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Spinal cord stimulation for low back pain (Review)

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[Intervention Review]

Spinal cord stimulation for low back pain

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ABSTRACT

Background

Spinal cord stimulation (SCS) is a surgical intervention used to treat persistent low back pain. SCS is thought to modulate pain by sending electrical signals via implanted electrodes into the spinal cord. The long term benefits and harms of SCS for people with low back pain are uncertain.

Objectives

To assess the effects, including benefits and harms, of SCS for people with low back pain.

Search methods

On 10 June 2022, we searched CENTRAL, MEDLINE, Embase, and one other database for published trials. We also searched three clinical trials registers for ongoing trials.

Selection criteria

We included all randomised controlled trials and cross-over trials comparing SCS with placebo or no treatment for low back pain. The primary comparison was SCS versus placebo, at the longest time point measured in the trials. Major outcomes were mean low back pain intensity, function, health-related quality of life, global assessment of efficacy, withdrawals due to adverse events, adverse events, and serious adverse events. Our primary time point was long-term follow-up (≥ 12 months).

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included 13 studies with 699 participants: 55% of participants were female; mean age ranged from 47 to 59 years; and all participants had chronic low back pain with mean duration of symptoms ranging from five to 12 years. Ten cross-over trials compared SCS with placebo. Three parallel-group trials assessed the addition of SCS to medical management.

Most studies were at risk of performance and detection bias from inadequate blinding and selective reporting bias. The placebo-controlled trials had other important biases, including lack of accounting for period and carryover effects. Two of the three parallel trials assessing SCS as an addition to medical management were at risk of attrition bias, and all three had substantial cross-over to the SCS group for time points beyond six months. In the parallel-group trials, we considered the lack of placebo control to be an important source of bias.

None of our included studies evaluated the impact of SCS on mean low back pain intensity in the long term (≥ 12 months). The studies most often assessed outcomes in the immediate term (less than one month). At six months, the only available evidence was from a single cross-over trial (50 participants). There was moderate-certainty evidence that SCS probably does not improve back or leg pain, function, or quality of life compared with placebo. Pain was 61 points (on a 0- to 100-point scale, 0 = no pain) at six months with placebo, and 4 points better (8.2 points better to 0.2 points worse) with SCS. Function was 35.4 points (on a 0- to 100-point scale, 0 = no disability or best function) at six months with placebo, and 1.3 points better (3.9 points better to 1.3 points worse) with SCS. Health-related quality of life was 0.44 points out of 1 (0 to 1 index, 0 = worst quality of life) at six months with placebo, and 0.04 points better (0.16 points better to 0.08 points worse) with SCS. In that same study, nine participants (18%) experienced adverse events and four (8%) required revision surgery. Serious adverse events with SCS included infections, neurological damage, and lead migration requiring repeated surgery. We could not provide effect estimates of the relative risks as events were not reported for the placebo period.

In parallel trials assessing SCS as an addition to medical management, it is uncertain whether, in the medium or long term, SCS can reduce low back pain, leg pain, or health-related quality of life, or if it increases the number of people reporting a 50% improvement or better, because the certainty of the evidence was very low. Low-certainty evidence suggests that adding SCS to medical management may slightly improve function and slightly reduce opioid use. In the medium term, mean function (0- to 100-point scale; lower is better) was 16.2 points better with the addition of SCS to medical management compared with medical management alone (95% confidence interval (CI) 19.4 points better to 13.0 points better; I^2 = 95%; 3 studies, 430 participants; low-certainty evidence). The number of participants reporting opioid medicine use was 15% lower with the addition of SCS to medical management (95% CI 27% lower to 0% lower; I^2 = 0%; 2 studies, 290 participants; low-certainty evidence). Adverse events with SCS were poorly reported but included infection and lead migration. One study found that, at 24 months, 13 of 42 people (31%) receiving SCS required revision surgery. It is uncertain to what extent the addition of SCS to medical management increases the risk of withdrawals due to adverse events, adverse events, or serious adverse events, because the certainty of the evidence was very low.

Authors' conclusions

Data in this review do not support the use of SCS to manage low back pain outside a clinical trial. Current evidence suggests SCS probably does not have sustained clinical benefits that would outweigh the costs and risks of this surgical intervention.

PLAIN LANGUAGE SUMMARY

Spinal cord stimulation for low back pain

Background

Low back pain is a leading cause of disability around the world. Spinal cord stimulation, a surgical treatment involving implantation of a device that applies electric impulses to the spinal cord, has been suggested to improve pain in people with long-term low back pain. This study aimed to review evidence regarding the benefits and harms of this procedure for people with low back pain.

Study characteristics

We searched online databases and registries for relevant studies on 10 June 2022. We found 13 trials with 699 participants. Of these, 55% were female and the average age of study participants ranged from 47 years to 59 years. The average duration of low back pain amongst study participants varied from 5 to 12 years. Ten of the 13 studies had financial ties to manufacturers of spinal cord stimulation systems.

Key findings

No studies have tested whether spinal cord stimulation surgery is better than placebo (sham or 'dummy' treatment) in people followed up for longer than 6 months. This means that the benefits of the treatment in the long term are unknown. Most of the available studies only measured outcomes at less than 1 month after treatment, and only 1 study measured outcomes at 6 months after treatment:

Pain intensity (0 to 100, lower scores mean less pain)

At 6 months, the only available study found no benefit of spinal cord stimulation on back pain compared with placebo (1 trial, 50 participants; moderate-certainty evidence). At 6 months, participants given placebo treatment reported that their average pain was 61 points, and those given spinal cord stimulation reported that their pain was 4 points better (8.2 points better to 0.2 points worse).

Function (0 to 100, lower scores mean better function)

At 6 months, one study found no benefit of spinal cord stimulation on function (that is, people's general physical function) compared with placebo (1 trial, 50 participants; moderate-certainty evidence). Participants given placebo treatment reported that their functioning was 35.4 points at 6 months, and those given spinal cord stimulation reported that their functioning was 1.3 points better (3.9 points better to 1.3 points worse).

Health-related quality of life (0 to 1, higher scores mean better quality of life)

At 6 months, one study found no benefit from spinal cord stimulation on health-related quality of life compared with placebo (1 trial, 50 participants; moderate-certainty evidence). Participants given placebo treatment reported that their health-related quality of life was 0.44 points at 6 months, and those given spinal cord stimulation reported that their health-related quality of life was 0.04 points better (0.16 points better to 0.08 points worse).

Global assessment of efficacy (number of participants with a 50% improvement in pain or better)

None of the placebo-controlled studies measured this outcome.

Withdrawals due to adverse events (i.e. an unwanted event that causes harm)

We are uncertain whether spinal cord stimulation caused people to withdraw from studies due to adverse events because there were few studies and the evidence was based on only a few cases.

Adverse events (e.g. increased pain)

One study that followed people for 12 months found 9 participants (18%) experienced adverse events such as infections, damage to the spine or nerves, bladder problems, and movement of very small parts of the devices that deliver the electrical impulses to the spinal cord (known as 'lead migration').

Serious adverse events (e.g. an infection requiring hospitalisation)

Some studies reported serious adverse events in people receiving spinal cord stimulation that required repeated surgery. The only placebo-controlled study that followed people for 12 months found 4 participants (8%) required repeated surgery. In the five other studies of people receiving a new spinal cord stimulation implant, the number of people requiring repeat surgery, due to adverse events such as infection or device problems, ranged from 4.1% at 8 weeks to 30.9% at 24 months. However, it was not possible to estimate how common these events were compared with placebo or no treatment, as limited information was available.

Limitations of the evidence

For people with low back pain, we are moderately confident that, at 6 months, spinal cord stimulation probably does not lead to lower pain, better function, or higher quality of life compared with placebo. We are uncertain whether spinal cord stimulation can improve outcomes in the immediate term compared with placebo. Little to no information is available regarding long-term efficacy or the risk of side effects and complications.

Summary of findings 1. Spinal cord stimulation versus placebo for low back pain in adults

Spinal cord stimulation (SCS) versus placebo for low back pain in adults

Patient or population: adults with low back pain

Setting: outpatient

Intervention: conventional, burst, or high-frequency SCS

Comparison: placebo

Outcomes	Anticipated absolute effects (95% CI)		Relative effect	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with SCS				
Pain intensity VAS, translated to a 0- to 100-point scale, where 0 is no pain **Medium-term follow-up** (≥ 3 months to < 12 months)	Mean back pain during placebo period was 61 points	Mean back pain was 4 points better (8.2 points better to 0.2 points worse)	-	50 participants (1 study)	Moderate[a]	SCS probably does not improve back or leg pain in the medium term. Data are based on a single trial of burst SCS at low risk of bias. The CIs excluded clinically important benefits. Eight of 10 available placebo-controlled trials measured low back pain outcomes in the immediate-term only. Based on those trials, it was uncertain whether SCS improves low back pain more than placebo in the immediate term (8 studies, 139 participants; very low-certainty evidence). Two trials measured leg pain in the immediate term. Based on those two trials, it was uncertain whether SCS improves leg pain more than placebo in the immediate term (2 studies, 39 participants; very low-certainty evidence).
Function Roland-Morris Disability Questionnaire & Oswestry Disability Index translated	Mean disability during placebo period was 35.4 points	Mean disability was 1.3 points better (3.9 points better to 1.3 points worse)	-	50 participants (1 study)	Moderate[a]	SCS probably does not improve function in the medium term. Data are based on a single trial of burst SCS at low risk of bias. The CIs excluded clinically important benefits. One other study measured function in the immediate-term only. Based on that trial, it was uncertain whether SCS improves function more than placebo

to a 0- to 100-point scale, where 0 is no disability or best function **Medium-term follow-up** (≥ 3 months to < 12 months)						in the immediate term (1 study, 20 participants; very low-certainty evidence).
Health-related quality of life EQ-5D, index from 0 to 1 where 0 is worst quality of life **Medium-term follow-up** (≥ 3 months to < 12 months)	Mean quality of life during placebo period was 0.44 points out of 1	Mean quality of life was 0.04 points better (0.16 points better to 0.08 points worse)	-	50 participants (1 study)	Moderate[a]	SCS probably provides little to no benefit for health-related quality of life in the medium term. Data are based on a single trial of burst SCS at low risk of bias. The CIs excluded clinically important benefits. Two other trials measured health-related quality of life in the immediate-term only. Both suggested no benefit, though we were unable to pool the results of those studies (2 studies, 52 participants; very low-certainty evidence).
Global assessment of efficacy ≥ 50% improvement in pain **Medium-term follow-up** (≥ 3 months to < 12 months)	Not estimable	Not estimable	-	(0 studies)	-	No data available
Withdrawals due to adverse events Follow-up: longest measured[b]	Not estimable	Not estimable	-	(0 studies)	Very low[e]	Poorly reported in included studies. We are uncertain whether SCS results in more people withdrawing due to adverse events. One small cross-over RCT with 6-week follow-up reported 2 withdrawals with placebo versus 1 withdrawal with SCS (1 study, 19 participants; very low-certainty evidence).
Adverse events[c] Follow-up: longest measured[b]	Not estimable	Not estimable	-	(0 studies)	Very low[e]	Poorly reported in included studies. One cross-over study at low risk of bias found 9 out of 50 (18%) people who received SCS experienced an adverse event over a 12-month period, but did not specify whether

						events occurred during the placebo or active SCS period.
Serious adverse events[d] Follow-up: longest measured[b]	Not estimable	Not estimable	-	(0 studies)	Very low[e]	Poorly reported in included studies. Although the incidence was uncertain, serious adverse events included infections, neurological damage, and lead migration requiring repeated surgery. One placebo-controlled study at low risk of bias found 4 out of 50 (8%) people who received SCS required surgical revision within 12 months. In the six trials in this review that followed people receiving a new SCS implant, surgical revision rates in the SCS group due to adverse events ranged from 4.1% at 8 weeks to 30.9% at 24 months.

CI: confidence interval; **VAS:** visual analogue scale

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for indirectness due to possible differences between the burst SCS regimen provided in the trial and other SCS regimens provided internationally.
[b]Long-term efficacy and safety were not estimable as no data were reported.
[c]Adverse events included increased pain, infection, unpleasant paraesthesia, incorrectly implanted electrode causing shocks, pain at internal pulse generator/incision site, neurostimulator pocket fluid collection.
[d]Serious adverse events included unintentional dural tears during lead placement, revision of leads, infection requiring surgery, pulse generator replacement, and micturition problems requiring explant or revision surgery.
[e]Downgraded one level for risk of bias, one level for imprecision, and one level for indirectness.

BACKGROUND

Description of the condition

Low back pain is the leading cause of years lived with disability worldwide (Global Burden of Disease Study 2018). Low back pain typically refers to pain between the twelfth rib and the buttock crease (Dionne 2008). Sometimes low back pain is associated with radiating leg pain or sciatica. In many cases, the source of low back pain cannot be established (Hartvigsen 2018). Instead, low back pain is classified in terms of duration: acute (fewer than six weeks' pain duration), subacute (six to 12 weeks' pain duration), or chronic (more than 12 weeks' pain duration). Some consider chronic low back pain that persists following back surgery to be a distinct syndrome known as 'failed back surgery syndrome' (FBSS) (Thomson 2013).

The mechanisms of chronic low back pain and associated leg pain are uncertain. Theories have suggested that persistent pain states, such as chronic low back pain, occur in part because of dysfunctional processing of pain-related information in the spinal cord (Nijs 2015). However, the clinical importance of abnormal spinal cord processing in people with chronic low back pain remains uncertain (Roussel 2013).

Description of the intervention

Spinal cord stimulation (SCS) involves implanting a device in the low back/trunk that generates electrical pulses and delivers them to the spinal cord via electrodes within the posterior epidural space (Kemler 2000). The ‘leads’, containing sets of electrodes, can be implanted via laminectomy or percutaneously. Depending on the location and intensity of the person's pain, a clinician may select from a varying number and type of leads (uni-, bi-, or multipolar), and parameters of stimulation (amplitude, pulse width, frequency). Parameters of stimulation can be adjusted wirelessly using a remote control (Mailis-Gagnon 2013).

Before a surgeon implants the device, current protocols usually require a trial screening period. Leads are temporarily placed percutaneously, and the clinician assesses the individual’s response to the stimulation while they continue with usual activities. The screening phase lasts from days to weeks. A positive response is often defined as at least 50% pain relief (Kemler 2000). If the screening phase is positive, a surgeon may offer a laminectomy to permanently implant a paddle lead or percutaneous leads which are anchored. Internal pulse generators (IPGs) are connected to the implanted leads via a tunnelling device such that the entire system is most often implanted under the skin. IPGs use rechargeable or primary cell batteries, depending on patient preference. The lifetime of an IPG is dependent upon multiple variables, including a person's use of the device. Replacement of IPGs is required for both rechargeable and primary cell types, though the former likely have a greater longevity.

How the intervention might work

The mechanism of action of SCS for low back pain is poorly understood. SCS was originally thought to work via the gate-control mechanism (Melzack 1965); that is, stimulation of part of the spinal cord would interrupt transmission of pain-related information to the cortex. However, evidence of the effects of SCS on the relay of pain-related information at the spinal cord in humans is limited (Meyerson 2000). In addition, SCS does not appear to influence pain in response to an experimentally induced noxious stimulus (Meyerson 2000). Other suggested mechanisms have included inhibition of the sympathetic nervous system (sympatholytic effect) (Kemler 2000), and interrupted transmission of pain-related nerve impulses by the brain (supraspinal inhibition) (Meyerson 2000). It is unclear whether the mechanism of action differs in people with chronic low back pain, compared to those with leg pain, or those diagnosed with failed back surgery syndrome (FBSS) (Meyerson 2000).

Why it is important to do this review

SCS is thought to be helpful for chronic low back pain, sciatica, and FBSS. The National Institute for Health and Care Excellence (NICE) recommends SCS for refractory neuropathic pain (NICE 2020). In 2014, the SCS market was estimated to be valued at 1.3 billion (i.e. 1300 million) US dollars (USD) (PRWeb 2015). In the USA, the average cost of implanting a stimulator is USD 30,000, plus USD 10,000 per annum for maintenance care if the person experiences complications. One study estimated that 12% of people who had SCS experienced at least one complication, such as lead migration or wound infection (Shamji 2015).

Evidence on the benefits and harms of SCS, compared with placebo or no treatment, is limited. A Cochrane Review of efficacy in chronic pain was withdrawn because the review was out of date (Mailis-Gagnon 2013). Grider 2016 conducted a systematic review of SCS for low back pain and focused on a wide range of trials, including those that compared SCS with different stimulation regimens and various other control treatments of unknown efficacy. This made the true efficacy of the procedure difficult to determine. Grider 2016 did find three small trials that compared SCS to no treatment or placebo/sham (160 participants in total). The trials had mixed results. One small trial (40 participants) found no effect on pain intensity at four weeks compared with placebo SCS (device switched off) (Perruchoud 2013). One hallmark 2007 trial by Kumar and colleagues ('PROCESS'; 100 participants), investigating SCS as an addition to 'conventional medical management', found a large effect on leg pain at six months (-26.7 points (95% confidence interval (CI) -40.4 to -13.0) on a 100-point scale) (Kumar 2007, primary reference). Because the 'conventional medical management' was not standardised or provided in a controlled way, this effect is challenging to interpret.

There have been additional trials since the Grider 2016 review. In 2019, Rigoard and colleagues reported on the PROMISE trial (Rigoard 2019). Similar to the Kumar 2007 trial, PROMISE compared SCS plus 'optimal medical management' with 'optimal medical management' alone. The 'optimal medical management' was not standardised or controlled by the investigators. At six months, the between-group difference in low back pain was 1.1 points (95% CI 0.6 to 1.6) on a 0 to 10 scale. The large effect on leg pain observed in the PROCESS trial by Kumar and colleagues in 2007 was not replicated: at six months the effect was 1.3 points (95% CI 0.7 to 1.9) on 0 to 10 scale (Rigoard 2019). In the Rigoard trial, 18% of participants experienced a stimulator-related adverse event. The SCS Frequency Study, a small study (24 participants) that compared SCS treatment at three different frequencies against 'sham' SCS treatment (device is switched on but not delivering any stimulation), found that some SCS regimens were not superior to sham (Al-Kaisy 2018). New trials are also underway (e.g. MODULATE-LBP (Al-Kaisy 2020)) or have overdue results.

To date, the evidence from trials of SCS suggests that, compared with placebo or no treatment, or as an addition to medical management, the effects on low back pain and leg pain are uncertain. A recent Cochrane Review of SCS interventions for any pain condition concluded that SCS may have clinically important effects when added to conventional medical management or physical therapy, but that effects over placebo may be much smaller and unimportant (O'Connell 2020). The certainty of evidence was low to very low. However, that review did not examine the evidence on SCS specifically for people with low back pain. A focused Cochrane Review will help resolve some of the uncertainty regarding efficacy of SCS for people with low back pain, and help clinicians, people with low back pain, and policymakers make decisions based on the best available evidence.

OBJECTIVES

To assess the effects, including benefits and harms, of SCS for people with low back pain.

METHODS

Criteria for considering studies for this review

Types of studies

We sought randomised controlled trials (RCTs), quasi-randomised trials (e.g. trials that use alternate allocation), and cross-over trials (e.g. trials in people with implanted stimulators that compare active stimulation with a period or periods where the stimulator is turned off or is inactive to act as a placebo stimulation) for this review. We considered studies published as full texts, abstracts only, and data found from unpublished sources. We did not limit inclusion by date or language of publication.

Types of participants

We considered studies in adult participants (≥ 18 years) of any gender with chronic low back pain (> 12 weeks' pain duration), with or without leg pain, including people classified as having FBSS. We excluded studies in participants who had pain conditions other than chronic low back pain, with or without leg pain, unless we could obtain separate data for the effects of treatment on participants with chronic low back pain, with or without leg pain, either from the published report or through contacting authors. We excluded studies in participants who had chronic low back pain caused by serious spinal pathology (e.g. fracture, cancer, infection). We did not place restrictions on study setting or the demographic characteristics of participants.

Types of interventions

We considered studies that compared SCS to placebo or no treatment or assessed SCS as an addition to medical management. We excluded studies that only compared different forms of SCS. We included studies using SCS procedures of any kind (e.g. using an implanted rechargeable or conventional (not rechargeable) pulse generator (IPG) or an older design of radiofrequency stimulator), and using any stimulation protocol. For analysis, we considered 'conventional' SCS to be tonic stimulation below 1 kHz, 'high-frequency' SCS to be tonic stimulation at 1 kHz to 10 kHz, and 'burst' SCS to be intermittent bursts of stimulation.

Comparator arms had to include a placebo or no treatment, or assess SCS as an addition to medical management. If no treatment was delivered by trial staff, we considered this a 'no treatment' group. Participants may have received co-interventions that could be considered usual care, such as oral medicines (i.e. opioids, non-steroidal anti-inflammatories, antidepressants, anticonvulsants, and other analgesics), physical therapies (e.g. massage, acupuncture, spinal manipulation), psychological therapies (e.g. cognitive behavioural therapy), and injection therapies (e.g. nerve blocks, epidural corticosteroids) (Kumar 2007). Although not strictly a 'no treatment' comparison, we included trials assessing the addition of SCS to medical management that was provided (at least in part) by investigators.

The following are examples of acceptable placebo SCS interventions that we considered for inclusion: i) the stimulator is switched off; ii) the stimulator is switched on initially for programming then switched off; iii) the stimulator is switched on but emits no electrical impulse to the spinal cord. There is debate in the field about whether very low-amplitude stimulation could also act as a placebo SCS stimulation (Tjepkema-Cloostermans 2016). However, because of uncertainty around the precise level of stimulation that should be considered 'subtherapeutic,' we excluded studies comparing SCS intervention to very low-amplitude stimulation, and considered studies that use such a comparator to be evaluating different forms of SCS.

Types of outcome measures

Major outcomes

For each outcome, we considered the hierarchy of pain and physical function outcomes provided by the Cochrane Musculoskeletal Group and the ranking of core outcome measures relevant to low back pain provided by Chiarotto and colleagues (Chiarotto 2018). Accordingly, where multiple outcomes were reported, we gave preference to the highest on the list. For each outcome, the hierarchy of outcomes is provided below in order of preference.

Outcomes assessing benefits

- Pain intensity: numeric rating scale (NRS); visual analogue scale (VAS); pain severity subscale of Brief Pain Inventory
- Function: Oswestry Disability Index version 2.1a or 24-item Roland-Morris Disability Questionnaire for physical functioning; NRS; global disability score; 36-item Short-Form (SF-36) (physical function); other validated functional scales
- Health-related quality of life: 12-item Short-Form questionnaire (SF-12); Patient-Reported Outcomes Measurement Information System Global-10 (PROMIS-GH-10); health-related quality of life survey (HRQoL); EuroQol-5D (EQ-5D); 36-item Short-Form questionnaire (SF-36) (mental health); other validated quality of life scale
- Global assessment of efficacy: participant-rated improvement measured as per cent improvement or on a categorical scale

Outcomes assessing harms

- Proportion of withdrawals due to adverse events
- Proportion of participants with adverse events: any adverse events reported (e.g. cardiovascular events, worsening of pain, fatigue, etc.)
- Proportion of participants with serious adverse events (defined as leading to hospitalisation, disability, or death)

Minor outcomes

- Medication use: number and proportion of participants taking any pain medication, daily dose of opioids as a morphine equivalent dose, or as reported in trials
- Health care use: number of visits to any healthcare provider for care related to participant's back pain or management of the SCS, or both
- Work status: number and proportion of participants reported to have returned to work, work absences, or as reported in trials

Timing of outcome assessment

We grouped outcome measures for outcomes assessing benefit (pain, disability, quality of life, medication use, health care use, work status) by timing of measurement as: immediate-term (< one month), short-term (≥ one month to < three months), medium-term (≥ three months to < 12 months), or long-term (≥ 12 months) follow-up. For cross-over trials, we used the duration of an SCS treatment to categorise timing of measurement. For example, if a trial had three treatment periods of two weeks each (placebo for two weeks versus high-frequency SCS for two weeks versus conventional SCS for two weeks, with outcomes collected at the end of each period), then we designated this as 'two-week follow-up' and it fell in the immediate-term category. If a trial had outcomes from multiple periods from the same SCS treatment (for example, a trial had two three-month periods of burst SCS and two three-month periods of placebo, pooling outcomes from both periods), then we designated this 'three-month follow-up' and it fell in the medium-term category. Long-term follow-up (≥ 12 months) was our primary time point. We chose this primary time point because SCS systems can degrade over time and require replacement. The impact of these events can only be captured with long-term follow-up. We collected adverse event outcomes at the last time point.

Search methods for identification of studies

Electronic searches

We searched the following databases, from their inception to 10 June 2022:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 6);
- MEDLINE via Ovid (1946 to 10 June 2022);
- Embase via Ovid (1947 to 10 June 2022);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) Complete via EBSCOhost (1982 to 10 June 2022).

We also searched the following trial registries for registered studies for which results have not yet been published:

- ClinicalTrials.gov (clinicaltrials.gov);
- Australian New Zealand Clinical Trials Register (anzctr.org.au);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/clinical-trials-registry-platform).

When we found unpublished studies, we contacted trialists to request data for inclusion if we deemed the studies complete. If we were unsuccessful in obtaining data, we listed these studies as 'awaiting classification'. Where studies were ongoing, we kept records and reported them as such. We did not limit our search by date or language. See Appendix 1 for our search strategy.

Searching other resources

To identify any additional references, we searched the reference lists of included studies and systematic reviews relevant to the treatment of low back pain. We included any references highlighted through discussion with experts in the field. We also used personal communication with experts working in the field of back pain or chronic pain and communicated directly with manufacturers of spinal cord stimulators (including Medtronic, Boston Scientific Corporation, Nalu Medical, and Saluda Medical) to identify unpublished reports. In addition, we searched grey literature sources, including Bielefeld Academic Search Engine (BASE), Open Grey (opengrey.eu), and e-thesis online (ethos.bl.uk).

Data collection and analysis

Selection of studies

Two review authors (AT and SG) independently screened titles and abstracts of all the potentially-relevant reports we identified from the searches. We coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications. Two review authors (AT and SG) independently screened these to identify studies for inclusion, and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third author (CM). We identified and excluded duplicate reports and collated multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (PRISMA Group 2009), and a Characteristics of excluded studies table. For screening of non-English language papers, we initially used Google Translate to assist eligibility assessment. We did not require translators to assist with assessing eligibility of studies or data extraction.

Data extraction and management

We built a custom data collection form using Covidence for study characteristics and outcome data, which we piloted on several studies. One review author (AT) extracted study characteristics from included studies. A second review author (SG) spot-checked study characteristics for accuracy against the trial report. We extracted the following study characteristics if available.

- Methods: study design, total duration of study, details of any 'run-in' or pre-implantation screening period, number of study centres and location, study setting, withdrawals, and date of study.
- Participants: N, mean age, age range, sex, socioeconomic status, back pain duration, pain severity, diagnostic criteria, inclusion criteria, exclusion criteria, and baseline pain, function, quality of life, pain medication use, healthcare use, and work status.
- Interventions: intervention (including brand and type of SCS device, duration of intervention, stimulation parameters), comparison, concomitant medications, excluded medications or procedures, and post-procedure care, as outlined in the TIDieR checklist (Hoffmann 2014).
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.

- Characteristics of the design of the trial as outlined below in the Assessment of risk of bias in included studies section.
- Notes: funding for trial and notable declarations of interest of trial authors.

Two review authors (AT and SG) independently extracted outcome data from included studies. We extracted the number of events and number of participants per treatment group for dichotomous outcomes, and means and standard deviations and number of participants per treatment group for continuous outcomes. We noted in the characteristics of included studies table if outcome data were not reported in a usable way or if we had to transform data or estimate it from a graph. We used the PlotDigitizer program to extract data from graphs or figures (PlotDigitizer) and performed this step in duplicate. We resolved disagreements by consensus or by involving a third review author (CM). One review author (AT) transferred data from Covidence into a Review Manager file (RevMan Web 2020). We double-checked that data were entered correctly by comparing the data presented in the analyses with the study reports.

We selected data to extract based on the following decision rules:

- Extract outcome data in the order of preference outlined in the Types of outcome measures section above.
- If both final values and change from baseline values are reported for the same outcome, extract the final values.
- If both unadjusted values and values that have been adjusted for baseline are reported for the same outcome, extract the adjusted values.
- For outcomes assessing benefits, give preference to intention-to-treat (ITT) analysis data rather than 'per protocol' or 'as treated' data, if available.
- If multiple time points are reported, use the one closest to the mid-point: two weeks for immediate term, two months for short term, eight months for medium term. For long-term outcomes, use the time point closest to 12 months.

Assessment of risk of bias in included studies

Two review authors (AT and SG) used the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to independently assess risk of bias for each study (Higgins 2011). We resolved disagreements by discussion or by involving another author (CM or IH). We assessed the risk of bias according to the following domains:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias), for self-reported outcomes;
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias);
- other bias: included if trials were stopped early, if there were differences between groups at baseline or differences between groups in timing of outcome assessment, and if there were co-intervention differences across groups.

For cross-over trials, we considered additional issues such as the impact of carryover and period effects, as suggested in Table 23.2a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

We graded each potential source of bias as high, low, or unclear risk. In our risk of bias table, we documented a quote from the study report, together with a justification for our judgement. For each of the domains listed, we summarised the risk of bias judgements across different studies. If information on risk of bias was based on unpublished data or correspondence with a trialist, we noted this in the risk of bias table. When evaluating treatment effects, we took into account the risk of bias for the studies that contribute to that outcome. To provide summary assessments of the risk of bias, we presented the figures generated by RevMan Web 2020.

Measures of treatment effect

We analysed dichotomous data as risk ratios, or Peto odds ratios when the outcome was a rare event (approximately less than 10%), and used 95% confidence intervals (CIs). Data were insufficient to calculate the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH).

We analysed continuous data as mean difference (MD) or standardised mean difference (SMD), depending on whether the same scale was used to measure an outcome, and 95% CIs. When studies used different scales to measure the same conceptual outcome (e.g. function), we calculated SMDs rather than MDs, with corresponding 95% CIs. We back-translated SMDs to a typical scale (e.g. 0 to 100 for pain) by multiplying the SMD by a typical among-person standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial) (Higgins 2021b). We entered data presented as a scale with a consistent direction of effect across studies. For analysis of cross-over studies, we used the generic inverse variance (GIV) approach, which allowed us to adjust mean differences for cross-over design and multiple comparisons to the placebo group (see Unit of analysis issues).

We defined effect sizes for continuous outcomes as small (MD < 10% of the scale), medium (MD 10% to 20% of the scale), or large (MD > 20% of the scale) (Rubinstein 2012). Because the evidence was of low or very low certainty, we did not calculate NNTB or NNTH. For all continuous outcomes (pain intensity, function, health-related quality of life), we considered a medium effect size (a difference of 15%) to be the minimum clinically important difference (MCID).

Unit of analysis issues

For all trials, the unit of analysis was the participant. Where a single trial reported multiple trial arms, we included only the relevant arms. If we combined two or more comparisons from the same study in a meta-analysis, we attempted to adjust the number of participants in the placebo period to avoid double- or triple-counting. For example, some studies compared multiple types of SCS to placebo. In each of these cases, we attempted to adjust for multiple comparisons to the placebo group. We adjusted results from Al-Kaisy 2018, Schu 2014, Sokal 2020, and Sweet 2016 by estimating the mean difference, where the n in the control arm is divided by the number of comparator groups used in our analysis. This method of accounting for multiple comparisons to the placebo period required studies to report either raw data or standard deviations. De Ridder 2013 and Eldabe 2020 reported insufficient information on variance and so we could not adjust the estimated

mean difference for multiple comparisons. For studies where multiplicity could not be adjusted for, it is likely that uncertainty is underestimated, increasing the chance of a type 1 error. We avoided analysing cross-over studies as parallel studies, in accordance with Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). None of the cross-over trials provided data from the first phase, so data extracted from these trials are at risk of bias from carryover effects. We recorded this as 'other bias' in our risk of bias assessment. For studies where the cross-over design could not be accounted for, the uncertainty is likely to be overestimated. Further information on data transformations used in our analysis of cross-over trials is available in Table 1.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where necessary (e.g. when we identified a study published as an abstract only or when data were not available for all participants). We did not identify cases where we thought the missing data could introduce serious bias, and therefore did not conduct a planned sensitivity analysis to explore the impact of missing data in the overall assessment of results.

For dichotomous outcomes that measure adverse events (e.g. number of withdrawals due to adverse events), we calculated the proportion using the number of participants that received treatment as the denominator.

For dichotomous outcomes that measure benefits (e.g. proportion of participants reporting pain medication use), we calculated the proportion using the number of randomised participants as the denominator.

For continuous outcomes (e.g. mean change in pain score), we calculated the MD or SMD based on the number of participants analysed at that time point. If the study did not present the number of participants analysed for each time point, we used the number of randomised participants in each group at baseline.

Where possible, we computed missing standard deviations from other statistics, such as standard errors, CIs or P values, according to the methods recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021c). If we could not calculate the standard deviations, we imputed them (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

We used the information in the data extraction tables to assess the included studies' clinical and methodological diversity, in terms of participants, interventions, outcomes, and study characteristics, to determine whether a meta-analysis was appropriate. To assess statistical heterogeneity, we visually inspected the forest plots to look for obvious differences in results between the studies; we also used the $I^2$and Chi^2 statistical tests.

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021), we interpreted an I^2 value of 0% to 40% as indicating that the heterogeneity 'might not be important'; of 30% to 60% as representing 'moderate' heterogeneity; of 50% to 90% as representing 'substantial' heterogeneity; and of 75% to 100% as representing 'considerable' heterogeneity. As noted in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), we kept in mind that the importance of I^2 depends on: (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity.

When interpreting the Chi^2 test, we took a P value of less than or equal to 0.10 to indicate evidence of statistical heterogeneity. If we identified substantial heterogeneity, we reported it and investigated possible causes by following the recommendations in the *Cochrane Handbook*.

Assessment of reporting biases

Because we were unable to pool more than 10 trials, we did not create funnel plots or undertake formal statistical tests to investigate funnel plot asymmetry, as planned (Page 2021). To assess outcome reporting bias, we checked published reports against trial protocols and registries, and prepared an Outcome Reporting Bias in Trials ('ORBIT') matrix (Table 2). For studies published after 1 July 2005, we screened the World Health Organization clinical trial register on the International Clinical Trials Registry Platform (trialsearch.who.int) to check for protocols.

Data synthesis

We undertook meta-analyses only where this was meaningful; that is, if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense. We pooled outcomes grouped by comparison; namely, SCS versus placebo and SCS plus medical management versus medical management alone. We used random-effects models where there were sufficient studies. In addition to the planned SCS versus placebo comparison, we conducted separate meta-analyses for each of the three distinct clinical types of SCS: conventional SCS (tonic stimulation at < 1 kHz), high-frequency SCS (tonic stimulation at 1 kHz to 10 kHz), or burst SCS (intermittent bursts of stimulation).

For our meta-analyses of cross-over trials (Analysis 1.1; Analysis 1.5; Analysis 1.3), we used the methods suggested in section 23.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a): we conducted a paired analysis where possible and adjusted for multiplicity by dividing the number of participants in the placebo period by the number of comparisons (see Table 1). We included results from paired analyses from cross-over studies where these were reported or calculable, and pooled studies using the generic inverse variance approach. We used paired results from Sokal 2020 and Perruchoud 2013, and conducted our own paired analysis using data reported by Wolter 2012. We excluded one study from the analyses because its approach to intervention and outcome collection (1-hour outcomes only) was substantially different to the other trials (Eisenberg 2015).

Our primary planned comparison and outcome was SCS versus placebo on low back pain intensity at long-term follow-up, for which there were no trials available. The other comparison of interest was SCS versus 'no treatment' on low back pain intensity. The latter analyses pooled all studies that assessed the addition of SCS to medical management. In all analyses, we included trials regardless of their risk of bias.

Subgroup analysis and investigation of heterogeneity

We did not locate a sufficient number of trials to allow formal subgroup analysis. As an exploratory analysis, we pooled outcomes separately for three distinct clinical types of SCS: conventional SCS,

high-frequency SCS, or burst SCS. We explored heterogeneity in our analysis of SCS as an addition to medical management, by examining the impact of removing one study that reported very large effects (Kapural 2022).

Sensitivity analysis

To investigate the robustness of the treatment effect on pain intensity and function for all time points, we had planned to carry out the following sensitivity analyses for the main comparison of SCS versus placebo:

- including only studies we judged as having a low risk of selection bias;
- including only studies we judged as having a low risk of detection bias.

Only two analyses, both at the immediate-term time point, had a sufficient number of studies to conduct this sensitivity analysis (Analysis 1.1; Analysis 1.3).

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table using the outcomes (as described under Types of outcome measures) below.

Outcomes assessing benefits:

- pain intensity;
- physical function;
- health-related quality of life;
- global assessment of efficacy.

Outcomes assessing harms:

- withdrawals due to adverse events;
- proportion with adverse events; and
- proportion with serious adverse events.

The main comparisons in the summary of findings table were SCS versus placebo in the medium-term (i.e. the longest measured time points in our included studies) for outcomes assessing benefits (pain, function, quality of life, global assessment of efficacy), and last follow-up for outcomes assessing harms (withdrawal due to adverse events, adverse events, serious adverse events). Because the intervention is a surgically-implanted device with substantial potential for adverse events (including revision surgery within two years), we considered that long-term outcomes were likely to be the most important to people undergoing spinal cord stimulation. However, because no long-term data were available, we decided (post hoc) to present data for the longest available time point (medium-term follow-up, i.e. ≥ 3months to < 12 months), rather than provide an empty summary of findings table.

Two people (AT and SG) independently assessed the certainty of the evidence. We used the five GRADE considerations (study limitations, inconsistency, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence as it relates to the studies which contributed data to the meta-analyses for the prespecified outcomes, and reported the certainty of evidence as high, moderate, low, or very low. We used methods and recommendations described in Chapters 14 and 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021a; Schünemann 2021b). We justified all decisions to downgrade the certainty of evidence for each outcome using footnotes, and we made comments to aid the reader's understanding of the review where necessary. Due to sparse data, we were unable to provide a NNTB or NNTH, absolute and relative per cent change in the summary of findings (SoF) table, as described in the Measures of treatment effect section above.

We considered the following when making judgements about the five GRADE considerations.

- Study design and risk of bias: we made an overall judgement on whether the certainty of the evidence for an outcome warranted downgrading on the basis of study limitations. To assist our interpretation of these biases, we referred to Table 14.2a in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021b). For example, we considered downgrading the certainty of the evidence by one level if most of the evidence came from individual studies either with a crucial limitation for one item, or with some limitations for multiple items.
- Inconsistency: we evaluated each direct comparison for consistency in the direction and magnitude of the effect sizes from individual trials, considering the width of the confidence interval and magnitude of the heterogeneity parameter. We downgraded comparisons by one level if we identified important and unexplained heterogeneity.
- Indirectness: although we used precise inclusion criteria to minimise the scope for this problem, indirectness in the evidence could still arise. We used Table 14.2b in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* to assist interpretation of issues with indirectness (Schünemann 2021b). For each outcome, we judged indirectness arising from, for example, differences in participant populations, SCS intervention parameters, and 'no intervention' comparator protocols.
- Imprecision: in cases where studies included relatively few participants and few events, and thus had wide confidence intervals around the estimate of the effect, the results of meta-analyses that include these studies are imprecise.
  - Dichotomous outcomes: when the 95% confidence interval around the pooled or best estimate of effect included benefits or harms that would lead to substantially different clinical decisions (e.g. the confidence interval includes both no benefit and large benefit), we downgraded the evidence.
  - Continuous outcomes: as with dichotomous outcomes, we downgraded the evidence if the confidence interval was so imprecise that it included effects that would lead to opposing clinical decisions. That is, if the lower and upper bounds of the confidence interval included effects that would lead a clinician or person undergoing spinal cord stimulation to make a substantially different clinical decision, we downgraded the evidence.
- Publication bias: because we found fewer than 10 studies examining the same intervention comparison, we used methods such as checking for unpublished trials in trial registries, examining protocol papers for outcome switching, and constructing an ORBIT matrix.

RESULTS

Description of studies

Results of the search

Our search, conducted up to 10 June 2022, yielded 6492 records across five databases and two clinical trials registers (CENTRAL = 921; MEDLINE = 1014; Embase = 2719; CINAHL = 54; Bielefield = 940; trials registers (WHO ICTRP, clinicaltrials.gov) = 844). After duplicates were removed, 4776 unique records remained. Of these, we retrieved 113 articles for full-text screening on the basis of their titles and abstracts. We deemed 13 trials eligible for inclusion (Al-Kaisy 2018; De Ridder 2013; Eisenberg 2015; Eldabe 2020; Hara 2022; Kumar 2007; Kapural 2022; Perruchoud 2013; Rigoard 2019; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012). Three trials are awaiting classification (see Characteristics of studies awaiting classification). We initially identified 14 relevant ongoing trials in clinical trials registries, one of which was published on 18 October 2022 and subsequently included in this review (Hara 2022). Thus, we have classified 13 studies as ongoing (see Characteristics of ongoing studies). We excluded 29 studies (see details in Excluded studies and Characteristics of excluded studies). We present a flow diagram of the study selection process in Figure 1.

