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Systematic review and network meta-analysis of randomized trial evidence of spinal cord stimulation for chronic pain

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ABSTRACT

Background/importance Existing systematic reviews and meta-analyses of randomized trials of spinal cord stimulation (SCS) for people with chronic pain have consistently excluded direct comparisons between different types of SCS and are therefore at major risk of publication bias.

Objective The aim of this systematic review and network meta-analysis (NMA) was to combine both direct and indirect randomized trial evidence on treatment effects of SCS for pain intensity, physical function, and health-related quality of life (HRQoL).

Evidence review MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and WikiStim were searched from inception to December 19, 2024 for parallel-arm randomized trials comparing SCS to conventional medical management (CMM), an active intervention (including other types of SCS) or placebo for adults with chronic pain. The measure of treatment effect for the primary outcome (pain intensity) and for secondary outcomes (physical function, HRQoL) was mean difference (MD) and 95% CI, and for responder rate was OR and 95% CI. NMA was performed in a frequentist framework.

Findings 23 reports of 16 unique randomized trials were included. All but one trial was assessed as having a high risk of bias. Results of NMA show significant reductions in pain intensity scores (0–10) at last follow-up (within the first 24 months) were observed with all types of SCS compared with CMM, with MD range from −2.37 (95% CI −3.54 to −1.20) to −5.55 (95% CI −7.34 to −3.76; 15 trials, 1479 participants; low certainty evidence). Improvements in physical function (MD range from −0.20, 95% CI −10.24 to 9.85) to −31.04 (95% CI −44.36 to −17.33; 8 trials, 837 participants; low certainty evidence) and HRQoL (MD range from 0.15 (95% CI 0.09 to 0.20) to 0.29 (95% CI 0.20 to 0.37; 8 trials, 942 participants; moderate certainty evidence) were observed for SCS compared with CMM at 6 months. Patients were found to have a higher likelihood to be a responder to treatment (ie, ≥50% reduction in pain intensity) with all forms of SCS in comparison to CMM at last follow-up (OR range from 9.75 (95% CI 4.07 to 23.25) to OR 63.4 (18.76 to 212.55; 13 trials, 1887 participants; very low certainty evidence). Clinically meaningful improvements were observed for pain intensity, HRQoL, and in some comparisons for physical function.

Conclusions There is low to moderate certainty of evidence that all types of SCS are superior to CMM for the management of chronic pain conditions.

INTRODUCTION

Spinal cord stimulation (SCS) is a treatment option for people with chronic pain who do not obtain satisfactory pain relief with conventional medical management (CMM). SCS is commonly indicated for chronic pain etiologies including persistent spinal pain syndrome type 1 and type 2 (PSPS-T1 and PSPS-T2), complex regional pain syndrome (CRPS), painful diabetic neuropathy (PDN), and other neuropathic pain syndromes.[1 2] The only type of stimulation available for several decades was low-frequency fixed-output stimulation (herein referred to as conventional SCS).[3] However, the last decade has seen the development and adoption of a number of novel and distinct SCS modalities such as high-frequency SCS (HF-SCS), burst SCS and differential target multiplexed (DTM) SCS, and also EVOKE closed-loop SCS (closed-loop system maintaining system amplitude at or above ECAP level).[4–8]

In order to demonstrate superiority, and in compliance with the US Food and Drug Administration standards, novel waveforms therapies have typically been compared with established therapies. However, recent systematic reviews of SCS have excluded randomized trials that compared different types of SCS with no clear justification for this omission; therefore, disregarding a considerable body of evidence.[9 10] Furthermore, these previous reviews, and others,[11–16] have been limited to meta-analysis of data based on head-to-head trials (or "direct") trial comparisons only. Network meta-analysis (NMA) allows a more comprehensive assessment by combination of direct and indirect evidence (eg, allowing estimation effect for treatment A vs C indirectly from a trial directly comparing treatment A vs B and a trial directly comparing B vs C), including all relevant data from studies with at least two treatment arms and producing a more precise treatment effect estimate than direct evidence from randomized trials or indirect evidence could alone.[17–19]

The aim of this study was to evaluate the relative effectiveness of the different types of SCS for the management of chronic pain. Considering the

findings of published randomized controlled trials (RCTs), we hypothesize that novel SCS modalities (HF-SCS, burst, DTM, and closed-loop SCS) provide superior pain relief and greater improvements in physical function and health-related quality of life (HRQoL) compared with conventional SCS and other comparators in patients with chronic pain conditions. The current systematic review and NMA overcomes the methodological limitations of previous reviews and provides the first assessment of the relative effectiveness of the different types of SCS currently used in clinical practice for the management of chronic pain.

METHODS

The systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses incorporating NMA (PRISMA-NMA).[20] The protocol for the review is registered on PROSPERO as CRD42023449215. A protocol was not submitted for publication in a peer-reviewed journal.

Search strategy

The databases MEDLINE (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL via The Cochrane Library), Embase, and WikiStim were searched from inception to December 19, 2024 by a reviewer (MMa). The search strategies were designed using a combination of both indexing and free-text terms with no restriction on language or date. Full translations of articles in languages other than those of the author's native languages would be obtained through native speakers in our institutions. The search strategies are presented in online supplemental material 1. Database searches were supplemented by screening reference lists of topic-relevant systematic reviews and eligible studies.

Study selection

The citations identified were assessed for inclusion in the review using a two-stage process. First, two reviewers (RVD and NS) independently screened all titles and abstracts identified by the database searches to identify potentially relevant articles to be retrieved. Second, full-text copies of these studies were obtained and assessed independently by two reviewers (RVD and NS) for inclusion, using consensus for any disagreements, and if necessary, a third reviewer (SE) would be consulted. Studies were eligible for inclusion if they met the following criteria: (1) adult patients (18 years of age or older) with chronic pain; (2) evaluation of SCS (any stimulation paradigm); (3) compared with CMM, an active intervention (including another stimulation paradigm) or placebo; (4) assessed pain intensity, physical function, or HRQoL; (5) in a parallel group randomized trial study design (ie, sample size estimation was based on a parallel-group design); and (6) reported in a full-text publication.

Outcomes

The primary outcome was pain intensity score measured with the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS). Secondary outcomes were:

- Responder rate (the proportion of patients achieving ≥50% reduction in pain).[21]
- Physical function (eg, Oswestry Disability Index scale).
- HRQoL (eg, EuroQol 5-Dimension questionnaire (EQ-5D) utility scores).

Primary and secondary outcomes were considered at last follow-up of the trial (within the first 24 months) and at 6 months postimplantation, where available. As patient treatment group crossover was permitted in 8 RCTs at 6 months postimplantation,[3 6 22–27] and in 1 RCT at 24 months,[8] only data before crossover were considered for inclusion in analysis.

Risk of bias assessment

Risk of bias (RoB) for the primary outcome was assessed by using the revised Cochrane RoB tool (RoB 2.0).[28] RoB assessment of the included studies was undertaken by one reviewer (RVD) and verified for agreement by a second reviewer (SN). Authors involved in the systematic review who were involved in the original studies did not assess RoB of included randomized trials. Any disagreements were resolved by consensus, and if necessary, a third reviewer (SE) would be consulted.

Data extraction and statistical analysis

Data extracted were study author and year of publication, study design characteristics, demographic data (ie, age and sex), details on the intervention and comparators, and outcome data, including the number of participants and the measurement time of the outcome. Data extraction was performed by one reviewer (SN) and checked for accuracy by a second reviewer (RVD).

Outcome data were extracted for inclusion in analysis in the first instance from intention-to-treat (ITT) populations with or without imputed missing data (eg, last value carried forward). Where data from ITT populations were not available, outcome data for those completing to 6 months and last follow-up in the trial, respectively, were included in analysis. Missing data were not requested from the original study authors. Outcome data available only in graphical format were extracted using WebPlot Digitizer (https://automeris.io/WebPlotDigitizer/).

To standardize outcome data to a single scale for pain intensity, it was assumed that the VAS scale (0–10 cm) and the NRS scale (0–10) were equivalent, and the VAS scale (0–100 mm) was converted by dividing pain scores by 10.[29] One RCT reported pain intensity separately during the day and during the night.[26] To allow pooling of pain intensity outcome data, an average of the day and night mean pain scores and data was used. Where included studies reported pain intensity scores and/or responder rates for (lower) back pain and for leg pain separately, in our primary approach, we included back pain scores in analysis and conducted sensitivity analysis including leg pain scores.

The measure of treatment effect for the primary outcome (pain intensity) and for continuous outcomes physical function and HRQoL was mean difference (MD) and 95% CI and for responder rate was OR and 95% CI.

Network meta-analysis

In addition to direct comparisons of SCS and CMM, and comparisons of SCS made within the included trials, NMA was performed to allow for indirect comparisons to be made between all interventions included within networks for each outcome (online supplemental figures S1 and S2).

Conventional low-frequency SCS delivers evenly spaced pulses at a fixed amplitude, while closed-loop SCS continuously adjusts amplitude in real time based on evoked compound action potentials (ECAPs), resulting in a non-constant waveform.[4] This dynamic modulation may affect clinical outcomes and patient experience, justifying its classification as a distinct SCS type rather than grouping it with conventional SCS.

