Narrative Review

Painful Diabetic Neuropathy - Spinal Cord Stimulation, Peripheral Nerve Stimulation, Transcutaneous Electrical Nerve Stimulation, and Scrambler Therapy: A Narrative Review

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Background: First-line medications for the treatment of painful diabetic neuropathy (PDN) are associated with a substantial rate of discontinuation due to adverse effects or insufficient efficacy. Neuromodulation techniques have been used for PDN, but a comprehensive review of the literature that incorporates several distinct device categories has yet to be undertaken.

Objectives: We aimed to summarize the evidence regarding 4 major types of neuromodulation devices for the treatment of PDN. We focused on spinal cord stimulators (SCS), peripheral nerve stimulators (PNS), transcutaneous electrical nerve stimulators (TENS), and scrambler therapy devices (ST) because they are often used for refractory neuropathic pain.

Study Design: Narrative Review.

Methods: A comprehensive and reproducible literature search was performed using PubMed with no search restrictions applied. The available Medical Subject Headings were used. Inclusion criteria included prospective studies, retrospective studies, case series, and case reports indexed from database inception to the search date (September 14, 2021).

Results: Seventeen studies met inclusion criteria, 10 of which were regarding SCS. Only 3 of the 10 were randomized controlled trials. We found no studies assessing contemporary PNS. Four studies assessed TENS, but the devices varied widely in voltages and waveforms. Two case reports described ST.

Limitations: Potential selection bias due to the nature of a narrative review, although a reproducible search strategy was utilized. Several neuromodulation modalities have minimal published evidence available.

Conclusions: The evidence for neuromodulation devices for the treatment of PDN mostly comprises open-label prospective trials or case reports. SCS has the most volume of evidence for efficacy. Studies regarding TENS show mixed results, possibly due to numerous device varieties. PNS and ST may hold promise based on their proposed mechanisms of action, but prospective controlled trials are needed.

Key words: Chronic pain, pain medicine, neuropathic pain, painful diabetic neuropathy, neuromodulation, spinal cord stimulation, peripheral nerve stimulation, transcutaneous nerve stimulation, scrambler therapy

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Over 300 million individuals worldwide are estimated to have diabetes mellitus (1), with the incidence likely increasing (2). At least half of all patients with diabetes develop neuropathy (3,4), which is painful in 50% of cases (1,5). This equates to a quarter of all patients with diabetes of any type developing painful diabetic neuropathy (PDN) (4-6). In addition to experiencing significant morbidity and decreased quality of life (6,7), diabetic patients with PDN incur greater healthcare costs (6). Compared to diabetic patients who do not have PDN, patients with PDN are estimated to spend up to twice as much on healthcare services and as much as 3 times more on outpatient medications (6).

The initial treatment strategy for PDN consists of optimizing glycemic control (1,5,8) and adding pharmacologic therapy, usually from among the anticonvulsant (e.g., pregabalin, gabapentin), antidepressant (e.g., duloxetine, amitriptyline), and topical agent (e.g., capsaicin cream, lidocaine patches) classes, and potentially opioids (1,4,5,8,9). Duloxetine, amitriptyline, and gabapentin or pregabalin are recognized as first-line agents (4,9). However, many patients have pain refractory to these medications (8,10-12), and adverse effects are common (10,13,14). Approximately 50% of patients with PDN who are prescribed gabapentin, pregabalin, or duloxetine will discontinue them within 3 months due to adverse effects, lack of efficacy, or both (15).

Because of these limitations with pharmacologic therapy and the need for alternative or adjunctive treatments, various neuromodulation modalities have been used to treat PDN (10,11,14,16). Four major classes of neuromodulation devices in clinical use are spinal cord stimulators (SCS), peripheral nerve stimulators (PNS), transcutaneous electrical nerve stimulators (TENS), and scrambler therapy devices (ST). To date, a comprehensive review of the literature encompassing the use of both invasive (SCS, PNS) and noninvasive (TENS, ST) devices specifically for the treatment of PDN has yet to be undertaken.

