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Systematic review and network meta-analysis of neurostimulation for painful diabetic neuropathy

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Short running title: Syst Review and NMA of neurostimulation for PDN

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ABSTRACT

Background: Different waveforms of spinal cord stimulation (SCS) have now been evaluated for the management of painful diabetic neuropathy (PDN). However, no direct or indirect comparison between SCS waveforms has been performed to date.

Purpose: To conduct a systematic review and network meta-analysis (NMA) to evaluate the effectiveness of SCS for PDN.

Data sources: MEDLINE, CENTRAL, Embase and WikiStim were searched from inception until December 2021.

Study selection: Randomised controlled trials (RCTs) of SCS for PDN were included.

Data extraction: Pain intensity, proportion of patients achieving at least a 50% reduction in pain intensity and health-related quality-of-life (HRQoL) data were extracted.

Data synthesis: Significant reductions in pain intensity were observed for low-frequency SCS (LF-SCS) (mean difference [MD] -3.13, 95% confidence interval [CI] -4.19 to -2.08, moderate certainty) and high-frequency SCS (HF-SCS) (MD -5.20, 95% CI -5.77 to -4.63, moderate certainty) compared to conventional medical management (CMM) alone. There was a significantly greater reduction in pain intensity on HF-SCS compared to LF-SCS (MD -2.07, 95% CI -3.26 to -0.87, moderate certainty). Significant differences were observed for LF-SCS and HF-SCS compared to CMM for the outcomes proportion of patients with at least 50% pain reduction and HRQoL (very low to moderate certainty). No significant differences were observed between LF-SCS and HF-SCS (very low to moderate certainty).

Limitations: Limited number of RCTs and no head-to-head RCTs conducted.

Conclusions: Our findings confirm the pain relief and HRQoL benefits of the addition of SCS to CMM for patients with PDN. However, in the absence of head-to-head RCT evidence the relative benefits of HF-SCS compared to LF-SCS for patients with PDN remains uncertain.

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The prevalence of diabetes has increased nearly four-fold from 108 million adults in 1980 to 422 million in 2014, equivalent to a global prevalence rate of 8.5%.(1) It is estimated that approximately 50% of people with diabetes will experience peripheral neuropathy(2; 3) and one-third will develop painful diabetic neuropathy (PDN).(4) PDN is associated with impairments on daily living and functioning, sleep disturbance and poor health-related quality of life (HRQoL).(5) The annual healthcare costs associated with the management of PDN are estimated to be approximately double those required for patients with diabetes without neuropathy or non-painful diabetic neuropathy.(6) Excluding diabetes treatment medications, patients with PDN were 2 to 3.5 times more likely to use opioids, anticonvulsant drugs and antidepressants, respectively when compared to patients with diabetes without neuropathy.(6)
Spinal cord stimulation (SCS) is a recommended intervention for the management of chronic neuropathic pain conditions.(7) Fixed output low frequency SCS (LF-SCS; frequency 10-100Hz, pulse width 100-1000μs, amplitude 1-10mA) delivers paraesthesia-based stimulation, where the patient feels a tingling sensation.(8) LF-SCS may on occasions cause paraesthesia that is uncomfortable for the patient.(9) High frequency SCS (HF-SCS; frequency 1-10kHz, pulse width 30-150μs, amplitude 1-5mA) typically produces stimulation below the paraesthesia threshold.(8)
The effectiveness of LF-SCS for PDN has been investigated in case reports, small case series, randomised controlled trials (RCTs) and systematic reviews.(10-18) The addition of HF-SCS has been demonstrated to provide superior pain relief and improvement in HRQoL than standard of care for patients with PDN in a US multicentre RCT.(19) However, a direct comparison of LF-SCS with HF-SCS for PDN has not been previously conducted and therefore their relative efficacy and safety remains uncertain. Network meta-analysis (NMA) can combine direct and indirect evidence, including all relevant data from studies with at least two treatment arms and therefore allow assessment of interventions that may not have been evaluated in a head-to-head comparison.
The aim of this systematic review and network meta-analysis was to evaluate the relative effectiveness of SCS for the management of PDN and compare the relative effects of LF-SCS versus HF-SCS.

RESEARCH DESIGN AND 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.(20) This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses incorporating NMA (PRISMA-NMA).(21) The protocol for this review is registered on PROSPERO as CRD42022299430.

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Search strategy

Electronic databases MEDLINE, CENTRAL, Embase and WikiStim were searched by an information specialist (MM) from inception to December 17, 2021. Electronic database selection follows Cochrane recommendations.(22) WikiStim was also searched as its focus is on neurostimulation studies. The search strategies were designed using a combination of both indexing and free-text terms with no restriction on language. The search strategies are presented in Supplementary material 1. Search results were exported to EndNote X9 library and de-duplicated. The reference lists of relevant systematic reviews and eligible studies were hand-searched to identify further potentially relevant studies.

Study selection

The citations identified were assessed for inclusion in the review using a two-stage process. First, two reviewers (RD and SC) independently screened all the titles and abstracts identified by the electronic database searches to identify the potentially relevant articles to be retrieved. Second, full-text copies of these studies were obtained and assessed independently by two reviewers (RD and SC) for inclusion. Any disagreements were resolved through discussion at each stage, and, if necessary, in consultation with a third reviewer (SE). Studies were eligible for inclusion if they met the following criteria: 1) adult patients (18 years of age or older) with a diagnosis of refractory diabetic neuropathic pain, 2) intervention was SCS (all stimulation protocols), 3) comparator was usual care, an active intervention or placebo, and 4) RCT study design.