Figure 1. PRISMA study flow diagram

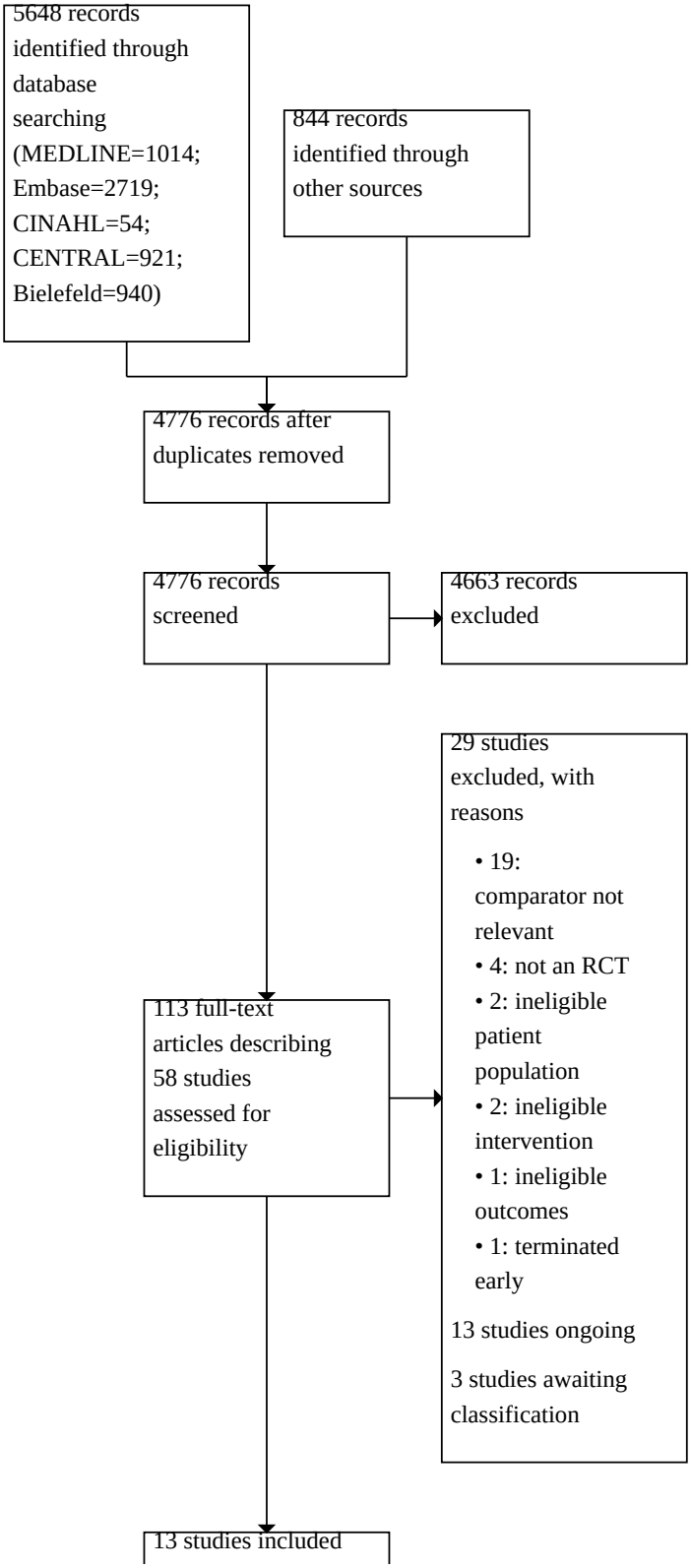
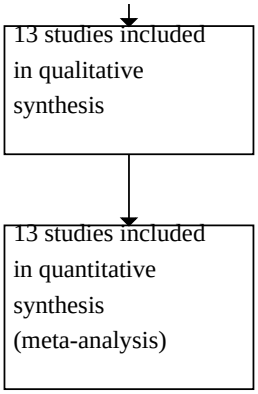


Figure 1. (Continued)



Included studies

Study design and setting

All thirteen studies were randomised controlled trials (RCTs). Ten used a cross-over design (Al-Kaisy 2018; De Ridder 2013; Eisenberg 2015; Eldabe 2020; Hara 2022; Perruchoud 2013; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012), and three used a parallel-group design (Kumar 2007; Kapural 2022; Rigoard 2019). Six studies had two intervention arms (Eisenberg 2015; Hara 2022; Kumar 2007; Kapural 2022; Rigoard 2019; Wolter 2012), four had three intervention arms (De Ridder 2013; Eldabe 2020; Schu 2014; Sweet 2016), and three had four intervention arms (Al-Kaisy 2018; Perruchoud 2013; Sokal 2020).

Three studies were multinational (Kumar 2007; Perruchoud 2013; Rigoard 2019). The other ten studies were conducted in seven different countries: Belgium (De Ridder 2013), Germany (Schu 2014; Wolter 2012), Israel (Eisenberg 2015), Poland (Sokal 2020), the UK (Al-Kaisy 2018; Eldabe 2020), Norway (Hara 2022), and the USA (Sweet 2016; Kapural 2022). The total duration of treatment with SCS in placebo-controlled trials varied between 2.5 hours and six months. Some parallel trials followed the SCS group for 24 months.

Six studies were funded by manufacturers of spinal cord stimulators (Al-Kaisy 2018; Eldabe 2020; Kumar 2007; Kapural 2022; Perruchoud 2013; Rigoard 2019); four did not report a funding source but had investigators with financial ties to manufacturers (De Ridder 2013; Schu 2014; Sokal 2020; Sweet 2016); and three appeared independent of industry funding (Hara 2022; Eisenberg 2015; Wolter 2012).

Participant characteristics

Thirteen studies randomised 699 participants with low back pain to receive spinal cord stimulation or a control intervention, with the sample size ranging from four to 218 participants per trial. The mean age of participants ranged from 47 years to 59 years. Six studies reported the mean duration of back pain symptoms before the trial (Al-Kaisy 2018; Eisenberg 2015; Kapural 2022; Rigoard 2019; Sokal 2020; Wolter 2012), which ranged from five to 12 years. Females accounted for 55% of the participants.

Inclusion criteria varied between studies. Eight studies included participants with chronic pain following spinal surgery or a previous diagnosis of 'failed back surgery syndrome' (FBSS) (Al-Kaisy 2018; De Ridder 2013; Eldabe 2020; Hara 2022; Rigoard 2019; Schu 2014; Sokal 2020; Sweet 2016), while one study only recruited participants who had not had any surgery for back or leg pain (Kapural 2022). Three studies stated participants should have stable medication for pain control (De Ridder 2013; Perruchoud 2013; Schu 2014). Seven studies required participants to already be implanted with an SCS and have achieved stable pain control (De Ridder 2013; Eisenberg 2015; Eldabe 2020; Perruchoud 2013; Schu 2014; Sweet 2016; Wolter 2012).

Interventions

Nine studies included an intervention arm delivering a conventional frequency stimulation (De Ridder 2013; Eisenberg 2015; Eldabe 2020; Kumar 2007; Rigoard 2019; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012), five studies included an intervention arm delivering high-frequency stimulation (Al-Kaisy 2018; Kapural 2022; Perruchoud 2013; Sokal 2020; Sweet 2016), and five studies included an intervention arm delivering burst stimulation (De Ridder 2013; Eldabe 2020; Hara 2022; Schu 2014; Sokal 2020) (see Table 3 for intervention characteristics). In 10 studies, the experimental arms were compared against a placebo/sham stimulation arm of the trial where an SCS was implanted but was switched off or not discharging (Al-Kaisy 2018; De Ridder 2013; Eisenberg 2015; Eldabe 2020; Hara 2022; Perruchoud 2013; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012). Only three of the placebo-controlled trials involved implantation of a new SCS device (Al-Kaisy 2018; Hara 2022; Sokal 2020). Three studies assessed SCS as an addition to trial care, labelled as "optimal medical management" or "conventional medical management" (Kumar 2007; Kapural 2022; Rigoard 2019). In these parallel-group trials, although guidelines were provided for medical management, it appears that the care was not clearly controlled or reported on by the trialists. As such, we considered this comparison to have been between SCS plus medical management and medical management alone. While this is not strictly a 'no intervention' comparison according to our prespecified entry criteria for the review, we decided to err on the side of including these studies.

In the three studies assessing SCS as an addition to medical management, the medical management options varied between studies and the non-SCS care actually received by participants in both groups was poorly reported. In the PROCESS trial (Kumar

2007), the medical management options were guided initially by investigators but were ultimately provided according to local clinical practice. As this was a multinational study, one would expect local clinical practice for back pain to vary considerably. Medical management in both groups could have included oral medications (i.e. opioid, non-steroidal anti-inflammatory drug, antidepressant, anticonvulsant/antiepileptic, and other analgesic therapies), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. In the SENZA trial (Kapural 2022), participants continued the medical management they had been receiving and received a treatment plan from investigators. Medical management in both groups could have included oral medications (including analgesic medication, non-steroidal anti-inflammatory drugs, neuromodulating agents, antidepressants), topical analgesics, compound creams, or counter-irritants, combined physical and psychological management, physical therapy, back rehabilitation program, spinal manipulation and spinal mobilisation, traction, acupuncture/acupressure, cognitive behavioral therapy, nerve blocks, epidural steroid injections, or transcutaneous electrical nerve stimulation. In the PROMISE trial (Rigoard 2019), an individual treatment plan was developed by investigators for each participant but the medical management was provided outside the trial. Out-of-trial care in both groups could have included noninvasive treatments such as acupuncture, psychological/behavioural therapy, and physiotherapy, or invasive treatments such as spinal injections/blocks, epidural adhesiolysis, and neurotomies. None of these three studies clearly reported on the medical management provided either by investigators or as out-of-trial care.

Pre-implantation trial periods

Studies that recruited participants without an SCS device already implanted tended to include a trial run-in period (Al-Kaisy 2018; Hara 2022; Kumar 2007; Kapural 2022; Rigoard 2019; Sokal 2020). Sweet 2016 included a run-in period in people with implanted stimulators and receiving conventional SCS to identify those most likely to respond to high-frequency SCS (of the 20 people recruited, only four responded and were included in the trial). Trial run-in periods ranged from 14 to 28 days in studies with run-in periods. The criteria used for successful completion of the trial period varied. Achieving a 50% reduction in pain was a requirement of most studies (Al-Kaisy 2018; Kumar 2007; Kapural 2022; Sokal 2020). Hara 2022 required a 2-point reduction in leg pain during the two-week run-in period to be included in their trial. In addition, one study required participants to have at least 80% coverage of their pain area with stimulation-induced paraesthesia (Kumar 2007). One study stated the criteria as having adequate low back pain relief with usual activity and appropriate analgesia in the context of postoperative pain (Rigoard 2019). In one study (De Ridder 2013), the experimental trial was conducted during the SCS trial period.

In the three studies using a parallel-group design (Kumar 2007; Kapural 2022; Rigoard 2019), the SCS trial period occurred after participants were randomised to their group. The SCS trial period success rate ranged from 82.7% to 92.5%. In the PROCESS study (Kumar 2007), 55.5% of those failing the SCS trial requested to still receive an SCS implant. In the PROMISE study (Rigoard 2019), participants who failed the SCS trial did not have an SCS implanted but were still followed as part of the study and included within the intention-to-treat analysis.

Outcomes

We present an Outcome Reporting Bias In Trials (ORBIT) matrix for the included studies in Table 2, with outcomes measured and level of reporting for each trial.

Major outcomes

Low back pain intensity

All thirteen trials measured mean low back pain intensity using a 0- to 10-point or 0- to 100-point visual analogue scale (VAS) or numeric rating scale (NRS). Six trials did not clearly report measures of variance (Al-Kaisy 2018; De Ridder 2013; Eldabe 2020; Kumar 2007; Perruchoud 2013; Sweet 2016).

Function

Seven of thirteen trials measured function outcomes: six of the seven used the Oswestry Disability Index (ODI) questionnaire (Hara 2022; Kumar 2007; Kapural 2022; Rigoard 2019; Schu 2014; Sokal 2020); and one used the Pain Disability Index (Wolter 2012). Of these seven, three did not clearly report measures of variance (Kumar 2007; Sokal 2020; Wolter 2012). One study was registered and measured ODI at baseline, but it was unclear if ODI outcomes were collected at follow-up (Al-Kaisy 2018). The remaining five trials did not have prospective registry records or study protocols, so it was unclear if they measured function outcomes (De Ridder 2013; Eisenberg 2015; Eldabe 2020; Perruchoud 2013; Sweet 2016).

Health-related quality of life

Seven of thirteen trials measured health-related quality of life (Eldabe 2020; Hara 2022; Kumar 2007; Kapural 2022; Perruchoud 2013; Rigoard 2019; Sokal 2020), but only three fully reported their results (Eldabe 2020; Hara 2022; Rigoard 2019). Six trials used the EQ-5D instrument (Eldabe 2020; Hara 2022; Kapural 2022; Perruchoud 2013; Rigoard 2019; Sokal 2020), and one used SF-36 (Kumar 2007). One study planned to measure health-related quality of life but did not provide results in the trial report (Sokal 2020).

Global assessment of efficacy (≥ 50% better)

Three of thirteen trials assessed the number of people who reported a 50% or higher improvement in pain (Kumar 2007; Kapural 2022; Rigoard 2019). One trial provided insufficient data at long-term follow-up for inclusion in a meta-analysis (Kumar 2007).

Withdrawals due to adverse events

Six of thirteen trials reported on withdrawals due to adverse events (Al-Kaisy 2018; Eldabe 2020; Kumar 2007; Kapural 2022; Perruchoud 2013; Rigoard 2019), although only two of the six provided complete data suitable for meta-analysis (Eldabe 2020; Kapural 2022).

Adverse events

Eight of thirteen trials appeared to collect data on number of adverse events (Al-Kaisy 2018; Eldabe 2020; Hara 2022; Kapural 2022; Kumar 2007; Rigoard 2019; Schu 2014; Sokal 2020), though reporting of proportions of adverse events in each study arm was generally poor. Several studies reported adverse events only for the as-treated participants (Al-Kaisy 2018; Kumar 2007; Schu 2014; Sokal 2020). Only two trials fully reported the number of adverse events in each study arm (Kapural 2022; Rigoard 2019).

Serious adverse events

Only one trial clearly reported serious adverse events in each study arm (Kapural 2022).

Minor outcomes

Medication use

Three trials reported on the number of participants using opioid medicines and daily morphine milligram equivalents (Kapural 2022; Rigoard 2019; Kumar 2007).

Health care use

No trials clearly reported on health care use.

Work status

One trial reported on the number of participants who returned to work (Kumar 2007).

Excluded studies

We excluded 29 studies for the following reasons: 19 due to an ineligible comparator; four because they were not RCTs; two because they included an ineligible study population; two due to an ineligible intervention; one due to ineligible outcomes; and one because it was terminated early. See Characteristics of excluded studies for details.

Risk of bias in included studies

We provide a summary of our judgements of the risk of bias in the included studies in Figure 2. Of the thirteen included trials, five (38%) were at risk of selection bias, ten (77%) were at risk of performance and detection bias, three (23%) were at risk of attrition bias, eleven (84%) were at risk of selective reporting bias, and twelve (92%) were at risk of other potential bias (Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

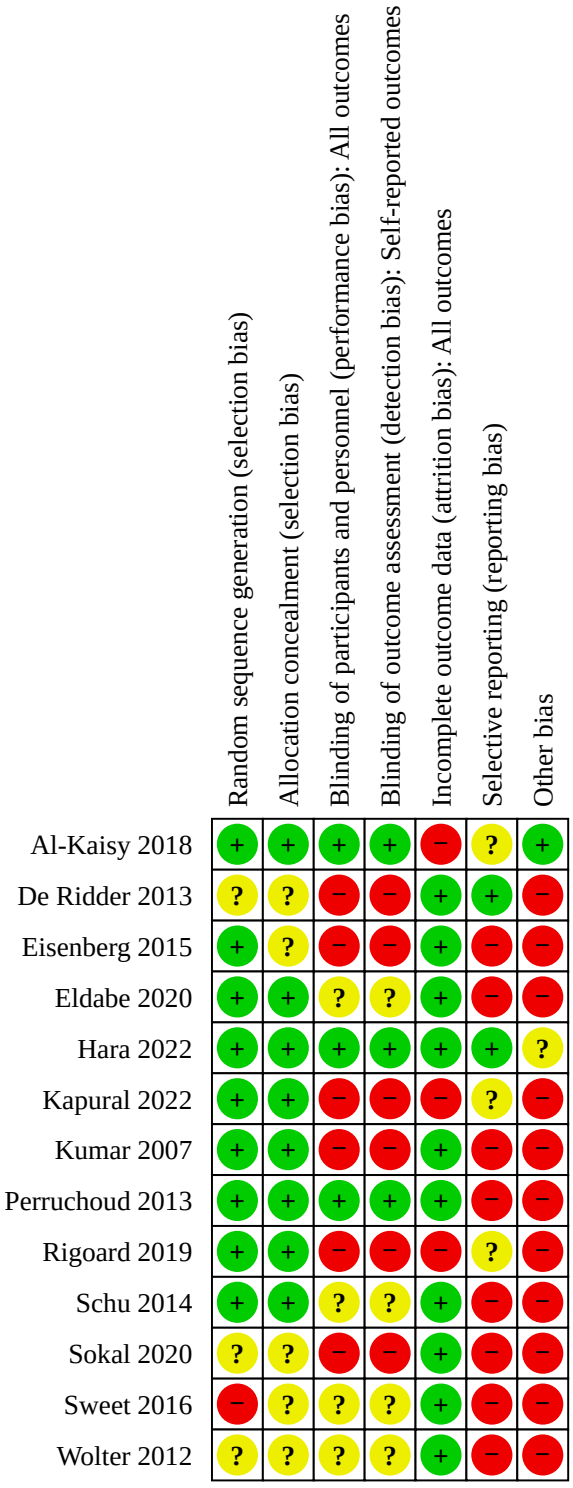
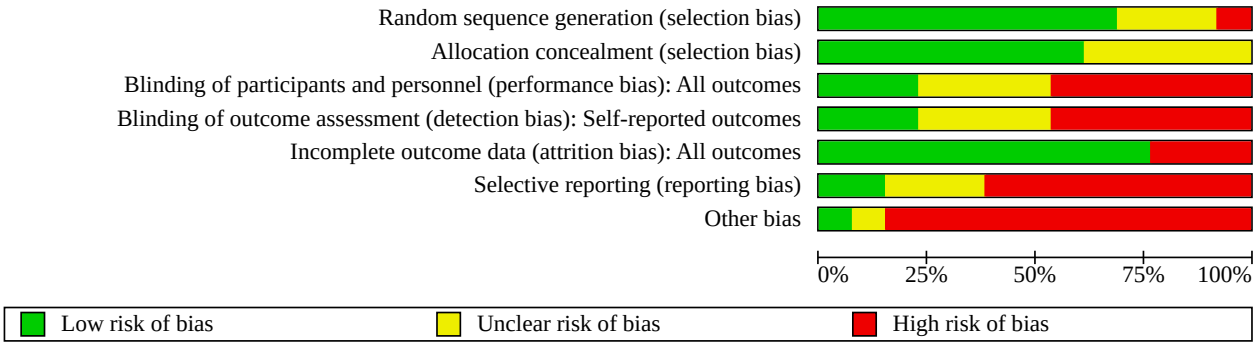


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

We rated eight studies as having a low risk of selection bias, with appropriate methods described for both the generation and concealment of the allocation sequence (Al-Kaisy 2018; Eldabe 2020; Hara 2022; Kumar 2007; Kapural 2022; Perruchoud 2013; Rigoard 2019; Schu 2014).

In one study (Eisenberg 2015), we considered generation of the randomisation sequence as low risk. However, authors provided no details on this sequence being kept offsite or otherwise blinded to the research team. As such, we considered this study as having an unclear risk of bias for allocation concealment.

We rated three studies as having an unclear risk of sequence generation (De Ridder 2013; Sokal 2020; Wolter 2012). The De Ridder 2013 and Wolter 2012 studies stated that participants were randomly assigned to groups, but provided no detail on the randomisation process. The Sokal 2020 study described how notes were drawn for group allocation by an independent examiner, but it was unclear whether this was a random process. We also rated Sokal 2020 as having an unclear risk of bias for allocation concealment because it did not provide details about whether the independent person was blinded to the sequence of treatment allocations. We also rated the De Ridder 2013 and Wolter 2012 studies as having an unclear risk of bias for allocation concealment because they provided no details on the method. We judged the remaining study as having a high risk of selection bias due to its very small sample and highly enriched design (only participants responding to high-frequency SCS were included) (Sweet 2016).

Blinding

We judged three studies to be at low risk of performance and detection bias (Al-Kaisy 2018; Hara 2022; Perruchoud 2013). All three studies described clear methods to ensure blinding to group allocation, and the investigators documented patient responses to show blinding was successful.

We considered all three parallel-group studies to have a high risk of performance and detection bias due to the inability to blind participants or investigators to group allocation (Kumar 2007; Kapural 2022; Rigoard 2019). The process of implanting and managing the SCS meant that group allocation could not be concealed.

Of the other seven cross-over trials, we rated four as having an unclear risk of performance and detection bias (Eldabe 2020; Schu 2014; Sweet 2016; Wolter 2012), and three as high risk (De Ridder 2013; Eisenberg 2015; Sokal 2020). In the studies rated as unclear risk, efforts were made to ensure blinding to treatment allocation by programming stimulation to sub-sensory amplitude, but no detail was provided to confirm participants were not able to distinguish between trial arms to confirm these efforts were successful. Conversely, in the studies we rated as having a high risk of bias, participants were reported to experience paraesthesia during at least one of the active stimulation trial arms, allowing identification of stimulation phases. As a result, participants would be able to identify receipt of active treatment during this phase of the trial.

Incomplete outcome data

We judged ten studies to have a low risk of attrition bias (De Ridder 2013; Eisenberg 2015; Eldabe 2020; Hara 2022; Kumar 2007; Perruchoud 2013; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012). In six very small studies with immediate-term follow-up, all randomised participants completed all aspects of the trial and were included in the analysis (De Ridder 2013; Eisenberg 2015; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012). In the PROCESS trial (Kumar 2007), 88% of participants recruited were available for the 12-month analysis and 87% of participants were available for the 24-month analysis. Furthermore, the rate of attrition was comparable between groups. Eldabe 2020 lost three participants from an initial sample of 19 (16%), all of whom were reported as withdrawing from the study after different treatment exposures. Similarly, Perruchoud 2013 reported the loss of five participants from 38 randomised (13%), which was attributed to SCS lead breakage, battery exhaustion during the second treatment phase, pulse generator flipping, and the withdrawal of consent after randomisation.

We judged the remaining three trials to have a high risk of attrition bias (Al-Kaisy 2018; Kapural 2022; Rigoard 2019). In Al-Kaisy 2018, only 24 (80%) of the 30 participants randomised contributed to the analysis. Reasons for exclusion were given as early discontinuations, deviations associated with randomisation and programming affecting the ability to evaluate participant data, and lack of device use. However, there was insufficient detail to consider this study as having a low risk of bias in this domain.

We judged the PROMISE trial as high risk due to a marked difference in attrition between groups and limited justification provided for participant exclusion (Rigoard 2019). At the six-month analysis, only one participant had discontinued in the study from the 'no intervention' group but 13 had discontinued from the SCS group. Furthermore, over the duration of the study, 21 participants (12 from the 'no intervention' group, 9 from the SCS group) were reported as being discontinued due to "withdrawal by the investigator", with no further information provided to justify this exclusion.

At the six-month assessment of the SENZA trial (Kapural 2022), one participant from the medical management group had been lost since randomisation but 17 had been lost from the SCS group. Although six of these participants were excluded due to an unsuccessful SCS trial, the other 11 were lost due to a mix of having withdrawn consent (n = 4), adverse events (n = 2), physician decision (n = 3), or were just reported as "lost to follow up" (n = 2). The lack of explanation of physician decisions to withdraw participants and the loss to follow-up meant that we considered this trial as having a high risk of attrition bias.

Selective reporting

We considered only two studies to have a low risk of selective reporting bias (De Ridder 2013; Hara 2022). Of the remaining 11 studies, we rated three as having an unclear risk of selective reporting (Al-Kaisy 2018; Kapural 2022; Rigoard 2019). In two studies (Al-Kaisy 2018; Rigoard 2019), the trial registration did not fully match the information provided in the study report. In Al-Kaisy 2018, the published report included outcomes (e.g. leg pain, adverse events) which had not been described in the trial registry. Conversely, in the Rigoard 2019 parallel-group study, data on several outcomes were presented 'as treated' only, despite some participants switching from the group to which they were originally randomised after the six-month follow-up assessment. We also rated the SENZA trial as having an unclear risk of bias because it presented data only for the 'as treated' group (Kapural 2022).

We judged eight studies in total as having a high risk of reporting bias due to: not providing any details about trial registration (Eisenberg 2015; Eldabe 2020; Perruchoud 2013; Schu 2014; Wolter 2012); discrepancies between the trial registration and the study report (Sokal 2020); a lack of clarity in data provided (Perruchoud 2013); or retrospective publication of the trial protocol or registry (Kumar 2007; Sweet 2016). In Sokal 2020, the trial registry described use of the EuroQol group - 5 Dimensions (EQ-5D) for the assessment of quality of life; however, these data were not presented in the study report. For the Perruchoud 2013 study, in addition to providing no information on study registration, the authors also reported medication use and side-effects as part of the study outcomes but provided no timings for these findings. We considered retrospective publication of the protocol of the PROCESS trial as representing a high risk of reporting bias: the study reported recruitment was completed in 2003 but the protocol was not published until 2005 (Kumar 2007).

Other potential sources of bias

We judged 12 of the 13 trials to be at high risk of 'other' sources of bias. Eight studies using a cross-over design did not describe the methods they used to account for the carryover and period effects between the treatment phases of the study (De Ridder 2013; Eisenberg 2015; Eldabe 2020; Perruchoud 2013; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012). Hara 2022 reported accounting for carryover effects in their analysis and period effects in their study design (they implemented long (three month) intervention periods), but it was unclear if they formally tested for period effects. Thus, we rated this study as having an unclear risk of bias on this item. The only study that clearly reported accounting for both carryover and period effects in their design and analysis was the SCS-Frequency trial (Al-Kaisy 2018), which we assessed as having a low risk for other sources of bias. They collected outcome measures over the last three days of the final week from each of the three-week cross-over assignments to minimise the cross-over effects from the previous phases, accounted for the paired nature of their data, and adjusted their analysis for multiple comparisons.

In the parallel-group trials (Kumar 2007; Kapural 2022; Rigoard 2019), we considered the lack of placebo control to be an important source of bias, leading to a judgement of high risk of bias. Additionally, in all three trials, participants were given the option to switch between SCS and medical management after six months, which would bias any effects observed beyond six months.

Effects of interventions

See: **Summary of findings 1** Spinal cord stimulation versus placebo for low back pain in adults

See Summary of findings 1 for the main comparison of SCS versus placebo.

Comparison 1: SCS versus placebo

No trials assessed SCS versus placebo at long-term follow-up. Only the Hara 2022 study assessed the benefits of SCS versus placebo using a treatment period of longer than three weeks. We judged eight of the 10 placebo-controlled trials to be sufficiently similar to warrant pooling of data in a meta-analysis of immediate-term outcomes (Al-Kaisy 2018; De Ridder 2013; Eldabe 2020; Perruchoud 2013; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012). The one trial which we excluded from that meta-analysis of immediate-term outcomes – Eisenberg 2015, with 18 participants – measured outcomes on the same day of the experiment, a substantially shorter gap than the other studies. The longest duration of treatment in any placebo-controlled trial of SCS for low back pain was six months (i.e. medium-term follow-up) (Hara 2022).

Benefits

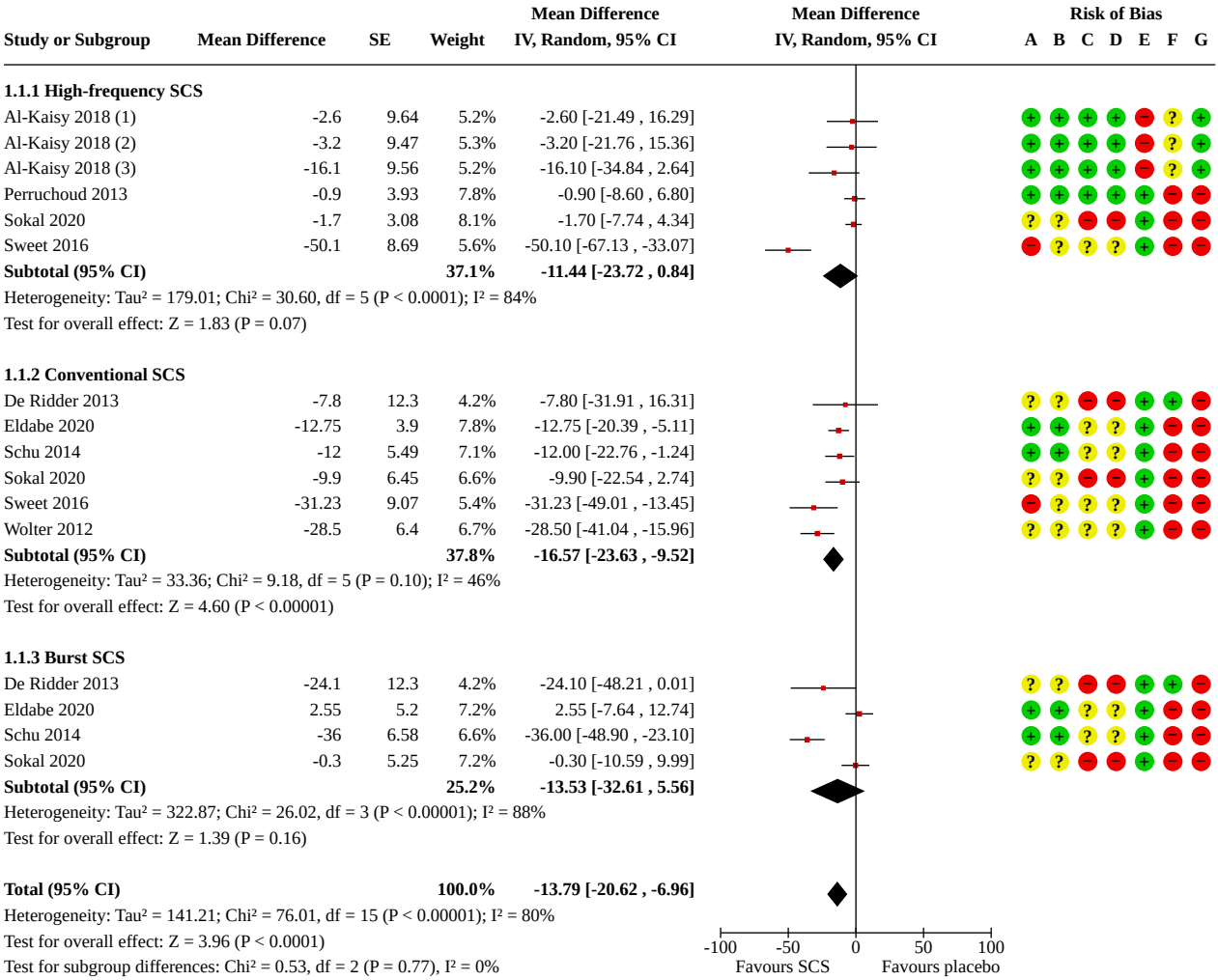
Pain intensity

Low back pain at immediate-term follow-up

Based on data from eight trials (Al-Kaisy 2018; De Ridder 2013; Eldabe 2020; Perruchoud 2013; Schu 2014; Sokal 2020; Sweet 2016; Wolter 2012), it is uncertain whether SCS improves low back pain intensity compared with placebo at immediate-term follow-up, because the certainty of the evidence was very low. At one month follow-up, mean back pain (0 to 100; higher is worse) was 13.8 points better with SCS compared to placebo (95% CI 20.6 points better to 7.0 points better; I^2 = 80%; 8 studies, 139 participants; very low-certainty evidence; Analysis 1.1; Figure 4). Our sensitivity analysis found this effect was robust to removal of trials that were at high or unclear risk of selection bias (De Ridder 2013; Sokal 2020; Sweet 2016; Wolter 2012) (MD 10.0 points better, 95% CI 18.4 points better to 1.6 points better; I^2 =76%; 4 studies, 96 participants), but not to removal of trials that were at high or unclear risk of detection

bias (i.e. all but Al-Kaisy 2018 and Perruchoud 2013). In trials at low risk of detection bias, there was no benefit with SCS in the immediate term (MD 3.00 points better, 95% CI 9.3 points better to 3.2 points worse; I^2 =0%; 2 studies, 62 participants).

Figure 4. Comparison 1: spinal cord stimulation versus placebo. Outcome 1.1: low back pain intensity (0-100) at immediate-term follow-up (< 1 month)



Footnotes

(1) 3030 Hz
(2) 1200 Hz
(3) 5882 Hz

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

It is uncertain whether different types of SCS differed in efficacy. At one month, mean back pain was 11.4 points better with high-frequency SCS (95% CI 23.7 points better to 0.8 points worse; I^2 = 84%; 4 studies, 79 participants; very low-certainty evidence; Analysis 1.1.1) compared with placebo. Conventional SCS may slightly improve low back pain intensity in the immediate term compared with placebo. At one month, mean back pain was 16.5 points better with conventional SCS (95% CI 23.6 points better to 9.5 points better; I^2 = 46%; 6 studies, 82 participants; low-certainty evidence; Analysis 1.1.2) compared with placebo. It is

uncertain whether burst SCS improves low back pain intensity in the immediate term compared with placebo because the certainty of the evidence was very low. At one month, mean back pain was 13.5 points better with burst SCS (95% CI 32.6 points better to 5.6 points worse; I^2 = 88%; 4 studies, 72 participants; very low-certainty evidence; Analysis 1.1.3) compared with placebo.

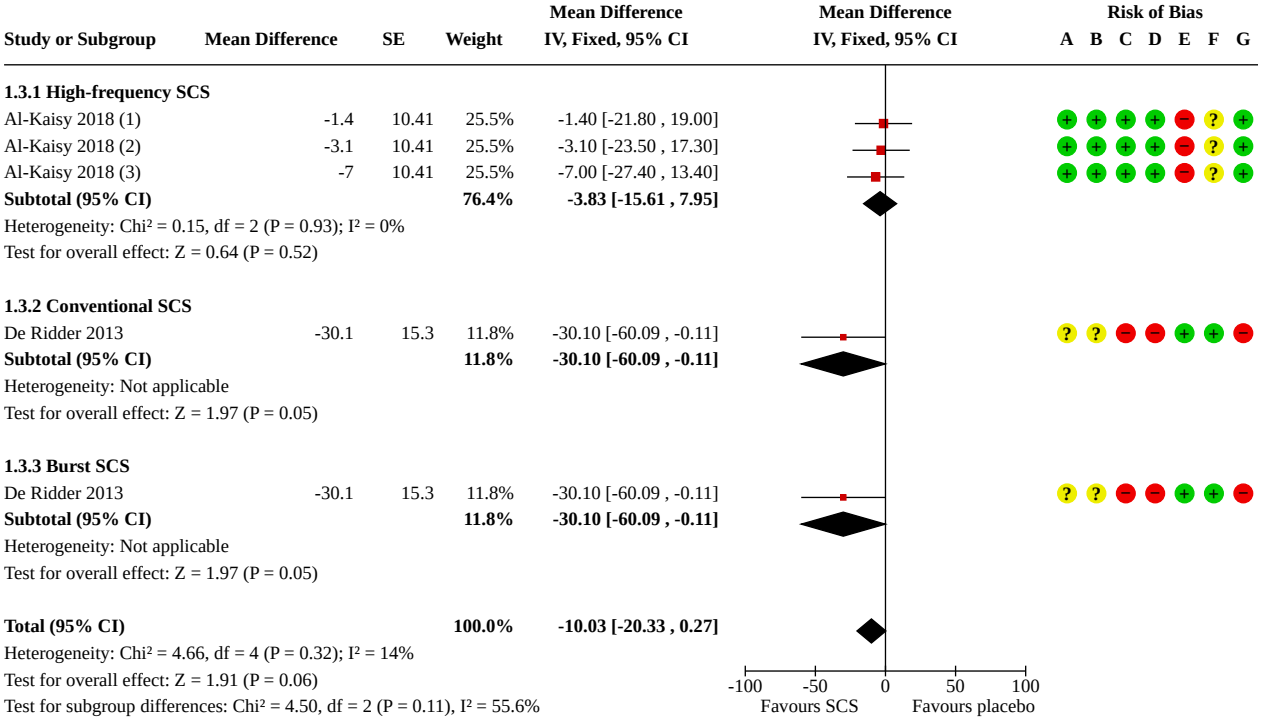
Low back pain at medium-term follow-up

At six months, one trial provided moderate-certainty evidence that SCS was probably not superior to placebo in reducing low back pain intensity (MD 4.00 points better, 95% CI 8.9 points better to 0.19 points worse; Analysis 1.2) (Hara 2022).

Leg pain at immediate-term follow-up

Two trials assessed benefits on leg pain intensity in the immediate term (Al-Kaisy 2018; De Ridder 2013). It is uncertain whether SCS improves leg pain intensity in the immediate term compared with placebo. At one month, mean leg pain (0 to 100; higher is worse) was 10.0 points better with SCS (95% CI 20.3 points better to 0.3 points worse; I^2 = 14%; 2 studies, 39 participants; very low-certainty evidence; Analysis 1.3; Figure 5) compared with placebo. Our sensitivity analysis found this effect was not robust to removal of one study at unclear risk of selection bias and high risk of detection bias (De Ridder 2013). After omitting De Ridder 2013, the estimated effect on leg pain intensity in the immediate term approached zero (MD 3.8 points better, 95% CI 15.6 points better to 8.0 points worse; Analysis 1.3.1).

Figure 5. Comparison 1: spinal cord stimulation versus placebo. Outcome 1.3: leg pain intensity (0-100) at immediate-term follow-up (< 1 month)



Footnotes

(1) 1200 Hz
(2) 3030 Hz
(3) 5882 Hz

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
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(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Leg pain at medium-term follow-up

One trial assessed this outcome in the medium term (Hara 2022). At six months, one trial provided moderate-certainty evidence that SCS was probably not superior to placebo in reducing leg pain intensity (MD 2 points better, 95% CI 6.47 points better to 2.47 points worse; Analysis 1.4).

Function

Two placebo-controlled trials reported on mean function (0 to 100; higher is better) in a way we could use in our analysis (Schu 2014; Hara 2022). It is uncertain whether SCS improves function compared with placebo in the immediate term, because the certainty of the evidence was very low. At one month, mean function was 15.1 points better with SCS compared with placebo (95% CI 4.5 points better to 25.7 points better; 1 study, 20 participants; very low-certainty evidence; Analysis 1.5). Sweet 2016 provided function scores from the SF-36 questionnaire in their trial of four participants, but we were unable to pool these results with other studies because they did not account for the paired nature of the data. In that study, there was no statistically significant effect of SCS compared to placebo on function at immediate-term follow-up. At six months, one trial provided moderate-certainty evidence that SCS was probably not superior to placebo in improving function (Analysis 1.6) (Hara 2022).

Health-related quality of life

Two placebo-controlled trials, both at high risk of bias for selective reporting and 'other' bias, measured health-related quality of life in the immediate term (Eldabe 2020; Perruchoud 2013). It is uncertain whether SCS improves health-related quality of life compared with placebo, because the certainty of the evidence was very low. Both studies measuring health-related quality of life suggested no benefit, though we were unable to pool the results of those studies. Perruchoud 2013 estimated there was no effect of high-frequency SCS compared with placebo on health-related quality of life in the immediate term, measured using the EQ-5D (index scored from 0 to 1, 1 indicates full health; mean difference, adjusted for period effects, was 0.02; 95% CI −0.10 to 0.13; Analysis 1.7). At immediate-term follow-up, Eldabe 2020 reported the median EQ-5D index scores to be 0.656 for placebo (interquartile range (IQR) 0.516 to 0.691), 0.620 for conventional SCS (IQR 0.516 to 0.691) and 0.516 for burst SCS (IQR 0.002 to 0.705). Sweet 2016 evaluated SF-36 (role emotional) and found no statistically significant effect of SCS compared to placebo at immediate-term follow-up. At six months, one trial provided moderate-certainty evidence that SCS was probably not superior to placebo in improving health-related quality of life (MD 0.04, 95% CI -0.08 to 0.16; Analysis 1.8) (Hara 2022).

Global assessment of efficacy (≥ 50% better)

None of the placebo-controlled trials reported on this measure of global assessment.

