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EVIDENCE REVIEW 323

ISCRR
Institute for Safety, Compensation and Recovery Research

Clinical effectiveness of spinal cord stimulators for persistent pain

A review of the evidence

The safety and effectiveness of spinal cord stimulators for persistent pain, function, quality of life, return to work, and medication use.

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A joint initiative of WorkSafe VICTORIA and MONASH University

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ABBREVIATIONS

Abbreviation	
CI	confidence interval
CMM	conventional medical management
CRPS	Complex Regional Pain Syndrome
ECAP	evoked compound action potential
EPHPP	Effective Public Health Practice Project
FBSS	Failed Back Surgery Syndrome
HD-SCS	high density spinal cord stimulation
HF-SCS	high frequency spinal cord stimulation
HRQoL	health-related quality of life
ISCRR	Institute for Safety, Compensation and Recovery Research
LF-SCS	low frequency spinal cord stimulation
NRS	numeric response scale
OR	odds ratio
QoL	quality of life
RCT	randomised control trial
SCS	spinal cord stimulator
TGA	Therapeutic Goods Administration
VAS	visual analogue scale

EXECUTIVE SUMMARY

Spinal Cord Stimulators (SCSs) are surgically implanted neurostimulation devices that are used to treat chronic or persistent pain. In addition to relieving pain, the secondary effects of spinal cord stimulation are suggested to include reductions in pain medication and physical therapy use, improvements in return to work capacity, and improvements in mental health outcomes such as depression and anxiety.

In Victoria, injured workers can receive an SCS funded through the Victorian Workers Compensation scheme to treat chronic pain conditions that have not responded to other treatments. However, the medium and long-term outcomes for people with an SCS implant are uncertain. Available trials are small, typically at high risk of bias and test brief treatment regimens.

The purpose of the current project was to conduct a review of the latest evidence for the clinical effectiveness of spinal cord stimulators for persistent pain.

Method

This Evidence Review involved a systematic search of three databases (Medline, Cochrane, Embase) to identify relevant synthesised research (i.e. evidence-based guidelines, systematic reviews), and any relevant randomised controlled trials (RCTs) and controlled clinical trials that assessed the effectiveness of SCS for treating persistent pain.

What is the effectiveness of spinal cord stimulator implants on persistent pain?

The primary aim was to examine the effectiveness of SCS implants on persistent pain in the short, medium, and long-term. There were 12 systematic reviews and 30 primary studies (10 RCTs and 20 prospective cohort studies) with pain reduction as the primary outcome of interest. Each of the studies reviewed looked at a variety of pain producing conditions in isolation and in combination.

Short-term outcomes (up to 3 months):

- Largest body of evidence from RCTs, systematic reviews and prospective cohort studies showing reductions in pain up to three months post implant
- Overall low level of certainty of evidence, moderate level of bias of included studies

Medium-term outcomes (3 to 6 months):

- Limited evidence from a smaller number of RCTs, systematic reviews and prospective cohort studies showing reductions in pain at six months post implant
- Overall low level of certainty of evidence, moderate level of bias of included studies

Long-term outcomes (12 months or more):

- Limited evidence from a smaller number of RCTs, systematic reviews and prospective cohort studies showing reductions in pain at 12+ months post implant
- Conflicting results at longer time frames from limited number of RCTs
- Overall low level of certainty of evidence, high to moderate level of bias of included studies

Major limitations:

- High heterogeneity of included pain conditions
- Moderate to high risk of bias among studies
- Methodological issues (e.g., blinding, small case numbers, lack of placebo controls)
- High risk of bias from industry funding.

What are the effects of spinal cord stimulator implants on functioning, quality of life, return to work and medication use?

The second research question of the evidence review was to examine evidence for the effects of SCS implants on function (physical, psychological, social), quality of life, return to work, medication and healthcare use. A small amount of supporting evidence was found for the effects of SCS on secondary outcomes with minor improvements in functioning, health related quality of life and return to work rates. Improvements in the reduction of medication use were identified by a small number of authors.

What do we know about adverse events associated with SCS implants?

Reporting on adverse events was less common in earlier studies but more frequent in recent studies. Overall proportions of patients experiencing an adverse event ranged considerably from as low as 9% to as high as 51%. Pain was commonly reported as an adverse event followed by lead migration. Much higher rates of adverse events have been reported in Australia.

Implications

Overall, the evidence suggests that SCS implants for persistent pain are clinically effective in the short and medium-term, but evidence is lacking on the long-term outcomes for patients. The quality of RCTs is improving leading to decreased risks of bias although the results are low to moderate certainty given continuing issues with industry funding, lack of effective blinding and high heterogeneity.

SCS implants have also shown limited, but positive, effects on quality of life, improving disability and functioning, and reducing medication use. The effects of SCS implants on return to work are much less certain with limited research available.

The high rate of adverse events reported in Australia, including the large proportion of SCS implants being removed, continue to be of concern. The outcomes of the recently announced Therapeutic Goods Administration (TGA) post market review of spinal cord stimulators should provide more information in order to allow judgements to be made regarding the true risks and benefits for patients.

BACKGROUND

Spinal cord stimulators are surgically implanted neurostimulation devices that are used to treat chronic or persistent pain. In 2018, chronic pain cost an estimated $139 billion in Australia, mostly through reduced quality of life and productivity losses[1]. The financial cost of chronic pain in 2018 was an estimated $73.2 billion[2] and this included $48.3 billion (66%) for productivity costs, reflecting the impact on a person's ability to work, work performance and employment outcomes.

In addition to relieving pain, the secondary effects of SCSs are suggested to include reductions in pain medication and physical therapy use, improvements in return to work capacity, and improvements in mental health outcomes such as depression and anxiety.

The efficacy of spinal cord stimulation is uncertain because available trials are small, typically at high risk of bias and test brief treatment regimens. Uncertainty about the efficacy of SCSs is also reflected in guideline recommendations; some guidelines endorse their use whereas others do not. In addition, SCSs require ongoing maintenance, reprogramming and replacement often via repeat surgeries, can cause several different adverse events, and are costly.

A recent Australian study, that analysed SCS implant adverse events reported to the TGA, found that from July 2012 to January 2019, 520 adverse events were reported, most events rated as severe or life-threatening[3]. Forty percent of SCSs that were implanted were removed.

In Victoria, injured workers can receive an SCS implant funded through WorkSafe Victoria to treat chronic pain conditions that have not responded to other treatments. Injured workers undergo a trial period with a temporary SCS implant. During this time, they undergo daily assessments completing a range of measures on well-being, functioning and experience of pain. The medium and long-term outcomes across these measures after implant in injured workers are currently unknown. There is a significant need for up-to-date quality information on postoperative outcomes for SCS implant recipients across a range of outcome parameters.

Types of pain conditions and treatments

The types of conditions that SCS has been reported to help include failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS). SCS has also been applied to conditions including refractory angina, diabetic neuralgia, post-herpetic neuralgia, and visceral or peripheral ischemic pain. The focus of this evidence review will be on compensable type pain conditions experienced by injured workers such as FBSS, CRPS and other chronic peripheral neuropathies with an injurious onset.

Opioids have been a common treatment for chronic pain and are often used in conjunction with conventional medical management therapies such as cognitive behavioural therapy, physical rehabilitation, non-opiate pharmacology, and integrative therapies. However, with increasing understanding of the levels of addiction, abuse, tolerance, and dependence associated with long-term opioid use, alternative treatments such as SCS are considered safer.

Spinal cord stimulation

Spinal cord stimulation has been in use since 1967 however its mechanism of action remains poorly understood. The technique is originally based on the gate control theory of pain, which suggests that non-painful inputs, such as electrical pulses emitted from the SCS implant, inhibit painful inputs, thereby preventing pain sensation from reaching the central nervous system[4].

Spinal cord stimulation consists of the placement of leads in the epidural space alongside the dorsal column. The leads are then connected to an implantable pulse generator. The generators are similar

to pacemakers and contain a battery and microprocessor. The generators are implanted either within the abdominal wall or posteriorly in the flank or gluteal region. Programming can occur transcutaneously, with adjustments made with a remote control by the physician or patient[5].

Implantable pulse generators last 5–10 years, depending on rechargeability, and are replaceable. The generators emit electrical pulses that mask pain signals travelling up the spinal cord. The coverage of pain by the electrical pulses can be affected by changes in the distance between the electrode and SCS generators from normal physiological activity (e.g., breathing and heartbeat) and movement. These changes in the level of neural activation can lead to overstimulation (uncomfortably strong stimulation) or under stimulation (lack of therapeutic benefit)[6].

Four main types of SCS implants

TONIC	HF-SCS
Traditional SCS system focuses on paraesthesia-inducing stimulation. Uses lower frequencies in the range of 40-60 Hz. This mode relies on the adequacy and durability of paraesthesia coverage as well as patient tolerance to achieve effectiveness. Some people find the paraesthesia unpleasant.	High frequency SCS delivers higher pulse rates of 10 kHz or more. HF-SCS involves the delivery of stimulation below the threshold of patient perception (e.g., 'subperception') so paraesthesia is not felt by patients.
BURST	**CLOSED LOOP**
The use of stimulation in the form of discrete 'BURSTs'. BURST stimulation delivers a train of five 500-Hz pulses at a frequency of 40 Hz. Like HF-SCS, BURST SCS does not evoke paraesthesia, allowing for placebo-controlled studies for comparison with tonic stimulation.	Closed-loop SCS is a relatively new form of neuromodulation that measures the evoked compound action potentials (ECAPs) elicited by each stimulus pulse and drives a feedback loop to maintain the ECAP amplitude near constant.

OBJECTIVES AND METHODS

The main objective of this Evidence Review was to examine the latest evidence for the clinical effectiveness of spinal cord stimulators for persistent pain with a particular focus on medium and long-term outcomes.

Research questions

1. What is the effectiveness of spinal cord stimulator implants on persistent pain?
2. What are the effects of spinal cord stimulator implants on function (physical, psychological, social), quality of life, return to work, medication and healthcare use?
3. What are the risks and inconveniences associated with use and maintenance of spinal cord stimulation implants?

Methods

This Evidence Review involved a systematic search of three databases (Medline, Cochrane, Embase) to identify relevant synthesised research (i.e. evidence-based guidelines (EBGs), systematic reviews), and any relevant randomised controlled trials and controlled clinical trials that assessed the effectiveness of SCS implants for treating persistent pain. The reference lists of relevant articles were scanned for additional studies not identified in initial searches and supplementary searches were conducted in the most recent issues (2022) of relevant journals.

Search strategy

A search strategy was developed according to the criteria shown in Table 1. Details of the search strategy can be found in Appendix A. Searches were limited to evidence published in English between April 2014 and August 2022. Given the large evidence base on this topic, data were extracted primarily from systematic reviews and RCTs. Information from controlled clinical trials was used in the absence of other information. Primary studies that were not included in existing systematic reviews supplemented the synthesis. Figure 1 shows the PRISMA flowchart of the search process identifying relevant articles on the effectiveness of SCS implants on persistent pain.

Quality assurance was undertaken for systematic reviews and RCTs by a single reviewer with a second reviewer undertaking a random sample to ensure consistency.

Table 1. Criteria for literature searches

Population	Adults (and those aged 15+) with chronic neuropathic pain due to conditions including (but not limited to) failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), phantom limb or stump pain. *Excluded*: Children under 15 Cancer pain, angina pain, diabetic neuropathy, post-herpetic neuralgia and post-stroke pain. SCS to treat Restless Legs Syndrome, Multiple Sclerosis, Parkinson's disease, incontinence issues and other non-compensable type conditions. People with spinal cord injury (unless SCS used for treating neuropathic pain)
Intervention	Spinal cord stimulation implant, all types. *Excluded: Dorsal root ganglion stimulation*
Comparator	Placebo or sham stimulation; or usual standard of care
Outcomes	Pain intensity, medication use (including opioids), healthcare use, function in daily activities, quality of life, social functioning, return to work, adverse events
Setting	Inpatient or outpatient
Study design	Systematic reviews or meta-analyses, controlled trials (randomised or non-randomised), evidence-based guidelines. Cohort studies can be included but flagged as lower quality evidence. *Excluded: Non-evidence-based guidelines, non-systematic reviews, case studies, editorials, letters and commentaries*
Search terms	Combinations of the following terms and synonyms were used to search the databases: • spinal cord stimulation OR spinal cord stimulator OR spinal neuromodulation OR implantable pulse generator • pain OR back pain OR chronic pain OR myalgia OR neck pain OR Low Back Pain OR Failed Back Surgery Syndrome OR neuralgia OR Complex Regional Pain Syndromes

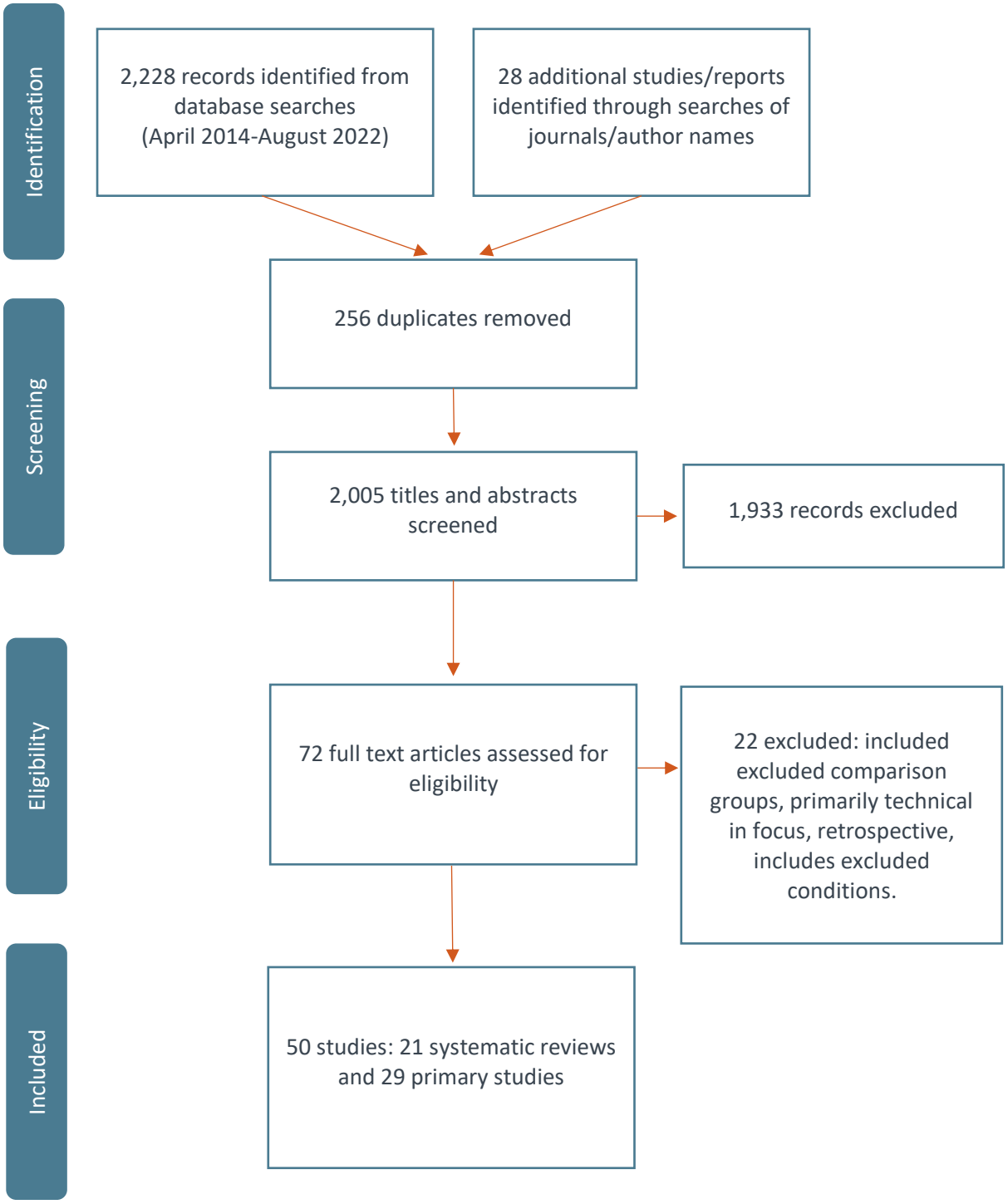

Figure 1. PRISMA flowchart depicting the search process identifying relevant articles on the effectiveness of SCS for treating persistent pain

QUALITY OF INCLUDED STUDIES

The quality of included studies was assessed using two different tools. Systematic reviews were assessed using the McMaster's Health Evidence Checklist[7] while the randomised control trial studies (RCTs) were assessed using the Quality Assessment Tool for Quantitative Studies[8]. Controlled clinical trials were not formally assessed as they are known to be of lower quality. Details of the results of the quality assessment can be found in Appendix B.