Risk of bias assessment

Risk of bias was assessed by using the revised Cochrane risk of bias tool (RoB 2.0).(23) Risk of bias assessment of the included studies was undertaken by one reviewer (RD) and assessed for agreement by a second reviewer (SN). Any disagreements were resolved by discussion and, if necessary, in consultation with a third reviewer (SE).

Outcomes

The primary outcome was pain intensity measured on a visual analogue scale (VAS) or numeric rating scale (NRS) at the last follow-up time point available. Where cross-over from the control group to SCS was allowed after primary study endpoint, data from the last follow-up before cross-over only were considered for inclusion in the analysis.

Secondary outcomes were proportion of patients achieving at least a 50% reduction in pain intensity and HRQoL

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Data extraction and statistical analysis

Individual patient data (IPD) were obtained from the authors of one of the three RCTs meeting the inclusion criteria(16) and data items were extracted at study level from the other two eligible RCTs.(17; 19)

Data extracted or provided within IPD were study author and year of publication, country where the study was conducted, study design characteristics (i.e., randomisation procedure and duration of follow-up), demographic data (i.e., age and sex), type of diabetes, duration of diabetes, duration of pain due to diabetes, details on the intervention procedure, and outcome data including the number of participants included in the analysis and the measurement time of the outcome. IPD were cross-checked and outcomes calculated as previously reported.(18)

Pain intensity outcome data (VAS or NRS) were reported or could be calculated at 3 and 6 months for the three RCTs. HRQoL outcome data (EQ-5D VAS scale and EQ-5D Index Scale) and the proportion of patients with at least a 50% reduction in pain intensity at 6 months were reported or could be calculated 6 months for the three RCTs. Outcome data available only in graphical format were extracted using WebPlot Digitiser (https://automeris.io/WebPlotDigitizer/).

The measure of treatment effect for pain intensity and HRQoL outcomes was mean difference (MD) and 95% confidence interval (CI), and for at least a 50% reduction in pain intensity was risk ratio (RR). Details on how outcomes were calculated are presented in Supplementary material 2.

In addition to the direct comparisons of LF-SCS versus conventional medical management (CMM) and HF-SCS versus CMM made within the three RCTs, NMA was performed to allow for an indirect comparison of LF-SCS and HF-SCS to be made (Figure 1).

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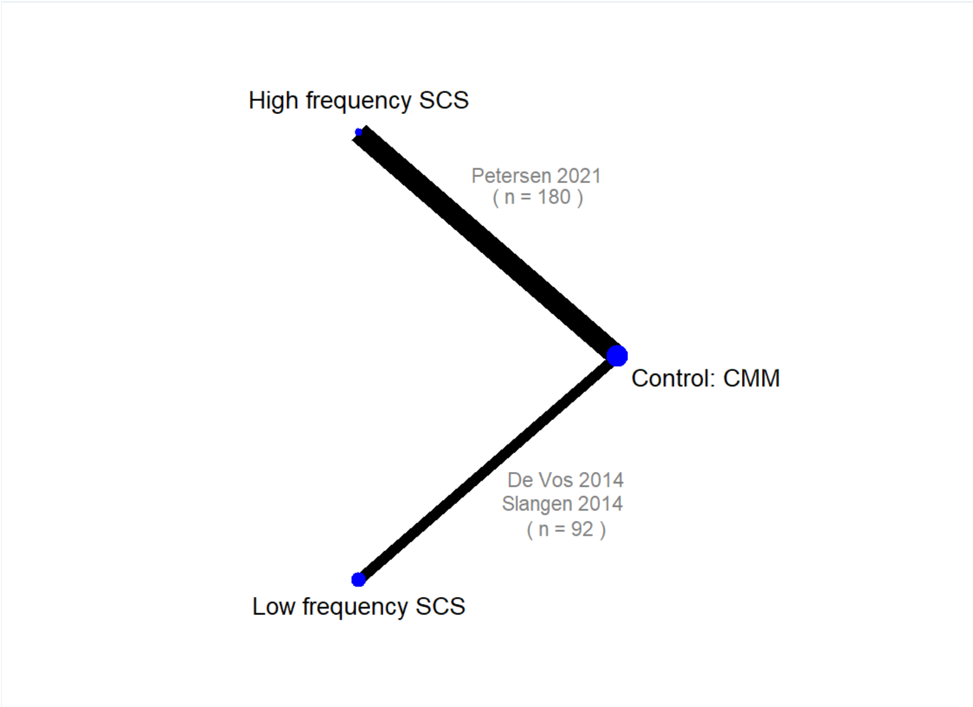

Figure 1. Network plot of SCS (low frequency and high frequency) and CMM

Owing to the similarities in the populations, designs, and treatment protocols of the three RCTs,(16; 17; 19) clinical and statistical heterogeneity was not anticipated and statistical heterogeneity was not observed within our previous analysis(18) for most outcomes. Therefore, in the first instance, NMA was performed using a fixed-effects model.

We assessed the level of statistical heterogeneity present between trials by comparison of trial and participant characteristics and trial results and formally according to the I^2 statistic (the percentage of variability between trials that is due to statistical heterogeneity) and the Tau^2 statistic (an estimate of the between-study variance in the NMA). If any important heterogeneity was deemed to be present for any outcome, NMA was also performed using a random-effects model as a sensitivity analysis.

