Invasive Electrical Neuromodulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: Neuromodulation is a treatment option for people suffering from painful diabetic neuropathy (PDN) unresponsive to conventional pharmacotherapy. We systematically examined the pain outcomes of patients with PDN receiving any type of invasive neuromodulation for treatment of neuropathic pain.

Materials and Methods: MEDLINE and Embase were searched through 10 January 2020, without language restriction. All study types were included. Two reviewers independently screened publications and extracted data. Quantitative meta-analysis was performed with pain scores converted to a standard 100-point scale. Randomized controlled trial (RCT) scores were pooled using the inverse variance method and expressed as mean differences.

Results: RCTs of tonic spinal cord stimulation (t-SCS) showed greater pain improvement than best medical therapy at six months (intention-to-treat: 38/100, 95% CI: 29–47). By per-protocol analysis, case series of t-SCS and dorsal root ganglion stimulation (DRGS) showed improvement by 56 (95% CI: 39–73) and 55 (22–87), respectively, at 12 months. For t-SCS, the rate of failing a therapeutic stimulation trial was 16%, the risk of infection was 4%, and the rate of lead problems requiring surgery to resolve was 4% per year of follow-up. High-frequency SCS and burst SCS both showed efficacy, with few patients studied.

Conclusion: Efficacious, lasting and safe surgical pain management options are available to diabetic patients suffering from PDN. Tonic-SCS is the established standard of treatment; however, other SCS paradigms and DRGS are emerging as promising treatments offering comparable pain benefits, but with few cases published to date. Randomized controlled trials are ongoing to assess their relative merits.

Keywords: Chronic pain, meta-analysis, neuropathic pain, neurostimulation, peripheral neuropathy, SCS

Conflict of Interest: Prof. Green reports personal fees from Executive Advisory Board Abbott, personal fees from Faculty on Courses for Abbott, personal fees from Data Monitoring Committee—trial of CDNF for PD, outside the submitted work; Dr. Rea reports grants from NovoNordisk, outside the submitted work; Prof. FitzGerald reports grants and personal fees from Abbott, personal fees from Medtronic, outside the submitted work; Dr Rea and Prof. FitzGerald are co-investigators in the PENTAGONS

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INTRODUCTION

Diabetic neuropathy is the most common peripheral neuropathy in the United States and globally. With the prevalence of diabetes in adults rising to 10.8% in the United States and 4.3% in the United Kingdom (1), improving the management of peripheral neuropathy has never been more important.

The principal pathology is a length-dependent neuropathy, estimated to affect around 30% of people with diabetes and more than half of those 60 years or older (2). It involves distal autonomic and sensory dysfunction, predominantly affecting the feet, but often progressing proximally and/or involving the upper limbs as time passes (3). The process initially affects small fibers (protopathic, autonomic: C, A?) and progresses to involve large fibers (epicritic: Aα, Aβ) to generate a classic pan-modal pathological pattern. Clinically, damage can lead to symptoms of neuropathic pain, paraesthesia, and numbness, which can progress to further complications such as neuropathic arthropathy and ulceration.

Painful diabetic neuropathy (PDN) affects around 26% of people with diabetes, resulting in significant physical and social morbidity and impairing quality of life (4). PDN has escaped categorization to specific pathomorphological findings, however, neurophysiologically is likely to involve dysfunctional processing at multiple levels including the dorsal root ganglia (DRG), ventrolateral periaqueductal gray, and autonomic nervous system (5,6). Patients are typically managed with anticonvulsant analgesic medications such as gabapentin or pregabalin and/or antidepressants such as amitriptyline or duloxetine (7,8). However, around 50% of patients are refractory (9), resulting in prescriptions of opioid analgesics and patients seeking alternative therapies.

Noninvasive and minimally invasive neuromodulation techniques may benefit some patients, but their analgesia is very limited and of short duration (10–13). Invasive neuromodulation with an implanted stimulator device may offer longer-term relief to refractory patients with poorly controlled pain. Given the prevalence of PDN, it has the potential to be one of the commonest indications for such treatments.

The neurophysiology of chronic stimulation and how it achieves analgesia is poorly understood. The classic treatment, tonic spinal cord stimulation (t-SCS), involves regular electrical pulses ($\sim$50 Hz) delivered to the dorsal columns through epidural electrodes. Tonic stimulation evokes paraesthesia in the area of pain, traditionally thought to function through a gate control mechanism to compete out pain signals (14). However, multiple stimulation methods that can achieve analgesia, but without generating paraesthesia, are now available, casting doubt on these long-held beliefs (15–17). The field continues to evolve. New stimulation methods including burst spinal cord stimulation (b-SCS), high-frequency spinal cord stimulation (HF-SCS), and dorsal root ganglion stimulation (DRGS), have all been shown to be highly effective as treatments for pain within the last decade (15,16,18).