Harms

Withdrawals due to adverse events

Only one placebo-controlled trial reported on withdrawals due to adverse events, by stimulation condition, at any time point (Eldabe 2020). It is uncertain whether SCS increases withdrawals due to adverse events compared with placebo at any time point, because the certainty of the evidence was very low. In their cross-over trial of 19 participants, Eldabe 2020 reported two withdrawals during the placebo SCS phase, one withdrawal during the conventional SCS phase, and zero withdrawals during the burst SCS phase.

Adverse events

None of the placebo-controlled trials clearly reported on the number of participants with any adverse event in each study arm. The certainty of the evidence for adverse events with SCS versus placebo at six weeks was very low (one trial, 19 participants) (Eldabe 2020). Eldabe 2020 provided a count of total adverse events associated with conventional SCS, burst SCS, and sham SCS. There were 15 adverse events during the two-week conventional SCS period; 11 adverse events during the two-week burst SCS period, and 12 adverse events during the two-week sham SCS period. The most common adverse event was increased pain: 35% had increased pain with conventional SCS, 24% with burst SCS and 24% with sham SCS. Hara 2022 reported on adverse events after 12 months of placebo and burst SCS and found nine of 50 participants (18%) experienced adverse events, including infection.

Serious adverse events

None of the placebo-controlled trials reported on serious adverse events by stimulation condition. Hara 2022 found four participants (8%) required surgical revision over 12 months. Two other studies, where participants received a new SCS implant, reported on the number of people requiring surgical revision in the short term. Al-Kaisy 2018 found one of 24 participants (4.1%) required surgical revision at 12 weeks and Sokal 2020 found one of 18 participants (5.5%) required surgical revision at eight weeks. Serious adverse events included unintentional durotomy during lead placement, revision of leads, infection requiring surgery, infection requiring antibiotics, pulse generator replacement, and micturition problems.

Minor outcomes

None of the placebo-controlled trials reported on medication use, health care use, or work status.

Comparison 2: SCS plus medical management versus medical management alone

Benefits

Pain intensity

No trials of SCS plus medical management versus medical management alone reported on mean low back pain intensity in both groups at long-term follow-up.

Low back pain at short-term follow-up

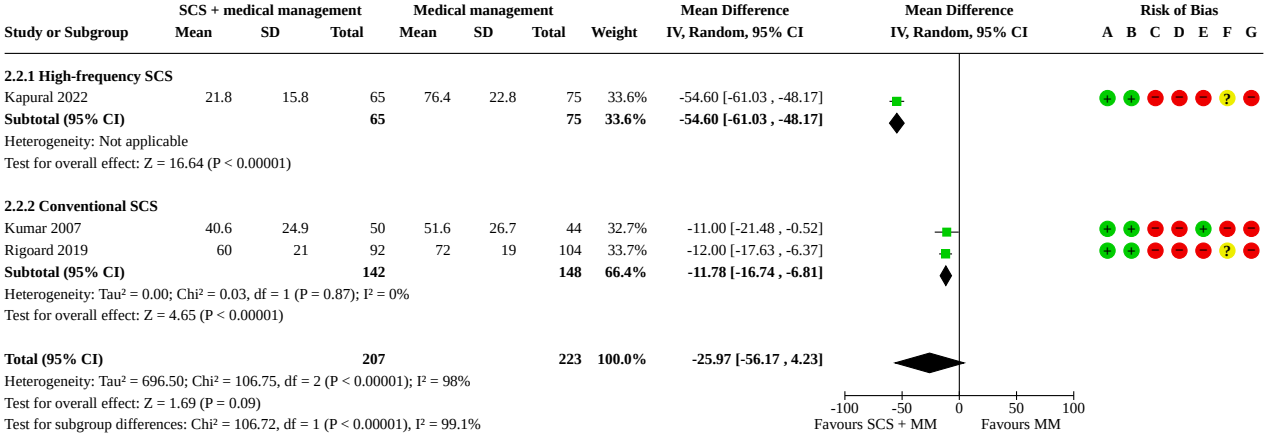
At short-term follow-up, one trial found the addition of SCS to medical management may slightly improve back pain intensity (Kumar 2007). At three months, mean back pain was 8.7 points better with the addition of SCS (95% CI 19.0 points better to 1.6 points worse; 1 study, 98 participants; low-certainty evidence; Analysis 2.1).

Low back pain at medium-term follow-up

Three trials reported on mean low back pain intensity at medium-term follow-up (≥ 3 months to < 12 months) (Kapural 2022; Kumar 2007; Rigoard 2019). It is uncertain whether the addition of SCS to medical management reduces back pain intensity, because the certainty of the evidence was very low. In the medium term, mean pain was 26.0 points better with the addition of SCS, though the estimate was uncertain (95% CI 56.2 points better to 4.2 points worse; I^2 = 98%; 3 studies, 430 participants; very low-certainty evidence; Analysis 2.2; Figure 6). One trial, which added high-frequency SCS to medical management, reported a very large effect size (Kapural 2022), which explained most of the heterogeneity.

When we excluded this trial from the analysis, the estimated benefit with SCS at medium-term follow-up was 11.8 points on a 100-point scale (95% CI 16.7 points better to 6.8 points better; I^2 = 0%; 2 studies, 290 participants; Analysis 2.2.2)

Figure 6. Comparison 2: spinal cord stimulation plus medical management versus medical management alone. Outcome 2.2: low back pain intensity at medium-term follow-up (≥ 3 months to < 12 months)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

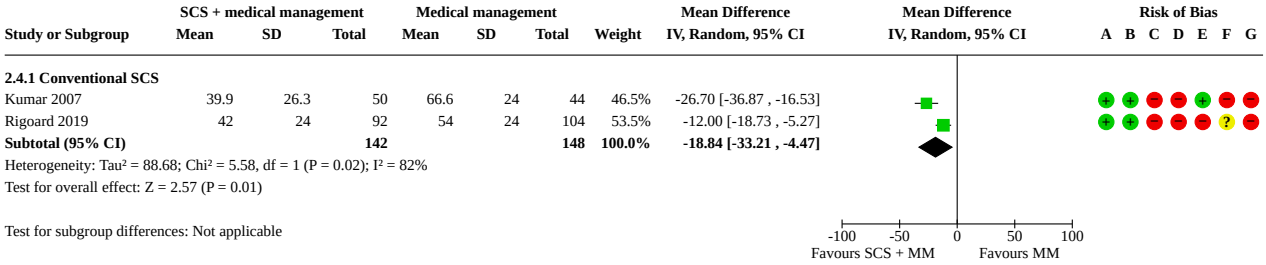
Leg pain at short-term follow-up

One trial reported on benefits for leg pain intensity in the short term (Kumar 2007). The addition of SCS to medical management may improve leg pain intensity in the short term. At three months, mean leg pain intensity was 32.3 points better with the addition of conventional SCS (95% CI 42.3 points better to 22.3 points better; 1 study, 98 participants; low-certainty evidence; Analysis 2.3).

Leg pain at medium-term follow-up

Two trials reported on benefits for leg pain intensity in the medium term (Kumar 2007; Rigoard 2019). It is uncertain whether adding SCS to medical management improves leg pain intensity in the medium term, because the certainty of the evidence was very low. In the medium term, mean leg pain intensity was 18.8 points better with the addition of SCS (95% CI 33.2 points better to 4.5 points better; I^2 = 82%; 2 studies, 290 participants; very low-certainty evidence; Analysis 2.4; Figure 7).

Figure 7. Comparison 2: spinal cord stimulation plus medical management versus medical management alone. Outcome 2.4: leg pain intensity at medium-term follow-up (≥ 3 months to < 12 months)



Risk of bias legend
(A) Random sequence generation (selection bias)
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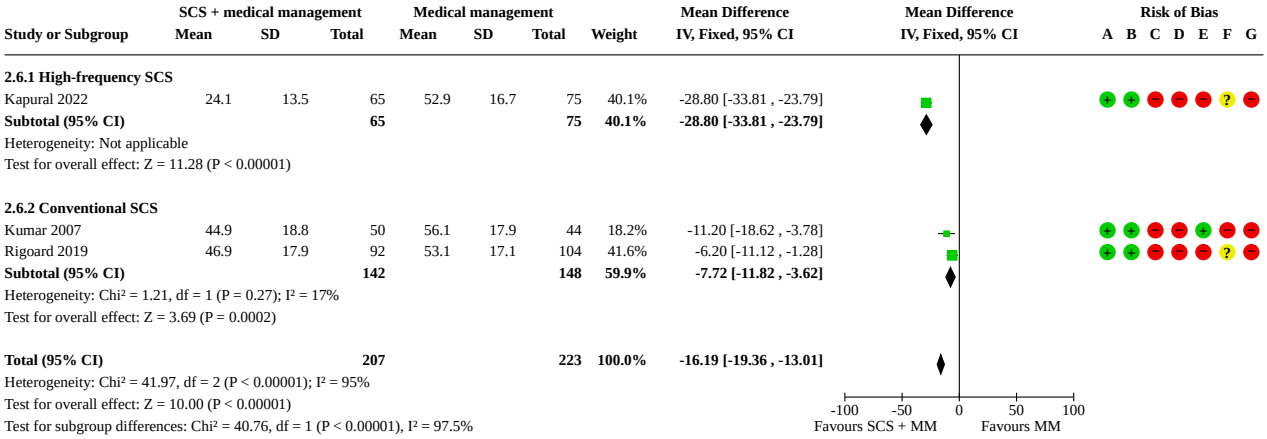
(F) Selective reporting (reporting bias)
(G) Other bias

Function

No trials of SCS plus medical management versus medical management alone reported on function in both groups at long-term follow-up.

Three trials reported on mean function at medium-term follow-up, and one trial at short-term follow-up. Adding SCS to medical management may slightly improve function in the short term. At three months, mean function, measured on a 100-point scale, was 12.6 points better with the addition of SCS (95% CI 20.1 points better to 5.2 points better; 1 study, 94 participants; low-certainty evidence; Analysis 2.5). In the medium term, mean function was 16.2 points better with the addition of SCS (95% CI 19.4 points better to 13.0 points better; I^2 = 95%; 3 studies, 430 participants; low-certainty evidence; Analysis 2.6; Figure 8). As with the pain outcomes, most of the heterogeneity was due to one trial reporting a large effect size (Kapural 2022). When we excluded this trial from the analysis, the estimated benefit of SCS on function in the medium term was 7.7 points on a 100-point scale (95% CI 11.8 points better to 3.6 points better; I^2 = 15%; 2 studies, 290 participants; Analysis 2.6.2).

Figure 8. Comparison 2: spinal cord stimulation plus medical management versus medical management alone. Outcome 2.6: function at medium-term follow-up (≥ 3 months to < 12 months)



Risk of bias legend
(A) Random sequence generation (selection bias)
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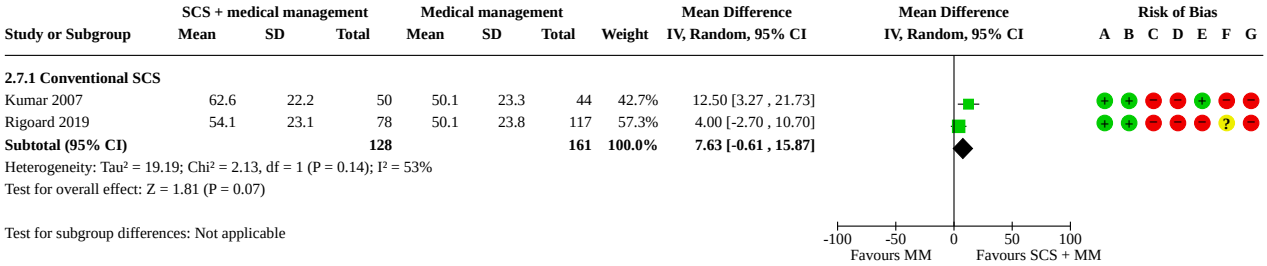
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Health-related quality of life

No trials of SCS plus medical management versus medical management alone reported on health-related quality of life in both groups at long-term follow-up.

Two trials of conventional SCS reported on health-related quality of life at medium-term follow-up. It is uncertain whether adding SCS to medical management improves health-related quality of life in the medium term, because the certainty of the evidence was very low. In the medium term, mean health-related quality of life, measured on a 100-point scale, was 7.6 points better with SCS (95% CI 15.8 points better to 0.6 points worse; I^2 = 53%; 2 studies, 289 participants; very low-certainty evidence; Analysis 2.7; Figure 9).

Figure 9. Comparison 2: spinal cord stimulation plus medical management versus medical management alone. Outcome 2.7: health-related quality of life at medium-term follow-up (≥ 3 months to < 12 months)



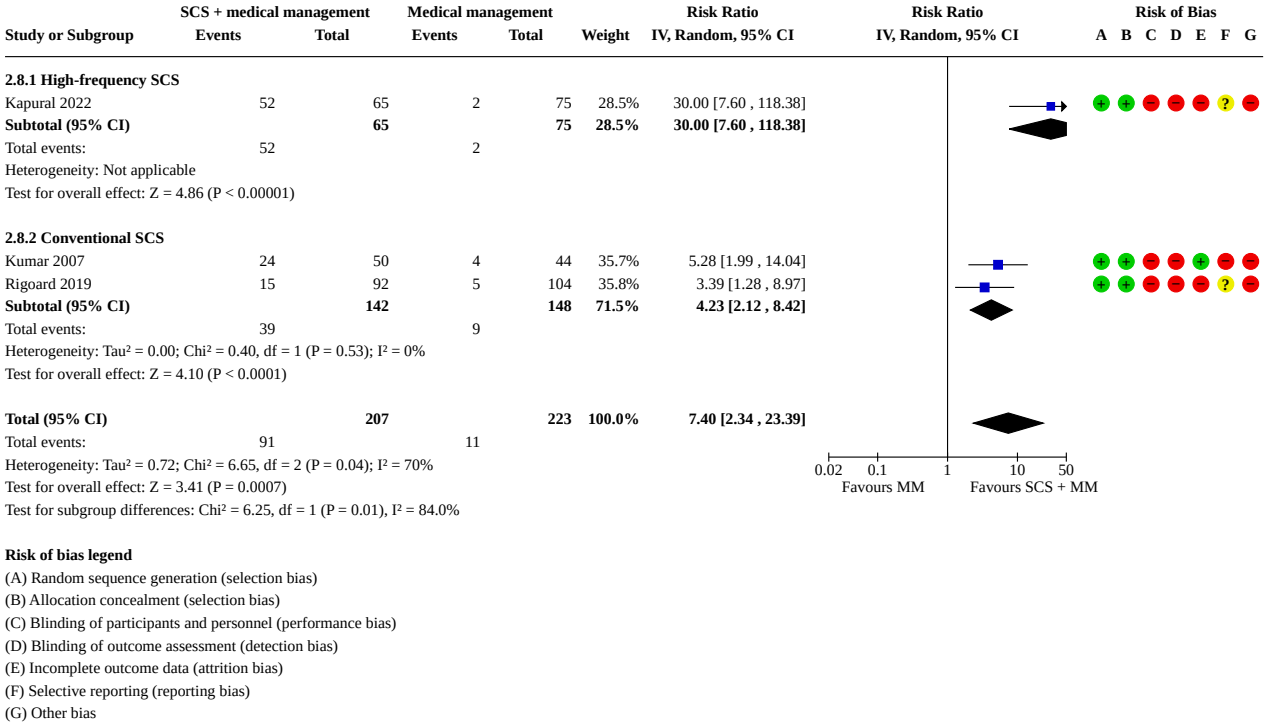
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Global assessment of efficacy (≥ 50% better)

One trial of SCS plus medical management versus medical management alone reported on global assessment of efficacy (≥ 50% improvement) in both groups at long-term follow-up (Kumar 2007). At their 24-month follow-up, Kumar 2007 estimated that 17 of 52 participants in the SCS group achieved 50% or better improvement compared with eight of 48 participants in the medical management group (risk ratio (RR) 1.96, 95% CI 0.93 to 4.12; very low-certainty evidence; Analysis 2.9).

Three trials of SCS plus medical management versus medical management alone reported on the number of participants who perceived a 50% or better improvement in pain at medium-term follow-up. It is uncertain whether the addition of SCS increases the number of people reporting a 50% or better improvement in the medium term, because the certainty of the evidence was very low. In the medium term, participants receiving SCS were 7.4 times as likely to report a 50% or better improvement in pain with SCS compared with participants in the control group (95% CI 23.4 times more likely to 2.3 times more likely; I^2 = 70%; 3 studies, 430 participants; very low-certainty evidence; Analysis 2.8; Figure 10). Most of the heterogeneity could be explained by one trial reporting a very large effect size (Kapural 2022). When we excluded this trial from the analysis, the estimated risk ratio for having a 50% or better improvement in the medium term was 4.2 (95% CI 2.1 times more likely to report being a 50% or better improvement to 8.4 times more likely; I^2 = 0%; 2 studies, 290 participants; Analysis 2.8.2).

Figure 10. Comparison 2: spinal cord stimulation plus medical management versus medical management alone. Outcome 2.8: global assessment of efficacy at medium-term follow-up (≥ 3 months to < 12 months)



Risk of bias legend
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(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Harms

Withdrawals due to adverse events

One trial reported on withdrawals due to adverse events (Kapural 2022). It is uncertain whether the addition of SCS increases the risk of withdrawals due to adverse events, because the certainty of the evidence was very low. In the medium term, two of 83 participants allocated to high-frequency SCS withdrew due to adverse events compared with zero of 76 participants in the control group.

Adverse events

Two trials which added SCS to medical management reported on the proportion of participants who experienced at least one adverse event in each group (Kapural 2022; Rigoard 2019). It is uncertain whether the addition of SCS increases the risk of experiencing an adverse event because the certainty of the evidence was very low. In the medium term, 65 of 157 (41.4%) participants randomised to SCS plus medical management experienced an adverse event compared with 49 of 179 (27.4%) participants randomised to medical management alone (RR 2.32, 95% CI 0.39 to 13.79; I^2 = 90%; 2 studies, 336 participants; very low-certainty evidence; Analysis 2.11).

Kumar 2007 reported on adverse events at 12 and 24 months but did not include the proportion of participants who experienced at least one adverse event in each group. Adverse events in those receiving SCS at 12 months included: lead migration (eight of 84 participants, 10%), lead/extension fracture/torqued contacts (two of 84 participants, 2%); IPG migration (one of 84 participants, 1%); loss of therapeutic effect/unpleasant paraesthesia (six of 84 participants, 7%); technique-related events such as incorrectly implanted electrode causing shocks and dural tears (four of 84 participants, 5%); infections (seven of 84 participants, 8%); pain at IPG/incision site (five of 84 participants, 6%); neurostimulator pocket fluid collection (four of 84 participants, 5%).

Serious adverse events

One trial reported on serious adverse events in both treatment arms (Kapural 2022). It is uncertain whether SCS increases the risk of serious adverse events compared with no SCS, because the certainty of the evidence was very low. In the medium term, six of 65 participants in a high-frequency SCS group who were followed up experienced a serious adverse event compared with four of 75 in the control group (RR 1.73, 95% CI 0.51 to 5.87; one study, 140 participants; I^2 = 0%; Analysis 2.12). Serious adverse events in the SCS arm included: osteomyelitis, severe lethargy, surgical revision/explant due to infection, and surgical revision/explant due to delayed wound healing. It was unclear how many participants receiving SCS required surgical revision due to device issues or adverse events.

Kumar 2007 reported on the number of participants requiring surgery due to an adverse event in those who received SCS at 12 months, but did not include proportions in each group that would allow estimation of risk. At 12 months, 20 of the 84 participants receiving SCS (24%) experienced a serious adverse event that required surgery to resolve. Of the 42 participants receiving SCS who were followed up at 24 months, 19 (45%) had experienced a total of 34 adverse events, and 13 (31%) had required surgical revision.

Rigoard 2019 found that of the 102 participants receiving SCS who were followed up at six months, 12 (12%) had required surgical revision.

Minor outcomes

Three trials of SCS plus medical management versus medical management alone reported on medication use at medium-term follow-up (Kapural 2022; Kumar 2007; Rigoard 2019). The addition of SCS to medical management may slightly reduce the proportion of participants taking opioid medicines in the medium term. At medium-term follow-up, the number of participants taking opioid medicines was 15% lower with SCS compared with no SCS (95% CI 27% lower to 0% lower; I^2 = 0%; 2 studies, 290 participants; low-certainty evidence; Analysis 2.13). The addition of SCS to medical management may slightly reduce daily morphine equivalents (MME) in the medium term. In the medium term, daily MMEs were 9.4 points lower with SCS compared with no SCS (95% CI 19.9 points lower to 1.2 points higher; I^2 = 0%; 3 studies, 430 participants; low-certainty evidence; Analysis 2.14).

One trial reported on the number returning to work (Kumar 2007). The addition of SCS to medical management may slightly increase the number of people returning to work. In the medium term, four of 52 participants in the SCS group had returned to work at medium-term follow-up compared with one of 48 participants in the control group (RR 3.7, 95% CI 0.4 to 31.9; 1 study, 100 participants; low-certainty evidence; Analysis 2.15).

None of the trials clearly reported on health care use in the study groups.

DISCUSSION

Summary of main results

SCS versus placebo

There is no evidence on the benefits or harms of SCS compared with placebo in the long term. Most trials have only assessed low back pain outcomes in the immediate term (8 trials, 139 participants). Based on these trials, it is uncertain whether SCS reduces back pain intensity compared with placebo because the certainty of the evidence is very low. Only one trial investigated the efficacy of SCS beyond three weeks of treatment. There is moderate-certainty evidence that, at six months, SCS is not superior to placebo for pain, function, and health-related quality of life outcomes.

Due to poor reporting in the included studies, we are uncertain to what extent SCS increases the risk of harms compared with placebo.

The uncertainty of the evidence was mostly due to study limitations, very small studies with imprecise estimates of effect, and inconsistency in the effects reported. None of the studies we located had a low risk of bias across all domains. It is also uncertain whether different types of SCS (i.e. burst, high-frequency or conventional) differ in efficacy. An exploratory subgroup analysis of trials comparing high-frequency SCS to placebo in the immediate term suggested no benefit. Analysis 1.1 included one study of four participants reporting a very large effect size (Sweet 2016), as well as the only two studies we considered to have achieved adequate blinding (Al-Kaisy 2018; Perruchoud 2013). When we removed Sweet 2016 from that analysis, the I^2 statistic dropped from 91% to 0% and the 95% confidence interval suggested no clinical benefit of high-frequency SCS compared with placebo at less than one month of follow-up.

SCS plus medical management versus medical management alone

We are uncertain whether the addition of SCS to medical management is beneficial for back pain intensity in the medium term because the certainty of the evidence was very low. Similarly, we are uncertain whether adding SCS to medical management improves function, leg pain intensity, global assessment of improvement, health-related quality of life, return to work, or opioid medicine use, because the certainty of the evidence was very low.

Due to poor reporting in the included studies, we are uncertain to what extent adding SCS to medical management increases the risk of harms. The proportion of people receiving an SCS implant who were followed for up to two years and required surgical revision due to adverse events ranged from 11.7% to 30.9%.

Although the three parallel-group trials that added SCS to medical management appeared to show clinical benefits for some outcomes, one study had results that differed widely from the other studies. When we excluded this study from analysis, the I^2 statistic reduced to 0% and effect sizes were more modest (e.g. for low back pain intensity in the medium term, the effect was 12 points on a 100-point scale, based on the two published trials). The two trials contributing to this estimate had critical study limitations. These included lack of blinding, attrition bias, and an enrichment-type design where, after randomisation, the trialists excluded participants who did not respond to SCS, but did not take the same approach to those who did not respond in the control arm. This design feature essentially disrupts the benefits of randomisation, and the 12-point benefit for pain in the medium term may therefore be an overestimate. Another challenge to the interpretation of these trials is the reporting of the medical management provided to both groups. From reading the trial reports, it is not possible to know precisely what medical management was provided or whether this care was consistently provided across the study groups. Any differences between the groups could be explained by differences in the medical management provided rather than the addition of SCS. We therefore suggest caution when interpreting the estimated benefits in trials of SCS compared with "conventional" or "optimal" medical management, as they were based on very low-certainty evidence.

Overall completeness and applicability of evidence

Our findings likely apply to the typical person with low back pain with or without leg pain who is being considered for a new SCS intervention or for changes to parameters of a previously implanted stimulator. Studies included participants from 12 countries and mean age ranged from 48 years to 59 years. Mean back pain intensity at baseline was above 50 points on a 100-point scale in six of 13 trials (range of mean back pain intensity at baseline: 36 points to 84 points on a 100-point scale). Duration of low back pain at baseline was on average more than six months in all six trials reporting these data (range of mean pain duration at baseline: 5.1 years to 12.3 years).

Although some studies reported that both study arms received "optimal medical management", in no studies was this controlled as part of the trial or audited to ensure it was applied equally across groups. This means that the true benefit of adding SCS to optimal

care consistent with clinical guidelines for low back pain remains unknown.

We found no evidence that newer approaches to SCS – for example, using burst or high-frequency stimulation patterns – were superior to conventional SCS interventions.

Due to the small number of studies and participants, we were unable to determine if the estimated benefits and harms of SCS differ in subgroups of people with low back pain (e.g. people classified as having 'refractory neuropathic pain' or 'failed back surgery syndrome').

Certainty of the evidence

SCS versus placebo

We located no evidence for our primary comparison of SCS versus placebo at long-term follow-up.

For immediate-term pain and function outcomes, the evidence was of very low certainty. We downgraded the evidence due to risk of bias (primarily from insufficient blinding, and potential for period and cross-over effects), imprecision, inconsistency, and indirectness (eight out of ten studies did not assess medium- or long-term efficacy). Given the small size of the effects observed in trials that we judged to be at high risk of bias, we consider it unlikely that future trials with a low risk of bias will show larger effects. Indeed, the only trial we rated as having an overall low risk of bias suggested no benefit of SCS. Hara 2022 provided moderate-certainty evidence for medium-term pain and function outcomes. We downgraded the evidence for medium-term outcomes due to potential indirectness (we could not be certain the results of Hara 2022 could be applied to all types of SCS).

There was too little data on health-related quality of life, global assessment of efficacy, and our minor outcomes (healthcare use, medication use, work status) to make any conclusions about benefits.

For harms in trials of SCS versus placebo, there were either no data (i.e. number of adverse events; number of serious adverse events, by treatment condition) or the certainty of the evidence was very low and based on only one very small study (i.e. withdrawals due to adverse events).

SCS plus medical management versus medical management alone

For pain and function outcomes in trials that added SCS to medical management, the certainty of the evidence ranged from low to very low. We downgraded the evidence due to bias (primarily due to lack of blinding and attrition bias), imprecision, and inconsistency.

There were sparse data on health-related quality of life, global assessment of efficacy, and our minor outcomes (healthcare use, medication use, work status) from trial that added SCS to medical management, and the certainty of the evidence ranged from low to very low.

Most of the information on the incidence of harms was from one trial at high risk of bias. We are therefore very uncertain about the risk of harms when SCS is added to medical management.

Potential biases in the review process

We conducted a comprehensive search of major databases, clinical trials registries, and consulted with experts to try to ensure we identified all relevant trials. Two review authors independently performed key steps in the review process, including: assessing trials for inclusion, extracting data, conducting risk of bias assessments, and grading the certainty of the evidence. In all cases, a third review author adjudicated if there were discrepancies in judgements.

We identified 13 ongoing studies (ACTRN12620000720910; Ahmadi 2021; Al-Kaisy 2020; ISRCTN10663814; ISRCTN33292457; NCT03419312; NCT03462147; NCT03718325; NCT03858790; NCT04479787; NCT04676022; NCT04732325; Reiter 2019). When published, the results from these trials may change the estimates from our analyses. However, given the small, inconsistent, immediate-term-only effects we observed in trials with biases that would tend to inflate effects (e.g. detection bias), we consider it unlikely that future well-designed, placebo-controlled trials will result in large, clinically important effects. Several ongoing trials are testing SCS versus medical management; it is unclear from their registry records whether these trials will overcome some of the important biases we identified in the parallel-groups trials included in this review.

Agreements and disagreements with other studies or reviews

Two recent systematic reviews (Duarte 2020; O'Connell 2021), one of which was a Cochrane Review (O'Connell 2021), have examined the effects of SCS versus placebo in people with chronic pain. Neither review estimated effects in populations with low back pain. Duarte 2020 concluded that SCS leads to reduced pain intensity when compared to placebo. However, they did not grade the certainty of evidence. Our review, along with that of O'Connell 2021, suggests that the certainty of the evidence for the efficacy of SCS in the immediate term is very low and the effect size uncertain. In the medium term, a recent high-quality trial not included in either of those reviews suggests that the true effect size of SCS over placebo is probably not clinically important (Hara 2022). Duarte 2020 did note that success of blinding probably influenced treatment effects observed in the placebo-controlled trials. We also note that trials with adequate blinding in our analysis tended to produce lower estimates for benefits on back pain.

O'Connell 2021 reported low- to very low-certainty evidence that, in people with chronic pain, SCS could provide clinically important benefits for pain intensity when added to conventional medical management or physical therapy. Our analysis of effects of adding SCS to medical management on low back pain intensity in the medium term was also based on very low-certainty evidence and had 95% confidence intervals that included both a large benefit and no benefit at all. Together the reviews suggest that we are still very uncertain about the magnitude of clinical benefits of SCS as an addition to medical management. We would also point out that the reported large effects of SCS in some isolated studies were essentially observed in comparison to no treatment, and in trials at high risk of performance, detection, attrition and other biases, including uneven application of co-interventions. We could not locate any study where trialists controlled and reported on the medical management provided to the study groups, to make it possible to estimate the benefit of adding SCS to conventional

or "optimal" non-SCS care. Therefore, the clinical benefit of adding SCS to optimal care for low back pain remains unknown.

Although we located almost no evidence on risk of adverse events with SCS versus placebo or no intervention, other studies have provided estimates of potential harms. In both ours and the O'Connell 2021 review, there was very low-certainty evidence that the incidence of adverse events (e.g. infection) and serious adverse events (e.g. re-operation) was higher with SCS than with no intervention, though the estimates were imprecise. A recent analysis of adverse events reported to the Australian Therapeutic Goods Administration found there were 520 adverse events reported between 2012 and 2019 of which 79% were "severe" and 13% were "life-threatening" (Jones 2022). Future trials should report on the incidence of adverse events and serious adverse events in all study arms and at long-term follow-up to determine the risk of harms with SCS.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence on the benefits and harms of spinal cord stimulation (SCS) compared with placebo in the long term for people with low back pain. Moderate-certainty evidence suggests there is probably no benefit of SCS over placebo on pain, function, or health-related quality of life in the medium term. Most placebo-controlled trials to date have examined immediate-term outcomes (less than one month) only, and although there appeared to be initial benefits on pain and function in some studies, the evidence was of very low certainty. Taken together, our findings suggest SCS probably has little to no sustained benefit over placebo for people with low back pain.

It is uncertain whether adding SCS to medical management improves low back pain intensity or health-related quality of life, or whether it increases the number of people reporting a 50% improvement or better, because the certainty of the evidence is very low. Low-certainty evidence suggests adding SCS to medical management may slightly improve function and slightly reduce opioid use in the medium term. Harms of SCS included infection, lead migration, and dural tear, some of which required repeat surgery. However, adverse events and serious adverse events were poorly documented and the magnitude of risk therefore remains uncertain.

The data in this review do not support the use of SCS for people with low back pain outside a randomised, placebo-controlled trial.

Implications for research

The long-term benefits and harms of SCS for people with low back pain are essentially unknown. Future trials should compare back pain outcomes with SCS versus placebo in the long term (i.e. at 12 months' follow-up or longer), in people naive to the intervention, and use robust methods to minimise risk of bias. We cannot see value in new trials comparing different SCS types or comparing SCS to uncontrolled and unreported medical management, until any efficacy over placebo has been proven. To allow better evaluation of risk for adverse events and comparison with other treatment options, future trials should clearly document the number of people in each group who experience any adverse event, a serious adverse event, or withdraw due to an adverse event. Based on the data in this review, we cannot say if a specific subset of people with low back pain benefit from SCS and others do not benefit or are harmed; this could be investigated in future high-quality trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Kaisy 2018

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Trial duration:** follow-up to 12 weeks: 4 x 3-week periods (participants followed for 12 months but outcomes not reported) **Trial aim:** evaluate the safety and efficacy of SCS using subperceptual threshold amplitude levels at four different frequencies and pulse widths settings (sham stimulation, 1200 Hz at 180 µs (microseconds), 3030 Hz at 60 µs, and 5882 Hz at 30 µs) in individuals diagnosed with FBSS who respond to conventional stimulation settings during a SCS trial **Sample size calculation:** to allow for a completely balanced design and each of the unique sequences to be used, 24 participants were needed for the study. Based on the PROCESS study, in which a mean (+/-SD) of 2.62 cm (+/-2.65, on a 0 cm to 10 cm scale) reduction in pain score was observed from baseline at four weeks of conventional SCS treatment, and with the placebo effect expected from sham stimulation, a mean pain score difference of 2 cm (on a 0 cm to 10 cm scale) between the sham and the active treatment groups was considered clinically significant. Accepting a mean difference of 2 cm, and a conservatively estimated standard deviation of 3 cm, a sample size of 24 would provide more than 85% power using an alpha = 0.05 in a two-sided test.

Al-Kaisy 2018 *(Continued)*

Analysis: "A generalized linear model of repeated measures for the four-period crossover design was used to estimate the treatment difference of stimulation delivered at different frequency/pulse width combinations for both back pain and leg pain. The final model had the average back pain score as the dependent variable, while baseline, treatment (frequency groups), and period (visits) were the independent variables. The treatment by period interaction term, carryover effect, was tested and removed from the final model as being not statistically significant. The Type 3 test was used to test the effects of stimulation delivered at the 4 frequencies. The pair-wise comparisons from the generalized linear mixed model using least square means were used to test the difference of treatment effects among the frequency groups, with the Bonferroni adjustment used for multiple comparisons. Descriptive statistics were used to summarize subjects' change of back and leg pain scores from baseline and percent reduction on pain from baseline. A paired t-test was used to compare the change in pain score from baseline. A p-value less than 0.05 was considered statistically significant."

Participants

Baseline characteristics

Overall

- Age: mean (range) = 47.9 (33 to 60), SD not reported
- Sex: n (%): M = 16 (66.7%) and F = 8 (33.3%)
- Back pain duration: mean (range) years = 5.1 (0.5 to 19.5)
- Baseline back pain score: 7 day 0-10 cm VAS. Mean (SD) = 7.75 (1.13)
- Baseline function score: mean (range) ODI = 53 (32-78)
- QoL score: not measured
- Baseline leg pain score: 7 day 0-10 cm VAS. Mean (SD) = 3.06 (2.55)
- Work status: not measured
- No. of participants: 24
- Socioeconomic status: not measured
- Pain medication use: on a stable dose of pain medications for at least four weeks prior to screening and willing to only maintain or decrease the pain medication dose during the cross-over phase of the study
- Diagnostic criteria: diagnosed with FBSS and had 0-10 cm VAS back pain scores > 6 for at least six consecutive months
- Healthcare use: not measured

Inclusion criteria: participants needed to meet all of the following inclusion criteria:

- at least 18 years old at the time of informed consent;
- willing and able to provide a signed and dated informed consent;
- capable of comprehending and consenting in English;
- willing and able to comply with all study procedures, study visits, and be available for the duration of the study;
- on a stable dose (no new, discontinued, or changes) of all prescribed pain medications for at least four weeks prior to screening and willing to maintain or only decrease the dose of all prescribed pain medications through the end of the cross-over visit;
- has tried appropriate conventional medical management for their pain;
- not indicated for additional surgical treatment (e.g. fusion for spinal instability) in the opinion of the referring physician or spinal surgeon
- has undergone previous spinal surgery;
- has been diagnosed with FBSS with VAS back pain scores ≥ 6 for at least 6 consecutive months and VAS leg pain scores, if present, lower than back pain scores;
- has primary back pain such that two 1 × 8 compact leads will be placed and the leads will not be placed above vertebral level T1 or below S2
- able to use the recharging equipment and willing to recharge up to 2 times per day

Exclusion criteria:

- an active implanted device, whether turned on or off
- current signs of a systemic infection;

Al-Kaisy 2018 *(Continued)*

- pregnant or lactating, inadequate birth control, or the possibility of pregnancy during the study;
- untreated major psychiatric comorbidity;
- serious drug-related behavioral issues (e.g. alcohol dependency, illegal substance abuse);
- neurological abnormalities unrelated to FBSS;
- diagnosed with Raynaud disease;
- diagnosed with fibromyalgia;
- any active malignancy or has been diagnosed with cancer and has not been in remission for at least one year prior to screening;
- secondary gains which, in the opinion of the investigator, are likely to interfere with the study;
- participating or planning to participate in another clinical trial;
- characteristics/limits of household or close contacts involved in study (e.g. family member already a study participant where blind could be broken);
- average VAS back pain score lower than 6 on the baseline multiday diary;
- requires an amplitude greater than 3 V in the supine position during the device trial period to achieve optimal pain relief with conventional stimulation unless the perceptual threshold (at 1000 Hz andsec) is 6 V or less (regardless of group impedance), or 9 V or less with a group impedance of 750 ohms or greater.

Pretreatment: n/a

Number of participants: 53 screened, 50 baseline, 39 device trial, 33 SCS implanted, 30 randomised, 24 end of cross-overs

Minimum pain intensity: VAS back pain scores ≥ 6 for at least 6 consecutive months and VAS leg pain scores, if present, lower than back pain scores

Source of participants: "Eligible patients were recruited and treated in a single center (Pain Management and Neuromodulation Centre, Guy's & St Thomas NHS Trust, London, United Kingdom), and written informed consent was obtained from all the study subjects"

Interventions	High-frequency spinal cord stimulation #1

- *Frequency*: 5882 Hz at 30 µs (microseconds)
- *Stimulator type*: rechargeable implanted pulse generator (IPG)
- *Lead number and type*: dual octapolar leads (Octad, Medtronic, Minneapolis, MN, USA)
- *Manufacturer*: Medtronic
- *Description*: "All subjects were implanted with dual octapolar leads. The rostral tip of the implanted epidural leads was located approximately between the vertebral body of T7 and T10 to achieve an optimal overlap between the painful area and the stimulation induced paraesthesia (60–80 Hz, 300–450 µs), using a maximum of three active contacts per subject. Trial leads were connected to a temporary external stimulator for the duration of the trial period (up to 17 days). Those subjects experiencing an average reduction in VAS back pain scores ≥50% of their baseline values in a pain diary during the last seven days of the trial period were permanently implanted with a rechargeable implanted pulse generator (RestoreSensor, Medtronic, Minneapolis, MN, USA). The AdaptiveStim feature remained off during the cross-over phase of the study. The IPG was positioned subcutaneously in the abdomen or gluteal region and connected to the implanted leads used during the device trial. After implantation, all subjects were given a four-week period of recovery without any active stimulation to allow for wound healing and to avoid any interference with the cross-over stage of the study. The implanted SCS device was activated during the first visit of the cross-over phase, using a maximum of three active contacts to achieve optimal paraesthesia coverage of the lower back. This contact configuration was then used throughout the whole cross-over phase without further modifications. Subjects received, in a randomised order, the four tested frequency/pulse width settings: sham (with the generator turned on and discharging, but without electricity transmitted to the lead), 1200 Hz @ 180 µs, 3030 Hz @ 60 µs, and 5882 Hz @ 30 µs; each combination was tested for three weeks and then reprogrammed. The higher frequencies of stimulation (up to 5882 Hz) and sham (no stimulation) settings were generated using a custom-made programmer used exclusively for clinical investigation. The amplitude was set for the sham mode in the same manner as it was for the active settings, to produce a recharge interval similar to that of the active settings in the 1200 Hz and 3030 Hz frequency groups; however, the 5882 Hz group required more recharging."