Methods

An evidence-based literature review using a reproducible search strategy (Supplemental Table 1) was performed via PubMed, with the keywords "painful diabetic neuropathies," "diabetic neuralgia," "diabetic neuropathies," "spinal cord stimulation," "peripheral nerve stimulation," "transcutaneous electrical nerve stimulation," and "scrambler therapy." The available Medical Subject Headings for these keywords were used. No search restrictions were applied. Inclusion criteria included any prospective studies, retrospective studies, case series, and case reports indexed in PubMed from database inception to the search date (September 14, 2021) that discussed the usage of SCS, PNS, TENS, or ST for the treatment of PDN. Exclusion criteria included abstracts, conference reports, reviews, and commentaries, as well as articles that did not pertain to the usage of SCS, PNS, TENS, or ST for the treatment of PDN. The search protocol describing our reproducible search strategy is summarized in Supplemental Table 1. Table 1 summarizes the studies meeting the inclusion criteria.

Results

Spinal Cord Stimulation

Spinal cord stimulation (SCS) was first introduced in 1967 (17), based on the premise of the gate control theory. Melzack and Wall proposed that the stimulation of non-nociceptive A-beta fibers results in the activation of inhibitory dorsal horn interneurons, thereby impeding the transmission of afferent nociceptive signals from A-delta and C-fibers (18). Several SCS systems have since been developed, using varying types of waveforms to stimulate the A-beta fibers of the dorsal column-medial lemniscus pathway. Although the gate control theory remains a useful means of conceptualizing afferent pathways in the central nervous system, it does not fully explain the mechanism of SCS. Patients implanted with SCS devices demonstrate no difference in sensory and pain thresholds (19), and SCS has been shown to affect supraspinal pain pathways within the thalamus and somatosensory cortex (20), sensorimotor circuits in the central nervous system (21), and neurotransmitter levels (e.g., GABA) (22).

SCS is indicated for severe neuropathic pain, most commonly for post-laminectomy pain and complex regional pain syndrome (23,24). SCS has also been used for PDN refractory to medications (e.g., gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) and noninvasive treatments (e.g., physical therapy, acupuncture, exercise) (25,26).

Several SCS devices are in clinical use, differentiated from each other by the type of electrical waveform generated. The tonic waveform has been utilized for decades. By providing repetitive electrical pulses to the dorsal column, patients experience a non-noxious, paresthesia-like sensation instead of pain (27). Recently, additional waveforms have been developed to minimize paresthesia-like sensations. The burst stimula-

Table 1. *Clinical studies regarding neuromodulation devices for painful diabetic neuropathy.*

