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Systematic review and meta-analysis of conventional medical management in a patient population with refractory chronic pain suitable to receive a spinal cord stimulation system

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Abstract

Aim

The aim of this review was to systematically identify all evidence that used conventional medical management (CMM) as a comparator in randomised controlled trials (RCTs) of spinal cord stimulation (SCS) therapy, and to conduct a meta-analysis to investigate if continued CMM provides statistical or clinically meaningful pain relief and whether CMM effects have improved over the last few decades.

Methods

Databases were searched from inception to June 2024 for RCTs that compared SCS to CMM. The primary outcome of the review was absolute change in pain intensity from baseline to the last available follow-up in the CMM group, measured using a visual analogue scale or numerical rating scale. The measure of treatment effect for absolute change and percentage change in pain intensity from baseline was mean difference (MD) and 95% confidence interval (CI). Risk of bias (RoB) was assessed by using the revised Cochrane RoB tool. The protocol for this review is registered on PROSPERO (CRD42023449215).

Results

Meta-analysis of absolute change in pain intensity from baseline to last follow-up shows that CMM is not associated with any significant reductions in pain intensity (MD -0.11; 95% CI: -0.32 to 0.11; moderate certainty). Similar results were observed for percent change in pain intensity from baseline to last follow-up (MD -3.22%; 95% CI: -12.59% to 6.14%; moderate certainty). No significant differences were observed when considering decade of publication of the RCT for absolute (p=0.065; moderate certainty) or percent change in pain intensity (p=0.524; moderate certainty). Meta-analysis for 6-month follow-up and sensitivity analysis shows similar numerical results.

Conclusion

Our findings show that continued CMM for a population eligible for SCS does not provide meaningful pain relief and has not considerably changed over the last few decades. The use of CMM as the control to evaluate relative SCS treatment effects should be reassessed.

Keywords: conventional medical management; meta-analysis; spinal cord stimulation; standard of care; systematic review

INTRODUCTION

Conventional medical management (CMM), also known as usual care, optimal or optimized medical management, has served as a benchmark control group (i.e., standard of care) in comparative effectiveness trials assessing neuromodulation for chronic pain since the early 2000's.[1] CMM consists of a range of non-neuromodulation treatment options, such as oral medications, epidural injections, nerve blocks, rehabilitative physical and psychological therapies, as well as a range of alternative therapies.[2] Oral medications often include opioids, non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants, and other analgesic drugs, depending on the condition.[3] CMM is normally defined by the trial investigators and tailored to the individual patient, often with minimal guidance provided in the trial protocol.[4-6]

Patients with chronic pain who become refractory to existing CMM may be suitable for a trial of neuromodulation, such as spinal cord stimulation (SCS). SCS is commonly indicated for the management of persistent spinal pain syndrome type 1 and type 2 (PSPS-T1 and PSPS-T2), complex regional pain syndrome (CRPS), peripheral vascular disease, painful diabetic neuropathy (PDN), and other neuropathic or ischaemic pain syndromes.[7,8] Typically, in trials evaluating SCS (usually in combination with CMM) versus CMM, once the neuromodulation therapy is deployed, medical management becomes fixed. In the CMM group, however, treatments can be initiated and adapted during the trial for optimisation (i.e., 'optimal medical management'). In this regard, CMM represents a real-world clinical approach to treating patients, prioritizing conservative options over invasive interventions. Examining the outcomes of CMM over time should therefore be highly instructive for evaluating medical progress and gauging patient responses to modern conservative management. The objectives of this study were two-fold: 1) to evaluate if CMM provides statistically and clinically meaningful improvements in pain relief for a population eligible for SCS, either across all studies, or, at the very least, within the most recently conducted randomised controlled trials (RCTs); and 2) to investigate whether advances in CMM suggest a need for additional comparative evidence on the effectiveness of SCS versus CMM. To address these objectives, this study aimed to

determine if further CMM provides statistical or clinically meaningful pain relief for patients suitable to receive SCS therapy, and whether this approach has improved over the last three decades.

METHODS

The systematic review methods followed the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care.[9] This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10] The protocol for the review is registered on PROSPERO as CRD42023449215.

Search strategy

The databases MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and WikiStim were searched from inception to 5th June 2024. The search strategies were designed using a combination of both indexing and free-text terms with no restriction on language or date. The search strategies are presented in Supplementary 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 (DS, RVD) 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 (DS, RVD) for inclusion, using consensus for any disagreements. Studies were eligible for inclusion if they met the following criteria: i) adult patients (18 years of age or older) with refractory chronic pain; ii) evaluation of SCS (any stimulation paradigm); iii) compared to CMM; iv) in a parallel group RCT design; and v) reported in a full-text manuscript in a peer-reviewed journal.

Outcomes

The primary outcome of the review was absolute change in pain intensity from baseline to the last available follow-up in the CMM group of the trial, measured using a visual analogue scale (VAS) or numerical rating scale (NRS). Additional outcomes included percentage change in pain intensity from baseline to the last follow-up in the CMM group, and absolute change and percentage change in pain intensity from baseline to 3-months and to 6-months post-treatment in the CMM group.

Data extraction

Data extracted were study author and year of publication, country where the study was conducted, funding sources, demographic data (i.e., age, sex), details on the intervention and comparator, duration of follow-up, type and duration of pain, number of participants included in the analysis, pain outcomes and safety. Data extraction was performed by one reviewer (SN) and checked for accuracy by a second reviewer (RVD).

Risk of bias assessment

Risk of bias (RoB) was assessed by using the revised Cochrane RoB tool (RoB 2.0).[11] RoB assessment of the included studies was undertaken by one reviewer (RVD) and verified for agreement by a second reviewer (SN). Any disagreements were resolved by discussion, and, if necessary, in consultation with a third reviewer (MR).

Data synthesis

The measure of treatment effect for absolute change and percentage change in pain intensity from baseline was mean difference (MD) and 95% confidence interval (CI). Absolute change in pain intensity (i.e. difference from baseline in cm or points on the VAS or NRS scale) and percentage change from baseline in pain intensity were considered as separate outcomes, where data were available.

Individual participant data (IPD) were obtained from the authors of one RCT[12] meeting the inclusion criteria and cross-checked as previously reported,[13] and data items were extracted at study level from the other eligible RCTs. Outcome data available only in graphical format were extracted using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/).

Outcome data were prepared for synthesis using a consistent approach to our previous analyses (see Supplementary Material 2 for details).[13-15]

Clinical heterogeneity of included studies was assessed by comparing study design characteristics, characteristics of CMM groups, participant characteristics and definitions of outcomes. Random-effects meta-analysis was performed to pool the CMM groups of included RCTs using the generic inverse variance method, using the updated metan command[16] in Stata version 18,[17] with restricted maximum likelihood (REML) used to estimate heterogeneity variance.[18] We assessed statistical heterogeneity in meta-analysis according to the I^2 statistic (the percentage of variability between trials that is due to statistical heterogeneity) with higher values corresponding to higher levels of statistical heterogeneity.

Subgroup meta-analyses were conducted according to decade of publication of the RCT (before 2010, 2010-2020 and after 2020) and by pain diagnosis (e.g., CRPS, PSPS-T1, PSPS-T2, PDN). Subgroup differences were tested according to the test of heterogeneity between subgroups.[19] Statistical significance was assessed at the 5% level (i.e. $p<0.05$).

We assessed the certainty of the evidence for the comparisons and outcomes included in meta-analysis using the GRADE framework.[20] Magnitude of effect and certainty of the evidence were considered when drawing conclusions.

RESULTS

The searches resulted in the identification of 2,249 potentially eligible records after deduplication. Following screening of titles and abstracts, 22 records were retrieved for

assessment of the full-text publication. After review of the full-text publications, 10 unique studies (612 participants in CMM groups) were included in the review.[1,12,21-28] Twelve studies were excluded on review of the full-text publication; two studies were not RCT in design,[29,30] one study did not include CMM as a control group,[31] two studies did not report outcomes of interest for this review,[32,33] two studies were only available as conference abstracts,[34,35] five studies were follow-up reports of studies following crossover.[3,36-39] The PRISMA flow diagram detailing the study selection process is presented in Figure 1.