There is growing evidence to suggest that invasive neuromodulation may be an effective therapy for patients with debilitating PDN. We therefore performed a systematic review and meta-analysis of all original published literature on the outcomes of invasive neuromodulation for the treatment of PDN.

MATERIALS AND METHODS

Data Sources and Searches

Search strings for MEDLINE and Embase were devised by authors A.L.B.R. and T.P. with assistance from a medical sciences librarian of the Bodleian Libraries of Oxford (Table S1). The review was prospectively registered on PROSPERO (CRD42019135591) and databases searched from inception to 10 January 2020.

Study Selection

Deduplication was carried out on Mendeley (Elsevier) and remaining publications imported to Covidence (Veritas Health Innovation) for further deduplication and study selection. There were no restrictions on study types, publication types or the language of publication. Abstract and full-text screening were carried out independently by two authors (A.L.B.R., T.P.), with disagreement resolved by a senior third author (J.J.F.). Publications were included that reported PDN patients with extractable, unduplicated pain outcomes, quality of life outcomes, or surgical complications data attributable solely to PDN patients. Reasons for exclusion at full-text screening were reported hierarchically (Fig. 1). Efforts were made to prevent duplication of patients/data between publications with common authors, including the construction of a publication timeline among common authors, and contacting authors where clarity was necessary.

Data Extraction and Quality Assessment

A spreadsheet of selected publications was constructed, including authors, year of publication, study type and surgical device. Two authors (A.L.B.R., T.P.) independently extracted data into copies of this spreadsheet including number of PDN patients, baseline pain, pain outcomes with time points, quality of life outcomes, complications of treatment and risk of bias. The Cochrane risk of bias tool was used to assess randomized controlled trials (RCTs). For other studies, except case reports, risk of bias was assessed as high, low or unclear on five categories: selection bias, performance bias, attrition bias, detection bias, and reporting bias, with study design specific criteria as described by others (19).