NMA was performed in a frequentist framework using the netmeta command(24) in R version 4.0.2. The network diagram and forest plots of results for all pairwise comparisons were produced in Stata version 14.1.

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.(25) We assessed the confidence in the NMA results (i.e., a framework similar to GRADE certainty of the evidence) according to the CINeMA approach,(26) 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'.

RESULTS

Study selection

After de-duplication, the search identified a total of 132 potentially eligible records. Following initial screening of titles and abstracts, five records were potentially relevant and were retrieved to allow assessment of the full-text publication. After review of the full-text publications, three studies were included in the review.(16; 17; 19) Two studies(27; 28) were excluded at the full-text paper screening stage because data presented were for the follow-up of one of the RCTs(17) after patients crossed-over from the control group to SCS. The PRISMA flowchart detailing the screening process for the review is shown in Figure 2.

Characteristics of included studies

The characteristics of the included RCTs are summarised in Table 1. The RCTs were multicentre, one performed in 2 centres in the Netherlands,(17) one across 7 pain clinics in the Netherlands, Denmark, Belgium, and Germany,(16) and one in 18 research sites across the United States.(19) The populations and study design were similar in the included RCTs. Ethnicity was only reported in the Petersen RCT with a broadly white population.(19) The time since diagnosis of diabetes was longer in the RCT by De Vos.(16) Two of the RCTs evaluated paraesthesia-inducing LF-SCS(16; 17) and one investigated paraesthesia-free HF-SCS(19). Patients allocated to the SCS arm could also receive CMM, while patients in the control group received CMM alone. All RCTs included a temporary screening trial prior to implantation of the permanent SCS device. The randomisation ratios were 2:1, 3:2, and 1:1 in the De Vos,(16) Slangen(17) and Petersen(19) RCTs, respectively. The primary outcome for the RCTs evaluating LF-SCS(16; 17) was the proportion of patients with at least 50% pain reduction at 6-month follow-up. The primary outcome in the RCT of HF-SCS(19) was a composite outcome of effectiveness and stable neurological examination requiring 50% or more pain relief by VAS without a meaningful worsening of baseline neurological deficits at 3-month follow-up. Proportion of patients with at least 50% pain reduction at 6-month follow-up was a secondary outcome in this RCT.

[Insert Table 1 here]

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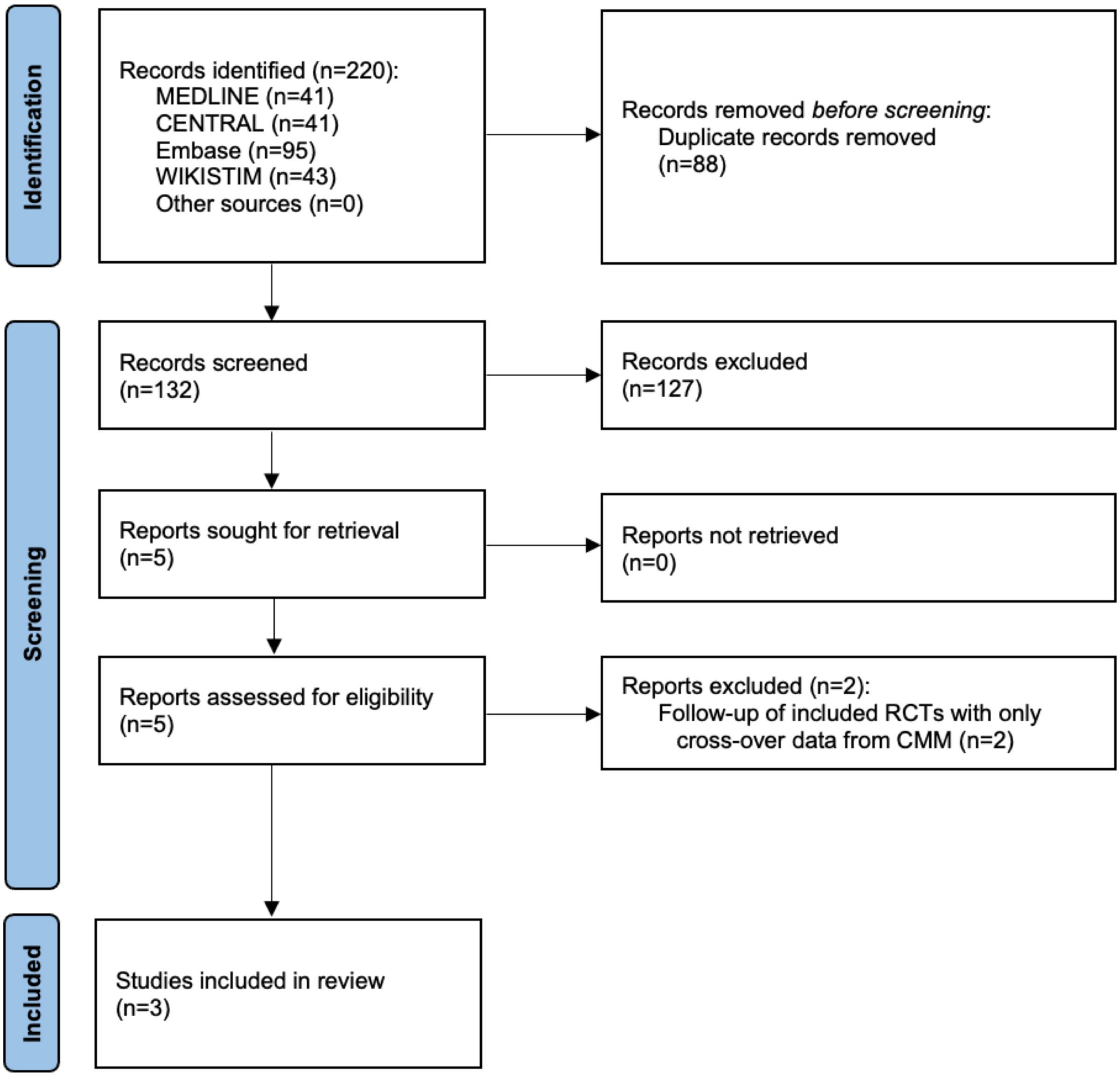