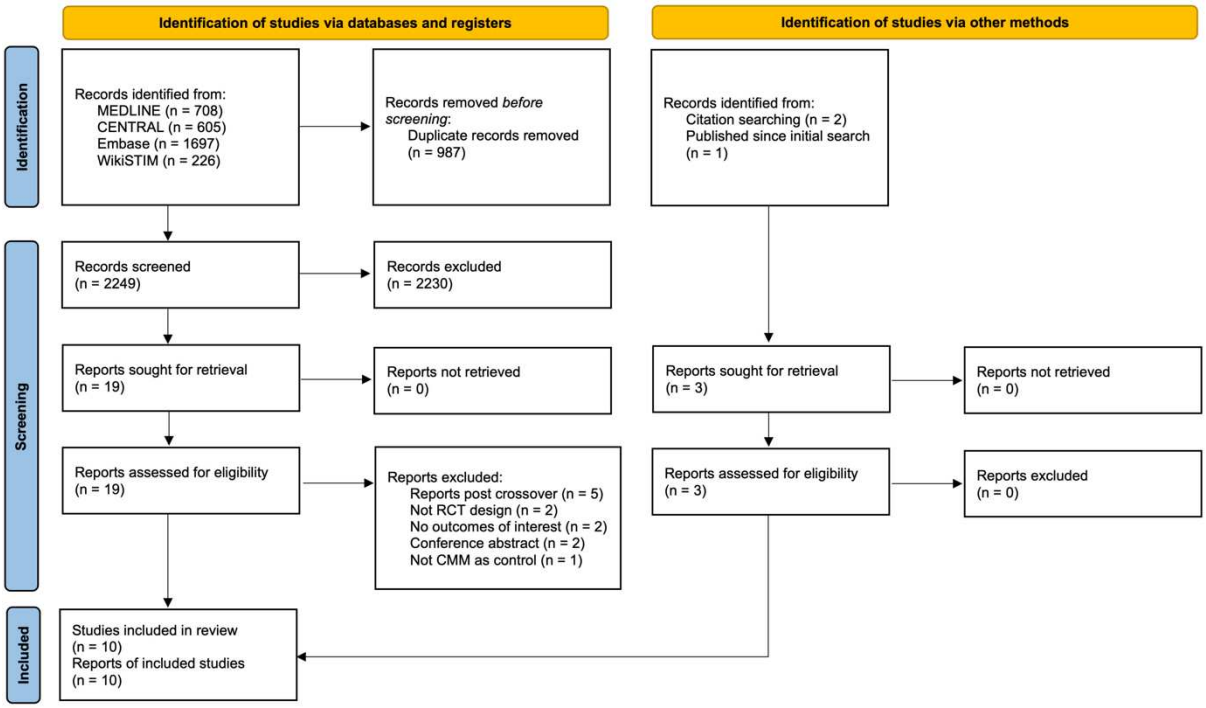

Figure 1. PRISMA 2020 flow diagram

The characteristics of the 10 included RCTs, including details on CMM provided, are summarised in Table 1. Nine of the studies were multicentre and funded by industry,[1,12,22-28] while 1 study was single centre with no industry funding received or declared.[21] Studies were conducted across several European countries, United States, Canada, Australia and Israel. The types of SCS evaluated were low-frequency (LF-SCS) in 5 studies,[1,12,21,26,27] high-

frequency (HF-SCS) in 3 studies,[21,24,25] and burst,[22] and differential target multiplexed (DTM),[28] in 1 study each. One study evaluated subcutaneous nerve stimulation;[23] however, we considered the study population of PSPS-T2 similar to the populations suitable for SCS. Diagnoses included CRPS type 1 in 1 study,[21] PDN in 3 studies,[12,25,27] PSPS-T1 in 3 studies,[22,24,28] and PSPS-T2 in 3 studies.[1,23,26] Duration of pain in the CMM group was considerably lower (i.e., 2.3 years) and proportion of females greater (i.e., 89.5%) in the study that included patients with CRPS type 1,[21] than in the remaining studies. One study was conducted before 2010,[1] four studies between 2010 and 2020,[12,23,26,27] and five since 2020.[21,22,24,25,28] CMM generally consisted of pain medications (e.g., opioids, non-opioids, muscle relaxants and non-steroidal anti-inflammatory agents), noninterventional therapies (e.g., physical therapy, chiropractic care, cognitive behavioural therapy, massage, and acupuncture), and interventional therapies (e.g., radiofrequency, and spinal injections).

Risk of bias assessment

The summary of the RoB assessment is presented in Table 2. One study was judged as presenting some concerns for the randomisation process domain due to some baseline imbalances observed between the groups, including pathology and years since diagnosis.[21] All of the included studies were judged to have a high risk of bias for outcome measurement as all were open-label trials with patients, clinicians, and outcome assessors aware of the interventions received. 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 intervention and beliefs of beneficial effect could have influenced the outcomes. Five studies were judged as presenting some concerns for the selection of the reported results domain where no study protocol was available, or it was not explicitly mentioned that a prespecified analysis plan was followed.[1,12,21,22,27] The overall bias for all included studies was high because at least one domain was judged to have a high risk of bias.

Table 1. Characteristics of included trials with a CMM control group

Author (y), country, setting, and funding	Intervention	Control	Follow-up duration*	Intervention – Number in analysis, sex, and mean age±SD	Control – Number in analysis, sex, and mean age±SD	Diagnosis and mean±SD duration of pain
Canós-Verdecho (2021)[21] Spain Single centre No industry funding	LF-SCS, HF-SCS	CMM (pharmacological, physical, and blockages) Pharmacological treatments: yes; physical therapy: yes; procedural treatments: yes; psychological therapy: NR	12 months	HF-SCS N=10, F=7 (70%), 46.3±10.0y LF-SCS N=12, F=8 (66.7%), 48.7±8.8y	N=19, F=17 (89.5%), 51.2±11.1y	**CRPS Type I** with upper limb involvement HF-SCS 4.7±6y (range 1-19) LF-SCS 1.8±0.9y (range 1-3) CMM 2.3±0.5y (range 2-3)
De Vos (2014)[12] Netherlands, Denmark, Belgium, and Germany Multicentre Industry funded	LF-SCS	CMM (medication adjustments and other conventional pain treatments, such as physical therapy) Pharmacological treatments: yes; physical therapy: yes; procedural treatments: NR; psychological therapy: NR	6 months	N=40, F=15 (37.5%), 58±11y	N=20, F=7 (35%), 61±12y	**PDN** LF-SCS 7±6y CMM 7±6y
Deer (2023)[22] United States Multicentre Industry funded	BurstDR	CMM (supervised medical care, including physical modalities, medication optimisation, noninterventional therapies and interventional therapies depending on the diagnosis and as decided by the investigator) Pharmacological treatments: yes; physical therapy: yes; procedural treatments: yes; psychological therapy: NR	6 months	N=162, F=96 (59%), 58.1±13.0y	N=107, F=52 (51%), 59.1±12.4y	**PSPS-T1** BurstDR 11.9±10.6y CMM 13.1±12.4y
Eldabe (2019)[23] Europe, Israel, and Australia Multicentre Industry funded	SQS	CMM (medical management optimisation; specifically excluded additional back surgery or the implantation of medical devices [e.g., other neurostimulation or intrathecal drug delivery therapies]) No additional detail reported	9 months	N=56, F=32 (57%), 50.9±10.9y	N=60, F=34 (57%), 52.2±11.4y	**PSPS-T2** SQS 13.5±11.0y CMM 13.1±9.9y
Kallewaard (2024)[28] Belgium, Germany, Netherlands, and Spain Multicentre Industry funded	DTM	CMM (treatment options reimbursed as per the regulations of each country, included interventional procedures (radiofrequency, steroid injections) as well as pain medications and physical therapy among others, CMM therapeutic options could be modified on an individual basis at the investigator's discretion) Pharmacological treatments: yes; physical therapy: yes; procedural treatments: yes; psychological therapy: NR	6 months	N=51, F=29 (57%), 55.9±13.0y	N=57, F=28 (49%), 56.9±12.8y	**PSPS-T1** DTM 10.4±10.9y CMM 11.6±10.8y
Kapural (2022)[24] United States Multicentre Industry funded	HF-SCS	CMM (best standard of care as determined for each individual patient by the study investigator; required to be generally consistent with clinical guidelines and interventional pain management guidelines) No additional detail reported	6 months	N=83, F=50 (60%), Mdn=53y (29-87)	N=76, F=40 (53%), Mdn=58.5y (26-77)	**PSPS-T1** HF-SCS Mdn=8.5y (0.5-52) CMM Mdn=8y (1-59)

Kumar (2007)[1] Europe, Canada, Australia, and Israel Multicentre Industry funded	LF-SCS	CMM (included oral medications, nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care; excluded other invasive therapy, such as spinal surgery or implantation of an intrathecal drug delivery system) Pharmacological treatments: yes; physical therapy: yes; procedural treatments: yes; psychological therapy: yes	6 months	N=52, F=22 (42.3%), 48.9±10y	N=48, F=27 (56.2%), 52.0±10.7y	**PSPS-T2** LF-SCS and CMM ≥ 6 months
Petersen (2021)[25] United States Multicentre Industry funded	HF-SCS	CMM (treatments include, but are not limited to, pharmacological agents, physical therapy, cognitive therapy, chiropractic care, nerve blocks, and other non-invasive or minimally invasive therapies) Pharmacological treatments: yes; physical therapy: yes; procedural treatments: yes; psychological therapy: yes	6 months	N=113, F=43 (38.1%), 60.7±11.4y	N=103, F=37 (35.9%), 60.8±9.9y	**PDN** HF-SCS 7.4±5.7y CMM 7.1±5.1y
Rigoard (2019)[26] Belgium, Canada, Colombia, France, Germany, Netherlands, Spain, United Kingdom, and United States Multicentre Industry funded	LF-SCS	CMM (individual treatment plan developed for each patient and optimized at each visit; could include treatments ranging from non-invasive treatments such as acupuncture, psychological/ behavioural therapy, and physiotherapy to invasive treatments such as spinal injections/blocks, epidural adhesiolysis, and neurotomies) Pharmacological treatments: yes; physical therapy: yes; procedural treatments: yes; psychological therapy: yes	6 months	N=110, F=68 (61.8%), 52.8±12.5y	N=108, F=64 (59.3%), 55.1±10.2y	**PSPS-T2** LF-SCS 6.4±7.4y CMM 7.0±7.1y
Slangen (2014)[27] Netherlands Multicentre Industry funded	LF-SCS	CMM (according to international guidelines and a treatment algorithm for the management of diabetic peripheral neuropathic pain; Invasive therapy, such as intrathecal drug delivery, was not allowed) No additional detail reported	6 months	N=22, F=7 (31.8%), 57.1±12.4y	N=14, F=5 (35.7%), 56.5±8.0y	**PDN** LF-SCS 6.0±5.1y CMM 4.9±3.6y

CMM=conventional medical management; CRPS=complex regional pain syndrome; DTM=differential target multiplexed; F=female; HF-SCS=high-frequency spinal cord stimulation; LF-SCS=low frequency spinal cord stimulation; Mdn=median; NR=not reported; PDN=painful diabetic neuropathy; PSPS-T1=persistent spinal pain syndrome type 1; PSPS-T2=persistent spinal pain syndrome type 2; SCS=spinal cord stimulation; SQS=subcutaneous nerve stimulation; y=years

