the validity of findings, facilitate comparisons across studies, and increase the probability that results are clinically valuable so that effective SCS treatments and settings are identified for this evolving method of neuromodulation.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2020.05.001.

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