The assumption of transitivity was considered within our specific inclusion criteria and outcome definitions to ensure consistent study designs and patient populations when

constructing treatment networks. We assessed the level of clinical heterogeneity present between trials by comparison of trial (eg, comparator type, duration of follow-up) and participant characteristics (eg, age, sex, duration of pain) and deemed that some clinical heterogeneity of trial designs (including control groups, see below), patient populations, and treatment protocols was present, but included studies were not so inconsistent to violate the assumption of transitivity. Due to the presence of this clinical heterogeneity, random-effects NMA was used as a conservative approach, and heterogeneity was assessed statistically according to the I^2 statistic (the percentage of variability between trials that is due to statistical heterogeneity) and the τ^2 statistic (an absolute estimate of the between-study variance in the NMA).

Inconsistency (incoherence) was assessed globally across networks with at least one closed loop of evidence by testing between-designs based on a design-by-treatment interaction random-effects model (ie, a design-based decomposition of Cochran's Q statistic).[30] Where global inconsistency was detected (ie, p value between-designs <0.05), incoherence within loops of evidence was further explored by comparing direct and indirect estimates using node-splitting[31] using a back-calculation method[32] based on the direct evidence proportion to calculate the contribution indirect evidence had to the NMA estimates. Publication bias and small study effects were assessed using comparison-adjusted funnel plots for all outcomes,[33] including Egger's test for asymmetry for NMAs with at least 10 comparisons.

NMA was performed in a frequentist framework using the netmeta command[34 35] in RStudio V.4.3.1. The method assumes a common heterogeneity variance for tau-squared. We used the default settings in netmeta, including the default method for estimating tau-squared (a special case of DerSimonian-Laird estimate) as we had no grounds or a good reason for selecting any alternative methods.

Control group responder rates and pain intensity scores

Nine included trials used CMM, one trial used physical therapy, and seven included trials used conventional SCS (compared with other types of SCS) as a control group. Therefore, we anticipated variability in control group responder rates and pain intensity scores, which may impact relative treatment effect sizes estimated within the NMA of different types of SCS compared with CMM and different types of SCS compared with each other. We calculated responder rates and mean (95% CI) values for each control group and compared these results by type of control group and over time using forest plots (produced in Stata V.18),[36] to aid with interpretation of NMA results.

Certainty of evidence

We present NMA results for all outcomes in a summary of findings table, adapted from the template tables developed by Yepes-Nuñez *et al*.[37] Comparisons are presented for SCS interventions against CMM as reference treatment, and for other SCS interventions against conventional SCS (ie, low-frequency fixed-output SCS). We assessed the confidence in the NMA results (ie, a framework similar to Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of the evidence) according to the Confidence in Network Meta-Analysis (CINeMA) approach,[38] which assesses six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (inconsistency). We downgraded evidence by one level if we considered the limitation relating to a domain to be "serious" and two levels if we considered it to be "very serious." Certainty of evidence was assessed by SN and RVD with input from coauthors.

Deviations from protocol: In addition to reporting outcomes at 6-month follow-up, we elected to report pain intensity at the last available follow-up because some studies did not report data at the 6-month time point. To maximize data inclusion and provide a more comprehensive analysis, we also used the longest follow-up within the first 24 months for each study. We did not evaluate the proportion of patients with ≥80% reduction in pain intensity due to limited reporting of this outcome. Subgroup meta-analyses by pain diagnosis were not conducted as these have been previously conducted for PSPS-T1,[39] PSPS-T2,[40] and PDN.[41] An NMA evaluating SCS for CRPS may be addressed in a future manuscript. Finally, the current manuscript does not explore whether the effectiveness of SCS varies by type of pain; this may also be the subject of subsequent work.

RESULTS

The searches resulted in the identification of 2548 potentially eligible records after deduplication. Following the screening of titles and abstracts, 32 records were retrieved for assessment of the full-text publication. After review of the full-text publications, 23 reports of 16 unique studies were included in the review and NMA. All the reports included for each of the studies identified are cited in table 1. Citations and reasons why studies were excluded on review of the full-text publication are listed in online supplemental material 2. The PRISMA flow diagram detailing the study selection process is presented in figure 1.

The characteristics of the included randomized trials are summarized in table 1. In the included trials, conventional SCS as the intervention of interest or comparator was evaluated versus CMM in 4 RCTs,[3 25 26 42] dorsal root ganglion stimulation (DRGS) in 1 RCT,[43] DTM SCS in 2 RCTs,[7 27] HF-SCS in 2 RCTs,[5 44] closed-loop SCS in 1 RCT,[8] and physical therapy in 1 RCT.[45] Comparisons of HF-SCS vs CMM were performed in 2 RCTs,[23 24] DTM SCS versus CMM in 1 RCT,[22] and burst SCS versus CMM in 1 RCT.[6] One three-armed randomized trial compared HF-SCS, conventional SCS, and CMM.[46] Network plots for the different outcomes evaluated are presented in online supplemental figures S1 and S2. All two-arm RCTs with CMM as a comparator and follow-up longer than 6 months included optional crossover at the 6 months time point.[3 6 22–26] Only two RCTs that compared different types of SCS included an optional crossover at 6 months[27] and at 24 months.[8] Participants in the randomized trials presented with chronic pain conditions commonly managed with SCS including CRPS with upper or lower limb involvement, PSPS-T1 (chronic low back pain with or without radiculopathy and no prior surgery), PSPS-T2 (chronic low back pain with or without radiculopathy after or as a consequence of surgery), and PDN. Commonly reported pain etiologies are presented in table 1.

Risk of bias assessment

The RoB summary table for the primary outcome is presented in table 2. One study was judged as presenting some concerns for the randomization process domain due to some baseline imbalances observed including pathology and years since diagnosis.[46] There is often a lack of detail when describing the comparator, particularly if this consists of CMM. RoB due to deviations from intended interventions was not considered to be present in these instances as the population in SCS studies would already have tried several, if not all types of CMM. Further, for SCS, it is plausible for deviations from the intended intervention to occur

Table 1 Characteristics and outcomes of randomized controlled trials included in the systematic review