Al-Kaisy 2018 *(Continued)*

- *Burst or tonic stimulation*: not stated
- *Duration*: 12 weeks, 4 periods (? 3 weeks per study period though not specified?)
- *Co-interventions*: instructed to maintain or decrease pain medications only

High-frequency spinal cord stimulation #2

- *Frequency*: 3030 Hz at 30 µs;
- *Stimulator type*: rechargeable implanted pulse generator (IPG)
- *Lead number and type*: dual octapolar leads (Octad, Medtronic, Minneapolis, MN, USA)
- *Manufacturer*: Medtronic
- *Description*: see description for high-frequency spinal cord stimulation #1
- *Burst or tonic stimulation*: not stated
- *Duration*: 12 weeks, 4 periods (? 3 weeks per study period though not specified?)
- *Co-interventions*: instructed to maintain or decrease pain medications only

High-frequency spinal cord stimulation #3

- *Frequency*: 1200 Hz at 180 µs
- *Stimulator type*: rechargeable implanted pulse generator (IPG)
- *Lead number and type*: dual octapolar leads (Octad, Medtronic, Minneapolis, MN, USA)
- *Manufacturer*: Medtronic
- *Description*: see description for high-frequency spinal cord stimulation #1
- *Burst or tonic stimulation*: not stated
- *Duration*: 12 weeks, 4 periods (? 3 weeks per study period though not specified?)
- *Co-interventions*: instructed to maintain or decrease pain medications only

Placebo

- *Frequency*: sham (with the generator turned on and discharging, but without electricity transmitted to the lead)
- *Stimulator type*: rechargeable implanted pulse generator (IPG)
- *Lead number and type*: dual octapolar leads (Octad, Medtronic, Minneapolis, MN, USA)
- *Manufacturer*: Medtronic
- *Description*: the generator turned on and discharging, but without electricity transmitted to the lead. "The amplitude was set for the sham mode in the same manner as it was for the active settings, to produce a recharge interval similar to that of the active settings in the 1200 Hz and 3030 Hz frequency groups; however, the 5882 Hz group required more recharging. The “sham mode” of the device was designed to deplete the battery without either delivering any electrical charge to the epidural leads (bench-side testing was used to verify the electrodes to be “off” in sham mode) or causing any noticeable heating of the IPG. Subjects were not provided with a patient programmer during the cross-over phase; therefore, the amplitude was unable to be altered during each follow-up period. To program subperception settings for each of the tested frequency/pulse width combinations, the perceptual threshold amplitude was identified by increasing the amplitude for each setting, including sham, with the subject in the supine position until it reached 10.5 V or the subjects reported any stimulation sensation. The amplitude was then reduced until they no longer felt any stimulation sensation or (when a perceptual threshold was not reached or exceeded 10.5 V) to a level that did not require them to recharge more than twice per day. Although the amplitude remained variable between the groups, the frequency, pulse width remained defined for each period."
- *Burst or tonic stimulation*: not stated
- *Duration*: 12 weeks, 4 periods (? 3 weeks per study period though not specified?)
- *Co-interventions*: instructed to maintain or decrease pain medications only

Outcomes	Outcomes measured at 3 weeks (immediate-term outcomes) **Outcomes included in review** • Low back pain intensity on 10 cm VAS, measured daily for the last 3 days of the trial period • Leg pain on 10 cm VAS

Al-Kaisy 2018 *(Continued)*

- Adverse events and device deficiencies
- Global impression of change (PGIC): categorical "no change", "somewhat better", "better"

Outcomes excluded from review

- Treatment satisfaction
- Presence and quality of stimulation sensations

Identification	**Sponsorship source:** sponsored by Medtronic Inc (Minnesota, USA) **Country:** United Kingdom **Setting:** Pain Management and Neuromodulation Centre, Guy's & St Thomas NHS Trust, London, United Kingdom **Comments:** no comments **Author's name:** Adnan Al-Kaisy **Institution:** Guy's and St. Thomas' Hospital NHS Trust, London, UK **Email:** alkaisy@aol.com **Address:** Pain Management & Neuromodulation Centre, St Thomas' Hospital, Westminster Bridge Road, London SE17EH, UK. **Start date - End date:** January 2013 to April 2015 **Trial registration:** NCT01750229
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects received, in a randomized order, the four tested frequency/pulse width settings..." Quote: the "randomization scheme was generated by the sponsor for the study that allocated subjects in a 1:1:1:1 fashion to each of the 4 different frequency/pulse width settings... The site received a box of envelopes, with each envelope containing a randomization sequence. Randomization sequences were assigned in sequential order until each unique sequence was distributed. If subjects did not complete their assigned sequence at the end of the crossover period, additional subjects were then enrolled and received their randomization assignment until all 24 unique randomization assignments were completed."
Allocation concealment (selection bias)	Low risk	Quote: "A randomization scheme was generated by the sponsor for the study that allocated subjects in a 1:1:1:1 fashion to each of the 4 different frequency/pulse width settings... . There were a total of 24 unique sequences of those four frequency groups. The site received a box of envelopes, with each envelope containing a randomization sequence. Randomization sequences were assigned in sequential order until each unique sequence was distributed. If subjects did not complete their assigned sequence at the end of the crossover period, additional subjects were then enrolled and received their randomization assignment until all 24 unique randomization assignments were completed."

Al-Kaisy 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study subjects and all site personnel treating and administering questionnaires to subjects, including the principal investigator, were blinded to the order of the frequencies being tested and to the frequency being used to treat subjects during the long-term of low-up period. The efficacy of the blinding process was not formally tested. Two members of the local research team were unblinded to the frequencies being tested to perform the programming. These unblinded personnel were not involved in any other study procedures (including collecting outcome data). Two databases were used to store blinded and unblinded data separately."
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "Subjects were asked to record once a day on a multiday paper diary their pain scores using a 0–10 cm VAS (for both back and leg separately) for seven days at baseline and during the last week of the device trial period, and for the entire duration of the randomized crossover period. The average pain scores for back pain from the last three days of complete diary data during the last week of each blinded crossover assignment was the primary efficacy outcome." Comment: stimulation sensation similar across groups except those receiving 1200 Hz
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Fifty-three subjects were enrolled in the study between January 2013 and April 2015. Of the 53 enrolled, 36 completed a SCS device trial, 33 were implanted with a full SCS system (92% trial to permanent conversion rate) and 30 were randomized. Of these 30 randomized subjects, six were excluded from analysis (due to early discontinuations, deviations associated with randomization and programming affecting the ability to evaluate subjects' data, and lack of device use), and 24 contributed to the analysis." Comment: 24/30 followed up (80%)
Selective reporting (reporting bias)	Unclear risk	Comment: trial registry outcomes (back pain, 0-10 scale, one month) matches paper. However, no information in trial registry about outcomes included in the trial report (leg pain, adverse events, function)
Other bias	Low risk	Quote: "The use of only the last three days data (instead of all data from the three-week period) was an intentional attempt to minimize any "carryover" effect, despite there being no scientific data available to substantiate the validity of this choice. The treatment by period interaction term, carryover effect, was tested and removed from the final model as being not statistically significant. These results seem to be independent from any period effect (i.e., regardless of the randomization order)." Comment: no evidence of carryover or period effects

De Ridder 2013

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Analysis:** not described **Sample size calculation:** not described

De Ridder 2013 *(Continued)*

Study design: a randomised placebo-controlled trial; tonic versus burst versus sham immediate-term outcomes

Trial aim: to find out whether SCS is indeed capable of suppressing neuropathic limb pain in a placebo-controlled way

Trial duration: conducted from 1 January 2011 until 30 September 2011. 1 week with burst mode, 1 week in tonic mode, and 1 week with placebo

Participants

Baseline characteristics

Overall

- *Age*: mean (SD) = 54.0 years (8.6)
- *Sex*: female = 11 (73%), male = 4 (27%)
- *Pain duration*: not reported
- *Baseline back pain score*: mean (0-10) = 7.35 (2.49)
- *Baseline function score*: not reported
- *QOL score*: not reported
- *Baseline leg pain score*: mean (0-10) = 7.50 (1.63)
- *Work status*: not measured
- *Pain medication use*: not measured
- *Healthcare use*: not measured
- *Number of participants*: 15
- *Diagnostic criteria*: "who presented to the BRAI^{2}N neuro-modulation clinic were eligible for SCS according to the Belgian requirements for the reimbursement for SCS, which states that the patient has to be medically intractable to opioids and antiepileptic drugs. All patients were selected by the first author, and after a multidisciplinary discussion with a specialized pain physician, a psychological and psychiatric evaluation was performed to rule out psychogenic pain as well as other psychiatric morbidity contraindicating an implant."
- *Socioeconomic status*: not measured

Inclusion criteria: extracted from clinicaltrials.gov/ct2/show/record/NCT01486108.

- able to provide informed consent to participate in the study;
- between the age of 18 and 75;
- has FBSS;
- has a simulator implanted at the dorsal column spinal cord powered by an EON/EON Mini internal pulse generator;
- medication has remained stable for at least 4 weeks prior to baseline data collection;
- agrees not to add or increase medication throughout the randomisation trial period of the study;
- willing to cooperate with the study requirements including compliance with the treatment regimen and completion of all office visits.

Exclusion criteria: "A patient will be excluded from participation in this study if they meet any one of the following criteria":

- current evidence of any psychiatric disorder;
- history of life-threatening severe illness or is suffering from severe chronic disease other than the indication for the study;
- history of substance abuse or substance dependency in the past 6 months prior to baseline data collection;
- currently participating in another clinical study;
- has a demand-type cardiac pacemaker, an infusion pump, or any other implantable neurostimulator device except for the spinal cord stimulator under study;
- not willing to maintain current medication regimen;

De Ridder 2013 *(Continued)*

- female candidates of child bearing potential who are pregnant (confirmed by positive urine/blood pregnancy test), not using adequate contraception as determined by the investigator, or nursing (lactating) a child.

Pretreatment: n/a (cross-over)

Minimum pain intensity: not stated, only that "Belgian requirements for the reimbursement for SCS, which states that the patient has to be medically intractable to opioids and antiepileptic drugs."

Number of participants: 15

Source of participants: Antwerp University Hospital. "All patients were selected by the first author, and after a multidisciplinary discussion with a specialized pain physician, a psychological and psychiatric evaluation was performed to rule out psychogenic pain as well as other psychiatric morbidity contraindicating an implant. After authorization by the psychologist and psychiatrist, an implant was offered to the patient"; presented to the BRAI^{2}N neuro-modulation clinic

Interventions	Placebo • *Frequency*: zero amplitude (IPG not discharging) • *Stimulator type*: stimulation was performed with a nonsterile EON IPG System (St. Jude Medical) via externalised extension wires • *Lead number and type*: Lamitrode tripole, 88, penta, 44 • *Manufacturer*: St Jude Medical • *Description*: placebo stimulation was performed in the following way: burst stimulation was applied on the predefined electrode contacts until the participant experienced paraesthesia. Subsequently the stimulator intensity was decreased exactly like in burst programming but continued until zero amplitude • *Burst or tonic stimulation*: not applicable • *Duration*: 1 week • *Co-interventions*: not reported Conventional spinal cord stimulation • *Frequency*: classical tonic stimulation (40 Hz or 50 Hz) • *Stimulator type*: stimulation was performed with a nonsterile EON IPG System (St. Jude Medical) via externalised extension wires • *Lead number and type*: Lamitrode tripole, 88, penta, 44 • *Manufacturer*: St Jude Medical • *Description*: stimulation intensity for tonic and burst mode during randomised stimulation was selected on the basis of the maximal pain suppression as determined by the participant • *Burst or tonic stimulation*: tonic • *Duration*: 1 week • *Co-interventions*: not reported Burst spinal cord stimulation • *Frequency*: "Burst stimulation consists of intermittent packets of closely spaced, high-frequency stimuli, for instance, 40-Hz burst mode with five spikes at 500 Hz per burst, with a pulse width of 1 ms [1000 µs] and 1-ms interspike intervals delivered in constant current mode. The cumulative charge of the five 1-ms spikes is balanced during 5 ms after the spikes, which differentiates it from high-frequency clustered firing, in which each pulse is immediately charge balanced" • *Stimulator type*: EON IPG System (St Jude Medical) • *Lead number and type*: Lamitrode tripole, 88, penta, 44 • *Manufacturer*: St Jude Medical • *Description*: "The stimulation intensity for tonic and burst mode during randomized stimulation was selected on the basis of the maximal pain suppression as determined by the patient. The burst mode was programmed by use of a custom-made software and programming device. Typically, burst stimulation is characterized by a lower amplitude but larger pulse width, which results in a similar energy

De Ridder 2013 *(Continued)*

	delivery per pulse. In burst mode, the amplitude was increased up to the moment that paraesthesias were elicited. Subsequently, the amplitude was decreased to a level below paraesthesia threshold." • *Burst or tonic stimulation*: burst • *Duration*: 1 week • *Co-interventions*: not reported
Outcomes	Outcomes measured at one week (immediate-term outcome) **Outcomes included in review** • Back pain intensity (100 mm VAS) • Leg pain intensity (100 mm VAS); both measured at immediate outcome time points **Outcomes excluded from review** • 100 mm VAS for "general pain", worst pain, least pain during past week • Preoccupation with or attention to pain (Pain vigilance and awareness questionnaire) • Paraesthesias caused by the stimulation • Electroencephalogram and source localisation
Identification	**Sponsorship source:** none stated **Country:** Belgium **Setting:** Neuromodulation clinic; approved by the Antwerp University Hospital Institutional review board **Comments:** "Conflict of interest statement: Dr. De Ridder has obtained a patent for burst stimulation. The remaining authors have no conflicts of interest." **Author's name:** Dirk De Ridder **Institution:** Department of Surgical Sciences, Section of Neurosurgery, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand **Email:** dirk.deridder@otago.ac.nz **Address:** Department of Surgical Sciences, Section of Neurosurgery, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand **Start date - End date:** conducted from 1 January 2011 until 30 September 2011 **Trial registration:** registered at ClinicalTrials.gov (NCT01486108).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: report states that study is randomised, but provides no detail on method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no mention of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: differences in paraesthesia tonic vs placebo but not burst vs placebo. Participants able to identify when active treatment being received.

De Ridder 2013 *(Continued)*

Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: subjective measures of paraesthesia reported by participants. Participants able to identify when active treatment being received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 15 patients were included in the study" Comment: all participants recruited completed the study.
Selective reporting (reporting bias)	Low risk	Comment: outcomes appear to reflect what is reported in trial registry.
Other bias	High risk	Comment: no mention of dealing with period and carry-over effects and no methods employed to mitigate for these factors.

Eisenberg 2015

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Analysis:** "Because the study population included 18 subjects, the Shapiro–Wilk test of normality was performed and showed that both TS [temporal summation] values and clinical pain intensities did not distribute normally. Therefore, the Wilcoxon signed rank test was used in the comparisons of TS values and clinical pain intensities between the SCS “ON” and “OFF” conditions." **Sample size calculation:** not reported **Study design:** cross-over design with immediate-term (< 2 hour) outcome **Trial aim:** "to test the effect of spinal cord stimulation (SCS) on temporal summation, the clinical correlate of the wind-up phenomenon in patients with radicular leg pain" **Trial duration:** 2 hours
Participants	**Baseline characteristics** Overall • *Age*: mean (SD); range = 59 years (7); 47 to 72 years • *Sex*: 17 men (94%); 1 woman (6%) • *Back pain duration*: mean = 11.3 years (5.3) • *Baseline back pain score*: not reported • *Baseline function score*: not reported • *QOL score*: not reported • *Baseline leg pain score*: not reported • *Work status*: not reported • *Number of participants*: 18 • *Socioeconomic status*: not reported • *Pain medication use*: opioids: n = 13, antidepressants: n = 6, anticonvulsants: n= 10, NSAIDS/simple analgesics: n = 5, baclofen: n = 1, medical marijuana: n = 2 • *Diagnostic criteria*: they had either temporary or permanent SCS implants for the treatment of otherwise intractable unilateral radicular leg pain, after at least 1 back surgery • *Healthcare use*: not reported

Eisenberg 2015 *(Continued)*

Inclusion criteria: "Patients aged 18 to 80 years were considered eligible if: (1) they provided written informed consent before enrolment, (2) they had either temporary or permanent SCS implants for the treatment of otherwise intractable unilateral radicular leg pain, after at least 1 back surgery, and (3) the SCS could be programmed in such a way that the perceived sensation of paraesthesia was restricted to the affected leg."

Exclusion criteria: "Patients were excluded if: (1) they had a neurological condition causing symmetrical polyneuropathy (ie, diabetes mellitus), (2) they had received a new pain therapy within 2 weeks before enrolment, (3) they had any other pain elsewhere in the body, unrelated to the radicular pain, and (4) exhibited a higher heat pain threshold than 46.5℃ at the most painful site in the affected limb."

Pretreatment: not applicable (cross-over design)

Minimum pain intensity: nil

Number of participants: 18

Source of participants: volunteers to Pain Research Unit, Institute of Pain Medicine, Rambam Health Care Campus, Haifa, Israel

Interventions	Conventional spinal cord stimulation • *Frequency*: not reported; study report states high-frequency stimulation was not possible using conventional device • *Stimulator type*: conventional implanted device; temporary or permanent SCS implants • *Lead number and type*: not reported • *Manufacturer*: not reported • *Description*: "Patients were then randomized to undergo the tests according to 1 of the following 2 orders: either 30 minutes after SCS activation (SCS “ON”) first and then 2 hours after turning it off (SCS “OFF”) or in a reversed order (SCS “OFF” first, followed by SCS “ON”). The randomization sequence was computer-based (blocks of 4). Heat stimuli were applied first to the contralateral leg (in the area corresponding to the most painful site in the affected leg) and to the most painful site in the affected leg 10 minutes later. The perceived heat pain intensity was continuously recorded (computerized visual analog scale). The intensity of the clinical (radicular) pain was assessed immediately before the initiation of the TS test in the affected leg, with both SCS “ON” and “OFF".” • *Burst or tonic stimulation*: not reported • *Duration*: 2 hours • *Co-interventions*: "Patients were requested not to take any analgesic medication for at least 2 hours before testing initiation" Placebo • *Frequency*: switched OFF • *Stimulator type*: conventional implanted device; temporary or permanent SCS implants • *Lead number and type*: not reported • *Manufacturer*: not reported • *Description*: "Patients were then randomized to undergo the tests according to 1 of the following 2 orders: either 30 minutes after SCS activation (SCS “ON”) first and then 2 hours after turning it off (SCS “OFF”) or in a reversed order (SCS “OFF” first, followed by SCS “ON”). The randomization sequence was computer-based (blocks of 4). Heat stimuli were applied first to the contralateral leg (in the area corresponding to the most painful site in the affected leg) and to the most painful site in the affected leg 10 minutes later. The perceived heat pain intensity was continuously recorded (computerized visual analog scale). The intensity of the clinical (radicular) pain was assessed immediately before the initiation of the TS test in the affected leg, with both SCS “ON” and “OFF".” • *Burst or tonic stimulation*: not reported • *Duration*: 2 hours • *Co-interventions*: "Patients were requested not to take any analgesic medication for at least 2 hours before testing initiation"
Outcomes	Outcomes measured at 2 hours (immediate-term outcome)

Eisenberg 2015 *(Continued)*

Outcomes included in review

- Clinical (radicular) pain (0-100 numeric pain scale)

Outcomes excluded from review

- Temporal summation

Identification	**Sponsorship source:** "The authors have no conflicts of interest to declare." No other sponsorship source stated. **Country:** Israel **Setting:** conducted at the Pain Research Unit, Institute of Pain Medicine, Rambam Health Care Campus, Haifa, Israel **Comments:** no industry funding reported **Author's name:** Elon Eisenberg **Institution:** Israel Institute of Technology, Haifa, Israel **Email:** e_eisenberg@rambam.health.gov.il **Address:** Pain Research Unit, Institute of Pain Medicine, Rambam Health Care Campus, PO Box 9602, Haifa 3109601, Israel **Start date - End date:** not reported **Trial registration:** not registered
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomized to undergo the tests according to 1 of the following 2 orders: either 30 minutes after SCS activation (SCS “ON”) first and then 2 hours after turning it off (SCS “OFF”) or in a reversed order (SCS “OFF” first, followed by SCS “ON”). The randomization sequence was computer-based (blocks of 4)."
Allocation concealment (selection bias)	Unclear risk	Comment: no mention of offsite list; potential for researcher to know sequence at enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The new high-frequency stimulation that does not produce paresthesia seems to overcome this bias and has already been used in a recent double-blind study on SCS. Unfortunately, conventional implanted devices cannot produce such high- frequency stimulation." Comment: unable to control for paraesthesias in ON (low-frequency stimulation) mode vs OFF mode. Therefore, participants were likely unblinded.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: participants likely unblinded from paraesthesias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all 18 participants enrolled provided outcome data (at 2 hrs). No baseline data against which to be able to compare the effects of the two conditions.

Eisenberg 2015 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no detail on trial registration or published protocol paper provided
Other bias	High risk	Comment: design involved switching off a device in participants who were treated successfully; and comparing pain with device ON vs OFF. In addition to bias from unblinding, the enrichment design (testing SCS in those who have responded) would bias results in favour of SCS. Also 2-hour outcomes have little clinical relevance and would not give time for participants to acclimate to the therapy. This would also bias in favour of SCS. No mention of carry-over and period effects but risk with this design would be high.

Eldabe 2020

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Trial duration:** 3 x 2 week study periods (6 weeks) **Trial aim:** compare sham (i.e. no stimulation) to the analgesic efficacy of two modes (patterns) of active SCS at sub-threshold current intensity (i.e. burst stimulation [BST] and 500 Hz [T500]) in a double-blind, three-period, three-treatment cross-over multicentre RCT. **Analysis:** "Log-transformed Pain VAS data were analyzed using a linear mixed model with restricted maximum likelihood and an identity covariance structure, including fixed effects for treatment, period, treatment×period, study site and sex, and a random intercept by participant. There were two planned primary comparisons: BST vs. sham and T500 vs. sham. Differences in pain VAS on a logscale were back-transformed to provide ratio (percentage) differences between conditions. Point estimates and 95% confidence intervals together with the two-sided p-value are presented. We also conducted purely exploratory sub-group analyses, by including site×treatment and sex×treatment interaction terms in the model." **Sample size calculation:** "The primary outcome is the patient's mean pain intensity score (VAS) over five days of monitoring. In individuals, a reduction in pain VAS of 30% typically defines a clinically important response. At the group level our targeted effect size was a mean reduction (vs. sham stimulation) of 25% in pain VAS (a ratio of BST: sham or T500: sham of 0.75), assuming a small improvement (5%) in the sham condition. With 90% power, two-sided p= 0.05, and a coefficient of variation for pain VAS on the logged scale of 0.37, 35 patients were required to detect the targeted difference for the two planned comparisons. We made no adjustment for multiple comparisons in either the sample size estimation or the subsequent analysis. The coefficient of variation representing the within-patient variability for pain VAS scores over the course of repeat measurements in a crossover trial was derived from a previous study. Given that patients were randomized to all six possible sequences of BST, T500, and sham, a multiple of six patients was required for the overall sample size. Hence, the required N was 42 allowing for missing data or withdrawals in up to six patients. Sample size estimation was conducted using PASS software."
Participants	**Baseline characteristics** Overall • Age: Mean (SD) = 54.0 (9.0) years • Sex: 12 women (63%); 7 men (37%) • Pain duration: not reported • Baseline back pain score: mean (SD) VAS = 4.4 (2.2) • Baseline function score: not reported • QOL score: median (IQR) EQ-5D = 0.620 (0.516 to 0.691)

Eldabe 2020 *(Continued)*

- Baseline leg pain score: not reported
- No. of participants: 19
- Socioeconomic status: not reported
- Pain medication use: not reported
- Diagnostic criteria: FBSS
- Healthcare use: not reported

Included criteria: "adults (≥18 years) with leg and back pain (whether unilateral or bilateral), who achieved stable pain relief with conventional SCS (i.e. paraesthesia inducing stimulation with frequency < 150 Hz) using the Medtronic's rechargeable spinal cord stimulator RestoreSensor® and with either 1 or 2 epidural leads, not requested reprogramming in the three months prior to study participation, confirmed they received pain relief from the device and reported constant ≥70% paraesthesia coverage."

Excluded criteria: "participants with an SCS device other than the one aforementioned, not capable of using or understanding how to handle the equipment or not capable to complete the study measures."

Pretreatment: n/a cross-over trial

Minimum pain intensity: nil

Number of participants: 19 recruited and randomised. 16 completed trial

Source of participants: two sites in the United Kingdom: South Tees Hospitals NHS Foundation Trust (The James Cook University Hospital) JCUH and Newcastle-upon-Tyne NHS Trust (Royal Victoria Infirmary) NuTH

Interventions

Intervention Characteristics

Placebo

- Frequency: nil
- Stimulator type: Medtronic's rechargeable spinal cord stimulator RestoreSensor
- Lead number and type: 1 or 2 epidural leads
- Manufacturer: Medtronic
- Description: "Subjects receiving Sham SCS underwent the programming steps [described in the description of the Burst stimulation arm below] by the non-blinded investigator. However, the stimulator was switched off after completing. During either sham or active stimulation phases, patients were able to revert to conventional stimulation at any time should they experience pain or side effects by contacting the pain clinic."
- Burst or tonic stimulation: Nil
- Duration: 2 weeks
- Co-interventions: not measured

Conventional spinal cord stimulation

- Frequency: 500 Hz with a pulse width of 480 µs
- Stimulator type: Medtronic's rechargeable spinal cord stimulator RestoreSensor
- Lead number and type: 1 or 2 epidural leads
- Manufacturer: Medtronic
- Description: "Subjects receiving T500 SCS underwent the programming steps [described in the description of the Burst stimulation arm below] by the non-blinded investigator. However, a continuous tonic stimulation at 500 Hz with a pulse width of 480 µs was programmed."
- Burst or tonic stimulation: tonic
- Duration: 2 weeks
- Co-interventions: not measured

Burst spinal cord stimulation

- Frequency: 40 Hz burst of four spikes of 1000 µs at 500 Hz per burst

Eldabe 2020 *(Continued)*

- Stimulator type: Medtronic's rechargeable spinal cord stimulator RestoreSensor
- Lead number and type: 1 or 2 epidural leads
- Manufacturer: Medtronic
- Description: "Subjects receiving BST underwent programming by the non-blinded member of the clinical team using the following steps: 1. Using no more than three active contacts with one cathode, paraesthesia covering as much as possible of the area of pain area should be elicited with"conventional stimulation"(i.e., frequency < 150 Hz) with the patient lying on his back; 2. while keeping the voltage setting below sensory threshold, the burst mode is programmed (40 Hz burst of four spikes of each 1000 µs at 500 Hz per burst); 3. the voltage amplitude is progressively increased to the sensory threshold where stimulation is expected to be reported as an uncomfortable dull ache; 4.. the voltage amplitude is decreased again to the sensation threshold amplitude. The amplitude is set at 10% below the sensory threshold and recorded in the software of the stimulator; 5. the same procedure is repeated with the patient in the following posture: standing, lying on the left side, lying on the right side, lying prone."
- Burst or tonic stimulation: Burst
- Duration: 2 weeks
- Co-interventions: not measured

Outcomes	Outcomes measured at 2 weeks (immediate-term outcome) **Outcomes included in review** • Pain intensity • Global impression of change (not reported) • HRQoL (EQ-5D) • Safety **Outcomes excluded from review** • Nil
Identification	**Sponsorship source:** Medtronic **Country:** United Kingdom **Setting:** patients treated with SCS were recruited from two sites in the United Kingdom: South Tees Hospitals NHS Foundation Trust (The James Cook University Hospital) JCUH and Newcastle-upon-Tyne NHS Trust (Royal Victoria Infirmary) NuTH **Comments:** - **Author's name:** Sam Eldabe **Institution:** Department of Pain and Anaesthesia, The James Cook University Hospital **Email:** seldabe@mac.com **Address:** Department of Pain and Anaesthesia, The James Cook University Hospital, Cheriton House, Marton Road, MiddlesbroughTS4 3BW, UK. **Start date - End date:** October 2014 and July 2017 **Trial registration:** not registered
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Eldabe 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomly assigned to treatment sequence by means of a central randomization service using text message randomization via a nonblinded investigator."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible patients were randomly assigned to treatment sequence by means of a central randomization service using text message randomization via a nonblinded investigator. Patients and outcome assessors were blind to treatment assignment (order)."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "To ensure blinding of participants, a current leak was programmed during sham phases so that the charging time (and the possible skin heating) were similar regardless of whether BST, T500, or sham was delivered. For BST, a four-spiked burst was used with passive charge balanced at the end of the four-spiked burst. Patients were not provided with a handheld patient programmer, but all had access to a modified recharging unit for the dura- tion of the study. The "study unit" had a disabled screen and alarms and no information about the battery charge was avail- able. Patients in all study phases were asked to recharge their device daily for 2 hours." Comment: attempts to blind participants, but no evidence provided of the success of this to show blinding successful
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Quote: "Nursing staff were split into two groups with no cross over allowed between the groups. Group one was blinded outcome assessors and group two consisted of unblinded nurse programmers." Comment: attempts to blind participants, but no evidence provided of the success of this to show blinding successful
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 16/19 (84%) completed the trial.
Selective reporting (reporting bias)	High risk	Comment: not registered; some outcome data not reported
Other bias	High risk	Comment: included washout period to account for carry-over effects; no mention of looking for period effects

Hara 2022

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Trial duration:** follow-up to 12 months **Trial aim:** "evaluate the effects of spinal cord burst stimulation compared with placebo stimulation in patients with chronic radicular pain after lumbar spine surgery who underwent placement of a spinal cord stimulator" **Study design:** single-centre, randomised, placebo-controlled study with a quadruple-blinded, four phase, 12-month, cross-over design **Sample size calculation:** "The trial was designed to detect a between-group difference of 10 points, corresponding to the MCID, in change in the mean ODI score between periods with burst stimulation

Hara 2022 *(Continued)*

and periods with placebo stimulation. Assuming that the population mean was 10 and the SD was 18 for the differences, a 1-sample t test of the differences at the.05 significance level needed 34 patients to achieve 90% power. Due to expected rates of 10% to 20% for patients lost to follow-up and potential breakthrough of paresthesia with risk of unblinding during burst stimulation in 20% to 30% of patients, we aimed at including 50 trial participants"

Analysis: "Sensitivity analyses were performed in the complete case set, which included the subset of patients in the full analysis set that had ODI measurements at all follow-up visits. The 2 interventions were compared using a linear mixed model, accounting for repeated measurements in each patient. The fixed effect was the combination of time (baseline vs follow-up) and treatment, yielding 3 levels representing baseline, burst stimulation, and placebo stimulation. Due to variance heterogeneity over time, the covariance structure for the repeated measurements for each patient was handled as unstructured. Statistical tests for the primary and secondary outcomes were performed at the 2-sided significance level of.05. The absolute between-intervention differences and 95% CIs were determined for the self-reported outcomes and daily physical activity. Missingness of data was handled with the use of mixed modeling and no imputations were performed. Period and sequence effects were not assessed in the statistical analyses."

Participants

Baseline characteristics

Overall

- Age: median, (inter-quartile range) = 50 (45-59)
- Sex: n (%): M = 23 (46%) and F = 27 (54%)
- Back pain duration: not reported
- Baseline back pain score: 0–10 NRS. Mean (95% CI) = 6.8 (6.4 to 7.3)
- Baseline function score: ODI. Mean (95% CI) = 44.7 (41.4 to 47.9)
- QOL score: EuroQol 5-D. Mean (95% CI) = 0.21 (0.13 to 0.28)
- Baseline leg pain score: 0–10 NRS. Mean (95% CI) = 7.3 (6.8 to 7.7)
- Work status: not reported
- No. of participants: 50
- Socioeconomic status: not reported
- Pain medication use: on any pain medication: n = 32, opioid analgesics: n = 18, gabapentinoids: n = 17, acetaminophen: n = 17, non-steroidal anti-inflammatory drugs: n = 5, antidepressants: n = 3
- Diagnostic criteria: (1) they had undergone at least 1 decompressive or fusion procedure for degenerative lumbar spine disease, (2) they experienced postoperative chronic radicular pain refractory to nonsurgical treatment for a minimum of 6 months, (3) they reported average pain intensity with a minimum of 5 on scale of 1 to 10 for leg pain using the Numeric Rating Scale, and (4) no additional spine surgery or pharmacological treatment was assumed to be beneficial
- Healthcare use: number of prior procedures: median (IQR) = 2 (1-3), discectomy: n = 38, fusion: n = 13, decompressive surgery: n = 11

Inclusion criteria: "To be eligible to participate in the study, a subject must meet all of the following inclusion criteria:

- Subject is at least 18-year old at the time of informed consent;
- Had undergone at least 1 decompressive or fusion procedure for degenerative lumbar spine disease
- Experienced postoperative chronic radicular pain refractory to nonsurgical treatment for a minimum of 6 months
- Reported average pain intensity with a minimum of 5 on scale of 1 to 10 for leg pain using the Numeric Rating Scale (higher scores indicate more severe pain; 0 meant "no pain" and 10 meant the "worst pain imaginable")
- No additional spine surgery or pharmacological treatment was assumed to be beneficial
- A successful 2-week spinal cord stimulation test with an external neurostimulator and epidural leads providing a reduction of at least 2 points for leg pain using the Numeric Rating Scale"

Exclusion criteria: "A subject will be excluded from participating in the study if they meet any of the following criteria:

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- previously treated with spinal cord stimulation or subcutaneous nerve stimulation.
- abnormal pain behaviour
- unresolved psychiatric illness
- unresolved issues of possible secondary gain
- inappropriate medication use (eg, misuse of sedatives or substance use disorders)."

Pretreatment: n/a

Number of participants: 112 screened, 65 device trial, 50 enrolled and randomised to first 3-month period, 47 randomised to second 3-month period, 44 randomised to third 3-month period, 42 randomised to fourth 3-month period

Minimum pain intensity: average pain intensity with a minimum of 5 on scale of 1 to 10 for leg pain using the Numeric Rating Scale

Source of participants: "Assessment of trial eligibility and postoperative follow-up appointments were performed at the multidisciplinary outpatient clinic for back, neck, and shoulder rehabilitation at St Olavs University Hospital in Trondheim, Norway"

Interventions

Intervention Characteristics

Burst spinal cord stimulation

- Frequency: 40 Hz of constant current with 4 spikes per burst at an amplitude corresponding to 50% to 70% of paraesthesia perception threshold
- Stimulator type: nonrechargeable implantable pulse generator
- Lead number and type: 16-contact lead (Infinion CX, Boston Scientific, Inc) was implanted for unilateral leg pain or two 8-contact leads (Linear ST, Boston Scientific, Inc) were implanted for bilateral leg pain
- Manufacturer: Precision Novi, Boston Scientific, Inc
- Description: “Epidural surgical lead insertion was performed while patients were in the prone position using local anesthetics and mild intravenous sedation to enable patient feedback and cooperation. The aim was to optimize lead placement over the dorsal columns of the spinal cord so that paresthesia occurred in the targeted spinal dermatome (ie, tonic conventional stimulation). A 16-contact lead (Infinion CX, Boston Scientific, Inc) was implanted for unilateral leg pain or two 8-contact leads (Linear ST, Boston Scientific, Inc) were implanted for bilateral leg pain through a small skin incision at the L1/L2 or L2/L3 vertebral levels and placed in the epidural space at the T9/T10 level under fluoroscopic guidance. Intraoperative electrophysiological testing and stimulation were performed during longitudinal lead navigation. The leads were anchored at the optimal localization and their positions were confirmed with x-ray imaging. Leads were then connected to an external neurostimulator using extension cords. Programming software (Illumina 3D, Boston Scientific, Inc) was used to optimize tonic conventional stimulation and determine paresthesia thresholds during the testing period. If there was insufficient improvement in leg pain during the testing period, the leads were removed and the patients were excluded. If there was sufficient improvement in leg pain during the testing period, the patients were included in the trial and their external neurostimulator was replaced with a nonrechargeable implantable pulse generator (Precision Novi, Boston Scientific, Inc) placed subcutaneously on the upper buttock or abdomen under local anesthesia. A nonrechargeable pulse generator was chosen to avoid unblinding of patients. Immediately after implantation of the stimulator, eligible patients underwent four 3-month periods of treatment. All patients underwent burst stimulation and placebo stimulation in a randomized order for two 3-month periods for each intervention. Burst stimulation consisted of closely spaced, high-frequency stimuli delivered to the spinal cord. The stimulus consisted of a 40-Hz burst mode of constant current stimuli with 4 spikes per burst and an amplitude corresponding to 50% to 70% of the paresthesia perception threshold.”
- Burst or tonic stimulation: burst stimulation
- Duration: 12 months, 4 periods of 3 months of treatment
- Co-interventions: not reported

Placebo

- Frequency: no stimulation provided

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- Stimulator type: nonrechargeable implantable pulse generator
- Lead number and type: 16-contact lead (Infinion CX, Boston Scientific, Inc) was implanted for unilateral leg pain or two 8-contact leads (Linear ST, Boston Scientific, Inc) were implanted for bilateral leg pain
- Manufacturer: Precision Novi, Boston Scientific, Inc
- Description: "Epidural surgical lead insertion was performed while patients were in the prone position using local anesthetics and mild intravenous sedation to enable patient feedback and cooperation. The aim was to optimize lead placement over the dorsal columns of the spinal cord so that paresthesia occurred in the targeted spinal dermatome (ie, tonic conventional stimulation). A 16-contact lead (Infinion CX, Boston Scientific, Inc) was implanted for unilateral leg pain or two 8-contact leads (Linear ST, Boston Scientific, Inc) were implanted for bilateral leg pain through a small skin incision at the L1/L2 or L2/L3 vertebral levels and placed in the epidural space at the T9/T10 level under fluoroscopic guidance. Intraoperative electrophysiological testing and stimulation were performed during longitudinal lead navigation. The leads were anchored at the optimal localization and their positions were confirmed with x-ray imaging. Leads were then connected to an external neurostimulator using extension cords. Programming software (Illumina 3D, Boston Scientific, Inc) was used to optimize tonic conventional stimulation and determine paresthesia thresholds during the testing period. If there was insufficient improvement in leg pain during the testing period, the leads were removed and the patients were excluded. If there was sufficient improvement in leg pain during the testing period, the patients were included in the trial and their external neurostimulator was replaced with a nonrechargeable implantable pulse generator (Precision Novi, Boston Scientific, Inc) placed subcutaneously on the upper buttock or abdomen under local anesthesia. A nonrechargeable pulse generator was chosen to avoid unblinding of patients. Immediately after implantation of the stimulator, eligible patients underwent four 3-month periods of treatment. All patients underwent burst stimulation and placebo stimulation in a randomized order for two 3-month periods for each intervention. Burst stimulation consisted of closely spaced, high-frequency stimuli delivered to the spinal cord. The stimulus consisted of a 40-Hz burst mode of constant current stimuli with 4 spikes per burst and an amplitude corresponding to 50% to 70% of the paresthesia perception threshold."
- Burst or tonic stimulation: not reported
- Duration: 12 months, 4 periods of 3 months of treatment
- Co-interventions: not reported

Outcomes	Outcomes measured at 3 months (short-term outcomes) **Outcomes included in review** • Back pain intensity (0 to 10 NRS) • Leg pain intensity (0-10 NRS) • Physical function (Oswestry Disability Index) • Quality of life (EuroQoL 5D index) • Surgical revisions and adverse events **Outcomes excluded from review:** • Physical activity level (steps per day and time spent standing or walking per day) • Cost-effectiveness
Identification	**Sponsorship source:** trial was funded by the Liaison Committee for Education, Research, and Innovation in Central Norway. **Country:** Norway **Setting:** Department of Neurosurgery, St Olavs University Hospital, Norway **Comments:** no comments **Author's name:** Sozaburo Hara **Institution:** Department of Neurosurgery, St Olavs University Hospital, Trondheim, Norway **Email:** (sasha.gulati@ntnu.no)

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Address: Department of Neurosurgery, St Olavs University Hospital, Trondheim, Norway

Start date - End date: participants enrolled from 5 September 2018 through to 28 April 2021. The 12-month follow-up finished on 20 May 2022.

Trial registration: NCT03546738

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: block randomization sequence was generated manually (block size of 6)
Allocation concealment (selection bias)	Low risk	Comment: allocation envelopes were made before commencement of the trial and concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: all were blinded except for trial nurse
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Comment: self-reported by blinded participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 47 of 50 randomised participants completed at least 1 follow-up
Selective reporting (reporting bias)	Low risk	Comment: reported as per trial registry
Other bias	Unclear risk	Comment: unclear if period and carryover effects accounted for in the analysis

Kapural 2022

Study characteristics

Methods

Study design: randomised controlled trial

Study grouping: parallel group

Analysis: "Analysis populations defined for the study include intention-to-treat (ITT) and per protocol (PP). The ITT population includes all randomized subjects, while the PP population includes subjects who completed the visit corresponding to the endpoint being analyzed. Note that subjects who fail the temporary trial will be included in the ITT population for the high-frequency stimulation at 10 kHz (HF10)+CMM arm. The primary endpoint will be evaluated with a Fisher's exact test comparing the percentage of subjects in each group who achieve a 50% improvement in their back pain VAS score at the primary efficacy assessment in the ITT population. The following secondary endpoints will be successively evaluated (hierarchical closed test approach) at study completion in the order shown with a 0.05 significance level for difference between groups in the PP population until statistical significance is not achieved"

Sample size calculation: "Assuming a 60% responder rate in the stimulation group (10-kHz SCS+CMM) and 36% in the control group (CMM), a sample size of 98 subjects in each group is enough to detect a

Kapural 2022 *(Continued)*

	significant difference with a power of 90% and a 2-sided type I error of 0.05. Assuming a 10% attrition rate, a total of 108 subjects per group need to be randomized. The sample size computation is based on the 2-sided Fisher's exact test, used for comparing 2 independent proportions, following an equal allocation randomization ratio of 1:1. Sites will be enrolling in the study a maximum of 54 subjects (25%) per site of the total number of study subjects (216 subjects)" **Study design:** 1:1 parallel randomised controlled trial **Trial aim:** "to evaluate the clinical effectiveness of the addition of 10-kHz SCS therapy to current conventional medical management (CMM) for non-surgical refractory back pain. Clinical efficacy will be measured in terms of patient-reported pain relief, disability, quality of life, and change in opioid use. Secondly, the investigation will generate data on the cost effectiveness of the addition of 10-kHz SCS therapy to CMM in terms of healthcare utilization (HCU) and productivity." **Trial duration:** "The total follow-up period is 12 months for all participants, with an optional crossover at 6 months." Primary outcome was 3 months.
Participants	**Baseline characteristics** High frequency spinal cord stimulation • Age: mean (range) = 53.0 (29 to 87) • Sex: 50 female (60.2%); 33 male (39.8%) • Back pain duration: median (range) = 8.5 years (0 to 52 years) • Baseline back pain score: mean (SD) on 10 cm VAS = 7.4 (1.2) • Baseline function score: mean (SD) ODI = 46.8 (10.3) • QOL score: not reported • Baseline leg pain score: not reported • Work status: not reported • No. of participants: 83 • Socioeconomic status: not reported • Pain medication use: not reported • Diagnostic criteria: diagnosis of chronic axial low back pain with aneuropathic component. Candidates will complete the PainDETECT questionnaire for assessment of a neuropathic pain component • SE status: not reported • Pain medication use: not reported No intervention • Age: mean (range) = 58.5 (26 to 77) • Sex: 40 female (52.6%); 36 male (47.4%) • Back pain duration: median (range) = 8.0 years (1 to 59 years) • Baseline back pain score: mean (SD) on 10 cm VAS = 7.2 (1.0) • Baseline function score: mean (SD) ODI = 47.4 (10.3) • QOL score: not reported • Baseline leg pain score: not reported • Work status: not reported • No. of participants: 76 • Socioeconomic status: not reported • Pain medication use: not reported • Diagnostic criteria: diagnosis of chronic axial low back pain with a neuropathic component. Candidates will complete the PainDETECT questionnaire for assessment of a neuropathic pain component • Healthcare use: not reported **Inclusion criteria:** • Have been diagnosed with chronic, refractory axial low back pain and are not a candidate for surgery based on a spine surgeon's assessment.