Overall, the quality of the systematic reviews was strong with only three of 21 receiving a rating indicating the review had quality limitations resulting in a weak or moderate rating. It should be noted that although the majority of systematic reviews were rated highly, the quality of the studies included in each of the systematic reviews varied considerably and was generally low.

One potential source of bias not assessed by the Health Evidence Checklist should be considered when interpreting these results. Just over half of the systematic reviews with pain as a primary outcome declared some funding or sponsorship from industry entities with an interest in the manufacture and sale of SCS equipment, and the sponsor's role in the study was not always made clear. Seven of the nine systematic reviews with primary outcomes other than pain declared industry sponsorship of one or more authors.

The quality of RCTs was weak to moderate with only four of ten studies receiving a strong rating. Lack of blinding was the largest source of bias for five RCTs. Selection bias was another area of concern primarily driven by recruitment of participants less likely to be representative of the target population.

Like the Health Evidence Checklist, the Quality Assessment Tool for Quantitative Studies does not assess bias potentially caused by funding or sponsorship from industries with an interest in the manufacture and sale of SCS equipment. Of the 30 primary studies, all but two declared some form of funding or sponsorship of individual authors or the study itself.

EFFECTIVENESS OF SPINAL CORD STIMULATORS ON PAIN

Key findings	There were very few systematic reviews or RCTs reporting on the short, medium, and long-term outcomes of SCSs on pain reduction. In contrast there were many prospective cohort studies, reporting clinically significant improvements in pain intensity at all time points.
Short-term outcomes	• Largest body of evidence from RCTs, systematic reviews and prospective cohort studies showing reductions in pain up to three months post implant. • Overall low level of certainty of evidence, moderate level of bias of included studies.
Medium-term outcomes	• Limited evidence from smaller number of RCTs, systematic reviews and prospective cohort studies showing reductions in pain at six months post implant. • Overall low level of certainty of evidence, moderate level of bias of included studies.
Long-term outcomes	• Limited evidence from smaller number of RCTs, systematic reviews and prospective cohort studies showing reductions in pain at 12+ months post implant. • Conflicting results at longer time frames from limited number of RCTs. • Overall low level of certainty of evidence, high to moderate level of bias of included studies.
Major limitations	• High heterogeneity of included pain conditions. • Moderate to high risk of bias of among studies. • Methodological issues (e.g., blinding, small case numbers, lack of placebo controls) • High risk of bias from industry funding.

The primary aim of the evidence review was to examine the effectiveness of SCS implants on persistent pain in the short, medium, and long-term. There were 12 systematic reviews and 29 primary studies (9 RCTs and 20 prospective cohort studies) with pain reduction as the primary outcome of interest. Summary tables of the included systematic reviews and primary studies are located in Appendix C.

The studies reviewed looked at the effect of SCSs on a variety of pain producing conditions in isolation and in combination. The included conditions were:

- Lower back pain
- Leg pain
- Lower back pain and leg pain combined
- Upper limb pain
- Neck pain
- Upper limb pain and neck pain combined
- Neuropathic pain (unspecified)
- Failed Back Surgery Syndrome (FBSS)
- Chronic Regional Pain Syndrome (CRPS)

Due to the wide heterogeneity of conditions and the small number of studies contributing evidence for each condition, an overall conclusion regarding the effectiveness of SCS implants by time frame on condition specific pain is not possible. A brief discussion of the evidence available for some specific conditions is provided later in this report.

Systematic review evidence

There were 12 systematic reviews with pain intensity as a primary outcome. Authors used a range of time periods to define short, medium and long-term outcomes. Several of the systematic reviews made no distinction based on time using only the final study timepoint to report outcomes on pain reduction. Where meta-analyses have reported pain outcomes at different timepoints, the small number of contributing studies have different outcome timepoints but generally fall within a range of three months and less for short-term, 3-6 six months for medium-term, and 12 months or more for long-term outcome reporting. Overall, the systematic reviews report on improvements in pain scores for a variety of neuropathic pain conditions over different time periods using various types of SCS devices.

Primary study evidence

There were 26 primary studies with pain intensity as the primary outcome of interest, seven of which were RCTs and 19 prospective cohort studies. The primary studies looked at a large number of different pain-producing conditions in isolation and in combination. In addition, there was a range of types of SCS implants utilised, with some studies directly comparing different types and others to placebo or other control conditions. Due to the wide heterogeneity of pain conditions and SCS implant types, evidence for the effectiveness of SCSs on pain intensity over the short, medium and long-term is presented in general terms.

Short-term pain outcomes

Systematic reviews

Only four systematic reviews[9-12] reported specifically on short-term pain outcomes, all of which were meta-analyses (Table 2). All four reported statistically or clinically significant improvement in pain outcomes in the short-term. Two of the systematic reviews included data from prospective and retrospective cohort studies[11, 12], while the remaining two included only data from RCTs. Pain intensity was measured in five different ways; visual analogue scale (VAS), numeric response scale (NRS) 0 to 10, NRS 0 to 100, and proportion of patients achieving pain reduction of ≥50%. The time since implant measure varied from one week to three months.

O'Connell et al. (2021)[10] found very low certainty evidence for the effectiveness of SCSs versus placebo (sham stimulation) and for SCS plus other intervention (medical management or physical therapy) vs other intervention alone within a month of implant. The average reduction in pain intensity for SCS versus placebo on the VAS (0-100) was 8.73 points lower (95% CI -15.67, -1.78) than in the control group. For SCS plus other intervention (medical management or physical therapy) vs other intervention alone, the mean pain intensity in the intervention groups was 37.4 points lower (95% CI -46.4 to -28.4) than in the control group. The proportion of SCS plus other intervention subjects with ≥50% pain relief was 69.6%. The authors suggest that compared to receiving medical management or physical therapy alone, people treated with the addition of SCS may experience less pain and higher quality of life after one month of stimulation.

Kurt et al (2022)[13] reported on pain outcomes for subjects at 6 and 12 months for all low back pain and leg pain patients combined but not for short-term outcomes at three months. The weighted mean difference at three months compared to baseline was 3.52 for low back pain subjects and 4.40 for leg pain subjects using the VAS (0-10) and based on just two studies.

Baranidharan et al. 2021[11] reported pain outcomes at 12 months for patients with combined upper limb and neck pain but not for short-term outcomes at three months. The proportion of patients achieving ≥50% pain relief at three months was 81% with upper limb pain and 72% for neck pain based on three studies.

Duarte et al (2020)[9] demonstrated a statistically significant reduction in pain intensity (VAS 0-10 cm or NRS 0-10) at three months during the active stimulation treatment periods compared with the control (sham/placebo) treatment periods, with a pooled mean difference of -1.15 (95% CI -1.75 to -0.55).

None of the narrative systematic reviews reported specifically on short-term outcomes of SCS implants, although Eckermann et al. (2022)[12] reported that in a majority of studies included in the review, reductions in pain were observed as early as three months after treatment. One narrative review specifically excluded studies with outcome measures at less than six months[14].

Primary studies

Four RCTs and six prospective cohort studies reported primary outcomes in the short-term, all reported at three months post permanent implant (Table 2). In three RCTs, pain intensity was measured as the proportion of patients achieving pain reduction of ≥50%, while one RCT measured mean VAS over a 5-day period. All but one of the prospective cohort studies used a visual analogue scale to measure pain intensity with one reporting the proportion of patients achieving pain reduction of ≥50%.

Three[15-17] of the four RCTs found significant improvements in pain intensity at three months using different types of SCS implants across different pain conditions. One RCT found significant improvement in pain intensity at three months for one of two types of SCS implants tested[18]. No significant difference was found when BURST SCS was compared to a sham control condition. All of the four RCTs were funded by device manufacturers or had authors who had been or were currently being funded in some way by a device manufacturer. Each of the four RCTs had a moderate quality rating.

All the prospective cohort studies listed in Table 2 found significant improvements in pain intensity at three months using different types of SCS implants across different pain conditions. One of the studies, Leong et al. 2021[19], reported results of a post hoc cross-sectional analysis across two different trials comparing two types of SCS (BURST vs tonic).

The number of subjects enrolled in the studies ranged from 23 to 99, and two studies reported limitations associated with small case numbers[20, 21]. One study employed a lower threshold of pain reduction for inclusion of patients' post-trial (≥40%)[22]. All the studies were funded by device manufacturers or had authors who had been or were currently being funded in some way by a device manufacturer.

Table 2. Summary of evidence on the effects of SCS implants on pain in the short-term

Author	Condition(s)	Comparator	**Number of studies/** patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Systematic reviews						
Duarte et al. 2020a[9]	Neuropathic pain	Control	6	VAS/NRS (0-10)	Evidence for statistically or clinically significant pain reduction	Moderate to high risk
O'Connell et al. 2021[10]	Neuropathic pain	Placebo	6	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	High risk
Baranidharan et al. 2021[11]	Upper limb or neck pain, upper limb pain alone, neck pain alone	Baseline	≤ 5	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	Moderate to high risk
Eckermann et al. 2022[12]	Chronic back pain without previous surgery	Various	9	≥50% pain relief, VAS (0-10), NRS	Studies consistently show reductions in pain scores with SCS. Reductions in pain were seen as early as three months after treatment.	Moderate to high risk
Randomised control trials						
Kapural et al. 2022[15]	Nonsurgical refractory back pain	CMM vs SCS+CMM	159	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	No blinding between treatment groups CMM had already been tried and failed by many subjects

Author	Condition(s)	Comparator	**Number of studies/** patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
						Funded by device manufacturer
Eldabe et al. 2021[18]	FBSS	HF-SCS, BURST-SCS vs Sham	19	Mean VAS over five days (0-100)	Evidence for statistically or clinically significant pain reduction for HF-SCS but not BURST	Small sample size Study population already achieved stable pain relief with tonic stimulation Funding to authors by device manufacturer
Fishman et al. 2021[16]	Chronic low back and leg pain	Differential Target Multiplexed (DTM)-SCS or SCS	124	VAS (0-100)	Evidence for statistically or clinically significant pain reduction. DTM SCS was statistically superior to SCS.	No blinding Funded by device manufacturer
North et al. 2020[17]	Chronic low back and leg pain	SCS subperception vs supraperception	140	≥50%	Evidence for statistically or clinically significant pain reduction. Subperception SCS patients achieved larger gains in of pain relief than supraperception SCS patients.	No blinding Sample used subjects with existing SCS implants Funding to authors by device manufacturer
Prospective cohort studies						
Deer et al. 2021[23]	Various conditions	None	50	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Funded by the device manufacturer

Author	Condition(s)	Comparator	**Number of studies/** patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Leong et al. 2021[19]	Chronic, intractable pain in the limbs and trunk	Cross over Comparison between two types of SCS not SCS vs baseline	99	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Post hoc cross-sectional analysis Funding to authors by device manufacturer, one author patent owner
Tate et al. 2021[20]	Chronic pelvic pain various causes	None	23	VAS (1-10)	Evidence for statistically or clinically significant pain reduction	Small sample size Funded by the device manufacturer
Benyamin et al. 2020[21]	FBSS	None	64	NRS (0-10)	Evidence for statistically or clinically significant pain reduction	High dropout rate Funding to authors by device manufacturer
Gupta et al. 2020[24]	Chronic postsurgical neuropathic pain	None	41	≥50%	Evidence for statistically or clinically significant pain reduction	Did not monitor medication use Funded by the device manufacturer
Russo et al. 2020[22]	Chronic back and/or leg pain (with or without previous back surgery)	None	50	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Low responder (≥40%) definition used Funded by the device manufacturer

Notes: CMM = conventional medical management; SCS = spinal cord stimulation; FBSS = Failed Back Surgery Syndrome; VAS = visual analogue scale; NRS = numeric rating scale; DTM = Differential Target Multiplexed.

Medium-term pain outcomes

Systematic reviews

Six of seven meta-analytic systematic reviews reported on medium-term pain outcomes (Table 3). All six reported statistically significant improvements in pain intensity at six months.

Four[2, 11-13, 25] of the systematic reviews included data from RCTs, prospective and retrospective cohort studies, while the remaining two[10, 26] included only data from RCTs. Inclusion of the same studies across the systematic reviews was common. Pain intensity was measured in five different ways; visual analogue scale (VAS), numeric response scale (NRS) 0 to 10, NRS 0 to 100, and proportion of patients achieving pain reduction of ≥50%.

O'Connell et al. (2021)[10] demonstrated a (very low certainty) clinically important mean difference in favour of SCS plus other intervention (medical management or physical therapy) versus other intervention alone at six months. The mean pain intensity (VAS 0-100) in the intervention groups was 31.22 points lower (95% CI -47.34 to -15.10) than in the control group, and 46.1% of patients achieved ≥50% pain relief. Results were based on five studies, all RCTs.

Kurt et al. (2022)[13] reported significant decreases (VAS 0-10) in overall pain, low back pain and leg pain combined, at six months compared with baseline (95% CI 2.81, 1.70–3.93) based on four studies. Three of the four included studies were rated as moderate risk of bias, with one considered at low risk of bias.