Author (y), follow-up duration	Country	Intervention vs comparator	Number randomized, sex, and mean age±SD	Most common diagnosis and duration of pain	Pain intensity, physical function, and HRQoL Outcomes	Key findings
Canós-Verdecho *et al* (2021)[46] 12 months	Spain	HF-SCS vs C-SCS, CMM	HF-SCS N=10, F=7 (70%), 46.3±10.0 y C-SCS N=12, F=8 (66.7%), 48.7±8.8 y CMM N=19, F=17 (89.5%), 51.2±11.1 y	CRPS Type I with upper limb involvement HF-SCS 4.7±6 y (range 1–19) C-SCS 1.8±0.9 y (range 1–3) CMM 2.3±0.5 y (range 2–3)	Pain intensity (NRS) Improvement in ODI Absolute improvement in pain Relative improvement in pain (%)	(-) p=0.257 (-) p=0.089 ↑ p=0.019 (-) p=0.097
De Andres *et al* (2017)[44] 12 months	Spain	HF-SCS vs C-SCS	HF-SCS N=26, F=11 (42.3%), 51.6±9.3 y C-SCS N=29, F=18 (62.1%), 53.8±11.4 y	PSPS-T2≥6 months	Reduction in pain Improvement in ODI	(-) p=0.560 (-) p=0.059
de Vos *et al* (2014)[42 73] 6 months	The Netherlands, Denmark, Belgium, and Germany	C-SCS vs CMM	C-SCS N=40, F=15 (37.5%), 58±11 y CMM N=20, F=7 (35%), 61±12 y	PDN C-SCS 7±6 y CMM 7±6 y	Proportion of patients with ≥50% pain reduction Pain intensity (VAS) HRQoL (EQ-5D utility)	↑ p<0.001 ↑ p<0.001 ↑ p<0.05
Deer *et al* (2017)[43] 12 months	USA	DRGS vs C-SCS	DRGS N=76, F=39 (51.3%), 52.4±12.7 y C-SCS N=76, F=39 (51.3%), 52.5±11.5 y	CRPS Type I or causalgia in the lower extremities DRG 7.5y C-SCS 6.8y	Proportion of patients with ≥50% pain reduction	↑ p<0.004
Deer *et al* (2023)[6] 12 months Crossover option at 6 months	USA	Burst SCS vs CMM	Burst SCS N=162, F=96 (59%), 58.1±13.0 y CMM N=107, F=52 (51%), 59.1±12.4 y	PSPS-T1 – nonspecific low back pain, lumbar spondylosis, radiculopathy, degenerative disc disease, spinal stenosis Burst SCS 11.9±10.6 y CMM 13.1±12.4 y	Percent pain reduction from baseline Proportion of patients with ≥50% pain reduction Improvement in ODI	↑ p<0.001 ↑ p<0.001 ↑ p<0.001
Fishman *et al* (2021)[7] 12 months	USA	DTM SCS vs C-SCS	DTM SCS N=67, F=34 (50.7%), 61.3±12.2 y C-SCS N=61, F=34 (55.7%), 60.7±11.8 y	PSPS-T2, radiculopathy, degenerative disc disease, spondylosis, mild to moderate spinal stenosis, and other DTM SCS 12.6±13.1 y C-SCS 12.9±11.2 y	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥50% LP reduction Minimal or moderate disability in ODI	DTM SCS 84%/C-SCS 51% DTM SCS 80%/C-SCS 75% DTM SCS 76%/C-SCS 62%
Kallewaard *et al* (2024)[22] 12 months Crossover option at 6 months	Belgium, Germany, the Netherlands, and Spain	DTM SCS vs CMM	DTM SCS N=51, F=29 (57%), 55.9±13.0 y CMM N=57, F=28 (49.1%), 56.9±12.8 y	PSPS-T1 – degenerative disc disease, lumbar-facet-mediated pain, radiculopathy, mild/moderate spinal stenosis, internal disc disruption/ annular tear DTM SCS 10.4±10.9 y CMM 11.6±10.8 y	Proportion of patients with ≥50% pain reduction Improvement in ODI HRQoL (EQ-5D utility)	↑ p<0.0001 ↑ p<0.001 ↑ p<0.001
Kapural *et al* (2015/2016)[5 74] 24 months	USA	HF-SCS vs C-SCS	HF-SCS N=92, F=57 (62%), 54.6±12.4 y C-SCS N=87, F=51 (58.6%), 55.2±13.4 y	PSPS-T2, radiculopathy, degenerative disc disease, spondylosis, mild to moderate spinal stenosis, and other HF-SCS 13.0±10.4 y C-SCS 14.2±12.2 y	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥50% LP reduction Minimal or moderate disability in ODI	↑ p<0.001 ↑ p=0.003 HF-SCS 65%/C-SCS 49%
Kapural *et al* (2022)[23] 24 months Crossover option at 6 months	USA	HF-SCS vs CMM	HF-SCS N=83, F=50 (60%), Mdn=53 y (29–87) CMM N=76, F=40 (53%), Mdn=58.5 y (26–77)	PSPS-T1 – degenerative disc disease, spondylosis, radiculopathy, mild/moderate spinal stenosis, spondylolisthesis, sacroiliac dysfunction HF-SCS Mdn=8.5 y (0.5–52) CMM Mdn=8 y (1–59)	Proportion of patients with ≥50% pain reduction Percentage reduction in VAS back pain HRQoL (EQ-5D utility)	↑ p<0.001 ↑p<0.001 ↑ p<0.001
Kemler *et al* (2000/2004/2008)[45 75 76] 60 months	The Netherlands	C-SCS vs PT	C-SCS N=36, F=22 (61%), 40±12 y PT N=18, F=15 (83%), 35±8 y	CRPS Type I C-SCS 40±28 m PT 34±22 m	Pain intensity (VAS) Proportion of patients with ≥50% pain reduction HRQoL	(-) p=0.25 LF-SCS 23% (7/31)/PT NR (-) p=0.80
Kumar *et al* (2007)[3 77] 24 months Crossover option at 6 months	Australia, Belgium, Canada, Israel, Italy, Spain, Switzerland, and UK	C-SCS vs CMM	C-SCS N=52, F=22 (42.3%), 48.9±10 y CMM N=48, F=27 (56.2%), 52.0±10.7 y	PSPS-T2≥6 months	Proportion of patients with ≥50% LP reduction Reduction in LBP Reduction in LP Improvement in ODI HRQoL (EQ-5D utility)	↑ p<0.001 ↑ p=0.008 ↑ p<0.0001 ↑ p<0.001 ↑ p<0.001

Continued

Table 1 Continued

Author (y), follow-up duration	Country	Intervention vs comparator	Number randomized, sex, and mean age±SD	Most common diagnosis and duration of pain	Pain intensity, physical function, and HRQoL Outcomes	Key findings
Mekhail *et al* (2020/2022/2024)[8 50 78] 36 months Crossover option at 24 months	USA	CL-SCS vs C-SCS	CL-SCS N=25, F=12 (48%), 53.0±8.3 y C-SCS N=25, F=12 (48%), 55.6±11.3 y	Degenerative disc disease, mild-moderate spinal stenosis, radiculopathy, spondylosis without myelopathy CL-SCS 17.2±12.1 y C-SCS 12.4±10.6 y	Proportion of patients with ≥50% pain reduction Percentage reduction in overall pain Improvement in ODI HRQoL (EQ-5D utility)	↑ p=0.001 ↑ p=0.01 (-) (-)
Petersen *et al* (2021)[24] 24 months Crossover option at 6 months	USA	HF-SCS vs CMM	HF-SCS N=113, F=43 (38.1%), 60.7±11.4 y CMM N=103, F=37 (35.9%), 60.8±9.9 y	PDN HF-SCS 7.4±5.7 y CMM 7.1±5.1 y	Proportion of patients with ≥50% pain reduction Pain intensity (VAS) HRQoL (EQ-5D utility)	↑ p<0.001 ↑ p<0.001 ↑ p<0.001
Rigoard *et al* (2019)[25] 12 months Crossover option at 6 months	Belgium, Canada, Colombia, France, Germany, the Netherlands, Spain, UK and USA	C-SCS vs CMM	C-SCS N=110, F=68 (61.8%), 52.8±12.5 y CMM N=108, F=64 (59.3%), 55.1±10.2 y	PSPS-T2 C-SCS 6.4±7.4 y CMM 7.0±7.1 y	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥50% LP reduction Reduction in LBP Reduction in LP Improvement in ODI	↑ p=0.036 ↑ p<0.0001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001
Slangen *et al* (2014)[26] 60 months Crossover option at 6 months	The Netherlands	C-SCS vs CMM	C-SCS N=22, F=7 (31.8%), 57.1±12.4 y CMM N=14, F=5 (35.7%), 56.5±8.0 y	PDN C-SCS 6.0±5.1 y CMM 4.9±3.6 y	Proportion of patients with ≥50% pain reduction (day) Proportion of patients with ≥50% pain reduction (night) Pain intensity during the day (NRS) Pain intensity during the night (NRS) HRQoL (EQ-5D utility)	↑ p<0.001 ↑ p<0.01 ↑ p<0.001 ↑ p<0.003 (-)
White *et al* (2024)[27] 12 months Crossover option at 6 months	USA	DTM SCS vs C-SCS	DTM SCS N=51, F=29 (56.9%), 62.9±13.5 y C-SCS N=54, F=33 (61.1%), 59.6±12.1 y	PSPS-T1—radiculopathy, degenerative disc disease, spondylosis, mild/moderate stenosis DTM SCS 9.5±8.0 y C-SCS 9.4±8.4 y	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥50% LP reduction Improvement in ODI HRQoL (EQ-5D utility)	DTM SCS 88%/C-SCS 28% DTM SCS 93%/C-SCS 36% ↑ p<0.01 ↑ p<0.01

(-) no statistically significant differences between groups.↑ statistically significant between groups in favor of intervention group.
.CL-SCS, closed loop SCS; CMM, conventional medical management; CRPS, complex regional pain syndrome; C-SCS, conventional SCS; DRGS, dorsal root ganglion stimulation; DTM, differential target multiplexed; F, female; HF-SCS, high-frequency spinal cord stimulation; HRQoL, health-related quality of life; LBP, low back pain; LP, leg pain; Mdn, median; NR, not reported; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; PDN, painful diabetic neuropathy; PSPS-T1, persistent spinal pain syndrome type 1; PT, physiotherapy; VAS, Visual Analog Scale; y, years.