* final trial follow-up or until crossover

** SCS included LF-SCS, HF-SCS and burst SCS

Table 2. Risk of bias assessment

Author (year)	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Canós-Verdecho (2021)[21]	Some concerns	Low	Low	High	Some concerns	High
De Vos (2014)[12]	Low	Low	Low	High	Some concerns	High
Deer (2023)[22]	Low	Low	Low	High	Some concerns	High
Eldabe (2019)[23]	Low	Low	Low	High	Low	High
Kallewaard (2024)[28]	Low	Low	Low	High	Low	High
Kapural (2022)[24]	Low	Low	Low	High	Low	High
Kumar (2007)[1]	Low	Low	Low	High	Some concerns	High
Petersen (2021)[25]	Low	Low	Low	High	Low	High
Rigoard (2019)[26]	Low	Low	Low	High	Low	High
Slangen (2014)[27]	Low	Low	Low	High	Some concerns	High

Outcomes

Pain-related outcomes observed in the CMM groups of the included studies are presented in Table 3. Pain intensity (VAS or NRS) was collected in all the included studies. Most studies reported no adverse events in the CMM groups. One study reported three cases of neurological deficit in the CMM group, motor (n=1) and sensory (n=2), at 3 months, with one sensory deficit remaining at 6 months.[24]

For the primary outcome, 8 studies reporting data for 381 participants that received CMM could be included in the meta-analysis of absolute change in pain intensity from baseline to last available follow-up. The meta-analysis shows that CMM does not result in significant reductions in pain intensity at last follow-up compared to baseline across all decades (MD -0.11; 95% CI: -0.32 to 0.11) (Figure 2), and no statistically significant differences in absolute change in pain intensity are shown when considering decade of publication of the RCT (test for subgroup differences p=0.065). A statistically significant difference in absolute change in pain intensity is shown when considering the patient diagnosis (p=0.030) (Supplementary Material 3, Figure S1). Statistically significant differences in the absolute change in pain intensity were not observed between last available follow-up compared to baseline for patients with a diagnosis of PDN, PSPS-T1 or PSPS-T2. Significant reductions in pain with CMM were observed for patients with CRPS Type 1 at 12-months (MD -3.00; 95% CI: -5.09 to -0.91).

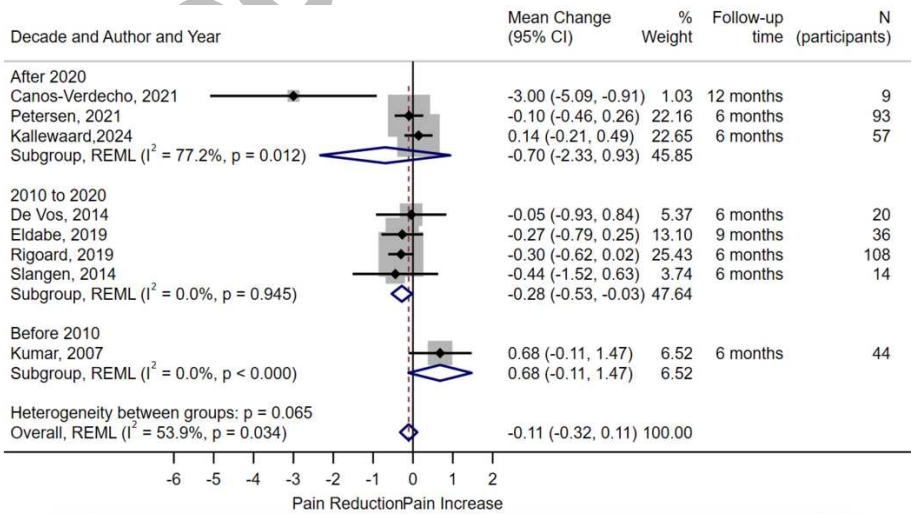

Figure 2. Absolute change in pain intensity from baseline to last follow-up according to decade of publication of the RCT (8 studies, 381 participants)

Similar results were observed for the meta-analysis of 5 studies reporting data for 221 participants to assess percent change in pain intensity, with no statistically significant differences observed between baseline and last available follow-up (MD -3.22%; 95% CI: -12.59% to 6.14%) and no statistically significant differences in the percent change according to decade of publication of the RCT (p=0.524) (Figure 3). Significant reductions in pain intensity were still observed for patients with CRPS Type 1 with CMM at 12 months (MD -37.30%; 95% CI: -63.04% to -11.56%) but not for patients with a diagnosis of PDN, PSPS-T1 or PSPS-T2 (test for subgroup differences p=0.051) (Supplementary Material 3, Figure S2).

Table 3. Outcomes of CMM groups of randomised controlled trials included in the systematic review

Author (y), follow-up	Pain-related outcomes
Canós-Verdecho (2021)[21]	Pain intensity (NRS) decreased from 8.3±0.5 to 5.3±0.8 at 12 months *
12 months	Absolute improvement in pain of 3.0±3.2
	Relative improvement in pain of 37.3±39.4%
De Vos (2014)[12]	Pain intensity (VAS) was 67±18 at baseline and 67±21 at 6 months
6 months	Absolute VAS reduction of 0±20
	Relative VAS reduction of 0±47%
	Proportion of patients with ≥50% pain reduction – 1 (5%) patient
Deer (2023)[22]	NRS % change of 5.6±21.3
6 months	Proportion of patients with ≥50% pain reduction – 5 (6.2%) patients
Eldabe (2019)[23]	Pain intensity (VAS) was 70.2±14.0 at baseline and 67.5±18.1 at 9 months
9 months	Absolute VAS reduction of 2.7±16.0
	VAS % change of 2.5±22.9%
	Proportion of patients with ≥50% pain reduction – 1 (2.8%) patient
Kallewaard (2024)[28]	Back pain intensity (VAS) was 7.76±1.03 at baseline and 7.90±2.96 at 6 months
6 months	Leg pain intensity (VAS) was 7.40±1.31 at baseline and 7.89±3.04 at 6 months
	Proportion of patients with ≥50% back pain reduction – 2 (3.6%) patients
Kapural (2022)[24]	VAS % change of 6.2±21.7
6 months	Proportion of patients with ≥50% pain reduction – 1 (1.3%) patient
Kumar (2007)[1]	Back pain intensity (VAS) was 44.8±23.2 at baseline and 51.6±26.7 at 6 months
6 months	Leg pain intensity (VAS) was 73.4±14.0 at baseline and 66.6±24.0 at 6 months
	Proportion of patients with ≥50% leg pain reduction – 4 (9%) patients
	Proportion of patients with ≥80% leg pain reduction – 3 (7%) patients
Petersen (2021)[25]	Pain intensity (VAS) was 7.0 at baseline and 6.9 at 6 months
6 months	Worsening pain for 48 (52%) patients
	Proportion of patients with ≥50% pain reduction – 5 (5%) patients
	Proportion of patients with VAS ≤3 for 6 consecutive months – 1 (1%) patient

Rigoard (2019)[26]	Back pain intensity (NRS) was 7.6±1.2 at baseline and 7.2±1.9 at 6 months
6 months	Leg pain intensity (NRS) was 5.3±2.1 at baseline and 5.4±2.4 at 6 months
	Proportion of patients with ≥50% back pain reduction – 5 (4.6%) patients
	Proportion of patients with ≥50% leg pain reduction – 9 (8.3%) patients
Slangen (2014)[27]	Pain intensity during the day (NRS) did not change from baseline
6 months	Pain intensity during the night (NRS) reduced by 0.9 points from baseline
	Proportion of patients with ≥50% pain reduction (day) – 0 (0%)
	Proportion of patients with ≥50% pain reduction (night) – 1 (7%) patient

CMM=conventional medical management; NRS=numeric rating scale; VAS=visual analogue scale
Data are mean ± standard deviation or n (%) unless specified otherwise
* mean ± standard error of the mean

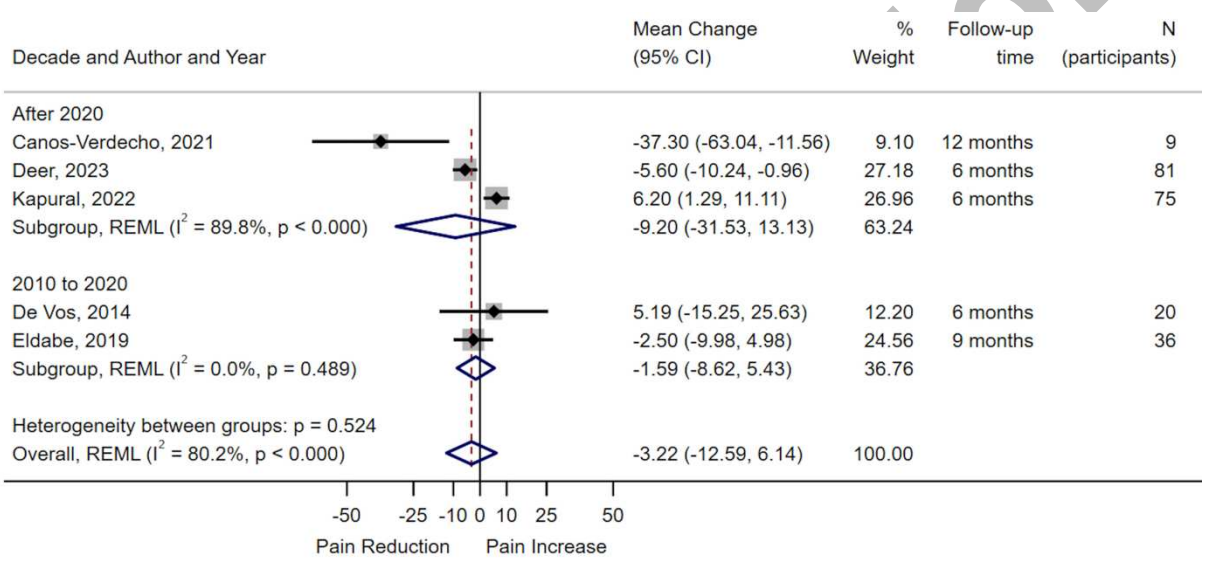

Figure 3. Percent change in pain intensity from baseline to last follow-up according to decade of publication of the RCT (5 studies, 221 participants)

Although there was a significant reduction in absolute change in pain intensity from baseline to 3-month follow-up (MD -0.40; 95% CI: -0.68 to -0.12) (Supplementary Material 4, Figure S3), the results were not statistically significant for percent change in pain intensity (MD -2.96%; 95% CI: -10.54% to 4.62%) (Supplementary Material 4, Figure S4). Test for subgroup differences show no statistically significant difference in absolute or percent change in pain intensity according to decade of publication of the RCT (p=0.123, and p=0.469, respectively). Test for subgroup differences shows no statistically significant differences in absolute change in pain intensity from baseline to 3-month follow-up when considering the patient diagnosis (p=0.103; Supplementary Material 4, Figure S5).

