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Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data

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Saluda Medical. 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. 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.

ABSTRACT

Spinal cord stimulation (SCS) has been suggested as a treatment option for patients with painful diabetic neuropathy (PDN). We conducted a systematic review and undertook a meta-analysis on individual patient data (IPD) from randomised controlled trials (RCTs) to assess the effectiveness of SCS for the management of PDN. Electronic databases were searched from inception until May 2020 for RCTs of SCS for PDN. Searches identified two eligible RCTs (total of 93 PDN participants) and two longer term follow-up studies of one of the RCTs. IPD were obtained from the authors of one of these RCTs. Meta-analysis showed significant and clinically meaningful reductions in pain intensity for SCS compared to best medical therapy alone, pooled mean difference (MD) -3.13 (95% confidence interval (CI): -4.19 to -2.08) on a 10-point scale at 6-months follow up. More patients receiving SCS achieved at least a 50% reduction in pain intensity compared to best medical therapy, pooled risk ratio 0.08 (95% CI: 0.02 to 0.38). Increases were observed for health-related quality of life assessed as EQ-5D utility score (pooled MD 0.16, 95% CI: 0.02 to 0.30) and visual analogue scale (pooled MD 11.21, 95% CI: 2.26 to 20.16). Our findings demonstrate that SCS is an effective therapeutic adjunct to best medical therapy in reducing pain intensity and

improving health-related quality of life in patients with PDN. Large well reported RCTs with long-term follow up are required to confirm these results.

Keywords: individual patient data; Meta-analysis; Painful diabetic neuropathy; Spinal cord; stimulation; Systematic review

INTRODUCTION

Diabetes mellitus is the most common cause of peripheral neuropathy in the developed world and the most common complication of diabetes affecting up to 50% of people with diabetes.[11; 34] Approximately one in three people with diabetes experience painful diabetic neuropathy (PDN).[1] PDN is defined as pain arising as a result of abnormalities in the peripheral somatosensory system in people with diabetes,[37] and has been found to significantly lower quality of life and substantially increase health costs associated with diabetes.[23] A recent cohort study reported that patients with PDN were 2 times more likely to use opioids and over 16 times more likely to have an amputation than patients with diabetes mellitus without neuropathy.[15]

Spinal cord stimulation (SCS) is a recognised option for the management of chronic neuropathic pain conditions such as failed back surgery syndrome (FBSS)[16] and complex regional pain syndrome (CRPS).[13] Several case series and case reports have suggested SCS as potentially effective for the management of PDN,[2; 5; 8; 18; 25; 35] but higher level evidence from randomised controlled trials (RCTs) is limited. A recent systematic review conducted a meta-analysis to evaluate change in pain severity based on two RCTs.[26] Pain severity is the only outcome evaluated in this systematic review. Health-related quality of life

(HRQoL) which can be significantly impacted by PDN has been shown to improve following SCS, would be an important addition.[10]

Individual patient data (IPD) from RCTs allow to collect, check, and reanalyse individual-level data from all studies addressing a similar research question.[31] The aim of this systematic review was to identify and conduct a meta-analysis on IPD from RCTs of SCS for PDN to assess the effectiveness of SCS compared to usual care and other treatment alternatives for the management of PDN.

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.[4] This systematic review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) of IPD.[31] The protocol for this review is registered on PROSPERO as CRD42020204390.

Search strategy

Electronic databases MEDLINE, CENTRAL and Embase were searched from inception until 21st May 2020. The search strategies were designed using a combination of both indexing and free text terms with no restriction on language. The search strategy used for the MEDLINE database is presented in supplementary material 1 of this manuscript (available at http://links.lww.com/PAIN/B325). The MEDLINE search strategy was adapted to enable similar searches of the other relevant electronic databases. 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 independently screened all the titles and abstracts identified by the electronic 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 for inclusion using the eligibility criteria outlined in Table 1. Any disagreements were resolved through discussion at each stage, and, if necessary, in consultation with a third reviewer.