Device Type	Authors	Study Design (Number of subjects)	Treatment Regimen	Notable Outcomes
Spinal cord stimulator (Tonic waveform)	Kumar et al 1996 (34)	Prospective open-label cohort study (N = 4)	After a 3-7 day trial stimulation, patients who experienced > 50% pain relief progressed to a permanent device implantation.	Three of the 4 patients (75%) in the PDN subgroup experienced pain relief > 50% for at least 36 months.
	Tesfaye et al 1996 (14)	Prospective open-label cohort study (N = 10)	After a 4-day trial stimulation (2 days with placebo stimulation, 2 days with active stimulation), patients who experienced > 50% pain relief progressed to a permanent device implantation.	Eight out of 10 patients (80%) reported > 50% pain relief during trial stimulation. Six out of eight patients (75%) who proceeded to permanent device implantation reported statistically significant pain relief at a median of 14 months postoperatively. One patient no longer reported pain relief for unknown reasons 4 months after permanent implantation.
	Daousi et al 2005 (35)	Prospective cohort study (N = 6)	Follow-up interviews and questionnaires.	The 6 patients who reported ongoing pain relief from Tesfaye et al (14) were reassessed at an average of 7.5 years after device implantation. Four patients continued to report > 50% pain relief. Two patients died of unrelated causes but had reported ongoing pain relief.
	Pluijms et al 2012 (36)	Prospective open-label cohort study (N = 15)	After a 2-week trial stimulation, patients who had successful stimulation (defined as > 50% pain relief or rated their symptoms as "much improved" or more on the patient global impression of change scale) progressed to permanent device implantation.	11 of 15 patients (73%) progressed to permanent implantation; 10 (67%) continued to meet criteria for successful stimulation at 12-month follow-up. EQ-5D quality of life scores increased at 2 week and 3-month follow-up, after which the increase was no longer statistically significant. However, the SF-36 physical component score showed statistically significant improvement compared to baseline at 3-month and 12-month follow-up.
	de Vos et al 2009 (37)	Prospective open-label cohort study (N = 11)	After a one-week trial stimulation, patients who experienced a reduction of > 30 points on VAS progressed to a permanent device implantation.	Nine out of 11 patients (82%) received permanent implantation. Six of these 9 patients (67%) had > 50% pain relief at 6-month follow-up. After lead revisions in 2 patients, at 30-month follow-up, 7 out of 9 patients (78%) had > 30% pain relief, six of whom had > 50% pain relief.
	de Vos et al 2014 (38)	Randomized controlled trial (N = 60)	Patients were randomized in 2:1 ratio to SCS therapy with conventional therapy (medications and physical therapy) or conventional therapy alone.	At 6-month follow-up, 65% of patients who received SCS had greater than 50% pain relief versus only 5% (1 patient) in the conventional therapy group. Statistically significant improvement in quality of life scores on McGill pain questionnaire and EQ-5D in the SCS group but not in the conventional therapy group.
	Slangen et al 2014 (10)	Randomized controlled trial (N = 36)	Patients were randomized in a 3:2 ratio to receive tonic SCS with medical therapy versus medical therapy alone.	At 6-month follow-up, > 50% pain relief was reported in 59% of the patients in the SCS group but only 7% (1 patient) were in the medical therapy group. Improved EQ-5D scores in the SCS group did not reach statistical significance. Defining "treatment success" as 50% pain relief on NRS scale or > 6 in the patient's global impression of change scale, > 60% of patients met these criteria at 24-month (40) and 36-month (41) follow-up and 55% at 5-year follow-up (42).
Spinal cord stimulator (Burst stimulation waveform)	de Vos et al 2014 (43)	Prospective, open-label cohort study (N = 48; N = 12 in PDN subgroup)	Patients who had been receiving tonic SCS therapy for at least 6 months were switched to a burst stimulation waveform for 2 weeks.	In the PDN subgroup, additional pain reduction of about 44%, especially for pain in the feet. One patient reported increased pain. Adverse effects included headaches, dizziness, and a sensation of "heavy legs."

Table 1 (continued). *Clinical studies regarding neuromodulation devices for painful diabetic neuropathy.*

Device Type	Authors	Study Design (Number of subjects)	Treatment Regimen	Notable Outcomes
Spinal cord stimulator (High-frequency [10-kHz] stimulation waveform)	Petersen et al 2021 (16)	Randomized controlled trial (N = 216)	Patients were randomized 1:1 to 10-kHz SCS plus CMM or CMM-only.	At 6-month follow-up, VAS pain scores of the lower extremities decreased by a mean of 76.3% (95% CI, 70.8-81.8) in the 10-kHz SCS + CMM group, with no change in the CMM-only group. The proportion of patients achieving > 50% pain reduction was 85% in the 10-kHz SCS + CMM group high-frequency waveform SCS group versus 5% in the CMM-only group. Improvement in neurological exam in 72% of 10-kHz SCS + CMM patients versus 6% in the CMM-only group. At 12-month follow-up, 86% of the 10-kHz SCS + CMM group continued to have > 50% pain relief (45).
	Sills S. 2020 (44)	Case series (N = 6; N = 3 in PDN subgroup)	After a 7-day trial stimulation of a 10 kHz SCS device, patients who experienced > 50% pain relief progressed to a permanent device implantation.	Patient #1 reported > 90% pain relief and quality of life at 36-month follow-up; Patient #5 reported ongoing pain relief >40% at 26-month follow-up; Patient #6 reported > 90% pain relief at 38-month follow-up.
Acupuncture-like needle probes	Hamza et al 2000 (58)	Prospective Crossover Study (N = 50)	Random assignment between active treatment (needles with electrical stimulation) or sham (needles only) for 30 minutes, 3x/week, for 3 weeks. Crossover of all participants occurred after a one-week washout period.	Improvement in VAS pain scores after 3 weeks of active treatment ($P < 0.05$). No further follow-up after completion of 3-week crossover.
Transcutaneous electrical nerve stimulation	Forst et al 2004 (63)	Randomized controlled trial (N = 19)	Randomized assignment between a proprietary, low-frequency TENS device (Salutaris) and placebo.	Statistically significant improvement with TENS on the Neuropathy Total Symptom Score-6 questionnaire after 6 weeks (-42%) and 12 weeks (-32%) of treatment. Improvements in numbness, lancinating pain, and allodynia. Statistically significant improvement in VAS after 6 weeks of TENS but not placebo ($P<0.05$).
	Reichstein et al 2005 (64)	Randomized controlled trial (N = 41; 21 received TENS)	Randomized assignment to either TENS or high-frequency external muscle stimulation. Treatments were daily 30-minute sessions for 3 consecutive days.	69% of patients in high-frequency external muscle stimulation group versus 25% in TENS group reported improvement in PDN ($P<0.05$). 100% of patients in the high-frequency external muscle stimulation group versus 44% in the TENS group ($P<0.05$) reported relief of non-painful neuropathy symptoms (defined as paresthesias and numbness).
	Gossrau et al 2011 (62)	Randomized controlled trial (N = 41; 22 received "micro-TENS")	Randomized assignment between low-voltage "micro-TENS" or placebo; 3 treatment sessions per week for 4 weeks.	At 4-week follow-up, no statistically significant differences between the micro-TENS group and placebo group on Pain Disability Index, neuropathic pain scores, or Center for Epidemiologic Studies Depression Scale.
	Upton et al 2017 (65)	Crossover Study (N = 5)	Randomized assignment to "traditional TENS" (80 Hz) or "acupuncture-like TENS" (2 Hz). Daily 30-minute treatments x10 days, followed by 7-day washout before crossover for 10 days.	All study participants reported "personally meaningful pain relief."
Scrambler therapy	Smith TJ 2021 (74)	Case report (N = 1)	Three daily 40-minute treatment sessions over 3 consecutive days, with identical operator and identical electrode placement.	Reduction of pain on NRS from eight out of ten to zero for 11 months, and ongoing.
	Lee YS et al 2019 (75)	Case report (N = 1)	One 45-minute treatment session every week over 10 consecutive weeks, with identical operator and identical electrode placement.	Reduction of pain on NRS from six out of ten to two out of ten, for potentially 6 months (uncertain if patient lost to follow-up).