Data Synthesis and Analysis

For RCTs, quantitative meta-analysis was performed on RevMan 5.3 (The Cochrane Collaboration), calculating mean difference using random effects modeling to compare best medical therapy (BMT) to neuromodulation for RCTs. Other studies were pooled for similar likelihood of bias and post-operative follow-up, then means and 95% CI calculated (z-distribution: $n \geq 30$, t-distribution: $n < 30$) for improvement of pain from baseline. Otherwise, a narrative synthesis was carried out. For purposes of meta-analysis, 10-point scores were converted to
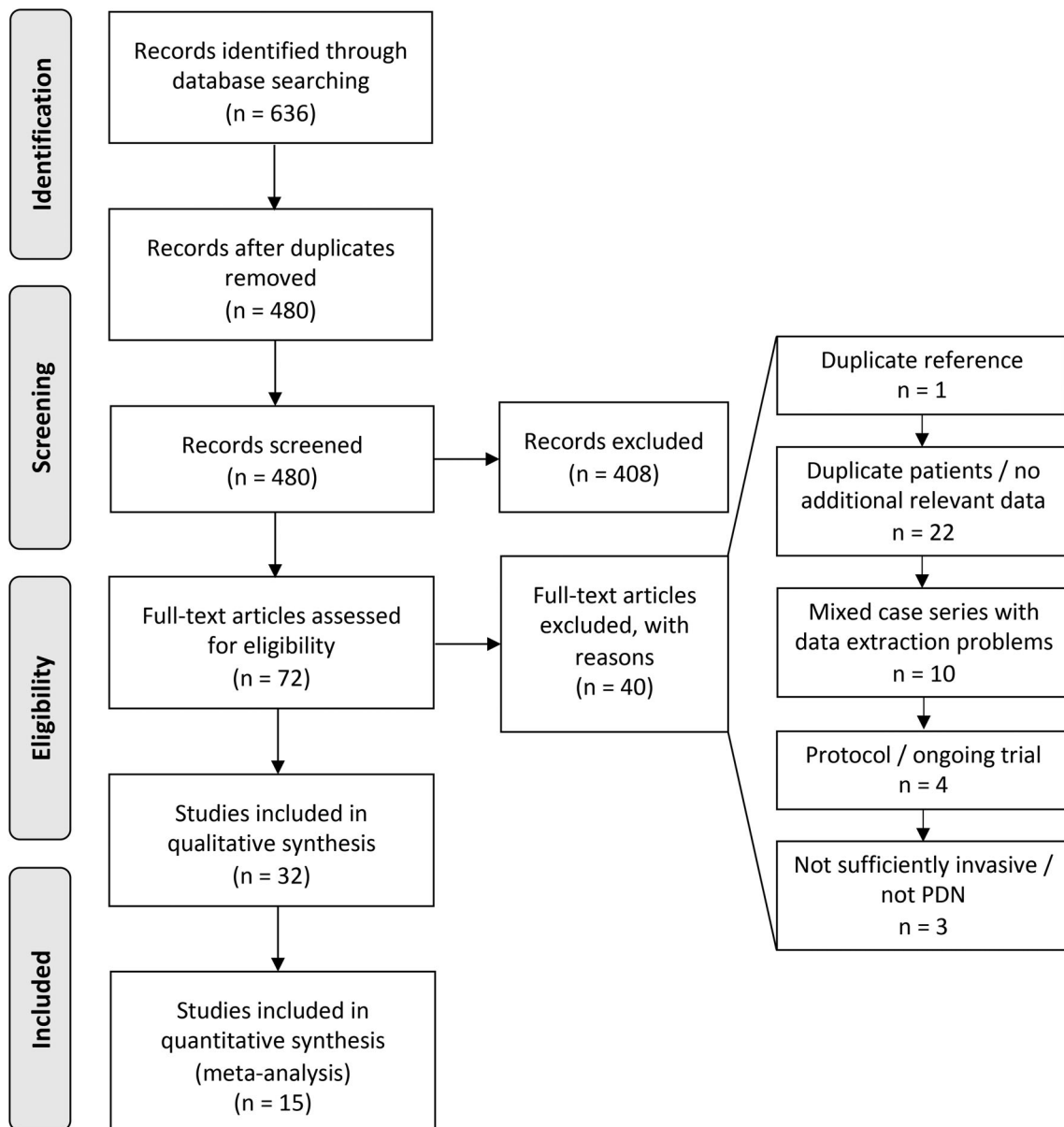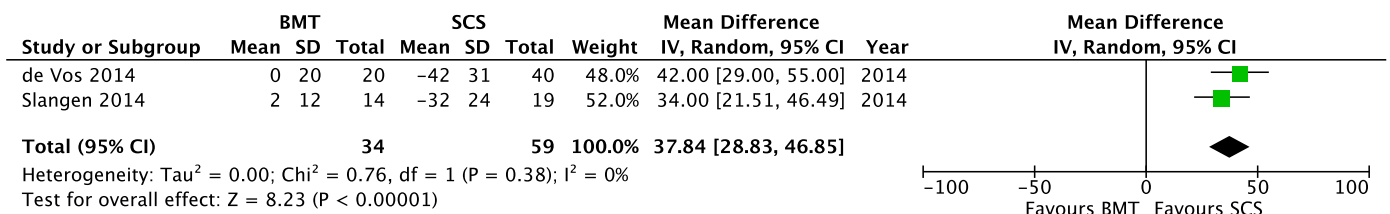
Figure 1 PRISMA flow diagram.

Figure 2 Intention-to-treat analysis of RCTs comparing best medical therapy (BMT) and t-SCS for change in pain severity from baseline on 100-point scale at six-month follow-up. [Color figure can be viewed at wileyonlinelibrary.com]

100-point scores, day pain scores were used when both day and night scores were reported, and peak pain scores were used when both background and peak scores were reported. Visual analogue scale (VAS), numerical rating scale (NRS), and pain severity scores from the brief pain inventory for diabetic peripheral neuropathy (BPI-DPN) were used. Authors were contacted when desired data were omitted. Distinction was made between intention to treat (ITT), modified-ITT (mITT), and per protocol analysis (PPA). There is no consensus definition of mITT (20,21). For the setting of invasive neuromodulation, we

Table 1 Meta-Analytic Comparison Between t-SCS and Dorsal Root Ganglion Stimulation.

Intervention	Analysis	Absolute pain improvement (95% CI)	Follow-up (mts)	n
t-SCS (36,37)	ITT	39 (32–46)	6	59
t-SCS (42,44)	mITT	38 (26–50)	6	16
t-SCS (28,44)	PPA	56 (39–73)	12	10
DRGS (51,52)	PPA	57 (37–76)	1	7
DRGS (51)	PPA	49 (26–73)	6	5
DRGS (51)	PPA	55 (22–87)	12	5*