[Insert Table 1 here]

Risk of bias assessment

Risk of bias was assessed by using the revised Cochrane risk of bias tool (RoB 2.0).[30] Risk of bias assessment of the included studies was undertaken by one reviewer and checked by a second reviewer. Any disagreements were resolved by discussion, and, if necessary, in consultation with a third reviewer.

Outcomes

The primary outcome was pain intensity 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 prior to cross-over were considered for inclusion in the analysis.

Secondary outcomes were proportion of patients achieving at least 50% reduction in pain intensity and HRQoL (EQ-5D-3L).

Data extraction and statistical analysis

IPD were obtained from the authors of one of the two RCTs meeting the inclusion criteria.[7] Data items were extracted at study level from the eligible RCTs where participant level data were not provided.[29] Data extracted or requested within IPD were study author and year of publication, country where the study was conducted, study design characteristics (i.e. randomisation procedure, duration of follow-up), demographic data (i.e. age, 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. Treatment related adverse events were extracted from the published reports of both RCTs and reported narratively.

IPD provided were cross-checked against the published report of De Vos [7]; baseline demographic information and outcome results were reproduced where possible. Following cross-checks, outcomes for this meta-analysis (pain intensity, HRQoL) were calculated at 3 months and 6 months using a complete-case analysis approach (i.e., those with missing data at 3 months or 6 months were excluded from the analysis) and also using an intention-to-treat (ITT) approach where missing outcome data at 3 or 6 months was imputed from earlier values. This was consistent with the approaches used in the original analysis of De Vos.[7]

Outcome data (pain intensity, HRQoL) at 3 months and 6 months were extracted from the published report by Slangen and colleagues.[29] Outcome data available only in graphical format were extracted using WebPlot Digitiser (https://automeris.io/WebPlotDigitizer/).

Slangen [29] reported mean pain intensity separately during the day and during the night according to the Numeric Rating Scale (NRS, 0 to 10) and De Vos [7] reported mean pain intensity according to the Visual Analogue Scale (VAS, 0 to 100). To allow pooling of pain intensity outcome data on a common scale (0 to 10), mean VAS pain scores were divided by 10 for De Vos [7] and an average of the day and night mean NRS pain scores was calculated for Slangen.[29]

Both studies also reported the proportion of patients with at least a 50% reduction in pain intensity at 6 months on the NRS or VAS respectively. Data were pooled with De Vos [7] separately for at least 50% reduction in daytime pain and at least 50% reduction in nighttime pain for Slangen.[29]

The measure of treatment effect for pain intensity and HRQoL outcomes was mean difference (MD) and 95% confidence interval (CI), pooled via the generic-inverse variance method of meta-analysis and for at least 50% reduction in pain intensity was risk ratio (RR) and 95% CI, pooled via the Mantel-Haenzel method of meta-analysis.[9] Due to similarities in the populations, designs and treatment protocols of the De Vos [7] and Slangen [29] RCTs, heterogeneity was not anticipated, therefore fixed-effects meta-analyses were performed. We assessed the level of heterogeneity present between trials by visual inspection of forest plots and formally according to the I^2 statistic (the percentage of variability between trials that is due to statistical heterogeneity), and if any important heterogeneity was present, random-effects meta-analysis were performed as a sensitivity analysis.

RESULTS

Study selection

After the removal of duplicate records, the searches resulted in the identification of 86 citations. Following initial screening of titles and abstracts and review of the full-text publications, four studies providing results for two unique RCTs were included in the review.[7; 29; 38; 39] IPD were provided by the authors of one RCT [7] but not for the other RCT identified.[29] The remaining two studies identified were follow-up studies of the RCT by Slangen and colleagues.[38; 39] The data from the follow-up studies was extracted from the publications but was not sought for the IPD meta-analysis due to crossover and unavailability of follow-up data for patients allocated to the control group. The PRISMA flow chart detailing the screening process for the review is shown in Figure 1.