PDN, painful diabetic neuropathy; EQ-5D, EuroQol 5 dimensions questionnaire; SF-36, 36-Item Short Form Survey; VAS, visual analog scale; SCS, spinal cord stimulation; NRS, numerical rating scale; CMM, conventional medical management; TENS, transcutaneous electrical nerve stimulation

tion waveform consists of train-of-five high-frequency pulses occurring at 40Hz (28,29), with the goal of mimicking endogenous neural discharge patterns and possibly influencing the emotional component of pain perception (30). The high-frequency waveform (generally defined as between 1000 Hz and 10KHz) generates a uniform pulse width to desynchronize communication between C-fibers and nociceptive neurons (31) and is touted to be paresthesia-free (32,33).

Tonic Waveform

One prospective open-label study assessed the use of tonic SCS for patients with chronic neuropathic pain from various etiologies, with the PDN subgroup experiencing greater than 50% pain relief for at least 36 months (34). Tesfaye et al were the first to specifically assess the use of tonic SCS for PDN (14). Ten patients with PDN refractory to medical management received a trial SCS implantation, 8 of whom experienced greater than 50% pain relief and proceeded to permanent implantation. Six of the 8 patients continued to report statistically significant pain relief at a median of 14 months after permanent implantation. In a follow-up study of the same cohort 7 years later, 4 of the 6 patients continued to report greater than 50% pain relief (35). Two subsequent prospective open-label studies also reported significant pain relief using tonic SCS, with a duration of follow-up ranging from 12 months (36) to 30 months (37).

The first randomized control trial assessing the use of tonic SCS for PDN was performed by de Vos et al (38). In a 2:1 ratio, 60 patients with PDN were randomized to receive SCS therapy with conventional therapy (medications and physical therapy) or conventional therapy alone. At 6-month follow-up, 65% of patients who received SCS had greater than 50% pain relief versus only 5% of patients in the conventional therapy group. A quality-of-life analysis of the same cohort also found statistically significant improvements in the SCS group (39). In a multicenter, randomized controlled trial by Slangen et al (10), 36 patients with PDN were randomized to receive tonic SCS with medical therapy versus medical therapy alone. Greater than 50% pain relief was observed in 59% of the patients in the SCS group, but only 7% in the medical therapy group. Defining "treatment success" as either a 50% pain score reduction in the numerical rating scale (NRS) or a score of > 6 in the Patient's Global Impression of Change scale, greater than 60% of patients met these criteria at 24-month (40) and 36-month (41) follow-up. In a 5-year follow-up analysis that pooled 48 patients from both Slangen et al (10) and Pluijms et al (36), 55% of patients still met "treatment success" criteria, and 80% of patients were still using their SCS devices (42).