Baranidharan et al. (2021)[11] reported pain outcomes at six months based on the results of two studies for upper limb pain and neck pain separately; a post hoc analysis of a prospective observational and a prospective cohort study. The proportion of patients with upper limb pain achieving ≥50% pain relief at six months was 82% and 73% for neck pain.

The meta-analysis carried out by Karri et al. (2020)[25] compared tonic and BURST SCS but did not report change from baseline for either form of SCS separately. Results were pooled from five studies, two of which were RCTs. A significant reduction in pain scores favoring BURST over tonic waveforms was found (mean difference –1.64 points; 95% CI –2.43 to –0.84).

Lamer et al. (2019)[26] compared conventional SCS implants versus medical management in three studies and reported conventional SCS implants significantly increased the odds of reducing pain by 50% or more (OR, 13.01; CI 95%, 4.96-34.17) in the medium-term. Two of three included trials contained patients with lower extremity painful diabetic neuropathy.

Primary studies

Two RCTs and eight prospective cohort studies reported primary outcomes in the medium-term, all reported at six months post permanent implant (Table 3). Pain intensity was measured as the proportion of patients achieving pain reduction of ≥50% in one RCT[15] and on a visual analogue scale in the other[27]. The prospective cohort studies primarily used VAS.

Both RCTs found significant reductions in pain intensity at six months using two different types of implants (HF-SCS and tonic SCS) for two different pain conditions (non-surgical refractory back pain and FBSS)[15, 27].

All of the prospective cohort studies found significant improvements in pain intensity at six months using different types of SCS implants across different pain conditions. One study employed a lower threshold of pain reduction for inclusion of patients post-trial (≥40%)(Russo et al. 2020)[22]. All but one study (Hamm-Faber et al 2020)[28] was funded by device manufacturers or had authors who had been or were currently being funded in some way by a device manufacturer. The number of patients recruited for the prospective cohort studies ranged from 13 to 100.

Table 3. Summary of evidence on the effects of SCS implants on pain in the medium-term

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Systematic reviews						
Eckermann et al. 2022[12]	Chronic back pain without previous surgery	Various	9	≥50%, VAS (0-10), NRS	Studies consistently show reductions in pain scores with SCS. Reductions in pain were seen at six months.	Moderate to high risk
Kurt et al. 2022[13]	Lower back pain, leg pain, combined	Baseline	≤ 4	VAS/NRS (0-10)	Evidence for statistically or clinically significant pain reduction	Low to moderate risk
Baranidharan et al. 2021[11]	Upper limb or neck pain, upper limb pain alone, neck pain alone	Baseline	≤ 5	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	Moderate to high risk
O'Connell et al. 2021[10]	Neuropathic pain	Other	≤ 5	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	High risk

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Karri et al. 2020[25]	Chronic lower back pain	BURST vs Tonic	5	VAS/NRS (0-10)	Evidence for statistically or clinically significant pain reduction	High risk
Lamer et al. 2019[26]	Refractory spine and/or limb pain	Medical therapy & new SCS technology	3	OR ≥50%	Evidence for statistically or clinically significant pain reduction	Moderate risk
Randomised control trials						
Kapural et al. 2022[15]	Nonsurgical refractory back pain	CMM vs SCS+CMM	159	≥50%	Evidence for statistically or clinically significant pain reduction	No blinding between treatment groups CMM had already been tried and failed by many subjects Funded by device manufacturer
Rigoard et al. 2021[27]	FBSS	SCS Monocolumn programming (Mono-group) or multicolumn programming (Multigroup)	115	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Complexity of programming Patient fatigue Funding to authors by device manufacturer
Prospective cohort studies						

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Deer et al. 2022a[29]	Various conditions	BURST 1:3 vs BURST 1:12 cycle	100 & 95	NRS (0-10)	Evidence for statistically or clinically significant pain reduction	Retrospective analysis of prospectively collected data from two different studies
Bolash et al. 2022[30]	Chronic back pain, or back and leg pain	None	49	≥50%	Evidence for statistically or clinically significant pain reduction	Funded by the device manufacturer
Paz-Solis et al. 2022[31]	FBSS or chronic radiculopathy	None	30	NRS (0-10)	Evidence for statistically or clinically significant pain reduction	Small sample size No wash-out periods between frequencies Funding to authors by device manufacturer
Deer et al. 2021[23]	Various conditions	None	50	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Funded by the device manufacturer
Motov et al. 2021[32]	FBSS	None	39	VAS (1-10)	Evidence for statistically or clinically significant pain reduction	Used an averaged follow-up time Funding to one author by device manufacturer

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Tate et al. 2021[20]	Chronic pelvic pain various causes	None	23	VAS (1-10)	Evidence for statistically or clinically significant pain reduction	Small sample size Funded by the device manufacturer
Hamm-Faber et al. 2020[28]	FBSS	None	13	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Small sample size Pilot study
Russo et al. 2020[22]	Chronic back and/or leg pain (with or without previous back surgery)	None	50	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Low responder (≥40%) definition used Funded by the device manufacturer

Notes: OR = odds ratio; CMM = conventional medical management; SCS = spinal cord stimulation; FBSS = Failed Back Surgery Syndrome; VAS = visual analogue scale; NRS = numeric rating scale; DTM = Differential Target Multiplexed.

Long-term pain outcomes

Systematic reviews

Four meta-analytic and three narrative systematic reviews reported on long-term outcomes of SCS implants for pain reduction (Table 4).

O'Connell et al. (2021)[10] found no clear evidence for an effect of SCS implants at five-year long-term follow-up when comparing SCS plus other intervention versus other intervention alone. However, evidence of a large effect on the proportion of participants experiencing ≥50% pain relief after 24 months of stimulation was demonstrated by one study. O'Connell et al. (2021) graded the evidence in that study as very low certainty with serious limitations identified for imprecision and inconsistency in reporting.

Kurt et al. (2022)[13] reported significant decreases (VAS 0-10) in overall pain, low back pain and leg pain combined, at 12 months compared with baseline (95%CI 2.68, 1.58–3.77) based on two prospective cohort studies. One study was rated as having a high risk of bias, and the other as having a moderate risk of bias.

Baranidharan et al. (2021)[11] reported long-term pain outcomes for patients with combined upper limb and neck pain. The final follow-up time points were 12 months in three studies, 6 months in one, and a median of 19.4 months in another. The proportion of patients with combined upper limb and neck pain achieving ≥50% pain relief was 83%.

Lamer et al. (2019)[26] provided a meta-analysis of three studies with varying long-term time points (6, 12 and 24 months) for HF-SCS versus tonic SCS, and reported HF-SCS significantly increased the odds of reducing pain by 50% or more (OR, 2.07; CI 95%, 1.35-3.19). Lamer et al. (2019)[26] also reported on the outcomes of two separate trials, one comparing tonic SCS with repeat spine surgery and one comparing HF-SCS with tonic SCS. Increased odds of achieving 50% or greater pain relief was reported for tonic SCS versus repeat spine surgery (OR, 6.90; CI 95%, 1.54-31.01) but no significant difference in NRS reduction from tonic SCS versus HF-SCS at 12-month follow-up was reported (weighted mean difference = 0.43; CI 95%, -0.72 to 1.58).

The three narrative systematic reviews offered summary comments on the effectiveness of SCS implants in the long-term. Eckermann et al. (2022)[12] suggested that pain reductions in SCS patients with chronic back pain without prior surgery are sustained in the long-term, however evidence was only presented from one proof of concept prospective cohort study. Conger et al. (2020)[14] found only two RCTs measuring axial back pain reduction beyond six months and identified a lack of quality RCTs examining long-term outcomes as a deficiency. Deer et al. (2020)[33] reported on long-term outcomes for some specific pain conditions but came to no definitive conclusions regarding long-term efficacy. One study reviewed for axial back pain and radicular pain found no significant reduction in VAS pain scores five years out.

Primary studies

Two RCTs[34, 35] found long-term significant reductions in pain intensity using different comparisons of types of implants for three different pain conditions (chronic back and leg pain, CRPS and FBSS) (Table 4). Two of the RCTs reported primary outcomes at 12 months[34, 35] and one at 24 months[34].

Mekhail et al. (2022)[34] compared closed-loop to open-loop SCS in patients with chronic, intractable back and leg pain refractory to conservative therapy and reported results to 24 months. At 24 months, 79% of closed-loop patients remained responders (≥50% reduction in pain) compared with 54% of open-loop patients. The study by Mekhail et al. (2022)[34] was assessed as being of strong quality although the study was funded by the device manufacturer and the authors declared conflicts of interest relating to personal sponsorship or funding from device manufacturers.

Canos-Verdecho et al. (2021)[35] compared LF-SCS (12 patients), HF-SCS (10 patients) and conventional treatment (19 patients) in patients with complex regional pain syndrome. At the primary endpoint of 12 months, patients in each of the treatment groups achieved a significant reduction in pain as measured with an NRS. Treatment with LF-SCS (5.6) resulted in the highest minimal clinically important difference threshold followed by HF-SCS (4.8) then conventional management (3.0). The minimal clinically important difference (MCID) in chronic pain reduction was reported to be two points on the numerical rating scale (out of a 10-point scale maximum) or 30%. The study by Canos-Verdecho et al. (2021)[35] was not funded by any device manufacturer and the authors did not declare any conflicts of interest relating to personal sponsorship or funding from device manufacturers. An assessment of the quality of the Canos-Verdecho et al. (2021)[35] study found deficiencies in handling of confounders and a lack of blinding.

All of the prospective cohort studies (12 studies) found significant improvements in pain intensity at 12+ months using different types of SCS implants across different pain conditions. The majority of prospective cohort studies reporting long-term outcomes tested the effectiveness of HF-SCS (eight studies). Eight of the 12 studies had a primary endpoint of 12 months, three had primary endpoints of two years and one followed patients up to six years post-implant (Remacle et al. 2020)[36]. Only 15 of the original 62 patients in the study by Remacle et al. (2020)[36] were available for follow-up and the authors reported high complication rates and withdrawals by patients as a major limitation.

One study employed a lower threshold of pain reduction for inclusion of patients post-trial (≥40%) (Russo et al. 2020)[22] and another included patients with a very low pain response (≥30%) (Goudman et al. 2021)[37]. All but one study (Hamm-Faber et al. 2020)[28] was funded by device manufacturers or had authors who had been or were currently being funded in some way by a device manufacturer. The number of patients recruited for the prospective cohort studies ranged from 13 to 194.

Table 4. Summary of evidence on the effects of SCS implants on pain in the long-term

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Systematic reviews						
Eckermann et al. 2022[12]	Chronic back pain without previous surgery	Various	9	≥50% pain relief, VAS (0-10), NRS	Studies consistently show reductions in pain scores with SCS. Reductions in pain were seen at 12, 24 and 3six months.	Moderate to high risk
Kurt et al. 2022[13]	Lower back pain, leg pain, combined	Baseline	≤ 4	VAS/NRS (0-10)	Evidence for statistically or clinically significant pain reduction	Low to moderate risk
Baranidharan et al. 2021[11]	Upper limb or neck pain, upper limb pain alone, neck pain alone	Baseline	≤ 5	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	Moderate to high risk
O'Connell et al. 2021[10]	Neuropathic pain	Other	≤ 5	≥50% pain relief, VAS (0-100)	Very low certainty evidence for statistically or clinically significant pain reduction	High risk
Deer et al. 2020[33]	Axial Back Pain, Radicular Pain, CRPS	Various	6	≥50% pain relief, VAS (0-10)	SCS for the treatment of failed back surgery syndrome (FBSS) and neuropathic pain and CRPS is safe and effective. In the early phase of CRPS, SCS with physical	Low to moderate risk

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
					therapy resulted in better functional outcomes vs physical therapy alone; however, the treatment difference faded by 3six months	
Lamer et al. 2019[26]	Refractory spine and/or limb pain	Medical therapy & new SCS technology	3	OR ≥50% pain relief	Evidence for statistically or clinically significant pain reduction	Moderate risk
Randomised control trials						
Mekhail et al. 2022[38]	Chronic, intractable back and leg pain refractory to conservative therapy	Closed loop vs open-loop SCS	134	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	Funded by device manufacturer
Canos-Verdecho et al. 2021[35]	Complex Regional Pain Syndrome of the upper limb	LF-SCS vs HF-SCS vs CMM	50	NRS (0-10)	Evidence for statistically or clinically significant pain reduction	No blinding
Prospective cohort studies						
Deer et al. 2022b[29]	Chronic, intractable pain of the trunk, and/or lower limbs	None	128	NRS (0-10)	Evidence for statistically or clinically significant pain reduction	Funded by the device manufacturer

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Brooker et al. 2021[6]	Chronic back and/or leg pain (with or without previous back surgery)	None	50	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	24 month follow-up AVALON study, same patient cohort as Russo et al. 2020
Cordero Tous et al. 2021[39]	FBSS or CRPS	None	18	NRS (0-10)	Evidence for statistically or clinically significant pain reduction	Funding to authors by device manufacturer Original study funded by the device manufacturer
Galan et al. 2021[40]	Peripheral polyneuropathy	None	26	VAS (0-10)	Evidence for statistically or clinically significant pain reduction	Small sample size
Goudman et al. 2021[37]	FBSS	None	194	NRS (0-10)	Evidence for statistically or clinically significant pain reduction	High heterogeneity of pain conditions
Kallewaard et al. 2021[41]	FBSS	None	68	≥50% pain relief	Evidence for statistically or clinically significant pain reduction	Small sample size
Perez et al. 2021[42]	FBSS	CMM	85	PainDETECT Questionnaire	Evidence for statistically or clinically significant pain reduction	Did not monitor medication use
Tate et al. 2021[20]	Chronic pelvic pain various causes	None	23	VAS (1-10)	Evidence for statistically or clinically significant pain reduction	Funded by the device manufacturer

Author	Condition(s)	Comparator	Number of studies/ patients	Primary Outcome measure	Summary finding	Risk of bias of included studies/limitations
Gupta et al. 2020[24]	Chronic postsurgical neuropathic pain	None	41	≥50%	Evidence for statistically or clinically significant pain reduction	Low responder (≥30%) definition used
Hamm-Faber et al. 2020[28]	FBSS	None	13	VAS (0-100)	Evidence for statistically or clinically significant pain reduction	Funded by the device manufacturer
Remacle et al. 2020[36]	FBSS	None	62	VAS (0-10)	Evidence for statistically or clinically significant pain reduction	Funding to authors by device manufacturer

Notes: OR = odds ratio; CMM = conventional medical management; SCS = spinal cord stimulation; FBSS = Failed Back Surgery Syndrome; VAS = visual analogue scale; NRS = numeric rating scale; LF-SCS = low frequency spinal cord stimulation; HF-SCS = high frequency spinal cord stimulation.

Summary of short, medium, and long-term outcomes of SCS implants on pain

Evidence from systematic reviews

Evidence for the efficacy of SCS implants for pain reduction over different time periods is sparse based on recently published systematic reviews. In the short-term, a small number of meta-analyses identified significant improvements in pain intensity scores and higher proportions of participants experiencing ≥50% pain relief. However, studies contributing data to the meta-analyses were often at moderate risk of bias and the Cochrane review[10] graded the evidence as very low certainty.