[Insert Figure 1 here]

Characteristics of included studies

The characteristics of the two included RCTs evaluating the effectiveness of SCS for PDN and follow-up studies are summarised in Table 2. One of the RCTs was performed in 2 centres in the Netherlands,[29] while one RCT was conducted across 7 pain clinics in the Netherlands, Denmark, Belgium, and Germany.[7] The RCTs were similar in the populations, designs and treatment protocols. Both RCTs included a larger proportion of patients with type II diabetes than type I diabetes. The time since diagnosis of diabetes and duration of painful symptoms was longer in the RCT by De Vos than in the RCT by Slangen. The two RCTs included a screening trial prior to implantation of the SCS device. The type of stimulation

investigated in both RCTs was conventional stimulation (i.e., paraesthesia inducing). The duration of the screening trial was seven days maximum in the De Vos RCT and two-weeks in the Slangen RCT. The randomisation ratios were 2:1 and 3:2 in the De Vos and Slangen RCTs, respectively. Both RCTs allowed for patients allocated to the SCS intervention to also receive best medical therapy (BMT) with the control group receiving BMT alone.

[Insert Table 2 here]

Risk of bias assessment

The summary of the risk of bias assessment is presented in Table 3. The full assessment for each included study is presented in supplementary material 2 (available at http://links.lww.com/PAIN/B325). Both 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, both RCTs were judged to have a high risk of bias for outcome measurement as these were open label trials. The outcome assessors were aware of the interventions received in the two RCTs. 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 either RCTs if the statistical analyses followed a pre-specified statistical analysis plan. This resulted in the domain selection of the reported result being judged as presenting some concerns. The overall bias for the included studies was considered to be high.

[Insert Table 3 here]

Outcomes

Meta-analysis of outcome data at 6 months, from the ITT approach in De Vos 2014 are presented below. Meta-analysis of outcome data at 3 months, and from the complete-case approach for De Vos 2014 are presented within supplementary material 3 (available at http://links.lww.com/PAIN/B325).

[Insert Figure 2 here]

Figure 2 shows the results of fixed effects meta-analysis of pain intensity and EQ-5D outcomes at 6 months. There was a statistically significant reduction in pain intensity (pooled MD -3.13, 95% CI -4.19 to -2.08, I^2 = 0%) on SCS treatment compared to BMT. Significantly more patients on SCS treatment achieved at least a 50% reduction in pain intensity compared to patients receiving BMT (pooled RR 0.08, 95% CI 0.02 to 0.38, I^2 = 0%). However, only one patient on BMT in each of the studies achieved at least a 50% reduction in pain intensity, resulting in a wide confidence interval around the pooled RR. Therefore, the magnitude of treatment effect of SCS over BMT is unclear for this outcome.

Meta-analysis also showed a statistically significant increase in EQ-5D utility index (pooled MD 0.16, 95% CI 0.02 to 0.30, I^2 = 0%) and in EQ-5D VAS score (pooled MD 11.21, 95% CI 2.26 to 20.16, I^2 = 68.6%) on SCS treatment compared to BMT.

Results of additional fixed effects meta-analyses at 3 months and sensitivity analyses were numerically similar and conclusions were unchanged (see supplementary material 3, Figure S1, Figure S2, available at http://links.lww.com/PAIN/B325).

Substantial heterogeneity was present between the EQ-5D VAS score results of the two studies for all analyses of this outcome. Therefore, random-effects meta-analysis was also conducted for EQ-5D VAS score, resulting in no statistically significant difference between treatment groups for any of the analyses (see supplementary material 3, Figure S3, available at http://links.lww.com/PAIN/B325).

The follow-up studies of the RCT by Slangen and colleagues reported outcomes after the six-month primary endpoint. The patients allocated to BMT were given the option to cross-over to SCS after the primary endpoint. Only two of the patients in the BMT group did not want to cross-over to SCS.[39] Therefore, no comparisons are possible between SCS and BMT after six-months. In addition, the five-year follow-up includes patients reported in a previous case series,[25] hence the total number of patients in this follow-up is greater than the total number of patients in the RCT.