It should be noted that attrition among study participants as the length of follow-up increased may limit conclusions regarding the longevity of benefit from tonic SCS. In the study by de Vos et al (38), 36 out of 40 patients (90%) randomized to SCS completed the final 6-month follow-up visit. Similarly, a high percentage of patients (19 out of 22 [86%]) randomized to SCS in the study by Slangen et al (10) completed their 6-month follow-up visit. However, only 15 out of these 22 patients (68%) returned for follow-up at 24 months (40). In a pooled analysis (42) that also included patients from Pluijms et al (36), only 22 out of 48 patients (46%) returned for 5-year follow-up.

Burst Stimulation Waveform

One prospective open-label study by de Vos et al (43) examined the burst stimulation SCS waveform in 12 patients with PDN who had previously been receiving tonic SCS therapy for at least 6 months. Prior to the initiation of any SCS therapies, these 12 patients had an average score of 70 on the visual analog scale (VAS) for pain. Using tonic SCS, their average VAS score was reduced to 28, which was further reduced to 16 after switching to the burst stimulation waveform ($P < 0.05$), representing additional pain reduction of greater than 40%. However, the clinical implications of these results are uncertain, as VAS scores of 16 and 28 are both generally considered as representing mild pain, and the study only included a follow-up period of 2 weeks. We did not find additional studies specifically examining the use of the burst stimulation waveform for PDN.

High-Frequency Waveform

Pain relief with high-frequency stimulation has been described in a case series of 3 patients with PDN (44), as well as in the SENZA-PDN randomized controlled trial (13,16). In the SENZA-PDN trial, 216 patients with PDN were randomized to receive either a high-frequency (10-kHz) waveform SCS device combined with conventional medical management or conventional medical management alone. At 6-month follow-up, the proportion of patients achieving more than 50% pain reduction was 85% in the high-frequency waveform SCS group versus 5% in the medical management group. Meaningful improvement in neurological exam findings (e.g., motor function, light

touch sensation, and reflexes) was observed in 72% of patients who received high-frequency SCS versus only 6% in the medical management group. A significant improvement in quality of life, pain, and sleep in the high-frequency SCS group was also reported. However, blinding was not performed because patients randomized to the high-frequency SCS group required percutaneous device implantation, and sham implantation was not a part of the study design. At 12-month follow-up, 86% of patients in the high-frequency SCS group continued to have greater than 50% pain relief, and 68% reported ongoing improved sensory function (45).

Adverse Effects and Cost-Effectiveness of SCS Devices

Adverse effects and complications from SCS devices include lead migration, implantable pulse generator site pain, wound dehiscence, infection, and reoperations for electrode or battery repositioning (10,16,38). One case of death due to a subdural hematoma following a dural puncture during SCS electrode placement has been reported (10).

Utilization rates of SCS devices continue to rise in the United States. In 2018, over 36,000 SCS device trials were reported to Medicare, surpassing one billion dollars in fees (46). A review of cost-effectiveness studies found SCS therapy to be overall cost-saving in the treatment of chronic low back pain, though most of the studies only assessed data for up to 24 months (47). Regarding the use of SCS for PDN, one analysis shows that despite an improvement in patients' quality of life, SCS is not cost-effective within the first 12 months of implantation due to the substantial initial cost (48). We found no additional studies assessing whether SCS may become cost-effective for PDN over a lengthier period of time.

Peripheral Nerve Stimulation

Peripheral nerve stimulation (PNS) was first described in the 1960s to treat head and neck pain, using a surgical approach to place an electrode adjacent to a nerve under direct visualization (49,50). However, PNS was not widely adopted due to a relatively high rate of adverse effects, including lead malfunction, lead migration, infection, and the need for repeat surgeries for lead repositioning (51,52). Further attempts to stimulate peripheral nerves involved adapting percutaneous electrodes originally developed for other uses (e.g., SCS leads). In 2016, Deer and colleagues published their findings of a novel device specifically designed for the stimulation of peripheral nerves in the lower and upper extremities, pelvis, or trunk (53). There are now several PNS devices on the market, with an expanding number of uses (54), including post-amputation pain (55), chronic low back pain (56), and postoperative knee pain (57).