No statistically significant differences were observed from baseline to 6-month follow-up for absolute change in pain intensity (MD -0.20; 95% CI: -0.67 to 0.28) (Supplementary Material 4, Figure S6), or for percent change in pain intensity (MD -3.81%; 95% CI: -14.81% to 7.19%) (Supplementary Material 4, Figure S7). Test for subgroup differences show no statistically significant difference in absolute or percent change in pain intensity according to decade of publication of the RCT (p=0.065, and p=0.414, respectively). Tests for subgroup differences show significant differences in absolute and percent change in pain intensity from baseline to 6-month follow-up when considering the patient diagnosis (p=0.004, and p=0.018, respectively; Supplementary Material 4, Figure S8 and S9), with statistically significant reductions in pain intensity with CMM for CRPS Type 1, but not for patients with PDN, PSPS-T1 and PSPS-T2.

Sensitivity analysis including leg pain scores in meta-analysis show similar numerical results, and conclusions were unchanged (Supplementary Material 5).

The GRADE certainty of the evidence is moderate for changes in pain intensity with CMM from baseline to 3-, 6-month and last available follow-up and for respective subgroup analysis considering decade of publication of the RCT. Downgrades to the certainty of the evidence were made because of the high risk of bias within the studies included in the meta-analysis. Although substantial heterogeneity is present within some analyses, overall and within subgroups, this inconsistency seems to mostly be driven by one study[21] (as discussed below), and the results of other studies are mostly consistent, therefore, no downgrade was made due to unexplained heterogeneity. The overall and subgroup results are generally precise and therefore raise no concerns about imprecision.

The GRADE certainty of the evidence is low when considering subgroup analysis according to patient diagnosis due to high risk of bias; additional downgrade to the certainty of the evidence was made due to the impact on findings from one study recruiting patients with CRPS Type 1 with imprecise results, which appears inconsistent with the remaining included studies and which may not be reflective of the patient population usually considered for SCS.[21]

DISCUSSION

The results of our systematic review and meta-analysis show that the impact of CMM on pain intensity in patients eligible for SCS has not significantly changed over the last decades. No statistically significant differences were observed across decade of publication of the RCTs at 3-, 6-month, and last follow-up with CMM for absolute or percent change in pain intensity. Overall, CMM resulted in statistically significant reductions in (absolute) pain at 3-month follow-up compared to baseline, however, reductions in pain were not statistically significant at 6-month or last follow-up. Taking into consideration commonly used thresholds for a minimal clinically important difference of 2 points in NRS for absolute change or 20% to 30% for percent change,[40-42] CMM in patients eligible for SCS did not result in clinically meaningful improvements across decade of publication of the RCTs. Clinically meaningful reductions with CMM were not observed at any timepoint compared to baseline, nor across decade of publication for patients eligible for SCS.

Statistically significant reductions in pain with CMM at all timepoints, and clinically meaningful reductions at 6-month and last follow-up were observed within a single study for a population with CRPS. This study is dissimilar to all other included studies in multiple ways: it was the only study not funded by industry, only study conducted at a single centre, only study in a CRPS population, and the included patients presented the shortest duration of pain and greatest proportion of female patients. Because there were no statistically significant or clinically meaningful reductions observed in any of the other studies, this study may not reflect the population usually considered for SCS.[21] No statistically significant or clinically meaningful reductions were observed for populations of PDN, PSPS-T1 or PSPS-T2.

Recent systematic reviews concluded there were no significant differences in findings between SCS studies funded by industry and those not funded by industry.[15,43] CMM participants in the study by Canós-Verdecho et al. presented continuing improvements in pain

relief over time (i.e., improvement in pain from baseline increased from 3- to 6-months and then to last follow-up).[21] The results of the remaining included studies suggest worsening of pain from 3-months to subsequent follow-ups. Nevertheless, the authors reported that the types of SCS evaluated within this trial produced considerable improvements when compared with CMM in a CRPS population.[21]

CMM is valuable and may provide satisfactory pain relief. There are novel, promising non-invasive interventions for chronic pain, such as cognitive functional therapy with or without movement sensor biofeedback,[44] prehabilitation for patients undergoing surgery,[45] and pain reprocessing therapy.[46] These novel therapies demonstrate that CMM will continue to evolve. However, even though CMM has also evolved over the past several decades, we did not find significant changes in effect size with CMM by decade of study publication. Further, and similarly to any therapy, a proportion of patients do not respond to these interventions. The same occurs with pharmaceutical therapies which have limited long-term benefits for chronic pain.[47-50] In addition, interventions for chronic pain are further limited by patients' intentional or unintentional nonadherence to therapy. SCS is a treatment option for these patients with pain refractory to already deployed CMM.

Historical trials of SCS have used CMM as the comparator, which was the standard of care at the time.[1] Since patients with chronic pain are considered for SCS only if their pain is refractory to CMM, once superiority of SCS was observed versus CMM and SCS approvals were obtained for an indication (e.g., PSPS-T2), the new standard of care became the type of SCS available at the time of approval. Subsequent trials for a PSPS-T2 population have compared novel types of SCS to the type of SCS with approval for use.[51-53] Given the results of our current systematic review and meta-analysis, we believe that once superiority of a type of SCS over CMM is demonstrated for a specific patient population, that type of SCS should become the standard of care to be used as the comparator of subsequent evaluations of novel types of SCS in the same patient population. Consideration of SCS as standard of care is essential to enable comparisons of different forms of SCS to be considered for decision-making.[54] There

are challenges for comparisons of different forms of SCS that need to be considered such as selection of appropriate non-inferiority margin when comparing "standard" SCS to a novel type of SCS, determination of which SCS type(s) should be considered standard of care, risk of comparison to an active comparator that is later found not to be truly efficacious (or efficacious only in more selected circumstances), possible implications for assessment of other types of neuromodulation like PNS, DBS, DRG, and others. Although based on the authors knowledge of the evidence, SCS technology and approval processes in different geographies, we appreciate this is only one possible solution and would welcome discussion of other alternatives. As previously discussed, although feasible, the conduct of rigorous sham-controlled trials is complex.[55] In addition, not all types of SCS can be evaluated in a blinded sham-controlled trial. An alternative may be the use of an open-label sham comparator arm. Such a comparator arm may be another source of criticism, nevertheless, a recent study showed that open-label placebo may perform as well as a deceptive placebo.[56]

From our results that show no additional benefit of continued CMM in an SCS eligible population it is ethically difficult to recommend a therapy (i.e., further CMM) that has now been shown to have no additional clinical meaningful benefit for such patients. A reappraisal of this clinical choice by the pain treatment community would now seem to be a relevant informed discussion. Conversely, it needs to be said that this meta-analysis provides no insight on treatment options for a patient at the beginning of the therapeutic journey who has not had optimal CMM applied to them.

All included studies were judged as having a high risk of bias. It is not possible to blind patients, clinicians or outcome assessors (when using participant-reported outcomes, the outcome assessor is the study participant) to comparisons of SCS to CMM. We only evaluated pain intensity-related outcomes as this was the primary outcome in the included studies. Nevertheless, significant effects in secondary outcomes were seldomly observed in the included studies, the exceptions being the study by Canós-Verdecho et al,[21] and the general health dimension of the SF-36 in the study by Kumar et al.[1] Our meta-analysis was limited to

comparisons between baseline and follow-up timepoints as the aim of the systematic review was to evaluate whether the potential effects of CMM on pain reduction had changed over the last few decades. We cannot exclude the impact of a nocebo effect on the results observed due to potential negative expectations associated with undertaking a previously failed treatment within the setting of these RCTs where most patients will have tried most CMM options.[57] Such a potential nocebo effect may not be applicable to a population that is not refractory to CMM.

We do not intend to imply that any treatment options within CMM do not provide satisfactory pain relief for patients with chronic pain, nor that CMM does not provide a meaningful level of pain relief for any individual patient; simply that a proportion of patients with chronic pain may not obtain satisfactory pain relief with conservative treatment options (i.e., those eligible for SCS). For these patients, as shown in this systematic review, CMM options have limited effect for reduction in pain intensity. Nonetheless, patients that respond to conservative treatment options are not eligible for SCS and as such, these interventions would not be appropriate as a comparator to SCS.

CONCLUSION

Current evidence shows that CMM for a population eligible for SCS has not changed over the last few decades. Although novel conservative treatment options continue to be developed and show promise for people with chronic pain, a proportion of patients may not obtain satisfactory pain relief over the long-term. It is this patient population that shows a lack of response to conservative treatment options that is considered for SCS. The enduring consideration of CMM as standard of care to evaluate relative SCS treatment effects should be reassessed.