CI, confidence interval of the mean.
*Includes one patient from our group.
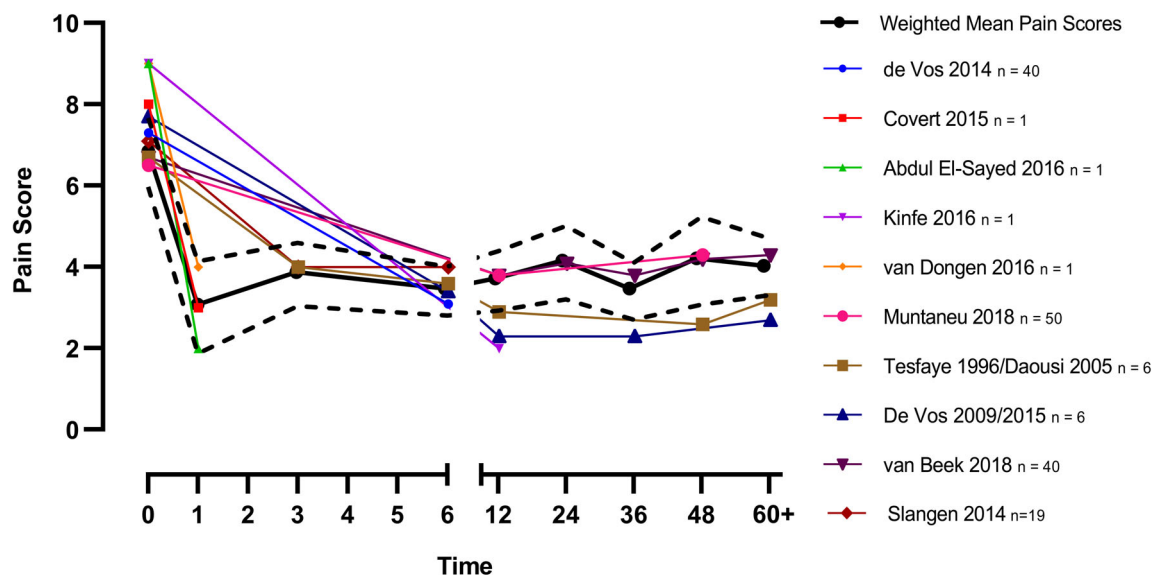
Figure 3 Composite of change in standardized mean pain scores over time (mts) with t-SCS. Dotted black line represents 95% confidence interval. "n" is number at last follow-up. [Color figure can be viewed at wileyonlinelibrary.com]

defined mITT as attempted analysis of everyone who received a permanent implant following trial stimulation. PPA is defined as attempted analysis of everyone with an implant at a given time point.

RESULTS

The search strategy retrieved 180 and 456 results from MEDLINE and Embase, respectively (Fig. 1). Following deduplication, 480 abstracts were reviewed, with 72 publications proceeding to full-text evaluation. Thirty-two publications (including seven conference abstracts) remained after full-text screening (Supporting Information Table S2), including reports of t-SCS (n = 21), high-frequency spinal cord stimulation (hf-SCS) (n = 2), burst spinal cord stimulation (b-SCS) (n = 2), dorsal root ganglion stimulation (DRGS) (n = 5), deep brain stimulation (DBS) (n = 1) and selective nerve root stimulation (n = 1). Among these, there was one erratum (22), and 13 single cases (Supporting Information Table S3 for summary) (23–35). 17 publications were inappropriate for meta-analysis.

Meta-Analysis

Quantitative meta-analysis of t-SCS RCTs showed superiority to BMT at six-month follow-up by ITT (Fig. 2). Likewise, meta-analysis demonstrated significant improvement in pain from baseline at 6- and 12-month post-operative follow-up in t-SCS case series by mITT and PPA, respectively (Table 1). Long-term case follow-up demonstrates that clinical benefit appears to continue for many years (Fig. 3). DRGS showed significant pain improvement from baseline at 1-, 6- and 12-month follow-up by PPA (Table 1). Mean improvement was similar for DRGS and t-SCS by PPA, however very broad 95% CIs, due to the small number of patients, limit the comparison.

Tonic Spinal Cord Stimulation
Controlled Trials

Two unblinded multicenter RCTs compare t-SCS to BMT at six months. Both reported outcomes on an intention-to-treat (ITT) basis. de Vos et al. (n = 40) used a primary outcome of >50% VAS reduction (36), and Slangen et al. (n = 19) used a broader primary outcome of "treatment success": >50% pain relief during daytime or night-time on an NRS scale, or "(very) much improved" for pain and sleep on the patient global impression of change (PGIC) scale (37). de Vos et al. reported 93% having successful trial stimulation

and implantation, with 60% having a > 50% VAS reduction compared to 5% for BMT ($p < 0.001$) at six months. Slangen et al. reported 77% having successful trial stimulation and implantation, with 59% having treatment success at six months, compared to 7% for BMT ($p < 0.01$). Follow-up of the successfully implanted patients (mITT) showed treatment success decrease from 76% at six months to 65% at 24 months.