Kapural 2022 *(Continued)*

- Pain should have a predominant neuropathic component as per the investigator's clinical assessment.
- Have not had any surgery for back or leg pain, or any surgery resulting in back or leg pain.
- Considering daily activity and rest, have average back pain intensity of ≥ 5 out of 10 cm on the VAS at enrolment.
- Be on no or stable pain medications, as determined by the investigator, for at least 28 days prior to enroling in this study.
- Be 18 years of age or older at the time of enrolment.
- Be willing and capable of giving informed consent
- Be willing and able to comply with study-related requirements, procedures, and visits.
- Be capable of subjective evaluation, able to read and understand written questionnaires in the local language, and able to read, understand, and sign the written inform consent

Exclusion criteria:

- "Have a diagnosed back condition with inflammatory causes of back pain (eg, ankylosing spondylitis or diseases of the viscera).
- Have a medical condition or pain in other areas, not intended to be treated with SCS, that could interfere with study procedures or accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the investigator.
- Have evidence of an active disruptive psychological or psychiatric disorder identified as the primary condition or other known condition significant enough to impact perception of pain, compliance of intervention, and/or ability to evaluate treatment outcome, as determined by the investigator in consultation with a psychologist.
- Have a current diagnosis of a progressive neurological disease, spinal cord tumor, or severe/critical spinal stenosis.
- Have a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease, or uncontrolled diabetes mellitus that would add unacceptable risk to the procedure.
- Be benefitting within 30 days prior to enrollment from an interventional procedure to treat back and/or leg pain
- Have an opioid addiction or drug-seeking behavior as determined by the investigator.
- Have an existing drug pump and/or SCS system or another active implantable device such as a pacemaker.
- Have prior experience with neuromodulation devices (SCS, PNS, DRG stimulation, multifidus muscle stimulation).
- Have a condition currently requiring or likely to require the use of diathermy or MRI that is inconsistent with Senza system guidelines in the physician's manual.
- Have metastatic malignant disease or active local malignant disease.
- Have a life expectancy of less than 1 year.
- Have an active systemic or local infection
- Be pregnant (participants of child-bearing potential that are sexually active must use a reliable form of birth control).
- Have within 6 months of enrollment a significant untreated addiction to dependency-producing medications or have been a substance abuser (including alcohol and illicit drugs).
- Be concomitantly participating in another clinical study.
- Be involved in an injury claim under current litigation
- Have a pending or approved worker's compensation claim"

Pretreatment: groups similar at baseline on key variables

Minimum pain intensity: average back pain intensity of ≥ 5 out of 10 cm on the VAS

Number of participants: 211 enrolled, 38 did not meet criteria, 13 withdrew consent, 1 excluded for "other" reason; 159 randomised (76 to CMM; 83 to SCS), 75 followed up in CMM group at 6 months (99%), 65 followed up in SCS group at 6 months (78%)

Kapural 2022 *(Continued)*

Source of participants: "15 centers in the United States. In all centers, patients who have not obtained satisfactory results with CMM and have not had previous major lumbar surgery will be screened for eligibility by medical record review."

Interventions

Intervention characteristics

High frequency spinal cord stimulation

- Frequency: 10 kHz
- Stimulator type: IPG, 10 kHz SCS system (Senza, Nevro Corp., Redwood City, CA, USA)
- Lead number and type: two percutaneous leads with 8 contacts each
- Manufacturer: Senza, Nevro Corp., Redwood City, CA, USA
- Description: "Participants randomized to 10-kHz SCS+CMM will undergo a 14-day SCS trial phase. Two percutaneous leads with 8 contacts each will be placed in the epidural space spanning vertebral levels T8 to T11. Stimulation at a frequency of 10 kHz and pulse width of 30 µs will be delivered from an external pulse generator. The stimulation target and current amplitude will be adjusted until at least 50% self-reported back pain reduction from baseline is achieved, defined as trial success, or until conclusion of the trial phase. Subjects who pass the trial phase will be scheduled for permanent implantation of the 10-kHz SCS system (Senza, Nevro Corp., Redwood City, CA, U.S.A.) with investigator and participant agreement. Participants who fail the trial phase will have leads explanted and will not receive a permanent SCS system but will be followed-up for 6 months. The permanent device implantation procedure will be per the manufacturer's physician implant manual and standard of care. The leads will be placed trans-fascially and anchored to the fascia, and will be tunneled to a subcutaneous pocket where the implantable pulse generator (IPG) is housed. The IPG is typically implanted in the lower back/buttock region. The device will be activated 0 to 14 days following permanent implantation. The subject will be instructed on the use of the IPG charger and remote control. Programming adjustments will be made at scheduled follow-ups as needed."
- Burst or tonic stimulation: assumed tonic
- Duration: 6 months
- Co-interventions: not reported. Options were: oral medications (including analgesic medication, non-steroidal anti-inflammatory drugs, neuromodulating agents, antidepressants); topical analgesics, compound creams, or counter-irritants; combined physical and psychological management; physical therapy; back rehabilitation program; spinal manipulation and spinal mobilisation; traction; acupuncture/acupressure; cognitive behavioral therapy; nerve blocks; epidural steroid injections; transcutaneous electrical nerve stimulation

No intervention

- Frequency: n/a
- Stimulator type: n/a
- Lead number and type: n/a
- Manufacturer: n/a
- Description: "All subjects will continue with their CMM, defined as the best standard of care for each individual patient, as determined by the investigator.... Previously beneficial treatments may be continued. Conservative care should have been rendered that was generally consistent with the American College of Physicians and the American Pain Society Guidelines as published in the Anals of Internal Medicine and an interventional pain management guideline from the American Society of Interventional Pain Physician"
- Burst or tonic stimulation: n/a
- Duration: 6 months
- Co-interventions: not reported. Options were: oral medications (including analgesic medication, non-steroidal anti-inflammatory drugs, neuromodulating agents, antidepressants); topical analgesics, compound creams, or counter-irritants; combined physical and psychological management; physical therapy; back rehabilitation program; spinal manipulation and spinal mobilisation; traction; acupuncture/acupressure; cognitive behavioral therapy; nerve blocks; epidural steroid injections; transcutaneous electrical nerve stimulation

Outcomes

Outcomes measured at 3, 6, and 12 months. Primary outcome was 3 months.

Kapural 2022 *(Continued)*

Outcomes included in review

- Back pain VAS
- ODI
- Global improvement (≥ 50% pain relief)
- Daily does opioids (MME)
- Using opioids (%)
- Adverse events
- % change in EQ-5D
- Work status
- Healthcare use

Outcomes excluded from review

- ODI responders (≥ 10 point reduction)
- Change in back pain VAS
- SF-12 (not reported)
- PHQ (not reported)
- Satisfaction (not reported)
- Physical performance (not reported)
- Sleep (not reported)

Identification

Sponsorship source: Nevro Corp

Country: United State of America

Setting: 15 specialist spine centers in the United States

Comments: selected patients who "have not obtained satisfactory results with CMM and have not had previous major lumbar surgery"; stopped early due to "superiority of treatment at the primary endpoint"; also, "This study was funded by Nevro Corp. N.P., C.W., and T.C. have nothing to disclose. J.P. has received a research grant and honorarium from Nevro Corp. and consulting fees from Boston Scientific and Abbott. A.C., L.K., and N.L. serve as scientific consultants to Nevro Corp. D.C., R.P.A., J.S., and B.G. are employees of Nevro Corp."

Author's name: Leonardo Kapural

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Address: Carolina's Pain Institute, 145 Kimel Park Drive, Suite 330,Winston-Salem, NC 27103, USA

Start date - End date: "Enrollment was initiated on September 10, 2018. Prespecified independent interim analysis at 40% of the enrollment target indicated the sample size was sufficient to show superiority of treatment at the primary endpoint; therefore, enrollment was stopped at 211"

Trial registration: NCT03680846

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomization will be used to help maintain balance in allocation at each site. Randomization assignments will be computer generated and allocated via an electronic data capture system. Randomization is 1:1 to either the 10-kHz SCS + CMM group or the CMM group."

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Allocation concealment (selection bias)	Low risk	Quote: "Block randomization will be used to help maintain balance in allocation at each site. Randomization assignments will be computer generated and allocated via an electronic data capture system."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not possible to blind CMM vs SCS
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: subjective outcomes - unblinded. Outcome assessment carried out by assessors aware of group allocation of participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: substantially different loss to follow-up in SCS vs CMM groups. Loss in 76 randomised to CMM group = 1 at 3 months and 6 months (1.3%); loss in 83 randomised to SCS = 15 at 3 months (18.1%) and 18 at 6 months (21.6%).
Selective reporting (reporting bias)	Unclear risk	Comment: outcomes in preliminary report matched those in registry. Only per-protocol results provided (ITT unavailable) so far
Other bias	High risk	Comment: enrichment-type design: sample selected based on going poorly with CMM. Control group then receives treatment they are going poorly with. Intervention arm is given SCS and followed up only if they respond. Those who are in the n = 65 are only those who responded. No such treatment given to control arm (i.e. delete those who do not respond to CMM, keep those who do). Plan was to randomise 216 participants but stopped trial after randomising 159. Co-interventions not controlled between groups. Range of co-interventions included within CMM aspect of trial. Participants also able to maintain other treatment that was previously effective.

Kumar 2007

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Analysis:** primary analysis: ITT; secondary analysis: as-treated and ITT **Sample size calculation:** "A total of 80 patients (40 in the SCS arm and 40 in the CMM [conventional medical management] arm) will need to be included in the ITT analysis. This sample size calculation is based upon the assumption that the proportion of patients successfully treated will be 42.5% in the SCS arm and 14.5% in the CMM arm, with a power of 80% and an alpha < 0.05.... Taking into account a drop-out rate of 20%, a total of 100 patients need to be included in this study." **Study design:** parallel RCT, SCS versus no treatment **Trial aim:** to test the hypothesis that SCS in addition to conventional medical management (CMM) is more effective in people with FBSS than CMM alone. **Trial duration:** 12 months
Participants	**Baseline characteristics** 'No intervention' group • Age: mean (SD) = 52.0 (10.7)

Kumar 2007 *(Continued)*

- Sex: male = 21 (44%), female = 27 (56%)
- Pain duration: not reported
- Baseline back pain score: mean (SD) 0-100 = 44.8 (23.2)
- Baseline function score: mean ODI = 54 (SD not reported)
- QoL score: SF-36 (mental component SDs not reported at baseline); mental health = 55; role emotional = 35; social functioning = 36; vitality = 32
- Baseline leg pain score: mean (SD) 0-100 = 73.4 (14.0)
- Work status: 10 currently employed (21%)
- No. of participants: 48
- Healthcare use: 22 had > 1 surgery (46%)
- Pain medication use: not reported
- Socioeconomic status: not reported

Conventional spinal cord stimulation group

- Age: mean (SD) = 48.9 (10.0)
- Sex: 22 female (42%)
- Pain duration: not reported
- Baseline back pain score: mean (SD) 0-100 = 54.5 (24.3)
- Baseline function score: mean ODI = 56 (SD not reported)
- QoL score: SF-36 (mental component SDs not reported at baseline); mental health = 50; role emotional = 37; social functioning = 34; vitality = 30
- Baseline leg pain score: mean (SD) 0-100 = 76.0 (13.0)
- Work status: 12 currently employed (23%)
- No. of participants: 52
- Healthcare use: 28 had > 1 surgery (54%)
- Pain medication use: not reported
- Socioeconomic status: not reported

Inclusion criteria: "Eligible patients were at least 18 years of age. They suffered from neuropathic pain of radicular origin (radiating in dermatomal segments L4 and/or L5 and/or S1) predominantly in the legs (exceeding back pain), of an intensity of at least 50 mm on a visual analogue scale (VAS: 0 equalling no pain, to 100 mm representing the worst possible pain) for at least 6 months after a minimum of one anatomically successful surgery for a herniated disc. Thus all patients had a documented history of nerve injury, i.e. root compression by herniated disc, competent to explain the complaint of radiating pain. In addition the neuropathic nature of pain was checked as per routine practice at the centre (i.e. by clinical investigation of pain distribution, examination of sensory/motor/reflex change, with supporting tests such as X-ray, MRI and EMG). Some of the eligible patients had undergone additional procedures, namely repeat lumbar disc operations, laminectomies with or without foraminotomies or spinal fusion"

Exclusion criteria: "Patients were excluded if they had another clinically significant or disabling chronic pain condition; an expected inability to receive or operate the SCS system; a history of a coagulation disorder, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis, or ankylosing spondylitis; evidence of an active psychiatric disorder, another condition known to affect the perception of pain, or inability to evaluate treatment outcome as determined by the principal investigator; life expectancy of less than 1 year; or an existing or planned pregnancy"

Pretreatment: "Baseline characteristics were relatively well balanced in the two groups, the only exception being a slightly higher back pain score in the CMM group. Although a low proportion of patients were receiving non-drug treatment (such as physical rehabilitation) at baseline, many of these treatments had been tried in the past"

Minimum pain intensity: leg pain ≥ 50 on 100-point VAS

Number of participants: 214 participants assessed, 51 excluded due to predominant back pain, 28 excluded for other reasons, 35 refused randomisation, 100 participants randomised. 94 participants at

Kumar 2007 *(Continued)*

	6-month analysis, 88 at 12-month analysis, 52 at 24-month analysis (42 in the SCS and 10 in the CMM group). **Source of participants:** specific locations for recruitment not stated
Interventions	'No intervention' group • Frequency: not applicable • Stimulator type: not applicable • Lead number and type: not applicable • Manufacturer: not applicable • Description: "At baseline, the non-SCS therapy received by both groups was reviewed and actively managed, at the discretion of the study investigator and according to local clinical practice. Non-SCS therapy included oral medications (i.e. opioid, non-steroidal anti-inflammatory drug, antidepressant, anticonvulsant/antiepileptic and other analgesic therapies), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. The protocol excluded other invasive therapy, such as spinal surgery or implantation of an intrathecal drug delivery system." • Burst or tonic stimulation: not applicable • Duration: 12 months • Co-interventions: drug therapies at 6 months: 31 taking opioids (70%); 22 taking NSAIDs (50%); 24 taking antidepressants (55%); 22 taking anticonvulsants (50%). Main non-drug therapies at 6 months: 8 physical rehabilitation (18%); 5 psychological rehabilitation (11%); 3 acupuncture (7%); 4 massage (9%); 5 transcutaneous electrical nerve stimulation (TENS) (11%) Conventional spinal cord stimulation group • Frequency: mean (SD) settings were an amplitude of 3.7 V (2.0), a pulse width of 350 µs (95.5) and a rate of 49 Hz (16.4). Almost half (45%) required an amplitude of 4 V or more • Stimulator type: implantable neurostimulation system (Synergy system, Medtronic, Inc., Minneapolis, MN). • Lead number and type: not specified • Manufacturer: Medtronic • Description: all participants assigned to the SCS group underwent a screening trial. Those experiencing stimulation-induced paraesthesia covering at least 80% of their pain area (ie, pins and needles in the same area of the back and leg that they were feeling pain) and at least 50% leg pain relief, received an implantable neurostimulation system • Burst or tonic stimulation: not specified; assumed tonic • Duration: 12 months • Co-interventions: drug therapies at 6 months: 28 taking opioids (56%); 17 taking NSAIDs (34%); 17 taking antidepressants (34%); 13 taking anticonvulsants (26%). Main non-drug therapies at 6 months: 3 physical rehabilitation (6%); 1 psychological rehabilitation (2%); 0 acupuncture (0%); 0 massage (0%); 0 TENS (0%)
Outcomes	Outcomes measured at 6 months (ITT) and 12 months (after cross-over allowed) **Outcomes included in review** • Self-completed VAS (100 mm) separately for back pain and leg pain; n (%) who achieved at least 50% leg pain relief • Quality of life (SF-36 - mental health component) • Function (Oswestry Disability Index) • Use of pain medication and non-drug therapies • Opioid use (MME) • Nature and frequency of treatment related events and complications **Outcomes excluded from review** • Treatment satisfaction

Kumar 2007 *(Continued)*

Identification	**Sponsorship source:** Medtronic **Country:** 12 centres across Europe, Canada, Australia, Israel **Setting:** 100 participants in a total of 12 centres in Europe, Canada, Australia, and Israel **Author's name:** Krishna Kumar **Institution:** Department of Neurosurgery, Regina General Hospital, Regina, Sask., Canada **Email:** krishna.kumar@rqhealth.ca; krishnakumar9@hotmail.com **Address:** Department of Neurosurgery, Regina General Hospital, 1440 14th Avenue, Regina, Sask., Canada S4P OW5 **Start date - End date:** April 2003 to June 2005 **Trial registration:** ISRCTN 77527324
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomly assigned in a 1:1 ratio to conventional medical management with SCS (SCS group) or without SCS (CMM group). A biostatistician prepared random computer-generated blocks (random sequence of either 2 or 4 patients) on a per site basis. The randomisation was electronically locked and could only be accessed after a patient entered the trial."
Allocation concealment (selection bias)	Low risk	Quote: "A biostatistician prepared random computer-generated blocks (random sequence of either 2 or 4 patients) on a per site basis. The randomisation was electronically locked and could only be accessed after a patient entered the trial." Comment: randomisation schedule was locked until after a person was included in the trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Given the nature of the intervention, it was impossible to blind patients and difficult to blind investigators during the trial." Comment: participants not blinded; could influence self-assessment of pain and function
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Quote: "Given the nature of the intervention, it was impossible to blind patients and difficult to blind investigators during the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "By 12-months follow-up: 16 received CMM only (includes 4 patients who requested to cross to SCS but failed trial screening) 28 crossed to SCS." Quote: "Primary outcome data were therefore available for 93 patients (50 SCS group and 43 CMM group) at 6 months." Comment: 88 of 100 randomised therefore adequate follow-up
Selective reporting (reporting bias)	High risk	Comment: some time points and reports of variation missing. Retrospectively registered (www.isrctn.com/ISRCTN77527324?q=77527324&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=ba-

Kumar 2007 *(Continued)*

		sic-search). Primary outcome and time point matches protocol but this was published in 2005 after recruitment had finished in 2003
Other bias	High risk	Comment: co-interventions differently applied across groups

Perruchoud 2013

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Analysis:** "responder analysis, with a responder (treatment benefit) defined as a patient reporting at least 'minimally improved' on the PGIC scale [patient's global impression of change]" ; "Pain VAS and EQ-5D index values were analyzed using a conventional within-subjects model, accounting for the 'period effect' and utilizing the baseline scores before each treatment (visits 2 and 4) in an analysis of covariance model (regarded as the most efficient model)" **Sample size calculation:** "For the purposes of the sample size estimation, we assume that the proportion of patients who respond in the sham condition (but not in the HFSCS [high-frequency spinal cord stimulation] condition) is essentially zero, and the proportion of patients responding in the HFSCS condition and not in the sham is 25% (0.25). The difference in proportion of responders is 0.25, number needed to treat (NNT)=4. In stricter terminology, the probability of success (responder) in the sham treatment is zero and the probability of success in the HFSCS is 0.25. For our statistical analysis plan, we adopt the recently presented methods of Schouten and Kester, in which the treatment difference (HFSCS sham) for each of the two treatment sequences is computed and then averaged. In this analysis, the mean treatment effect is not confounded by any 'period effect'; opposite 'period effects' in each sequence cancel out. The mean difference in proportions together with its 95% confidence interval (CI) and two-sided p-value will be presented. Schouten and Kester also provide a formula—matched directly to their analysis strategy—for sample size estimation for crossover designs with a binary outcome. With 90% power, 2 p=0.05, 38 patients are required to detect a difference in the proportions, responding (HFSCS sham) to 0.25 (as detailed above)" **Study design:** "randomized double-blind two-period crossover study" **Trial aim:** "Determine effect of high-frequency stimulation vs placebo on a patient's global impression of change at 2 week follow-up" **Trial duration:** 2 weeks (8 weeks of cross-overs: 4 x 2 week periods with outcomes collected at end of 2-week period)
Participants	**Baseline characteristics** Overall • Age: Mean (SD) = 54.2 (10.7) • Sex: 17/33 female (51.5%); 16/33 male (48.5%) • Back pain duration: not reported • Baseline back pain score: 10 cm VAS for back AND leg pain = 4.0 (2.2) • Baseline function score: not reported • QOL score: EQ-5D = 0.468 (0.312) • Baseline leg pain score: 10 cm VAS for back AND leg pain = 4.0 (2.2) • Work status: not reported • n: 38 • SE status: not reported

Perruchoud 2013 *(Continued)*

- Pain medication use: Statement on medication use in results "Overall medication use remained unchanged in all but one patient who modestly increased the dose of oral morphine (2 x 10 mg/day) at visit 3"
- Diagnostic criteria: be treated with SCS for chronic low back pain radiating in one or both legs, and have stable pain control
- Healthcare use: not reported

Inclusion criteria: "To be included in the study, patients had to

- sign informed consent,
- be able to understand the study and its implication as well as be able and willing to comply with the outcome measurements,
- be treated with SCS for chronic low back pain radiating in one or both legs,
- have stable pain control, and
- be implanted with a Medtronic (Minneapolis, MN, USA) impulse generator, either rechargeable or battery powered"

Exclusion criteria: "We excluded patients who were unable to understand the method used of keep a diary and those with limited autonomy or availability for the study"

Pretreatment: n/a; cross-over trial

Minimum pain intensity: not stated. Only report participants must have 'stable pain control'

Number of participants: 40 enrolled; 2 withdrew before randomisation; 5 excluded: 1x lead breakage; 1 x battery exhaustion; 1 x pulse generator flipping; 2 x withdrew consent; 33 provided data at (immediate) follow-up. 38 randomised and 33 followed up

Source of participants: "Forty patients already treated with SCS were recruited for the study at the Department of Anaesthesia and Pain Management Hôpital de Morges (Switzerland) and the Pain Clinic at the James Cook University Hospital Middlesbrough (UK)"

Interventions

Intervention characteristics

High-frequency spinal cord stimulation

- Frequency: 5000 Hz; pulse width is adjusted to 60 ms [milliseconds]
- Stimulator type: "Medtronic(Minneapolis, MN, USA) impulse generator, either rechargeable (RestoreADVANCED®, RestoreSensor®, or RestoreUltra®)or battery powered (PrimeADVANCED®)"
- Lead number and type: not stated
- Manufacturer: Medtronic
- Description: "Subjects randomized to receive HFSCS were programmed by the nonblinded investigator following four steps: 1) using no more than three active contacts, paresthesia covering as much as possible the area of pain is elicited with conventional stimulation; 2) while keeping the current amplitude below sensory threshold, the stimulation frequency is increased to 5000 Hz; 3) the current amplitude is progressively increased to the sensory threshold; and 4) the current amplitude is decreased again below threshold amplitude until the patient is unable to feel paresthesias regardless of the position. Pulse width is adjusted to 60 ms [milliseconds] under HFSCS"
- Burst or tonic stimulation: not stated
- Duration: 2-week periods of stimulation; 8 weeks' study duration i.e. 2 weeks' current stimulation, 2 weeks' HF or sham, 2 weeks' current stimulation, 2 weeks' HF or sham
- Co-interventions: co-interventions not reported according to intervention period. General statement only "Overall medication use remained unchanged in all but one patient who modestly increased the dose of oral morphine (2×10 mg/day) at visit 3."

Placebo

- Frequency: nil
- Stimulator type: "Medtronic(Minneapolis, MN, USA) impulse generator, either rechargeable (RestoreADVANCED®, RestoreSensor®, or RestoreUltra®)or battery powered (PrimeADVANCED®)"

Perruchoud 2013 *(Continued)*

- Lead number and type: not stated
- Manufacturer: Medtronic
- Description: "Subjects randomized to receive sham underwent the programming steps 1–4 as described above by the nonblinded investigator. However, the stimulator was switched off after completing step 4."
- Burst or tonic stimulation: N/A
- Duration: 2-week periods of stimulation; 8 weeks' study duration i.e. 2 weeks' current stimulation, 2 weeks' HF or sham, 2 weeks' current stimulation, 2 weeks' HF or sham
- Co-interventions: co-interventions not reported according to intervention period

Outcomes	Outcomes measured at 2 weeks (immediate-term outcome) **Outcomes included in review** • Patient's global impression of change (7-point Likert scale) • Back and leg pain VAS; 5-day average at end of two-week period • EQ-5D • Adverse events • Medication use **Outcomes excluded from review** • Nil
Identification	**Sponsorship source:** "Medtronic funded the study and the manufacturer provided the technical support for IPG programming. However, no member of Medtronic personnel contributed to the design of the study or the collection or analysis of the data." Also, "Dr. C. Perruchoud, Dr. S. Eldabe, and Pr. E. Buchser consult for and are members of advisory boards for Medtronic. Dr. C. Perruchoud, Dr. S. Eldabe, and Pr. E. Buchser received consulting fees, honoraria, speaking fees, and travel fees from Medtronic." **Country:** Switzerland and UK **Setting:** recruited for the study at the Department of Anaesthesia and Pain Management Hôpital de Morges (Switzerland) and the Pain Clinic at the James Cook University Hospital Middlesbrough (UK) **Comments:** - **Author's name:** Christophe Perruchoud **Institution:** Department of Anaesthesia and Pain Management, EHC—Hôpital de Morges, Morges, Switzerland **Email:** christophe.perruchoud@chuv.ch **Address:** Department of Anaes-thesia and Pain Management, EHC—Hôpital de Morges, Ch. du Crêt 2, 1110 Morges, Switzerland. **Start date - End date:** not provided **Trial registration:** not registered
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomized at baseline to receive either HFSCS or no stimulation (sham) using a central randomization service. Non-blinded investigators have provided clinical care for the patients in the study but have taken

Perruchoud 2013 *(Continued)*

		no part in any study data collection, which has been performed exclusively by blinded investigators." Comment: randomisation performed by central service and applied by investigators independent of those collecting outcome data
Allocation concealment (selection bias)	Low risk	Quote: "Subjects were randomized at baseline to receive either HFSCS or no stimulation (sham) using a central randomization service. Non-blinded investigators have provided clinical care for the patients in the study but have taken no part in any study data collection, which has been performed exclusively by blinded investigators". Quote: "For the purpose of the study, teams were divided into unblinded clinical care teams who did the programming and instructed the patients and the blinded observers who collected the study outcome measures with no input into the patient care." Comment: enrolment performed by blinded investigator
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "We asked all patients to guess which group they were in at the end of two weeks and the percentage guessing correctly is what can be expected from chance (45% guessed correctly at visit 3 and 55% at visit 5); none described paresthesias. This was consistent across both centers." Quote: "A major priority of this study was to ensure proper blinding as the paresthesia-free stimulation (HFSCS) would, for the first time ever, allow a comparison with true sham conditions, i.e., the absence of stimulation. We took every precaution to conceal the nature of the treatment applied and research teams were split into two groups of blinded and unblinded personnel with no crossover, and only personnel blinded to the therapy collected outcome data from the patients. In patients with rechargeable devices, we have programmed the IPG to have a current leakage in the sham period to mirror the current usage during HFSCS period. This maintained the requirement for identical recharging times whether sham or HFSCS was delivered. Results show that blinding was successful as four out of eight patients responding favorably to sham treatment at visit 3 indicated that they thought they were on sham and the other four that they had received HFSCS." Comment: blinding appeared to be successful (owing to low paraesthesias and matched recharging time in sham and high frequency periods)
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "Results show that blinding was successful as 4/8 patients responding favourably to sham at visit 3 indicated that they thought they were on sham and the other four that they had received HFSCS"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data provided on 33 of 38 randomised (87%). Justification given for participant lost.
Selective reporting (reporting bias)	High risk	Comment: measures of variation not reported. No trial registration, no protocol paper. Outcomes on medication use and adverse events do not specify timings to distinguish what treatment these reactions were in response to.
Other bias	High risk	Quote: "A further limitation of our study is the short (two-week) duration of treatment with HFSCS and sham. It is apparent, particularly from the VAS score results, that a carryover effect of conventional SCS may have played a significant role. It is also plausible that expectation for a better result in a subsequent period may have led to an unwillingness to disrupt the study by opting out of the treatment period. In future studies, it may be desirable to consider a longer duration of treatment in order to avoid this “carryover effect."

Perruchoud 2013 *(Continued)*

	Quote: "There was an obvious 'period effect' in the sense that effect of HFSCS and sham seems to be equal and only the order in the sequence, not the nature of the treatment, appears to dictate the effect." Comment: evidence of carryover effects and period effects (though period effect were controlled for statistically by using paired data?)

Rigoard 2019

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Analysis:** "For the primary and secondary objectives at 6 months, the primary analysis followed the ITT principle. In addition, completers and as-treated analyses were undertaken. The following analysis definitions were applied: ITT, between-group comparison based on random allocation of all patients; completers, between-group comparison based on random allocation of patients with complete data; and as-treated, between-group analysis based on the treatment received at 6 months and on patients with complete data. Patients with missing data were treated as non-responders for the primary objective and no-change for secondary objectives for the ITT analysis. For additional outcome measures, the as-treated populations were used." **Sample size calculation:** "The primary hypothesis was that the proportion of LBP responders in the SCS group would be greater than that in the OMM group. A minimum sample of 212 was required to provide 90% power to detect a between-group difference of 20% in responder rates. The assumptions of between-group difference were based on results of the PROCESS RCT. Sample size re-estimation was conducted by an independent statistician when 140 patients reached 6 months of follow-up using Lan-DeMets with O'Brien-Fleming boundary methods. No adjustments to sample size resulted from this analysis." **Study design:** "PROMISE was a multicentre, prospective, randomized, open-label, parallel-group, controlled trial conducted at 28 investigational sites." **Trial aim:** "confirm the effectiveness and cost-effectiveness of SCS in the population with predominant LBP" **Trial duration:** 24 months
Participants	**Baseline characteristics** No intervention group • Age: mean (SD) = 55.1 (10.2) years • Sex: n (%). Female = 64 (59.3%). Male = 44 (40.7%) • Back pain duration: mean (SD) years = 7.0 (7.1) • Baseline back pain score: mean (SD) 0-10 = 7.6 (1.2) • Baseline function score: mean (SD) ODI = 54.8 (14.4) • QOL score: mean (SD) EQ-5D index value = 0.36 (0.24) • Baseline leg pain score: mean (SD) Leg pain 0-10 = 5.3 (2.1) • Work status: 47 unable to work (43.5%) • No. of participants: 108 • Socioeconomic status: not measured • Pain medication use: not provided for ITT population • Diagnostic criteria: "for the purposes of this study, FBSS is defined as persistent or recurrent low back and leg pain of at least 6 months duration, following at least one decompression and/or fusion procedure"

Rigoard 2019 *(Continued)*

- Healthcare use: not reported

Conventional spinal cord stimulation group

- Age: mean (SD) = 52.8 (12.5) years
- Sex: n (%). Female = 68 (61.8%). Male = 42 (38.2%)
- Back pain duration: mean (SD) years = 6.4 (7.4)
- Baseline back pain score: mean (SD) 0-10 = 7.5 (1.2)
- Baseline function score: mean (SD) ODI = 55.0 (14.6)
- QOL score: mean (SD) EQ-5D index value = 0.34 (0.27)
- Baseline leg pain score: mean (SD) Leg pain 0-10 = 5.4 (1.9)
- Work status: 64 unable to work (58.2%)
- No. of participants: 110
- Socioeconomic status: not measured
- Pain medication use: not provided for ITT population
- Diagnostic criteria: "for the purposes of this study, FBSS is defined as persistent or recurrent low back and leg pain of at least 6 months duration, following at least one decompression and/or fusion procedure"
- Healthcare use: not reported

Overall

- Age: mean (SD) = 53.9 (11.5) years
- Sex: 132 female (60.6%)
- Back pain duration: mean (SD) years = 6.7 (7.2)
- Baseline back pain score: mean (SD) 0-10 = 7.5 (1.2)
- Baseline function score: mean (SD) ODI = 54.9 (14.4)
- QOL score: mean (SD) EQ-5D index value = 0.35 (0.26)
- Baseline leg pain score: mean (SD) Leg pain 0-10 = 5.3 (2.0)
- Work status: 111 unable to work (50.9%)
- No. of participants: 218
- Socioeconomic status: not measured
- Pain medication use: not provided for ITT population
- Diagnostic criteria: "for the purposes of this study, FBSS is defined as persistent or recurrent low back and leg pain of at least 6 months duration, following at least one decompression and/or fusion procedure"
- Healthcare use: not collected (apart from medication use in 'as treated' population

Inclusion criteria: "The subject is a candidate for SCS with the multicolumn Specify® 5-6-5 surgical lead; has FBSS and does not require further surgery (for the purposes of this study, FBSS is defined as persistent or recurrent low back and leg pain of at least 6 months duration, following at least one decompression and/or fusion procedure); presents average low back pain ≥5 and that is greater than leg pain as assessed by the baseline NPRS [Numeric Pain Rating Scale]; and has persistent low back and leg pain."

Exclusion criteria: "The subject is being treated or has been treated with SCS, subcutaneous or peripheral nerve stimulation, being treated with an intrathecal drug delivery system or requires back surgery at the location related to his/her original back pain complaint or experimental therapies; had most recent back surgery less than 6 months ago; has low back pain only (no leg pain) as assessed by the baseline NPRS; is suspected by the investigator of substance abuse that might confound the study results; has unresolved major issues of secondary gain, as determined by the investigator; exhibits major psychiatric morbidity, untreated or refractory to treatment as determined by the investigator; has consistent severe pain (that is, 10 out of 10) without fluctuation, which might confound the results of this study; has radiographic evidence of instability requiring fusion; has pain relieved completely by recumbency (mechanical pain); has a serious neurologic deficit; has a history of coagulation disorder, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis, or ankylosing spondylitis;has calcific arachnoiditis; has severe thoracic stenosis; has life expectancy < 24 months beyond study enrolment; is <18 years of age; is pregnant or planning to become pregnant during the course of the study; is enrolled

Rigoard 2019 *(Continued)*

in or plans to enroll in any study that might confound the results of this study; would be unable to operate the SCS equipment, based on the opinion of the principal or subinvestigator; is unwilling to be treated with SCS, attend visits as scheduled, and/or comply with study requirements; is unable to undergo study assessments or complete questionnaires independently (for example, is illiterate); and is a member of a vulnerable population."

Pretreatment: no clinically important differences in ITT population shown

Minimum pain intensity: ≥ 5/10

Number of participants: 2858 = screened, 278 = enrolled, 218 = randomised, 196 = completed 6 month assessment, 174 = completed 12 month assessment, 154 = completed 24 month visit

Source of participants: 28 investigational sites in Belgium, Canada, Colombia, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States.

Interventions

Intervention characteristics

No intervention

- Frequency: n/a
- Stimulator type: n/a
- Lead number and type: n/a
- Manufacturer: n/a
- Description: "Pain treatment will be evaluated, and medical management of patient's pain will be optimized in both arms. As part of the confirmation of eligibility (prior to randomization), the investigator and subject will determinean individual OMM treatment plan, which should include non-investigational pharmacologic agents (for example, tricyclic antidepressants, opioid analgesics or tramadol, antiepileptics, or lidocaine) and/or interventional therapies (for example, therapeutic injections, radiofrequency, acupuncture, functional restoration, physical therapy, and psychological interventions, such as cognitive behavioral therapy) as appropriate. The following treatments are excluded from OMM: intrathecal drug delivery, peripheral nerve stimulation (not an approved indication in the United States), back surgery at the location related to the patient's original back pain complaint, and experimental therapies. Data regarding pain treatments implemented during the study will be collected to reveal how medical management was optimized. After randomization, as well as at all scheduled follow-up visits, the subject and physician will further discuss OMM to determine the best course of continued action."
- Burst or tonic stimulation: n/a
- Duration: 6 months (then allowed to cross and followed to 24 months)
- Co-interventions: provided, but only for 'as treated' population. Medication use appears slightly higher in control group in the as treated population

Conventional spinal cord stimulation

- Frequency: 20-1200 Hz
- Stimulator type: multicolumn surgical lead and a compatible neurostimulator (model 97714, n = 49; 37702, n = 39; 97702, n = 27; 37714, n = 12; 97712, n = 4; 37713, n = 3; 97713, n = 3; 37712, n = 2; and 37701, n = 1)
- Lead number and type: multicolumn surgical lead (Specify 5-6-5; Medtronic)
- Manufacturer: Medtronic
- Description: "In addition to OMM, patients randomized to the SCS arm will undergo an SCS screening test (3-day minimum). The screening test may be conducted with the Specify® 5-6-5 surgical lead or with a percutaneous lead(s). If successful, a SCS system will be implanted. A screening test will be determined to be successful if the subject finds the feeling of paresthesia acceptable and has adequate low back pain relief with usual activity and appropriate analgesia as assessed by the physician. Physicians can consider a conducting second screening test with the Specify® 5-6-5 lead if a screening test with a percutaneous lead led to inadequate paresthesia coverage of low back pain and/or painful extraneous stimulation (for example, chest wall pain, pressure or sharp mid-back pain). The final system implanted will consist of a Medtronic pulse generator (rechargeable or primary cell) and a Specify® 5-6-5 surgical lead. Subjects should receive their permanent implant within 60 calendar days from

Rigoard 2019 *(Continued)*

	randomization. They will be programmed to their optimal programming parameters and will be able to ad-just their stimulation with the patient programmer,within the settings programmed in the clinic. Subjects will be provided with a patient programmer manual and will be instructed on the proper use and handling of the patient programmer." • Burst or tonic stimulation: not mentioned • Duration: 6 months (then allowed to cross and followed to 24 months) • Co-interventions: provided, but only for 'as treated' population. Medication use appears slightly higher in control group in the as treated population
Outcomes	Outcomes measured at 6, 12, and 24 months. Cross-over allowed from 6 months. Primary analysis performed on 6 month outcomes. **Outcomes included in review** • Global improvement (≥ 50% pain relief) • Back pain VAS • Leg pain VAS • Function (ODI) • HRQOL (EQ5-D) **Outcomes excluded from review** • SF-36 PCS score (QOL captured by EQ-5D)
Identification	**Sponsorship source:** "Medtronic funded the study and was involved in the study design, data collection, data analysis, data interpretation, and writing of the report." **Country:** Belgium, Canada, Colombia, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States **Setting:** Neurosurgical departments **Comments: -** **Author's name:** Phillippe Rigoard **Institution:** Department of Neurosurgery, Poitiers University Hospital **Email:** philipperigoard@yahoo.fr **Address:** Department of Neurosurgery, Poitiers University Hospital, CHU de Poitiers, Laboratoire PRISMATICS Bâtiment CCV Etage 0 2, rue de la Milétrie CS 90577 86000 Poitiers, France **Start date - End date:** screened from 8 January 2013 through 31 August 2015, with the last patient enrolled on 15 August 2015 and the final patient visit on 20 June 2017 **Trial registration:** NCT01697358
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated (1:1 ratio) to SCS 1 OMM (SCS group) or OMM alone (OMM group) using random, permuted blocks of 4 and 2 stratified by investigational site."
Allocation concealment (selection bias)	Low risk	Quote: "To maintain allocation concealment, randomization assignments were provided using an electronic data management system."