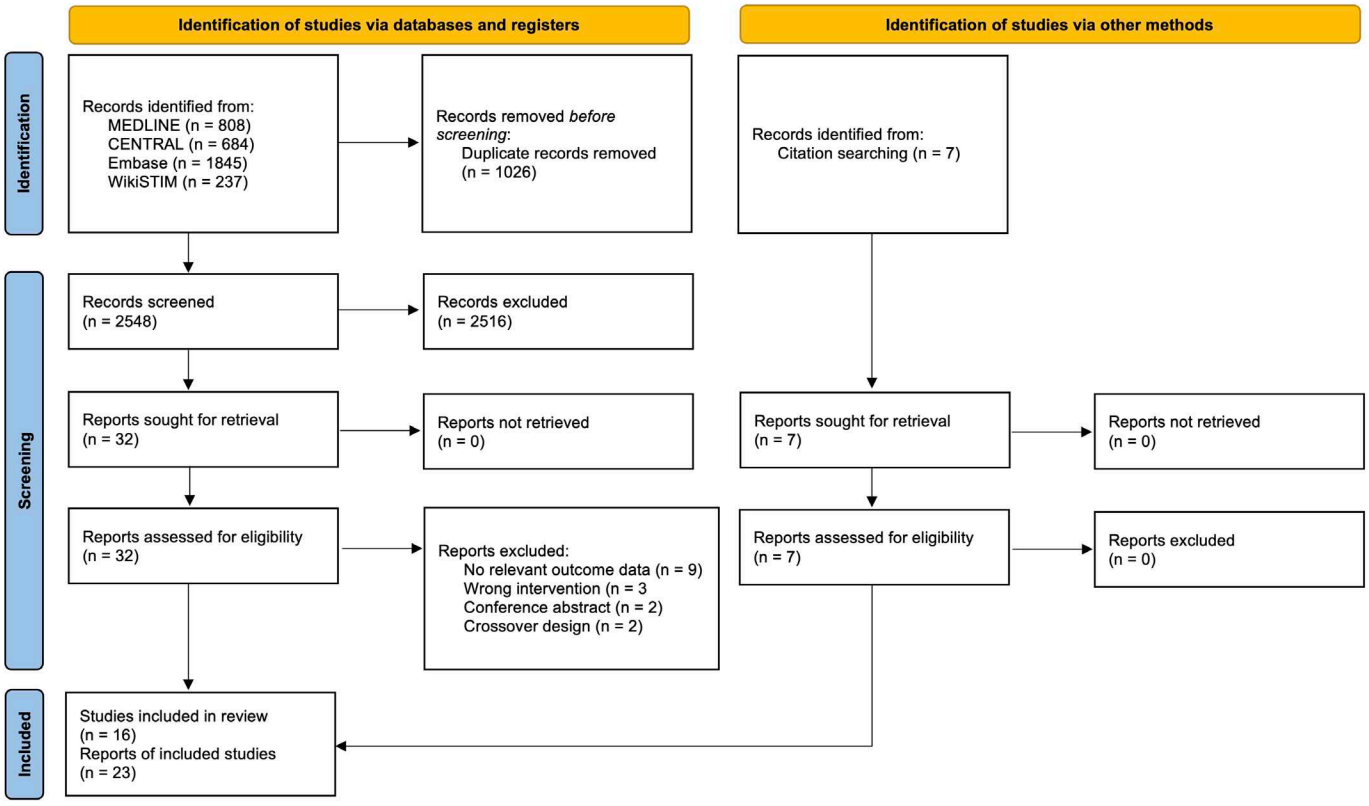

Figure 1 PRISMA 2020 flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(eg, variation in stimulation received due to postural changes or limited use of the device). Only one study[8] reported device metrics or use of the SCS system throughout the study. Such information is essential to evaluate adherence to the intervention. Most studies were open-label trials with outcome assessors aware of the interventions received and were therefore judged to have a high RoB for outcome measurement. For participant-reported outcomes, the outcome assessor is the study participant; therefore, the subjective nature of the pain assessments and the plausibility that knowledge of the received intervention and beliefs of potential beneficial effects could have influenced these outcomes. As such, open-label trials were judged to have high risk of bias for the outcome measurement domain. In one study, patients, investigators, and staff, including outcome assessors, were blinded, and the study was therefore judged to have low RoB for the outcome measurement domain.[8] Studies were judged as presenting some concerns for the selection of the reported results domain where no study protocol was available or not explicitly mentioned that a prespecified analysis plan was followed. The overall bias for 15 studies was high because at least one domain was judged to have a high RoB, and the overall bias for 1 study was low.

Table 2 Risk of bias assessment

Author (year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Canós-Verdecho *et al* (2021)[46]	Some concerns	Low	Low	High	Some concerns	High
De Andres *et al* (2017)[44]	Low	Low	Low	High	Some concerns	High
de Vos *et al* (2014)[42]	Low	Low	Low	High	Some concerns	High
Deer *et al* (2017)[43]	Low	Low	Some concerns	High	Some concerns	High
Deer *et al* (2023)[6]	Low	Low	Low	High	Low	High
Fishman *et al* (2021)[7]	Low	Low	Some concerns	High	Low	High
Kallewaard *et al* (2024)[22]	Low	Low	Low	High	Low	High
Kapural *et al* (2015)[5]	Low	Low	Low	High	Some concerns	High
Kapural *et al* (2022)[23]	Low	Low	Low	High	Low	High
Kemler *et al* (2000)[45]	Low	Low	Some concerns	High	Some concerns	High
Kumar *et al* (2007)[3]	Low	Low	Low	High	Some concerns	High
Mekhail *et al* (2020)[8]	Low	Low	Low	Low	Low	Low
Petersen *et al* (2021)[24]	Low	Low	Low	High	Low	High
Rigoard *et al* (2019)[25]	Low	Low	Low	High	Low	High
Slangen *et al* (2014)[26]	Low	Low	Low	High	Some concerns	High
White *et al* (2024)[27]	Low	Low	Low	High	Low	High

NMA results

Pain intensity score

15 trials (1479 participants),[3 5–8 22–27 42 44–46] including conventional SCS, HF-SCS, Burst SCS, closed-loop SCS, DTM SCS, physical therapy, and CMM groups, reported pain intensity at last follow-up time and at 6 months (online supplemental figure S1A).

Statistically significant reductions in pain intensity scores at last follow-up were observed with all types of SCS compared with CMM (figure 2A). Reductions in pain intensity with SCS ranged between MD −2.37 (95% CI −3.54 to −1.20) and MD −5.55 (95% CI −7.34 to −3.76). Burst SCS, DTM SCS, and HF-SCS significantly reduced pain intensity at last follow-up compared with physical therapy, and DTM SCS was statistically significantly superior to both conventional SCS and HF SCS. No other statistically significant differences in pain intensity score were observed between other types of SCS (online supplemental table S1). Results for pain intensity score at 6-month follow-up are presented in online supplemental table S2.

The certainty of the evidence was low, due to serious risk of bias due to lack of blinding of pain outcomes and substantial heterogeneity. Therefore, although it is likely that SCS interventions reduce pain compared with CMM and that some types of SCS may be superior to conventional SCS, the magnitude of pain reduction is uncertain (online supplemental summary of findings table 1).

Responder rates

13 trials (1887 participants),[3 5–8 22–27 42 43] including evaluations of conventional SCS, HF-SCS, burst SCS, closed-loop SCS, DTM SCS, DRGS, and CMM groups, reported responder rates at last follow-up (online supplemental figure S1B) and 12 trials (1735 participants),[3 5–8 22–27 42] including conventional SCS, HF-SCS, burst SCS, closed-loop SCS, DTM SCS, and CMM groups, reported responder rates at 6 months (online supplemental figure S1C).

NMA results show that it is statistically significantly more likely for a patient to be considered a responder (ie, ≥50% reduction in pain intensity) with any type of SCS compared with CMM at last follow-up (figure 2B). ORs of response for different types of SCS were large and imprecise, ranging from OR 9.75 (95% CI 4.07 to 23.25) and OR 63.4 (18.76 to 212.55), likely due to very low response rates, including no responders, observed in CMM groups within the included RCTs.

There were no statistically significant differences between any type of SCS or DRGS at last follow-up (online supplemental supplement table S3). Results for the proportion of patients with ≥50% reduction in pain intensity at 6-month follow-up were similar, with the exceptions of statistically significant advantages for HF-SCS and DTM SCS over conventional SCS (online supplemental table S4).

Sensitivity analysis of the proportion of patients with ≥50% reduction in pain intensity and pain intensity scores showed similar results, and conclusions were unchanged (online supplemental table S5 to S8).

Certainty of the evidence was very low, due to serious risk of bias due to lack of blinding of pain outcomes, substantial heterogeneity, and imprecision, likely due to very low response rates, including no responders, observed in CMM groups within the included RCTs. Therefore, although it is likely that SCS interventions reduce pain by ≥50% compared with CMM and that some types of SCS may be superior to conventional SCS, the magnitude of improvement in responder rates is very uncertain (online supplemental summary of findings table 2).

Physical function

Eight trials (837 participants),[3 5 6 8 22 25 44 46] including conventional SCS, HF-SCS, Burst SCS, closed-loop SCS, DTM SCS, and CMM groups, reported physical function at 6 months (online supplemental figure S2A).