Up to three-years follow-up the proportion of patients with 50% pain reduction and pain intensity during the day or night remains fairly similar. There is a small but continuous reduction in the proportion of patients with 50% pain reduction and an increase in pain intensity at four and five-years follow-up (see Table 2). Likewise, treatment success decreased from 77% to 55% at three and five-years follow-up, respectively. Only a small reduction was observed in the proportion of patients reporting improvement in the PGIC for pain from 59% to 53% and 50% at six-months, two and five-years respectively.

Treatment related adverse events were reported in both trials. De Vos reported 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.[7] One patient in the Slangen RCT 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,[29] one patient developed an infection two months after implant which led to an explant eight months following implantation.[38] Over five-years follow-up, ten patients reported pain in the battery pocket, nine patients experience uncomfortable stimulation requiring adjustments to SCS programming and lead revision or lead replacement was required by four and three patients respectively.[38] Eight patients required one SCS device replacement and five patients underwent two battery replacements.[38]

DISCUSSION

We present the first meta-analysis of IPD and aggregate data in the field of SCS. Our meta-analysis of 2 RCTs and a total of 93 participants have shown a mean reduction in pain intensity of -3.13 (95% CI -4.19 to -2.08) for management of PDN with SCS when compared to BMT. Statistically significant differences were also observed for the proportion of patients achieving at least 50% pain reduction, EQ-5D utility index and EQ-5D VAS, all showing beneficial effects of SCS compared with BMT for patients with PDN. In both RCTs, the patients allocated to BMT were eligible to cross-over to SCS after the six-months primary endpoint. Therefore, longer-term follow-ups currently available and future follow-up assessments will only enable evaluation of outcomes for patients with SCS with no long-term comparison with patients with PDN managed with BMT. Long-term assessments of patients

in the Slangen trial [29] suggest a small but continuous increase in pain when compared with the six-month assessment, and consequently a reduction in the proportion of patients obtaining 50% pain relief up to five-years follow-up.[38] These findings are similar to those observed on the long-term impact of SCS for other neuropathic pain conditions where loss of efficacy has been reported for a proportion of patients when compared to the primary endpoint.[12; 14; 17; 21]

The results of the meta-analysis for reduction in pain intensity are in line with the pooled MD of 37.84 (95% CI 28.83 to 46.85) reported in a previous systematic review and meta-analysis.[26] Differences in numerical estimates are likely due to differences in pain scales pooled. Raghu et al [26] seem to have pooled the results of the VAS from the De Vos trial [7] with the results of the modified Brief Pain Inventory- Diabetic Peripheral Neuropathy pain severity scale presented in the Slangen trial.[29] We extracted NRS data for daytime pain scores which was only reported in graphical format in the Slangen trial[29] and pooled with VAS scores from the ITT approach calculated using the IPD of the De Vos trial.[7] Sensitivity analysis with complete case data from De Vos et al [7] and night pain scores from Slangen et al [29] performed within this systematic review provide similar results with conclusions unchanged.

RCTs evaluating other types of SCS such as high-frequency SCS at 10kHz for PDN are being conducted.[19] Preliminary reports suggest that the primary endpoint (i.e. proportion of patients with at least 50% reduction in lower limb pain without a clinically meaningful neurological deficit compared with baseline at 3-months) was achieved in a significantly greater proportion of patients receiving 10KHz SCS (86%) when compared with patients receiving conventional medical management alone (5%).[24] Encouraging results have also been reported in a case series [6] and a small cross-over RCT evaluating burst SCS for PDN.[36] RCT evidence is required to ascertain the effectiveness of burst SCS for PDN. SCS

devices that can accommodate different types of stimulation may enable the use of N-of-1 clinical trials to identify the type of stimulation more effective for each individual in a randomised, cross-over trial evaluating different types of stimulation as well as placebo controls. It is possible but not certain that identifying the most effective stimulation paradigm for each patient may result in improved long-term outcomes. However, both patients and clinicians need to consider the potential long duration of carryover effects in the neurostimulation setting and therefore the need for long washout periods before assessment of the effectiveness of the different stimulation types.

