















A Systematic Guideline by the ASPN Workgroup on the Evidence, Education, and Treatment Algorithm for Painful Diabetic Neuropathy: SWEET

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Introduction: Painful diabetic neuropathy (PDN) is a leading cause of pain and disability globally with a lack of consensus on the appropriate treatment of those suffering from this condition. Recent advancements in both pharmacotherapy and interventional approaches have broadened the treatment options for PDN. There exists a need for a comprehensive guideline for the safe and effective treatment of patients suffering from PDN.

Objective: The SWEET Guideline was developed to provide clinicians with the most comprehensive guideline for the safe and appropriate treatment of patients suffering from PDN.

Methods: The American Society of Pain and Neuroscience (ASPN) identified an educational need for a comprehensive clinical guideline to provide evidence-based recommendations for PDN. A multidisciplinary group of international experts developed the SWEET guideline. The world literature in English was searched using Medline, EMBASE, Cochrane CENTRAL, BioMed Central, Web of Science, Google Scholar, PubMed, Current Contents Connect, Meeting Abstracts, and Scopus to identify and compile the evidence for diabetic neuropathy pain treatments (per section as listed in the manuscript) for the treatment of pain. Manuscripts from 2000-present were included in the search process.

Results: After a comprehensive review and analysis of the available evidence, the ASPN SWEET guideline was able to rate the literature and provide therapy grades for most available treatments for PDN utilizing the United States Preventive Services Task Force criteria.

Conclusion: The ASPN SWEET Guideline represents the most comprehensive review of the available treatments for PDN and their appropriate and safe utilization.

Keywords: diabetes, painful diabetic neuropathy, neuropathy, spinal cord stimulation, chronic pain, diabetic neuropathy

Introduction and Methodology

Development Process

The American Society of Pain and Neuroscience (ASPN), through its mission to increase evidence-based access to treatment, has commissioned a systematic guideline process to outline the current state of the art in treatment of painful diabetic neuropathy (PDN) (SWEET guidelines). Members of the SWEET consensus group were selected from among the thought leaders across a broad spectrum of specialties interested in the treatment of diabetic neuropathy within both ASPN and other societies. A diverse authorship included experts from the specialties of Pain Medicine, Neurology, Podiatry, Primary Care, Neurosurgery, Physiatry, Psychology, and Anesthesiology. The current guideline will examine the evidence, education and current treatment options. The SWEET consensus work group was convened and at regular intervals, members have evaluated the level of current evidence in the peer-reviewed literature for topics that have been identified as critical for treatment.

Work groups were convened to conduct literature searches and examine the evidence for the topics developed by lead authors in outline form. After the literature search was completed, each author was asked to provide cited references, and evidence rank. The section leaders then formulated the recommendation grade, based on the evidence, which were reviewed by at least three different, nonconflicted SWEET working group members. If conflicts of interest were identified, recusal was required as outlined below. ASPN utilizes the United States Preventative Services Task Force (USPSTF) format with slight modification for interventional pain treatment. This process has been established in previous ASPN publications.¹ Once literature was reviewed, consensus statements were created and graded based upon the ASPN-USPSTF criteria listed in Table 1. The process by which section leaders then created consensus points included in-person meetings, teleconference, or other electronic or audio-video communications to define the consensus; agreement by at least 80% of the contributing authors was considered a quorum. Consensus strength was defined, as described in previous ASPN guidelines.¹ If a recommendation was proposed with <50% consensus, based on assigned evidence rank and recommendation grade, then no consensus was achieved.

This consensus guideline gives guidance to clinicians concerning painful PDN treatment and evidence-based practice and outcome optimization. However, these recommendations should not be construed as a standard of care, but instead represent best practices. This guidance is based on several factors and peer-reviewed evidence, and regardless of the strength of evidence, requires interpretation for clinical application.

Table 1 Quality of Evidence Ranking Using United States Preventative Services Task Force Criteria Modified for Therapy

Grade	Definition	Suggestions for Practice
A	ASPN recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	ASPN recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	ASPN recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	ASPN recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	ASPN concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

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Abbreviations: ASPN, American Society of Pain and Neuroscience; USPSTF, United States Preventative Services Task Force.

Management of Conflict of Interest

All authors were required to disclose conflicts of interest prior to assignment of topics. The senior authors determined the extent of the conflict of interest ensuring balanced inquiry and evaluation for each manuscript section. One of the co-primary authors without conflict was identified for each section and is the adjudication determination official for any issues of potential conflict. All authors were asked to recuse themselves on any recommendation potentially affected by a disclosed conflict. Additionally, authors without conflict vetted all recommendations for bias.

Methodology: Literature Search, Evidence Ranking

The world literature in English was searched using Medline, EMBASE, Cochrane CENTRAL, BioMed Central, Web of Science, Google Scholar, PubMed, Current Contents Connect, Meeting Abstracts, and Scopus to identify and compile the evidence for diabetic neuropathy pain treatments (per section as listed in the manuscript) for the treatment of pain. Manuscripts from 2000-present were included in the search process. Search words were selected based upon the section represented. Identified peer-reviewed literature was critiqued using the USPSTF criteria for quality of evidence,² with modifications for neuromodulation studies (Table 1). After USPSTF letter grading was assigned, the working subgroup then assigned the “level of certainty regarding benefit” as described in Table 2.

For each major section or topic, ASPN formulated consensus points. Consensus points should not be confused with recommendations based on consensus alone (Evidence Level II), which were rendered as clinical guidance in the situations where, due to the lack of evidence-based literature (such as randomized controlled trials [RCTs]), prospective observational studies, and retrospective cohort/case series), the best available guidance is expert opinion.

Table 2 Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies. Evidence Level: I-A - At least one controlled and randomized clinical trial, properly designed
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: <ul style="list-style-type: none"> • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. Evidence Level I-B- Well-designed, controlled, non-randomized clinical trials (prospective observational studies conforming to STROBE criteria) or Evidence Level I-C – Retrospective cohort or large case studies (>20 subjects)
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: <ul style="list-style-type: none"> • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcome Evidence Level II- Expert opinion based of risk:benefit or based upon case reports

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Abbreviation: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Painful Diabetic Neuropathy

Background

PDN is a common and distressing complication of diabetes mellitus (DM), characterized by chronic pain and sensory abnormalities in the extremities. PDN is reported in as many as 16%–26% of patients with diabetes, yet often not discussed with the patients and continues to remain untreated,³ negatively affecting the patient's quality of life, both physically and psychologically.⁴

The pathophysiology of PDN is multifactorial, involving both metabolic and vascular mechanisms. Chronic hyperglycemia, oxidative stress, and neuroinflammation contribute to nerve damage in a length-dependent manner and subsequent development of pain, with variety of clinical manifestations, ranging from mild discomfort to severe debilitating pain, often accompanied by sleep disturbances, anxiety, and depression.

The diagnosis of PDN involves a comprehensive evaluation of a patient's symptoms, medical history, physical examination, and additional diagnostic tests.

1. Patient's history: including detailed information about the symptoms, underlying medical conditions, and evaluation of potential causes for neuropathic pain.
2. Physical examination: assessment of neurological function including sensory perception, reflexes, and motor strength.
3. Diagnostic criteria, such as the Toronto Diabetic Neuropathy Expert Group criteria.⁵
4. Nerve conduction studies: helps to assess the nerve damage and rule out other possible causes of neuropathy.
5. Quantitative sensory testing: measuring the perception of various sensory stimuli to evaluate the function of small nerve fibers.
6. Laboratory testing: to assess patient's blood glucose control, kidney function, and rule out other potential causes of neuropathy such as vitamin deficiency and autoimmune disorders.
7. Imaging studies: such as magnetic resonance imaging (MRI) or nerve ultrasound to assess for structural abnormalities or nerve compression.

The management of PDN requires a multimodal approach, that combines pharmacological, topical analgesics, interventional therapies, and non-pharmacological therapies. Pharmacological treatments include tricyclic antidepressants, anti-convulsants, serotonin-norepinephrine reuptake inhibitors, and opioids. Topical analgesics include 8% capsaicin, lidocaine and amitriptyline. Non-pharmacological interventions such as physical therapy, transcutaneous electrical nerve stimulation, and acupuncture can also provide some relief. Additionally, interventional procedures like nerve blocks and spinal cord stimulation have been on emerging rise, in treatment of refractory cases.

Despite a position statement from multiple national associations, including the Centers for Disease Control and Prevention (CDC) as well as American Academy of Neurology (AAN),^{6,7} opioids continue to remain the most commonly prescribed medication for PDN, followed by gabapentin, pregabalin, duloxetine, amitriptyline, and venlafaxine.⁸

PDN continues to remain a challenging condition to manage effectively. Tailoring treatment to individual patients, considering their comorbidities and preferences, is crucial for optimizing outcomes. Additionally, a multidisciplinary approach involving collaboration between primary care physicians, endocrinologists, interventional pain specialists, podiatrists, and other healthcare professionals is essential for comprehensive PDN management.

Physical Exam

Early detection of PDN is challenging due to the insidious nature of PDN and nonspecific symptoms. Patients frequently experience symptoms such as pins and needles, shocks, numbness, a feeling of walking on sandpaper or extra socks, and burning sensations. These symptoms often worsen at night and follow a stocking-glove distribution, initially affecting the feet and toes before progressing proximally.⁹ Evaluating medical history, family history, alcohol use, and medications, along with thorough physical exam is vital for early stage PDN identification. The American Diabetes Association recommends sensory tests such as the 128 Hz tuning fork, monofilament testing, thermal testing, pinprick sensations, deep tendon reflexes, and proprioceptive testing; see [Figure 1](#).¹⁰ Additionally,

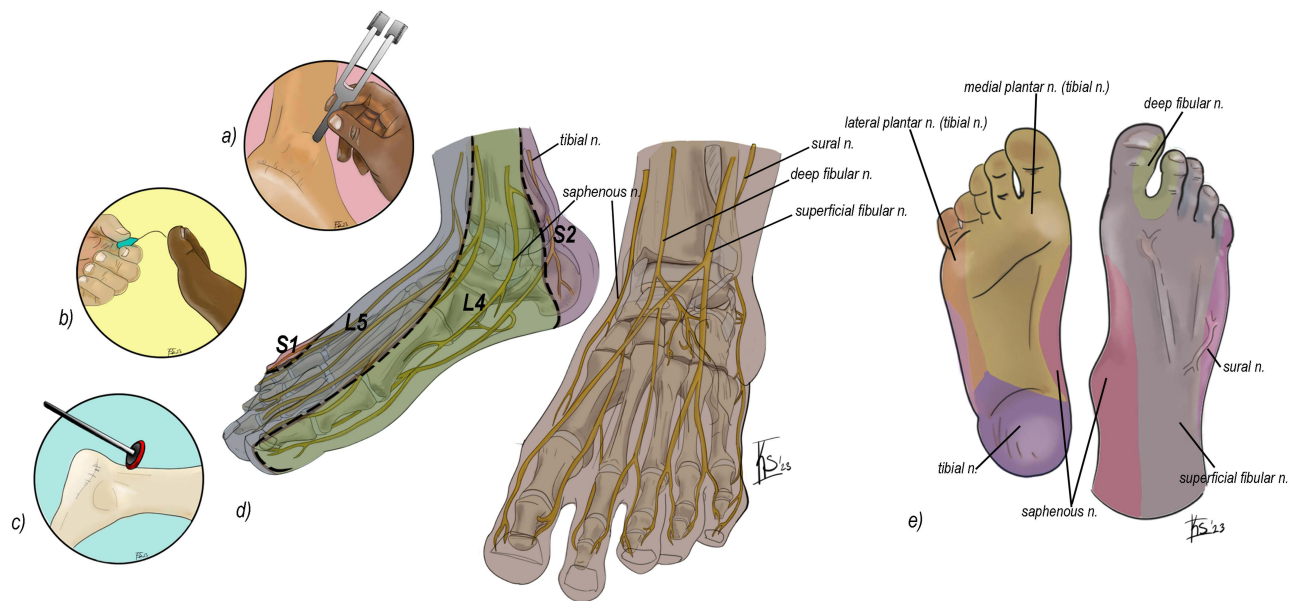


Figure 1 (a) 128Hz Tuning fork for vibratory testing. (b) 10g Semmes Weinstein monofilament test evaluates light touch perception. (c) Achilles reflex testing. (d) Normal foot anatomy and innervation to the foot. Right includes a dermatomal overlay. (e) Corresponding sensory territories of the main nervous supply to the foot.