In the medium-term, the most recent systematic review with a meta-analysis, Kurt et al. (2022)[13] found significant decreases in pain for low back pain and leg pain combined, measured using the VAS (0-10), with the four included studies (controlled clinical trials) rated as having a low to moderate risk of bias. The Cochrane review[10] found a clinically important mean difference at six months based on five RCTs although the evidence was graded of low certainty.

The least amount of RCT evidence was available for long-term outcomes of SCS implants for pain reduction. Conger et al. (2020)[14] found only two RCTs measuring axial back pain reduction beyond six months and identified a lack of quality RCTs examining long-term outcomes as a deficiency. The Cochrane review[10] identified two RCTs examining long-term outcomes with conflicting results.

The validity of recommendations of SCS implants as a safe and effective therapy for neuropathic pain by the majority of systematic reviews, contrasts with the almost universal acknowledgement among the authors of the low certainty of the evidence due to high heterogeneity and the moderate to high risk of bias of the included studies. The risk of bias from industry funding was not assessed consistently, if at all, in most of the systematic reviews although many acknowledged it was a significant issue.

Evidence from primary studies

There is evidence for the efficacy of SCS implants for pain reduction over different time periods based on seven RCTs and 19 prospective cohort studies. However, the strength of the evidence from the small number of RCTs and the lower level of evidence offered by prospective cohort trials is weak. In the short-term, four RCTs and six prospective cohort studies reported significant reductions in pain achieved at three months post-implant. One non-significant result was found in an RCT when comparing BURST SCS to a sham control condition[18]. All of the four RCTs were funded by device manufacturers or had authors who had been or were currently being funded in some way by a device manufacturer. All had a moderate quality rating. All of the prospective cohort studies found significant improvements in pain intensity at 3 months using different types of SCS implants across different pain conditions. All of the studies were funded by device manufacturers or had authors who had been or were currently being funded in some way by a device manufacturer.

In the medium-term, two RCTs[15, 27] and eight prospective cohort studies reported significant reductions in pain achieved at six months post permanent implant. Both RCTs[15, 27] found significant reductions in pain intensity at 6 months using two different types of implants (HF-SCS and tonic SCS) for two different pain conditions (non-surgical refractory back pain and FBSS). All but one study (Hamm-Faber et al 2020)[28], including the RCTs, was funded by device manufacturers or had authors who had been or were currently being funded in some way by a device manufacturer.

In the long-term, two RCTs[34, 35] and 12 prospective cohort studies reported significant reductions in pain achieved at 12+ months post implant. One of the RCTs[35] demonstrated a significant reduction in pain under a conventional management condition without SCS implants. All of the prospective cohort studies (12 studies) found significant improvements in pain intensity at 12+ months using different types of SCS implants across different pain conditions. All but one of the prospective cohort studies (Hamm-Faber et al 2020)[28] were funded by device manufacturers or had authors who had

been or were currently being funded in some way by a device manufacturer. One of the two RCTs[35] had no conflict of interest with respect to funding source for the study or the study authors. The prospective cohort studies were not formally assessed in terms of their quality and risk of bias, but as lower level studies they lack the scientific rigour afforded to RCTs.

EFFECTIVENESS OF SCS ON OUTCOMES OTHER THAN PAIN

Key findings	In addition to the systematic reviews and RCTs reporting on secondary outcomes of SCSs, there were 10 systematic reviews and three RCTs with a primary focus on outcomes other than pain reduction.
Disability and functioning	A small number of systematic reviews reported on disability and functioning as secondary outcomes. Improvements in disability and functioning were noted in all but one of the studies included in the systematic reviews.
Health related quality of life	HRQoL was the most reported secondary outcome of SCS implants. Evidence for improvement of HRQoL in the short and medium-term was reported in several systematic reviews and RCTs. Where longer term outcome data was available, the systematic reviews identified declines or improvements that failed to reach significance at 12+ months. In contrast, recent RCTs reported improvements in HRQoL out to 12+ months, particularly for high responders (those achieving ≥80% pain relief).
Medication use	Four systematic reviews and three RCTs reported specifically on SCS implants on opioid use. Reports on reductions in opioid consumption ranged between 17% to 67%. However, the Cochrane review found no clear evidence regarding the effects of SCS implants on medication use in the short or medium-term.
Return to work	Return to work was very rarely reported as an outcome in the literature. A systematic review and meta-analysis by Moens et al. (2019) examined evidence on return to work in patients with chronic pain treated with SCSs. The mean percent return to work among the included studies was 14% with the measure varying between 10% and 47%. Two other studies reported return to work proportions after 12 months of 14% and 21%.
Adverse events	Reporting on adverse events was common practice in more recent studies. Six systematic reviews and seven RCTs reported on adverse events occurring due to SCS implants. Overall proportions of patients experiencing an adverse event ranged considerably from 9% to 51%. Pain was commonly reported as an adverse event followed by lead migration.

The secondary effects of SCS implants are suggested to include improvements in return to work capacity, reductions in pain medication, physical therapy use and improvements in mental health outcomes such as depression and anxiety. The second research question of the evidence review is to examine evidence for the effects of SCS implants on function (physical, psychological, social), quality of life, return to work, and medication and healthcare use. There were no papers identified which examined the effects of SCS implants on healthcare use beyond a small number of studies examining increases in healthcare use associated with SCS implantation and adverse events in the context of cost utility analyses. The evidence review will also examine the risks and inconveniences (adverse events) associated with use and maintenance of SCS implants.

There were nine systematic reviews and three primary studies of the effects of SCS implants where the primary outcome of interest was not pain intensity. Three of these systematic reviews had a

primary focus on the methodological issues in SCS implant research[43-45], two focused on associated healthcare costs[46, 47], and the remaining four focused on adverse events[48], return to work[49], opioid use[50], and patient satisfaction[51] among SCS implant recipients. Two of three primary studies examined the impact of SCS implants on quality of life[52, 53] and one focused on methodology[54].

In addition to these studies, a number of the systematic reviews and primary studies with a primary focus on pain examined secondary outcomes on one or more of the associated outcomes.

Disability and functioning

Key findings	• Some improvements • Small evidence base • Weak support

A small number of systematic reviews reported on disability and functioning as secondary outcomes. Improvements in disability and functioning were noted in all but one of the studies included in the systematic reviews.

Disability and functioning were mostly measured using the Oswestry Disability Index (ODI) in the literature; however a number of other tools were employed across different studies.

There were no systematic reviews with a primary focus on the effects of SCS implants on disability and functioning, but some provided a narrative summary of findings. In addition, few of the systematic reviews with pain as a primary outcome examined improvements in disability and functioning as a secondary outcome. Systematic reviews by Eckermann et al. (2022)[12], Kurt et al. (2021)[13] and Baranidharan et al. (2021)[11] all found positive effects on disability and functioning attributed to SCS implants in the studies reviewed. However, one of the five studies reviewed by Eckermann et al. (2022)[12] showed ODI scores relative to baseline were not statistically significant.

The Cochrane review by O'Connell et al. (2021)[10] included five studies that measured disability as an outcome. In the short-term only one study contained sufficient information to allow an analysis of the results. A small significant effect of improvement in ODI was found in an SCS implant versus sham condition. No clear evidence of an effect of SCS implants on disability was found in the medium-term and no studies included information on the effects of SCS implants on disability in the long-term.

Quality of life

Key findings	• Improvements in HRQoL • Small evidence base • Moderate support

HRQoL was the most reported secondary outcome of SCS. Evidence for improvement of HRQoL in the short and medium-term was reported in several systematic reviews and RCTs. Where longer term outcome data was available, the systematic reviews identified declines or improvements that failed to reach significance at 12+ months. In contrast, recent RCTs reported improvements in HRQoL out to 12+ months, particularly for high responders (those achieving ≥80% pain relief).

The EQ-5D is the most commonly used generic preference-based health-related quality of life (HRQoL) measure in the literature although a number of other measures have been used. None of the systematic reviews had a primary focus on the effects of SCS implants on HRQoL but five reported on HRQoL as a secondary outcome. The Cochrane review[10] found a positive effect on

HRQoL in the short and medium-term, based on one and five RCTs respectively. There was no evidence of improvement in HRQoL in the long-term with only one RCT identified. Of the other systematic reviews, improvements in HRQoL compared to baseline were reported by three authors on data out to six months post implant[11-13, 33]. Eckermann et al (2022)[12] found significant improvements in HRQoL in two of four studies reviewed. Where longer term outcome data was available, the systematic reviews identified declines or improvements that failed to reach significance at 12+ months.

Two RCTs[52, 53] reported on HRQoL as a primary outcome and a further six RCTs as a secondary outcome. Duarte et al (2021)[52] examined the differences in HRQoL among pain relief responders (those achieving ≥50% pain relief) and high responders (those achieving ≥80% pain relief) using closed loop SCS implants. Greater improvements in HRQoL were found among high responders and the authors[52] noted that the improvement in HRQoL in people treated with closed loop SCS implants is directly associated with their level of pain relief. Amirdelfan et al. (2018)[53] reported on patients randomized to either traditional (tonic SCS) or HF-SCS. Both groups showed significant improvements in SF-12 scores from baseline.

All but one of the remaining six RCTs examined reported improvements in HRQoL out to 12+ months. However, Eldabe et al. (2021)[18] found that, on average, HRQoL was substantially worse in the BURST condition versus either sham control or HF-SCS.

Medication use

Key findings	• Qualified reductions in opioid use • Small to medium evidence base • Moderate support

Four systematic reviews and three RCTs reported specifically on SCS implants on opioid use. Reports on reductions in opioid consumption ranged between 17% to 67%. However, the Cochrane review found no clear evidence regarding the effects of SCS on medication use in the short or medium-term.

Medication use was reported in various ways, for specific classes of drugs (e.g., pain medications), for non-specific drugs (e.g., all medications) and occasionally for specific drugs such as opioids. Four systematic reviews[10-12, 50] reported on medication use, one of which examined the effects of SCS implants on reduction of opioid use as a primary outcome[50].

O'Connell et al. (2021)[10] found no clear evidence regarding the effects of SCS implants on medication use in the short or medium-term. In contrast, Eckermann et al. (2022)[12] reported a decline in opioid consumption following SCS implants among the prospective cohort studies included in their systematic review. Overall, the proportion of patients who had ceased opioid use at 12 months ranged from 16.7% to 66.7%. Baranidharan et al. (2021)[11] pooled data from five studies to report an average of 39% of patients reducing or eliminating the use of pain medication.

The systematic review by Smith et al. (2022)[50] examined research on the impact of SCS implants on opioid dose from pre-implantation to post-implantation. The 17 studies examined demonstrated an ability of SCS implants to aid in the reduction of opioid use over a wide range of pre-implantation doses at 12 months post-implantation. The authors[50] concluded that spinal cord stimulation is most effective when used in patients who have lower daily doses of opioids pre-implantation.

Three RCTs[15, 27, 34] were identified with medication use as a secondary outcome. Kapural et al. (2022)[15] compared clinical management with and without 10-kHz SCS in non-surgical refractory back pain patients. Changes in daily opioid use were reported at six months. The mean daily intake in the 10-kHz SCS treatment group decreased on average by 45.8% at the six month follow-up compared

with 12.1% among the control group. After six months of treatment, 21.9% (7/32) of patients who received 10-kHz stimulation had stopped taking opioid analgesics, and a further 44% (14/32) of patients experienced a decrease in their daily dose.

Mekhail et al. (2022)[34] reported on 24-month outcomes from an RCT examining closed-loop versus open-loop SCS implants for chronic back and leg pain. Reduction of opioid use or cessation was seen in 67% (18/27) and 61% (14/23) of closed-loop and open-loop patients, respectively.

Rigoard et al. (2021)[27] assessed the impact of multicolumn lead programming on the clinical efficacy of SCS implants in a double-blind RCT among FBSS patients. Medication use as a secondary outcome was assessed using the Medication Quantification Scale. Overall medication consumption decreased in both multicolumn programming groups from baseline with no significant difference between the two groups.

Return to work

Key findings

- Average return to work (14%)
- Very small evidence base
- Low support

Return to work was very rarely reported as an outcome in the literature. A systematic review and meta-analysis examined evidence on return to work in patients with chronic pain treated with SCS. The percent return to work mean among the included studies was 14% with the measure varying between 10% and 47%.

Return to work was very rarely reported as an outcome in the literature. Three studies, a systematic review[49], an RCT[27] and a prospective cohort study[55], were identified which reported on the impact of SCS implants on return to work.

The aim of the systematic review and meta-analysis undertaken by Moens et al. (2019)[49] was to identify and summarize evidence on return to work in patients with chronic pain treated with SCS implants. Return to work was defined as the percentage of patients going back to work who were unemployed before treatment. No further information about the type of work or fractional time worked was provided. Moens et al. (2019)[49] identified one RCT, five retrospective case series and one prospective cohort study that contained enough data to calculate a percentage of patients who returned to work. The return to work mean was 14% with the measure varying between 10% and 47%.

Rigoard et al. (2021)[27] assessed the impact of multicolumn lead programming on the clinical efficacy of SCS implants in a double-blind randomized control trial among FBSS patients and reported return to work at 12 months. Of the 75 unemployed working-aged patients at inclusion, 16 patients (21.3%) had returned to work at 12 months. No further information was provided.

Goudman et al. (2020)[55], in a secondary analysis of an existing dataset, aimed to see whether patients with FBSS who received SCS implants resumed work, at what intensity and under what circumstances. Patients were retrospectively questioned at 12 months after SCS implantation. Eleven of the 80 patients resumed work (13.75%), 42 patients (52.5%) received workers compensation, 25 (31.25%) reached retirement age, and two (2.5%) were not actively seeking employment. Of the 11 patients who resumed work at 12 months, 10 returned to their previous place of employment. Information available from nine of the 11 patients who returned to work showed three patients returning to full-time work with the rest working between 12 and 34 hours per week.

Adverse events

Six systematic reviews and seven RCTs reported on adverse events occurring due to SCS implants. Only two of the RCTs included in this evidence review failed to report on adverse effects experienced by patients during the studies.

Evidence from systematic reviews

The Cochrane review by O'Connell et al. (2021)[10] concluded that "SCS is associated with a reasonably common incidence of procedure and device-related complications including infection, lead failure or displacement, and the need for further surgical procedures" (page 27). Evidence among studies reporting medium-term outcomes (six months post implantation) reviewed by O'Connell et al. (2021)[10] suggested a 4.6% risk of infection, a 4% risk of lead failure/ displacement and an 10% risk of requiring reoperation/reimplantation. The authors[10] noted that information on how and when adverse events occurred in RCTs was lacking.

In 2021, Blackburn et al.[48] published a systematic review and meta-analysis of complication rates with the intent to compare percutaneous versus open SCS implantation. With comparatively few open SCS implantations in the literature results were also presented in aggregate. The overall complication rate associated with SCS implants was 21.1%. Results were also provided on the complication rate due to equipment-related causes (12.1%) such as uncomfortable paresthesia and lead migration, followed by medical (e.g., implant site pain and infection) and technical complications at 6.3% and 1.1%, respectively.