Prospective Case Series

Pluijms et al. ($n = 15$) reported 73% having successful trial stimulation and implantation (22,38). Treatment was successful (>50% pain relief) in 82% of patients at six months, 91, 55, and 64% at one, two, and three years follow-up (mITT) (39). The cohorts of Slangen et al. (including cross-over patients from medical arm) (37) and Pluijms et al. (38) ($n = 48$) have combined longer-term follow-up, following 83% trial success (40). Treatment success was achieved in 87, 71, 77, 67, and 55% at one, two, three, four, and five years follow-up (PPA) (39–41). At five years, 80% of patients implanted were still using their device (40). Tesafye et al. ($n = 10$) reported eight patients undergoing permanent implantation after trial, all reporting >50% relief during active stimulation (42). Peak pain improved from a baseline mean VAS of 64.5 (SD = 12.2) to 35.6 (SD = 32.6) at six months, while 72.3 (SD = 15.5) with stimulation *off*. VAS was 27 (SD = 22.5, $n = 6$) at 3.3 years and 42.3 (SD = 11.3, $n = 4$) at 7.5 years (43). De Vos et al. ($n = 11$) reported 82% having successful trial stimulation (44). Implanted patients improved from 77.2 (SD = 9.4) to 34.4 (SD = 16.5), 22.8 (SD = 24.4) and 22.5 (SD = 19.8) at 6, 12, 30 months follow-up. Munteanu ($n = 50$) reports success rates of 85% at one year, 69% at two years, 75% at three years, and 55% at four years follow-up (45).

Mixed Series

Richardson et al. reported two patients who were afforded total pain relief with surgery. One patient was still implanted and pain free at one-year follow-up (46). The other patient was explanted within the year as they became pain free, remaining so at two and three years follow-up. Kumar et al. ($n = 4$) reported success in all patients at internalization and 75% at longer-term follow-up (47).

Quality of Life

One trial was significant for improvement of quality of life, with EQ-5D increasing by 11 with t-SCS and decreasing by four with BMT ($p < 0.01$) (36). McGill Pain Questionnaire Quality of Life decreased by 8 for t-SCS and by 1 for BMT ($p < 0.001$) and satisfaction with treatment was significantly higher with t-SCS: 8 vs. 4/10 ($p < 0.001$). Another trial was not significant for t-SCS improving quality of life (EQ-5D) or perceived health (EQ-VAS, Medical Outcomes Study SF-36) (37). Pluijms et al. also did not show improvement of quality of life (EQ-5D, SF-36) at six months, only the physical component of SF-36 at 12 months ($p < 0.01$) (mITT) (22,38).

Risk of Bias

Both RCTs had a low risk of bias in multiple categories (Supporting Information Table S4). However, allocation concealment and blinding to outcome were unclear, and the nature of t-SCS necessitates a high risk of performance bias.

The majority of the published data were from case series and case reports. Inherent in these study designs (level IV evidence) is a high risk of bias (Supporting Information Fig. S1).

Complications

Risk of failing therapeutic trial was 16%, and risk of infection was 4% (Supporting Information Table S5). Risk of lead problems requiring surgery to resolve were 13%: 4% per year of follow-up. Implanted pulse generator (IPG) replacement was 0% at six months, 12% at two years, 17% at three years, and 45% at five years. Following "permanent" implantation, likelihood of explanation was 20% by five years (40). One patient died from subdural haematoma (37).

Burst Spinal Cord Stimulation

De Vos et al. reported 12 patients receiving b-SCS, after prior t-SCS for a minimum of six months (mean = 2.5 years) (48). Prior to t-SCS, mean baseline pain was VAS 70 (SD = 9), which subsequently improved to 28 (SD = 23). Following b-SCS implantation, mean score improved to 16 (SD = 18) ($p < 0.05$) at two weeks. Of the patients, 67% found their pain improved with b-SCS, while 8% worsened; 67% of patients reported preferring b-SCS to t-SCS, and 33% vice versa. One patient reported having lower and more stable blood glucose during b-SCS. Tjepkema-Cloostermans et al. conducted a double-blind randomized cross over study assessing t-SCS, high- and low-amplitude b-SCS in a mixed pain cohort of 40 patients (49). Of the three PDN patients, one preferred each condition.