Conventional SCS (MD −7.31, 95% CI −14.28 to −0.33), burst SCS (MD −31.04, 95% CI −44.36 to −17.33), DTM (−24.00, 95% CI −35.01 to −12.99), and closed-loop SCS (MD −16.01, 95% CI −29.13 to −2.88) were found to provide a statistically significant improvement in physical function compared with CMM at 6-month follow-up (figure 2C). No

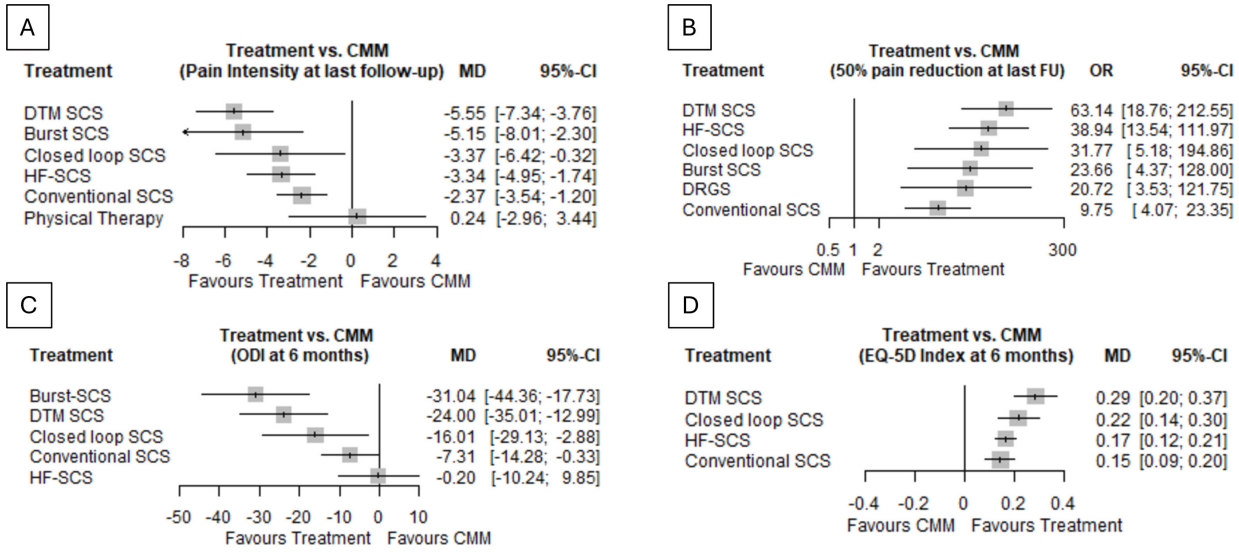

Figure 2 Network meta-analysis of (A) pain intensity score (VAS, 0–10 cm) at last follow-up; (B) proportion of patients with ≥50% reduction in pain intensity at last follow-up (ITT analysis); (C) physical function at 6-month follow-up; and (D) EQ-5D utility scores at 6-month follow-up. CMM, conventional medical management; DRGS, dorsal root ganglion stimulation; DTM, differential target multiplexed; EQ-5D, EuroQol 5-Dimension scale; FU, follow-up; HF-SCS, high-frequency spinal cord stimulation; ITT, intention-to-treat; MD, mean difference; ODI, Oswestry Disability Scale; VAS, Visual Analog Scale.

statistically significant differences were observed for HF-SCS compared with CMM (MD −0.20, 95% CI −10.24 to 9.85). Burst SCS results in statistically significant improvements in physical function compared with conventional SCS and HF-SCS. No significant differences in physical function improvements were observed between burst SCS, DTM, and closed-loop SCS (online supplemental table S9).

The certainty of the evidence was low, due to serious risk of bias due to lack of blinding and substantial heterogeneity. Therefore, although it is likely that SCS interventions improve physical function compared with CMM and that some types of SCS may be superior to conventional SCS, the magnitude of improvement is uncertain (online supplemental summary of findings table 3).

Health-related quality of life

Eight trials (942 participants),[3 8 22–26 42] including conventional SCS, HF-SCS, closed-loop SCS, DTM SCS, and CMM groups, reported EQ-5D utility scores at 6 months (online supplemental S2B).

Statistically significant improvements in EQ-5D utility scores were observed for all types of SCS compared with CMM (figure 2D). Improvements in EQ-5D utility scores ranged between MD 0.15 (95% CI 0.09 to 0.20) and MD 0.29 (95% CI 0.20 to 0.37). Statistically significant advantages for closed-loop SCS and DTM SCS over conventional SCS and for DTM SCS over HF-SCS were also observed at 6 months (online supplemental table S10).

The certainty of the evidence was moderate, due to serious risk of bias. SCS interventions probably improve HRQoL compared with CMM, and some types of SCS may be superior to conventional SCS (online supplemental summary of findings table 4).

Heterogeneity, inconsistency (incoherence), and publication bias/small study effects

Substantial statistical heterogeneity was present in the NMAs of pain outcomes; for responder rates, I^2 statistics ranged between 58% and 70% and τ^2 statistics ranged from 0.50 to 0.78 and for pain intensity outcomes I^2 statistics ranged between 85% and 90% and τ^2 statistics ranged from 1.5 to 2 (online supplemental table S11). Statistically significant global incoherence was also detected for pain intensity outcomes (online supplemental table S11), but when further examining this global incoherence via node splitting of the comparisons forming closed loops in the network, no statistically significant differences were found between direct and indirect evidence contributing to the NMA estimates for these comparisons (online supplemental table S12).

Similarly, substantial statistical heterogeneity (I^2=60%, τ^2=22.09) and statistically significant global incoherence (p=0.04) was present in the NMA of physical function (online supplemental table S11), but no statistically significant differences were found between direct and indirect evidence contributing to the NMA estimates for the comparisons forming closed loops in node-splitting analyses (online supplemental table S12). There was no evidence of statistical heterogeneity in the analyses of HRQoL, and incoherence could not be assessed for this outcome due to lack of closed loops in the network (online supplemental figure S2B), (online supplemental table 11).

Therefore, we conclude that heterogeneity and global incoherence present within these analyses likely originates from differences in study and participant characteristics (table 1) and due to differences in control group results within different types of control group, particularly for pain outcomes (see Control group results section).

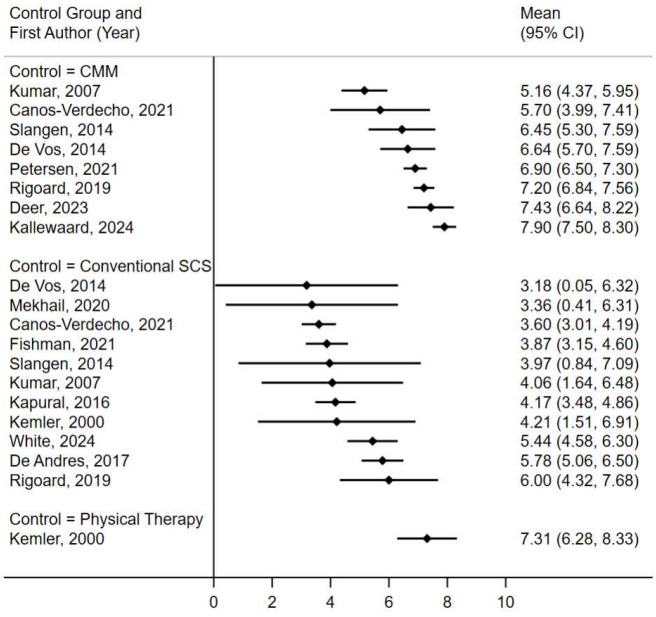

Figure 3 Pain intensity scores observed in control groups at 6 months follow-up. CMM, conventional medical management; SCS, spinal cord stimulation.

There is no evidence of publication bias or small study effects (i.e. comparison-adjusted funnel plot asymmetry) for any outcome (online supplemental figure S3 and S4). However, assessments are limited for Physical Function and HRQoL due to fewer than 10 RCTs (comparisons) contributing data to these outcomes.

Control group results

The pain intensity scores at 6-month follow-up were consistently greater with CMM and physical therapy than with conventional SCS as the control group (figure 3). While pain intensity scores for CMM at 6 months ranged between mean 5.16 (95% CI 4.37 to 5.95)[3] and mean 7.90 (95% CI 7.50 to 8.30),[22] there was generally more variability in conventional SCS groups with pain intensity scores ranging between mean 3.18 (95% CI 0.05 to 6.32)[42] and mean 6.00 (95% CI 4.32 to 7.68).[25]

In line with the pain intensity scores observed, the responder rate with CMM at 6 month follow-up ranged between 0% (95% CI 0% to 23%)[26] and 8% (95% CI 2% to 20%)[3] (figure 4). Although the responder rates with conventional SCS as the control group were generally higher, these were very variable and ranged between 14% (95% CI 8% to 21%)[25] and 60% (95% CI 43% to 75%).[42]

Similar patterns were observed for conventional SCS groups irrespective of time point of follow-up based on pain intensity scores (figure 5A) and responder rates (figure 5B).