laboratory investigations, electrodiagnostic studies, and skin biopsies may aid diagnosis and assess disease progression.¹⁰

Diagnostic Approaches

Sensory Testing

Sensory testing plays a crucial role in evaluating peripheral nerve function in PDN. The 128 Hz tuning fork is utilized to assess vibratory sensation, reflecting the integrity of large sensory nerve fibers. The absence of perceived vibratory sensation indicates sensory impairment.¹¹ The 10-g Semmes Weinstein monofilament test evaluates light touch perception and is used to assess large nerve fibers. The mono filament is designed to buckle under 10 g of pressure. Various testing sites, including the plantar aspect of the toes, metatarsal heads, dorsum of the hallux, midfoot, and plantar aspect of the heel, are recommended.¹² Because the aforementioned exams test the large nerve fibers, positive tests are usually in the irreversible late stage of the disease progression.¹³

Thermal Testing

Thermal testing, which assesses temperature perception, has shown promise in early detection of PDN, as it tests the small nerve fibers that are affected early in the disease progression. Reduced temperature sensations have been associated with up to 93% of individuals with glucose intolerance or DM.¹³ However, standardization and subjectivity remain challenges in this diagnostic modality.

Pinprick Sensations

The evaluation of pinprick sensations provides insight into the functionality of small myelinated A-delta fibers. By applying pressure using a pin or small gauge needle, the ability to perceive sharp stimuli is assessed. Inability to perceive the sharp sensation indicates abnormal sensory function. Despite its subjective nature, the pinprick test demonstrates high positive predictive value in diagnosing PDN.¹⁴

Deep Tendon Reflexes

Deep tendon reflexes, particularly the Achilles and patellar reflexes, exhibit acceptable sensitivity, specificity, and predictive values associated with abnormal nerve conduction velocity (NCV). Impaired reflexes in these regions warrant further investigation, but evidence proposes deep tendon reflex testing as a valuable tool for early detection of PDN.¹⁵

Proprioceptive Testing

Assessment of joint position sense provides valuable information regarding the effect of PDN on proprioceptive accuracy. Studies have shown a correlation between proprioceptive inaccuracy and altered diabetic neuropathy scores, supporting its utility as a diagnostic tool.¹⁶

Laboratory Testing

Initial laboratory testing should include a complete blood count, comprehensive metabolic profile, fasting blood glucose, thyroid-stimulating hormone, and vitamin B12 levels.¹⁷ Serum protein electrophoresis with immunofixation is suggested by the AAN due to the association of monoclonal gammopathies with peripheral neuropathy. Laboratory testing should be performed on initial presentation/diagnosis. Although laboratory testing alone cannot diagnose PDN, it can be utilized as a screening test for etiologies attributed to peripheral neuropathy.¹⁷

Electrodiagnostic Studies

Nerve conduction velocities and electromyography can aid in treatment planning once a comprehensive history and physical examination have been conducted. However, the utility of electrodiagnostic studies in the absence of suspicion of demyelinating disorders, nerve entrapment, or nerve injury remains debatable.⁹

Skin Biopsies

Analysis of intraepidermal nerve fiber densities through small punch biopsy has emerged as a valuable and promising modality for the diagnosis and monitoring of early-stage PDN. This technique provides a distinct advantage over NCV studies, as it allows for the evaluation of small intraepidermal nerve fibers that are susceptible to early disease involvement.^{18,19} The biopsy procedure is easily performed, exhibits good reproducibility, and offers the capability to assess disease progression and potentially serve as an indicator of treatment response.¹⁸

Section I. Pharmacotherapy

All patients with diabetes should be screened for PDN and, if present, should be appropriately treated. There are three classes of medications that are primarily used for the treatment of PDN. These classes include serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, and tricyclic antidepressants (TCAs).²⁰ The individual medications belonging to each of these classes are presented later in this section. Of all these oral agents, duloxetine, pregabalin, and tapentadol are approved by the FDA for the treatment of painful diabetic neuropathy.^{21–24} Drugs belonging to the TCA class are often used and effective for various neuropathic pain conditions; however, these agents have not been studied in randomized control trials specifically for the treatment of PDN.²⁰

Opioids, while effective in the short term, are discouraged for use in the treatment of chronic noncancer pain.⁶ In a systematic review by the CDC, there was weak to nonexistent evidence for the long-term efficacy of opioids for the treatment of chronic pain.^{6,7} Instead, long-term opioid use was found to be associated with adverse consequences including addiction and opioid-induced hyperalgesia. Interestingly, tapentadol which exerts its effect by both opioids and SNRI-based mechanisms was found to be effective in the treatment of painful diabetic neuropathy and has an FDA indication for this condition.²⁵ However, due to the adverse consequences of long-term opioid use, this medication is discouraged by several societies.

At large, all the agents from the SNRI, gabapentinoids, and TCA classes have similar efficacy on neuropathic pain.²⁰ However, there are agent-specific differences in side effects. Additionally, some of the agents have multiple indications, including depression and anxiety. Clinicians should be mindful of these differences in selecting appropriate medication. While many of these medications are effective for the treatment of PDN, complete elimination of pain is not realistic. Clinicians should have a discussion with patients in setting reasonable analgesic expectations. When initiating an agent, it is advisable to slowly titrate the agent to the effective dose to avoid intolerance and if therapeutic efficacy is not achieved after increasing the dose to the maximum allowable dose for the duration of 12 weeks, the medication can be considered ineffective. Clinicians should not prematurely declare an agent ineffective when the dose has not been escalated to an appropriate level and the agent has not been tried for an appropriate duration.

Combination therapy with agents from different classes has not been studied extensively in well-designed trials. One study evaluated the efficacy of combined duloxetine (60 mg/day) and pregabalin (300 mg/day) to high-dose duloxetine (120 mg/day) and pregabalin (600 mg/day).²⁶ The combination therapy was no more effective than individual agent therapy. Given the paucity of data on combination therapy, a clinician should carefully weigh the pros and cons before initiating such therapy.

Individual Pharmacotherapy Agents

Duloxetine

Duloxetine is a serotonin and norepinephrine reuptake inhibitor.²¹ It has a balanced activity when it comes to serotonin and norepinephrine reuptake inhibition. Serotonin and norepinephrine are important neurotransmitters and modulate descending inhibitory pain pathways in the brain and spinal cord, and this underlies the analgesic mechanism of duloxetine.²⁷ Duloxetine is approved for use in PDN by the FDA.²¹ It is available in 20 mg, 30 mg, and 60 mg strength capsules. For the treatment of PDN, FDA recommends a target dose of 60 mg daily; however, in clinical practice, the dose varies between 20 mg and 120 mg daily. Numerous well-designed studies support the use of duloxetine for the treatment of PDN.^{28,29} In a parallel-group, double-blind, placebo-controlled study, various doses and regimens of duloxetine were compared to placebo in subjects with PDN. After 12 weeks of treatment, the 24-hour average pain score was significantly improved in subjects taking duloxetine 60 mg daily or 60 mg twice daily compared to those taking duloxetine 20 mg daily or placebo group. In another open-label, randomized, parallel study, subjects were randomized to receive either duloxetine 60 mg twice daily or 120 mg once daily.²⁸ Subjects were followed for 28 weeks. Both regimens were equally effective as measured by the Brief Pain Inventory (BPI) scale. Additionally, both regimens were safe and well tolerated by patients. There is evidence that duloxetine may be a better option compared to other choices such as pregabalin.²⁶ In a multicenter, double-blind, parallel-group study in PDN, subjects were randomized to duloxetine 60 mg daily or pregabalin 300 mg daily, and after 8 weeks those who received duloxetine performed significantly better than pregabalin on all domains of the BPI scales. In addition to PDN, duloxetine is approved for a few other indications including depression, anxiety, fibromyalgia, and generalized musculoskeletal pain. Therefore, duloxetine can be an ideal choice for individuals with PDN with concomitant depression, anxiety, fibromyalgia, or musculoskeletal pain.

Gabapentin

Gabapentin belongs to a class of medication called anticonvulsants. It exerts its analgesic effect by binding to and inhibiting $\alpha 2\delta$ -1 receptor which is a voltage-gated calcium channel.^{30,31} Gabapentin is approved for use in the treatment of seizures and post-herpetic neuralgia by the FDA. Gabapentin is often used for the treatment of PDN though it is not FDA-approved for PDN.³⁰ Gabapentin is available in capsule form in 100 mg, 300 mg, and 400 mg strength, and in tablet form in 600 mg and 800 mg strength.³⁰ Gabapentin also has a liquid formulation for those who cannot swallow pills and is available in 250 mg/5 mL strength.³⁰ The efficacy of gabapentin for PDN has been studied in randomized control trials.^{32,33} In one trial, subjects with PDN were randomized to receive gabapentin or placebo.³² All patients were given 3600 mg of gabapentin each day divided into three doses. Subjects who could not tolerate the 3600 mg per day dose received a reduced dose (900 mg/day, 1200 mg/day, 1800 mg/day, and 2400 mg/day). After 8 weeks of treatment, gabapentin was found to be effective in reducing symptoms of PDN compared to placebo as measured on a VAS. In another trial, gabapentin was compared to amitriptyline and found to be superior in controlling pain and paresthesia on an NRS.³³ Despite the analgesic advantages of gabapentin, amitriptyline should be considered in patients in patients with concomitant mood disorder because of its effectiveness in treating depression. Gabapentin dose and regimen vary from patient to patient when it comes to the treatment of PDN. In clinical practice, the dose and regimen range from 300 mg three times daily to 1200 mg three times daily. The maximum dose of gabapentin is 3600 mg/day.³⁰ Gabapentin is primarily eliminated through the kidney; therefore, the dose needs to be adjusted in individuals with renal insufficiency.³⁰ Gabapentin can lead to peripheral edema and should not be used in patients who have pre-existing peripheral edema.