Figure 2. PRISMA 2020 flow diagram

Risk of bias assessment

The summary of the risk of bias assessment is presented in Table 2. All RCTs were judged to have a low risk of bias for the domains of the process of randomisation, deviations from intended interventions, and level of missing outcome data. However, all RCTs were judged to have a high risk of bias for outcome measurement as these were open label trials with outcome assessors aware of the interventions received. Also contributing to the high risk of bias in this domain is 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. There was no mention in two of the RCTs(16; 17) if the statistical analyses followed a pre-specified statistical analysis plan which resulted in the domain selection of the reported result being judged as presenting some concerns. The other RCT(19) followed a statistical analysis plan finalised before data were available for analysis. The overall bias for the included studies was considered to be high because at least one domain was judged to have a high risk of bias.

[Insert Table 2 here]

Outcomes

Figure 3 shows the results of fixed-effects NMA of pain intensity and EQ-5D outcomes at 6 months. For all outcomes and analyses conducted, HF-SCS has the highest probability of being the best treatment option (Supplementary Table 1).

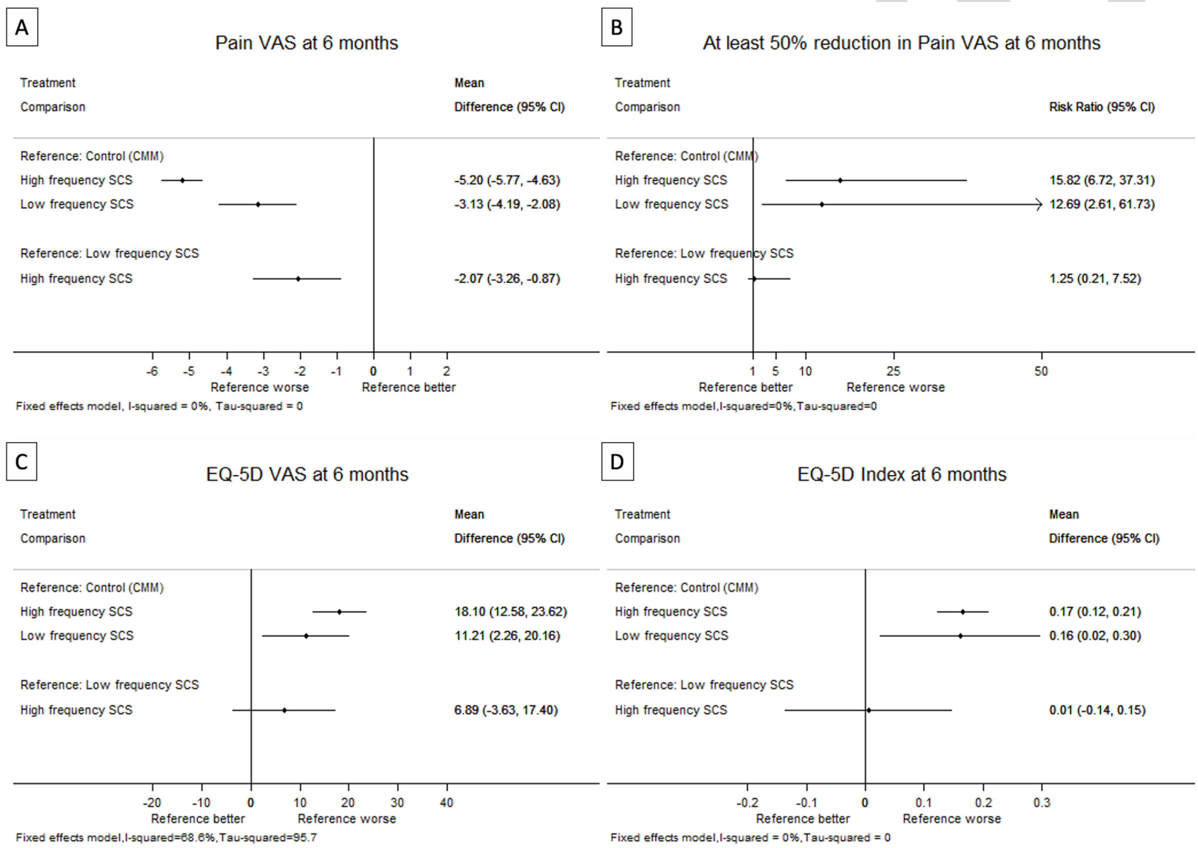

Figure 3. Direct treatment comparisons of low frequency and high frequency SCS versus CMM and indirect treatment comparison of low frequency versus high frequency SCS at 6 months for pain intensity (0-10 scale) (A), at least 50% pain reduction (0-100% scale) (B), EQ-5D VAS scale (0-100 scale) (C) and EQ-5D utility index (0-1.00 scale) (D)

Pain intensity

There was a statistically significant reduction in pain intensity on both LF-SCS (MD -3.13, 95% CI -4.19 to -2.08, moderate certainty) and HF-SCS (MD -5.20, 95% CI -5.77 to -4.63, moderate certainty) compared to CMM at 6 months follow-up. There was a significantly greater reduction in pain intensity on HF-SCS compared to LF-SCS (MD -2.07, 95% CI -3.26 to -0.87, moderate certainty) (Figure 3A).