Although the effectiveness of conventional paraesthesia inducing SCS for PDN has been demonstrated, its cost-effectiveness has not yet been established. A cost-utility analysis from a societal perspective was conducted based on the outcomes of the Slangen RCT indicating that SCS was not cost-effective at 12-months follow-up, but suggesting that SCS is likely to become cost-effective in the long-term i.e. >48 months follow up.[28] Economic evaluations of SCS for other neuropathic pain conditions indicate that when long-term time horizons of 15 years to lifetime are considered, SCS is cost-effective or dominant (i.e. more effective at a lower cost).[20; 22; 27; 32; 33] It is plausible that SCS is cost-effective for PDN, however, it still needs to be demonstrated. The economic evaluation should consider the progressive nature of diabetes and PDN, how it would affect the effectiveness of SCS and impact on people's health and pain severity.

There are potentially some limitations in the use of SCS for PDN. Although SCS has been shown to work in upper as well as lower limb pains [3; 16] we are not aware of it being used to treat upper and lower limb pains simultaneously since targeting would be different and would necessitate placement of a lead in the cervical as well as lower thoracic spine posing some limitations to the system.

Strengths and weaknesses

This is the first systematic review and meta-analysis of IPD in the field of SCS. The review was registered a priori in PROSPERO and the process, including study identification, selection, and data extraction, was performed in line with CRD guidance [4] and reported in line with PRISMA-IPD.[31] Risk of bias assessment was performed using the revised Cochrane risk of bias tool (RoB 2.0).[30] The methods for the meta-analysis are transparent, reproducible and follow best practice recommendations. The results of the meta-analysis are more comprehensive, considering multiple time point and the influence of missing data, and therefore provide more certainty on the effect of SCS in reduction of pain intensity and improvement in HRQoL.

Two RCTs, recruiting a total of 93 participants, to date have evaluated SCS for the management of PDN. Therefore, the sample size of eligible participants for this meta-analysis is limited. IPD from additional RCTs would provide opportunities for analyses of predictors of success and greater certainty of the generalised treatment effect.

Despite being well designed, the two current RCTs are both at high risk of bias is due to the open label nature of the trials but also due to pain assessment being subjective and plausibility that knowledge and beliefs of beneficial effect from SCS could have influenced the outcomes. Design of future trials of SCS should take into account that given the subjectivity of pain measurement and potential beliefs of effectiveness, RCTs of populations with chronic pain evaluating the effectiveness of medical devices where it is not possible to blind outcome assessors will be considered to be at high risk of bias in the domain measurement of the outcome and overall risk of bias based on the revised Cochrane RoB 2.0 tool. Comparison of paraesthesia-free waveforms provide opportunities for adequately blinded trials.

Future trials should also consider baseline characteristics that are lacking from the currently available RCTs that could be helpful to distinguish responders from non-responders such as neuropathic pain assessment, presence of allodynia, comorbidities, psychological factors, glucose control and also objective outcomes of improvement in function such as actigraphy and gait analysis. Some of these baseline characteristics and objective outcomes of function have been collected as part of the RCT evaluating high-frequency SCS for PDN.[19]

We performed a meta-analysis of IPD and aggregate data due to obtaining IPD from only one of the RCTs. Meta-analysis including IPD of both RCTs would not affect the conclusions of this review but would potentially enable additional analysis to investigate demographic data (i.e. age, sex), type of diabetes, duration of diabetes and duration of pain due to diabetes as potential modifiers of the effect of SCS. These factors should be considered in future IPD meta-analysis, potentially including IPD from the ongoing RCT of high-frequency SCS for PDN.[19]

CONCLUSION

In conclusion, we found that SCS is more effective than BMT in reducing pain intensity and improving HRQoL in people with PDN. Long-term follow-ups up to five-years suggest a small but continuous decrease in the proportion of patients with SCS achieving at least 50% pain reduction and an increase in pain intensity.