High-Frequency Spinal Cord Stimulation

Galan et al. ($n = 9$) reported one patient failing trial stimulation, and the rest improving from mean baseline pain of VAS 8.1 (SD = 1.0) to 1.9 (SD = 1.4) at three months and 2.0 (SD = 1.3) at six months, with 88% achieving >50% pain relief (50). Sisson et al. presented a case where the patient also had painful Scheuermann's disease, with 10/10 pain overall (30). An implant at T9-10 gave excellent back relief and good lower limb PDN relief (5/10) at six months.

Dorsal Root Ganglion Stimulation

Eldabe et al. ($n = 10$) reported 50% receiving long-term DRGS, after two failing intraoperative therapeutic trial, one having operative lead placement problems (previously failed t-SCS), one requesting explant for personal reasons, and one explanted for therapeutic failure at one week having suffered lead dislodgement and a dural puncture (51). Mean pain reduced by VAS 48 (SD = 18) at one month and 49 (SD = 19) at six months from a baseline of 77 (SD = 14). Falowski et al. reported two patients with baseline pain of 8 on VAS, improved by 75 and 100% at six-week follow-up (52). Yelle et al. presented a case showing 40% pain reduction five days after surgery, despite SCS previously failing (32). This case was complicated by bilateral lead fracture, for which leads were replaced. Belani et al. reported a complication of thecal sac puncture with neurologic deficits resolving on explant (33). Logé et al. reported improvement of lower limb transcutaneous oxygen pressure in a patient with L4-DRGS (31).

Deep Brain Stimulation

A single case of DBS was identified. The surgical target was the left periaqueductal gray matter, confirmed at autopsy at the level of the posterior commissure (35). The authors reported complete resolution of the patient's severe preoperative perineal pain.

Stimulation was used two hours a day at 20 Hz, and the analgesia was naloxone-reversible.

Selective Nerve Root Stimulation

A single case of this unusual surgical technique was reported (34). Bilateral epidural multicontact electrodes were placed to stimulate right L4/L5, and left L5/S1 nerve roots. Stimulation produced bilateral paraesthesia and reduced baseline lower extremity pain from 8 to 1 on VAS. Pain control remained excellent at six months.

DISCUSSION

PDN accounts for approximately 10% of the healthcare burden of chronic pain (53). Our review demonstrates that there is good evidence for the efficacy of neurosurgical techniques to treat PDN. By far the most explored technique to date is t-SCS. Patients undergoing this surgery are medically refractory and have suffered for an average of five to seven years (36–38,42). For 60% of these patients, t-SCS surgery offers a meaningful reduction in their debilitating pain (36,37), which can last for many years, perhaps indefinitely (40). Both the growing prevalence of PDN and the opioid epidemic have made the exploration of advanced methods of pain relief in this condition increasingly relevant. In addition, the anticonvulsants, which have been a cornerstone of PDN management, have recently been classified as class C drugs in the United Kingdom, due to risk of abuse and dependence (54). This development further highlights the need for therapeutic alternatives.

Technical and biological factors may, over time, attenuate the therapeutic benefits of neuromodulation (55). Late failure is recognized, whether idiopathic or due to lead migration, fracture or other hardware issues. Lead problems requiring revision surgery were 13% in this meta-analysis, equivalent to SCS reports for other indications (56,57).

Assessment of the results of published neuromodulation studies is complicated by a major difference in the type of intention-to-treat (ITT) analysis typically performed in RCTs compared to case series. This stems from the nearly universal practice of performing trial stimulation prior to a decision on full-system implantation. RCTs adopt a formal ITT approach where all patients who have trial stimulation are followed up as being surgically treated. Case series generally do not follow up trial failures, and analyses of surgically treated patients therefore include only those patients who proceeded to full implantation; this has sometimes been called "modified intention-to-treat" (mITT). One problem with strict ITT is that the rate of conversion from trial to permanent implantation is highly dependent on patient selection, which is a subjective clinical judgment, and the permanent/trial ratio has an overwhelming impact on ITT results. Even in the two major RCTs where the selection process was formalized using clear inclusion and exclusion criteria, permanent implantation rates differed substantially (15%) (36,37). This is likely to be a critical factor in their different QoL results. Outside RCTs, mITT, while being a less well-established means of assessment, does at least have the advantage of starting from a semi-objective patient group, that is, those who respond to initial trial stimulation. mITT effectively considers trial stimulation as a pre-intervention investigation to assess for eligibility, rather than a part of the treatment itself. Ultimately, interpreting the results of a neuromodulation study depends on understanding both the permanent-to-trial case ratio (i.e., efficacy of patient selection) and the long-term effects in those who receive permanent implants (i.e., efficacy of the treatment in well-selected patients).