Pregabalin

Pregabalin also belongs to the anticonvulsant categories of medication. Pregabalin acts similarly to gabapentin mechanistically.³¹ Pregabalin is FDA-approved for use in the treatment of neuropathic pain from PDN, post-herpetic

neuralgia, and spinal cord injury.²² It is also used for fibromyalgia and partial onset seizure.² Pregabalin is available in 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules as well as a liquid formulation in 20 mg/mL dosage.²² The FDA recommends a maximum of 300 mg per day divided into 3 doses for the treatment of PDN; however, in clinical practice, the regimen is more nuanced and varies with patients with a maximum of 300 mg per day. The effectiveness of pregabalin for the treatment of PDN is demonstrated in randomized clinical trials.³⁴ In one trial, subjects with PDN were randomized to pregabalin 300 mg per day (100 mg three times daily) and a placebo group. After 8 weeks of treatment, the pregabalin group has significantly improved pain VAS scores compared to the placebo group.

Tricyclic Antidepressants

TCAs are a class of antidepressant medication that can be used to alleviate neuropathic pain. It is believed that the mechanism of action of TCAs in neuropathic pain involves multiple pharmacological effects. TCAs are believed to function primarily by inhibiting the reuptake of norepinephrine and serotonin, two neurotransmitters implicated in pain modulation. By increasing the concentrations of these neurotransmitters in the synaptic cleft, TCAs can enhance the inhibitory pathways that modulate pain transmission. This modulation of neurotransmitter activity may contribute to the analgesic properties of TCAs.³⁵ Moreover, sodium channel-blocking properties have been discovered in TCAs. By inhibiting sodium channels, particularly voltage-gated sodium channels, TCAs can reduce the aberrant discharge of neurons in neuropathic pain states. By inhibiting the transmission of pain signals, this action functions to decrease pain perception.³⁵

Amitriptyline was initially studied to evaluate the efficacy in individuals with PDN and either normal or depressed mood. A crossover study was done with 29 patients that were randomly assigned to receive amitriptyline or a placebo for six weeks. During the third to sixth week of treatment, amitriptyline was found to be more effective than the placebo at reducing discomfort. In addition, patients who could tolerate higher concentrations of amitriptyline experienced greater pain relief, with 150 mg per day identified as the optimal daily dose.³⁶

In another study conducted by Max et al, there was a comparison of the efficacy of amitriptyline and desipramine in 38 PDN patients in a randomized, double-blind, crossover study. At 6 weeks 74% of patients treated with amitriptyline and 61% of patients treated with desipramine experienced moderate or greater pain relief. They concluded that both drugs were equally effective in treating PDN, with desipramine functioning as an alternative for patients who were unable to tolerate amitriptyline.³⁷ Furthermore, a randomized double-blind study was conducted comparing amitriptyline and pregabalin for the pain relief of PDN. Fifty-one patients were administered either amitriptyline or pregabalin. Response rates of 73% for amitriptyline and 77% for pregabalin on the McGill and Likert pain scales revealed no statistically significant differences between the two treatments.³⁸

Another study conducted, compared the effectiveness of amitriptyline and gabapentin in treating neuropathic pain in a prospective, randomized, double-blind study. Half of the 28 patients received amitriptyline (25 to 75 mg per day) for six weeks, while the other half received gabapentin (900 to 1800 mg per day). There was no significant difference in pain relief between the two regimens, according to the study.

As an alternative to other recommended treatments, TCAs such as amitriptyline may be considered. Despite the limited evidence, TCAs, particularly amitriptyline, may have a positive effect on neuropathic pain reduction. TCA therapy may be challenging for some patients, as one in five individuals cannot tolerate it. Clinicians need to be cautious and monitor for potential adverse effects, particularly in patients with specific conditions such as narrow-angle glaucoma, benign prostatic hypertrophy, orthostasis, urinary retention, impaired liver function, or thyroid disease.³⁹ Patients with additional cardiovascular risk factors should have their QTc interval assessed to avoid the risk of torsades de pointes, and alternative treatments may be considered if prolongation is present.³⁹

Tapentadol

Tapentadol is a centrally-acting analgesic agent with dual mechanisms of action. It is an m-opioid receptor agonist and norepinephrine reuptake inhibitor.²⁵ Both mechanisms are well established for pain control.²⁷ Tapentadol is approved for use in PDN by the FDA.²⁵ There are two randomized control trials that evaluated the efficacy and tolerability of tapentadol in patients with PDN.^{25,40} In both trials, subjects with PDN were titrated to tapentadol during a three-week open-label period. Subjects with ≥ 1 -point reduction in pain intensity on 11 NRS at the end of the titration period were

randomized to tapentadol versus the placebo group. After 12 weeks of a double-blinded maintenance phase, both trials found tapentadol to be effective and safe for the management of moderate-to-severe PDN. Despite FDA indication, the American Association of Clinical Endocrinology clinical Practice Guideline recommends against the use of opioids (including tapentadol) for the treatment of PDN due to the risks of addiction with long-term use of opioids.⁴¹

Tables 3 and 4 summarize the literature and ASPN recommendations for this section.

Section 2. Topical Treatments

While oral medications are commonly used to treat painful diabetic neuropathy, their use is typically limited by significant side effects, a high number-needed-to-treat (NNT), and a high non-responder rate. As such, the application of topical medications is gaining significant interest and has in many instances become a routine aspect of patient care in patients with PDN. While many medications are used in the topical treatment of PDN, this section focuses on the most commonly utilized medications including, lidocaine, capsaicin, and amitriptyline.

Topical Lidocaine

Though not specifically mentioned in the 2021 American Diabetes Association guidelines for standard of care management of PDN, topical lidocaine presents a low-risk option for patients refractory to FDA approved treatments.⁴³ Lidocaine, an amide local anesthetic, mitigates neuropathic pain by reversibly blocking voltage-gated sodium channels on neuronal membranes.⁴⁴ This action inhibits sodium influx during action potential generation, dampening nerve impulse transmission and inducing a numbing state. Lidocaine preferentially targets channels in hyperexcitable, pathologically signaling neurons, due to its

Table 3 Literature Summary for Pharmacotherapy in PDN

Study Author	Study Type	Study Size	Evidence Level	Notes
Goldstein et al ²⁹	RCT	457	I	Compared efficacy of duloxetine (20 mg/day, 60 mg/day, and 120 mg/day) to placebo after 12 weeks of treatment.
Raskin et al ²⁸	RCT	449	I	Compared analgesic efficacy of duloxetine 60 mg/day to 120 mg/day after 28 weeks of treatment.
Backonja et al ³²	RCT	165	I	Compared analgesic efficacy of gabapentin (maximum effective dose) to placebo after 8 weeks of treatment
Dalocchio et al ³³	RCT	25	I	Compared analgesic efficacy of gabapentin (1200 mg/day to 2400 mg/day) to amitriptyline (30 mg/day to 90 mg/day) after 12 weeks of treatment
Rosenstock et al ³⁴	RCT	146	I	Compared analgesic efficacy of pregabalin (300 mg/day) to placebo after 8 weeks of treatment
Max et al ³⁶	RCT	29	I	Amitriptyline was superior to placebo in relieving pain from the third to the sixth week of treatment for patients with PDN.
Max et al ³⁷	RCT	36	I	Amitriptyline and desipramine experienced moderate or greater pain relief in patients with PDN. They concluded that both drugs were equally effective in treating PDN.
Bansal et al ³⁸	RCT	51	I	When comparing amitriptyline and pregabalin for the pain relief of PDN, no statistically significant differences were found between the two treatments
Morello et al ⁴²	RCT	28	I	When comparing amitriptyline and gabapentin in treating PDN no significant difference was found between treatments.
Vinik et al ⁴⁰	RCT	358	I	All patients were treated with tapentadol and titrated to an efficacious dose for 3 weeks. Subsequently, subjects were randomized to either continue tapentadol or receive a placebo for 8 additional weeks. Changes in pain intensity the end of titration period to the end of trial was assessed.

Abbreviations: RCT, randomized controlled trial; PDN, painful diabetic neuropathy.

Table 4 ASPN Recommendations on Pharmacotherapy in PDN

Recommendation	Grade	Level	Level of Certainty Net Benefit
Clinicians should carefully evaluate all patients with diabetes for the presence of painful diabetic neuropathy and its impact on function and quality of life.	A	I	High
Clinicians should discuss the goals of pain control and functional improvement with patients.	A	I	High
Clinicians should assess patients for co-morbidities such as depression, anxiety, seizure disorder, peripheral edema, and renal failure, and use this information for the selection of appropriate therapeutic agents.	A	I	High
Clinicians should offer agents from SNRI, gabapentinoids, and TCAs classes of medication.	A	I	Moderate
Opioids offer modest to moderate relief of pain from PDN, although they are often accompanied by side effects and therefore their use is not recommended.	B	I	Moderate
Clinicians should slowly titrate the dose of an agent until therapeutic efficacy or a maximum dose is achieved. An agent can be considered ineffective after it has been trialed for an appropriate time at the appropriate dose.	A	II	High
There is inadequate evidence to recommend or advise against using combination therapy. Clinicians should weigh the pros and cons when making such a decision.	C	II	Low

Abbreviations: SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; PDN, painful diabetic neuropathy.

higher affinity for open and inactivated states. This selective targeting lends to its effectiveness in managing chronic neuropathic pain.^{44,45}

Topical lidocaine has been the subject of significant clinical research in the management of PDN for years. In 2004, Argoff et al performed an open-label, non-randomized prospective study with 41 subjects which demonstrated that a 5% lidocaine patch significantly improved pain scores as compared to baseline, with no systemic side effects or drug interactions over a 2-week observation period.⁴⁴ Barbano et al observed a similar pain reduction (VAS 68.6 at baseline vs 42.4 at 3 weeks, $p < 0.001$) in a 3-week trial with 56 participants in an open-label, flexible-dosing prospective study.⁴⁶ While effective as proof of concepts for the utilization of topical lidocaine in the management of PDN, both of these studies had significant limitations in that they were non-randomized, non-blinded, and did not have a control arm.

In 2009, Baronet al conducted the only study to-date evaluating the efficacy of topical lidocaine as a monotherapy for PDN. A randomized, open-label, multicenter, non-inferiority study was performed comparing 5% lidocaine plaster, which is commercially available in Europe, to pregabalin in patients with PDN.^{47–49} The results of this study were initially reported as an interim analysis, which found similar pain relief in the two groups but that the lidocaine plaster arm ($n = 47$) experienced fewer drug-related adverse events (DRAE, 3.9% in the lidocaine arm vs 39.2% in the pregabalin arm).⁴⁷ There was also a substantially higher discontinuation rate due to DRAE in the pregabalin group ($n = 44$) as compared to the lidocaine group (20.3% vs 13%).⁴⁷ While the subsequently published full analysis substantiated the results found in the interim analysis, the authors also reported quality of life measures in the full analysis.^{48,49} Subjects in the lidocaine arm ($n = 105$) reported significantly greater improvements in quality of life (QOL) based on the EuroQOL 5-dimension questionnaire (EQ-5D) as compared to the pregabalin group ($n = 105$).^{48,49}

Although significant limitations exist to the broad applicability of these results, there are sufficient data in the literature to support the use of topical lidocaine in an individualized treatment plan for patients with PDN. Given the low incidence of DRAE in studies evaluating the efficacy of topical lidocaine, it is a worthwhile consideration in patients who are either refractory to traditional FDA approved medications for PDN or in whom side effects limit their use (see Table 5).