At 3 months, statistically significant reductions in pain intensity on both LF-SCS and HF-SCS were observed compared to CMM, but there was no statistically significant difference between HF-SCS and LF-SCS (Supplementary Figure 1A). Sensitivity analyses of pain intensity at 3 and 6 months including an additional 7 participants excluded from the per-protocol analyses of the Petersen(19) RCT showed very similar results to the main analysis, and conclusions were unchanged (Supplementary Figure 1C, 1D).

Proportion of patients achieving at least 50% reduction in pain intensity

Significantly more patients on both LF-SCS (RR 12.69, 95% CI 2.61 to 61.73, very low certainty) and HF-SCS (RR 15.82, 95% CI 6.72 to 37.31, very low certainty) achieved at least a 50% reduction in pain intensity compared with patients receiving CMM. There was no statistically significant difference between HF-SCS and LF-SCS in the proportion of participants achieving at least a 50% reduction in pain intensity (RR 1.25, 95% CI 0.21 to 7.52, very low certainty) (Figure 3B). However, the numbers of participants, particularly within the CMM groups of the studies, achieving at least a 50% reduction in pain intensity were low, resulting in wide 95% CIs intervals around the RRs. Therefore, the magnitude of treatment effect of SCS over CMM and of HF-SCS versus LF-SCS are uncertain for this outcome.

Health-related quality of life

Statistically significant increases in EQ-5D VAS scale scores and in EQ-5D utility index scores were observed on both LF-SCS and HF-SCS compared to CMM, but no statistically significant differences between HF-SCS and LF-SCS were observed for these HRQoL outcomes (Figure 3C and Figure 3D).

Substantial heterogeneity was present in the analysis of EQ-5D VAS score results (I^2 = 68.6%, Tau^2 = 95.7). Therefore, random-effects meta-analysis was also conducted for EQ-5D VAS score, resulting in no statistically significant difference for any of the comparisons (Supplementary Figure 1B). No heterogeneity was present in the analyses for any other outcomes (I^2 = 0%, Tau^2 = 0).

Adverse events

Treatment related adverse events reported in the De Vos RCT(16) were one infection during the screening trial, two patients who perceived an incomplete overlap of the paraesthesia with the painful area during the screening trial, two patients with pain due to the implanted pulse generator and one patient that coagulopathy complicating the implantation procedure; all resolved and not requiring explant of the SCS device. One patient in the Slangen RCT(17)

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developed postdural puncture headache following a dural puncture, which was complicated by a lethal subdural hematoma 3 days after the procedure, one patient required device explant due to an infection six weeks after implantation of the SCS system. Two treatment related serious adverse events (device extrusion and wound infection) and 18 adverse events in 14 HF-SCS patients were reported in the Petersen RCT.(19) The most frequent adverse events were infection (n=3) and wound dehiscence (n=2) while a paraesthesia related adverse event was reported by 1 patient. Device explant was required for 2 patients following infection.(19)

Certainty of evidence

Figure 4 presents the certainty of evidence for the outcomes evaluated. There was moderate certainty evidence for the outcomes pain intensity VAS and EQ-5D utility index and low certainty evidence for EQ-5D VAS due to risk of bias, imprecision or serious heterogeneity being present. There were very low numbers of patients in the CMM group obtaining at least 50% reduction in pain intensity, which resulted in very wide 95% CIs around the RR and therefore very low certainty evidence for this outcome.

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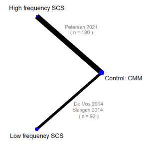
Patient or Population: adults with a diagnosis of refractory diabetic neuropathic pain
Interventions: High Frequency SCS, Low Frequency SCS
Comparator (reference): Conventional Medical Management (CMM)
Total number of studies: Three RCTs
Total number of participants: 272 participants