The economic standing of neuromodulation in PDN is not yet clear. The only published cost-effectiveness analysis concluded that t-SCS was not cost-effective in the short-term, modeling a 23% trial stimulation failure rate (58). Much lower rates can be achieved (36), with strict patient selection criteria, screening carefully for evidence of mechanical pain and major psychological morbidity. Carrying out trial stimulation and implantation at the same visit also improves the economic profile, although presently this is rarely done. The major cost of the treatment is that of the initially implanted hardware and any subsequent battery replacements. Current IPG batteries using newer stimulation modes such as cycling may extend battery life to over a decade. Transcutaneous induction-rechargeable batteries are now commonplace and, although more expensive than nonrechargeable batteries initially, are now marketed with a 25-year lifespan. Finally, in the broader context of the opioid epidemic, the potential socio-economic cost of escalating medicines should also be taken into account. The prevalence of PDN is closely linked to poor diabetic control (59), and so PDN patients typically also have burdensome micro- and macrovascular morbidity, unfortunately limiting the probable longevity of treatment. In one series, there was a 37.5% mortality by 7.5-year follow-up (43).

Tonic-SCS trials cannot be blinded as stimulation leads to paraesthesia over the targeted area. This may well generate important placebo and nocebo bias. HF-SCS and b-SCS do not typically result in paraesthesia, so that the presence of stimulation is imperceptible to the patient in every respect other than the pain relief that it may provide. From a researcher's perspective this offers a major advantage, as double-blind trials can be designed where all participants have a system implanted but stimulation is initially randomized to *on* or *off*. Those participants in the *off* group are effectively sham operated controls, but without the ethical concerns that sham surgery normally raises as they have working systems which can all eventually be activated. Crossover designs are also possible. The relative efficacy of these different SCS paradigms is unknown, but preliminary research suggests that they could be noninferior to t-SCS, and preferable for some patients (30,48–50). An RCT of HF-SCS for PDN is currently underway (clinicaltrials.gov: NCT03228420).

The DRG is a well-recognized locus of dysfunction in neuropathic pain syndromes (60). The ACCURATE trial demonstrated that DRGS was superior to t-SCS for treatment of complex regional pain syndrome (CRPS) (18), another cause of neuropathic pain in the foot. This was achieved whilst largely avoiding common side effects of t-SCS, including paraesthesias outside the target area and postural variation in stimulus intensity. Although CRPS and PDN are both neuropathic pain syndromes, their peripheral pathology is very different, and at present it is unclear whether or not the results of the ACCURATE trial will be replicated for PDN. Our analysis of a small number of patients suggests that DRGS is likely to have similar efficacy to t-SCS, although the large CI's make this comparison largely speculative. The ongoing UK multicenter PENTAGONS trial (isrctn.com: ISRCTN40062191) aims to evaluate DRGS for PDN compared to BMT. DRGS is a slightly more technically challenging procedure than SCS, for which there is a learning curve for individual surgeons. In the ACCURATE RCT, there was a higher rate of procedure-related nonserious adverse events in the DRGS group than the SCS group; however, there

was no difference in serious adverse event rates (18). Complications of dural puncture have been reported, however in experienced centers, these are rare occurrences when implanting DRGS electrodes (61), and safety is reportedly on par with SCS (62,63). Although more economical stimulation paradigms for SCS are being developed, DRGS benefits from markedly (~90%) lower energy consumption than typical SCS, largely due to the negligible layer of subdural cerebrospinal fluid at the DRG. This can be further optimized with prudent DRG electrode placement (64). This decreases the clinical and economic burden of IPG replacements: the most expensive hardware component.

Diabetic neuropathy is frequently accompanied by peripheral vascular disease (PVD), and both pathologies, in variable combinations, may contribute to an individual's limb pain. SCS is licensed to treat ischaemic pain due to medically refractory PVD and in that setting has long been recognized as vasoactive, improving microcirculatory blood flow (65). While the pathology of peripheral diabetic vasculopathy/neuropathy has been shown to involve both sympathetic and parasympathetic abnormalities (66), their relative mechanistic contributions to microcirculatory deficits remain uncertain. Arterio-venous shunts in the skin are under the control of the sympathetic nervous system (67). However by the time a patient develops PDN, their small-fiber loss will have left them largely peripherally sympathectomized, with highly impaired cutaneous microvascular dilatation and constriction, and compromised tissue perfusion (68). The demonstration of SCS-induced vasodilation at high intensities in sympathectomized animal models (69,70) provides evidence that stimulation may improve cutaneous oxygenation by non-autonomically mediated means. DRGS may also improve tissue oxygenation (31). Retrograde firing in sensory fibers triggering vasodilator release, such as CRGP, may underpin such vasodilatation (71–74). Physiologically this is part of the axon reflex that causes increased perfusion in the skin surrounding an area of injury.