Topical Capsaicin

Capsaicin, a naturally occurring compound of chili peppers, treats neuropathic pain by interacting with sensory neurons involved in pain transmission.^{50,51} It is a highly selective agonist for the transient receptor potential vanilloid 1 (TRPV1)

Table 5 Literature Summary of Topical Lidocaine in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Follow Up Duration	Results
Argoff et al, 2004 ⁴⁴	Non-randomized, prospective study	41	Level I-B	NPS score	2 Weeks	Patients with PDN reported improved pain control with lidocaine patch when added to their current regimen.
Barbano et al, 2004 ⁴⁶	Non-randomized, prospective study	56	Level I-B	Reduction in mean daily pain diary readings by 30% using VAS	Up to 5 weeks	70% of PDN patients showed at least a 30% reduction in average pain scores.
Baron et al, 2009 ⁴⁷	Randomized controlled trial, non-inferiority study (interim results)	91	Level I-A	Reduction of >2 or an absolute value < 4 on NRS-3 pain scale	4 Weeks	65.3% of patients in the lidocaine arm achieved the primary endpoint vs 62.0% in the pregabalin group
Baron et al, 2009 ⁴⁸	Randomized controlled trial	204	Level I-A	Reduction of >2 or an absolute value < 4 on NRS-3 pain scale, QOL parameters (EQ-5D), patient satisfaction, incidence of DRAE	4 Weeks	69.1% of patients in the lidocaine arm achieved primary endpoint vs 62.0% in the pregabalin group. Lidocaine group achieved greater improvement in QOL, patient satisfaction, and lower incidence of DRAE

Abbreviations: PDN, painful diabetic neuropathy; QOL, quality of life; DRAE, drug-related adverse event.

receptor. Nociceptive (C and A-delta) fibers expressing TRPV1 are responsible for transmitting pain signals to the brain. Upon entering the epidermal layers, high concentrations of capsaicin (8% prescription dose) bind and activate the TRPV1 receptors.⁵⁰

As a TRPV1 agonist, capsaicin initially causes depolarization and action potential propagation, which desensitizes the nociceptive fibers, triggering sensations of warmth, itching, or pain.^{50–52} This chemical cascade is associated with a marked increase of intracellular calcium, and sustained capsaicin exposure in high doses results in “dysfunctionalization”, or reversible ablation of the nociceptive fibers, characterized by loss of cell membrane potential, receptor desensitization, substance P depletion, and reduced nerve fiber density, thus decreasing pain signals sent to the brain.⁵⁰ Additionally, capsaicin-activated TRPV1 in immune cells can mitigate inflammation, further contributing to its analgesic and potential anti-inflammatory effects.⁵¹

Topical capsaicin’s role in the management of PDN has been substantiated by many clinical trials. The Capsaicin Study Group and Tandan et al demonstrated that 0.075% capsaicin cream significantly improved pain compared to placebo in 8 and 12-week trials, respectively.^{53,54} Biesbroeck et al reported similar results in an 8-week trial.⁵⁵ However, these studies noted high dropout rates due to side effects, such as skin irritation.⁵¹

While lower doses have been around for much longer, a critical advancement was reported by Mou et al in their comprehensive review.⁵⁶ They presented evidence that a single application of a higher dose, 8% capsaicin patch, could provide pain relief for up to 12 weeks in patients with focal neuropathic pain.⁵⁶ Subsequently, in a randomized controlled trial by Simpson et. al, in a study of 369 patients, the mean percentage change in “average daily pain” score from baseline to weeks 2–8 was significantly greater in the capsaicin group (–27.4%) than in the placebo group (–20.9%) (p<0.001).⁵¹ Moreover, the incidence of adverse events was similar in both groups, suggesting that this high-concentration capsaicin patch provided substantial pain relief without increasing side effects.⁵¹

Anand et al reported similar results in a randomized control trial with 50 participants in which patients were randomized to either 8% capsaicin patch along with standard of care (SOC) medication management or SOC alone.

Patients in the capsaicin plus SOC group fared significantly better with a clinically and statistically meaningful improvement in NRS pain scores at 3-month follow-up, as compared to SOC alone.⁵⁰

On the basis of this clinical evidence, 8% capsaicin patch is an FDA approved treatment for PDN and should be considered as a treatment option that can provide moderate relief, especially when initial oral agents are ineffective or provide only partial pain relief (see Table 6).

Topical Amitriptyline

Amitriptyline, a tricyclic antidepressant, is used topically for neuropathic pain, including diabetic neuropathy.^{57,58} Its analgesic action primarily stems from inhibiting norepinephrine and serotonin reuptake, enhancing their neurotransmission and reducing pain perception.^{57,58} It also antagonizes peripheral and central N-methyl-D-aspartate (NMDA) receptors,

Table 6 Literature Summary of Topical Capsaicin in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Follow Up Duration	Results
Capsaicin Study Group, 1991 ⁵²	Multi-center, placebo controlled, randomized controlled trial	277	I-A	Percent change in VAS pain score and physician's global evaluation scale.	8 weeks	69.5% vs 53.4% improvement in pain as per physician's global evaluation scale for capsaicin vs placebo group, respectively. 38.1% decrease in VAS pain score in capsaicin group vs 27.4% in the placebo group.
Tandan et al, 1992	Double-blind, randomized controlled trial	22	I-A	Percent change in VAS pain score.	12 weeks	44.6% reduction in VAS score in capsaicin group vs 23.2% in the placebo group.
Biesbroeck, et al, 1995 ⁵⁵	Double-blind, randomized controlled trial	235	I-A	Percent change in VAS pain score and measurement of interference by pain with functional activities at baseline and 2-week intervals.	8 weeks	76% of all subjects (capsaicin group and oral amitriptyline group) reported pain improvement. Mean reduction in pain intensity of 40%. Statistically significant reduction in interference with daily activities by pain in both groups as well.
Simpson et al, 2017 ⁵¹	Randomized control trial	369	I-A	Percent reduction in VAS pain scores between week 2 through 8.	8 weeks	27.4% reduction in VAS pain score in capsaicin group vs 20.9% in placebo group. Capsaicin group also had shorter median time to treatment response compared to placebo (19 vs 72 days).
Anand et al, 2022 ⁵⁰	Randomized controlled trial	50	I-A	Percent reduction in NRS daily pain score.	12 weeks	Capsaicin group reported a statistically and clinically significant improvement in NRS scores between baseline and 12 week follow up (-1.87, p=0.0001). No statistically significant difference in the placebo group (-.58, p=0.11)

Abbreviations: VAS, visual analogue scale; NRS, numeric rating scale.

inhibiting excitatory neurotransmitter glutamate release. Furthermore, amitriptyline blocks voltage-gated sodium and calcium channels, reducing neuronal excitability, particularly relevant in hyperglycemia-induced neuropathic pain.⁵⁷ The exact mechanism of the topical formulation remains unclear, but it is suggested that the drug penetrates the skin to exert local and potentially systemic effects.

The effectiveness of topical amitriptyline is not well delineated in the literature. In a double-blind, randomized, placebo-controlled crossover trial by Ho et al, 35 subjects with postsurgical neuropathic pain, postherpetic neuralgia, or PDN were randomized to receive either topical 5% amitriptyline or placebo.⁵⁷ The study did not show any clinically meaningful difference in pain scores between the two groups. Certainly, these results are marred by a small sample size overall and an even smaller group of PDN patients within the overall cohort.⁵⁷ However, a double-blind, randomized controlled trial by Kiani et al compared topical 2% amitriptyline to 0.75% capsaicin cream. The results showed that while both were effective in managing the painful symptoms of PDN, amitriptyline did so with fewer DRAE and improved patient compliance.⁵⁸

Given there is conflicting evidence in the literature regarding the efficacy of topical amitriptyline, this medication should not be used as a first line treatment for PDN. However, its use may certainly be warranted in patients refractory to first- and second-line therapeutic agents, as the drug does have a favorable side effect profile (see Table 7). Overall, there is moderate evidence for topical medications in the treatment of PDN (see Table 8).

Table 7 Literature Summary of Topical Amitriptyline in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Follow Up Duration	Results
Ho et al, 2008 ⁵⁷	Randomized, placebo-controlled trial	35	Level I-A	VAS pain score	6 Weeks	No change in pain intensity with topical amitriptyline as compared to topical lidocaine or placebo.
Kiani et al, 2015 ⁵⁸	Double blinded, randomized controlled trial	56	Level I-A	50% or greater improvement in VAS pain score	12 weeks	No significant difference in pain relief between amitriptyline or capsaicin group (43.1% vs 37.3%, respectively, achieved the primary endpoint). Topical amitriptyline arm reported fewer DRAE and improved patient compliance.

Abbreviations: VAS, visual analogue scale; DRAE, drug-related adverse event.

Table 8 ASPN Recommendations for Topical Medications in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
Topical lidocaine may be offered as an adjunct therapy to patients who have failed conservative and FDA approved treatments for PDN, or in whom DRAE limit dose titration of oral agents.	B	I-B	Moderate
Topical capsaicin 0.75% ointment may be offered to patients as a 2nd line treatment in patients who have failed conservative and FDA approved treatments for PDN, or in whom DRAE limit dose titration of oral agents.	B	I-A	Moderate
Topical capsaicin 8% patch may offer moderate benefit in patients with PDN in conjunction with FDA approved oral medications.	A	I-A	Strong
Topical amitriptyline may provide marginal pain improvement in patients with PDN and may be better tolerated with less DRAE as compared to most oral and select.	C	I-A	Low

Abbreviations: FDA, Food and Drug Administration; PDN, painful diabetic neuropathy; DRAE, drug-related adverse event.