Rigoard 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Due to the nature of the treatments, the treating physicians and patients could not be blinded to the treatment group." Comment: no blinding of participants due to undergoing surgery for implantation of SCS device
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Quote: "Regarding assessment bias, due to the nature of the treatments, the study cannot be blinded (the form of SCS used in this trial requires paresthesia); however, to minimize potential assessment bias, questionnaires will be completed by patients without study staff consultation or visibility, using a secured electronic tablet." Comment: no blinding of participants or the assessors. Assessors linked to funding body and deemed likely to increase risk of bias due to conflict of interest Comment: patients (outcome assessors) were providing subjective reports of pain
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: different loss of data in the two groups for ITT 6-month outcomes: 18 did not provide data in SCS group (16.3%) versus 3 in OMM group (2.8%)
Selective reporting (reporting bias)	Unclear risk	Comment: outcomes reported reflect those described through texts and in trials registry but some outcomes have 'as treated' analysis only
Other bias	High risk	Quote: "Medtronic funded the study and was involved in the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication." Comment: this judgement concerns outcomes beyond 6 months. Substantial cross-over to SCS at 6 months - becomes a cohort study for 12- month and 24-month outcomes. Only 29 of 108 randomised to OMM remained in the group at 12 months.

Schu 2014

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** Cross-over **Analysis:** all analyses were intention-to-treat and involved all enroled participants **Sample size calculation:** "Ethics committee approval was conditional upon including a maximum of 20 patients in the study. Utilizing a one-way ANOVA [analysis of variance] as the primary analysis to detect the difference between the stimulation groups as described above, the power to detect a difference of 2.0 on the pain intensity NRS was calculated as 80% with a sample size of 20 and an observed average standard deviation for the three stimulation groups of 2.0." **Study design:** prospective, randomised, double-blind, placebo-controlled cross-over design **Trial aim:** "...evaluate the effectiveness of burst stimulation for the treatment of failed back surgery syndrome." **Trial duration:** 3-week intervention duration - cross-over of 3 treatment arms all of 1-week duration

Schu 2014 *(Continued)*

Participants	**Baseline characteristics** Overall • Age: mean (SD) = 58.6 (10.2) • Sex: 7 male (35%), 13 female (65%) • Back pain duration: not measured • Baseline back pain score: mean (SD) NRS = 5.6 (1.7) • Baseline function score: mean (SD) ODI = 22.3 (8.0) • QOL score: not measured • Baseline leg pain score: not measured • Work status: not measured • No. of participants: 20 • Socioeconomic status: not measured • Pain medication use: not measured • Diagnostic criteria: "a diagnosis of FBSS" • Healthcare use: not measured **Inclusion criteria:** "Eligible participants were all adults aged 18 to 75 years who had a diagnosis of FBSS, had been implanted with a St. Jude Medical SCS system at least three months previously, and were receiving conventional tonic stimulation at a frequency of 40 to 50 Hz. In order to participate, patients were required to have had stable medication for at least four weeks prior to data collection and to agree not to increase medication consumption during the study period." **Exclusion criteria:** "Patients were excluded from the study if they suffered from a psychiatric disorder, had a medical history that included a life-threatening illness, had documented drug abuse/addiction in the six months prior to the collection of baseline data, or had another severe chronic illness. Patients were also excluded if they were participating in another clinical study or had a pre existing implanted demand cardiac pacemaker, intrathecal drug pump, or any neurostimulation device other than the spinal cord stimulator required for the study." **Pretreatment:** n/a; cross-over trial **Minimum pain intensity:** none **Number of participants:** 150 assessed for eligibility, 20 consented, randomised and completed. **Source of participants:** conducted at Düsseldorf University Hospital in Germany
Interventions	**Intervention characteristics** Placebo group • Frequency: no stimulation was programmed (the device was switched off) • Stimulator type: St. Jude Medical SCS system • Lead number and type: SCS leads located at the mid-thoracic position (vertebral level T7–10) • Manufacturer: St Jude Medical • Description: placebo stimulation, where no stimulation was programmed (the device was switched off) • Burst or tonic stimulation: n/a • Duration: 1 week • Co-interventions: instructed to not increase pain medication during the study Conventional spinal cord stimulation • Frequency: 500 Hz. Mean (SD) pulse width under 500-Hz tonic stimulation = 370.8 (135.4) µs [microsecond], and mean (SD) amplitude = 5.5 (3.6) mA. • Stimulator type: St. Jude Medical SCS system • Lead number and type: SCS leads located at the mid-thoracic position (vertebral level T7–10)

Schu 2014 *(Continued)*

- Manufacturer: St Jude Medical
- Description: tonic stimulation at a frequency of 500 Hz (subsensory amplitude)
- Burst or tonic stimulation: tonic
- Duration: 1 week
- Co-interventions: participants agree not to increase medication consumption during the study period

Burst spinal cord stimulation group

- Frequency: 500 Hz, pulse width 1000 µs;
- Stimulator type: St. Jude Medical SCS system
- Lead number and type: SCS leads located at the mid-thoracic position (vertebral level T7–10)
- Manufacturer: St Jude Medical
- Description: burst stimulation—packets of five pulses (pulse width 1 ms [millisecond]) at 500 Hz, delivered 40 times per second (subsensory amplitude)
- Burst or tonic stimulation: burst
- Duration: 1 week
- Co-interventions: participants agree not to increase medication consumption during the study period

Outcomes	Outcomes measured at one week (immediate-term outcome) **Outcomes included in review** • Pain (NRS) • Function (ODI) • Safety (adverse events) **Outcomes excluded from review** • Pain quality • Patient stimulation preference • Pain catastrophising • Pain vigilance
Identification	**Sponsorship source:** none stated **Country:** Germany **Setting:** Neurosurgical clinic; Düsseldorf University Hospital in Germany **Comments:** funding for trial not stated. Jan Vesper is a consultant for St. Jude Medical, receiving payment for preparing and giving educational presentations, as well as reimbursement for travel expenses. Philipp Slotty received a fellowship training program from St. Jude Medical. Gregor Bara received a fellowship grant from St. Jude Medical. Stefan Schu is a consultant for St. Jude Medical and Spinal Modulation Inc., receiving payment for preparing and giving educational presentations, as well as reimbursement for travel expenses. **Author's name:** Jan Vesper **Institution:** Department of Functional Neurosurgery and Stereotaxy, Neurosurgical Clinic, Heinrich Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany **Email:** jan.vesper@uniklinik-duesseldorf.de **Address:** Jan Vesper, MD, PhD, Department of FunctionalNeurosurgery and Stereotaxy, Neurosurgical Clinic, Heinrich Heine UniversityDüsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany **Start date - End date:** enrolled between February 2013 and May 2013 **Trial registration:** not stated

Schu 2014 *(Continued)*

Notes	This study contributed two estimates to both Analyses 1.1 and 1.5, one for each of the two types of SCS provided versus placebo. To account for multiplicity in our analysis, we divided n for the placebo group by two when calculating each mean difference and 95% CI derived from that study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "independent pain nurse allocated a colored ballot to each of the six possible treatment sequences and drew lots in order to prepare the randomization table." Comment: sequence prepared manually rather than by computer
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes containing colored ballots were then prepared by the independent pain nurse according to the randomization table and subsequently stored by the independent pain nurse in a secure location to ensure that the randomization envelopes remained concealed until treatment assignment. The independent pain nurse had no contact with the patient prior to randomization."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Both the investigator and patient were blinded to the treatment allocation throughout the study. The patients were not given a programming device to take home in order to ensure that they remained blinded." Comment: placebo-controlled; stimulation was "subsensory" therefore minimal paraesthesia and lower chance of patient knowing when the SCS system was turned off. However, no information provided to confirm attempts at blinding successful.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Quote: "Both the investigator and patient were blinded to the treatment allocation throughout the study." Comment: self-reported outcomes; therefore if patient was blind to SCS settings, low risk of bias during outcome assessment. However, no detail provided on assessment of whether blinding was successful
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data from all participants (n = 20) included in ITT analyses
Selective reporting (reporting bias)	High risk	Comment: no trial registry or protocol paper
Other bias	High risk	Comment: high risk of carryover and period effects; not accounted for in design (e.g. no washout period between cross-overs)

Sokal 2020

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Analysis:** "Statistical analyses and data manipulation and visualisation was conducted using R 3.6.2 statistical environment. To determine the effects of treatment type, we used Bayesian multilevel re-

Sokal 2020 *(Continued)*

gression models... We also used linear models for average daily pain and a zero-inflated negative binomial for total number of drugs taken. For both models, we used a stepwise procedure of testing the effects. First, a null model was fit to the data with the entire set of subject-level effects and population-level intercept. Second, main effects of the tested factors were added to the model (the "ME model"). Finally, interaction terms were added, resulting in the full model. Goodness of fit of each model was measured with leave-one-out information criterion (LOOIC). Lower values of LOOIC indicate better model fit, and a significant difference between two models occurs when the absolute difference in LOOIC of the models exceeds two times the standard error the difference."

Sample size calculation: not reported

Study design: randomised, semi-double-blind, cross-over, placebo-controlled trial

Trial aim: "The objective of this study was to evaluate the effectiveness of currently available types of SCS. We tested three available waveforms: (1) low frequency (LF), (2) 1 kHz, and (3) clustered tonic. We additionally tested sham stimulation to assess the placebo effect. We aimed to examine the effects of various stimulation modes on levels of pain and disability, as well as, assess the amount of analgesic medication required during each mode"

Trial duration: conducted from August 2018 to January 2020. Cross-over took a total of 8 weeks and consisted of four 2-week periods of (1) LF, (2) clustered tonic, (3) 1 kHz, and (4) sham (inactive) stimulation, each.

Participants

Baseline characteristics

Overall

- Age: mean (SD) = 57.4 (10.1) years
- Sex: 11/23 female (47.8%); 12/23 male (52.2%)
- Back pain duration: mean (SD) = 7.70 (6.28) years
- Baseline back pain score: mean (SD) Back and leg pain VAS (0-10) = 8.4 (1.0)
- Baseline function score: median Oswestry (IQR) = 19 (15)
- QOL score: not measured
- Baseline leg pain score: mean (SD) back and leg pain VAS (0-10) = 8.4 (1.0)
- Work status: not recorded
- No. of participants: 18
- Socioeconomic status: not recorded
- Pain medication use: not recorded at baseline
- Diagnostic criteria: "diagnosed with FBSS and five (22%) were diagnosed with CRPS, and pain was distributed in the lumbosacral area"
- Healthcare use: not recorded

Inclusion criteria: "Key inclusion criteria consisted of (1) patients with FBSS or CRPS with neuropathic and mixed pain in the low-back and/or legs that is refractory to conservative therapy, (2) chronic pain reported for at least 6 months, and (3) 18–80 years of age."

Exclusion criteria: "Exclusion criteria were (1) active malignancy, (2) addiction to alcohol and/or medication, (3) evidence of an active disruptive psychiatric disorder, (4) local infection at the site of surgical incision, and (5) pregnancy."

Pretreatment: n/a; cross-over

Minimum pain intensity: nil

Number of participants: 23 recruited, 5 participants were subsequently excluded from analyses for the following reasons: 1 failed a trial period after percutaneous electrode implantation (i.e. did not achieve satisfactory pain relief; patient 21); 3 participants (patients 1, 22, and 23) did not agree to further evaluation; and in 1 participant, feedback data were deemed irrelevant and unreliable (patient 12). Thus, 18 participants entered the randomisation phase two weeks after last surgery. All 18 participants were evaluated for a minimum of eight weeks in a prospective randomised trial.

Sokal 2020 *(Continued)*

Source of participants: "Patients were recruited in the Department of Neurosurgery and Neurology of University Hospital nr 2 of Collegium Medicum of Nicolaus Copernicus University in Bydgoszcz, Poland"

Interventions

Intervention characteristics

High-frequency spinal cord stimulation

- Frequency: 1000 Hz
- Stimulator type: non-rechargeable IPG (Precision Novi™) and in one case (patient 11), a rechargeable IPG (Montage™)
- Lead number and type: either one or two linear lead 8- or 16-contact (Infinion 16™) electrodes on [vertebral] levels T7–T10
- Manufacturer: Boston Scientific Co.
- Description: the 1 kHz waveform was programmed with f = 1 kHz, PW = 120 µs, and amplitude = 3 Amp. Stimulation of 1 kHz was below perceptual threshold (i.e. 6 Amp)
- Burst or tonic stimulation: tonic
- Duration: 2 weeks
- Co-interventions: participants recorded the number and type of medications taken during the trial

Placebo

- Frequency: IPG deactivated
- Stimulator type: non-rechargeable IPG (Precision Novi™) and in one case (patient 11), a rechargeable IPG (Montage™)
- Lead number and type: either one or two linear lead 8- or 16-contact (Infinion 16TM) electrodes on levels T7–T10
- Manufacturer: Boston Scientific Co.
- Description: during the control arm (i.e. sham), IPG was deactivated except for emergency shutdown of stimulation
- Burst or tonic stimulation: n/a
- Duration: 2 weeks
- Co-interventions: participants recorded the number and type of medications taken during the trial

Conventional spinal cord stimulation

- Frequency: 40-60 Hz
- Stimulator type: non-rechargeable IPG (Precision Novi™) and in one case (patient 11), a rechargeable IPG (Montage™)
- Lead number and type: either one or two linear lead 8- or 16-contact (Infinion 16™) electrodes on levels T7–T10
- Manufacturer: Boston Scientific Co.
- Description: Patients assigned to the LF treatment arm received tonic stimulation with frequencies typically between 40–60 Hz. The pulse width in the LF treatment arm ranged between 250–500 µs, and the amplitude produced comfortable paraesthesia
- Burst or tonic stimulation: tonic
- Duration: 2 weeks
- Co-interventions: participants recorded the number and type of medications taken during the trial

Burst spinal cord stimulation

- Frequency: 450–550 Hz in a cluster activated with f = 40–60 Hz
- Stimulator type: non-rechargeable IPG (Precision Novi™) and in one case (patient 11), a rechargeableIPG (Montage™)
- Lead number and type: either one or two linear lead 8- or 16-contact (Infinion 16™) electrodes on levels T7–T10
- Manufacturer: Boston Scientific Co.

Sokal 2020 *(Continued)*

- Description: "in burst stimulation, the same patients received intermittent packets of burst stimuli delivered using the neural targeting algorithm, which consisted of several pulses per packet with PW 250–500 µs repeated with f = 40 Hz. Target amplitude was tailored to patient comfort level and at 50% below perception in a continuous mode"
- Burst or tonic stimulation: burst
- Duration: 2 weeks
- Co-interventions: participants recorded the number and type of medications taken during the trial

Outcomes	Outcomes measured at 2 weeks (immediate-term outcome) **Outcomes included in review** • Back pain VAS • Function (Oswestry) • Medication use (% using opioids) • Complications **Outcomes excluded from review** • Average daily VAS scores • Change in VAS from baseline
Identification	**Sponsorship source:** "This research received no external funding" **Country:** Poland **Setting:** participants were recruited in the Department of Neurosurgery and Neurology of University Hospital nr 2 of Collegium Medicum of Nicolaus Copernicus University in Bydgoszcz, Poland **Comments:** "Acknowledgments: The authors would like to acknowledge Mateusz Wabnyc from Boston Scientific for assistance with evaluation and data collection. Conflicts of Interest: Paweł Sokal reports non-financial support from Medtronic and Boston Scientific. Agnieszka Malukiewicz and Marcin Rudaś report non-financial support from Boston Scientfic. Sara Kierońska, Joanna Murawska, Cezary Guzowski, Marcin Rusinek, Dariusz Paczkowski, and Mateusz Krakowiak report no conflicts of interest." **Author's name:** Pawel Sokal **Institution:** Department of Neurosurgery and Neurology, Jan Biziel University Hospital **Email:** pawel.sokal@cm.umk.pl **Address:** Department of Neurosurgery and Neurology, Jan Biziel University Hospital Nr 2, Ujejskiego 75 Street, 85-168 Bydgoszcz, Poland **Start date - End date:** conducted from August 2018 to January 2020 **Trial registration:** NCT03957395
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was performed by drawing notes with the name of the modality or treatment arm (i.e., LF tonic, 1kHz, clustered tonic, sham) by an independent examiner." Comment: notes drawn but unclear whether this was a totally random process

Sokal 2020 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "The independent representative was responsible for the programming and allocation of the stimulation paradigm." Comment: allocation performed by independent person; unclear whether sequence concealed from the independent person
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The consulting physician present during each visit did not know the kind of waveform that had been programmed by the representative. Thus, participants in the study and the examining physician were both blinded to the type of waveform applied. Stimulators were programmed in such a way that patients did not feel paraesthesia in three of the four modes (1 kHz, clustered tonic, and sham)." Quote: "Patients only felt paraesthesia during the tonic LF stimulation condition. Therefore, the present trial can be considered to be semi-blinded. In tonic mode patients were always aware of active stimulation and knew when it was switched off." Comment: there would be paraesthesias in the low frequency group, and participants may have been unblinded.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: as above - low paraesthesias and attempt at blinding to IPG setting.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Figure 1 suggests all 18 followed-up after each 2-week phase completed
Selective reporting (reporting bias)	High risk	Comment: no reporting of disability scores or EQ-5D as specified in protocol. Also 12-month outcomes are the primary but recruitment appears ongoing (estimated completion 2022).
Other bias	High risk	Comment: very short-term outcomes only; no mention of period or carry-over effects or design features to deal with these.

Sweet 2016

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Analysis:** "The mean and standard error were calculated across all conditions. A paired-sample two-tailed Student's t-test was used for all parametric data, and Fisher's exact test was used for categorial data. For the PGIC [patient's global impression of change], a 'responder' to the therapy was defined as an individual who experienced at least 'minimal improvement' over the conventional stimulation period immediately prior to the test period. All other measures were compared between subthreshold HD and sham stimulation conditions. A two-sided p-value of 0.05 or less was defined as statistically significant". **Sample size calculation:** not described **Study design:** randomised, double-blind, cross-over, placebo-controlled trial **Trial aim:** "The purpose of this study is to evaluate the effects of subthreshold HD stimulation (1200 Hz, 200 µs, amplitude below sensory threshold) in a population of patients who are confirmed to respond to the therapy"

Sweet 2016 *(Continued)*

	Trial duration: conducted from August 2018 to January 2020; cross-over took a total of 8 weeks and consisted 2-weeks of subthreshold high density stimulation and 2-weeks of sham stimulation, with each experimental conditions preceded by 2 weeks of conventional stimulation.
Participants	**Baseline characteristics** Overall • Age: mean (SD) = 50.7 (17.0) years • Sex: 2/4 female (50%); 2/4 male (50%) • Back pain duration: mean (SD) = not reported • Baseline back pain score: mean (SD) Back and leg pain VAS (0-10) = not reported • Baseline function score: median Oswestry (IQR) = not reported • QOL score: not reported • Baseline leg pain score: mean (SD) Back and leg pain VAS (0-10) = not reported • Work status: one retired (25%), one employed in a physical job (25%), two registered disabled (50%). • No. of participants: 4 • Socioeconomic status: not recorded • Pain medication use: not recorded at baseline • Diagnostic criteria: "treated with SCS for postlaminectomy syndrome involving back pain radiating to one or both lower extremities" • Healthcare use: not recorded **Inclusion criteria:** "To be eligible, subjects needed to have been implanted with two epidural 8-contact Medtronic Compact percutaneous SureScan leads (electrode contacts 3 mm long and 1.3 mm diameter, 4 mm intercontact spacing) implanted in the midline with the end of the lead at the [vetebral level] T7-T8 interspace, with a RestoreSensor implanted pulse generator (Minneapolis, MN, USA), have stable pain control for at least 6 months, and have evidence of at least 50% benefit using a one-week trial of subthreshold HD stimulation, defined as 1200 Hz frequency, 200 µs pulse width, and an amplitude 90% of the threshold for detection of a sensory percept" **Exclusion criteria:** not reported **Pretreatment:** n/a; cross-over **Minimum pain intensity:** nil **Number of participants:** 15 screened for enrollment, 11 were excluded for sub-optimal pain relief during the 1-week trial. Four participants were randomised. All 4 participants completed the cross-over arms of the trial. **Source of participants:** not reported
Interventions	Subthreshold high density spinal cord stimulation • Frequency: 1200 Hz • Stimulator type: a RestoreSensor implanted pulse generator (Minneapolis, MN, USA) • Lead number and type: "two epidural 8-contact Medtronic Compact percutaneous SureScan leads (electrode contacts 3 mm long and 1.3 mm diameter, 4 mm intercontact spacing) implanted in the midline with the end of the lead at the T7-T8 interspace" • Manufacturer: Medtronic • Description: subthreshold HD stimulation was 1200 Hz, 200 µs, amplitude 90% of threshold for sensory percept • Burst or tonic stimulation: tonic • Duration: 2 weeks • Co-interventions: none reported Placebo

Sweet 2016 *(Continued)*

- Frequency: IPG deactivated
- Stimulator type: a RestoreSensor implanted pulse generator (Minneapolis, MN, USA)
- Lead number and type: "two epidural 8-contact Medtronic Compact percutaneous SureScan leads (electrode contacts 3 mm long and 1.3 mm diameter, 4 mm intercontact spacing) implanted in the midline with the end of the lead at the T7-T8 interspace"
- Manufacturer: Medtronic
- Description: same settings as subthreshold high density stimulation but amplitude 0 V.
- Burst or tonic stimulation: n/a
- Duration: 2 weeks
- Co-interventions: none reported

Outcomes

Outcomes measured at 2 weeks (immediate-term outcome)

- Back pain (VAS)
- Quality of life (SF-36)
- Patient's global impression of change
- Pain vigilance and awareness

Outcomes included in review

- Back pain VAS

Outcomes excluded from review

- SF-36 (no paired data available)
- Patient's global impression of change (no paired data available)
- Pain vigilance and awareness

Identification

Sponsorship source: none reported

Country: USA

Setting: not reported

Comments: "Jonathan Miller serves as a consultant for Medtronic Neuromodulation"

Author's name: Jonathon Miller

Institution: Department of Neurological Surgery, University Hospitals Case Medical Center

Email: Jonathan.Miller@UHHospitals.org

Address: Department of Neurological Surgery, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106, USA.

Start date - End date: not reported

Trial registration: not reported

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: highly enriched sample: 15 people trialled, only 4 responders to high-frequency SCS included in RCT
Allocation concealment (selection bias)	Unclear risk	Comment: not reported

Sweet 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "participants may have been aware that much less current was delivered during the sham phase, with significant implications for blinding; we did not formally assess the effectiveness of blinding for this study."
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Quote: "participants may have been aware that much less current was delivered during the sham phase, with significant implications for blinding; we did not formally assess the effectiveness of blinding for this study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 4 of 4 randomised were followed
Selective reporting (reporting bias)	High risk	Comment: retrospective registration; adverse effects measured but not reported
Other bias	High risk	Comment: order and period effects likely

Wolter 2012

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Analysis:** "For statistical analyses, computer software packages (Graph Pad Prism, Version 5.01; GraphPad Software, Inc., La Jolla, CA, USA, and R, Version 2.11.1; R Foundation for Statistical Computing, Vienna, Austria) were used. First, descriptive statistics were computed for all items. Due to the small number of observations, non-parametric statistics were used. To calculate the statistical significance of the differences of mean NRS scores, first a one-way analysis of variance (Friedmann test) was used. The differences between the mean NRS scores of each stimulation modality (supra-threshold vs. sub-threshold stimulation, sub-threshold vs. no stimulation, supra-threshold vs. no stimulation) were analysed by means of the Wilcoxon matched pairs test (two sided). Due to the closed testing principle, an adjustment of a was not required. Spearman correlations were calculated between the pain scores, the effects of supra-threshold and sub-threshold stimulation, and the HADS, BDI and PDI scores." **Sample size calculation:** "With α = 0.05 and a power of 0.8, and given a standard deviation of 1.25 NRS points with supra-threshold stimulation, sub-threshold stimulation and without stimulation, with a detectable alternative of 1.2 NRS points the sample size for the two-sided Wilcoxon matched pairs test was estimated to be 10." **Study design:** blinded, randomised cross-over design **Trial aim:** to determine the effect of sub-perception threshold stimulation (sub-threshold stimulation) in neuropathic pain conditions compared with conventional supra-perception threshold stimulation (supra-threshold stimulation). **Trial duration:** intervention period: 2 arm cross-over each of 1 week duration.
Participants	**Baseline characteristics** Overall • Age: mean (SD) = 54 (6.2) years. Range 44-62 years. • Sex: 3 women (50%), 3 men (50%) • Back pain duration: mean (range) = 12.3 years (5 - 19 years) • Baseline back pain score: pts III, IV, VI VIII-X mean = 3.6 (1.3)

Wolter 2012 *(Continued)*

- Baseline function score: not provided for FBSS subgroup
- QOL score: not measured
- Baseline leg pain score: not measured
- Work status: not measured
- No. of participants: 6
- Socioeconomic status: not measured
- Pain medication use: not provided for FBSS subgroup
- Diagnostic criteria: not reported
- Healthcare use: not reported

Inclusion criteria: SCS for neuropathic pain, prior SCS for at least 3 months with significant (> 50%) pain relief, capacity to understand the study design and willingness to fill in pain questionnaires

Exclusion criteria: myocardial infarction in the preceding 3 months, cerebral ischaemia in the preceding 3 months, and degenerative central nervous system disease

Pretreatment: n/a; cross-over trial

Minimum pain intensity: none

Number of participants: 10

Source of participants: Interdisciplinary Pain Center, University Hospital Freiburg, Germany

Interventions

Intervention characteristics

Placebo

- Frequency: n/a
- Stimulator type: "All patients were implanted with percutaneous-type electrodes. With one exception (patient 6), all patients had a non-rechargeable implantable pulse generator (IPG). In patient 6, the battery state of the IPG was checked to rule out inadvertent discharge during the trial."
- Lead number and type: percutaneous-type electrodes
- Manufacturer: Medtronic (n=5) or Boston scientific (n=1)
- Description: "the device was randomly switched to zero or to stimulation directly below perception threshold in a blinded manner. Patients were asked to walk and make trunk movements in order not to miss any kind of stimulation paraesthesia which would have led to unblinding. If paraesthesia could be elicited under any condition, the amplitude was reduced until paraesthesia disappeared."
- Burst or tonic stimulation: n/a
- Duration: 1 week
- Co-interventions: not reported in FBSS subgroup

Conventional spinal cord stimulation

- Frequency: 25-100 Hz
- Stimulator type: "All patients were implanted with percutaneous-type electrodes. With one exception (patient 6), all patients had a non-rechargeable implantable pulse generator (IPG). In patient 6, the battery state of the IPG was checked to rule out inadvertent discharge during the trial."
- Lead number and type: percutaneous-type electrodes
- Manufacturer: Medtronic (n=5) or Boston scientific (n=1)
- Description: "stimulation directly below perception threshold in a blinded manner. Patients were asked to walk and make trunk movements in order not to miss any kind of stimulation paraesthesia which would have led to unblinding. If paraesthesia could be elicited under any condition, the amplitude was reduced until paraesthesia disappeared. The lowest threshold voltage measured in the prior two assessments was used as threshold."
- Burst or tonic stimulation: mixed
- Duration: 1 week
- Co-interventions: not reported in FBSS subgroup

Wolter 2012 *(Continued)*

Outcomes	Outcomes measured at one week (immediate-term outcome) **Outcomes included in review** • Pain intensity **Outcomes excluded from review** • Hospital Anxiety and Depression Score (HADS) • Pain Disability Index (PDI) • Beck Depression Inventory (BDI)
Identification	**Sponsorship source:** none **Country:** Germany **Setting:** Interdisciplinary Pain Center **Comments: -** **Author's name:** Tilman Wolter **Institution:** University Hospital Freiburg **Email:** tilman.wolter@uniklinik-freiburg.de **Address:** Interdisciplinary Pain Center, University Hospital Freiburg, Freiburg, Germany **Start date - End date:** not reported (published 2011) **Trial registration:** not registered
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: mentions study is randomised but no description of method of randomisation sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: used placebo control - SCS switched off. Attempts to blind participants but no assessment of whether blinding was successful.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Comment: minimised paraesthesia in intervention periods to maintain blinding; primary endpoint subjective and self-reported. However, no assessment of success of blinding methods, thus unclear whether blinding maintained/successful.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all 10 participants (including the 6 with FBSS) followed up
Selective reporting (reporting bias)	High risk	Comment: not registered; effect of different stimulation forms on disability and depression outcomes not described with clarity

Wolter 2012 *(Continued)*

Other bias	High risk	Comment: high risk of bias from crossover and period effects - not accounted for in design

CMM: conventional medical management
EMG: electromyography
EQ-5D: EuroQol 5-dimension quality of life questionnaire
FBSS: failed back surgery syndrome
HRQoL: health-related quality of life
IPG: internal pulse generator
IQR: interquartile range
ITT: intention-to-treat
LBP: low back pain
MCID: minimal clinically important difference
MD: mean difference
MME: morphine milligram equivalents
MRI: magnetic resonance imaging
ms: millisecond
n/a: not applicable
NRS: numeric rating scale
NSAID: non-steroidal anti-inflammatory drug
ODI: Oswestry Disability Index
OMM: optimal medical management
QOL: quality of life
SCS: spinal cord stimulation
SD: standard deviation
SE: standard error
SF-12: Short-form 12-item quality of life questionnaire
SF-36: Short-form 36-item quality of life questionnaire
VAS: visual analogue scale
µs: microsecond

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12614000236695	Ineligible comparator: study did not have a 'no intervention' group
ACTRN12617001541392	Ineligible comparator: control group was given surgery
Amirdelfan 2018	Ineligible intervention: not spinal cord stimulation
Andersen 2009	Ineligible intervention: not spinal cord stimulation
Baranidharan 2020	Not an RCT
Billot 2020	Ineligible comparator: study did not have a 'no intervention' group
De Andres 2017	Ineligible comparator: study did not have a 'no intervention' group
Deer 2014	Ineligible comparator: study did not have a 'no intervention' group
Deer 2015b	Ineligible comparator: study did not have a 'no intervention' group
Eldabe 2020b	Ineligible comparator: study did not have a 'no intervention' group
ISRCTN13607429 2016	Not an RCT

Study	Reason for exclusion
Kapural 2015	Ineligible comparator: study did not have a 'no intervention' group
Kriek 2017	Ineligible population: did not have low back pain
MacIver 2010	Not an RCT
Meier 2015	Ineligible population: did not have low back pain
Mekhail 2020	Ineligible comparator: study did not have a 'no intervention' group
NCT00200122	Ineligible comparator: unclear control group
NCT01550562 2012	Terminated early
NCT02837822	Ineligible outcomes: study did not present outcomes relevant to this review
NCT03312010	Ineligible comparator: study did not have a 'no intervention' group
North 1994	Ineligible comparator: control group was given surgery
North 2005	Ineligible comparator: control group was given surgery
North 2020	Ineligible comparator: study did not have a 'no intervention' group
Roulaud 2015	Ineligible comparator: study did not have a 'no intervention' group
Thomson 2017	Ineligible comparator: study did not have a 'no intervention' group
Tjepkema-Cloostermans 2016	Ineligible comparator: study did not have a 'no intervention' group
Veizi 2017	Not an RCT
Vesper 2017	Ineligible comparator: study did not have a 'no intervention' group
Vesper 2019	Ineligible comparator: study did not have a 'no intervention' group

Characteristics of studies awaiting classification *[ordered by study ID]*

Mekel-Bobrov 2017

Methods	RCT with cross-over design (SCS with stimulation switched off versus standard SCS versus subperceptual SCS)
Participants	Unknown
Interventions	SCS with stimulation switched off versus standard SCS versus subperceptual SCS
Outcomes	Brain activation; other measures not specified
Notes	Conference abstract - insufficient detail on participant population to determine eligibility

Miller 2015

Methods	Cross-over RCT
Participants	20 participants
Interventions	3 days subperceptual SCS versus 3 days sham stimulation or vice versa
Outcomes	Average back pain intensity (0- to 10-point VAS)
Notes	Conference abstract - insufficient detail on control condition to determine eligibility

Miller 2016

Methods	Cross-over RCT
Participants	4 people with "post-laminectomy syndrome"
Interventions	Conventional stimulation versus subthreshold stimulation versus sham stimulation
Outcomes	Back pain 0- to 10-point VAS
Notes	Conference abstract - insufficient detail on control condition to determine eligibility

RCT: randomised controlled trial
SCS: spinal cord stimulation
VAS: visual analogue scale

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12620000720910

Study name	An evaluation of spinal cord stimulation for the treatment of chronic pain, also its effect on mood, sleep, physical activity and analgesic medicine requirements
Methods	Randomised controlled trial
Participants	"Patients will have been implanted with a BurstDr electrical stimulator, and will report significant pain relief (defined as average pain less than 3/10 from their stimulator) and minimal requirements for analgesic medication (defined as less than 20 Morphine Equivalent Dose (MEq)) and without any accompanying sensation from electrical stimulation."
Interventions	Device switched ON versus OFF
Outcomes	**Primary** • Brief pain inventory • Sleep diary • Medication **Secondary** • Depression Anxiety and Stress Scale (DASS)-21 • Activity (pedometer) • Pain catastrophizing scale • Pressure-pain threshold

ACTRN12620000720910 *(Continued)*

Starting date	10 September 2020
Contact information	Dr Salmons Rooms Specialist in Pain Management Parkland House 2/89 Forrest Street Cottesloe WA 6011 johnsalmon@bigpond.com
Notes	

Ahmadi 2021

Study name	Efficacy of different spinal cord stimulation paradigms for the treatment of chronic neuropathic pain (PARS-trial): study protocol for a double-blinded, randomized, and placebo-controlled crossover trial
Methods	Randomised, placebo-controlled, multicenter cross-over study
Participants	Key inclusion criteria • Gender: male and female • Minimum age: 18 years • Maximum age: no maximum age Additional inclusion criteria • Suffering from intractable neuropathic pain, who have been considered for SCS therapy according to current German treatment guidelines and, within 48 of study enrolment, were already implanted with a wireless SCS device (Stimwave) • Placement of the distal tip of the electrode between upper level of thoracic vertebra (Th) 8 and lower level of Th12 • Leg pain > back pain • Written consent • Duration of pain history > 6 months and < 5 years Exclusion criteria • Covering of the pain area with the SCS stimulation device < 90% • Ischaemic pain • Chronic primary pain • Implantation of several SCS electrodes • Coagulopathy • Any planned changes in existing pain medication for the duration of trial participation (period of 35 days) • Pregnancy • Neurodegenerative disease • Lack of understanding of the trial and the individual consequences of participating in the trial • Expected lack of compliance (i.e. not able to complete the trial questionnaires)
Interventions	Burst SCS versus 1 kHz SCS versus 1.499 kHz SCS versus placebo SCS

Ahmadi 2021 *(Continued)*

Outcomes	**Primary** • VAS **Secondary** • Pain quality (painDETECT - screener to identify neuropathic pain) • EQ-5D • HADS • ODI
Starting date	1 April 2020
Contact information	Rezvan.Ahmadi@med.uni-heidelberg.de Neurochirurgische UniversitätsklinikUniversitätsklinikum Heidelberg Ms. PD Dr. med. Rezvan Ahmadi Im Neuenheimer Feld 400 69120 Heidelberg Germany
Notes	

Al-Kaisy 2020

Study name	Multicentre, double-blind, randomised, sham-controlled trial of 10 khz high-frequency spinal cord stimulation for chronic neuropathic low back pain (MODULATE-LBP): a trial protocol
Methods	Multicentre, double-blind, randomised, sham-controlled trial with a parallel economic evaluation
Participants	96 patients with CNLBP who have not had spinal surgery
Interventions	"Patients will be randomised 1:1 to 10 kHz SCS plus usual care (intervention group) or to sham 10 kHz SCS plus usual care (control group) after receiving the full implant"
Outcomes	**Primary** • Mean VAS back pain (7-day participant VAS pain diary; time frame: 6 months post randomisation) **Secondary** • Oswestry Disability Index • Complications • EQ-5D-5 L • Health and social care costs
Starting date	14 August 2018
Contact information	Contact: Samuel J Wesley 07561062944 samuel.wesley@gstt.nhs.uk Contact: Ramla A Abuukar Abdullahi 02071883237 ext 83237 ramla.abuukarabdullahi@gstt.nhs.uk

Al-Kaisy 2020 *(Continued)*

Notes	clinicaltrials.gov/ct2/show/NCT03470766

ISRCTN10663814

Study name	Comparison of spinal cord stimulation in combination with standard pain treatment versus standard pain treatment only in patients with intractable chronic back pain without previous history of spine surgery
Methods	Multicentre prospective randomised study
Participants	Inclusion criteria • Be a candidate for SCS system (trial and implant) • Diagnosed with chronic, refractory axial low back pain with or without lower limb pain with a neuropathic component as assessed by the investigator, and not eligible for spine surgery (e.g. lumbar fusion, discectomy, laminectomy, laminotomy) at the time of enrolment • Average back pain intensity ≥ 6.0 cm on the 10.0 cm VAS at the time of enrolment • Willing and capable of giving written informed consent to participate in study based on voluntary agreement after a thorough explanation of participation has been provided • Willing and capable of subjective evaluation, of reading and understanding written questionnaires, and reading, understanding and signing the written informed consent • 18 years of age or older at the time of enrolment • On a stable pain medication regimen, as determined by the study investigator, for at least 30 days prior to enroling • Willing and able to comply with study-related requirements, procedures, and visits
Interventions	SCS therapy versus CMM
Outcomes	**Primary** • Individual responder rate measured using VAS (as defined by at least a 50% reduction in pain) at 6 months **Secondary** • VAS • ODI • EQ-5D • SF-12 • Adverse events
Starting date	29 June 2020
Contact information	Mr Wim Laloo clinical@sgx-international.com
Notes	"AIM: evaluate SCS programming with conventional medical management in comparison to conventional medical management alone for chronic back pain sufferers with or without leg pain and who are not considered candidates for spine surgery."

ISRCTN33292457

Study name	Senza spinal cord stimulation system for the treatment of chronic back and leg pain in failed back surgery syndrome (FBSS) patients
Methods	Single-centre, double-blind, three-period, prospective, randomised, placebo-controlled cross-over study
Participants	Inclusion criteria • Adults (at least 18 years of age) • Capable of giving informed consent • An appropriate candidate for implantation of a spinal cord stimulator • Able to comply with the requirements of the study visits and self-assessment questionnaires • On stable pain medications for at least 4 weeks prior to the baseline visit • FBSS patient with back pain intensity of at least 5 cm out of 10 cm, with radiating pain that originates from lumbar, L3, L4, L5, and/or S1 regions of the spine.
Interventions	SCS ON versus OFF
Outcomes	**Primary** • VAS • Adverse events **Secondary** • VAS • Sleep • ODI • Medication
Starting date	13 April 2011
Contact information	Dr Jean-Pierre Van Buyten (no further details)
Notes	https://doi.org/10.1186/ISRCTN33292457

NCT03419312

Study name	Cerebral PET patterns, inflammatory biomarkers and outcome in patients treated with burst spinal cord stimulation for chronic low back and leg pain: a randomized controlled clinical trial
Methods	Randomised cross-over trial (burst SCP versus washout versus sham)
Participants	12 people with FBSS/chronic low back pain/radicular pain/neuropathic pain Inclusion criteria • Occurrence of chronic pain in the lumbosacral region, as well as unilateral or bilateral leg pain. • Prior lumbar surgery in medical history. • Diagnosed with neuropathic pain in the lower extremities and graded as probable neuropathic pain or definite neuropathic pain according International Association for the Study of Pain criteria. • Patient reports largely unchanged pain condition last 6 months. • ≥ 18 years of age and < 60 years of age. • Willing participation in all parts of the study, as well as having the ability to complete the entire study plan.