The appropriate timing of treatment with neuromodulation is a long-standing question in pain management. Surgical treatments are usually reserved for the most refractory patients, who have been suffering the longest. However, it is recognized that the more long-standing pain syndromes are, the more psychological morbidity accumulates as well as plastic changes in the brain that ultimately make pain more difficult to treat (75,76). As invasive neuromodulation has demonstrated superiority to continued medical treatment in poorly responding cases, it may be prudent to offer surgical treatments as soon as it becomes clear that medical treatments are not working satisfactorily, with cessation of nonbeneficial medications as soon as possible. It is increasingly clear that opioids do not provide effective long-term symptom control in chronic neuropathic pain syndromes. The opioid epidemic has brought into focus the need for more judicious prescribing and the dangers of insidiously escalating doses, which are far greater than risks from surgery (77).

LIMITATIONS AND RECOMMENDATIONS

Treatment with t-SCS has level 1 evidence, accumulated in two trials, across multiple centers, showing superiority to BMT. However, these were necessarily unblinded and performance bias is important to acknowledge. The treatment effect calculated in this meta-analysis is likely to include a placebo effect. However, such effects can be long lasting, and the aim in highly refractory patients with severe pain is simply to leverage pain relief. On these grounds, t-SCS can be recommended. There is only level 4 evidence for longer term benefit, so the clinician must be cautious with a patient's

expectations on duration of effect, while acknowledging the increasing possibility of complications over time.

For b-SCS, HF-SCS, and DRGS, only a small amount of level 4 evidence is available, insufficient for routine recommendation for PDN. These can only be recommended on a research or exceptional basis. However, SCS devices can operate with multiple programs interchangeably, allowing the patient to select programs based on observed relief and side effects. In this setting, devices providing b-SCS or HF-SCS can be recommended provided that they have a tonic program as default, and other optional programs used at patient's preference.

CONCLUSION

As a leading cause of neuropathic pain worldwide, the effective treatment of PDN is of high societal and economic importance. Meta-analysis of the existing evidence provided by two randomized controlled trials supports the use of t-SCS in the treatment of medication refractory severe PDN. Other newer stimulation modalities such as high-frequency SCS, burst SCS, and DRGS show promise but require formal trial evaluation. We suggest that the available evidence should encourage healthcare professionals to consider neuromodulation in any case where there is severe pain unresponsive to anticonvulsant and antidepressant medications, and before prescription of strong opioids, certainly well before such drugs reach guideline dose limits.

Authorship Statement

Mr. Raghu and Mr. Parker conceived the topic for review. The concept, scope, and design was developed by Mr. Raghu, Mr. Parker, and Prof. FitzGerald. Prof. FitzGerald supervised the study. Prof. Aziz and Prof. Green helped supervise the study. Mr. Parker and Mr. Raghu underwent Cochrane approved systematic review and meta-analysis training in order to carry out the study. Mr. Raghu, Mr. Parker and Prof. FitzGerald carried out the study as described in Methods. Dr. Hadjipavlou consulted on all statistics. The manuscript was primarily written by Mr. Raghu, Mr. Parker, and Prof. FitzGerald. Dr. Rea consulted on and revised the manuscript primarily relating to diabetes physiology and medical aspects of diabetes. All authors contributed to and revised the manuscript, and approved the final manuscript.

How to Cite this Article:

Raghu A.L.B., Parker T., Aziz T.Z., Green A.L., Hadjipavlou G., Rea R., FitzGerald J.J. 2021. Invasive Electrical Neuromodulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis. Neuromodulation 2021; 24: 13–21

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENTS

The edits have improved the paper, but it still relies heavily on a meta-analysis of just two studies. The authors chose to ignore my comments on the inconsistency of adopting a random effects meta-analysis, which assumes and aims to quantify between-study heterogeneity of effect size, when quantifying heterogeneity is not possible with just two studies.

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Peripheral neuropathic pain caused by diabetes is often a sign of poorly controlled diabetes and implanters should work closely with the diabetologist and the general practitioners when considering implant procedure. The added complications associated with the procedure in these patients should be acknowledged and addressed appropriately. In carefully selected patients SCS therapy can be life-changing. The available literature is not sufficient to advocate SCS therapy in all cases of peripheral diabetic neuropathy. It should be undertaken by experienced clinicians providing multidisciplinary care.

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This is a very interesting publication demonstrating the impact of multiple potential neuromodulation techniques for painful diabetic neuropathy. It demonstrates also that we need more RCT with larger number of patients to explore new therapies and compare them to tonic spinal cord stimulation.

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