As with SCS devices, the physiological foundation of PNS devices is the gate control theory by Melzack and Wall. However, there is evidence that PNS exerts numerous effects on both the peripheral and central nervous systems. It has been found to alter the concentration of inflammatory mediators, endorphins, and prostaglandins adjacent to the stimulated nerve, as well as reduce nociceptive activity in the dorsal horn, prefrontal cortex, and limbic system (49,54). The exact mechanism by which PNS exerts analgesia is likely multimodal (54).

In our literature search, there were zero studies that used a PNS device for the treatment of PDN. The most similar study we found was from 2000, in which Hamza et al describe the use of acupuncture-like needles to administer electrical stimulation to the tibial and deep peroneal nerves (58). Patients had an improvement in pain scores, physical activity, and sleep, but the outcomes were only followed for 3 weeks. In addition, the needles were placed solely by anatomic landmarks without a means of confirming adequate proximity to the target nerves. Current PNS devices require fluoroscopic or ultrasonographic guidance to confirm proper electrode positioning.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive method of neuromodulation with a mechanism of action that is also based on the gate control theory. There is significant variation in electrical waveform frequencies, intensities, and pulse widths among TENS devices, but all of them use cutaneous adhesive electrodes to stimulate A-beta fibers with the goal of indirectly inhibiting nociceptive transmission in the spinal cord dorsal horn (59-61). TENS may also induce the release of endogenous opioids, further contributing to pain relief (59,62).

Forst et al conducted a placebo-controlled randomized controlled trial using a proprietary, low-frequency TENS waveform (63). A group of 19 patients with mild-to-moderate diabetic neuropathy was randomized to either TENS therapy or sham via an identical but inactive device. In both groups, stimulation pads were placed over the anatomical distribution of the

peroneal nerve. The patients that received TENS therapy reported statistically significant reductions in total symptomatology scores at 6- and 12-week follow-ups, as well as improvements in numbness, lancinating pain, and allodynia. The authors did not provide additional details describing the treatment regimen (e.g., number of hours of stimulation per day).

However, other studies have yielded mixed or negative results. Reichstein et al randomized a group of 41 patients with diabetic sensory polyneuropathy to receive either TENS or high-frequency external muscle stimulation (64). In the TENS group, pads were placed over the anatomic distribution of the peroneal nerves, and a biphasic waveform with a frequency of 180 Hz and intensity of 20-30 mA was administered. In the high-frequency external muscle stimulation group, electrodes were wrapped over the femoral muscles, and pulses ranging from 4,096 Hz to 32,768 Hz were delivered. Only 33% of the patients who received TENS reported an overall improvement in symptoms versus 80% of the external muscle stimulation group. Among patients with specifically PDN, the response rate to TENS was even lower, with only 25% of patients in the TENS group experiencing benefit versus 69% of patients in the external muscle stimulation group. The patients who received external muscle stimulation therefore appeared to experience greater pain relief than those who had received TENS, though the authors state that the underlying mechanism for analgesia from muscle stimulation is unclear. Gossrau et al assessed the use of a low-current waveform, called "micro-TENS," in a randomized placebo-controlled trial involving 41 patients with PDN (62). The placebo group and the micro-TENS group experienced statistically equivalent pain relief. A small pilot crossover study by Upton et al compared "traditional TENS" (defined by the investigators as having a frequency of 80 Hz) to "acupuncture-like TENS" (2 Hz) and found that both modalities provided pain relief for patients with PDN (65). However, there was no placebo group, and only 5 patients were enrolled.

Of note, 2 of the earliest studies describing the use of "transcutaneous electrostimulation" for treating PDN utilized H-wave technology, rather than TENS (66,67). In these 2 studies, patients who received H-wave therapy reported a statistically significant improvement in pain, but sample sizes were relatively small. Although H-wave devices and TENS units both administer electrical signals to the skin, H-wave devices generally have a lower frequency range (1-60Hz for H-wave compared to 1-250Hz for TENS) and a fixed pulse duration and can be considered distinct from TENS devices (68). The appearance of these 2 studies pertaining to H-wave therapy in our literature search underscores how a variety of waveforms, frequencies, and devices may be described as TENS or in terminology similar to that of TENS.