Four other systematic reviews[11, 12, 43, 56] reported or commented on adverse events. McNicol's et al. (2021)[43] systematic review examined the methodology and reporting quality of SCS implant RCTs and studies. They[43] found most studies reviewed did not report SCS implant related adverse events or reported that none occurred. Interestingly, paresthesia was sometimes reported as an adverse effect/event but at other times described as an indicator of SCS implant efficacy. In summary, the following proportions of adverse events were reported across three of the four systematic reviews:

- **Pain at device location:** Both Eckermann et al. (2022)[12] and Baranidharan et al. (2021)[11] reported that pain at the site of the SCS device was the most reported adverse event with 10% to 25%, and 2% to 27%, respectively.
- **Lead migration:** Three of the systematic reviews reported on the incidence of lead migration with reported proportions of 8.3% to 15%[12], 0% to 14%[11], and 3% to 14%[56].
- **Surgical revision:** The proportion of surgical revisions were reported as 5% to 8.3% and 0% to 29% by Eckermann et al. (2022)[12] and Baranidharan et al. (2021)[11], respectively.
- **Explantation:** Explantation rates of 5% to 16%[12] and 0% to 13%[11] were reported. Eckermann et al.[12] noted that not all explants occur for safety reasons with some being removed for loss of efficacy or a need for magnetic resonance imaging.

Evidence from primary studies

The majority of RCTs included in this evidence review reported adverse events within their studies with some providing quite detailed information in supplementary online tables. Table 5 lists the types of adverse events reported and the proportions by patient where available. The proportion of patients experiencing an adverse event across the studies was 9% to 51%, one study[27] provided information on the number of adverse events but not by patient. Five of the seven RCTs reported incidences of serious adverse events with an average of 3 patients per study experiencing a serious adverse event.

Overall, the largest proportion of patients (51%) experiencing an adverse event occurred in a crossover RCT comparing two different types of stimulation carried out by Eldabe et al. (2021)[18]. All of the patients in this[18] study already had a permanent SCS device and had previously achieved

stable pain relief with tonic stimulation. Twenty four of the 27 reported adverse events were described as pain events.

Table 5. Adverse event reporting in randomised control trials

Authors	Number of patients	Number of adverse events	Number of patients with adverse events	Serious adverse events by number of patients
Mekhail et al. (2022)	134	42	28 (20.9%)	4 (3.0%)
Kapural et al. (2022)	145	41	35 (24.1%)	5 (3.4%)
Canos-Verdecho et al. (2021)	22	7	7 (31.8%)	NR
Eldabe et al. (2021)	53	38	27 (50.9%)	NR
Fishman et al. (2021)	128	12	11 (8.6%)	2 (1.6%)
Rigoard et al. (2021)	108	65	NR	2 (1.8%)
Eldabe et al. (2020)	105	41	17 (16.2%)	1 (0.9%)

Therapeutic Goods Administration review

In 2022, Jones and colleagues[3] published an analysis of the adverse events reported to the TGA between July 2012 and January 2019. During this period there were a total of 26,786 devices implanted, 10,702 devices removed, and 520 reported adverse events. Adverse events were coded by seriousness, severity, body system affected, type of event, action taken, and attribution of fault. Of the 520 events most were rated as severe (79%) or life-threatening (13%). Device malfunction was the most common event (56.5%). The authors estimated that each year in Australia, for every 10 spinal cord stimulators implanted, approximately 4 are removed.

Partly in response to the concerns regarding long-term safety and performance of SCS implantable raised by Jones et al (2022)[3], the Therapeutic Goods Administration announced it is undertaking a post market review of spinal cord stimulators. The review includes the impulse generator devices as well as the leads. Device manufacturers included in the Australian Register of Therapeutic Goods will be asked to provide information about their product, including:

- Supply within Australia;
- Indications and contraindications for use;
- Advertising material;
- All domestic and international incidents, adverse events and complaints;
- Any investigations for each kind of incident and the outcomes in response to each category of adverse event or complaint received; and
- Any corrective actions taken by the manufacturer in response to investigations of adverse events and complaints.

OTHER CONSIDERATIONS

Guidelines

A number of health technology appraisals from around the world recommend SCS implants for patients with chronic neuropathic back or leg pain, chronic post-surgical back and leg pain and CRPS. These include:

- The National Institute for Health and Care Excellence, UK[57, 58]
- European Academy of Neurology[59]
- Ontario Health, Canada[60]

The majority of guidelines acknowledge the limitations of the existing body of research, particularly for long-term outcomes.

Pain conditions

In a paper on trends in clinical trials for spinal cord stimulation, Harmsen et al. (2021)[4] identified 212 relevant clinical trials between the years 2000 and 2020. Approximately two-thirds of all studies had commenced within the last 5 years. The studies spanned 27 different disorders, with most registered clinical trials examining the effects of SCS implants on chronic pain syndromes, including back/extremity pain (44 trials), SCI (33 trials), FBSS (28 trials), neuropathy (28 trials), and CRPS (16 trials).

All of the systematic reviews included in this evidence review conclude that spinal cord stimulation is effective for reducing chronic neuropathic pain from a variety of chronic pain syndromes. The clinical efficacy of SCS implants for intractable back pain, FBSS, neuralgia and CRPS is generally accepted within the literature although caveats regarding long-term outcomes and the quality of evidence remain.

Types of SCS implant

What is evident from this review is that SCS technologies have expanded significantly, particularly in the last 5 years. SCS technologies now utilise a variety of different waveforms, lead configurations and different programming options[56, 61].

According to the review of clinical trials by Harmsen et al. (2021)[4], a quarter of trials were parameterization studies that involved testing different stimulation settings (i.e., conventional vs. burst or high frequency stimulation) to optimize therapeutic outcomes. Previous to 2007, only one study was identified that examined the effect of varying SCS parameters. In contrast, 53 such studies were commenced between 2008 and 2019 with over half (56%) of parameter-related studies initiated in the last 3 years. Replication studies are in decline.

As each technological advance has been made, claims of improved outcomes have followed[56, 62]. The systematic reviews[14, 25, 56] and RCTs[16-18, 35] included in this evidence review provide evidence of increased efficacy in pain reduction using HF-SCS and BURST and other stimulation parameters over traditional tonic SCS.

Limitations

This review was based primarily on systematic reviews and RCTs and additionally benefited from the presence of a Cochrane review on the effectiveness of SCS implants. The quality of the systematic

reviews was strong according to the McMaster's Health Evidence Checklist[7], however the quality of the studies included in the reviews was judged as low grade by the majority of authors.

Half of the systematic reviews with pain reduction as a primary focus restricted their analysis to RCTs. There was a high degree of duplication of included studies across the systematic reviews. The Cochrane review[10] rated the overall evidence within the RCTs as being of low, or very low certainty, and all results that were evaluated as being at high risk of bias overall.

High levels of industry funding of studies and investigators were identified by the systematic reviews and were common (6 out of 7) among the RCTs included in the current evidence review. While industry funding does not negate the results of the studies it is a consideration when considering the magnitude of the effects that are reported.

Some of the limitations of the RCTs include:

- Many of the RCTs included in the systematic reviews were limited by small sample size. The systematic reviews found trials with fewer than 50 participants were common and led to larger effect estimates when compared with the largest trials[9, 10]. It should be noted that the more recent RCTs included in this evidence review have reported much larger sample sizes. In Harmsen's et al. (2021)[4] review of 212 registered clinical trials, a quarter of trials had planned an enrolment of 10 or less subjects; in a quarter of trials (47%) enrolment of between 11 to 150 subjects was most common.
- Most of the RCTs consisted of short-term interventions with short follow-up periods.
- A small number of studies included patients who were already stabilized and using SCS devices which makes the generalizability of the results to de novo populations problematic, and may underestimate the adverse effects and overestimate the beneficial effects of the implants.
- Lack of blinding was an issue with many of the RCTs included in the systematic reviews. In particular, patient blinding with paraesthesia inducing tonic SCS was rare due to the difficulties of establishing a placebo arm. However, even with the advent of paraesthesia free SCS modalities the quality of blinding of participants has been identified as an issue[9, 10, 44]. The quality of blinding of subjects in SCS trials is particularly important as the magnitude of treatment effect has been shown to vary by quality of blinding[9]. Lack of blinding was the largest source of bias for four out of the seven RCTs included in the current evidence review reporting pain as a primary outcome.
- The lack of a washout period or inadequate washout periods in crossover studies was also a common issue identified with RCT trials included in the systematic reviews[9, 10]. Inadequate or absent washout periods increase the chances of carry-over effects. Only two crossover RCT trials were included in the current evidence review. One had a nine-day washout period, the other had a variable washout period of three to seven days and reported variable medication use among patients during the washout period.
- The heterogeneity between RCTs limits comparisons and impacts on the level of evidence ratings in systematic reviews or meta-analyses. Heterogeneity occurs between study designs, SCS modalities, control groups, and included pain conditions. As the pace of change in device development increases there are less replications to confirm original findings, as device manufacturers move on to fund different SCS parameters and devices.

SUMMARY AND IMPLICATIONS

Summary

The purpose of this project was to conduct a review of the latest evidence for the clinical effectiveness of spinal cord stimulators for persistent pain. Based on a large evidence base of 21 systematic reviews (including the Cochrane review by O'Connell et al (2021)) and 29 primary studies (9 RCTs and 20 controlled clinical trials), the current review provides limited support for the efficacy of SCS implants for persistent pain in the short and medium-term. Larger, well controlled trials are still needed to determine longer-term effects.

Evidence for the effects of SCS implants on function (physical, psychological, social), quality of life, return to work, medication and healthcare use was sparse. Four systematic reviews focussed on secondary outcomes; adverse events, return to work, opioid use, and patient satisfaction. Two primary studies were found examining the impact of SCS implants on quality of life[52, 53]. In addition to these studies, several of the systematic reviews and primary studies with a primary focus on pain examined one or more of the associated, secondary outcomes. A small amount of supporting evidence was found for the effects of SCS on secondary outcomes.

The final question posed in this evidence review concerned the risks and inconveniences associated with use and maintenance of spinal cord stimulation implants. Reporting on adverse events was common practice in more recent studies, addressing one common criticism of the lack of information provided by authors on adverse events in the past. Overall proportions of patients experiencing an adverse event ranged from 9% to 51%. Pain was commonly reported as an adverse event followed by lead migration.

Implications

Overall, the evidence suggests that SCS implants for persistent pain are clinically effective in the short and medium-term, but evidence is lacking on the long-term outcomes for patients. The quality of RCTs is improving leading to decreased risks of bias although the results are still low to moderate certainty given continuing issues with industry funding, lack of effective blinding and high heterogeneity.

SCS implants have also shown limited, but positive, effects on improving disability and functioning, quality of life and reduction in medication use. The effects of SCS implants on return to work are much less certain with limited research available.

SCS implantation is an invasive medical procedure not without risk. The high rate of adverse events reported in Australia, including the large proportion of SCS implants being removed, are of concern.

APPENDIX A. LITERATURE SEARCH PROCESS

Search strategy

1. spinal neuromodulation.mp.
2. spinal cord stimulation/
3. electric stimulation therapy/
4. 1 OR 2 OR 3
5. pain*.ab,kf,ti.
6. Pain/
7. 5 OR 6
8. 4 AND 7
9. limit 8 to (english language and humans and yr="2014 -Current")

One reviewer conducted a comprehensive database search of Medline, Embase, and the Cochrane Library using the search strategy as mentioned above. A total of 2,228 references were identified, the number of outputs from each database accessed were as follows:

- Ovid Medline N = 1,107
- Embase (via Ovid) N = 1,005
- Cochrane N = 116

APPENDIX B. QUALITY OF INCLUDED STUDIES

Quality of systematic reviews

McMaster's Health Evidence Checklist[7] provides an overall summative score based on 10 assessment domains (yes/no):

1. Clearly focussed research question
2. Provision of inclusion criteria
3. Comprehensive search strategy
4. Search strategy covers adequate number of years
5. Level of evidence included
6. Quality assessment of included studies
7. Transparent quality assessments
8. Appropriateness of combining study results (heterogeneity check)
9. Weighting of results
10. Interpretation of results

Each systematic review was assessed against these 10 domains and the results are presented in Table 6. Overall, the quality of the systematic reviews was strong with only three receiving a rating indicating the review had quality limitations resulting in a weak or moderate rating. It should be noted that although the majority of systematic reviews were rated highly, the quality of the studies included in each of the systematic reviews varied considerably and was generally low.

One potential source of bias not assessed by the Health Evidence Checklist should be considered when interpreting these results. Just over half of the systematic reviews with pain as a primary outcome declared some funding or sponsorship from industry entities with an interest in the manufacture and sale of SCS equipment, and the sponsor's role in the study was not always made clear. Seven of the nine systematic reviews with primary outcomes other than pain declared industry sponsorship of one or more authors.

Table 6. Quality ratings for systematic review studies

Systematic Reviews	Primary outcome	Quality rating (score)	Type of included studies
Eckermann et al. 2022[12]	Pain	✓	RCTs or other trials
Hagedorn et al. 2022[63]	Patient satisfaction	✓	RCTs or other trials
Kurt et al. 2022[13]	Pain	✓	RCTs or other trials
Smith et al. 2022[50]	Opioid use	✗	RCTs or other trials
Baranidharan et al. 2021[11]	Pain	✓	RCTs or other trials
Blackburn et al. 2021[48]	Complications	✓	RCTs or other trials
McClure et al. 2021[46]	Cost-effectiveness	−	Other trials
McNicol et al. 2021[43]	Methods / quality	✓	RCTs
O'Connell et al. 2021[10]	Pain	✓	RCTs
Conger et al. 2020[14]	Pain	✓	RCTs or other trials
Chakravarthy et al. 2019[64]	Pain	−	RCTs, other trials, case series or expert opinion
Deer et al. 2020[33]	Pain	✓	RCTs
Duarte et al. 2020a[9]	Pain	✓	RCTs
Duarte et al. 2020b[44]	Methods / quality	✓	RCTs
Karri et al. 2020[25]	Pain	✓	RCTs or other trials
Niyomsri et al. 2020[47]	Cost-effectiveness	✓	RCTs, other trials, case series or expert opinion
Vallejo et al. 2020[45]	Methods / quality	✓	RCTs or other trials
Head et al. 2019[56]	Pain	✓	RCTs
Lamer et al. 2019[26]	Pain	✓	RCTs
Moens et al. 2019[49]	Return to work	✓	RCTs or other trials
Mekhail et al. 2018[65]	Pain	✓	RCTs

Notes. Other trials may include prospective, observational, or retrospective trials.

Legend: ✓ Strong quality, − Moderate quality, ✗ Weak quality

The 21 systematic reviews were examined to identify their currency, comprehensiveness and quality. All of the 21 reviews were published in the last five years, i.e., between 2018 and 2022. The most recent of these were Eckermann et al. 2022[12], Kurt et al. 2022[13], Hagedorn et al. 2022[63], and Smith et al. 2022[50]. A comprehensive Cochrane review by O'Connell[10] was published in 2021 and included papers published up to September 2021.