Section 3. Neuromodulation

Spinal Cord Stimulation

Spinal cord stimulation (SCS) for the treatment of PDN was initially thoroughly described in three different studies, all published in 2014. De Vos and colleagues performed a multicenter randomized controlled trial investigating the effectiveness of traditional SCS in patients with PDN.⁵⁹ Sixty patients with PDN in the lower extremities unresponsive to conventional medical therapy were enrolled and followed for six months. They were randomized 2:1 to conventional medical therapy with SCS (SCS group) or without SCS (control group) therapy. At each follow-up visit, the EQ-5D, the short form McGill Pain Questionnaire (SF-MPQ), and a 0–100 VAS to measure pain intensity were recorded. At baseline, the average VAS score for pain intensity was 73 in the SCS group and 67 in the control group. After six months of treatment, the average VAS score was reduced to 31 in the SCS group ($P < 0.001$) and remained 67 in the control group ($P = 0.97$). The reported responder rate was 69% in the SCS group. Similarly, the EQ-5D and SF-MPQ questionnaires also showed that patients in the SCS group experienced reduced pain and improved health and quality of life after six months of treatment, while those in the control group did not.⁵⁹

Slangen and colleagues published results from a two-center randomized controlled trial studying traditional SCS versus best conventional medical management for the treatment of PDN.⁶⁰ Thirty-six PDN patients with severe lower limb pain not responding to conventional medical therapy were enrolled. Twenty-two patients were randomly assigned to conventional medical therapy with SCS (SCS group) and 14 to best medical therapy only (BMT group). The SCS system was implanted only if trial stimulation was successful. Treatment success was defined as $\geq 50\%$ pain relief during daytime or nighttime or “(very) much improved” for pain and sleep on the patient global impression of change (PGIC) scale at six months. Trial stimulation was successful in 77% of the SCS patients. Treatment success was observed in 59% of the SCS and in 7% of the BMT patients ($P < 0.01$). Pain relief during daytime and during nighttime was reported by 41 and 36% in the SCS group and 0 and 7% in the BMT group, respectively ($P < 0.05$). Pain and sleep were “(very) much improved” in 55 and 36% in the SCS group, whereas no changes were seen in the BMT group, respectively ($P < 0.001$ and $P < 0.05$).⁶⁰

Also in 2014, de Vos et al published results from a study in which patients with PDN or failed back surgery syndrome (FBSS) treated for six months with traditional SCS were transitioned to burst SCS for two weeks.⁶¹ A total of 48 patients were in the overall study, of which 12 patients were diagnosed with PDN. At baseline, these patients had a VAS of 70. With traditional SCS, they reported a VAS of 28 ($P < 0.001$) and with burst SCS a VAS of 16 ($P < 0.001$), and this difference was statistically significant ($P < 0.05$). The effect of burst SCS was more evident in the PDN patients compared to the FBSS patients (77% vs 57%). Eight of the 12 patients had more pain reduction with burst stimulation as compared to traditional SCS.⁶¹ At this time, no other studies exploring burst SCS for use in PDN have been published.

In 2018, Van Beek et al reported the longest follow-up data for traditional SCS in treating PDN. Forty-eight patients with PDN were included in this prospective multicenter study.⁶² The Michigan Diabetic Neuropathy Score (MDNS) was used to assess the severity of neuropathy. During the five years of follow-up, the NRS score for pain, PGIC, and treatment success (50% reduction of NRS score or significant PGIC) were evaluated. Treatment success was observed in 55% of patients after five years. Of those patients that underwent a permanent implant, 80% were still using their SCS device after five years. Interestingly, higher MDNS was associated with treatment failure during the five-year follow-up time period ($P = 0.014$).⁶²

Recently, Petersen et al explored the benefit of 10 kHz high frequency (HF)-SCS in treating patients with PDN in the SENZA-PDN study.⁶³ In this multicenter, open-label, randomized controlled trial, a total of 216 patients were randomized 1:1 to either the HF-SCS with conventional medical management arm (treatment arm) or conventional medical management alone arm (control arm). Following randomization, 113 patients were included in the treatment arm and 103 in the control arm. They reported 78.9% (75/95) of the HF-SCS arm and 5.3% (5/94) of the conventional medical management (CMM) arm obtained $> 50\%$ pain relief and had no neurologic deterioration at six months ($P < 0.001$). After allowing crossover from the control arm to the treatment arm at six months, the same researchers reported the 12-month results following implantation for all implanted patients.⁶⁴ The average pain relief was 74.3%, and 85% of patients had $> 50\%$ pain relief without further neurological decline. Additionally, health-related quality of life measures, including EQ-5D-5L (baseline overall health), Diabetes Quality of Life score, Pain and Sleep Questionnaire 3-Item Index (sleep quality), BPI (pain interference), and Global Assessment of

Functioning (social, occupational, and psychological functioning) were all improved at six and 12 months. Recently, long-term efficacy of 10kHz was published in a 24-month publication on the previously described RCT. At 24 months, the investigators reported that 10kHz reduced pain by a mean of 79.9% compared to baseline, with 90.1% of participants experiencing greater than 50% pain relief. Participants also had improvements in quality of life, sleep, and neurological symptoms. Only 3.2% of implants were explanted due to infection, supporting the safety of implantable therapies in the diabetic population when appropriate measures are taken.⁶⁵

The findings of these studies were substantiated by a recent systematic review assessing the use of SCS for treatment of pain in length-dependent peripheral neuropathy.⁶⁶ Neuropathies included in this review extended beyond just PDN and included chemotherapy-induced neuropathy and other polyneuropathies. This systematic review comprising nineteen studies (376 participants who underwent SCS implantation) demonstrated that all studies reported significant improvement in pain intensity after 12 months of SCS therapy compared to baseline. However, the quality of evidence for this outcome per the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria was very low quality, indicating the need for future high-quality trials to strengthen the use of SCS for all neuropathies beyond just PDN.⁶⁶

Overall, SCS is a well-studied and proven intervention for the treatment of PDN. Both traditional SCS and the more contemporary HF-SCS have been studied in randomized controlled trials and shown to be more efficacious than conventional medical management for the relief of pain related to PDN (see [Tables 9 and 10](#)).

Table 9 Literature Summary for SCS in PDN

Author	Design	Sample Size	Level of Evidence	Pain Endpoint - Control	Pain Endpoint - SCS	Secondary Outcomes at Endpoint - Control	Secondary Outcomes at Endpoint - SCS
De Vos, 2014 ⁵⁹	RCT	60	I-A	0% VAS Reduction	59% VAS Reduction	No Improvement	Improvement
Slangen, 2014 ⁶⁰	RCT	36	I-A	7% Responder Rate	59% Responder Rate	No Improvement	Improvement
De Vos, 2014 ⁶¹	Prospective cohort study	12	I-B	60% VAS Reduction (Tonic)	77% VAS Reduction (Burst)	N/A	N/A
Van Beek, 2018 ⁶²	Prospective cohort study	48	I-B	N/A	55% Responder Rate at 5 Years	N/A	Improvement
Peterson, 2021 ⁶³	RCT	216	I-A	5.3% Responder Rate	78.9% Responder Rate	No Improvement	Improvement
Peterson, 2023 ⁶⁵	RCT	142	I-A	N/A	90.1% responder rate and 79.9% reduction in VAS	NA	Improvement

Abbreviation: VAS, visual analog scale.

Table 10 ASPN Recommendations for SCS in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
The SWEET Consensus Committee recommends consideration of SCS for patients with lower extremity PDN after the failure of other non-invasive FDA approved treatments.	A	I-A	High

Abbreviations: SWEET, systematic guideline process to outline the current state of the art in treatment of painful diabetic neuropathy; SCS, spinal cord stimulation; PDN, painful diabetic neuropathy.

Peripheral Nerve Stimulation

Background

Peripheral nerve stimulation (PNS) has emerged as a potential treatment modality for PDN, offering an alternative to conventional pharmacological approaches. The utility of PNS in various pain conditions including neuropathic pain,⁶⁷ complex regional pain syndrome (CRPS),⁶⁸ phantom and residual limb pain,⁶⁹ low back pain,^{70,71} and postoperative pain⁷² has been well described. The current state of the literature on PNS for PDN is limited; more study is needed to assess the utility of PNS in people with diabetes.

PNS may not be appropriate for managing symptoms in patients with diffuse PDN involving multiple nerve distributions with a sizeable dermatomal area. The limitation of PNS is that current systems can only accommodate 1 or 2 leads which may not be adequate to cover a patient's pain. In some cases, larger mixed motor-sensory nerves can be targeted (ie, the sciatic nerve). However, it can be difficult to selectively target afferent A β fibers and avoid stimulating efferent A α motor fibers.

Some of the benefits of PNS include use in patients who may not be candidates for SCS or dorsal root ganglion stimulation (DRG-S) because of complex spine anatomy, prior spinal surgery or fusion, or inability to discontinue anticoagulants. PNS is considered a low to intermediate risk depending on the location of lead placement and proximity to vasculature and other critical structures.⁷³ In many cases, PNS can be done safely without discontinuing blood-thinning medications.⁷⁴ Temporary and permanent options are commercially available, giving patients a variety of options for treatment.

Nerve Targets and Patient Considerations

PDN patients with relatively focal neuropathic pain may be good candidates for PNS. For example, if most of the pain is localized to the plantar surface of the foot, the tibial nerve could be targeted with PNS. The tibial nerve runs from the popliteal fossa through the deep posterior compartment of the leg before passing through the tarsal tunnel, dividing into the lateral plantar nerve (LPN), medial plantar nerve (MPN), and medial calcaneal nerve (MCN). Lead placement along the tibial nerve will generally occur proximal to the tarsal tunnel and posterior to the tibia.⁷⁵ Other potential nerve targets for treating PDN in the lower extremity include the common peroneal, superficial peroneal, and sciatic nerves. It should be noted that other neuromodulation modalities (SCS and DRG-S) have focused mainly on PDN in the lower extremities.^{63,76} Another benefit to PNS is that targets in the upper extremity, notably the median and ulnar nerves, could also be considered.

Peripheral nerves in the lower extremity, including the tibial and common peroneal nerves, are prone to entrapment at the tarsal tunnel and fibular head, respectively. It has been proposed that diabetic patients are at increased risk of complications due to increased compression in these areas, leading to nerve damage and irreversible sensory changes. Decompression neurolysis has been performed in diabetics in the upper (median, ulnar) and lower extremities (tibial, common peroneal, deep peroneal, superficial peroneal nerves) with promising results.^{77,78} PNS can be an option for patients who have undergone decompression surgery and continue to have focal pain. When planning the location of PNS placement, it is advisable to consider placing leads proximally to the suspected lesion, entrapment, or injury.

Current Evidence for PNS in PDN

The evidence for using PNS in PDN is evolving, and several challenges still need to be addressed. One key challenge is the need for standardized protocols and parameters for PNS treatment. A recent review of neuromodulation in PDN⁷⁹ found grade II-3 evidence across three retrospective and prospective cohort studies showing the benefit of using PNS to target the tibial nerve in the lower leg. In an older study examining percutaneous electrical nerve stimulation (PENS) of lower extremity nerves (tibial, deep peroneal) in PDN patients, positive improvements in pain were demonstrated.⁸⁰ Larger-scale, well-designed clinical trials with extended follow-up periods are needed to determine the durability of pain relief and potential adverse effects associated with PNS.