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REFERENCES

[1] Abbott CA, Malik RA, van Ross ERE, Kulkarni J, Boulton AJM. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes care 2011;34(10):2220-2224.

[2] Abd-Elsayed A, Schiavoni N, Sachdeva H. Efficacy of spinal cord stimulators in treating peripheral neuropathy: a case series. Journal of clinical anesthesia 2016;28:74-77.

[3] Amirdelfan K, Vallejo R, Benyamin R, Yu C, Yang T, Bundschu R, Yearwood TL, Sitzman BT, Gliner B, Subbaroyan J, Rotte A, Caraway D. High-Frequency Spinal Cord Stimulation at 10 kHz for the Treatment of Combined Neck and Arm Pain: Results From a Prospective Multicenter Study. Neurosurgery 2020;87(2):176-185.

[4] Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care, 2009.

[5] Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabetic medicine : a journal of the British Diabetic Association 2005;22(4):393-398.

[6] de Vos CC, Bom MJ, Vanneste S, Lenders MWPM, de Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation : journal of the International Neuromodulation Society 2014;17(2):152-159.

[7] de Vos CC, Meier K, Zaalberg PB, Nijhuis HJ, Duyvendak W, Vesper J, Enggaard TP, Lenders MW. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain 2014;155(11):2426-2431.

[8] de Vos CC, Rajan V, Steenbergen W, van der Aa HE, Buschman HPJ. Effect and safety of spinal cord stimulation for treatment of chronic pain caused by diabetic neuropathy. Journal of Diabetes and its Complications 2009;23(1):40-45.

[9] Deeks J, Higgins J, Altman D. Analysing data and undertaking meta-analyses. In: J Higgins, J Thomas, J Chandler, M Cumpston, T Li, M Page, V Welch, editors. Cochrane Handbook for Systematic Reviews of Interventions v60 (updated July 2019): Cochrane, 2019. pp. 241-284.

[10] Duarte RV, Andronis L, Lenders M, de Vos CC. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. Quality of life research 2016;25(7):1771-1777.

[11] England JD, Asbury AK. Peripheral neuropathy. Lancet 2004;363(9427):2151-2161.

[12] Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Yearwood TL, Bundschu R, Yang T, Benyamin R, Burgher AH. 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(5):667-677.

[13] Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnée CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343(9):618-624.

[14] Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. 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(2):292-298.

[15] Kiyani M, Yang Z, Charalambous LT, Adil SM, Lee HJ, Yang S, Pagadala P, Parente B, Spratt SE, Lad SP. Painful diabetic peripheral neuropathy: Health care costs and complications from 2010 to 2015. Neurol Clin Pract 2020;10(1):47-57.

[16] Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. 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(1-2):179-188.

[17] Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 2008;63(4):762-770; discussion 770.

[18] Kumar K, Toth C, Nath RK. Spinal cord stimulation for chronic pain in peripheral neuropathy. Surgical neurology 1996;46(4):363-369.

[19] Mekhail NA, Argoff CE, Taylor RS, Nasr C, Caraway DL, Gliner BE, Subbaroyan J, Brooks ES. High-frequency spinal cord stimulation at 10 kHz for the treatment of painful diabetic neuropathy: design of a multicenter, randomized controlled trial (SENZA-PDN). Trials 2020;21(1):87.

[20] Niyomsri S, Duarte RV, Eldabe S, Fiore G, Kopell BH, McNicol E, Taylor RS. A Systematic Review of Economic Evaluations Reporting the Cost-Effectiveness of Spinal Cord Stimulation. Value in Health 2020.

[21] North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery 2005;56(1):98-106; discussion 106-107.