Geometry of the network



Intervention	Comparator	Direct evidence	Network estimates (Fixed effects): Anticipated absolute effect (95% CI)	Network estimates (Fixed effects): Relative effect (95% CI)	Certainty of the evidence (GRADE / CINeMA)	Interpretation of Findings
Outcome: Pain Intensity (VAS 0 to 10 cm) at 6 months						
High Frequency SCS	CMM	1 RCT (180 participants)	Mean pain intensity is 5.20cm lower in the high frequency SCS group compared to the CCM group (5.77cm lower to 4.63cm lower)	NA	⊕⊕⊕○ Moderate[1,2,3]	High frequency SCS probably reduces pain intensity compared to CCM
Low Frequency SCS	CMM	2 RCTs (92 participants)	Mean pain intensity is 3.13cm lower in the low frequency SCS group compared to the CCM group (4.19 lower to 2.08 lower)	NA	⊕⊕⊕○ Moderate[1,2,3]	Low frequency SCS probably reduces pain intensity compared to CCM
High Frequency SCS	Low Frequency SCS	No direct evidence	Mean pain intensity is 2.07cm lower in the high frequency SCS group compared to the low frequency SCS group (4.19cm lower to 2.08cm lower)	NA	⊕⊕⊕○ Moderate[1,2,3]	High frequency SCS probably reduces pain intensity compared to low frequency SCS
Outcome: At least 50% reduction in Pain Intensity at 6 months						
High Frequency SCS	CMM	1 RCT (180 participants)	**Without intervention[4]:** 47 per 1000; **With intervention[5]:** 747 per 1000 (317 to 1000 per 1000)	RR 15.82 (6.72 to 37.31)	⊕○○○ Very low[1,2,6,7]	The effect of high frequency SCS compared CCM in reducing pain intensity by at least 50% is very uncertain
Low Frequency SCS	CMM	2 RCTs (92 participants)	**Without intervention[4]:** 47 per 1000; **With intervention[5]:** 599 per 1000 (123 to 1000 per 1000)	RR 12.69 (2.61 to 61.73)	⊕○○○ Very low[1,2,6,7]	The effect of low frequency SCS compared to CCM in reducing pain intensity by at least 50% is very uncertain
High Frequency SCS	Low Frequency SCS	No direct evidence	**Without intervention[4]:** 559 per 1000; **With intervention[5]:** 705 per 1000 (117 to 1000 per 1000)	RR 1.26 (0.21 to 7.52)	⊕○○○ Very low[1,2,6,7]	The effect of high frequency SCS compared low frequency SCS in reducing pain intensity by at least 50% is very uncertain
Outcome: EQ-5D VAS scale at 6 months						
High Frequency SCS	CMM	1 RCT (180 participants)	Mean EQ-5D VAS is 18.10 higher in the high frequency SCS group compared to the CCM group (12.58 higher to 23.62 higher)	NA	⊕⊕○○ Low[1,2,8,9]	It is uncertain whether high frequency SCS increases EQ-5D VAS compared to CCM
Low Frequency SCS	CMM	2 RCTs (92 participants)	Mean EQ-5D VAS is 11.21 higher in the low frequency SCS group compared to the CCM group (2.26 higher to 20.16 higher)	NA	⊕⊕○○ Low[1,2,8,9]	It is uncertain whether low frequency SCS increases EQ-5D VAS compared to CCM
High Frequency SCS	Low Frequency SCS	No direct evidence	Mean EQ-5D VAS is 6.89 higher in the high frequency SCS group compared to low frequency SCS group (3.63 lower to 17.40 higher)	NA	⊕⊕○○ Low[1,2,8,9]	It is uncertain whether there is a difference high frequency SCS and low frequency SCS in terms of EQ-5D VAS
Outcome: EQ-5D Utility Index at 6 months						
High Frequency SCS	CMM	1 RCT (180 participants)	Mean EQ-5D Utility Index is 0.17 higher in the high frequency SCS group compared to the CCM group (0.12 higher to 0.21 higher)	NA	⊕⊕⊕○ Moderate[1,2,3]	High frequency SCS probably increases EQ-5D Utility Index compared to CCM
Low Frequency SCS	CMM	2 RCTs (92 participants)	Mean EQ-5D Utility Index is 0.16 higher in the low frequency SCS group compared to the CCM group (0.02 higher to 0.30 higher)	NA	⊕⊕⊕○ Moderate[1,2,3]	Low frequency SCS probably increases EQ-5D Utility Index compared to CCM
High Frequency SCS	Low Frequency SCS	No direct evidence	Mean EQ-5D Utility Index is 0.01 higher in the high frequency SCS group compared to low frequency SCS group (0.14 lower to 0.15 higher)	NA	⊕⊕⊕○ Moderate[1,2,3]	There is probably no difference in terms of EQ-5D Utility Index between high frequency SCS and low frequency SCS

CI=confidence interval; CMM=conventional medical management; EQ-5D=EuroQol 5-Dimension scale; NA=not applicable; SCS=spinal cord stimulation; VAS=visual analogue scale

GRADE / CINeMA Working Group Grades of Evidence (or certainty of the evidence)
High quality: We are very confident the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect Is likely to be substantially different from the estimate of the effect.

Explanatory Footnotes
[1]Certainty of the evidence downgraded due to serious within-study bias; included RCTs are not blinded and outcomes assessed (pain intensity and HRQoL) are subjective
[2]No closed loops are present in the network, therefore inconsistency (incoherence) cannot be assessed
[3]No indication of reporting bias, indirectness, imprecision or heterogeneity; no downgrades to certainty of the evidence made for these criteria.
[4] Based on the pooled comparator group event rate (corresponding to 4.7% of CCM groups across three studies and 55.9% of low frequency SCS groups across two studies with at least 50% in pain intensity at 6 months)
[5]Based on the pooled comparator group event rate and the relative effect (RR and 95% CI)
[6]Certainty of the evidence downgraded twice due to very serious imprecision; the numbers of participants, particularly in the CCM groups of the studies achieving at least a 50% reduction in pain intensity were low, resulting in very wide 95% CIs around the RRs.
[7]No indication of reporting bias, indirectness, or heterogeneity; no downgrades to certainty of the evidence made for these criteria.
[8]Certainty of the evidence downgraded due to serious heterogeneity; Substantial heterogeneity was present in the analysis (I^2 = 68.6%, Tau^2 = 95.7). Network meta-analysis was repeated using a random-effects model. showing no statistically significant difference for any comparators
[9]No indication of reporting bias, indirectness, or imprecision; no downgrades to certainty of the evidence made for these criteria.