Future Directions

In conclusion, the evidence for using PNS in PDN is evolving but shows promise as a potential therapeutic option for managing pain associated with PDN (see [Table 11](#)). Patients who may benefit the most are those with localized pain that can be attributed to a single nerve. However, further research is needed to establish standardized protocols, evaluate long-term efficacy and safety, and assess cost-effectiveness. With continued advancements in PNS technology and more robust

Table 11 Literature Summary for PNS in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Dabby et al, 2017 ⁸¹	Prospective cohort	12 (all with PNP, 7 with PDN)	I-B	Patients completed the SF-MPQ before and after 6 stimulation sessions. Pre- and post-stimulation VAS were also recorded.	Pain reduced by 85% to 4.88 ± 3 after the final stimulation session. VAS pain scores were reduced by 54.85 to 87.50%. Efficacy of treatment was rated as excellent (n=4), very good (n=3), and poor (n=1).
Sokal et al, 2017 ⁸²	Prospective cohort	6 (4 PNP, 2 with PDN)	I-B	Pain assessment by VAS at 6 months post activation as compared to baseline and serious adverse event incidence.	Average baseline VAS score was 7.5 and after 6-months of stimulation decreased to 1.3. Average McGill scores decreased from 23.8 (baseline) to 4.5 (6-month follow-up). All patients had satisfying pain relief.
Hamza et al, 2000 ⁸⁰	Prospective crossover sham-controlled	50 (25 allocated to PENS, 25 to sham PENS with eventual crossover)	I-A	Levels of pain, physical activity, and quality of sleep were assessed using three separate 10-cm VASs, where 0 = minimal (lowest) and 10 = maximal (highest).	Compared with the pain VAS scores before active and sham treatments, pain scores after treatment were reduced to 2.5 ± 0.8 and 6.3 ± 1.1 , respectively. With active PENS treatment, the VAS activity and sleep scores were significantly improved from 5.2 ± 1.0 and 5.8 ± 1.3 to 7.9 ± 1.0 and 8.3 ± 0.7 , respectively.

Abbreviations: PNP, peripheral neuropathic pain; PDN, Painful diabetic neuropathy; SF-MPQ, Short form McGill Pain Questionnaire; VAS, visual analog scale; PENS, percutaneous electrical nerve stimulation.

clinical evidence, peripheral nerve stimulation has the potential to become an important tool in the multidisciplinary management of PDN. The SWEET Consensus Committee recommends consideration of PNS for patients with focal lower extremity PDN who have failed conservative therapies and are not candidates for SCS (see Table 12). (Grade C)

DRG Stimulation

DRG-S is approved for CRPS and/or peripheral causalgia in the groin and lower limb. Application of DRG-S to other painful conditions of the lower extremity, such PDN, is actively developing. The ability to directly modulate the A δ and C small fibers that innervate the skin and subcutaneous tissue, at level A β collaterals, and taking advantage of convergence in the dorsal horn, would appear to make DRG-S an optimal therapy for pain associated with peripheral neuropathic pain. Furthermore, DRG-S can normalize pathologic hypersensitivity of DRG neurons associated with neuropathic pain and suppress inflammatory responses, particularly those driven by glial cells. There are multiple experimental animal model studies testing stimulation paradigms at the DRG for PDN.^{83,84}

Table 12 ASPN Recommendations for PNS in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
The SWEET Consensus Committee recommends consideration of PNS for patients with focal lower extremity PDN who have failed conservative therapies and are not candidates for SCS.	C	I-C	Moderate

Abbreviations: SWEET, Systematic guideline process to outline the current state of the art in treatment of painful diabetic neuropathy; PNS, peripheral nerve stimulation; PDN, painful diabetic neuropathy; SCS, spinal cord stimulation.

Advantages of DRG-S relative to SCS are the ability to achieve focal coverage of concordant painful areas with minimal extraneous stimulation. This may be due to the direct recruitment of relevant primary sensory neurons that innervate the painful distal regions as opposed to more generalized stimulation of the dorsal column.

There is a small prospective study, three retrospective case series, and five case reports for the application of DRG-S for varying causes of peripheral neuropathy (PN).^{85–89} These studies included diagnoses of PDN, painful small-fiber PN, idiopathic PN, polysensory PN, hereditary sensory and autonomic PN, PN associated with Lyme's disease, and chemotherapeutic agent-induced PN. There are two additional DRG-S case series that included patients with multiple concomitant pain etiologies which included peripheral neuropathy. There are two retrospective studies^{76,90} and one case report⁸⁵ specifically for the indication of PDN.

Eldabe et al retrospectively reported on seven PDN patients having undergone device implantation.⁷⁶ Of the seven subjects that had stimulators implanted, two had the devices explanted at or before the one-week follow-up for either poor painful area coverage or personal reasons. Of the seven patients who underwent full implantation, three achieved $\geq 50\%$ pain reduction at the six-month follow-up, two of whom had a reduction of more than 80%. At 12-month follow-up, two patients achieved $\geq 50\%$ pain reduction, with one patient lost to follow-up.

A retrospective analysis on PDN patients was completed by Falowski et al.⁹⁰ Inclusion criteria included chronic intractable peripheral neuropathy of the legs and/or feet and responding successfully to a trial of DRG-S with leads at L4-S1. Eight consecutive patients across two study centers were included (7 males, 1 female; mean age: 64.8 ± 10.2 years). Two of the eight patients had PDN. Data pertaining specifically to PDN patients was not included. Visual analog scale pain scores and pain medication usage were collected at the baseline visit and after six weeks of treatment. Two patients reported complete (100%) pain relief, two patients reported better than 80% pain relief, and another three patients reported better than 50% pain relief. A single patient reported better than 40% pain relief.

Chapman et al published a case report of a patient with both PDN and low back pain.⁸⁵ He underwent a 7-day trial of unilateral DRG stimulation at T12 and S1, which allowed the untreated side to serve as the control. The trial resulted in significant pain relief in both feet and low back pain, with a VAS reduction from 9 to 0 for feet pain. Additional measures including the Oswestry Disability Index (ODI), EQ-5D and SF-36 all showed significant improvement. Implantation data was not made available.

Evidence for DRG-S for PDN is limited by retrospective nature of studies, lack of blinding, and limited number of patients. Despite these limitations, DRG-S is shown to be effective for not only pain but also function and quality of life measures (see Table 13). Further studies are needed to elucidate the efficacy of DRG-S applied to PDN. At this time, recommendation is for selective and judicious use of DRS-S to PDN patients based on professional judgment, along with previous treatments tried and failed (see Table 14).

Table 13 Literature Summary for DRG-S in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Eldabe et al, 2018 ⁷⁶	Retrospective case series	10	II	N/A	Of the seven patients who underwent full implantation, three achieved $\geq 50\%$ pain reduction at the six-month follow-up, two of whom had a reduction of more than 80%. At 12-month follow-up two patients achieved $\geq 50\%$ pain reduction, with one patient lost to follow-up.
Falowski et al, 2019 ⁹⁰	Retrospective case series	8	II	N/A	Two patients reported complete (100%) pain relief, two patients reported better than 80% pain relief, and another three patients reported better than 50% pain relief. A single patient reported better than 40% pain relief.
Chapman et al, 2020 ⁸⁵	Case report	1	II	N/A	VAS reduction from 9 to 0 for feet pain. Additional measures including ODI, EQ-5D and SF-36 all showed significant improvement. Implantation data was not made available.

Abbreviations: VAS, visual analogue scale; ODI, Oswestry Disability Index; EQ-5D, EuroQOL 5-dimension questionnaire; SF-36, Short Form 36-item questionnaire; health-related quality of life.

Table 14 ASPN Recommendations for DRG-S in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
DRG-S may be considered for the treatment of lower extremity PDN in patients who have failed other FDA approved treatments.	C	II	Low

Abbreviations: DRG-S, dorsal root ganglion stimulation; PDN, painful diabetic neuropathy.

Intrathecal Drug Delivery

Ziconotide is a nonopioid analgesic medication that reversibly blocks pronociceptive neurotransmitter release from afferent nerves in the dorsal horn of the spinal cord via binding of N-type voltage-sensitive calcium channels.⁹¹ Specifically, glutamate, calcitonin gene-related peptide (CGRP), and substance P from primary nociceptive afferents terminating in the superficial layers of the spinal cord dorsal horn are blocked from being released.⁹¹ The only clinically available route of administration is via the intrathecal route. Ziconotide does not affect mu-opioid receptors, and typical reversal agents such as naloxone have no effect. There is no evidence of tolerance with long-term administration, and sudden cessation does not cause withdrawal syndrome.⁹²

The medication's on-label FDA approval is for administration via a microambulatory delivery device with a recommended starting dose of 0.5–1.2 mcg/day per the Polyanalgesic Consensus Conference (PACC) but can be as high as 2.4 mcg/day per the product labeling. Upward titration of 0.5–1.0 mcg/day every several days is recommended as ziconotide has a narrow therapeutic window and a max dose of 21.6 µg/day.⁹³ Ziconotide carries a “black box warning” and is contraindicated in patients with a history of psychosis; thus, psychiatric evaluation should be completed before trialing medication. Side effects of ziconotide which are more common at higher doses include nausea, vomiting, confusion, postural hypotension, gait abnormality, urinary retention, nystagmus, drowsiness, dizziness, weakness, visual changes, and serum creatine kinase elevation.⁹⁴

There are three randomized, double-blinded, placebo-controlled studies that support the use of intrathecal ziconotide for non-cancer-related pain,^{95–97} with approximately 75% of patients having a neuropathic pain condition. In a 2021 prospective study of 14 patients, it was shown that ziconotide improves pain and emotional components and function, specifically improving disability, emotional well-being, and catastrophizing.⁹⁸ Based on the available evidence (see Table 15), the SWEET guidelines support careful selection of intrathecal therapy of diabetic neuropathic pain with ziconotide although there are no published studies that specifically investigate its effectiveness for PDN (see Table 16).

Table 15 Literature Summary of Intrathecal Drug Delivery in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Rauck et al, 2006 ⁹⁷	Randomized, Double-Blind, Placebo-Controlled	220	I-A	Mean percentage change as measured on the VASPI from baseline to Week 3.	Patients randomized to ziconotide (n = 112) or placebo (n = 108) started IT infusion at 0.1 µg/hour (2.4 µg/day), increasing gradually (0.05–0.1 µg/hour increments) over 3 weeks. The ziconotide mean dose at termination was 0.29 µg/hour (6.96 µg/day). Patients' baseline Visual Analogue Scale of Pain Intensity (VASPI) score was 80.7 (SD 15). Statistical significance was noted for VASPI mean percentage improvement, baseline to Week 3 (ziconotide [14.7%] vs placebo [7.2%]; P = 0.036)

(Continued)

Table 15 (Continued).

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Staats et al, 2004 ⁹⁵	Double-blind, placebo-controlled, randomized trial	111	I-A	Mean percentage change in VASPI score from baseline to the end of the initial titration period.	67 (98.5%) of 68 patients receiving ziconotide and 38 (95%) of 40 patients receiving placebo were taking opioids at baseline (median morphine equivalent dosage of 300 mg/d for the ziconotide group and 600 mg/d for the placebo group; P = 0.63, based on mean values), and 36 had used intrathecal morphine. Mean (SD) VASPI scores were 73.6 (1.8) mm in the ziconotide group and 77.9 (2.3) mm in the placebo group (P = 0.18). Mean VASPI scores improved 53.1% (95% confidence interval [CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group (P < 0.001), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group (P < 0.001). Five patients receiving ziconotide achieved complete pain relief, and 50.0% of patients receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo (P = 0.001).
Wallace et al, 2006 ⁹⁶	Randomized, Double-Blind, Placebo-Controlled	255	I-A	Mean percent reduction in VASPI.	The mean percent reduction in VASPI score from baseline was 31.2% and 6.0% for ziconotide- and placebo-treated patients, respectively (p ≤ 0.001).
Shao et al, 2021 ⁹⁸	Prospective	14	I-B	Examined the role of first-line ziconotide IDT on the tridimensional pain experience in ziconotide IDT-naive patients with neuropathic pain.	11 of 14 patients completed long-term follow-up. There were 7 responders based on NRS minimum clinically important difference. At a mean (±standard error of the mean) follow-up of 10.91 ± 0.70 months, SF-36 emotional well-being (P = 0.04), SF-36 pain (P = 0.02), and ODI (P = 0.03) significantly improved for the entire cohort and in responders (SF-36 emotional well-being, P = 0.01; SF-36 pain, P = 0.04; ODI, P = 0.02). Pain Catastrophizing Scale (PCS)-Rumination (P = 0.02), PCS-Helplessness (P = 0.02), and PCS-Total (P = 0.003) scores improved significantly for responders only.