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Conflict of Interest Statement: MR discloses nonpaid consultancies to Abbott, Boston Scientific, Mainstay Medical, Medtronic, Nevro, Presidio Medical, Saluda Medical, and Stimwave and research activities for Boston Scientific, Mainstay Medical, Medtronic, Nevro, Presidio Medical, and Saluda Medical. He has equity holdings in Lungpacer and SPR Therapeutics. He has options in Saluda Medical and Presidio Medical. SN discloses consultancy fees from Saluda Medical. DS discloses no conflict of interest. SE discloses consultancy fees from Medtronic, and Mainstay Medical outside the submitted work. He has received department research funding from the National Institute of Health Research, Saluda Medical and Medtronic. RVD is an employee of Saluda Medical, the employer had no role in this work. He has previously received consultancy fees from Mainstay Medical, Medtronic, and Saluda Medical.

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Supplementary Material 1

Ovid MEDLINE(R) ALL <1946 to June 05, 2024>

1 spinal cord stimulat*.ti,ab,kw.
2 dorsal column stimulat*.ti,ab,kw.
3 epidural stimulat*.ti,ab,kw.
4 exp Spinal cord stimulation/
5 HF10.ti,ab,kw.
6 ((burst or high-density or closed-loop or high-frequency) adj3 (stimulat* or SCS)).ti,ab,kw.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Neuralgia/
9 exp PERIPHERAL NERVOUS SYSTEM DISEASES/
10 exp SOMATOSENSORY DISORDERS/
11 ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).ti,ab,kw.
12 ((neur* or nerv*) adj6 (compress* or damag*)).ti,ab,kw.
13 non-surgical refractory back pain.ti,ab,kw.
14 persistent spinal pain syndrome.ti,ab,kw.
15 PSPS.ti,ab,kw.
16 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 7 and 16
18 randomized controlled trial.pt.
19 controlled clinical trial.pt.
20 randomized.ab.
21 placebo.ti,ab.
22 drug therapy.fs.
23 randomly.ab.
24 trial.ab.
25 groups.ab.
26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 exp animals/
28 humans/
29 27 not 28
30 26 not 29
31 clinical trial, phase iii/
32 ("phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
33 31 or 32
34 30 or 33
35 17 and 34

Cochrane Central Register of Controlled Trials CENTRAL (via The Cochrane Library)
Issue 5 of 12, May 2024

#1 (spinal NEXT cord NEXT stimulat*):ti,ab,kw
#2 (dorsal NEXT column NEXT stimulat*):ti,ab,kw
#3 (epidural NEXT stimulat*):ti,ab,kw
#4 MeSH descriptor: [Spinal Cord Stimulation] explode all trees
#5 (HF10):ti,ab,kw
#6 ((burst or high-density or closed-loop or high-frequency) NEAR/3 (stimulat* or SCS)):ti,ab,kw
#7 {OR #1-#6}
#8 MeSH descriptor: [Neuralgia] explode all trees
#9 MeSH descriptor: [Peripheral Nervous System Diseases] explode all trees

#10 MeSH descriptor: [Somatosensory Disorders] explode all trees
#11 ((pain* or discomfort*) NEAR/10 (central or complex or nerv* or neuralg* or neuropath*)):ti,ab,kw
#12 ((neur* or nerv*) NEAR/6 (compress* or damag*)):ti,ab,kw
#13 (non-surgical refractory back pain):ti,ab,kw
#14 (persistent spinal pain syndrome):ti,ab,kw
#15 (PSPS):ti,ab,kw
#16 {OR #8-#15}
#17 #7 AND #16

Embase
Embase <1974 to 2024 June 05>

1 spinal cord stimulat*.ti,ab,kw.
2 dorsal column stimulat*.ti,ab,kw.
3 epidural stimulat*.ti,ab,kw.
4 exp spinal cord stimulation/
5 HF10.ti,ab,kw.
6 ((burst or high-density or closed-loop or high-frequency) adj3 (stimulat* or SCS)).ti,ab,kw.
7 or/1-6
8 exp neuropathic pain/
9 exp neuralgia/
10 exp peripheral neuropathy/
11 exp somatosensory disorder/
12 ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).ti,ab,kw.
13 ((neur* or nerv*) adj6 (compress* or damag*)).ti,ab,kw.
14 non-surgical refractory back pain.ti,ab,kw.
15 persistent spinal pain syndrome.ti,ab,kw.
16 PSPS.ti,ab,kw.
17 or/8-16
18 7 and 17
19 Randomized controlled trial/
20 Controlled clinical study/
21 random*.ti,ab.
22 randomization/
23 intermethod comparison/
24 placebo.ti,ab.
25 (compare or compared or comparison).ti.
26 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
27 (open adj label).ti,ab.
28 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
29 double blind procedure/
30 parallel group$1.ti,ab.
31 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
32 (assigned or allocated).ti,ab.
33 (controlled adj7 (study or design or trial)).ti,ab.
34 (volunteer or volunteers).ti,ab.
35 human experiment/
36 trial.ti.
37 or/19-36

38 Animal experiment/ not (human experiment/ or human/)
39 37 not 38
40 18 and 39
41 "randomized controlled trial (topic)"/
42 18 and 41
43 40 or 42

WIKISTIM
Search SCS (spinal cord stimulation) entries

Neuropath*

Supplementary Material 2

In the first instance, we extracted outcome data calculated using an intention-to-treat (ITT) approach from the included studies and where outcome data from an ITT approach were not available, we extracted outcome data from complete-case approaches or per-protocol approaches, or for the populations who provided outcome data at specific follow-up times. Where cross-over from the CMM group to the SCS intervention group was allowed after primary study endpoint, data from the last follow-up before cross-over only were considered for inclusion in the analysis. Where pain intensity outcome data (i.e. means and standard deviations) were reported at baseline and at follow-up time points but change scores from baseline were not reported, mean change and associated standard errors were calculated according to formulae outlined in the Cochrane Handbook,[1] using correlation coefficients of 0.33 and 0.5 at 3-months and 6-months respectively, calculated from the CMM group of the RCT with IPD provided.[2]

To standardise outcome data to a single scale for pain intensity, we assumed that the VAS scale (0-10 cm) and the NRS scale (0-10) were equivalent, and we converted the VAS scale (0-100 mm) by dividing pain scores by 10. One RCT reported pain intensity separately during the day and during the night.[3] To allow pooling of pain intensity outcome data, an average of the day and night mean pain scores and data was used. Two studies included in meta-analysis reported pain intensity scores for (lower) back pain and for leg pain separately.[4,5] In our primary approach, we included back pain scores in meta-analysis and conducted sensitivity analysis including leg pain scores in meta-analysis. Numerical results of meta-analysis were similar, and conclusions were unchanged (Supplementary Material 4).

Supplementary Material 3

Change in pain intensity according to patient diagnosis

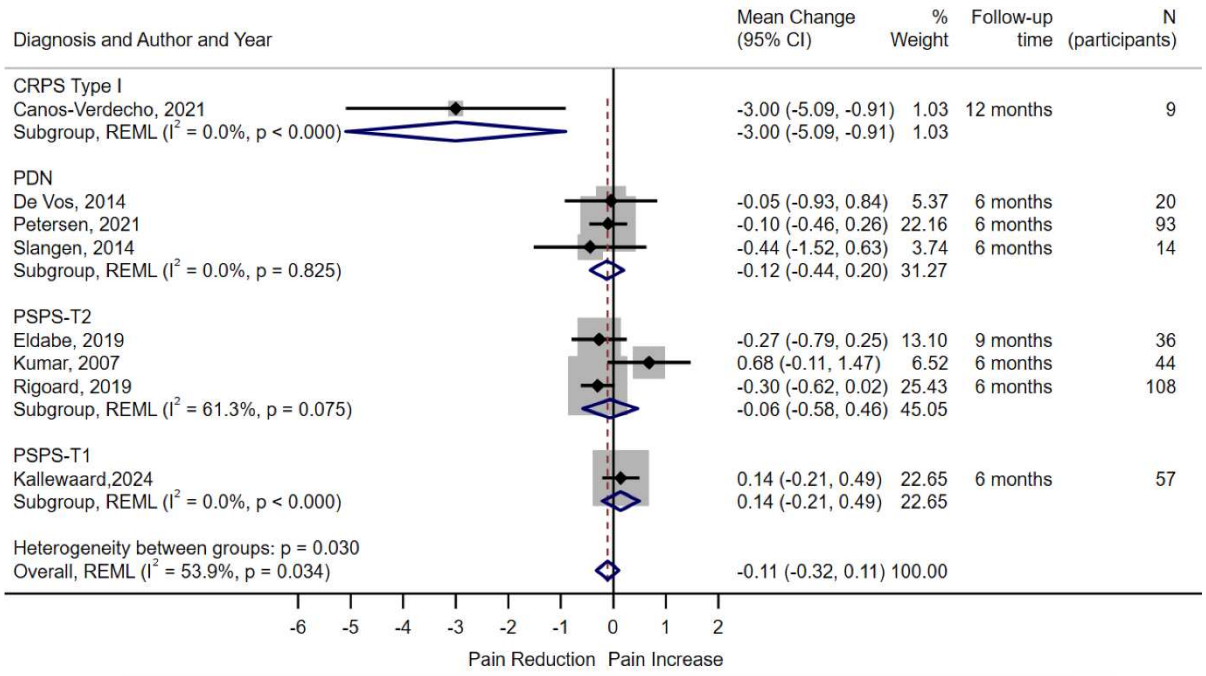

Figure S1. Absolute change in pain intensity from baseline to last follow-up according to patient diagnosis (8 studies, 381 participants)