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Figure 4. Certainty of evidence of impact of the different treatment options in the outcomes evaluated
CI=confidence interval; CMM=conventional medical management; EQ-5D=EuroQol 5-Dimension scale; NA=not applicable; SCS=spinal cord stimulation; VAS=visual analogue scale

GRADE / CINeMA Working Group Grades of Evidence (or certainty of the evidence)
High quality: We are very confident the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect Is likely to be substantially different from the estimate of the effect.
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[9]No indication of reporting bias, indirectness, or imprecision; no downgrades to certainty of the evidence made for these criteria.

DISCUSSION

The results of this NMA of 3 RCTs and a total of 272 participants show that LF-SCS and HF-SCS result in statistically significant reductions in pain intensity, a higher proportion of patients obtaining at least 50% pain reduction and improvements in EQ-5D VAS and EQ-5D utility index scores at 6 month follow-up compared with CMM for patients with PDN. There was a significantly greater reduction in pain intensity on HF-SCS compared to LF-SCS at 6 month but not at 3 month follow-up. No differences between LF-SCS and HF-SCS were observed for the outcomes proportion of patients obtaining at least 50% pain reduction or HRQoL outcomes.

The statistically significant difference in pain scores at 6 months between HF-SCS and LF-SCS is expected and aligns with previous RCT evidence comparing these waveforms in other indications.(29) However, the absence of differences between HF-SCS and LF-SCS at 3 months or in proportion of patients reporting at least 50% pain reduction does not align with results of studies comparing both waveforms in other indications(29) and may reflect the challenging nature of the PDN population. Given the subjective nature of pain assessment, the absence of a difference between both waveforms on the HRQoL outcomes and particularly EQ-5D utility index may provide a more reliable indicator of the closeness of the outcomes of both waveforms in this population.

The more recent Petersen RCT(19) represents outcomes of SCS using state of the art technology, while the De Vos(16) and Slangen(17) RCTs both characterise decade old technology. While the waveform comparison remains valid since no changes were introduced

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to paraesthesia-inducing LF-SCS, this may impact the rate and type of adverse events reported in the studies and the rates of response to SCS screening trial. The percentage of trial success is much higher in Petersen(19) (94%) than in De Vos(16) (85%) or in Slangen (77%). While this may reflect the overall higher success of trials with HF-SCS than LF-SCS, the difference between De Vos(16) and Slangen(17) possibly reflects the trial practice in the two centres involved in the Slangen RCT(17) or simply the smaller numbers recruited to the SCS intervention. Details on lead type and how this may affect outcomes were not included in the manuscripts. A previous report observed significant pain reduction both with percutaneous paddle leads and with cylindrical leads, although higher dislocation and infection rates were observed in those patients with cylindrical leads.(30)

A head-to-head trial of LF-SCS and HF-SCS and other waveforms in use in clinical practice for patients with PDN would provide greater clarity particularly if more objective outcomes such as actigraphy and continuous blood glucose monitoring were collected alongside pain scores. Burst SCS for PDN has shown promise in a case series(31) and a small cross-over RCT.(32) Different waveforms of SCS have been shown to act via different pathways in the central nervous system. Preclinical studies have shown that LF-SCS produces analgesia through segmental as well as supraspinal mechanisms. Segmental analgesia is enacted by GABA release from inhibitory interneurons at the level of the stimulated segment of the spinal cord. A supraspinal to spinal inhibitory feedback loop is mainly mediated by serotonergic pathways. The exact mechanism of action of HF-SCS remains unclear, theories formulated include the induction of a depolarisation blockade that prevents propagation of action potentials, the induction of a desynchronisation stochastic neuronal activity at the spinal gate and the induction of temporal summation of subthreshold activity to produce inhibitory neuronal activation. Future work is needed to clarify the exact mechanism of action of HF-SCS as well as clarify the implication of the recent ability to measure evoked compound action potentials (ECAPs) in the preclinical setting on mechanisms of action of LF-SCS.(33)

The cost-effectiveness of SCS for neuropathic pain has been demonstrated for LF-SCS(34; 35) and HF-SCS.(36) To date, the cost-effectiveness of SCS for PDN has only been investigated in a trial-based economic evaluation with a 12-month time horizon. The authors concluded that LF-SCS for PDN was not cost-effective in the short term.(37) Further research is required to evaluate the cost-effectiveness of both LF-SCS and HF-SCS for PDN with a time horizon adequate to capture the long-term costs, benefits and consequences of SCS.

Qualitative studies have previously detailed the patient experience with SCS.(38; 39) However, qualitative evidence on the patient experience specifically with HF-SCS or the use of SCS in patients with PDN is yet to be conducted.

The position of SCS in the treatment algorithm for PDN has not yet been formally recommended. NICE clinical guidelines provide recommendations on pharmacological

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management of neuropathic pain including diabetic neuropathy.(40) Given the inclusion criteria in the studies of SCS for PDN, it would be reasonable to conclude that lack of response or intolerance to at least two classes of analgesic medications could constitute an indication for SCS.