Abbreviations: VASPI, visual analogue scale of pain intensity; IT, intrathecal; SD, standard deviation; CI, confidence interval; IDT, intrathecal drug therapy; ODI, Oswestry Disability Index; SF-36, 36-item Short Form questionnaire on health-related quality of life; PCS, Pain Catastrophizing Scale.

Table 16 ASPN Recommendations for Intrathecal Drug Delivery in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
There is limited evidence to support intrathecal ziconotide for diabetic neuropathy.	C	I-C	Low

Sub-Topic: Special Considerations for Implantable Therapies in the Diabetic Patient

DM is an increasingly prevalent chronic multisystemic condition that is associated with increased perioperative morbidity and mortality. During periods of heightened stress, such as surgery, significant changes may occur in glucose metabolism leading to acute hyperglycemia. This occurs in up to 40% of patients undergoing noncardiac surgery.⁹⁹ Poorly controlled DM negatively impacts soft tissue and tendon healing, rendering diabetic patients at an increased risk of poor wound healing and surgical site infections. More specifically, chronic hyperglycemia is associated with impaired neutrophil phagocytic activity, increased inflammation and oxidative stress, and poor endothelial function.¹⁰⁰ These variables contribute to a relative immunocompromised state. Decreased innate immunity has been found to be the key factor in diabetic patients that results in increased infection in the setting of implanted devices. Being aware of surgical technique is important not only to help mitigate postoperative infections but also seromas and wound dehiscence. Diabetic patients have been found to be at an increased risk of these postoperative complications.¹⁰¹

Utilizing the data gathered from orthopedic and cardiac surgery literature, we can deduce the implications of DM on surgical outcomes within pain medicine and neurosurgery. While the incidence of surgical site infections is variable amongst chronic pain implantable devices (1% to 17%), diabetic patients are at increased risk of severe infection.¹⁰² More recent studies have revealed that the rate of SCS infections can be as high as 3.11% within a 12-month period.¹⁰³ Hoelzer et al reported an overall infection rate of 2.45% of SCS implants, which included diabetic patients, but did not further assess the role of uncontrolled versus controlled diabetes.¹⁰⁴ The pathogenesis of an infection relates to the initial innate immune response to the formation of a biofilm around the implanted device.¹⁰⁵ Multiple factors have been identified in impairing the innate immune response and include absence of vascularization at the interface with the device, disrupted blood flow in the vicinity of the device due to tissue damage during surgery, local hypoxia, dysregulation of phagocyte function on foreign materials, inadequate immune signaling between the inert biomaterial and host cells, and protection of contaminating microorganisms from phagocytosis due to attachment to the implant – all factors impacted by DM.¹⁰⁵ This highlights the systemic micro- and macrovascular implications of DM.

Lab markers, primarily hemoglobin A1C or glycated hemoglobin, may be used to identify diabetic patients with poorly controlled DM. A1C is commonly used as a surrogate for glycemic control, but there remains no clear consensus on A1C cutoff values for elective surgery. This is partly due to an ongoing debate regarding whether long-standing hyperglycemia or acute perioperative hyperglycemia has more significant implications on surgical outcomes. A study by Underwood et al conveys that A1C >8% is related to poor surgical results.¹⁰⁰ This cutoff was also found to be associated with an increased rate of postoperative surgical site infections by Gabriel et al.¹⁰⁶ Nonetheless, while variable cutoff target values of A1C may exist, severe and prolonged perioperative hyperglycemia may result in greater operative complications than acute hyperglycemia alone.¹⁰⁷ See Tables 17 and 18.

Non-Invasive Neuromodulation

The use of a time-varying magnetic field to induce a sufficiently strong current to stimulate living tissue was first reported by d'Arsonval in 1896.¹¹² Magnetic stimulation of nerve tissue was demonstrated by Oberg in 1973.¹¹³ The first magnetic stimulation of peripheral nerves (mPNS) was reported by Polson in 1982.¹¹⁴ He established that mPNS, as compared to electrical peripheral nerve stimulation (ePNS), was pain free and could reach deep nerves. Another advantage over electrical stimulation is that higher current densities near the surface of the skin which can cause tissue damage are not seen in magnetic stimulation as there is no hydrolysis and pH changes. mPNS induces a larger E field due to its time-varying, 3D magnetic field, whereas ePNS generates a smaller more 2D electrical field due to being a line

Table 17 Literature Summary Special Considerations for Implantable Therapies in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Underwood et al, 2014 ¹⁰⁰	Retrospective Study	622 patients	I-C	Hospital length of stay (LOS)	Individuals with A1C values ≤ 6.5 or $>8\%$, the hospital LOS was significantly longer compared with the control group ($P < 0.05$).
Gabriel et al, 2019 ¹⁰⁶	Retrospective study	1582 patients	I-C	Postoperative surgical site infections (SSI)	A HbA1c of 8.0% or higher significantly increased the odds ratio of developing postoperative SSI ($p < 0.05$)
Walid et al, 2010 ¹⁰⁸	Retrospective study	556 patients	I-C	Hospital length of stay and healthcare cost	Significant differences in the lumbar decompression and fusion group between the "No DM" and "Subclinical" groups ($P < 0.05$) in terms of cost and LOS ($P < 0.05$).
Adams et al, 2013 ¹⁰⁹	Retrospective cohort study	40,491 patients	I-C	Surgical outcomes, including revision arthroplasty and deep infection	No significantly increased risk of revision arthroplasty, deep infection, or deep venous thrombosis was found in patients with diabetes compared with patients without diabetes in patients who underwent elective total knee arthroplasty.
Bock et al, 2015 ¹¹⁰	Systemic Review	22 studies	I-C		Patients scheduled for vascular and orthopedic surgery carry an elevated risk justifying preoperative testing for blood glucose or HbA1c as a screening tool.
Kremers et al, 2015 ¹¹¹	Retrospective cohort study	20,171 procedures	I-C	Prosthetic joint injections (PJIs)	Although data were limited, there was no association between hemoglobin A1c values and PJIs.

Abbreviations: LOS, length of stay; A1C/HbA1c, glycated hemoglobin; SSI, surgical site infection; DM, diabetes mellitus; PJI, periprosthetic joint infection.

Table 18 ASPN Recommendations in Special Considerations for Implantable Therapies in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
Preoperative A1c should be obtained on diabetic patients undergoing elective surgery	B	I-C	Moderate
Elective surgery should be delayed for A1C above 8	B	I-C	Moderate

Abbreviation: A1C, glycated hemoglobin.

source electrode. Due to the differences in the resultant electrical fields, the stimulation threshold in mPNS recruits many more A β fibers without recruiting A δ fibers as compared to ePNS.

The first pilot study using a new mPNS device involved 24 patients with neuropathic pain, including those with painful diabetic neuropathy.¹¹⁵ The active treatment wand was placed on or just over the patient's skin. The treatment protocol consisted of three daily sessions in a row during the first week of therapy. This was followed by a weekly treatment for the remainder of the month totaling 6 treatments. There were treatments every second week in the second month. Monthly treatments were continued as needed for pain exacerbations. Two-thirds of patients were deemed responders, defined as 50% or more reduction in VAS pain scores, experiencing 87% reduction of pain scores. The average VAS pain reduction was 3.8 from baseline scores. Opioid reduction was achieved in 58.3% of responders.

A first randomized prospective study on mPNS, including patients with mono- and peripheral neuropathy, was recently conducted, and 90 days data are available in the form of an abstract to the 2023 ASPN meeting.¹¹⁶ There were 13 patients who had PDN in the active treatment arm (mPNS plus CMM), and 4 patients in the control arm (CMM only). Responders were defined as subjects who achieved $>50\%$ of pain relief at 3 months after the treatment initiation. There were 8 out of 8 responders in the treatment arm on a per-protocol basis, with reduction of their pain scores by 64.7%. In

the control arm, 1 out of 4 were responders, with an average increase of the pain scores by 2.4%. mPNS appears to be a very promising noninvasive, painless initial neuromodulation therapy for PDN as well as other neuropathic conditions. A randomized sham-controlled prospective study on use of mPNS for the lower extremity peripheral neuropathy in diabetes is ongoing, and enrollment completion is expected by the end of the year. See Tables 19 and 20.

Section 4. Alternative Approaches

Aside from implantable therapies for treatment of PDN, alternative treatment approaches have historically focused on non-implantable interventions, dietary supplementations, and lifestyle modifications. Such interventions trialed in the past include acupuncture, sympathetic nerve blocks, and botulinum toxin injections.

Moderate level evidence suggests favorable utilization of acupuncture as an optional treatment for PDN.^{117–120} Numerous prospective clinical studies and RCTs suggest a positive effect with relatively low adverse event rates.^{119,121–125} A single-blinded, placebo-controlled RCT compared acupuncture to sham acupuncture demonstrated low-moderate treatment effect without appreciable side effects, meanwhile another RCT found that pain was improved at week 12 of follow-up but efficacy waned by week 18 when acupuncture was compared to standard of care.^{123,124} Outside of traditional acupuncture, modifications of acupuncture have been proposed to be effective for treatment of PDN. Electroacupuncture whereby current applied to acupuncture needles was found to reduce neuropathic pain while improving sleep and overall quality of life. Laser acupuncture was found to improve nerve conduction velocities and patient reported outcomes compared to placebo for PDN.^{121,125} Other studies report improvement of PDN symptoms with injections of *Saussureae Involucratae Herba* (snow lotus; a herbal medicine suggested to accelerate blood circulation and have anti-oxidative properties) at acupuncture points and perineural platelet rich plasma, though further studies are needed to validate this approach.^{126,127} Meta-analyses support these findings, but suggestions have been made for further studies to assess the longitudinal efficacy of traditional acupuncture for treatment of PDN. If acupuncture is trialed, the semi-standardized acupuncture in diabetic peripheral neuropathy (ACUDPN) treatment protocol with bilateral acupuncture points is recommended.¹¹⁹

Few studies support the utilization of lumbar sympathetic ganglion block or neurolysis for PDN.^{128–131} One case report documented improvement in bilateral lower extremity PDN with a series of nine continuous lumbar sympathetic blocks over a 26-month period.¹²⁹ Another RCT suggested combining treatment with continuous lumbar sympathetic

Table 19 Literature Summary of Non-Invasive Neuromodulation in PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Bedder et al, 2022 ¹¹⁵	Case series	24	I-C	Success defined as >50% pain relief and opioid reduction	At 90 days, 67% of neuropathic pain patients had successful outcomes. 51% reduction in opioids.
Kapural et al, 2023 ¹¹⁶	Multi-site-randomized Double blind crossover controlled trial	54	I-A	Success defined as >50% pain relief and EQ-5D-3L data plus PGIC	At 3 months, 64% of neuropathic pain patients had successful outcome with mPNS vs CMM. PGIC 80.95% mPNS vs 6.25% for CMM.