NCT03419312 *(Continued)*

	• Must certify that he / she understands the study plan, as well as voluntarily signs informed consent. • Must be able to sit still for a minimum of 45 minutes and be able to follow restrictions related to the PET survey. Patient has undergone a 7-day SCS trial with epidural burst stimulation with the following results: • at least 75% coverage of the painful area of tonic stimulation before start of burst trial stimulation. • at least 50% reduction in pain intensity from baseline of trial to end of trial period. Exclusion criteria • Current pain conditions other than back and leg pain after back surgery. • Treated with opioids exceeding 80 milligrams of morphine per day or is considered at risk for development of problematic opioid use. • Untreated depression or anxiety. • Cannot complete the study plan. • Unable to read or write Swedish. • Participating in another clinical trial. • History of previous PET scan or other substantial radiation dose in the last 5 years. • Has claustrophobia. • Ongoing pregnancy or planned pregnancy during study time. • Contraindications for arterial catheterisation. • Previously treated with spinal cord stimulation.
Interventions	Experimental: Study sequence A Proclaim Elite 5: Burst - Washout - Sham 1. 14 days of burst stimulation. 2. 7 days washout. 3. 14 days of sham stimulation. Experimental: Study sequence B Proclaim Elite 5: Sham - Washout - Burst 1. 14 days of sham stimulation. 2. 7 days washout. 3. 14 days of burst stimulation.
Outcomes	**Primary** • Change in regional cerebral blood flow measured with 15O-water positron emission tomography (PET) **Secondary** • Back and leg pain (time frame: measured at visit day 0 (baseline), day 14 and day 35). Measured using a 100 mm VAS for back and leg pain, respectively. Scale range: 0 mm indicates no pain (minimum), 100 mm indicates worst imaginable pain (maximum).
Starting date	11 February 2018
Contact information	rolf.karsten@akademiska.se
Notes	

NCT03462147

Study name	The efficacy of spinal cord stimulation in patients with a failed back surgery syndrome
Methods	Randomised cross-over trial
Participants	Inclusion criteria • Patients with an implanted neurostimulation system Exclusion criteria • No knowledge of the Dutch language • Addicted to drugs
Interventions	Sham SCS versus high 'density' SCS versus conventional SCS
Outcomes	**Primary** • VAS **Secondary** • Medication • Quality of life • Quality of sleep
Starting date	1 October 2017
Contact information	Martine Puylaert, MD PhD +3289325407 martine.puylaert@zol.be
Notes	

NCT03718325

Study name	Burst Spinal Cord Stimulation (Burst-SCS) Study
Methods	Randomised; cross-over assignment; blinding of participants, investigators, outcomes assessors
Participants	20 participants Inclusion criteria • Men or women with chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome and intractable low back and leg pain, and for whom burst SCS has been recommended as a treatment option • Candidates who can speak, read, and understand English Exclusion criteria • "Subjects who are pregnant- as determined by verbal report or chart review • Subjects with current, habitual, or previous use within the last 12 months of artificial nails, nail enhancements, or nail extensions that cover any portion of either thumbnail. Exceptions, including brief and/or occasional use, may be permissible at the discretion of the principal investigator • Subjects who are unable or unwilling to cooperate with clinical testing

NCT03718325 *(Continued)*

	• Subjects having any impairment, activity or situation that, in the judgement of the study coordinator or PI, would prevent satisfactory completion of the study protocol"
Interventions	"First, participants will receive clinically-effective Burst-SCS per their standard of care. Study evaluations will be completed prior to and after stimulation. Then, participants will have their stimulation adjusted to receive sham (no) SCS. Study evaluations will be completed prior to and after this sham."
Outcomes	**Primary** • Change in VAS score (primary) **Secondary** • Change in Short-Form McGill Pain Questionnaire (SFMPQ) score • Change in General Pain Disability Index (PDI) score • Change in Brief Pain Inventory-Short Form (BPI-SF) score • Michigan Body Map (MBM) • Fibromyalgia Survey Questionnaire (FSQ)
Starting date	12 March 2019
Contact information	jloechli@med.umich.edu
Notes	Michigan, USA

NCT03858790

Study name	Efficacy and safety of spinal cord stimulation in patients with chronic intractable pain
Methods	Parallel RCT; target sample = 54
Participants	Inclusion criteria • Diagnosed with chronic, intractable pain of the trunk and/or limbs which has been refractory to conservative therapy for a minimum of 3 months • VAS ≥ 5 • 18 years of age or older at the time of enrolment • willing and able to comply with study-related requirements, procedures, and visits • willing and capable of giving informed consent
Interventions	"Experimental: Experimental Subjects' PINS spinal cord stimulator randomized to this arm is on always" "Sham Comparator: Control Subjects' PINS spinal cord stimulator randomized to this arm is off for a week"
Outcomes	**Primary** • Difference in VAS between the experimental and control group (time frame: 13 weeks) **Secondary** • Changes in VAS (time frame: 4, 12, 24 weeks) • Sleep quality (time frame: 4, 12, 24 weeks) • Changes in Beck Depression Inventory (time frame: 4, 12, 24 weeks) • Change in quality of life as measured by SF-36 (time frame: 4, 12, 24 weeks)

NCT03858790 *(Continued)*

	• Number of participants with adverse events (time frame: 24 weeks)
Starting date	February 2019
Contact information	pins_medical@163.con
Notes	

NCT04479787

Study name	Spinal cord stimulation vs. medical management for low back pain (DISTINCT)
Methods	Prospective, multicenter, randomised, controlled clinical study with an optional cross-over component
Participants	
Interventions	**SCS:** an SCS trial period followed by SCS implantation with the Abbott Proclaim XR Implantable Pulse Generator **Active comparator:** CMM, consisting of an array of therapies including, but not limited to, structured physical therapy, medications, injections, and complementary and alternative medicine (e.g. acupuncture, massage therapy)
Outcomes	**Primary** • Difference in responders between both groups (time frame: 6 months) • Improvement in function, defined as a ≥ 13% decrease on ODI or score ≤ 20%, OR Improvement in pain, defined as a ≥ 50% decrease on NRS **Secondary** • Proportion of participants who elect to cross-over after the primary outcome (time frame: 6 months)
Starting date	31 July 2020
Contact information	Abbott Medical Devices (no other details provided)
Notes	"The objective of this study is to evaluate the efficacy of BurstDR dorsal column stimulation, compared with comprehensive medical management, in improving pain and back-related physical function in subjects suffering with chronic, refractory axial low back pain with a neuropathic component, who have not had lumbar spine surgery and for whom surgery is not an option."

NCT04676022

Study name	SCS as an option for chronic low back and/or leg pain instead of surgery (SOLIS)
Methods	Parallel RCT
Participants	Key inclusion criteria • Chronic low back pain, with or without leg pain, for at least 6 months • Received at least 90 days of documented pain management care to address the primary pain complaint, prior to screening (e.g. medication, physical therapy)

NCT04676022 *(Continued)*

	• If female of childbearing potential: not pregnant, as evidenced by a negative pregnancy test at screening • Have signed a valid, Institutional review board-approved informed consent form (ICF) provided in English Key exclusion criteria • Primary pain complaint of vascular origin (e.g. peripheral vascular disease) • Require implantation of lead(s) in the cervical epidural space • Significant cognitive impairment at screening that, in the opinion of the investigator, would reasonably be expected to impair the study candidate's ability to assess pain intensity • Previous spinal cord stimulation trial or is already implanted with an active implantable device(s) (e.g. pacemaker, drug pump, implantable pulse generator)
Interventions	SCS vs CMM
Outcomes	**Primary** • Proportion of participants with 50% or greater reduction in pain
Starting date	26 March 2021
Contact information	Contact: Megan Cease megan.cease@bsci.com Contact: Diane Keesey 855-213-9890 BSNClinicalTrials@bsci.com
Notes	Email received from Dr Megan Cease (27 July 2022) stating: "The study is currently ongoing and we do not have results to include in a review at this time".

NCT04732325

Study name	Model-based characterization of spinal cord stimulation for pain
Methods	Randomised cross-over trial of SCS (burst versus high-frequency versus sham versus tonic)
Participants	25 people with chronic pain (including FBSS, complex regional pain syndrome, neuropathic pain) Inclusion criteria: people who: • have chronic intractable pain of the trunk and/or limbs • are undergoing SCS as part of standard clinical care for chronic pain management • have been implanted with a commercial SCS device • are 18 years or older and can speak, read, and understand English • understand study procedures and can comply with them for the entire length of the study • are willing to participate in COVID-19 symptom screening and answer questions about COVID-19 diagnosis 1 to 3 days before a scheduled visit • are willing to wear a face-covering during all study visits Exclusion criteria: people who: • are pregnant or nursing • have current, habitual, or previous use within the last 12 months of artificial nails, nail enhancements, or nail extensions that cover any portion of either thumbnail • are unable or unwilling to cooperate with clinical testing

NCT04732325 *(Continued)*

	• have any impairment, activity or situation that in the judgment of study personnel would prevent satisfactory completion of the study protocol • are unable or whose legal guardian/representative is unwilling to give written informed consent • have or have tested positive in the last 14 days for COVID-19, or are symptomatic for COVID-19
Interventions	"Participants will be randomized to one of six treatment arms. Participants will receive burst, kHz, tonic, and sham spinal cord stimulation (SCS). Each treatment will be applied for a duration of seven days. Participants will be blinded during programming."
Outcomes	**Primary** "SCS-induced changes in temporal summation (TS) [Time Frame: Baseline (At randomization) and at the end of each seven-day treatment] TS refers to an increased perception of pain in response to sequential stimuli of equal physical strength. At the end of each treatment period, TS scores will be calculated by subtracting the average pain rating of the single-stimulus trials from the average pain rating of the ten-stimuli trials. If the difference is a positive number, the researchers will conclude that there was pain summation, where larger numbers will indicate increased pain summation or TS. If the difference is zero or a negative number, the researchers will conclude that there was no pain summation or TS."
Starting date	No details given
Contact information	No details given
Notes	

Reiter 2019

Study name	High frequency spinal cord stimulation (HFSCS) at 10 kHz plus conventional medical management (CMM) versus conventional medical management alone for the treatment of non-surgical back pain
Methods	RCT
Participants	People with chronic refractory low back pain with or without leg pain; not surgical candidates; VAS ≥ 5
Interventions	High-frequency SCS plus conventional medical management (CMM) versus CMM
Outcomes	**Primary** • Number of participants with ≥ 50% improvement in pain **Secondary** • Pain • Disability • QoL • Satisfaction • Function • Healthcare use • Safety
Starting date	2017
Contact information	Jan Willem Kallewaard (co-author)

Reiter 2019 *(Continued)*	
	jkallewaard@rijnstate.nl
Notes	Email received from Dr Kallewaard (12 July 2021) stating this is an ongoing study that would not be completed within 6 months.

CMM: conventional medical management
CNLBP: chronic nonspecific low back pain
EQ-5D: EuroQoL 5-Dimension quality of life questionnaire
FBSS: failed back surgery syndrome
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
LBP: low back pain
MME: morphine milligram equivalent
NRS: numeric rating scale
ODI: Oswestry Disability Index
QoL: quality of life
RCT: randomised controlled trial
SCS: spinal cord stimulation
SF-36: Short-form 36-item quality of life questionnaire
VAS: visual analogue scale

DATA AND ANALYSES

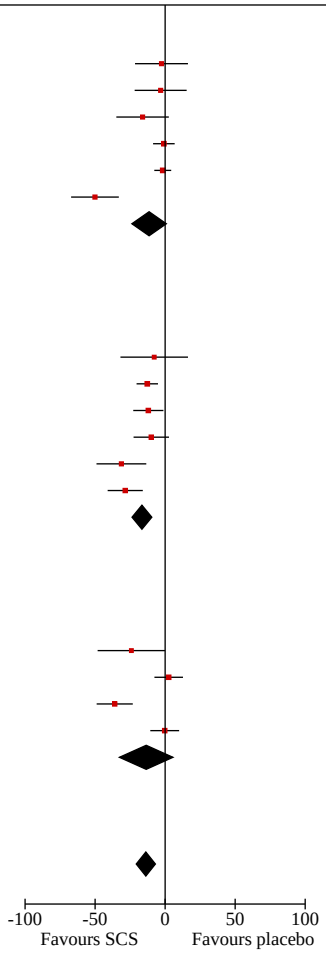
Comparison 1. Spinal cord stimulation (SCS) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Low back pain intensity (0-100) at immediate-term follow-up (< 1 month)	8		Mean Difference (IV, Random, 95% CI)	-13.79 [-20.62, -6.96]
1.1.1 High-frequency SCS	4		Mean Difference (IV, Random, 95% CI)	-11.44 [-23.72, 0.84]
1.1.2 Conventional SCS	6		Mean Difference (IV, Random, 95% CI)	-16.57 [-23.63, -9.52]
1.1.3 Burst SCS	4		Mean Difference (IV, Random, 95% CI)	-13.53 [-32.61, 5.56]
1.2 Low back pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Burst SCS	1		Mean Difference (IV, Fixed, 95% CI)	-4.00 [-8.19, 0.19]
1.3 Leg pain intensity (0-100) at immediate-term follow-up (< 1 month)	2		Mean Difference (IV, Fixed, 95% CI)	-10.03 [-20.33, 0.27]
1.3.1 High-frequency SCS	1		Mean Difference (IV, Fixed, 95% CI)	-3.83 [-15.61, 7.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.2 Conventional SCS	1		Mean Difference (IV, Fixed, 95% CI)	-30.10 [-60.09, -0.11]
1.3.3 Burst SCS	1		Mean Difference (IV, Fixed, 95% CI)	-30.10 [-60.09, -0.11]
1.4 Leg pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 Burst SCS	1		Mean Difference (IV, Fixed, 95% CI)	-2.00 [-6.47, 2.47]
1.5 Function (0-100) at immediate-term follow-up (< 1 month)	1		Mean Difference (IV, Random, 95% CI)	-15.10 [-25.69, -4.52]
1.5.1 Conventional SCS	1		Mean Difference (IV, Random, 95% CI)	-9.80 [-24.09, 4.49]
1.5.2 Burst SCS	1		Mean Difference (IV, Random, 95% CI)	-20.60 [-35.16, -6.04]
1.6 Function (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 Burst SCS	1		Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.91, 1.31]
1.7 Health-related quality of life (0-1 index) at immediate-term follow-up (< 1 month)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.7.1 High-frequency SCS	1		Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.10, 0.13]
1.8 Health-related quality of life (0-1 index) at medium-term follow-up (≥ 3 mo to < 12 mo)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.8.1 Burst SCS	1		Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.08, 0.16]

Analysis 1.1. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 1: Low back pain intensity (0-100) at immediate-term follow-up (< 1 month)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.1.1 High-frequency SCS					
Al-Kaisy 2018 (1)	-2.6	9.64	5.2%	-2.60 [-21.49 , 16.29]	+ + + + − ? +
Al-Kaisy 2018 (2)	-3.2	9.47	5.3%	-3.20 [-21.76 , 15.36]	+ + + + − ? +
Al-Kaisy 2018 (3)	-16.1	9.56	5.2%	-16.10 [-34.84 , 2.64]	+ + + + − ? +
Perruchoud 2013	-0.9	3.93	7.8%	-0.90 [-8.60 , 6.80]	+ + + + + − −
Sokal 2020	-1.7	3.08	8.1%	-1.70 [-7.74 , 4.34]	? ? − − + − −
Sweet 2016	-50.1	8.69	5.6%	-50.10 [-67.13 , -33.07]	− ? ? ? + − −
Subtotal (95% CI)			**37.1%**	**-11.44 [-23.72 , 0.84]**	
Heterogeneity: Tau² = 179.01; Chi² = 30.60, df = 5 (P < 0.0001); I² = 84%					
Test for overall effect: Z = 1.83 (P = 0.07)					
1.1.2 Conventional SCS					
De Ridder 2013	-7.8	12.3	4.2%	-7.80 [-31.91 , 16.31]	? ? − − + + −
Eldabe 2020	-12.75	3.9	7.8%	-12.75 [-20.39 , -5.11]	+ + ? ? + − −
Schu 2014	-12	5.49	7.1%	-12.00 [-22.76 , -1.24]	+ + ? ? + − −
Sokal 2020	-9.9	6.45	6.6%	-9.90 [-22.54 , 2.74]	? ? − − + − −
Sweet 2016	-31.23	9.07	5.4%	-31.23 [-49.01 , -13.45]	− ? ? ? + − −
Wolter 2012	-28.5	6.4	6.7%	-28.50 [-41.04 , -15.96]	? ? ? ? + − −
Subtotal (95% CI)			**37.8%**	**-16.57 [-23.63 , -9.52]**	
Heterogeneity: Tau² = 33.36; Chi² = 9.18, df = 5 (P = 0.10); I² = 46%					
Test for overall effect: Z = 4.60 (P < 0.00001)					
1.1.3 Burst SCS					
De Ridder 2013	-24.1	12.3	4.2%	-24.10 [-48.21 , 0.01]	? ? − − + + −
Eldabe 2020	2.55	5.2	7.2%	2.55 [-7.64 , 12.74]	+ + ? ? + − −
Schu 2014	-36	6.58	6.6%	-36.00 [-48.90 , -23.10]	+ + ? ? + − −
Sokal 2020	-0.3	5.25	7.2%	-0.30 [-10.59 , 9.99]	? ? − − + − −
Subtotal (95% CI)			**25.2%**	**-13.53 [-32.61 , 5.56]**	
Heterogeneity: Tau² = 322.87; Chi² = 26.02, df = 3 (P < 0.00001); I² = 88%					
Test for overall effect: Z = 1.39 (P = 0.16)					
Total (95% CI)			**100.0%**	**-13.79 [-20.62 , -6.96]**	
Heterogeneity: Tau² = 141.21; Chi² = 76.01, df = 15 (P < 0.00001); I² = 80%					
Test for overall effect: Z = 3.96 (P < 0.0001)					
Test for subgroup differences: Chi² = 0.53, df = 2 (P = 0.77), I² = 0%					



Footnotes

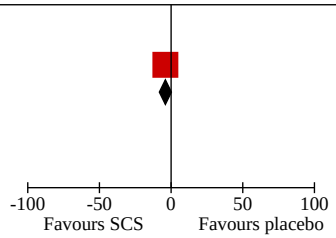
(1) 3030 Hz
(2) 1200 Hz
(3) 5882 Hz

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 2: Low back pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Burst SCS				
Hara 2022	-4	2.14	100.0%	-4.00 [-8.19 , 0.19]
Subtotal (95% CI)			**100.0%**	**-4.00 [-8.19 , 0.19]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.87 (P = 0.06)				
Test for subgroup differences: Not applicable				

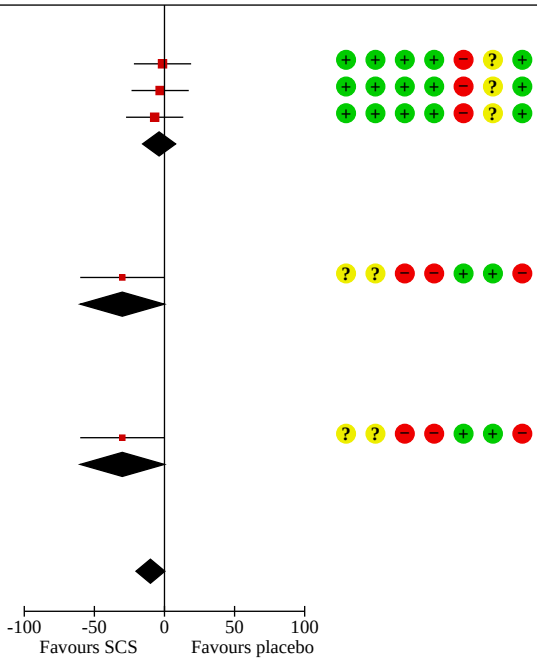


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 3: Leg pain intensity (0-100) at immediate-term follow-up (< 1 month)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 High-frequency SCS				
Al-Kaisy 2018 (1)	-1.4	10.41	25.5%	-1.40 [-21.80 , 19.00]
Al-Kaisy 2018 (2)	-3.1	10.41	25.5%	-3.10 [-23.50 , 17.30]
Al-Kaisy 2018 (3)	-7	10.41	25.5%	-7.00 [-27.40 , 13.40]
Subtotal (95% CI)			**76.4%**	**-3.83 [-15.61 , 7.95]**
Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² = 0%				
Test for overall effect: Z = 0.64 (P = 0.52)				
1.3.2 Conventional SCS				
De Ridder 2013	-30.1	15.3	11.8%	-30.10 [-60.09 , -0.11]
Subtotal (95% CI)			**11.8%**	**-30.10 [-60.09 , -0.11]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.97 (P = 0.05)				
1.3.3 Burst SCS				
De Ridder 2013	-30.1	15.3	11.8%	-30.10 [-60.09 , -0.11]
Subtotal (95% CI)			**11.8%**	**-30.10 [-60.09 , -0.11]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.97 (P = 0.05)				
Total (95% CI)			**100.0%**	**-10.03 [-20.33 , 0.27]**
Heterogeneity: Chi² = 4.66, df = 4 (P = 0.32); I² = 14%				
Test for overall effect: Z = 1.91 (P = 0.06)				
Test for subgroup differences: Chi² = 4.50, df = 2 (P = 0.11), I² = 55.6%				

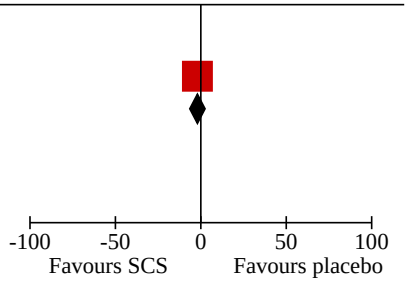


Footnotes
(1) 1200 Hz
(2) 3030 Hz
(3) 5882 Hz

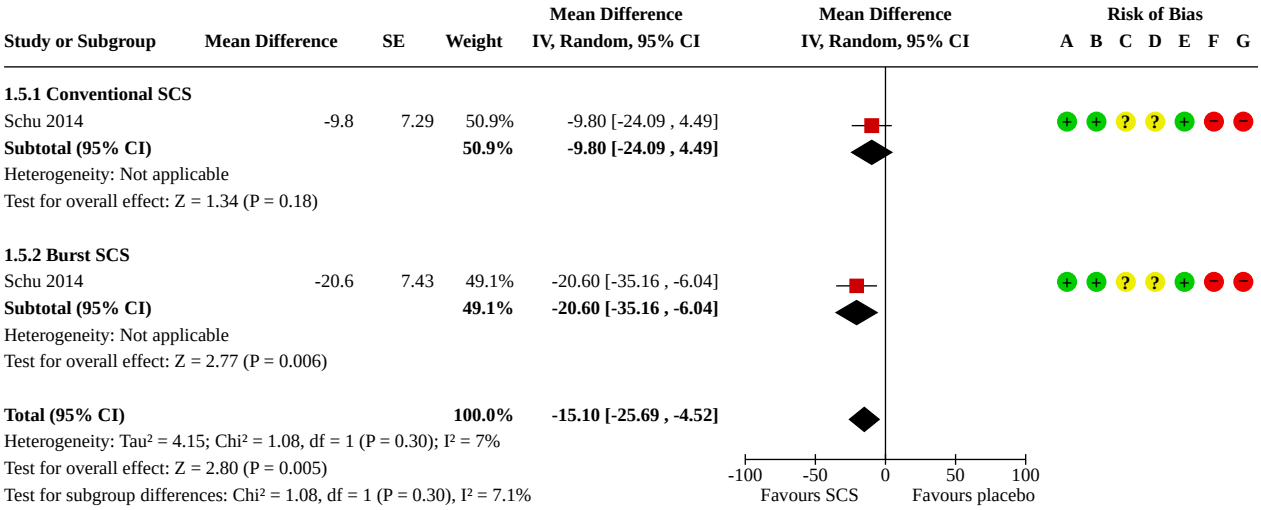
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 4: Leg pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Burst SCS				
Hara 2022	-2	2.28035	100.0%	-2.00 [-6.47 , 2.47]
Subtotal (95% CI)			**100.0%**	**-2.00 [-6.47 , 2.47]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.88 (P = 0.38)				
Test for subgroup differences: Not applicable				



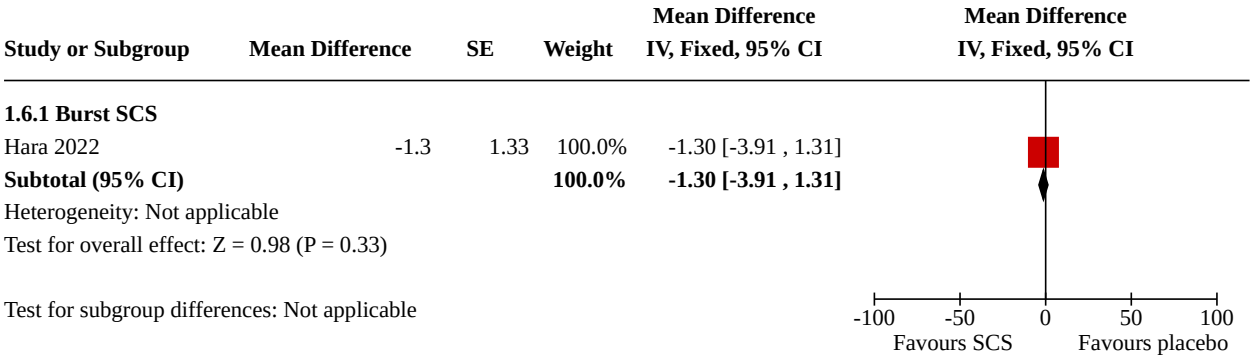
Analysis 1.5. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 5: Function (0-100) at immediate-term follow-up (< 1 month)



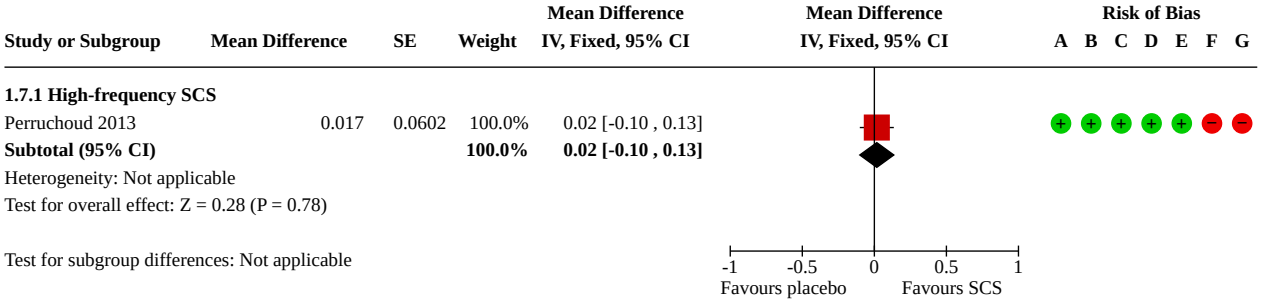
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 6: Function (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)

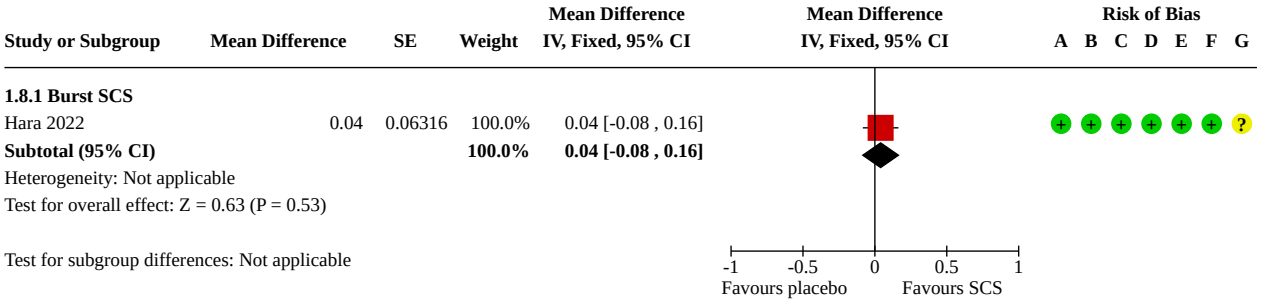


Analysis 1.7. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 7: Health-related quality of life (0-1 index) at immediate-term follow-up (< 1 month)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.8. Comparison 1: Spinal cord stimulation (SCS) versus placebo, Outcome 8: Health-related quality of life (0-1 index) at medium-term follow-up (≥ 3 mo to < 12 mo)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Spinal cord stimulation (SCS) plus medical management versus medical management alone

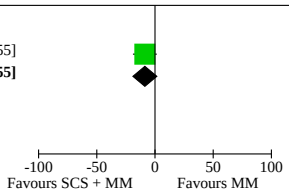
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Low back pain intensity (0-100) at short-term follow-up (≥ 1 mo to < 3 mo)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 Conventional SCS	1	98	Mean Difference (IV, Random, 95% CI)	-8.70 [-18.95, 1.55]

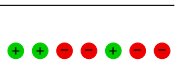
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Low back pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)	3	430	Mean Difference (IV, Random, 95% CI)	-25.97 [-56.17, 4.23]
2.2.1 High-frequency SCS	1	140	Mean Difference (IV, Random, 95% CI)	-54.60 [-61.03, -48.17]
2.2.2 Conventional SCS	2	290	Mean Difference (IV, Random, 95% CI)	-11.78 [-16.74, -6.81]
2.3 Leg pain intensity (0-100) at short-term follow-up (≥ 1 mo to < 3 mo)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Conventional SCS	1	98	Mean Difference (IV, Fixed, 95% CI)	-32.30 [-42.26, -22.34]
2.4 Leg pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 Conventional SCS	2	290	Mean Difference (IV, Random, 95% CI)	-18.84 [-33.21, -4.47]
2.5 Function (0-100) at short-term follow-up (≥ 1 mo to < 3 mo)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 Conventional SCS	1	94	Mean Difference (IV, Random, 95% CI)	-12.60 [-20.05, -5.15]
2.6 Function (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)	3	430	Mean Difference (IV, Fixed, 95% CI)	-16.19 [-19.36, -13.01]
2.6.1 High-frequency SCS	1	140	Mean Difference (IV, Fixed, 95% CI)	-28.80 [-33.81, -23.79]
2.6.2 Conventional SCS	2	290	Mean Difference (IV, Fixed, 95% CI)	-7.72 [-11.82, -3.62]
2.7 Health-related quality of life (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.7.1 Conventional SCS	2	289	Mean Difference (IV, Random, 95% CI)	7.63 [-0.61, 15.87]
2.8 Global assessment of efficacy at medium-term follow-up (≥ 3 mo to < 12 mo)	3	430	Risk Ratio (IV, Random, 95% CI)	7.40 [2.34, 23.39]
2.8.1 High-frequency SCS	1	140	Risk Ratio (IV, Random, 95% CI)	30.00 [7.60, 118.38]
2.8.2 Conventional SCS	2	290	Risk Ratio (IV, Random, 95% CI)	4.23 [2.12, 8.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9 Global assessment of efficacy at long-term follow-up (≥ 12 mo)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.93, 4.12]
2.10 Withdrawals due to adverse events at longest follow-up	1	159	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.02, 0.06]
2.10.1 High frequency SCS	1	159	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.02, 0.06]
2.11 Proportion with any adverse event at longest follow-up	2	336	Risk Ratio (M-H, Random, 95% CI)	2.32 [0.39, 13.79]
2.11.1 High-frequency SCS	1	140	Risk Ratio (M-H, Random, 95% CI)	5.77 [2.34, 14.20]
2.11.2 Conventional SCS	1	196	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.74, 1.42]
2.12 Proportion with serious adverse event at longest follow-up	1	140	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.51, 5.87]
2.12.1 High-frequency SCS	1	140	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.51, 5.87]
2.13 Medication use 1 (number (%) taking opioid medicines) at medium-term follow-up (≥ 3 mo to < 12 mo)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.13.1 Conventional SCS	2	290	Risk Ratio (IV, Random, 95% CI)	0.85 [0.73, 1.00]
2.14 Medication use 2 (daily MME) at medium-term follow-up (≥ 3 mo to < 12 mo)	3	430	Mean Difference (IV, Random, 95% CI)	-9.36 [-19.89, 1.16]
2.14.1 High-frequency SCS	1	140	Mean Difference (IV, Random, 95% CI)	-9.20 [-20.49, 2.09]
2.14.2 Conventional SCS	2	290	Mean Difference (IV, Random, 95% CI)	-10.46 [-39.55, 18.64]
2.15 Work status 1 (number returned to work) at medium-term follow-up (≥ 3 mo to < 12 mo)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.15.1 Conventional SCS	1	100	Risk Ratio (IV, Random, 95% CI)	3.69 [0.43, 31.89]

Analysis 2.1. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 1: Low back pain intensity (0-100) at short-term follow-up (≥ 1 mo to < 3 mo)

Study or Subgroup	SCS + medical management Mean	SD	Total	Medical management Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Conventional SCS								
Kumar 2007	38.9	24.9	51	47.6	26.7	47	100.0%	-8.70 [-18.95 , 1.55]
Subtotal (95% CI)			**51**			**47**	**100.0%**	**-8.70 [-18.95 , 1.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.66 (P = 0.10)								
Test for subgroup differences: Not applicable								

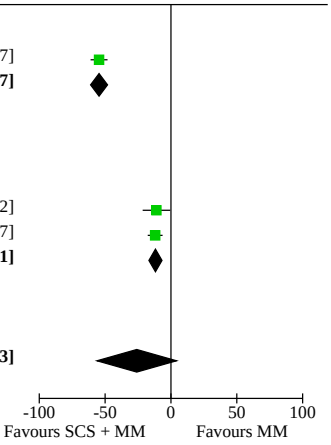




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

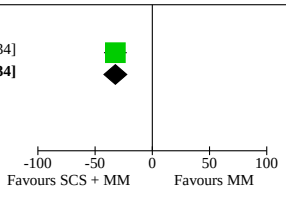
Analysis 2.2. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 2: Low back pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)

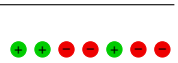
Study or Subgroup	SCS + medical management Mean	SD	Total	Medical management Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 High-frequency SCS								
Kapural 2022	21.8	15.8	65	76.4	22.8	75	33.6%	-54.60 [-61.03 , -48.17]
Subtotal (95% CI)			**65**			**75**	**33.6%**	**-54.60 [-61.03 , -48.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 16.64 (P < 0.00001)								
2.2.2 Conventional SCS								
Kumar 2007	40.6	24.9	50	51.6	26.7	44	32.7%	-11.00 [-21.48 , -0.52]
Rigoard 2019	60	21	92	72	19	104	33.7%	-12.00 [-17.63 , -6.37]
Subtotal (95% CI)			**142**			**148**	**66.4%**	**-11.78 [-16.74 , -6.81]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%								
Test for overall effect: Z = 4.65 (P < 0.00001)								
Total (95% CI)			**207**			**223**	**100.0%**	**-25.97 [-56.17 , 4.23]**
Heterogeneity: Tau² = 696.50; Chi² = 106.75, df = 2 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 1.69 (P = 0.09)								
Test for subgroup differences: Chi² = 106.72, df = 1 (P < 0.00001), I² = 99.1%								



Analysis 2.3. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 3: Leg pain intensity (0-100) at short-term follow-up (≥ 1 mo to < 3 mo)

Study or Subgroup	SCS + medical management Mean	SD	Total	Medical management Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 Conventional SCS								
Kumar 2007	36.7	26.3	51	69	24	47	100.0%	-32.30 [-42.26 , -22.34]
Subtotal (95% CI)			**51**			**47**	**100.0%**	**-32.30 [-42.26 , -22.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.36 (P < 0.00001)								
Test for subgroup differences: Not applicable								





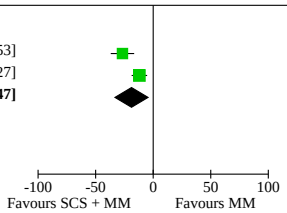
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

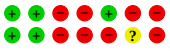
Analysis 2.4. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 4: Leg pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)

Study or Subgroup	SCS + medical management Mean	SD	Total	Medical management Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Conventional SCS								
Kumar 2007	39.9	26.3	50	66.6	24	44	46.5%	-26.70 [-36.87 , -16.53]
Rigoard 2019	42	24	92	54	24	104	53.5%	-12.00 [-18.73 , -5.27]
Subtotal (95% CI)			**142**			**148**	**100.0%**	**-18.84 [-33.21 , -4.47]**

Heterogeneity: Tau² = 88.68; Chi² = 5.58, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 2.57 (P = 0.01)

Test for subgroup differences: Not applicable





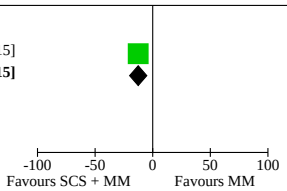
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.5. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 5: Function (0-100) at short-term follow-up (≥ 1 mo to < 3 mo)

Study or Subgroup	SCS + medical management Mean	SD	Total	Medical management Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.5.1 Conventional SCS								
Kumar 2007	42.7	17.9	50	55.3	18.8	44	100.0%	-12.60 [-20.05 , -5.15]
Subtotal (95% CI)			**50**			**44**	**100.0%**	**-12.60 [-20.05 , -5.15]**

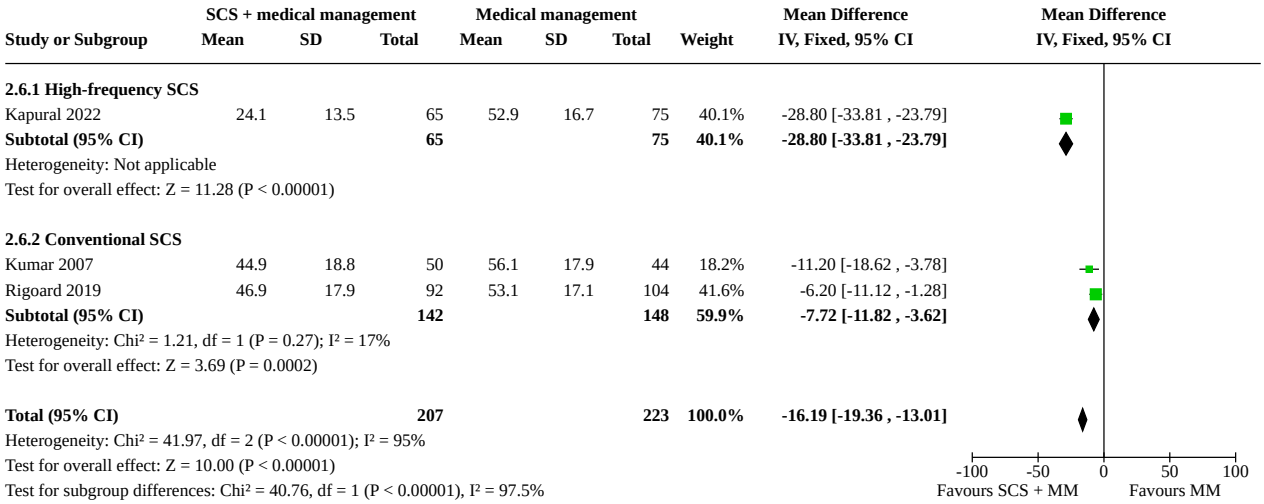
Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)

Test for subgroup differences: Not applicable

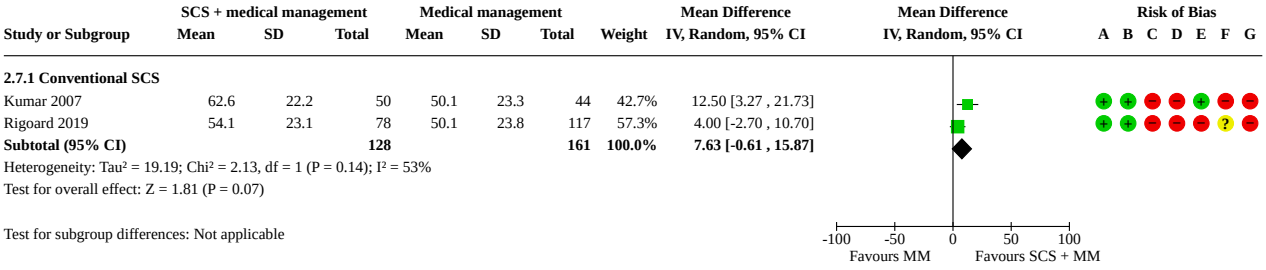


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.6. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 6: Function (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)



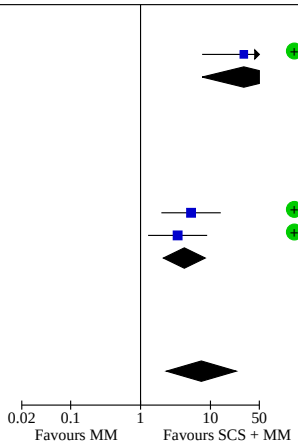
Analysis 2.7. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 7: Health-related quality of life (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)

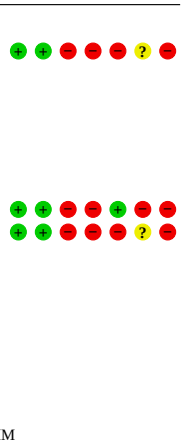


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.8. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 8: Global assessment of efficacy at medium-term follow-up (≥ 3 mo to < 12 mo)

Study or Subgroup	SCS + medical management Events	Total	Medical management Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.8.1 High-frequency SCS						
Kapural 2022	52	65	2	75	28.5%	30.00 [7.60 , 118.38]
Subtotal (95% CI)		**65**		**75**	**28.5%**	**30.00 [7.60 , 118.38]**
Total events:	52		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.86 (P < 0.00001)						
2.8.2 Conventional SCS						
Kumar 2007	24	50	4	44	35.7%	5.28 [1.99 , 14.04]
Rigoard 2019	15	92	5	104	35.8%	3.39 [1.28 , 8.97]
Subtotal (95% CI)		**142**		**148**	**71.5%**	**4.23 [2.12 , 8.42]**
Total events:	39		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 4.10 (P < 0.0001)						
Total (95% CI)		**207**		**223**	**100.0%**	**7.40 [2.34 , 23.39]**
Total events:	91		11			
Heterogeneity: Tau² = 0.72; Chi² = 6.65, df = 2 (P = 0.04); I² = 70%						
Test for overall effect: Z = 3.41 (P = 0.0007)						
Test for subgroup differences: Chi² = 6.25, df = 1 (P = 0.01), I² = 84.0%						