[22] North RB, Parihar HS, Spencer SD, Spalding AF, Shipley J. Cost-Effectiveness Model Shows Superiority of Wireless Spinal Cord Stimulation Implantation Without a Separate Trial. Neuromodulation 2020.

[23] O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics 2009;27(2):95-112.

[24] Petersen EA, Stauss T, Scowcroft J, White J, Sills S, Amirdelfa K, Guirguis M, Xu J, Yu C, Nairizi A, Patterson D, Galan V, Bundschu R, Mehta N, Sayed D, Lad NP, DiBenedetto D, Sethi KA, Wu P, Argoff C, Nasr C, Taylor R, Brooks E, Subbaroyan J, Gliner BE, Caraway D, Mekhail N. 10 kHz Spinal Cord Stimulation for Treatment of Painful Diabetic Neuropathy - A Multicenter Randomized Controlled Trial. Neurosurgery 2020;67(Supplement_1).

[25] Pluijms WA, Slangen R, Bakkers M, Faber CG, Merkies ISJ, Kessels AG, Dirksen CD, Joosten EA, Reulen JPH, van Dongen RT, Schaper NC, van Kleef M. Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: a pilot study. British journal of anaesthesia 2012;109(4):623-629.

[26] Raghu ALB, Parker T, Aziz TZ, Green AL, Hadjipavlou G, Rea R, FitzGerald JJ. Invasive Electrical Neuromodulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis. Neuromodulation 2020.

[27] Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. Health Technol Assess 2009;13(17):iii, ix-x, 1-154.

[28] Slangen R, Faber CG, Schaper NC, Joosten EA, van Dongen RT, Kessels AG, van Kleef M, Dirksen CD. A Trial-Based Economic Evaluation Comparing Spinal Cord Stimulation With Best Medical Treatment in Painful Diabetic Peripheral Neuropathy. The journal of pain : official journal of the American Pain Society 2017;18(4):405-414.

[29] Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, Kessels AG, van Kleef M. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes care 2014;37(11):3016-3024.

[30] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj 2019;366:l4898.

[31] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. Jama 2015;313(16):1657-1665.

[32] Taylor RS, Bentley A, Campbell B, Murphy K. High-frequency 10 kHz Spinal Cord Stimulation for Chronic Back and Leg Pain: Cost-consequence and Cost-effectiveness Analyses. Clin J Pain 2020;36(11):852-861.

[33] Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. Clin J Pain 2010;26(6):463-469.

[34] Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 2012;28 Suppl 1:8-14.

[35] Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet (London, England) 1996;348(9043):1698-1701.

[36] Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MWPM. Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation. Neuromodulation 2016;19(5):492-497.

[37] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70(18):1630-1635.

[38] van Beek M, Geurts JW, Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, van Kuijk SMJ, van Kleef M. Severity of Neuropathy Is Associated With Long-term Spinal Cord Stimulation Outcome in Painful Diabetic Peripheral Neuropathy: Five-Year Follow-up of a Prospective Two-Center Clinical Trial. Diabetes care 2018;41(1):32-38.

[39] van Beek M, Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, Kessels AGH, van Kleef M. Sustained Treatment Effect of Spinal Cord Stimulation in Painful Diabetic Peripheral Neuropathy: 24-Month Follow-up of a Prospective Two-Center Randomized Controlled Trial. Diabetes care 2015;38(9):e132-134.