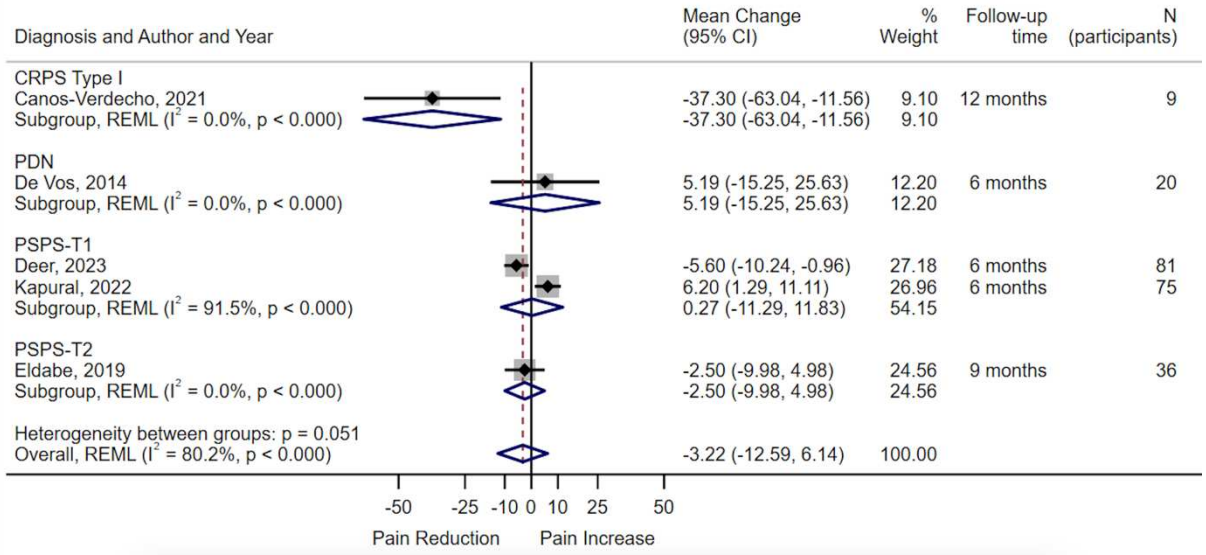

Figure S2. Percent change in pain intensity from baseline to last follow-up according to patient diagnosis (5 studies, 221 participants)

Supplementary Material 4

Change in pain intensity to 3- and 6-month follow-up

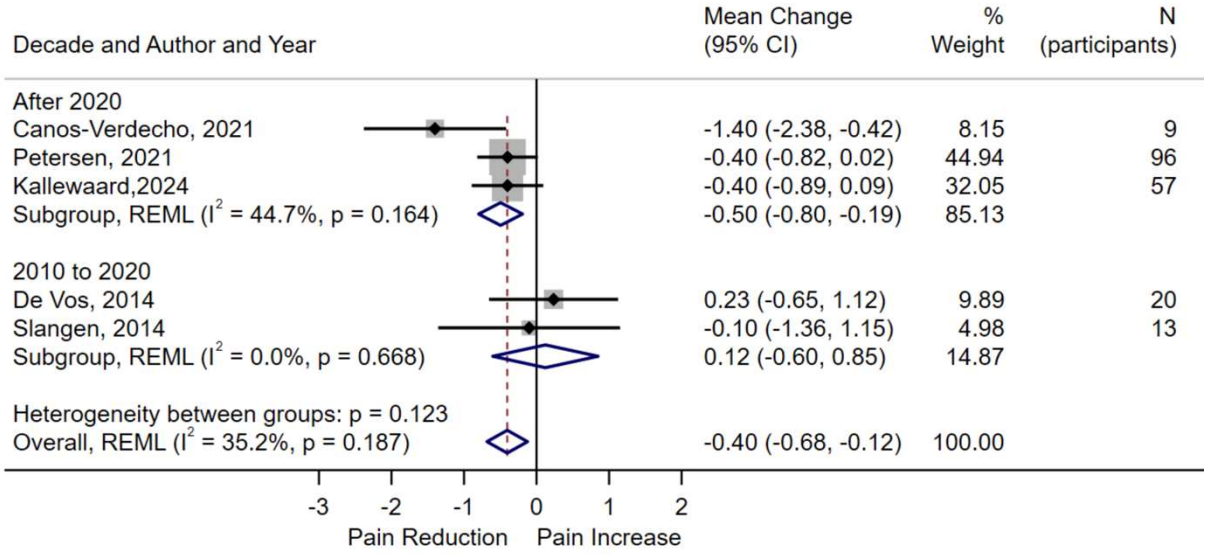

Figure S3. Absolute change in pain intensity from baseline to 3-month follow-up according to decade of publication of the RCT (5 studies, 195 participants)

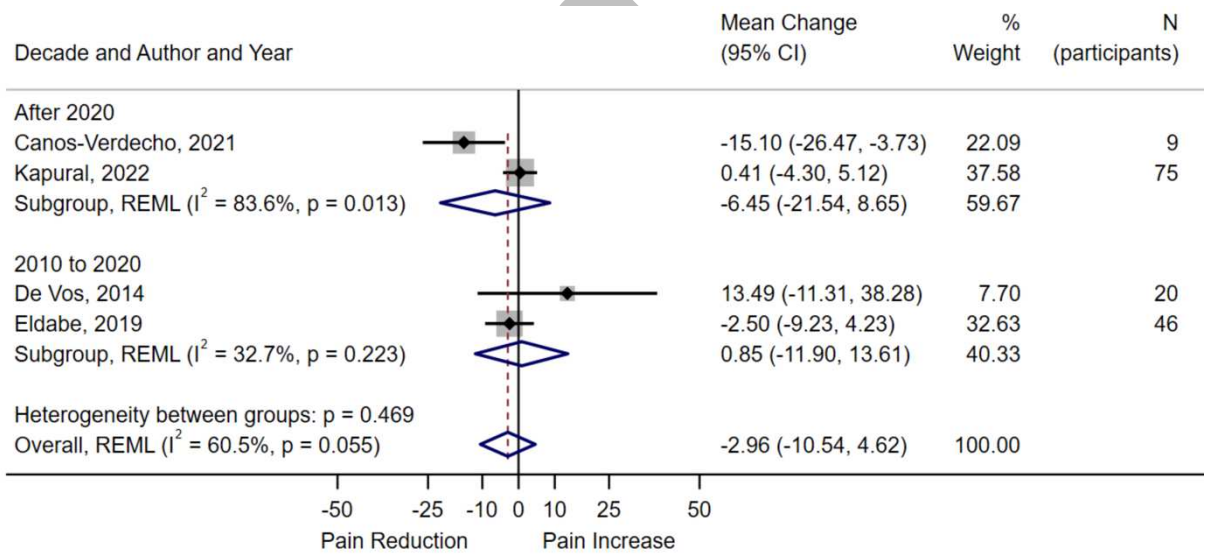

Figure S4. Percent change in pain intensity from baseline to 3-month follow-up according to decade of publication of the RCT (4 studies, 150 participants)

NB – Percent change in pain intensity from baseline to 3-month follow-up according to patient diagnosis were not performed because the 4 studies all have different diagnoses, so there are no 'subgroups' to test.

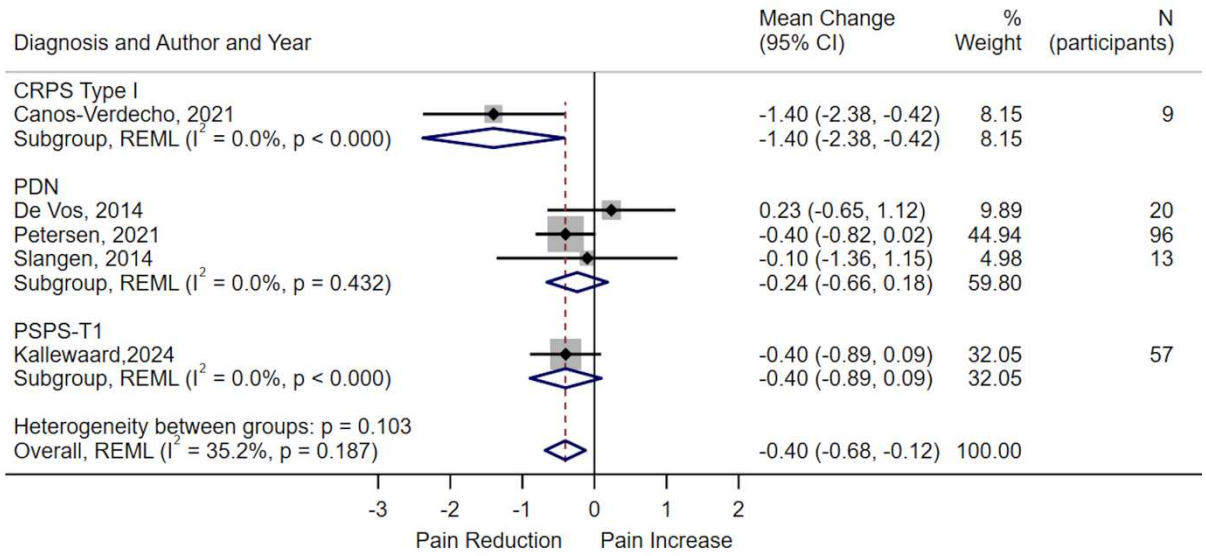

Figure S5. Absolute change in pain intensity from baseline to 3-month follow-up according to patient diagnosis (5 studies, 195 participants)