DISCUSSION

Overall findings

The results of this NMA show that all types of SCS currently used in clinical practice are superior to CMM and provide statistically and clinically significant reductions in pain intensity (we considered a minimal clinically important difference (MCID) of 2 points in a 0–10 NRS scale),[47] a greater proportion of patients with ≥50% pain reduction, and statistically and clinically significant improvements in HRQoL (we considered a MCID of 0.074).[48] Conventional SCS, closed-loop SCS, DTM, and burst

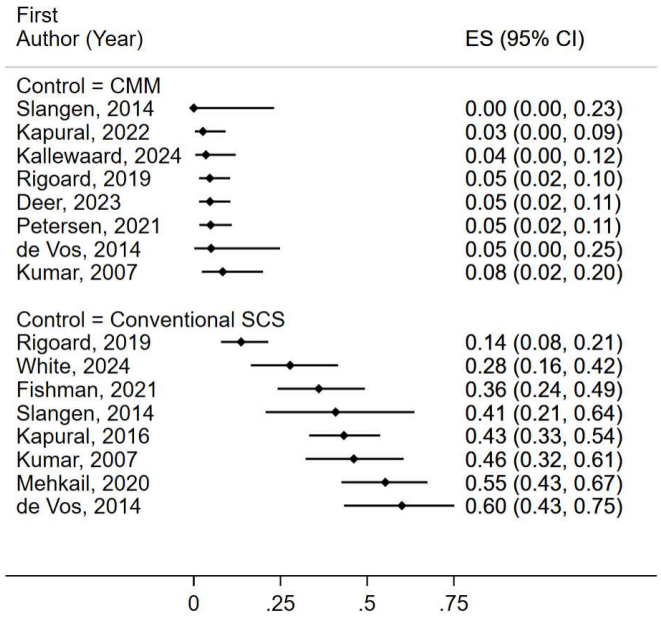

Figure 4 Responder rates observed in control groups at 6 months follow-up. ES (proportion of achieving ≥50% reduction in pain VAS or NRS score). CMM, conventional medical management; ES, effect size; NRS, Numeric Rating Scale; SCS, spinal cord stimulation; VAS, Visual Analog Scale.

SCS were found to provide a statistically significant improvement in physical function compared with CMM, with clinically meaningful improvements observed only for some comparisons (we considered a MCID of 10 points).[49] While some differences in outcomes were seen between novel types of SCS and conventional SCS, no statistically significant differences were observed between the different novel types of SCS for most outcomes evaluated.

Implications for research

The variability observed within CMM and conventional SCS groups can affect comparisons across the different novel SCS modalities. Generally, interventions compared head-to-head in trials with well-performing control groups will have less potential to demonstrate important relative treatment effects than interventions compared with poorer performing treatment groups. The impact of the variability of control group results on relative treatment effects can also be exacerbated within NMA where indirect comparisons are made; for example, an indirect comparison of two types of SCS anchored by a "common" comparison of conventional SCS from RCTs where the conventional SCS groups have performed differently. Across the different time points, the conventional SCS group that was used in an RCT as a comparator to closed-loop SCS[50] had consistently one of the highest responder rates and respective low pain intensity scores within conventional SCS groups. The results can, however, be explained due to the use of ECAPs to assist the programming of the conventional SCS arm (ie, it was possible to confirm neural activation in the conventional SCS arm). Therefore, it would be difficult to observe large advantages for closed-loop SCS when compared with conventional SCS within the RCT and for closed-loop SCS compared with other types of SCS in the NMA.

Conversely, when considering DTM, one study compared DTM to a CMM control group.[22] As shown in figure 4, CMM cohorts generally present lower rates of response and higher pain scores than conventional SCS as a control group. Two studies used conventional SCS as a control group.[7 27] However, the conventional SCS control groups in these studies did not perform as well as the conventional SCS control group in the trial of closed-loop SCS in terms of responder rates or of a reduction in pain intensity score. Therefore, it is more likely for DTM to show advantages over the other interventions evaluated within the respective trials and within the NMA. The same can be said for burst SCS, compared in an RCT to a CMM control group,[6] and also HF-SCS, where one RCT compared

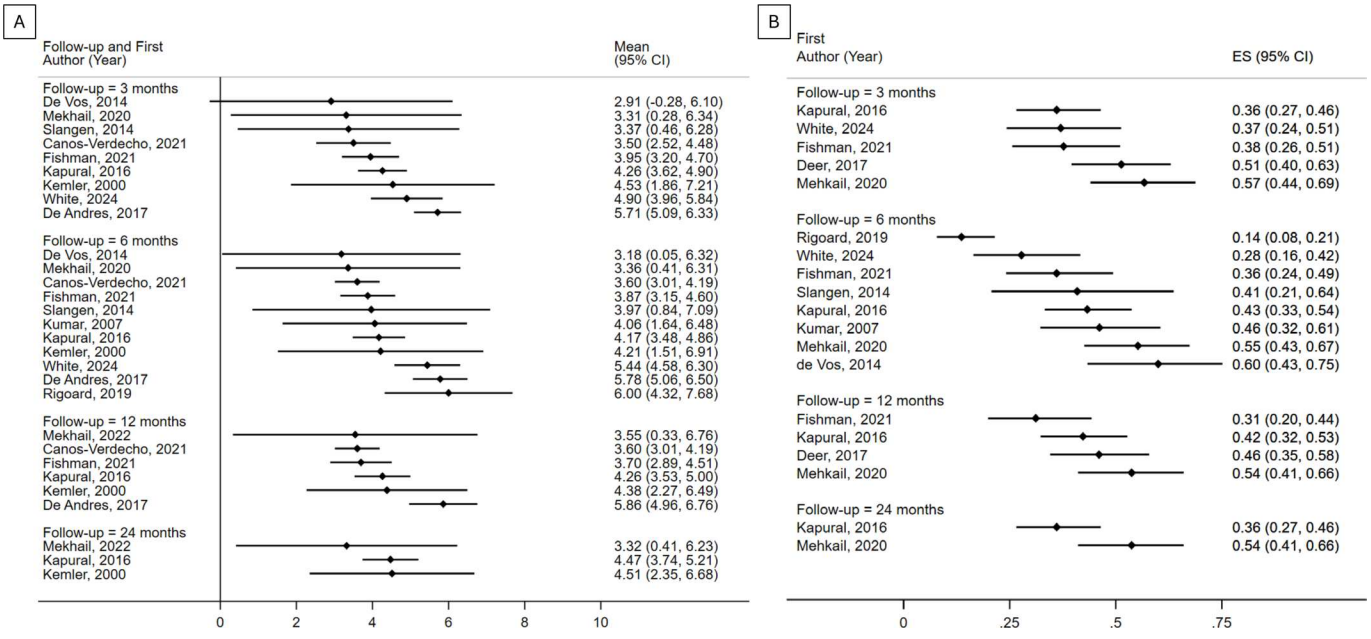

Figure 5 (A) Pain intensity scores observed in conventional SCS groups by time point; (B) Responder rates observed in conventional SCS groups by time point. ES (proportion of achieving ≥50% reduction) in pain VAS or NRS score. ES, effect size; NRS, Numeric Rating Scale; SCS, spinal cord stimulation; VAS, Visual Analog Scale.

the intervention to CMM,[23] and two RCTs had poor-performing conventional SCS as a control group.[5 44] In summary, NMA results should be interpreted in the context of control group responder rates and pain scores, due to variability in the types and performance of control groups. Further, a head-to-head trial with a poor-performing control group can lead to inflated effect sizes for the difference between groups and generate number needed to treat (NNT) estimates closer to 1 for an intervention. However, if the same intervention was compared with a well-performing control group, the difference between groups would be smaller and consequently NNT estimates would be further from 1. The variability observed for CMM and conventional SCS groups in this systematic review suggests that the choice of control group can substantially impact the outcomes of a trial. It is therefore essential that the control groups are adequately described, including the neural dose (eg, ECAP amplitude and time above ECAP threshold), or electrical dose (eg, charge per pulse [amplitude (mA)×pulse width (ms) or charge per second [amplitude (mA) x frequency (Hz)×pulse width (ms))[4 51 52] or system settings and system utilization when the comparator is a SCS modality. Future directions may include machine learning-driven dose response optimization and multisite ECAP mapping to address complex pain topographies.

Future studies should report the proportion of patients with≥80% reduction in pain intensity, which was not possible to evaluate in the current review given the limited data available.

Implications for practice

The variation observed in this study for conventional SCS suggests that treatment effects with this intervention may be inconsistent. Similar variation may occur in treatment effects for other types of SCS. Such variation without explanation as to the potential reasons has resulted in SCS being questioned as a treatment option for chronic pain. It should be noted that SCS is also used for the management of diverse conditions with beneficial treatment effects reported for restoration of sensory feedback from the missing foot following lower-limb amputations,[53] walking without falling in people with late-stage Parkinson's disease,[54] restoration of trunk and leg motor functions after complete paralysis,[55] recovery of over-ground walking,[56] restoration of walking after complete spinal cord injury,[57] and reduction of attack frequency in people with medically intractable chronic cluster headache.[58] The treatment effects of SCS in these areas have not been questioned. One of the reasons is the subjectivity of pain and of the outcomes used to evaluate treatment effects. Another reason has been the lack of transparency in reports of SCS (eg, in most instances, adherence to therapy is not reported and as such, it is not possible to confirm if the patients received a useful therapeutic dose). There have been concerted efforts to overcome limitations in the field of SCS, from the development and validation of composite outcomes to provide a comprehensive assessment of the chronic pain experience,[51 59] calls to report the device metrics,[4 60] and development of SPIRIT- and CONSORT-iNeurostim guidelines for the reporting of RCTs of implantable neurostimulation devices.[61–63] The authors expect these endeavors will promote increased transparency and completeness of SCS study reports and improve the reproducibility and consistency of SCS treatment effects.