FIGURE LEGENDS

Figure 1. PRISMA IPD flow diagram

Figure 2. Fixed effects meta-analysis of pain intensity and EQ-5D outcomes at 6 months

Table 1 Eligibility criteria

Inclusion criteria (if all of the following met)	**Exclusion criteria (if any of the following met)**
1. Population comprised patients with diabetic neuropathic pain	1. Neurostimulation intervention other than SCS
2. Intervention was SCS (all stimulation protocols)	2. Study design other than RCT (e.g., case series, case reports, cohort studies)
3. Comparator was usual care, an active intervention or placebo	3. No original data presented (e.g., design/protocol paper, [systematic] review, meta-analysis, commentaries/editorial)
4. Study design was an RCT	4. Insufficient information (e.g., study only available as a conference proceeding/ abstract)

RCT=randomised controlled trial; SCS=spinal cord stimulation

Table 2. Characteristics and outcomes of randomised controlled trials and follow-up studies included in the systematic review

Author (year) and setting	Number in analysis, sex and mean age ± SD		Diabetes and duration of pain		Follow-up duration	Outcomes	Key findings
	SCS	BMT	SCS	BMT			
De Vos (2014) [7] Netherlands, Denmark, Belgium, and Germany	N=40 F=15; M=25 58 ± 11 y	N=20 F=7; M=13 61 ± 12 y	Diabetes Type I – n=10 Type II – n=30 Duration – 16 ± 11 y Pain Duration – 7 ± 6 y	Diabetes Type I – n=5 Type II – n=15 Duration – 17 ± 12 y Pain Duration – 7 ± 6 y	6 months	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) [29] Netherlands	N=22 F=7; M=15 57 ± 12 y	N=14 F=5; M=9 57 ± 8 y	Diabetes Type I – n=3 Type II – n=19	Diabetes Type I – n=1 Type II – n=13	6 months	Proportion of patients with 50% pain reduction (day) Proportion of patients with 50% pain reduction (night)	↑ p<0.001 ↑ p<0.01 ↑ p<0.001

			Duration – 13 ± 10 y <u>Pain</u> Duration – 6 ± 5 y	Duration – 13 ± 7 y <u>Pain</u> Duration – 5 ± 4 y		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<0.003 (-) (-) ↑ p<0.001 ↑ p<0.05 ↑ p<0.01
Follow-up studies of Slangen (2014) RCT							
van Beek (2015) [39] Netherlands	N=17; N=15 at 2 y follow-up F=5; M=12 55 ± 12 y	NA	NR	NA	2 years	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	47% (8/17) 35% (6/17) 4.0 ± 3.0 3.5 ± 3.0 59.3 ± 20.6 0.40 ± 0.36 53% (9/17) 53% (9/17) 65% (11/17)

						Treatment success **	
van Beek (2018)* [38] Netherlands	N=40 F=13; M=27 57 ± 10 y	NA	<u>Diabetes</u> Type I – n=5 Type II – n=35 Duration – 14 ± 13 y <u>Pain</u> Duration – 6 ± 4 y	NA	5 years	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) PGIC pain	47% (16/34) at 3 y 37% (11/30) at 4 y 36% (8/22) at 5 y 35% (12/34) at 3 y 33% (10/30) at 4 y 32% (7/22) at 5 y 3.8 ± 2.6 at 3 y 4.2 ± 2.4 at 4 y 4.3 ± 2.2 at 5y 3.9 ± 2.7 at 3 y 4.4 ± 2.4 at 4 y 4.6 ± 2.5 at 5y

						PGIC sleep Treatment success **	53% (18/34) at 3 y 53% (16/30) at 4 y 50% (11/22) at 5 y 29% (10/34) at 3 y 47% (14/30) at 4 y 32% (7/22) at 5 y 77% (26/34) at 3 y 67% (20/30) at 4 y 55% (12/22) at 5 y

BMT=best medical therapy; F=female; HRQoL=health-related quality of life; M=male; MPQ=McGill Pain Questionnaire; NA=not applicable; NR=not reported; 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

* Includes 5-year follow-up of Slangen (2014) RCT after crossover from BMT group and additional patients reported in a case series [25]

** 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 improvements for SCS group

↓ statistically significant improvements for BMT group

Table 3. Risk of bias assessment

Author (year)	Outcome	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selecti the rep resu
De Vos (2014)[7]	Pain intensity	Low	Low	Low	High	Some co
Slangen (2014)[29]	Pain intensity	Low	Low	Low	High	Some co