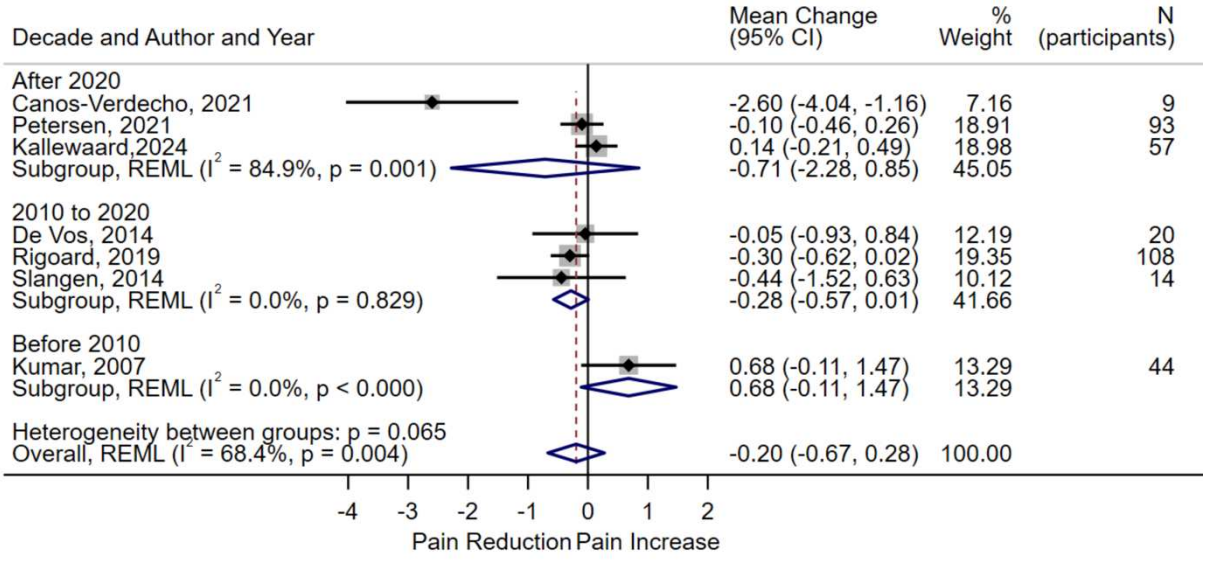

Figure S6. Absolute change in pain intensity from baseline to 6-month follow-up according to decade of publication of the RCT (7 studies, 345 participants)

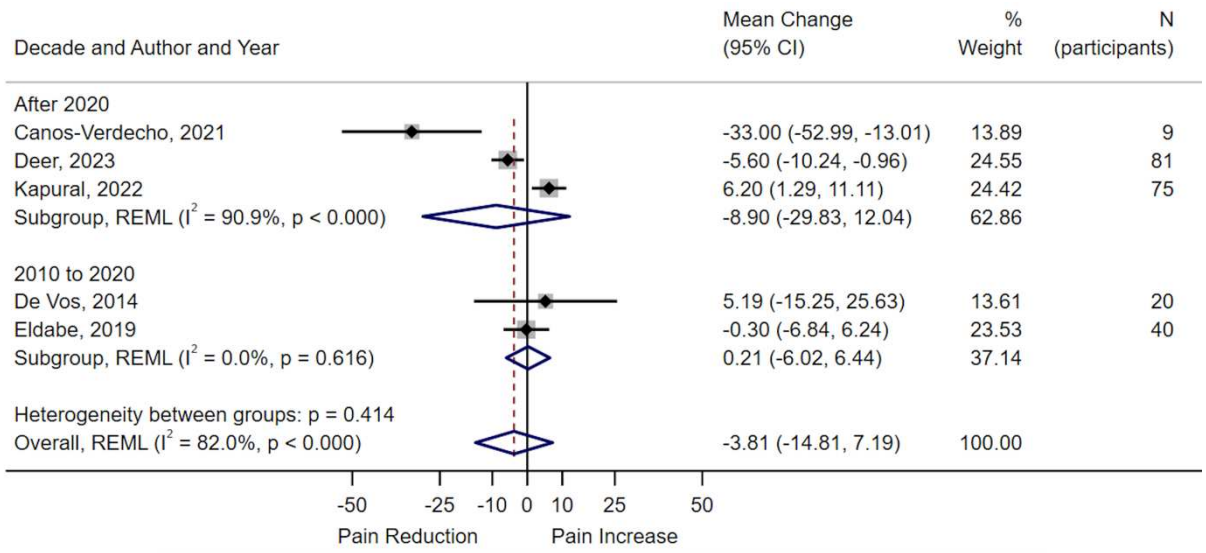

Figure S7. Percent change in pain intensity from baseline to 6-month follow-up according to decade of publication of the RCT (5 studies, 225 participants)

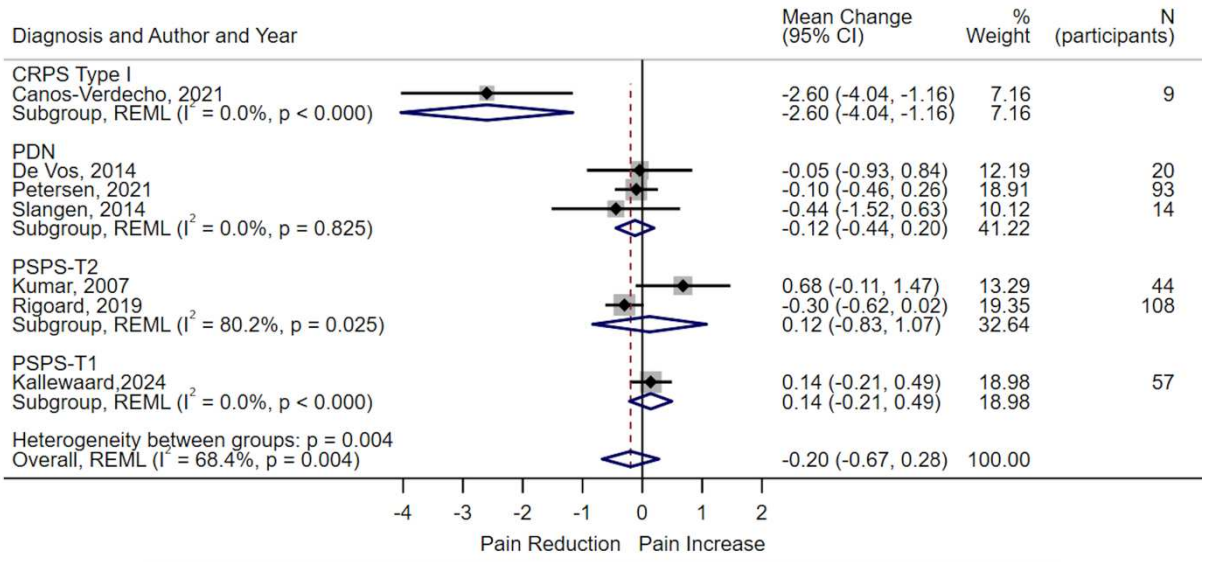

Figure S8. Absolute change in pain intensity from baseline to 6-month follow-up according to patient diagnosis (7 studies, 345 participants)

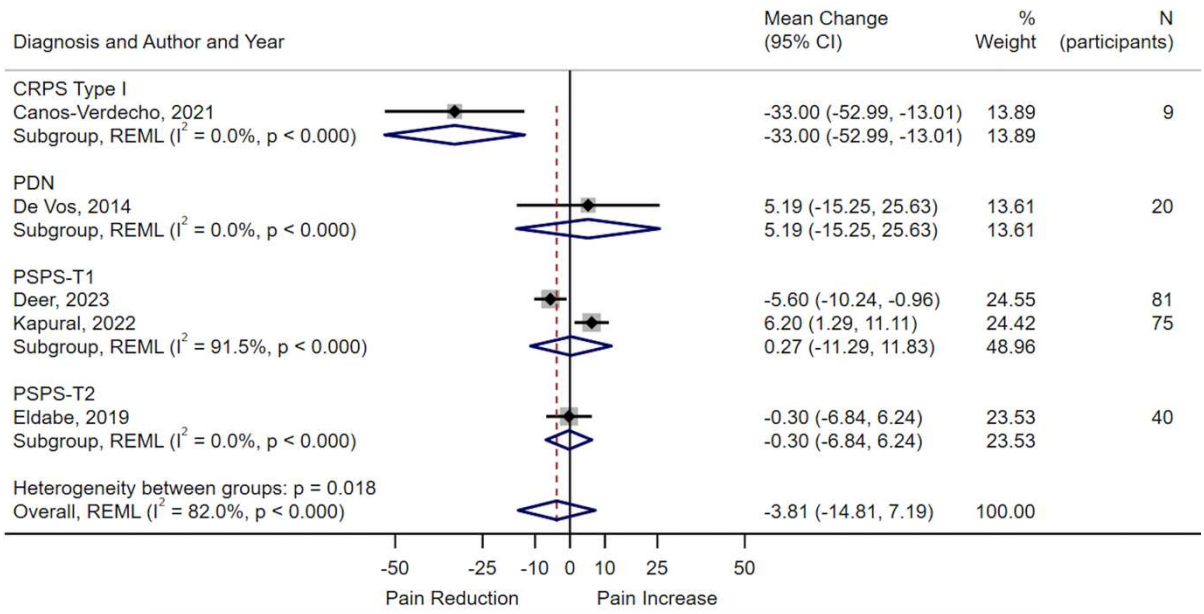

Figure S9. Percent change in pain intensity from baseline to 6-month follow-up according to patient diagnosis (5 studies, 225 participants)

Supplementary Material 5

Sensitivity analysis (change in pain intensity – leg pain)