Twelve of the systematic reviews focused on pain as the primary outcome, while nine reviews had primary outcomes including:

- Opioid use pre and post implant
- Patient satisfaction
- Complication rates and types of complications
- Methods and reporting quality
- Cost effectiveness
- Costs and health care utilisation
- Return to work

The 12 systematic reviews that focused on a primary outcome of pain varied in terms of their populations, interventions, comparators, and outcome measures. Seven conducted meta-analyses with the remaining five conducting narrative reviews.

For the meta-analyses, the majority of these included studies that were, on average, at moderate risk of bias, and had methodological limitations related to a range of issues including:

- Combining studies of different designs and follow-up durations.
- Poor quality of blinding and handling of carryover effects due to crossover designs.
- Large variation in pain conditions between studies.
- Variation in the type of stimulation investigated included a wide range of modalities such as paraesthesia stimulation, subthreshold, BURST, and varying kilohertz frequencies up to 5880 Hz.

The highest quality systematic review with a meta-analysis was the Cochrane review by O'Connell et al. (2021)[10].

Quality of primary studies

Twenty-nine primary studies were identified of which nine were Level II (RCTs) and 20 Level III (prospective cohort studies). Quality assessment was undertaken on the RCTs using the Quality Assessment Tool for Quantitative Studies[8]. The Quality Assessment Tool for Quantitative Studies allows for a mark to be assigned ranging between "strong," "moderate," and "weak" in eight categories:

1. Study design
2. Analysis
3. Withdrawals and dropouts
4. Data collection practices
5. Selection bias
6. Invention integrity
7. Blinding as part of a controlled trial
8. Confounders

A final global rating is assigned based on the number of weak ratings across the eight categories (strong: no weak ratings; moderate: one weak rating; weak; two or more weak ratings). The results of the quality assessments of RCTs are presented in Table 7. Three types of primary outcomes were examined in the RCTs: pain reduction (pain), the effectiveness of screening trials (methods) and quality of life (Qual).

Overall, the quality of RCTs was weak to moderate with only four studies receiving a strong rating. Lack of blinding was the largest source of bias for five out of the nine RCTs. Selection bias was

another area of concern primarily driven by recruitment of participants less likely to be representative of the target population.

Like the Health Evidence Checklist, the Quality Assessment Tool for Quantitative Studies does not assess bias potentially caused by funding or sponsorship from industries with an interest in the manufacture and sale of SCS equipment. Of the 30 primary studies, all but two declared some form of funding or sponsorship of individual authors or the study itself.

Table 7. Quality ratings for RCTs

Author	Primary outcome	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Global rating
Mikhail et al. 2022[34]	Pain	✓	✓	✓	✓	✓	✓	✓
Kapural et al. 2022[15]	Pain	✓	✓	✓	✗	✓	✓	−
Rigoard et al. 2021[27]	Pain	−	✓	✓	✓	✓	✓	✓
Canos-Verdecho et al. 2021[35]	Pain	−	✓	✗	✗	✓	✓	✗
Duarte et al. 2021[52]	Qual	−	✓	✓	✓	✓	−	✓
Eldabe et al. 2021[18]	Pain	−	✓	✗	✓	✓	−	−
Fishman et al. 2021[16]	Pain	−	✓	✓	✗	✓	−	−
Eldabe et al. 2020[54]	Methods	−	✓	✓	−	✓	✓	✓
North et al. 2020[17]	Pain	−	✓	✗	✗	✓	−	−
Amirdelfan et al. 2018[53]	Qual	−	✓	✓	✗	✓	−	−

Legend: ✓ Strong quality, − Moderate quality, ✗ Weak quality

APPENDIX C. KEY CHARACTERISTICS AND FINDINGS OF INCLUDED STUDIES

Table 8. Summary table of systematic reviews with pain as a primary outcome of interest

Reference Country	Type of review Databases searched Search period	Number of studies	Population Follow-up	Intervention Comparator	Key findings
O'Connell et al. 2021 [10] UK	Cochrane systematic review 7 Inception to September 2021	15 unique, 20 ongoing RCTs	Adults with non-cancer and non-ischaemic pain of longer than three months duration. Short (1 mth), medium (4 to 8 mths), long-term (12+ mths)	Implanted spinal neuromodulation any type Placebo (sham) stimulation, no treatment or usual care; or SCS interventions + another treatment versus that treatment alone.	• Low- to very low-certainty evidence for clinically important benefits for pain intensity and benefits on health-related quality of life (HRQoL) when added to conventional medical management or physical therapy. • Very low-certainty evidence for clinically important benefits on pain intensity or HRQoL when compared with placebo (sham) stimulation. • No clear evidence of benefit from SCS for disability or medication use.
Kurt et al. 2022 [13] The Netherlands	Systematic review and meta-analysis 3 Inception to November 2020	16 (11 quantitative, 5 qualitative)	Anyone with FBSS Up to six months	Spinal cord stimulation (any) None or any	• For those with low back and leg pain: Low back pain decrease 3, 6 , and 12mth; leg pain decrease 3, 6, 12 months. For those with overall pain: decrease at 6 and 12 months. • Patients report limitations in daily life and living with the SCS system.
Eckerman et al. 2022 [12]	Systematic review	10 primary studies and 6 secondary publications	Adults, suffering from chronic back pain no previous spine surgery	Spinal cord stimulation (any)	• Pain scores: 6/10 studies significant decrease in pain scores from baseline to final follow-up. 3/6 studies significant decrease in pain scores at 12 months.

Reference Country	Type of review Databases searched Search period	Number of studies	Population Follow-up	Intervention Comparator	Key findings
USA	4 Inception to February 2021		12 to 36 months	None or any	• Patient reported pain measure: HF-SCS at 12 months 3 studies 52% to 90% • The studies reported limited data supporting high patient satisfaction, reductions in opioid use, and an acceptable safety profile.
Baranidharan et al. 2021[11] UK	Systematic review and meta-analysis 4 May 2008 to November 2020	15 primary studies	Adults, suffering from neck/upper limb pain unresponsive to previous treatment, including traditional SCS. Minimum 3 month	10kHz SCS. None or any	• The proportion of patients who achieved ≥ 50% pain reduction was 83% (95% CI 77–89%). The proportion of patients who reduced/eliminated their opioid consumption was 39% (95% CI 31–46%). • The evidence derived from 15 studies consistently demonstrated favourable outcomes in terms of pain reductions, improvements in function, QoL, patient satisfaction, reductions in medication use, and an acceptable safety profile.
Conger et al. 2020[14]	Systematic review	17 RCTs and nonrandomized studies (cohort or case series)	Axial low back pain (LBP) with or without leg pain	LF-SCS, BURST, or HF-SCS	• Low-quality evidence that high-frequency SCS, compared with low-frequency SCS is effective in patients with axial LBP with concomitant leg pain. There is very low-quality evidence for low-frequency SCS for the treatment of axial LBP in patients with concomitant leg pain. • There is insufficient evidence addressing the effectiveness of BURST SCS to apply a GRADE rating.
USA	3		At least six months	None or any	
	Inception to September 2019				
Duarte et al. 2020a[9]	Systematic review and meta-analysis	8 RCTs using a placebo/sham control	Adults with neuropathic pain	SCS any type	• Statistically significant reduction in pain intensity during the active stimulation treatment periods compared with the control treatment periods on a 10-point scale.
UK	4		Any	Placebo or sham	

Reference Country	Type of review Databases searched Search period	Number of studies	Population Follow-up	Intervention Comparator	Key findings
	Inception to January 2019				• Limited evidence that SCS is effective in reducing pain intensity when compared with a placebo intervention.
Karri et al. 2020[25]	Systematic review and meta-analysis	RCTs and prospective cohort studies (N = 11)	Persons suffering with chronic LBP secondary to failed back surgery syndrome, axial LBP, lumbar radiculopathy, and spinal stenosis	Tonic, BURST, and HF-SCS — relative to each other	• Meta-analysis of tonic versus BURST stimulation revealed superiority of the BURST waveform across data pooled from 5 separate studies. • Evidence comparing BURST and HF stimulation is lacking, but findings from a small cohort suggest that BURST and HF are equally effective in reducing back pain. However, BURST demonstrated superiority to HF in reducing leg pain.
USA	2 1966 to July 2019		Up to 24 months		
Chakravarthy et al 2019[64] USA	Systematic review and meta-analysis 6 2010 to 2019	Level II, III, IV, or V (N = 15)	Various pain diagnoses including FBSS, CRPS and Radiculopathy. Up to 2 years	BURST SCS Tonic SCS	• The weighted pooled mean pain rating across articles at baseline was 76.7. Mean pain rating with tonic SCS was 49.2, and with BURST SCS it was 36.7. • In pooled analyses that incorporated all available published evidence, the improvement over baseline for BURST SCS was shown to have a clinically important incremental benefit over tonic SCS.
Head et al. 2019[56] USA	Systematic review 13 Inception to June 1 2019	RCTs (N = 11)	Adults, back and lower limb pain Any	SCS any type None or any	• SCS is an effective tool for treatment of chronic, intractable neuropathic low-back and leg pain. • Traditional SCS significantly decreases lower extremity pain and improves multiple other patient outcome metrics compared with reoperation and conventional medical management. • High frequency 10-kHz SCS is superior to traditional paraesthesia-based SCS at relieving both back and lower extremity pain.

Reference Country	Type of review Databases searched Search period	Number of studies	Population Follow-up	Intervention Comparator	Key findings
Lamer et al. 2019[26] USA	Systematic review and meta-analysis 6 January 1 1995 to December 31 2017	RCTs (N = 17)	Adults with intractable Spine and Limb Pain Greater than three months	SCS any type Any	• SCS was significantly more likely than medical therapy in relieving pain in a variety of chronic painful conditions. New SCS technology was associated with incremental improvement in chronic intractable pain compared with conventional SCS.
Mekhail et al. 2018[65] USA	Systematic review 4 1967 to September 2016	RCTs (N = 21)	Adults with pain-related indications Any	SCS any Placebo and active comparator	• Spinal cord stimulation, compared with conventional medical management for trunk and limb pain, demonstrated moderately strong evidence of efficacy with respect to pain reduction, functional outcomes, and patient satisfaction.
Deer et al. 2020[33]	Systematic review 6 January 1995 to October 2018	RCTs (N = 6)	Adults with chronic pain Minimum 6 mths	SCS any Any	• High level evidence supports SCS for treating chronic pain and complex regional pain syndrome. For patients with failed back surgery syndrome, SCS was more effective than reoperation or medical management.

Notes: CI = confidence interval; RCT=randomised control trial; LF-SCS = low frequency spinal cord stimulation; HF-SCS = high frequency spinal cord stimulation; FBSS = Failed Back Surgery Syndrome; CRPS = Complex Regional Pain Syndrome; HRQoL = health-related quality of life; QoL = quality of life; Level II = RCTs, Level III = prospective, observational studies retrospective, observational studies; Level IV case series; Level V = expert opinion.

Table 9. Summary table of primary studies examining the effectiveness of SCS on pain and other conditions.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
Bolash et al. 2022[30] USA	Prospective cohort SURF	Adults (N = 49) Chronic back pain, or back and leg pain	Tonic (suprathreshold), BURST and high density (subthreshold) None 1, 3, & 6 months	Pain intensity Quality of life, function, sleep, adverse events	• Spinal cord stimulation with multiple stimulation patterns demonstrate clinical and functional efficacy when using an externally powered stimulation system.
Deer et al. 2022a[29] USA	Prospective cohort TRIUMPH and REALITY	Adults (N = 215 & N = 312) FBSS/back pain/radiculopathy, CRPS I and CRPS II, Peripheral neuropathy, Neck/upper limb pain	BURST SCS None 6 months	Pain intensity Pain-related emotional distress, physical functioning, adverse events	• Mean pain intensity decreased by nearly 50% relative to baseline, PCS scores significantly decreased, and physical function improved.
Deer et al. 2022b[66] USA, Canada, Europe	Prospective cohort TRIUMPH	Adults (N = 128) Chronic, intractable pain of the trunk, and/or lower limbs	BURST SCS None 24 months	Pain intensity Mood and affect, anxiety, depression, fear avoidance, sleep, physical function, and pain-related medication use.	• Significant improvements in pain, physical, mental, and emotional functioning observed at six months of treatment were maintained at 2 years after implant. • Participants reported a significant decrease in the impact of pain on life and in the amount of medication consumed across all drug classes.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
Kapural et al. 2022[15] USA	RCT crossover	Adults (N = 159) Nonsurgical refractory back pain (NSRBP)	10kHz SCS CMM vs SCS+CMM 12 months	Pain intensity Disability, sleep, mental health, satisfaction, healthcare utilization, and quality of life.	• The addition of 10-kHz SCS to CMM resulted in profound improvements in pain relief, function, quality of life, and awareness of positive change, as well as reduction in daily opioid use, 12 months post implantation.
Mekhail et al. 2022[34] USA	RCT crossover EVOKE	Adults (N = 134) Chronic, intractable back and leg pain refractory to conservative therapy	SCS ECAP-controlled, closed-loop SCS was compared with fixed-output, open-loop SCS 24 months	Pain intensity Health-related quality of life, physical and emotional functioning, sleep, and drug use	• Closed-loop SCS delivered higher, more consistent neural response within the prescribed therapeutic window and demonstrated superior long-term improvements in pain relief and patient-reported outcomes, with meaningful opioid reduction.
Paz-Solis et al. 2022[31]	Prospective cohort	Adults (N = 30)	SCS low frequency	Pain relief	• Effective sub perception pain relief was achieved in SCS at sub-kHz frequencies (down to 10 Hz)
Spain, UK	HALO study	FBSS or chronic radiculopathy	None	Opioid use	
			24 months		
Brooker et al. 2021[6]	Prospective cohort	Adults (N = 50)	Closed loop SCS	Pain intensity	• Responder rates (≥ 50% pain reduction) and high responder rates (≥ 80% pain reduction) for overall pain were 89.5% and 68.4%, respectively.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
Australia	AVALON	Chronic back and/or leg pain (with or without previous back surgery)	None 24 months	Quality of life, function, sleep, and medication usage	• Significant improvements from baseline were observed in QOL, function, and sleep over the 24 months. At 24 months, 82.8% of patients with baseline opioid use eliminated or reduced their opioid intake.
Canos-Verdecho et al. 2021[35] Spain	RCT	Adults (N = 50) Complex Regional Pain Syndrome of the upper limb	LF-SCS vs HF-SCS vs CMM CMM 12 months	Pain intensity General health, quality of life, function, and sleep	• Patients with CRPS of the upper limb experienced considerable improvement 12-months after the start of both conventional treatment and treatment with SCS systems.
Cordero Tous et al. 2021[39]	Prospective cohort	Failed SCS adults (N = 18)	Tonic SCS vs HF-SCS	Pain intensity	• Eleven of the 18 (61%) patients included in the study were successfully rescued with HF-SCS. • Significant improvement in quality of life, including Sleeping and Walking, while there were no major differences in other categories such as Personal Care, Work or Recreation. • Analysis of opioid use at 12 months after treatment showed significant dose reduction in five patients (45%), opioid discontinuation in four patients (36%), no significant variations despite improvement in five patients (45%) and need to increase the dose of opioids in one case (9%).
Spain		FBSS or CRPS	None	Functionality, analgesics use and treatment safety	
			12 months		
Deer et al. 2021[23]	Prospective cohort	Adults (N = 50)	BURST SCS	Pain intensity	• BURST SCS can provide effective pain relief, increase quality of life, reduce disability, and decrease pain catastrophizing even