Scrambler Therapy

Scrambler therapy (ST) is a relatively new method of cutaneous neuromodulation initially studied in Italy in the late 1990s (69). ST devices are mechanistically distinct from TENS units and have 510(k) clearance from the United States Food and Drug Administration. ST devices synthesize 16 unique waveforms and combine them into 256 strings of information packets that are continually changed by a software algorithm. These signals are administered through cutaneous adhesive electrodes placed along the dermatomal distributions that most approximate the regions of pain (70). Rather than adhering to the gate control theory and inhibiting nociception through A-beta fiber stimulation, the goal of ST is to modulate nociceptive signals from C-fibers into sensations that are interpreted as both "non-painful" and endogenous by the central nervous system (69). ST has shown initial success in a variety of neuropathic pain conditions, such as chemotherapy-induced peripheral neuropathy (71), human immunodeficiency virus-related peripheral neuropathy (72), and postherpetic neuropathy (73).

In our literature search, no randomized controlled trials were found assessing the use of ST for PDN. However, 2 case reports were identified. In one case report, an 80-year-old woman with severe PDN in the upper and lower extremities received one 40-minute ST session per day over 3 consecutive days, and her NRS pain score decreased from 8 out of 10 to zero, with pain relief sustained at 11-month follow-up without any additional treatments and no adverse effects (74). In the other case report, a 45-year-old woman with bilateral lower extremity PDN refractory to pregabalin, posterior tibial nerve blocks, and lumbar sympathetic blocks received one 45-minute ST session every week over 10 consecutive weeks. By the end of her final treatment session, her NRS pain score had decreased from a baseline of 6 out of 10 to 2 out of 10. The patient was instructed to return for a repeat ST session if her pain were to worsen, but she had not returned after 6 months (75). It is not clear whether the patient continued to have sustained relief throughout this time or whether she was lost to follow-up.

Discussion

The evidence for neuromodulation devices for the treatment of PDN is surprisingly limited. There are very few randomized controlled trials in the literature, and nearly all prospective studies are open label.

SCS devices appear to have the strongest evidence regarding efficacy and duration of relief, and they have been in clinical use for the treatment of PDN for nearly 30 years. However, there are very few studies assessing the efficacy of the newer waveforms (e.g., burst, high frequency), and no studies have directly compared them to the "traditional" tonic waveform. The SENZA-PDN trial by Petersen et al (16) using the high-frequency (10-kHz) waveform is particularly noteworthy. It is the largest randomized controlled trial to date assessing the use of SCS for PDN, and at 6-month follow-up, patients in the 10-kHz SCS group experienced statistically significant improvements in their neurologic exam, especially in regard to sensory function. Because hemoglobin A1c levels among patients did not improve over the course of the trial, this suggests that 10-kHz stimulation had an independent effect on improving neurologic function, with the precise mechanism yet to be established (16) but possibly involving improvements in cutaneous blood perfusion (76). Based on these results, the United States Food and Drug Administration approved the use of 10-kHz stimulation for the treatment of PDN. However, no other studies reproducing and confirming the benefits of 10-kHz for PDN have yet been completed. As new waveforms continue to be developed, future studies should assess whether these waveforms are superior in efficacy to tonic stimulation and whether a particular waveform pattern may be especially beneficial for patients with PDN. Future studies should also address the question of whether SCS can induce measurable physiologic changes (e.g., electromyography and nerve conduction velocity [EMG/NCV] data) that are directly associated with improved neurologic function and in turn, whether particular EMG/NCV findings have prognostic value for particular waveforms.

The use of contemporary PNS devices for PDN has not been studied, but this may be a potentially important area of future investigation. The successful use of PNS for other refractory neuropathic conditions, including those that are not limited to a single nerve distribution, may bode success for PDN, but this remains to be seen.

The evidence base for TENS for the treatment of PDN is weakened by a wide variety of devices and waveforms that are all subsumed under the broad label of "TENS," making the generalizability of results challenging. Further, the available literature shows mixed results, with some studies showing only minimal analgesic benefit. However, TENS devices may still be a valuable adjunctive therapy for many patients due to their very low barrier to access, as they can be purchased over-the-counter without insurance, and they generally do not require clinician supervision for use.