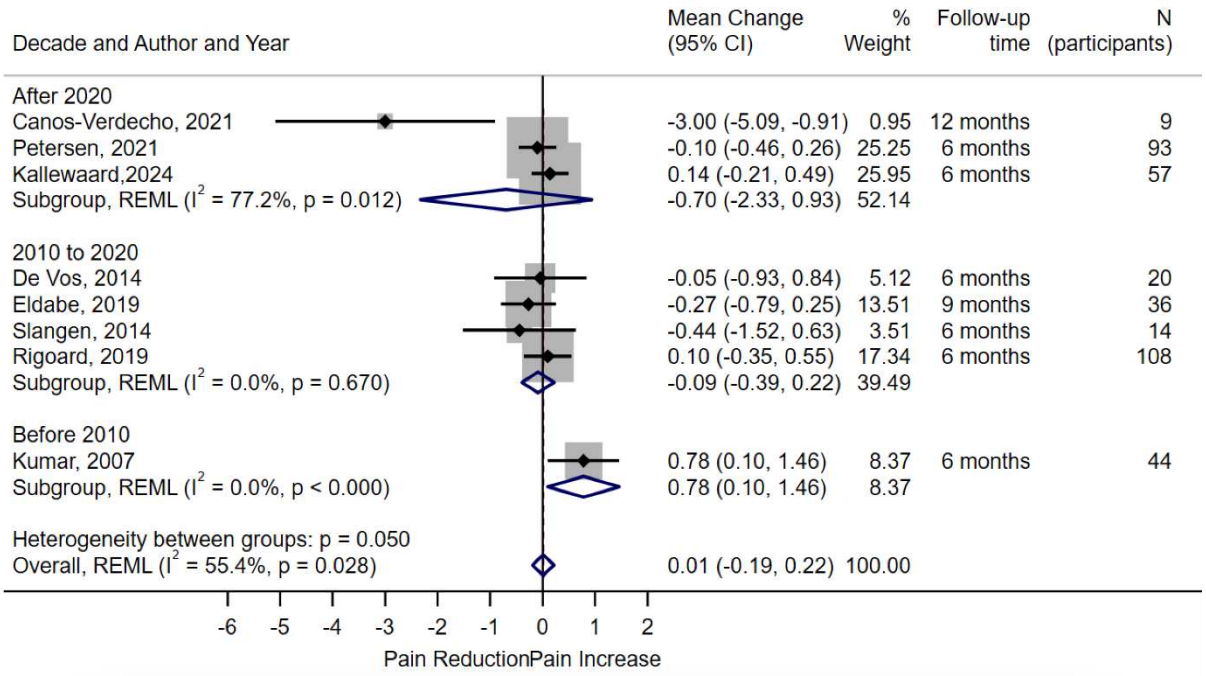

Figure S10. Sensitivity analysis of absolute change in pain intensity (leg pain) from baseline to last follow-up according to decade of publication of the RCT (8 studies, 381 participants)

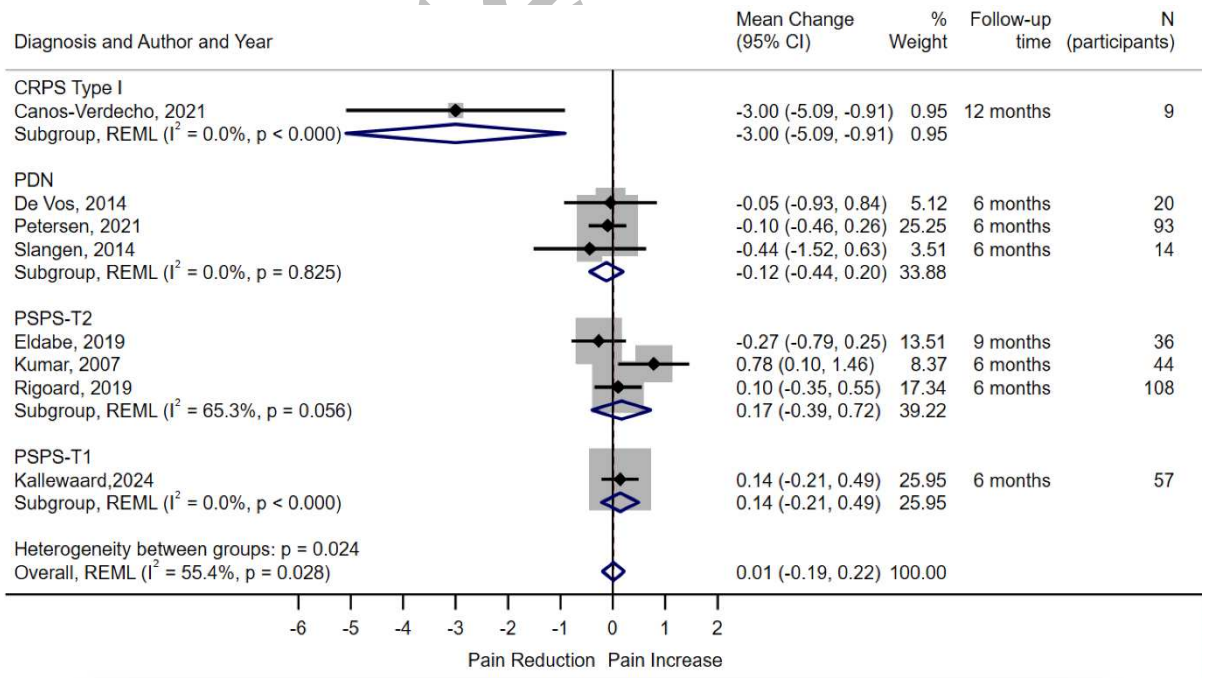

Figure S11. Sensitivity analysis of absolute change in pain intensity (leg pain) from baseline to last follow-up according to patient diagnosis (8 studies, 381 participants)

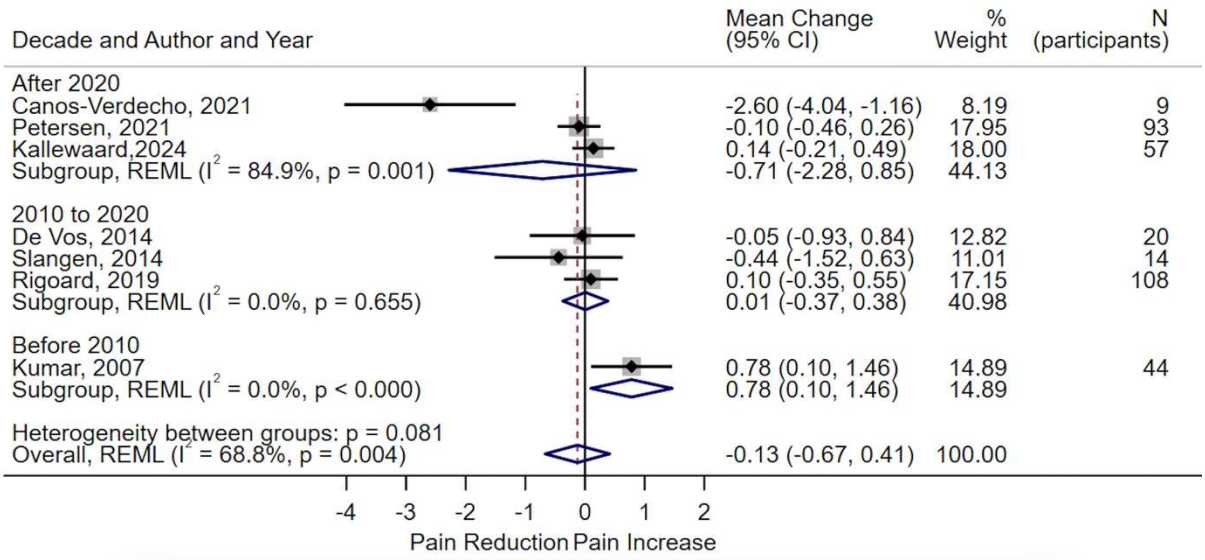

Figure S12. Sensitivity analysis of absolute change in pain intensity (leg pain) from baseline to 6-month follow-up according to decade of publication of the RCT (7 studies, 345 participants)

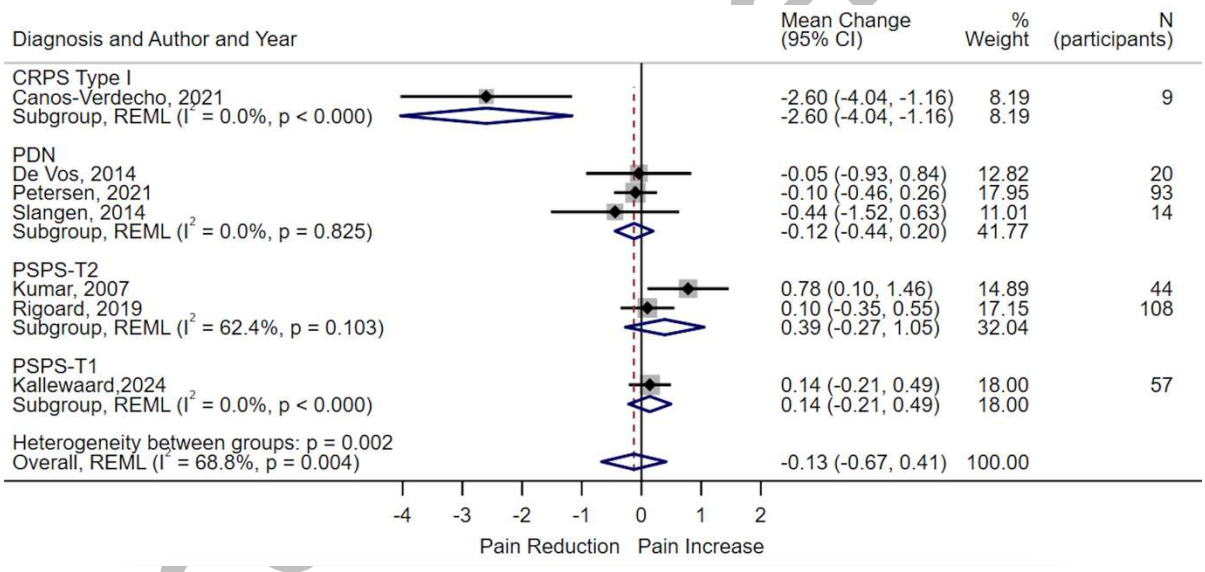

Figure S13. Sensitivity analysis of absolute change in pain intensity (leg pain) from baseline to 6-month follow-up according to patient diagnosis (7 studies, 345 participants)

References

1. Higgins J, Li T, Deeks J. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins J, Thomas J, Chandler J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 64 (updated August 2023)*. Cochrane; 2023.
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4. 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*. Nov 2007;132(1-2):179-88. doi:10.1016/j.pain.2007.07.028
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