Strengths and limitations

The methods for this NMA are transparent, reproducible and follow best practice recommendations. The review was registered a priori in PROSPERO and the review process, including study identification, selection and data extraction was performed in line with CRD guidance(20) and reported in line with PRISMA-NMA.(21)

The evidence base of SCS for patients with PDN is limited to 3 RCTs, therefore the sample size of eligible patients for this NMA is limited. Since the network is small and has no closed loops, inconsistency between 'direct' and 'indirect' evidence cannot be assessed, so it is unknown if any inconsistency is present in the results. Although the RCTs were well designed, the open label design and pain as a subjective outcome mean that the RCTs are at high risk of bias. Should it be possible to blind outcome assessors to treatment allocation in a direct comparison of LF-SCS to HF-SCS would result in the RCT being considered at low risk of bias for the outcome measurement domain.

SUMMARY

Current evidence shows that both LF-SCS and HF-SCS provide more benefits than CMM for patients with PDN. HF-SCS was found to have the highest probability of being the best treatment option. However, while HF-SCS may reduce pain intensity compared to LF-SCS, no differences were observed for the other outcomes including overall HRQoL. In the absence of head-to-head RCT evidence the relative benefits of HF-SCS compared to LF-SCS for patients with PDN remains uncertain.

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Guarantor statement: RVD and SN are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: RVD and SN conceptualised the study. MM conducted the electronic database searches. RD and SC screened the search results for eligibility. SC, RD and SN extracted the data. RD and SN conducted the risk of bias assessment. SN performed the data

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analysis. RVD and SN drafted the manuscript. All authors contributed to drafts, read and approved the final manuscript.

Conflicts of interest: RVD has received consultancy fees from Boston Scientific Corp, Mainstay Medical, Medtronic Ltd and Saluda Medical all unrelated with this work. RST has received consultancy fees from Medtronic Ltd, Nevro Corp and Saluda Medical all unrelated with this work. He is due to serve on a Medtronic Ltd advisory board of spinal cord stimulation for painful diabetic neuropathy and is a co-investigator for the SENZA-PDN trial. SE has received consultancy fees from Abbott, Boston Scientific Corp, Mainstay Medical and Medtronic Ltd all unrelated with this work. He has received Department Research funding from the National Institute of Health Research, Medtronic Ltd, and Nevro Corp. The other authors declare no competing interests.

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

Author (year) and country	Intervention	Comparator	Follow-up duration	Number in analysis, sex and mean age±SD	Type and duration of diabetes	Duration of pain	Outcomes	Key findings
De Vos (2014)(16) Netherlands, Denmark, Belgium, and Germany	LF-SCS	CMM	6 months	LF-SCS n=40 (F=15; M=25), 58±11 y CMM n=20 (F=7; M=13), 61±12 y	LF-SCS Type I n=10 Type II n=30 16±11 y CMM Type I n=5 Type II n=15 17±12 y	LF-SCS 7±6 y CMM 7±6 y	Proportion of patients with 50% pain reduction Pain intensity (VAS) MPQ NWC-T MPQ PRI-T MPQ QoL HRQoL (EQ-5D VAS) PGIC pain Satisfaction with treatment	↑p<0.001 ↑p<0.001 ↑p<0.01 ↑p<0.01 ↑p<0.001 ↑p<0.01 ↑p<0.01 ↑p<0.001
Slangen (2014)(17) Netherlands	LF-SCS	CMM	6 months	LF-SCS n=22 (F=7; M=15), 57±12 y CMM n=14 (F=5; M=9), 57±8 y	LF-SCS Type I n=3 Type II n=19 13±10 y CMM Type I n=1 Type II n=13 13±7 y	LF-SCS 6±5 y CMM 5±4 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 VAS) HRQoL (EQ-5D utility) PGIC pain PGIC sleep Treatment success *	↑p<0.001 ↑p<0.01 ↑p<0.001 ↑p<0.003 (-) (-) ↑p<0.001 ↑p<0.05 ↑p<0.01
Petersen (2021)(19) United States	HF-SCS	CMM	6 months	HF-SCS n=113 (F=43; M=70) 61±11y CMM n=103 (F=37; M=66) 61±10 y	HF-SCS Type I n=8 Type II n=105 13±9 y CMM Type I n=3 Type II n=100	HF-SCS 7±6 y CMM 7±5 y	Composite of 50% pain reduction and no deterioration on neurological examination Proportion of patients with 50% pain reduction Pain intensity (VAS) Proportion of patients with VAS ≤3 for 6 consecutive months HRQoL (EQ-5D VAS) HRQoL (EQ-5D utility)	↑p<0.001 ↑p<0.001 ↑p<0.001 ↑p<0.001 ↑p<0.001 ↑p<0.001

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					12±9 y			

CMM=conventional medical management; F=female; HF-SCS=high frequency spinal cord stimulation; HRQoL=health-related quality of life; LF-SCS=low frequency spinal cord stimulation; M=male; MPQ=McGill Pain Questionnaire; NRS=numeric rating scale; NWC-T=total number of words chosen; PGIC=patient global impression of change; PRI-T=total pain rating index of words chosen; SD=standard deviation; VAS=visual analogue scale; y=years

* Treatment success defined as ≥50% reduction in pain intensity during daytime or night-time, or an improvement for pain and sleep of ≥6 in the score of the PGIC scale

(-) no statistically significant differences between groups

↑ statistically significant between groups in favour of SCS group

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Table 2. Risk of bias assessment

Author (year)	Outcome	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
de Vos (2014)(16)	Pain intensity	Low	Low	Low	High	Some concerns	High
Slangen (2014)(17)	Pain intensity	Low	Low	Low	High	Some concerns	High
Petersen (2021)(19)	Pain intensity	Low	Low	Low	High	Low	High

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