Only one of the included RCTs was judged to have low RoB.[8] The high RoB in all but one study due to lack of blinding of pain outcomes, in addition to substantial heterogeneity, has resulted in the certainty of evidence to be judged as low for pain and physical function outcomes. Although SCS interventions likely improve pain and physical function compared with CMM and some types of SCS may be superior to conventional SCS, the magnitude of improvement remains uncertain. Importantly, the certainty of evidence for HRQoL was judged as moderate, indicating that SCS interventions probably improve HRQoL compared with CMM and some types of SCS may be superior to conventional SCS. Low certainty means that confidence in the effect estimate is limited and thus, the true effect may be substantially different from the estimate of effect observed in the current NMA. Moderate certainty means there is moderate confidence in the effect estimate and thus, the true effect is likely to be close to the estimate of effect, but there is the possibility that the effect could be substantively different. Instead of more RCT evidence, or trials independent from industry, what the field of SCS needs to improve the certainty of evidence is RCTs with low RoB that are reported appropriately to enable replication not only for other trials but also for clinical practice. Calls for additional RCT evidence when good quality RCTs with low RoB are available can be considered analogous to research waste. Recent systematic reviews of SCS have not observed differences between independent studies and those funded by industry.[13 15] Reporting guidelines for protocols and RCTs of implantable neurostimulation devices have now been developed to promote increased transparency, clarity, and completeness of reports.[62 63]

Strengths and potential limitations

Our findings are consistent with a recent NMA that showed that both conventional and novel types of SCS were superior to CMM.[64] However, important methodological differences distinguish our analysis. The previous NMA pooled all novel SCS types into a single node, precluding comparisons of the different novel SCS types with CMM and with conventional SCS, did not comment on potentially different treatment effects across conventional SCS or CMM nodes, and did not assess certainty of evidence or publication bias. Moreover, the systematic review was not registered, and the literature searches were up to September 2, 2022, with new evidence for novel SCS types published since. Similarly, another recent NMA combined all types of SCS into a single node and concluded that neuromodulation was the most effective treatment option for PSPS-T2 compared with conservative and minimally invasive treatment options, and placebo/sham.[40] Other NMAs have focused on specific pain conditions of PDN and PSPS-T1.[39 41] Importantly, all NMAs have included types of SCS that are used in clinical practice and consistently show that SCS is superior to CMM.

This study has some limitations that should be taken into consideration. All but one study was judged to have high RoB. No sham-controlled parallel arm RCTs were identified from which to draw any conclusions about the effectiveness of active SCS compared with sham stimulation. Our findings diverge notably from previous Cochrane reviews that included sham-controlled trials of SCS.[9 10] To date, all sham-controlled evidence of SCS for chronic pain conditions comes from crossover RCTs.[9–11] Besides the methodological shortcomings of this evidence (eg, short crossover phases, challenges in blinding of participants),[65] crossover RCTs have mostly evaluated experimental types of SCS of no proven clinical benefit to maintain the rigor of blinding. These experimental types of SCS are not used in clinical practice and, as such, have limited external validity or value to inform decision-making.[66–69] A notable example is the sham-controlled crossover trial that evaluated a type of burst SCS.[70] To maintain participant blinding, stimulation amplitude was set at 50%–70% of the paresthesia perception threshold.

Besides this approach not being used in routine clinical practice, a previous study reported that the same type of burst stimulation at 90% of paresthesia perception threshold was not superior to sham stimulation.[71] Although comparisons between SCS and sham stimulation are important, such evidence, and its inclusion in NMAs should be considered with caution. The relative effects of an experimental type of SCS vs sham stimulation can result in misleading findings when comparing SCS as used in clinical practice to sham stimulation in an NMA. In contrast, our analysis included only parallel-arm trials that evaluated SCS as intended for use in clinical practice, versus various comparators and conducted an NMA that distinguished between different SCS modalities. Substantial statistical heterogeneity and inconsistency were present in the NMAs of pain outcomes and physical function, likely due to differences in control group results. Eight of the included RCTs permitted crossover at the 6-month time point; therefore, analysis at later time points is limited. The networks were sparse due to limited evidence available. We did not present treatment rankings using surface under the cumulative ranking curve or other ranking methods, as such approaches can be easily misinterpreted, particularly likely in this scenario where some NMA results were associated with imprecision due to low response rates and variation of control groups. Instead, and in line with recommendations by Mbuagbaw *et al*,[72] we evaluated the relative effectiveness of different types of SCS through presentation of treatment effect estimates with measures of precision visually within forest plots and drawing conclusions based on these effect estimates and their associated uncertainty according to the CiNEMA framework. Certainty of the evidence was low for the primary outcome (pain intensity score), and physical function, very low for responder rate (≥50% reduction in pain intensity), and moderate for HRQoL. Finally, given that we conducted an aggregate data NMA, we acknowledge the potential for ecological fallacy.

CONCLUSIONS

This comprehensive systematic review and NMA shows that all types of SCS are superior to CMM for the management of chronic pain conditions with improvements in pain intensity (low certainty evidence), physical function (low certainty evidence), and HRQoL (moderate certainty evidence). Compared with conventional SCS, novel SCS modalities were found to provide statistically significant reductions in pain intensity (DTM SCS), greater proportion of patients with ≥50% reduction in pain intensity (DTM SCS and HF-SCS), greater improvements in physical function (burst SCS), and HRQoL (closed-loop SCS and DTM SCS). No statistically significant differences were observed between the different novel types of SCS for most outcomes evaluated. Examination of control groups shows variability within conventional SCS and CMM groups that can impact the magnitude of treatment effect observed not only in head-to-head trials but also within NMA comparisons between the different novel types of SCS. The results of our analysis support the continued policy of the use of SCS for people with chronic pain refractory to CMM.

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REFERENCES

1 Thomson S, Huygen F, Prangnell S, *et al*. Appropriate referral and selection of patients with chronic pain for spinal cord stimulation: European consensus recommendations and e-health tool. *Eur J Pain* 2020;24:1169–81.