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
USA		FBSS, radiculopathy, degenerative disk disease, Spondylosis, mild spinal stenosis, neuropathic pain, other	None 6 months	Quality of life, disability, pain catastrophizing, overall evaluation/satisfaction with treatment, medication usage, adverse events.	when low ON:OFF ID ratios (1:12, for a total of 8% on time) are used. • Results suggest that intermittent stimulation can be titrated to provide optimal pain relief while delivering the lowest possible dose of electricity to the spinal cord.
Duarte et al. 2021[52] USA & Australia	RCT & Prospective cohort EVOKE & AVALON	Adults (N = 204) Chronic back and leg pain	Closed loop SCS None 12 months	Quality of life and functioning Pain	• Patients in a remission health state report statistically and clinically significant better HRQoL than patients experiencing lesser pain relief.
Eldabe et al. 2021[18] UK	RCT	Adults with tonic SCS implant (N = 19) FBSS	BURST and Tonic SCS Placebo (sham) 6 weeks	Pain intensity Global impression of change and quality of life, adverse events.	• Findings suggest that T500 stimulation was superior to sham, but BST stimulation was not, in a group of subjects with leg and back pain habituated to tonic SCS.
Fishman et al. 2021[16] USA	RCT	Adults (N = 124) Chronic low back pain (LBP)	Differential Target Multiplexed (DTM)-SCS or SCS None 12 months	Pain intensity Disability and global health	• DTM SCS provided superior LBP relief compared with traditional SCS programming in patients with intractable LBP and LP at the 3-month visit in the intention-to-treat population. The study demonstrated sustained benefits with high efficacy in LBP out to 12 months. Both treatment groups experienced meaningful LP relief as well as improvements from baseline in measures of disability.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
Galan et al. 2021[40]	Prospective cohort	Adults (N = 26)	HF-SCS (10kHz)	Pain intensity	• Subjects experienced significant and sustained pain relief (at least 65% at all timepoints) whereas physicians noted improvements in neurological function. • Significant improvements in disability, function, sleep, sensory, and affective dimensions of pain were reported at all timepoints. • All adverse events were resolved without sequelae.
USA		Peripheral polyneuropathy, including Painful Diabetic Neuropathy	None	Adverse events, neurological assessments, disability, function, quality of life, pain interference, sleep, satisfaction, and global impression of change	
			12 months		
Goudman et al. 2021[67]	Prospective cohort	Adults (N = 194)	HD-SCS	Pain intensity	• The mean pain reduction for both back and leg pain reached a strong statistical significance after 12 months of HD-SCS. The mean reduction over time for leg pain was higher than for back pain. At 12 months, the mean leg pain reduction was 54% compared to 41% for the mean back pain reduction. • The study showed an overall statistically significant improvement in sleep quality, functionality, quality of life, and a decrease in pain medication usage.
Belgium & France	DISCOVER Registry	FBSS	None	Quality of life, functional disability, sleep quality, and a numerical representation of the negative impact of pain medication. Patient satisfaction	
			12 months		
Kallewaard et al. 2021[41]	Prospective cohort	Adults (N =68)	HF-SCS (10kHz)	Pain intensity	• After 12 months of treatment, 80% of patients experienced ≥ 50% reduction in baseline leg pain, and a similar proportion (76%) experienced ≥ 50% reduction in baseline back pain.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
The Netherlands		FBSS patients with predominant leg pain	None 12 months	Quality of life, opioid use, mental status, and adverse events	• The therapy was also associated with a general improvement in patients' quality of life, as measured by secondary outcomes including disability, perception of health improvement, mental well-being, and satisfaction. • A positive impact on opioid consumption was also observed.
Leong et al. 2021[19]	Cross-sectional analysis of RCT	Adults (N = 99)	BURST vs Tonic SCS	Pain intensity	• Significant positive correlations were identified between BURST amplitude and total, "worst," and "trunk" pain for VAS; all domains for pain catastrophising; and "Role-Physical," "Bodily Pain," and "General Health" for SF-36v2™ after 12-weeks of BURST stimulation.
USA	SUNBURST	Chronic, intractable pain in the limbs and trunk	Cross over	Pain catastrophizing, general health	
			3 months		
Motov et al. 2021[32]	Prospective cohort	Adults (N = 39)	HF-SCS	Pain intensity	• Significant VAS score reduction for lower back pain and for leg pain. Twenty-four percent of all patients were able to discontinue their opioids.
Germany		FBSS	None	Opioid use and adverse events	
			10 months		
Perez et al. 2021[42]	Prospective cohort	Adults (N = 85)	Tonic & HF-SCS	Pain intensity	• CMM patients maintained similar scores, while SCS patients reduced their overall score.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
Spain	SEFUDOCE	FBSS	CMM 24 months	Functioning, anxiety, depression and sleep.	• No significant inter-group differences were found for anxiety, depression, functioning and sleep. • Twenty-four-month follow-up showed unlikely presence of neuropathic pain and moderate disability in SCS patients, whereas the CMM patients maintained baseline health state.
Rigoard et al. 2021[27]	RCT	Adults (N = 115)	SCS Monocolumn programming (Mono-group) or multicolumn programming (Multigroup)	Pain intensity	• At six months, the decrease in back pain was greater for Multi-group (41.3%) than for Mono-group (35.5%), which was not statistically significant. However, there was significant global reduction in pain in both groups at six months (−45.9%). This was sustained after 12 months (−45.1%), accompanied by significant improvements in functional capacity (32.0%), depression (33.9%), anxiety (30.9%), and quality of life (50.0%). • Pain medication intake also decreased by 42.2% over 12 months.
France	ESTIMET	FBSS	Cross over	Functional improvement, quality of life, depression, anxiety, medication changes, and patient satisfaction.	
			12 months		
Tate et al. 2021[20]	Prospective cohort	Adults (N = 23)	HF-SCS (10 kHz)	Pain intensity	• The data reported here show that 10-kHz SCS is a safe and effective treatment option for treating symptoms of chronic pelvic pain. • Most subjects tested responded to stimulation with decreased pain levels and increased daily functioning with duration of benefits lasting through the end of the 12-month study period.
USA		Chronic pelvic pain various causes	None	Functional impairment, Global Impression of Change.	
			12 months		
Benyamin et al. 2020[21]	Prospective cohort	Adults (N = 64)	HF-SCS (10kHz)	Pain intensity	

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
USA	OPTIONS	FBSS	None 3 months	Global impression of change, health-related quality of life, functional disability, satisfaction/recommendation, stimulation perception, device programming, and adverse events.	• Improvements in pain relief, global impression of change, EQ-5D-5L, functional disability, and patient satisfaction were all clinically relevant and statistically significant.
Eldabe et al. 2020[54]	RCT	Adults (N = 105)	HF-SCS (10kHz) and BURST SCS Screening trial vs no screening trial	Screening trial effectiveness	• Results indicate that although an SCS screening trial may have some diagnostic utility, it provides no patient outcome benefits compared to a no screening trial and direct to permanent SCS implantation strategy. • The economic evaluation also shows that an SCS trial is not a cost-effective use of healthcare resources.
UK	TRIAL-STIM	Chronic pain of neuropathic origin	None	Pain intensity, quality of life, functioning, patient satisfaction, costs	
			6 months		
Goudman et al. 2020[55]	Prospective cohort	Adults (N = 194)	HD-SCS	Quality of life	• HD-SCS may lead to significantly increased HRQoL at 12 months in patients with FBSS. Despite the increase, reaching the HRQoL level of matched controls was not achieved. • Only a limited number of patients (14%) were able to return to work.
Belgium & France	DISCOVER Registry	FBSS	None	Return to work	
			12 months		
Gupta et al. 2020[24]	Prospective cohort	Adults (N = 41)	HF-SCS (10kHz)	Pain intensity	• 10-kHz SCS is effective and tolerated in patients with CPSP.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
USA		Chronic postsurgical neuropathic pain	None 12 months	Pain catastrophizing and vigilance, patient function, physical and mental well-being, and sleep quality	• Pain catastrophizing and vigilance, patient function, physical and mental well-being, and sleep quality all improved over the course of the study.
Hamm-Faber et al. 2020[28]	Prospective cohort (pilot)	Adults (N = 13)	LD-SCS vs HD-SCS	Pain intensity	• Leg pain at baseline was reduced at six months and at 12 months. Back pain at baseline was reduced at six months and at 12 months. • Pain medication was significantly reduced and the pain/disability measure showed improvements at 12 months. • Five patients returned to work and overall patient satisfaction at the end of the study was high.
Netherlands		FBSS	None	Pain medication use, pain disability, patient satisfaction, employment status, stimulation settings, and adverse events.	
			12 months		
North et al. 2020[17]	RCT	Adults with existing SCS implants (N = 140)	SCS subperception vs supraperception	Pain intensity	• Significant improvement in pain relief was sustained out to 12 months when using subperception SCS. • Access to more than one selectable treatment approach (sub- or supraperception) provided better outcomes when subjects could choose their most effective therapy.
USA	WHISPER	Chronic low back and leg pain	Crossover	Quality of life, disability, and adverse events	
			12 months		
Remacle et al. 2020[36]	Prospective cohort	Adults (N = 62)	HF-SCS	Pain intensity	• The study demonstrated a sustained beneficial effect of the multicolumn-lead SCS device on back and leg pain, daily activity limitation, quality of sleep, and analgesic and coanalgesic medication consumption in patients with FBSS for 72 months.

Reference Country	Study design Trial name	Population Pain type	Intervention Control Follow-up	Primary outcome Secondary	Key findings
Belgium		FBSS	None 6 years	Sleep quality, use of medications, daily activity and adverse events	• However, there were high complication and patient withdrawal rates with the SCS device.
Russo et al, 2020[22] Australia	Prospective cohort AVALON	Adults (N = 50) Chronic back and/or leg pain (with or without previous back surgery)	Closed loop SCS None 12 months	Pain intensity Quality of life, function, sleep, and medication use	• At 12 months, the proportion of patients with ≥50% relief was 76.9% (back), 79.3% (leg), and 81.4% (overall), and the proportion with ≥80% pain relief was 56.4% (back), 58.6% (leg), and 53.5% (overall). • 68.8% (22/32) eliminated or reduced their opioid intake. • Statistically significant improvements in secondary outcomes were observed.
Amirdelfan et al. 2018[53] USA	RCT SENZA	Adults (N = 198) Chronic back and leg	HF-SCS vs LF-SCS LF-SCS 12 months	Quality of life, disability, functioning, self-reported pain, sleep.	• At 12 months, a higher proportion of 10 kHz SCS subjects had marked improvement of their disability to a “moderate” or “minimal” impact on their daily function versus the control group. • The 10 kHz SCS subjects also reported far higher rates of both driving and sleeping with their device turned on, as well as reduced reliance on their programmers to adjust therapy settings.

Notes: CMM = conventional medical management; RCT=randomised control trial; LF-SCS = low frequency spinal cord stimulation; HF-SCS = high frequency spinal cord stimulation; HD-SCS = high density spinal cord stimulation; FBSS = Failed Back Surgery Syndrome; CRPS = Complex Regional Pain Syndrome; HRQoL = health-related quality of life; QoL = quality of life.

REFERENCES

1. AIHW. Chronic Pain in Australia. Canberra, Australian Institute of Health and Welfare; 2020.
2. Painustralia. The cost of pain in Australia. Canberra: Deloitte Access Economics; 2019.
3. Jones CMP, Shaheed CA, Ferreira G, Mannix L, Harris IA, Buchbinder R, et al. Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. Journal of Patient Safety. 2022;18(5):507-11.
4. Harmsen IE, Hasanova D, Elias GJB, Boutet A, Neudorfer C, Loh A, et al. Trends in Clinical Trials for Spinal Cord Stimulation. Stereotact Funct Neurosurg. 2021;99(2):123-34.
5. Hong A, Varshney V, Hare GMT, Mazer CD. Spinal cord stimulation: a nonopioid alternative for chronic pain management. Canadian Medical Association Journal. 2020;192(42):E1264-E7.
6. Brooker C, Russo M, Cousins MJ, Taylor N, Holford L, Martin R, et al. ECAP-Controlled Closed-Loop Spinal Cord Stimulation Efficacy and Opioid Reduction Over 24-Months: Final Results of the Prospective, Multicenter, Open-Label Avalon Study. Pain pract. 2021;21(6):680-91.
7. Health Evidence™ (2018). Quality Assessment Tool – Review Articles. . McMaster University; 2018.
8. Armijo-Olivo S, Stiles CR, Hagen NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. J Eval Clin Pract. 2012;18(1):12-8.
9. Duarte RV, Nevitt S, McNicol E, Taylor RS, Buchser E, North RB, et al. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. Pain. 2020;161(1):24-35.
10. O'Connell NE, Ferraro MC, Gibson W, Rice AS, Vase L, Coyle D, et al. Implanted spinal neuromodulation interventions for chronic pain in adults. Cochrane Database Syst Rev. 2021;12:CD013756.
11. Baranidharan G, Bretherton B, Montgomery C, Titterington J, Crowther T, Vannabouathong C, et al. Pain Relief and Safety Outcomes with Cervical 10 kHz Spinal Cord Stimulation: Systematic Literature Review and Meta-analysis. Pain and Therapy. 2021;10(2):849-74.
12. Eckermann JM, Pilitsis JG, Vannaboutathong C, Wagner BJ, Province-Azalde R, Bendel MA. Systematic Literature Review of Spinal Cord Stimulation in Patients With Chronic Back Pain Without Prior Spine Surgery. Neuromodulation: Technology at the Neural Interface. 2022;25(5):648-56.
13. Kurt E, Noordhof RK, van Dongen R, Vissers K, Henssen D, Engels Y. Spinal Cord Stimulation in Failed Back Surgery Syndrome: An Integrative Review of Quantitative and Qualitative Studies. Neuromodulation. 2022;25(5):657-70.
14. Conger A, Sperry BP, Cheney CW, Burnham TM, Mahan MA, Onofrei LV, et al. The Effectiveness of Spinal Cord Stimulation for the Treatment of Axial Low Back Pain: A Systematic Review with Narrative Synthesis. Pain Med. 2020;21(11):2699-712.
15. Kapural L, Jameson J, Johnson C, Kloster D, Calodney A, Kosek P, et al. Treatment of nonsurgical refractory back pain with high-frequency spinal cord stimulation at 10 kHz: 12-month results of a pragmatic, multicenter, randomized controlled trial. Journal of neurosurgery Spine. 2022:1-12.
16. Fishman M, Cordner H, Justiz R, Provenzano D, Merrell C, Shah B, et al. Twelve-Month results from multicenter, open-label, randomized controlled clinical trial comparing differential target multiplexed spinal cord stimulation and traditional spinal cord stimulation in subjects with chronic intractable back pain and leg pain. Pain pract. 2021;Vol.21(8):912-23p.
17. North J, Loudermilk E, Lee A, Sachdeva H, Kaiafas D, Washabaugh E, et al. Outcomes of a Multicenter, Prospective, Crossover, Randomized Controlled Trial Evaluating Subperception Spinal Cord Stimulation at ⩽1.2 kHz in Previously Implanted Subjects. Neuromodulation. 2020;Vol.23(1):102-8p.