The evidence for ST for the treatment of PDN is very limited. However, ST has shown initial success for the treatment of other refractory peripheral neuropathies. Also, ST is distinct among current neuromodulation therapies in that C-fibers are targeted rather than A-beta fibers, and ST is believed to modulate nociceptive signals rather than inhibiting them. Additional research is necessary to establish whether this unique mechanism of action is more efficacious for PDN than other neuromodulation techniques that are based upon the gate control theory. Particularly, placebo-controlled trials or non-inferiority trials comparing ST with more invasive neuromodulation devices (e.g., SCS) are likely necessary before ST can be widely adopted for treating PDN.

The potential benefits of ST and TENS are important to assess and maximize, as these therapies may hold promise for patients with pain that is refractory to SCS. Also, few treatment options exist for patients with pain refractory to medications or in whom medication use has been limited due to adverse effects from escalating dose requirements. Furthermore, many patients are unable to receive implanted neuromodulation devices due to medical comorbidities associated with diabetes (e.g., osteomyelitis, poor wound healing, recurrent infections secondary to immunodeficiency), excessive risk of bleeding from concomitant antiplatelet or anticoagulant usage, or personal preference.

In conclusion, the treatment of PDN remains a challenge, especially for the significant proportion of diabetic patients who either have pain refractory to neuropathic medications or have dose-limiting adverse effects. Neuromodulation devices can provide an avenue of hope when there may be few other treatment options. Further research is greatly needed to clarify which devices and waveforms are optimal, balancing the goals of efficacy, safety, and accessibility.

Supplementary material available at www.painphysicianjournal.com

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Supplemental Table .: ***Search protocol and reproducible search strategy.***

Review/Search Topic: Spinal Cord Stimulation, Peripheral Nerve Stimulation, Transcutaneous Electrical Nerve Stimulation, and Scrambler Therapy for the Treatment of Painful Diabetic Neuropathy	Searcher: Eric Wang
Investigators: Dr. Eric Wang, Dr. Lauren Berninger, Dr. Olga Komargodski, Dr. Thomas Smith	Date: September 14th, 2021

DATABASE	**Date of Search**	**Date Range Searched**	**Neuromodulation modality**	**Search Strategy**	**# Citations**
PubMed/MEDLINE	9/14/21	Inception to 9/14/21	Spinal cord stimulation	("diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms]) AND ("spinal cord stimulation"[MeSH Terms] OR ("spinal"[All Fields] AND "cord"[All Fields] AND "stimulation"[All Fields]) OR "spinal cord stimulation"[All Fields])	83
PubMed/MEDLINE	9/14/21	Inception to 9/14/21	Peripheral nerve stimulation	("diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms]) AND (("peripheral nerves"[MeSH Terms] OR ("peripheral"[All Fields] AND "nerves"[All Fields]) OR "peripheral nerves"[All Fields] OR ("peripheral"[All Fields] AND "nerve"[All Fields]) OR "peripheral nerve"[All Fields]) AND ("stimulate"[All Fields] OR "stimulated"[All Fields] OR "stimulates"[All Fields] OR "stimulating"[All Fields] OR "stimulation"[All Fields] OR "stimulations"[All Fields] OR "stimulative"[All Fields] OR "stimulator"[All Fields] OR "stimulator s"[All Fields] OR "stimulators"[All Fields]))	375
PubMed/MEDLINE	9/14/21	Inception to 9/14/21	Transcutaneous electrical nerve stimulation	("diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms]) AND ("transcutaneous electric nerve stimulation"[MeSH Terms] OR ("transcutaneous"[All Fields] AND "electric"[All Fields] AND "nerve"[All Fields] AND "stimulation"[All Fields]) OR "transcutaneous electric nerve stimulation"[All Fields] OR ("transcutaneous"[All Fields] AND "electrical"[All Fields] AND "nerve"[All Fields] AND "stimulation"[All Fields]) OR "transcutaneous electrical nerve stimulation"[All Fields])	57
PubMed/MEDLINE	9/14/21	Inception to 9/14/21	Scrambler therapy	("diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms] OR "diabetic neuropathies"[MeSH Terms]) AND (("scrambler"[All Fields] OR "scramblers"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]))	2
Total:					517
Comments: No search restrictions or filters applied.					