2 Goudman L, Rigoard P, Billot M, *et al*. Patient Selection for Spinal Cord Stimulation in Treatment of Pain: Sequential Decision-Making Model - A Narrative Review. *J Pain Res* 2022;15:1163–71.
3 Kumar K, Taylor RS, Jacques L, *et al*. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;132:179–88.
4 Katz N, Dworkin RH, North R, *et al*. Research design considerations for randomized controlled trials of spinal cord stimulation for pain: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials/Institute of Neuromodulation/ International Neuromodulation Society recommendations. *Pain* 2021;162:1935–56.
5 Kapural L, Yu C, Doust MW, *et al*. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. *Anesthesiology* 2015;123:851–60.
6 Deer T, Gilligan C, Falowski S, *et al*. Treatment of Refractory Low Back Pain Using Passive Recharge Burst in Patients Without Options for Corrective Surgery: Findings and Results From the DISTINCT Study, a Prospective Randomized Multicenter Controlled Trial. Neuromodulation. 2023;26:1387–99.
7 Fishman M, Cordner H, Justiz R, *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;21:912–23.
8 Mekhail N, Levy RM, Deer TR, *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. *Lancet Neurol* 2020;19:123–34.
9 O'Connell NE, Ferraro MC, Gibson W, *et al*. Implanted spinal neuromodulation interventions for chronic pain in adults. *Cochrane Database Syst Rev* 2021;12:CD013756.
10 Traeger AC, Gilbert SE, Harris IA, *et al*. Spinal cord stimulation for low back pain. *Cochrane Database Syst Rev* 2023;3:CD014789.
11 Duarte RV, Nevitt S, McNicol E, *et al*. Systematic review and meta-analysis of placebo/ sham controlled randomised trials of spinal cord stimulation for neuropathic pain. *Pain* 2020;161:24–35.
12 Duarte RV, Nevitt S, Maden M, *et al*. Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data. *Pain* 2021;162:2635–43.
13 Eldabe S, Nevitt S, Copley S, *et al*. Does industry funding and study location impact findings from randomized controlled trials of spinal cord stimulation? A systematic review and meta-analysis. *Reg Anesth Pain Med* 2024;49:272–84.
14 Raghu ALB, Parker T, Aziz TZ, *et al*. Invasive Electrical Neuromodulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis. *Neuromodulation* 2021;24:13–21.
15 Klasova J, Hussain N, Umer I, *et al*. Emotional and psychosocial function after dorsal column spinal cord stimulator implantation: a systematic review and meta-analysis. *Reg Anesth Pain Med* 2024;50:e105523:794–805:.
16 ElSaban M, Kleppel DJ, Kubrova E, *et al*. Physical functioning following spinal cord stimulation: a systematic review and meta-analysis. *Reg Anesth Pain Med* 2023;48:302–11.
17 Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017;12:103–11.
18 Chaimani A, Caldwell DM, Li T, *et al*. Undertaking network meta-analyses. In: *Cochrane handbook for systematic reviews of interventions*. 2019: 285–320.
19 Brignardello-Petersen R, Guyatt GH. Introduction to network meta-analysis: understanding what it is, how it is done, and how it can be used for decision-making. *Am J Epidemiol* 2025;194:837–43.
20 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
21 Dworkin RH, Turk DC, Wyrwich KW, *et al*. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–21.
22 Kallewaard JW, Billet B, Van Paesschen R, *et al*. European randomized controlled trial evaluating differential target multiplexed spinal cord stimulation and conventional medical management in subjects with persistent back pain ineligible for spine surgery: 24-month results. *Eur J Pain* 2024;28:1745–61.
23 Kapural L, Jameson J, Johnson C, *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. *J Neurosurg Spine* 2022;37:188–99.
24 Petersen EA, Stauss TG, Scowcroft JA, *et al*. Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial. *JAMA Neurol* 2021;78:687–98.
25 Rigoard P, Basu S, Desai M, *et al*. Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial. *Pain* 2019;160:1410–20.
26 Slangen R, Schaper NC, Faber CG, *et al*. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. *Diabetes Care* 2014;37:3016–24.
27 White T, Justiz R, Almonte W, *et al*. Twelve-month results from a randomized controlled trial comparing differential target multiplexed spinal cord stimulation and conventional spinal cord stimulation in subjects with chronic refractory axial low back pain not eligible for spine surgery. *N Am Spine Soc J* 2024;19:100528.
28 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
29 Wewege MA, Jones MD, Williams SA, *et al*. Rescaling pain intensity measures for meta-analyses of analgesic medicines for low back pain appears justified: an empirical examination from randomised trials. *BMC Med Res Methodol* 2022;22:285.
30 Higgins JPT, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98–110.
31 Dias S, Welton NJ, Caldwell DM, *et al*. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
32 König J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Stat Med* 2013;32:5414–29.
33 Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012;3:161–76.
34 Balduzzi S, Rücker G, Nikolakopoulou A, *et al*. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. *J Stat Softw* 2023;106:1–40.
35 Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012;3:312–24.
36 StataCorp. Stata statistical software: release 19. College Station, TX StataCorp LLC; 2025.
37 Yepes-Nuñez JJ, Li S-A, Guyatt G, *et al*. Development of the summary of findings table for network meta-analysis. *J Clin Epidemiol* 2019;115:1–13.
38 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al*. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082.
39 Eldabe S, Nevitt S, Bentley A, *et al*. Network Meta-analysis and Economic Evaluation of Neurostimulation Interventions for Chronic Nonsurgical Refractory Back Pain. *Clin J Pain* 2024;40:507–17.
40 Goudman L, Russo M, Pilitsis JG, *et al*. Treatment modalities for patients with Persistent Spinal Pain Syndrome Type II: A systematic review and network meta-analysis. *Commun Med (Lond)* 2025;5:63.
41 Duarte RV, Nevitt S, Copley S, *et al*. Systematic Review and Network Meta-analysis of Neurostimulation for Painful Diabetic Neuropathy. *Diabetes Care* 2022;45:2466–75.
42 de Vos CC, Meier K, Zaalberg PB, *et al*. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain* 2014;155:2426–31.
43 Deer TR, Levy RM, Kramer J, *et al*. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 2017;158:669–81.
44 De Andres J, Monsalve-Dolz V, Fabregat-Cid G, *et al*. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. *Pain Med* 2017;18:2401–21.
45 Kemler MA, Barendse GA, van Kleef M, *et al*. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;343:618–24.
46 Canós-Verdecho A, Abejón D, Robledo R, *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;24:448–58.
47 Farrar JT, Young JP Jr, LaMoreaux L, *et al*. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–58.
48 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523–32.
49 Ostelo RWJG, de Vet HCW. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol* 2005;19:593–607.
50 Mekhail N, Levy RM, Deer TR, *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;79:251–60.
51 Levy RM, Mekhail N, Abd-Elsayed A, *et al*. Holistic Treatment Response: An International Expert Panel Definition and Criteria for a New Paradigm in the Assessment of Clinical Outcomes of Spinal Cord Stimulation. *Neuromodulation* 2023;26:1015–22.
52 Miller JP, Eldabe S, Buchser E, *et al*. Parameters of Spinal Cord Stimulation and Their Role in Electrical Charge Delivery: A Review. *Neuromodulation* 2016;19:373–84.
53 Nanivadekar AC, Bose R, Petersen BA, *et al*. Restoration of sensory feedback from the foot and reduction of phantom limb pain via closed-loop spinal cord stimulation. *Nat Biomed Eng* 2024;8:992–1003.
54 Milekovic T, Moraud EM, Macellari N, *et al*. A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease. *Nat Med* 2023;29:2854–65.
55 Rowald A, Komi S, Demesmaeker R, *et al*. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. *Nat Med* 2022;28:260–71.
56 Angeli CA, Boakye M, Morton RA, *et al*. Recovery of Over-Ground Walking after Chronic Motor Complete Spinal Cord Injury. *N Engl J Med* 2018;379:1244–50.

57 Wagner FB, Mignardot J-B, Le Goff-Mignardot CG, *et al*. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature New Biol* 2018;563:65–71.
58 Wilbrink LA, de Coo IF, Doesborg PGG, *et al*. Safety and efficacy of occipital nerve stimulation for attack prevention in medically intractable chronic cluster headache (ICON): a randomised, double-blind, multicentre, phase 3, electrical dose-controlled trial. *Lancet Neurol* 2021;20:515–25.
59 Taylor RS, Neville Q, Mullin CM, *et al*. Validation of a holistic composite outcome measure for the evaluation of chronic pain interventions. *Pain Rep* 2024;9:e1202.
60 Levy RM. The need for mechanism-based medicine in neuromodulation. *Neuromodulation* 2012;15:273–9.
61 Duarte RV, Bresnahan R, Copley S, *et al*. Reporting Guidelines for Clinical Trial Protocols and Reports of Implantable Neurostimulation Devices: Protocol for the SPIRIT-iNeurostim and CONSORT-iNeurostim Extensions. *Neuromodulation* 2022;25:1045–9.
62 Bresnahan R, Copley S, Eldabe S, *et al*. Reporting guidelines for protocols of randomised controlled trials of implantable neurostimulation devices: the SPIRIT-iNeurostim extension. *EClinicalMedicine* 2024;78:102933.
63 Duarte RV, Bresnahan R, Copley S, *et al*. Reporting guidelines for randomised controlled trial reports of implantable neurostimulation devices: the CONSORT-iNeurostim extension. *EClinicalMedicine* 2024;78:102932.
64 Huygen FJPM, Soulanis K, Rtveladze K, *et al*. Spinal Cord Stimulation vs Medical Management for Chronic Back and Leg Pain: A Systematic Review and Network Meta-Analysis. *JAMA Netw Open* 2024;7:e2444608.
65 Duarte RV, McNicol E, Colloca L, *et al*. Randomized Placebo-/Sham-Controlled Trials of Spinal Cord Stimulation: A Systematic Review and Methodological Appraisal. *Neuromodulation* 2020;23:10–8.
66 Eldabe S, Gilligan C, Taylor RS, *et al*. Issues in design, conduct, and conclusions of JAMA's Hara et al.'s randomized clinical trial of spinal cord burst stimulation versus placebo stimulation on disability in patients with chronic radicular pain after lumbar spine surgery. *Pain Pract* 2023;23:232–3.
67 Staats PS, Taylor RS, Gilligan C, *et al*. Limitations of the Cochrane review of spinal cord stimulation for low back pain. *Pain Pract* 2023;23:868–72.
68 Durbhakula S, Broachwala MY, Schuster NM, *et al*. Striking errors in the methodology, execution, and conclusions of the Cochrane Library review of spinal cord stimulation for low back pain by Traeger et al. *Pain Med* 2023;24:923–5.
69 Eldabe S, Nevitt S, Bentley A, *et al*. Response to "Competing Narratives: Moving the Field Forward on Spinal Cord Stimulation". *Clin J Pain* 2024;40:557–60.
70 Hara S, Andresen H, Solheim O, *et al*. Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial. *JAMA* 2022;328:1506–14.
71 Eldabe S, Duarte R, Gulve A, *et al*. Analgesic Efficacy of "Burst" and Tonic (500 Hz) Spinal Cord Stimulation Patterns: A Randomized Placebo-Controlled Crossover Study. *Neuromodulation* 2021;24:471–8.
72 Mbuagbaw L, Rochwerg B, Jaeschke R, *et al*. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Syst Rev* 2017;6:79.
73 Duarte RV, Andronis L, Lenders MWPM, *et al*. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. *Qual Life Res* 2016;25:1771–7.
74 Kapural L, Yu C, Doust MW, *et al*. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. *Neurosurgery* 2016;79:667–77.
75 Kemler MA, De Vet HCW, Barendse GAM, *et al*. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2004;55:13–8.
76 Kemler MA, de Vet HCW, Barendse GAM, *et al*. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg* 2008;108:292–8.
77 Manca A, Kumar K, Taylor RS, *et al*. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). *Eur J Pain* 2008;12:1047–58.
78 Mekhail NA, Levy RM, Deer TR, *et al*. ECAP-controlled closed-loop versus open-loop SCS for the treatment of chronic pain: 36-month results of the EVOKE blinded randomized clinical trial. *Reg Anesth Pain Med* 2024;49:346–54.