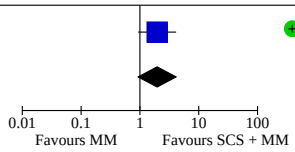


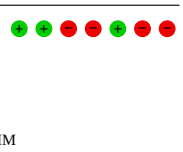


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.9. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 9: Global assessment of efficacy at long-term follow-up (≥ 12 mo)

Study or Subgroup	SCS + medical management Events	Total	Medical management Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2007	17	52	8	48	100.0%	1.96 [0.93 , 4.12]
Total (95% CI)		**52**		**48**	**100.0%**	**1.96 [0.93 , 4.12]**
Total events:	17		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.08)						
Test for subgroup differences: Not applicable						

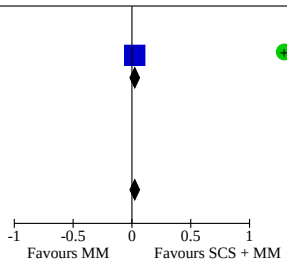


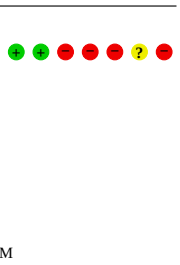


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.10. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 10: Withdrawals due to adverse events at longest follow-up

Study or Subgroup	SCS + medical management Events	Total	Medical management Events	Total	Weight	Risk Difference M-H, Random, 95% CI
2.10.1 High frequency SCS						
Kapural 2022	2	83	0	76	100.0%	0.02 [-0.02 , 0.06]
Subtotal (95% CI)		**83**		**76**	**100.0%**	**0.02 [-0.02 , 0.06]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**83**		**76**	**100.0%**	**0.02 [-0.02 , 0.06]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Not applicable						

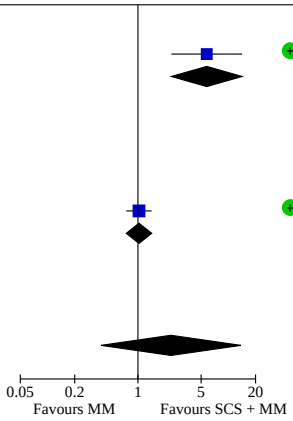


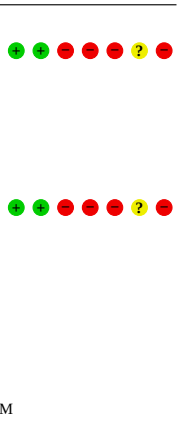


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.11. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 11: Proportion with any adverse event at longest follow-up

Study or Subgroup	SCS + medical management Events	Total	Medical management Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 High-frequency SCS						
Kapural 2022	25	65	5	75	47.2%	5.77 [2.34 , 14.20]
Subtotal (95% CI)		**65**		**75**	**47.2%**	**5.77 [2.34 , 14.20]**
Total events:	25		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.81 (P = 0.0001)						
2.11.2 Conventional SCS						
Rigoard 2019	40	92	44	104	52.8%	1.03 [0.74 , 1.42]
Subtotal (95% CI)		**92**		**104**	**52.8%**	**1.03 [0.74 , 1.42]**
Total events:	40		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						
Total (95% CI)		**157**		**179**	**100.0%**	**2.32 [0.39 , 13.79]**
Total events:	65		49			
Heterogeneity: Tau² = 1.54; Chi² = 13.91, df = 1 (P = 0.0002); I² = 93%						
Test for overall effect: Z = 0.93 (P = 0.35)						
Test for subgroup differences: Chi² = 12.48, df = 1 (P = 0.0004), I² = 92.0%						

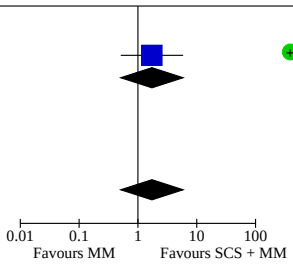




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.12. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 12: Proportion with serious adverse event at longest follow-up

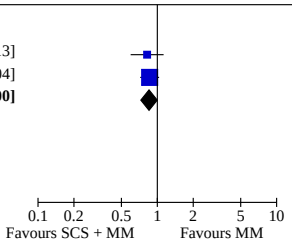
Study or Subgroup	SCS + medical management Events	Total	Medical management Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 High-frequency SCS						
Kapural 2022	6	65	4	75	100.0%	1.73 [0.51 , 5.87]
Subtotal (95% CI)		**65**		**75**	**100.0%**	**1.73 [0.51 , 5.87]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**65**		**75**	**100.0%**	**1.73 [0.51 , 5.87]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Not applicable						

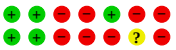


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.13. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 13: Medication use 1 (number (%) taking opioid medicines) at medium-term follow-up (≥ 3 mo to < 12 mo)

Study or Subgroup	SCS + medical management Events	Total	Medical management Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.13.1 Conventional SCS						
Kumar 2007	28	50	30	44	24.7%	0.82 [0.60 , 1.13]
Rigoard 2019	53	79	91	117	75.3%	0.86 [0.72 , 1.04]
Subtotal (95% CI)		**129**		**161**	**100.0%**	**0.85 [0.73 , 1.00]**
Total events:	81		121			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Test for subgroup differences: Not applicable						

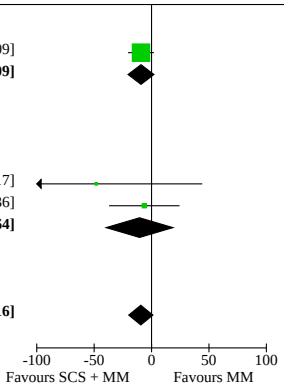


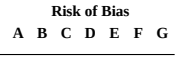


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.14. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 14: Medication use 2 (daily MME) at medium-term follow-up (≥ 3 mo to < 12 mo)

Study or Subgroup	SCS + medical management Mean	SD	Total	Medical management Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.14.1 High-frequency SCS								
Kapural 2022	24.6	37.5	65	33.8	29.4	75	86.9%	-9.20 [-20.49 , 2.09]
Subtotal (95% CI)			**65**			**75**	**86.9%**	**-9.20 [-20.49 , 2.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.60 (P = 0.11)								
2.14.2 Conventional SCS								
Kumar 2007	76.8	146	50	125	281	44	1.3%	-48.20 [-140.57 , 44.17]
Rigoard 2019	58.5	121.1	79	64.8	83.1	117	11.8%	-6.30 [-36.96 , 24.36]
Subtotal (95% CI)			**129**			**161**	**13.1%**	**-10.46 [-39.55 , 18.64]**
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%								
Test for overall effect: Z = 0.70 (P = 0.48)								
Total (95% CI)			**194**			**236**	**100.0%**	**-9.36 [-19.89 , 1.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 2 (P = 0.70); I² = 0%								
Test for overall effect: Z = 1.74 (P = 0.08)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%								

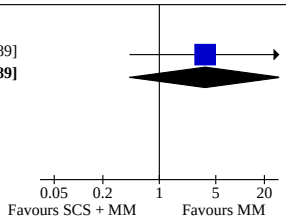




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.15. Comparison 2: Spinal cord stimulation (SCS) plus medical management versus medical management alone, Outcome 15: Work status 1 (number returned to work) at medium-term follow-up (≥ 3 mo to < 12 mo)

Study or Subgroup	SCS + medical management Events	Total	Medical management Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.15.1 Conventional SCS						
Kumar 2007	4	52	1	48	100.0%	3.69 [0.43 , 31.89]
Subtotal (95% CI)		**52**		**48**	**100.0%**	**3.69 [0.43 , 31.89]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.24)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Summary data extracted from cross-over trials and methods used to estimate mean difference and standard error

Analysis	Study	Mean (intervention)	SD (intervention)	N (intervention)	Mean (placebo)	SD (placebo)	N (Placebo)	Effect size (mean difference)	SE	Effect size adjusted for cross-over design?	Effect size adjusted for multiple comparisons to placebo group?	Notes
1.1 SCS versus placebo SCS, Outcome 1: Low back pain intensity (0-100) at immediate-term follow-up (< 1 month)												
1.1.1	Al-Kaisy 2018 (High-frequency SCS) (1)	45.1	18.7	24	48.3	24.5	8	-3.2	9.47	No	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo period by 3. Mean and SD were rescaled (x10)
1.1.1	Al-Kaisy 2018 (High-frequency SCS) (2)	45.7	20.7	24	48.3	24.5	8	-2.6	9.66	No	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo period by 3. Mean and SD were rescaled (x10)
1.1.1	Al-Kaisy 2018 (High-frequency SCS) (3)	32.2	19.8	24	48.3	24.5	8	-16.1	9.56	No	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo period by 3. Mean and SD were rescaled (x10)

Table 1. Summary data extracted from cross-over trials and methods used to estimate mean difference and standard error *(Continued)*

1.1.1	Perruchoud 2013 (High-frequency SCS)	43.5	19.2	33	42.6	21.4	33	-0.9	3.93	Yes. Means were from within subjects model	N/A	Effect size = -0.09 (95% CI -0.68 to 0.86) reported in paper. SE calculated from CI. Effect size and CI were rescaled (x10). Adjustment for period effects not required
1.1.1	Sokal 2020 (High-frequency SCS)	51.7	14	18	54.2	12.2	18	-1.7	2.20	Yes, using regression weights (β = -0.17) and SD of individual regression weight (τ = 0.68) provided by authors in Table A1	No	Effect size = -0.17, SE = 0.22 reported in paper Table A1. Effect size and SE were rescaled (x10). Effect size estimates are adjusted for cross-over. Unclear if multiplicity was accounted for.
1.1.1	Sweet 2016 (High-frequency SCS)	22.9	4.1	4	63.1	12.2	2	-50.1	6.44	Adjusted for cross-over, period and sequence effects	Yes	Patient level scores were digitally extracted from Figure 3. To estimate effect size, a mixed-effects model was fitted accounting for cross-over, period and sequence effects
1.1.2	De Ridder 2013 (Conventional SCS)	51.5	-	15	59.5	-	15	-7.8	12.30	No	No	Mean estimates digitally extracted from Figure 3. Mean difference was calculated, and SE was assumed equal to burst SCS estimate from

Table 1. Summary data extracted from cross-over trials and methods used to estimate mean difference and standard error *(Continued)*

												De Ridder. Results were rescaled (x10).
1.1.2	Eldabe 2020 (Conventional SCS)	51.0	-	19	38.0	-	19	-12.8	3.9	Yes	No	Means extracted from report. Mean percentage reduction and confidence interval were reported. These were converted to absolute values and rescaled (x10).
1.1.2	Schu 2014 (Conventional SCS)	71	19	20	83	11	10	-12.0	5.49	No	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo period by 2.
1.1.2	Sokal 2020 (Conventional SCS)	41.8	17.6	18	54.2	12.2	6	-9.9	5.6	Yes	Yes	Effect size = -0.99, SE = 0.56 reported in paper Table A1. Effect size and SE were rescaled (x10)
1.1.2	Sweet 2016 (Conventional SCS)	53.2	6.3	4	63.1	12.2	2	-31.2	7.2	Yes	No	Patient level scores were digitally extracted from Figure 3. To estimate effect size, a mixed-effects model was fitted, accounting for cross-over, period and sequence effects
1.1.2	Wolter 2012 (Conventional SCS)	56.8	22.4	6	63.7	20	6	-28.5	6.4	Yes	N/A	Patient level scores were reported in Table 3. A paired 2 sample t-test was performed (accounts for carryover). Estimates were rescaled (x10)
1.1.3	DeRidder 2013	35.5	-	15	59.5	-	15	-24.1	12.3	No	No	Mean estimates digitally extracted from Figure 3. Difference between

Table 1. Summary data extracted from cross-over trials and methods used to estimate mean difference and standard error *(Continued)*

	(Burst SCS)											burst SCS and placebo was reported statistically significant at 0.05 threshold. Mean difference was calculated, and conservatively assuming P = 0.05 allowed calculation of the standard error for back pain. Results were rescaled (x10)
1.1.3	Eldabe 2020 (Burst SCS)	54	-	19	51	-	19	2.55	5.2	Yes	No	Means extracted from report. Mean percentage reduction and confidence interval were reported. These were converted to absolute values and rescaled (x10).
1.1.3	Schu 2014 (Burst SCS)	47	25	20	83	11	10	-36	6.58	Yes	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo period by 2.
1.1.3	Sokal 2020 (Burst SCS)	52.7	13.3	18	54.2	12.2	6	-0.3	3.7	Yes	Yes	Effect size = -0.03, SE = 0.37 reported in paper Table A1. Effect size and SE were rescaled (x10). Effect size estimates are adjusted for cross-over. Unclear if multiplicity was accounted for.
1.4 SCS versus placebo SCS, Outcome 1: Low back pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)												
1.4.1	Hara 2022 (Burst SCS)	57	-	50	61	-	50	-4.0	2.14	Yes	N/A	Mean difference and confidence intervals were reported in Table 2. SE was calculated from confidence in-

Table 1. Summary data extracted from cross-over trials and methods used to estimate mean difference and standard error *(Continued)*

												terval. Results were rescaled (x10)
1.2 SCS versus placebo SCS, Outcome 2: Function (0-100) at immediate-term follow-up (< 1 month)												
1.2.2	Schu 2014 (Conventional SCS)	49.2	14.6	20	59	20.6	10	-9.8	7.29	Yes	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo by 2. Results were rescaled (x2).
1.2.3	Schu 2014 (Burst SCS)	38.4	16	20	59	20.6	10	-20.6	7.43	Yes	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo by 2. Results were rescaled (x2).
1.5 SCS versus placebo SCS, Outcome 2: Function (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)												
1.5.1	Hara 2022 (Burst SCS)	34.0	-	50	35.4	-	50	-1.3	1.33	Yes	N/A	Mean difference and confidence intervals are reported in Table 2. SE was calculated from confidence interval.
1.6 SCS versus placebo SCS, Outcome 3: Health-related quality of life (0-1) at immediate-term follow-up (<1 month)												
1.6.1	Perruchoud 2013 (High-frequency SCS)	0.48	-	33	0.46	-	33	0.017	0.0602	Yes	N/A	Means were from within subjects model. Effect size = 0.017 (95% CI -0.101 to 0.135) extracted from report. SE calculated from CI.
1.8 SCS versus placebo SCS, Outcome 3: Health-related quality of life (0-1) at medium-term follow-up (≥ 3 mo to < 12 mo)												

Table 1. Summary data extracted from cross-over trials and methods used to estimate mean difference and standard error *(Continued)*

1.8.1	Hara 2022 (Burst SCS)	0.48	-	50	0.44	-	50	0.04	0.0632	Yes	N/A	Mean difference and confidence intervals were reported in Table 2. SE was calculated from confidence interval.
1.3 SCS versus placebo SCS, Outcome 4: Leg pain intensity (0-100) at immediate-term follow-up (<1 month)												
1.3.1	Al-Kaisy 2018 (High-frequency SCS) (1)	18.1	25.5	24	25.1	25.5	8	-1.4	10.41	No	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo group by 3. Mean and SD were rescaled (x10). Follow-up SD values not reported; taken from baseline
1.3.1	Al-Kaisy 2018 (High-frequency SCS) (2)	23.7	25.5	24	25.1	25.5	8	-3.1	10.41	No	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo group by 3. Mean and SD were rescaled (x10). Follow-up SD values not reported; taken from baseline
1.3.1	Al-Kaisy 2018 (High-frequency SCS) (3)	22	25.5	24	25.1	25.5	8	-7.0	10.41	No	Yes	Mean difference and SE estimated from 2 sample t-test with unequal variance adjusted for multiplicity by dividing N of placebo group by 3. Mean and SD were rescaled (x10). Follow-up SD values not re-

Table 1. Summary data extracted from cross-over trials and methods used to estimate mean difference and standard error *(Continued)*

												ported; taken from baseline
1.3.2	DeRidder 2013 (Conventional SCS)	36	-	15	66	-	15	-30.1	15.3	No	No	Mean estimates digitally extracted from Figure 3 in report. Mean difference was calculated, and SE was assumed equal to burst SCS leg pain estimate from De Ridder. Results were rescaled (x10).
1.3.3	DeRidder 2013 (Burst SCS)	36	-	15	66	-	15	-30.1	15.3	No	No	Mean estimates digitally extracted from Figure 3. Difference between burst and placebo was reported statistically significant at 0.05 threshold. Mean difference was calculated, and conservatively assuming P = 0.05 allowed calculation of the standard error for leg pain. Results were rescaled (x10).
1.7 SCS versus placebo SCS, Outcome 4: Leg pain intensity (0-100) at medium-term follow-up (≥ 3 mo to < 12 mo)												
1.7.1	Hara 2022 (Burst SCS)	59	-	50	61	-	50	-2.0	2.28	Yes	N/A	Mean difference and confidence intervals were reported in Table 2. SE was calculated from confidence interval. Results were rescaled (x10).

Table 2. Outcome Reporting Bias In Trials (ORBIT) matrix

Study ID	Low back pain intensity	Function	Health-related quality of life	Global assessment (≥ 50% better)	Withdrawals due to adverse events	% with adverse events	% with serious adverse events
Al-Kaisy 2018	Partial	?	?	?	Partial	Partial	Partial
De Ridder 2013	Partial	?	?	?	?	?	?
Eisenberg 2015	Full	?	?	?	?	?	?
Eldabe 2020	Partial	?	Full	?	Full	Partial	?
Hara 2022	Full	Full	Full	Not measured	Full	Partial	Partial
Kumar 2007	Partial	Partial	Partial	Partial	Partial	Partial	Measured
Kapural 2022	Full	Full	Partial	Full	Full	Full	Full
Perruchoud 2013	Partial	?	Partial	?	Partial	?	?
Rigoard 2019	Full	Full	Full	Full	Partial	Full	Partial
Schu 2014	Full	Full	?	?	?	Partial	Partial
Sokal 2020	Full	Partial	Measured	?	?	Measured	?
Sweet 2016	Full	Partial	Partial	?	?	?	?
Wolter 2012	Full	Partial	?	?	?	?	?

'Full': sufficient data for inclusion in a meta-analysis were reported (e.g. mean, standard deviation, sample size per group for continuous outcomes).
'Partial': insufficient data for inclusion in a meta-analysis were reported (e.g. means only, with no measures of variance).
'Measured': outcome was measured but no outcome data were reported.
'Not measured': outcome was not measured by trialists.
'?': unclear whether the outcome was measured or not (as a trial protocol or prospective study registry entry was unavailable).

Table 3. Characteristics of SCS interventions in included studies

Study ID	Type of stimulation given	Device details	Electrode type/number	Stimulation parameters	Comparator	Details of pre-implantation trial period	Duration of stimulation

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

Al-Kaisy 2018	3 high-frequency stimulation waveforms	Rechargeable implanted pulse generator produced by Medtronic (Minneapolis, MN, USA).	Dual octapolar leads (Octad, Medtronic, Minneapolis, MN, USA).	High-frequency stimulation 1 included 5882 Hz for 30 µs; high-frequency stimulation 2 included 3030 Hz for 30 µs; high-frequency stimulation 3 included 1200 Hz for 180 µs	Placebo stimulation with the generator turned on and discharging, but without electricity transmitted to the lead	"All the recruited subjects received a trial of HF10 therapy for 7–14 days to assess efficacy and tolerability to the treatment. For every subject we initially activated a single bipole corresponding to the vertebral area of T9–T10, titrating up the HF10 SCS amplitude (1–5 mA range) during the first two to three days of the trial. If significant relief was not obtained (50%, but usually >70%), we activated a new bipole below the tested one for the following two to three days and, if again not successful, we moved to a new bipole higher than the one initially tested. At the end of the trial period, only those subjects reporting at least 50% or greater back pain VAS reduction from baseline were permanently implanted"	4 treatment arms, all of 3 weeks' duration
De Ridder 2013	Burst and conventional	Nonsterile EON IPG System (St. Jude Medical)	Externalised extension wires, Lamitrode tripole, 88, penta or 44	"Burst stimulation consists of intermittent packets of closely spaced, high-frequency stimuli, for instance, 40-Hz burst mode with five spikes at 500 Hz per burst, with a pulse width of 1 ms and 1 ms interspike intervals delivered in constant current mode. The cumulative charge of the five 1 ms spikes is balanced during 5 ms after the spikes." Conventional stimulation in-	Zero amplitude (IPG not discharging)	"During the mandatory period of external stimulation, which is a minimum of 28 days according to Belgian health care requirements for reimbursement, each patient was trialed by application of the classical tonic stimulation (40 or 50 Hz), burst stimulation with the same electrode configuration on separate days to prevent a carryover effect, and placebo. Patients were told they would receive three stimulation designs, some of which they might feel as paresthesias and some of which they might not feel as paresthesias. After an initial tonic programming session to define which electrodes needed activation as determined by paresthesia coverage, patients were programmed, lying down, randomly for 1 week with burst mode, 1 week in tonic mode, and 1 week with placebo".	3 treatment arms, all of 1 week duration

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

				cluded tonic stimulation of 40 Hz or 50 Hz			
Eisenberg 2015	Conventional	Conventional implanted device; temporary or permanent SCS implants	Not reported	Stimulator switched on or stimulator switched off	SCS device switched off	"Temporary or permanent SCS implants for the treatment of otherwise intractable unilateral radicular leg pain, after at least 1 back surgery was inclusion criteria for trial participation."	30 minutes
Eldabe 2020	Conventional and burst	Medtronic's rechargeable spinal cord stimulator, RestoreSensor	1 or 2 epidural leads	Conventional stimulation was a continuous tonic stimulation at 500 Hz with a pulse width of 480 µs. Burst stimulation was "40 Hz burst of four spikes of each 1000 µs at 500 Hz per burst".	The stimulator was switched off	"Achieved stable pain relief with conventional SCS (i.e., paraesthesia inducing stimulation with frequency < 150 Hz) using the Medtronic's rechargeable spinal cord stimulator RestoreSensor® and with either 1 or 2 epidural leads was inclusion criteria for trial participation".	3 treatment arms, each of 2 weeks' duration
Hara 2022	Burst	Precision Novi, Boston Scientific, Inc non-rechargeable implantable pulse generator	"A 16-contact lead (Infinion CX, Boston Scientific, Inc) was implanted for unilateral leg pain or two 8-contact leads (Linear ST, Boston Scientific, Inc) were implanted for bilateral leg pain"	"Closely spaced, high-frequency stimuli delivered to the spinal cord. The simulus consisted of 40 Hz of constant current with 4 spikes per burst at an amplitude corresponding to 50% to 70% of paraesthesia perception threshold."	No stimulation provided	"Epidural surgical lead insertion was performed while patients were in the prone position using local anesthetics and mild intravenous sedation to enable patient feedback and cooperation. The aim was to optimize lead placement over the dorsal columns of the spinal cord so that paresthesia occurred in the targeted spinal dermatome (ie, tonic conventional stimulation). A 16-contact lead (Infinion CX, Boston Scientific, Inc) was implanted for unilateral leg pain or two 8-contact leads (Linear ST, Boston Scientific, Inc) were implanted for bilateral leg pain through a small skin incision at the L1/L2 or L2/L3 vertebral levels and placed in the epidural space at the T9/T10 [vertebral] level under fluoroscopic guidance. Intraoperative electrophysiological testing and stimulation were performed during longitudi-	12 months: 4 periods of 3 months of treatment (6 months of SCS and 6 months of placebo)

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

						nal lead navigation. The leads were anchored at the optimal localization and their positions were confirmed with x-ray imaging. Leads were then connected to an external neurostimulator using extension cords. Programming software (Illumina 3D, Boston Scientific, Inc) was used to optimize tonic conventional stimulation and determine paresthesia thresholds during the testing period. If there was insufficient improvement in leg pain during the testing period, the leads were removed and the patients were excluded. If there was sufficient improvement in leg pain during the testing period, the patients were included in the trial and their external neurostimulator was replaced with a nonrechargeable implantable pulse generator (Precision Novi, Boston Scientific, Inc) placed subcutaneously on the upper buttock or abdomen under local anesthesia. A nonrechargeable pulse generator was chosen to avoid unblinding of patients. Immediately after implantation of the stimulator, eligible patients underwent four 3-month periods of treatment."	
Kumar 2007	Conventional	Implantable neurostimulation system produced by Medtronic (Synergy system, Medtronic, Inc., Minneapolis, MN)	Not specified	Mean (SD) settings were an amplitude of 3.7 V (2.0), a pulse width of 350 µs (95.5) and a rate of 49 Hz (16.4). Almost half (45%) of the participants required an amplitude of 4 V or more	”Non-SCS therapy received by both groups was reviewed and actively managed, at the discretion of the study investigator and according to local clinical practice. Non-SCS therapy included oral medications (i.e. opioid, non-steroidal anti-inflammatory drug, antidepressant, anticonvulsant/antiepilep-	“All patients assigned to the SCS group underwent a screening trial. Those experiencing at least 80% overlap of their pain with stimulation-induced paresthesia and at least 50% leg pain relief received an implantable neurostimulation system”	12 months

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

					tic and other analgesic therapies), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. The protocol excluded other invasive therapy, such as spinal surgery or implantation of an intrathecal drug delivery system".		
Kapural 2022	High frequency	IPG SCS system (Senza, Nevro Corp., Redwood City, CA, USA)	Two percutaneous leads with 8 contacts each placed in the epidural space spanning vertebral levels T8 to T11	10 kHz	"All subjects will continue with their CMM, defined as the best standard of care for each individual patient, as determined by the investigator." Options included, but were not limited to: oral medications (including analgesic medication, nonsteroidal anti-inflammatory drugs, neuromodulating agents, antidepressants); topical analgesics, compound creams, or counter-irritants; combined physical and psychological management; physical therapy; back rehabilitation program; spinal manipulation and spinal mo-	Stimulation at a frequency of 10 kHz and pulse width of 30 µs delivered from an external pulse generator. The stimulation target and current amplitude was adjusted until at least 50% self-reported back pain reduction from baseline achieved, defined as trial success, or until conclusion of the trial phase	6 months

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

					bilisation traction; acupuncture/acupressure; cognitive behavioural therapy; nerve blocks; epidural steroid injections; transcutaneous electrical nerve stimulation		
Perruchoud 2013	High frequency	Medtronic (Minneapolis, MN, USA) impulse generator, either rechargeable (RestoreADVANCED, RestoreSensor, or RestoreUltra) or battery-powered (PrimeADVANCED)	Not reported. No more than three active contacts	5000 Hz; with pulse width adjusted to 60 ms	The stimulator was switched off	"Currently implanted with suitable SCS device" was an inclusion criteria for study participants	2-week periods of stimulation; 8 weeks study duration; i.e. 2 weeks current stimulation, 2 weeks high-frequency (HF) or sham, 2 weeks current stimulation, 2 weeks HF or sham
Rigoard 2019	Conventional	Medtronic neurostimulator (model 97714, n = 49; 37702, n = 39;97702, n = 27; 37714, n = 12; 97712, n = 4; 37713, n = 3; 97713, n = 3; 37712, n = 2; and 37701, n = 1)	Multicolumn surgical lead (Specify 5-6-5; Medtronic)	20 Hz to 1200 Hz	"All patients received optimal medical management [OMM]. As part of the confirmation of eligibility (prior to randomization), the investigator and subject will determine an individual OMM treatment plan, which should include non-investigational pharmacologic agents (for example, tricyclic antidepressants, opioid analgesics or tramadol,	“The screening test may be conducted with the Specify® 5-6-5 surgical lead or with a percutaneous lead(s). If successful, a SCS system will be implanted. A screening test will be determined to be successful if the subject finds the feeling of paresthesia acceptable and has adequate low back pain relief with usual activity and appropriate analgesia as assessed by the physician. Physicians can consider a conducting second screening test with the Specify® 5-6-5 lead if a screening test with a percutaneous lead led to inadequate paresthesia coverage of low back pain and/or painful extraneous stimulation (for example, chest wall pain, pressure or sharp mid-back pain)”.	6 months (then allowed to cross to alternative trial arm and followed to 24 months)

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

				antiepileptics, or lidocaine) and/or interventional therapies (for example, therapeutic injections, radiofrequency, acupuncture, functional restoration, physical therapy, and psychological interventions, such as cognitive behavioural therapy) as appropriate. The following treatments are excluded from OMM: intrathecal drug delivery, peripheral nerve stimulation (not an approved indication in the United States), back surgery at the location related to the patient's original back pain complaint, and experimental therapies."		
Schu 2014	Conventional and burst	St. Jude Medical SCS system	SCS leads located at the mid-thoracic position (T7–T10 vertebral level)	For conventional stimulation, 500 Hz mean pulse width ± SD under 500-Hz tonic stimulation was 370.8 ± 135.4 µs, and mean amplitude ± SD was 5.5 ± 3.6 mA. For burst spinal cord stimulation, packets of five pulses (pulse width 1 ms) at	Device was switched off	Implanted "with a St. Jude Medical SCS system at least three months previously" was an inclusion criteria for study participants.	3 treatment arms, all of 1 week duration

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

				500 Hz, delivered 40 times per second			
Sokal 2020	High-frequency, burst, and conventional	Non-rechargeable IPG (Precision Novi™) and in one case, a rechargeable IPG (Montage™) produced by Boston Scientific Co.	Either one or two linear lead 8- or 16-contact (Infinion 16™) electrodes on vertebral levels T7–T10	High-frequency stimulation was programmed with frequency of 1 kHz, pulse width of 120 s, and amplitude = 3 Amp. Burst stimulation delivered intermittent packets using the neural targeting algorithm, which consisted of several pulses per packet with pulse width 250–500 s repeated with frequency of 40 Hz. Conventional stimulation included tonic stimulation with frequencies typically between 40 Hz and 60 Hz. The pulse width ranged between 250 s and 500 s, and the amplitude produced comfortable paraesthesia	IPG was deactivated	Participants underwent 2 weeks of trial stimulation. During the trial period, tonic low-frequency stimulation was used to check the coverage of pain area with paraesthesia induced by an external stimulator by adjusting the optimal settings of active electrode's contacts. After a successful 14-day trial period, participants who achieved at least a 50% reduction in pain were qualified to the second stage of the study, which involved the placement of a permanent internal pulse generator implantation under general anaesthesia.	4 treatment arms, all of 2-week duration
Sweet 2016	Sub-threshold high density (HD)	Medtronic RestoreSensor implanted pulse generator (Minneapolis, MN, USA).	"[Two] epidural 8-contact Medtronic Compact percutaneous SureScan	Subthreshold HD stimulation (1200 Hz, 200 µs, amplitude 90% of threshold for sensory percept)	"[Same] settings but amplitude 0 V"	"[One-week] trial of subthreshold HD stimulation, defined as 1200 Hz frequency, 200 µs pulse width, and an amplitude 90% of the threshold for detection of a sensory percept. At the end of the week, each potential participant was asked about pain relief using the sub-	2 treatment arms, each of 2 weeks' duration and both preceded by 2 weeks of conven-

Table 3. Characteristics of SCS interventions in included studies *(Continued)*

			leads (electrode contacts 3 mm long and 1.3 mm diameter, 4 mm intercontact spacing) implanted in the midline with the end of the lead at the T7-T8 [vertebral] interspace"			threshold parameters. Subjects were enrolled only if they reported significant pain relief using subthreshold HD stimulation, defined as 50% reduction in pain on the visual analog scale (VAS) compared with preoperative values."	tional stimulation
Wolter 2012	Conventional	"With one exception (patient 6), all patients had a nonrechargeable implantable pulse generator (IPG). In patient 6, the battery state of the IPG was checked to rule out inadvertent discharge during the trial". Stimulators were produced by Medtronic (n = 5) or Boston Scientific (n = 1).	All participants were implanted with percutaneous-type electrodes	25 Hz to 100 Hz	The device was switched to zero	Prior SCS for at least 3 months with significant (> 50%) pain relief was an inclusion criterion for trial participation	2 treatment arms, each of 1-week duration

CMM: conventional medical management; **IPG:** internal pulse generator or implantable pulse generator; **SCS:** spinal cord stimulation; **µs:** microseconds; **ms:** milliseconds

APPENDICES

Appendix 1. Search strategy

MEDLINE (Ovid) search strategy

Database: Ovid MEDLINE (R) <1946 to June 2022>

1. randomized controlled trial.pt.

2. exp randomized controlled trial/

3. "randomized controlled trial".mp.

4. exp random allocation/

5. placebo.mp.

6. exp placebos/

7. exp placebo effect/

8. (random* adj3 trial).ab,ti.

9. "controlled clinical trial".mp.

10. exp controlled clinical trial/

11. Random*.ab,ti.

12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. low back pain.mp.

14. exp Low Back Pain/

15. back pain.mp.

16. exp Back Pain/

17. sciatica.mp.

18. exp Sciatica/

19. lumbosacral region.mp.

20. exp Lumbosacral Region/

21. lower back pain.mp.

22. lower backache.mp.

23. low back ache.mp.

24. lumbago.mp.

25. exp Spine/

26. spine.mp.

27. lumbar spine.mp.

28. sciatic neuropathy.mp.

29. exp Sciatic Neuropathy/

30. (lumbar adj pain).mp.

31. backpain.mp.

32. lumbar spine.mp.

33. back disorder.mp.

34. coccyx.mp.

35. coccydynia.mp.

36. neuropathic.mp.

37. (failed adj back).mp.

38. FBSS.mp.

39. laminectomy syndrome.mp.

40. post surgery syndrome.mp.

41. regional pain syndrome.mp.

42. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

43. exp Electrodes

44. implanted/

45. exp Electric Stimulation Therapy/

46. spinal cord stimulat$.mp.

47. dorsal column stimulat$.mp.

48. epidural stimulat$.mp.

49. neuromodulat$.mp.

50. (stimulat$ adj frequency).mp.

51. (therapy adj frequency).mp.

52. (burst adj stimulat$).mp.

53. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52

54. 12 and 42 and 53

CENTRAL (Ovid) search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1. low back pain.mp.

2. exp Low Back Pain/

3. back pain.mp.

4. exp Back Pain/

5. sciatica.mp.

6. exp Sciatica/

7. lumbosacral region.mp.

8. exp Lumbosacral Region/

9. lower back pain.mp.

10. lower backache.mp.

11. low back ache.mp.

12. lumbago.mp.

13. exp Spine/

14. spine.mp.

15. lumbar spine.mp.

16. sciatic neuropathy.mp.

17. exp Sciatic Neuropathy/

18. (lumbar adj pain).mp.

19. backpain.mp.

20. lumbar spine.mp.

21. back disorder.mp.

22. coccyx.mp.

23. coccydynia.mp.

24. neuropathic.mp.

25. (failed adj back).mp.

26. FBSS.mp.

27. laminectomy syndrome.mp.

28. post surgery syndrome.mp.

29. regional pain syndrome.mp.

30. or/1-29

31. exp Electrodes

32. implanted/

33. exp Electric Stimulation Therapy/

34. spinal cord stimulat$.mp.

35. dorsal column stimulat$.mp.

36. epidural stimulat$.mp.

37. neuromodulat$.mp.

38. (stimulat$ adj frequency).mp.

39. (therapy adj frequency).mp.

40. (burst adj stimulat$).mp.

41. or/31-40

42. 30 and 41

Embase (Ovid) search strategy

Database: Embase <1974 to 2022 June>

1. randomized controlled trial.pt.

2. exp randomized controlled trial/

3. "randomized controlled trial".mp.

4. exp random allocation/

5. placebo.mp.

6. exp placebos/

7. exp placebo effect/

8. (random* adj3 trial).ab,ti.

9. "controlled clinical trial".mp.

10. exp controlled clinical trial/

11. Random*.ab,ti.

12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. low back pain.mp.

14. exp Low Back Pain/

15. back pain.mp.

16. exp Back Pain/

17. sciatica.mp.

18. exp Sciatica/

19. lumbosacral region.mp.

20. exp Lumbosacral Region/

21. lower back pain.mp.

22. lower backache.mp.

23. low back ache.mp.

24. lumbago.mp.

25. exp Spine/

26. spine.mp.

27. lumbar spine.mp.

28. sciatic neuropathy.mp.

29. exp Sciatic Neuropathy/

30. (lumbar adj pain).mp.

31. backpain.mp.

32. lumbar spine.mp.

33. back disorder.mp.

34. coccyx.mp.

35. coccydynia.mp.

36. neuropathic.mp.

37. (failed adj back).mp.

38. FBSS.mp.

39. laminectomy syndrome.mp.

40. post surgery syndrome.mp.

41. regional pain syndrome.mp.

42. or/13-41

43. exp Electrodes

44. implanted/

45. exp Electric Stimulation Therapy/

46. spinal cord stimulat$.mp.

47. dorsal column stimulat$.mp.

48. epidural stimulat$.mp.

49. neuromodulat$.mp.

50. (stimulat$ adj frequency).mp.

51. (therapy adj frequency).mp.

52. (burst adj stimulat$).mp.

53. or/43-52

54. 12 and 42 and 53

CINAHL (EBSCOhost) search strategy

1. randomized controlled trial

2. (MM "Randomized Controlled Trials+")

3. (MH "Random Assignment")

4. placebo

5. (MH "Placebos")

6. (MH "Placebo Effect")

7. ""controlled clinical trial""

8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7

9. (MH "Low Back Pain")

10. low back pain

11. back pain

12. (MH "Back Pain+")

13. (MH "Sciatica")

14. sciatica

15. lumbosacral region

16. (MH "Lumbosacral Plexus+")

17. lower back pain

18. "lower backache"

19. low back ache

20. lumbago

21. (MH "Spine+")

22. spine

23. lumbar spine

24. sciatic neuropathy

25. (MH "Sciatic Nerve+")

26. lumbar pain

27. back pain

28. lumbar spine

29. back disorder

30. coccyx

31. coccydynia

32. neuropathic

33. failed back

34. FBSS

35. laminectomy syndrome

36. post surgery syndrome

37. regional pain syndrome

38. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37

39. (MH "Electrodes+") OR (MH "Electrodes, Implanted+")

40. (MH "Electric Stimulation+")

41. spinal cord stimulat$

42. spinal cord stimulat

43. (MH "Spinal Cord Stimulation") OR "spinal cord stimulator"

44. dorsal column stimulation

45. epidural stimulation

46. neuromodulation

47. stimulation frequency

48. burst stimulation

49. 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48

50. 8 AND 38 AND 49

WHAT'S NEW

Date	Event	Description
1 August 2023	Amended	Corrected mislabelled graph axis in Figure 9.

HISTORY

Protocol first published: Issue 9, 2021
Review first published: Issue 3, 2023

CONTRIBUTIONS OF AUTHORS

Conceived the review: AT, SG, IH, CM

Drafted the protocol: AT and SG

Developed and ran search strategy: AT

Obtained studies: AT

Selected studies for inclusion (2 people): AT and SG

Extracted data from studies (2 people): AT and SG

Evaluated risk of bias, make GRADE judgements: AT and SG

Entered data into RevMan 5: AT

Carried out the analysis: AT

Interpreted the analysis: AT, SG, IH, CM

Drafted the review: AT and SG

Reviewed and approved final version: AT, SG, IH, CM

DECLARATIONS OF INTEREST

AT: provided paid consultancy on models of physiotherapy care to a health service provider in 2017.
SG: none known
IAH: employed by New South Wales (NSW) Ministry of Health, University of NSW, and Australian Orthopaedic Association, and received royalties for a 2016 book, *Surgery, the Ultimate Placebo,* and a 2021 book, *Hippocrasy, How Doctors Are Betraying Their Oath*.
CGM: has received competitive grants from government agencies and industry to support his research. As an invited speaker at conferences, he has had his expenses covered and also received small gifts, such as a box of chocolates or a bottle of wine. He has received honoraria for marking theses, reviewing grants, and preparing talks.

SOURCES OF SUPPORT

Internal sources

- National Health and Medical Research Council, Australia

  Fellowship support for Dr Traeger and Prof. Maher

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were some small differences between our protocol and the review. First, we planned to construct a funnel plot to explore possible small study biases; however, we decided against this due to the small number of studies located. Second, there were no long-term data available for us to include in our summary of findings table. At the suggestion of peer reviewers, we decided (post hoc) to present data from our analysis of the longest possible follow-up (i.e. medium-term outcomes), rather than an empty summary of findings table. Third, we specified comparator groups had to include placebo or no treatment but decided to include designs assessing the addition of SCS to medical management. Whether these studies reflect an SCS versus 'no treatment' comparison is open to interpretation, and so we erred on the side of inclusion. Finally, we did not prespecify that we would use the generic inverse variance approach to meta-analysis of cross-over trials. However, this approach was necessary for us to account for paired data and for multiplicity when studies provided more than one estimate of SCS versus placebo. As planned, we extracted the number of events and number of participants per treatment group for dichotomous outcomes, and means, standard deviations, and number of participants per treatment group for continuous outcomes. We used this information, along with data on paired analyses extracted from trial reports (see Table 1), to allow us to use the generic inverse variance approach.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid; *Low Back Pain [therapy]; Quality of Life; *Spinal Cord Stimulation [adverse effects]

MeSH check words

Female; Humans; Male; Middle Aged