18. Eldabe S, Duarte R, Gulve A, Williams H, Garner F, Brookes M, et al. Analgesic Efficacy of "Burst" and Tonic (500 Hz) Spinal Cord Stimulation Patterns: a Randomized Placebo-Controlled Crossover Study. Neuromodulation. 2021;Vol.24(3):471-8p.
19. Leong SL, De Ridder D, Deer T, Vanneste S. Potential Therapeutic Effect of Low Amplitude Burst Spinal Cord Stimulation on Pain. Neuromodulation. 2021;Vol.24(3):574-80p.
20. Tate JL, Stauss T, Li S, Rotte A, Subbaroyan J. A Prospective, Multi-Center, Clinical Trial of a 10-kHz Spinal Cord Stimulation System in the Treatment of Chronic Pelvic Pain. Pain pract. 2021;21(1):45-53.
21. Benyamin R, Galan V, Hatheway J, Kim P, Choi D, Falowski S, et al. Options: A Prospective, Open-Label Study of High-Dose Spinal Cord Stimulation in Patients with Chronic Back and Leg Pain. Pain physician. 2020;23(1):87-98.
22. Russo M, Brooker C, Cousins MJ, Taylor N, Boesel T, Sullivan R, et al. Sustained Long-Term Outcomes With Closed-Loop Spinal Cord Stimulation: 12-Month Results of the Prospective, Multicenter, Open-Label Avalon Study. Neurosurgery. 2020;87(4):E485-E95.
23. Deer TR, Patterson DG, Baksh J, Pope JE, Mehta P, Raza A, et al. Novel Intermittent Dosing Burst Paradigm in Spinal Cord Stimulation. Neuromodulation. 2021;24(3):566-73.
24. Gupta M, Scowcroft J, Kloster D, Guirguis M, Carlson J, McJunkin T, et al. 10-kHz Spinal Cord Stimulation for Chronic Postsurgical Pain: Results From a 12-Month Prospective, Multicenter Study. Pain pract. 2020;20(8):908-18.
25. Karri J, Orhurhu V, Wahezi S, Tang T, Deer T, Abd-Elsayed A. Comparison of Spinal Cord Stimulation Waveforms for Treating Chronic Low Back Pain: Systematic Review and Meta-Analysis. Pain physician. 2020;23(5):451-60.
26. Lamer TJ, Moeschler SM, Gazelka HM, Hooten WM, Bendel MA, Murad MH. Spinal Stimulation for the Treatment of Intractable Spine and Limb Pain: A Systematic Review of RCTs and Meta-Analysis. Mayo Clin Proc. 2019;94(8):1475-87.
27. Rigoard P, Billot M, Ingrand P, Durand-Zaleski I, Roulaud M, Peruzzi P, et al. How Should we Use Multicolumn Spinal Cord Stimulation to Optimize Back Pain Spatial Neural Targeting? A Prospective, Multicenter, Randomized, Double-Blind, Controlled Trial (ESTIMET Study). Neuromodulation. 2021;Vol.24(1):86-101p.
28. Hamm-Faber TE, Gultuna I, van Gorp EJ, Aukes H. High-Dose Spinal Cord Stimulation for Treatment of Chronic Low Back Pain and Leg Pain in Patients With FBSS, 12-Month Results: A Prospective Pilot Study. Neuromodulation. 2020;23(1):118-25.
29. Deer T, Wilson D, Schultz D, Falowski S, Tavel E, Moore G, et al. Ultra-Low Energy Cycled Burst Spinal Cord Stimulation Yields Robust Outcomes in Pain, Function, and Affective Domains: A Subanalysis From Two Prospective, Multicenter, International Clinical Trials. Neuromodulation. 2022;25(1):137-44.
30. Bolash R, Creamer M, Rauck R, Vahedifar P, Calodney A, Fox I, et al. Multi-waveform Spinal Cord Stimulation with High Frequency Electromagnetic Coupled (HF-EMC) Powered Implanted Electrode Array and Receiver for the Treatment of Chronic Back and Leg Pain (SURF Study). Pain physician. 2022;25(1):67-76.
31. Paz-Solis J, Thomson S, Jain R, Chen L, Huertas I, Doan Q. Exploration of High- and Low-Frequency Options for Subperception Spinal Cord Stimulation Using Neural Dosing Parameter Relationships: The HALO Study. Neuromodulation. 2022;25(1):94-102.
32. Motov S, Aftahy K, Jorger AK, Wagner A, Meyer B, Shiban E. High-frequency spinal cord stimulation in failed back surgery syndrome patients with predominant low back pain-single-center experience. Neurosurg Rev. 2021;44(5):2809-18.
33. Deer TR, Grider JS, Lamer TJ, Pope JE, Falowski S, Hunter CW, et al. A Systematic Literature Review of Spine Neurostimulation Therapies for the Treatment of Pain. Pain Med. 2020;21(7):1421-32.

34. Mekhail N, Levy RM, Deer TR, Kapural L, Li S, Amirdelfan K, et al. Durability of Clinical and Quality-of-Life Outcomes of Closed-Loop Spinal Cord Stimulation for Chronic Back and Leg Pain: a Secondary Analysis of the Evoke Randomized Clinical Trial. JAMA Neurol. 2022;Vol.79(3):251-60p.
35. Canos-Verdecho A, Abejon D, Robledo R, Izquierdo R, Bermejo A, Gallach E, et al. Randomized Prospective Study in Patients With Complex Regional Pain Syndrome of the Upper Limb With High-Frequency Spinal Cord Stimulation (10-kHz) and Low-Frequency Spinal Cord Stimulation. Neuromodulation. 2021;24(3):448-58.
36. Remacle T, Mauviel S, Renwart HJ, Ghassempour K, Belle F, Luckers O, et al. Long-Term Multicolumn-Lead Spinal Cord Stimulation Efficacy in Patients with Failed Back Surgery Syndrome: A Six-Year Prospective Follow-up Study. World Neurosurg. 2020;142:e245-e52.
37. Goudman L, De Smedt A, Eldabe S, Rigoard P, Linderoth B, De Jaeger M, et al. High-dose spinal cord stimulation for patients with failed back surgery syndrome: a multicenter effectiveness and prediction study. Pain. 2021;162(2):582-90.
38. Mekhail N, Levy RM, Deer TR, Kapural L, Li S, Amirdelfan K, et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. The lancet. 2020;Neurology. Vol.19(2):123-34p.
39. Cordero Tous N, Sanchez Corral C, Ortiz Garcia IM, Jover Vidal A, Galvez Mateos R, Olivares Granados G. High-frequency spinal cord stimulation as rescue therapy for chronic pain patients with failure of conventional spinal cord stimulation. Eur J Pain. 2021;25(7):1603-11.
40. Galan V, Scowcroft J, Chang P, Li S, Staats P, Subbaroyan J, et al. Ten kHz spinal cord stimulation for the treatment of chronic peripheral polyneuropathy: 12-Month results from prospective open-label pilot study. Pain pract. 2021;21(8):898-906.
41. Kallewaard JW, Gultuna I, Hoffmann V, Elzinga L, Munnikes R, Verbrugge L, et al. 10 kHz Spinal Cord Stimulation for the Treatment of Failed Back Surgery Syndrome with Predominant Leg Pain: Results from a Prospective Study in Patients from the Dutch Healthcare System. Pain pract. 2021;21(5):490-500.
42. Perez C, Rojo E, Margarit C, Sanchez N, Blanco T, Munoz M, et al. 24-month Real-World Study of Spinal Cord Stimulation in Failed Back Surgery Patients with Refractory Pain. Pain physician. 2021;24(6):479-88.
43. McNicol E, Ferguson M, Bungay K, Rowe EL, Eldabe S, Gewandter JS, et al. Systematic Review of Research Methods and Reporting Quality of Randomized Clinical Trials of Spinal Cord Stimulation for Pain. The Journal of Pain. 2021;22(2):127-42.
44. Duarte RV, McNicol E, Colloca L, Taylor RS, North RB, Eldabe S. Randomized Placebo-/Sham-Controlled Trials of Spinal Cord Stimulation: A Systematic Review and Methodological Appraisal. Neuromodulation. 2020;23(1):10-8.
45. Vallejo R, Gupta A, Cedeno DL, Vallejo A, Smith WJ, Thomas SM, et al. Clinical Effectiveness and Mechanism of Action of Spinal Cord Stimulation for Treating Chronic Low Back and Lower Extremity Pain: a Systematic Review. Curr Pain Headache Rep. 2020;24(11):70.
46. McClure JJ, Desai BD, Ampie L, You W, Smith JS, Buchholz AL. A Systematic Review of the Cost-Utility of Spinal Cord Stimulation for Persistent Low Back Pain in Patients With Failed Back Surgery Syndrome. Global Spine Journal. 2021;11(1_suppl):66S-72S.
47. Niyomsri S, Duarte RV, Eldabe S, Fiore G, Kopell BH, McNicol E, et al. A Systematic Review of Economic Evaluations Reporting the Cost-Effectiveness of Spinal Cord Stimulation. Value Health. 2020;23(5):656-65.
48. Blackburn AZ, Chang HH, DiSilvestro K, Veeramani A, McDonald C, Zhang AS, et al. Spinal Cord Stimulation via Percutaneous and Open Implantation: Systematic Review and Meta-Analysis Examining Complication Rates. World Neurosurg. 2021;154:132-43.e1.
49. Moens M, Goudman L, Brouns R, Valenzuela Espinoza A, De Jaeger M, Huysmans E, et al. Return to Work of Patients Treated With Spinal Cord Stimulation for Chronic Pain: A Systematic Review and Meta-Analysis. Neuromodulation. 2019;22(3):253-61.

50. Smith CA, Roman J, Mammis A. The Role of Spinal Cord Stimulation in Reducing Opioid Use in the Setting of Chronic Neuropathic Pain: A Systematic Review. Clin J Pain. 2022;38(4):285-91.
51. Hagedorn JM, Romero J, Ha CT, D'Souza RS. Patient Satisfaction With Spinal Cord Stimulation and Dorsal Root Ganglion Stimulation for Chronic Intractable Pain: A Systematic Review and Meta-Analysis. Neuromodulation.
52. Duarte RV, Soliday N, Leitner A, Taylor RS. Health-Related Quality of Life Associated With Pain Health States in Spinal Cord Stimulation for Chronic Neuropathic Pain. Neuromodulation. 2021;24(1):142-9.
53. Amirdelfan K, Yu C, Doust MW, Gliner BE, Morgan DM, Kapural L, et al. Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT. Qual Life Res. 2018;Vol.27(8):2035-44p.
54. Eldabe S, Duarte RV, Gulve A, Thomson S, Baranidharan G, Houten R, et al. Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility and cost-effectiveness (TRIAL-STIM)? A randomised controlled trial. Pain. 2020;Vol.161(12):2820-9p.
55. Goudman L, De Smedt A, Putman K, Moens M, Discover C. Long-term quality of life and work status after high-dose spinal cord stimulation in patients with failed back surgery syndrome: a secondary analysis of real-world data. J Neurosurg Spine. 2020;34(3):440-8.
56. Head J, Mazza J, Sabourin V, Turpin J, Hoelscher C, Wu C, et al. Waves of Pain Relief: A Systematic Review of Clinical Trials in Spinal Cord Stimulation Waveforms for the Treatment of Chronic Neuropathic Low Back and Leg Pain. World Neurosurg. 2019;131:264-74.e3.
57. NICE. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. Technology appraisal guidance (TA159). UK: National Institute of Health and Care Excellence (NICE); 2008.
58. NICE. Senza spinal cord stimulation system for delivering HF10 therapy to treat chronic neuropathic pain. Medical technologies guidance (MTG41). National Institute of Health and Care Excellence (NICE); 2019.
59. Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur J-P, Paulus W, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. Eur J Neurol. 2016;23(10):1489-99.
60. (Quality) OH. 10-kHz High-Frequency Spinal Cord Stimulation for Adults With Chronic Noncancer Pain: A Health Technology Assessment. Ont Health Technol Assess Ser. 2020;20(6):1-109.
61. Malinowski MN, Jain S, Jassal N, Deer T. Spinal cord stimulation for the treatment of neuropathic pain: expert opinion and 5-year outlook. Expert Rev Med Devices. 2020;17(12):1293-302.
62. Malinowski MN, Chopra PR, Tieppo Francio V, Budwany R, Deer TR. A narrative review and future considerations of spinal cord stimulation, dorsal root ganglion stimulation and peripheral nerve stimulation. Curr Opin Anaesthesiol. 2021;34(6):774-80.
63. Hagedorn JM, Falowski SM, Blomme B, Capobianco RA, Yue JJ. Burst spinal cord stimulation can attenuate pain and its affective components in chronic pain patients with high psychological distress: results from the prospective, international TRIUMPH study. Spine J. 2022;22(3):379-88.
64. Chakravarthy K, Malayil R, Kirketeig T, Deer T. Burst Spinal Cord Stimulation: A Systematic Review and Pooled Analysis of Real-World Evidence and Outcomes Data. Pain Med. 2019;20(Supplement_1):S47-S57.
65. Mekhail N, Visnjevac O, Azer G, Mehanny DS, Agrawal P, Foorsov V. Spinal Cord Stimulation 50 Years Later: Clinical Outcomes of Spinal Cord Stimulation Based on Randomized Clinical Trials-A Systematic Review. Reg Anesth Pain Med. 2018;43(4):391-406.
66. Deer TR, Falowski SM, Moore GA, Hutcheson JK, Pena I, Candido K, et al. Passive Recharge Burst Spinal Cord Stimulation Provides Sustainable Improvements in Pain and Psychosocial Function: 2-year Results From the TRIUMPH Study. Spine. 2022;47(7):548-56.
67. Goudman L, De Smedt A, Forget P, Eldabe S, Moens M. High-Dose Spinal Cord Stimulation Reduces Long-Term Pain Medication Use in Patients With Failed Back Surgery Syndrome Who Obtained at Least 50% Pain Intensity and Medication Reduction During a Trial Period: A Registry-Based Cohort Study. Neuromodulation. 2021;24(3):520-31.