Abbreviations: EQ-5D, EuroQOL 5-dimension questionnaire; PGIC, Patient Global Impression of Change; mPNS, magnetic peripheral nerve stimulation; CMM, conventional medical management.

Table 20 ASPN Recommendations for Non-Invasive Neuromodulation in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
mPNS may provide intermediate-term relief (3 months) for neuropathic pain arising from PDN.	B	I-B	Moderate

Abbreviation: mPNS, magnetic peripheral nerve stimulation.

block followed by alcohol neurolysis provided more benefit in pain scores versus sympathetic alcohol neurolysis alone, with benefits sustained at 6 months post treatment.¹³⁰ Similarly, another RCT compared alcohol neurolysis with radiofrequency thermocoagulation or both for treatment of PDN. Postoperative pain scores were significantly decreased from baseline with a 66.7%, 73.3% and 93.3% complete remission rate, respectively, without severe complications. However, pain returned at 3 months after alcohol neurolysis, 6 months after radiofrequency thermocoagulation and 1 year after combined treatment. The authors concluded that lumbar sympathetic ganglion block combined with radiofrequency was safe and effective in managing PDN.¹³¹ These interventions may be a viable option for selected patients with refractory PDN prior to other more invasive interventions.¹²⁸

Similarly, few studies have demonstrated optimistic results utilizing botulinum toxin injection for PDN without major complications. Botulinum toxin type A inhibits the release of acetylcholine at the neuromuscular junctions and may also have a modulatory effect on afferent sensory fiber firing by inhibiting glutamate release, decreasing calcitonin gene related peptide and substance P release.^{132–135} A double-blind RCT demonstrated that intradermal botulinum toxin type A injection into the foot reduced neuropathic pain and improved quality of life and sleep in people with PDN compared to control.¹³² Similarly, other studies have found that botulinum toxin type A is well tolerated and significantly reduced PDN, compared to normal saline placebo injections.^{133,134} One meta-analysis concluded that there are level I studies to support a correlation between botulinum toxin A injection and a small improvement in pain in diabetic neuropathy, particularly in the dorsum of the feet. However, given the small effect size, botulinum toxin A should only be considered as an adjunctive treatment to first-line modalities and further studies are needed.¹³⁵ Of note, botulinum toxin injection for PDN is not an FDA-approved indication.

The majority of supplements utilized to address PDN fall into the category of antioxidants and neuroprotective cofactors.¹³⁶ Alpha-lipoic acid, an antioxidant and chemoprotective compound, has been investigated in treatment of PDN. Studies have shown improvement of PDN symptoms with long-term use, however efficacy of this has yet to be compared to typical pharmacologic agents used for treatment of PDN.^{137–139} Acetyl-L-carnitine, an acetylated amino acid, has also been implicated in the treatment of PDN. It has been used for treatment of various forms neuropathic pain including PDN with success.^{140–142} However, high-grade evidence is not available to evaluate its efficacy compared to other pharmacologic agents. Some studies have evaluated the use of the vitamin B complex (B1, B6, B12) in treatment of PDN due to its antioxidant effects as well as its function in neural metabolism and neural protection. However, no recommended dosing is available for safe treatment as increased levels can cause neuropathy.¹⁴³ Benfotiamine, a lipid formulation of vitamin B1 has also been evaluated for treatment of PDN. High-level studies to validate its use are also lacking.¹³⁶

Lifestyle modifications remain one of the oldest and most traditional means of management for PDN, focusing on improved glycemic control, particularly in patients with type 1 DM (T1DM).¹⁴⁴ Though intensive glycemic control can help delay the development and progression of PDN in patients with T1DM, it has been found to have little effect on PDN in patients with type 2 DM (T2DM).^{145–148} The Diabetes Control and Complications Trial (DCCT) emphasized enhanced glycemic control in patients with T1DM with a -1.84 annualized risk difference with tight glycemic control, whereas the ACCORD and VADT studies reported an annualized risk difference of -0.058 for T2DM which was not statistically significant.^{144,145,149,150} Moreover, tight glycemic control of hemoglobin A1C less than 6.0 has been associated with increased mortality. As such, improved glycemic control with hemoglobin A1C between 7.0 and 8.0 has been recommended instead.¹⁴⁶ Weight loss as well as exercise has been shown to increase intraepidermal nerve fiber density which is normally reduced during PDN.^{151,152} In combination, an improved diet with active lifestyle has been advocated to help reduce the severity of PDN symptoms.

A summary of the literature cited in this section appears in [Table 21](#) and ASPN recommendations are in [Table 22](#).

Psychological/Behavioral

PDN is a complex condition with physical, social and psychological consequences.¹⁵³ Given its complexity, multidisciplinary treatment approaches are likely to be more effective than any monotherapy.

For many years, PDN's comorbidities with depression,^{154,155} anxiety,^{156,157} catastrophization,^{158,159} and impairment of patients' QOL^{160,161} have been identified in the literature, with these psychological factors thought to play a potential mediating role in patient's pain experiences. As a result, logic would suggest that these psychological sequelae of PDN should be treated in order to optimize patients' emotional comfort levels, at the least. For this review, however, the focus

Table 21 Literature Summary for Alternative Approaches in PDN

Author, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
<i>Acupuncture</i>					
Dietzel et al, 2023 ¹¹⁹	RCT	62	I-A	Visual analog scale, neuropathic pain symptom inventory, short-form 12 and diabetic peripheral neuropathic pain inventory	Favorability towards acupuncture group over control arm in reducing scores among all outcome measures immediately after the intervention and longitudinal follow-ups.
Feng et al, 2022 ¹²⁰	Meta-analysis	1021	I-A	n/a	A total of 16 studies with 1021 participants, including 8 RCTs with 338 participants. The acupuncture group was better than control group in improving pain intensity. Subgroup analysis revealed that the treatment group was superior to sham acupuncture. Two RCT demonstrated no significant difference between acupuncture and conventional treatments.
Meyer-Hamme et al, 2021 ¹²⁵	RCT	172	I-A	Delta of sural sensory nerve action potential (SNAP), conduction velocities, clinical scores, and patient-reported outcome measures (PROMs).	Sural SNAP and sural and tibial nerve conduction velocities improved significantly after 10 treatments when comparing needle acupuncture to placebo. PROMs showed larger improvements following needle and laser acupuncture than placebo.
Chao et al, 2019 ¹²⁴	RCT	40	I-A	Pain scale, physical function and quality of life	Acupuncture significantly reduced the average weekly pain score compares with usual care at week 12 but pain returns to baseline by week 18. Quality of life and physical functioning improved in the acupuncture group by week 18.
Shin et al, 2018 ¹²¹	RCT	98	I-A	McGill Pain Questionnaire, sleep interference and EuroQol-5 questionnaire, patient global impression of change	The electroacupuncture treatment group showed significantly greater improvement in pain, sleep, quality of life and more patients had a greater improvement in the global impression scale compared to control arm.
Garrow et al, 2014 ¹²³	RCT	45	I-A	Visual analog pain scale, Leeds assessment of neuropathic symptoms and signs, short-form 36	Acupuncture demonstrated small improvement in VAS compared to controls. There was little change in those receiving sham acupuncture and a moderate treatment effect in favor of active acupuncture was detected.
Hui-tian et al, 2004 ¹²⁶	RCT	104	I-A	Effective rate	At 2-month follow up the clinical effective rate in the acupuncture plus medication group was 51.9% and the total effective rate was 88.5%, both superior to those in the control group.
Abuaisha et al, 1998 ¹²²	RCT	46	I-A	Peripheral neurological exam scores, hemoglobin A1c levels	77% of participants had significant improvement in symptoms. And 67% were able to stop or reduce medication use.

(Continued)

Table 21 (Continued).

Author, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
<i>Botulinum toxin</i>					
Salehi et al, 2019 ¹³²	RCT	32	I-A	Visual analog scale, short-form 36, neuropathic pain scale, Pittsburgh sleep quality index	There was a statistical significant difference in the mean visual analog scale, physical dimension of the short form 36, sleep quality and some neuropathic pain scale indices at 12 week follow up. The results showed that botulinum toxin A reduced neuropathic pain and improved quality of life and sleep.
Ghasemi et al, 2014 ¹³⁴	RCT	40	I-A	Neuropathic pain scale and visual analog scale	Intradermal injection of botulinum toxin A reduced neuropathic pain scores in comparison to placebo arm.
Yuan et al, 2009 ¹³³	RCT	18	I-A	Visual analog scale	44% of participants in the treatment arm achieved a VAS reduction of 3 points within three-month post-procedure.
<i>Sympathetic nerve block or neurolysis</i>					
Sun et al, 2020 ¹³⁰	RCT	60	I-A	Visual analog scale	Pain scores of all patients decreased significantly compared with pre-treatment values, with lower pain scores in those treated with combined therapy (neurolysis and continuous lumbar sympathetic block) compared to sympathetic neurolysis only. Skin temperature, capillary filling time and blood oxygen saturation level were significantly improved in all participants.
Ding et al, 2018 ¹³¹	Retrospective study	90	II	Self-reported pain relief	Sustained pain relief was obtained up to 3 months with ethanol neurolysis, 6 months with radiofrequency thermocoagulation and 12 months with combined ethanol neurolysis and radiofrequency thermocoagulation.
<i>Alternative injections</i>					
Hassanien et al, 2020 ¹²⁷	RCT	60	I-A	Visual analog scale, Toronto clinical neuropathy score	Significant improvement was noted in pain and numbness scores in the ultrasound-guided perineural platelet rich plasma (PRP) injection and medical treatment group compared to the medical treatment only group.
<i>Supplementation</i>					
Garcia-Alcala et al, 2015 ¹³⁹	RCT	45	I-A	Total symptom score	Alpha-lipoic acid improved total symptom score at 4-week Phase 1 and up to 16 week Phase 2, compared to withdrawal control group at 16-week.
Ziegler et al, 2011 ¹³⁸	RCT	460	I-A	Neuropathy impairment score, quantitative sensory tests (QSTs) and nerve conduction velocities	Four-year treatment with alpha-lipoic-acid did not influence the primary end point but resulted in a clinically meaningful improvement and prevention of progression of neuropathic impairments.

(Continued)

Table 21 (Continued).

Author, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Ziegler et al, 2006 ¹³⁷	RCT	181	I-A	Total symptom score, neuropathic symptom and change score, neuropathy impairment score	Oral treatment with 600mg once daily alpha-lipoic acid for 5 weeks improved neuropathic symptoms.
De Grandis et al, 2002 ¹⁴¹	RCT	333	I-A	Nerve conduction velocity and amplitude, visual analog scale	Participants treated with acetyl-L-carnitine showed a statistically significant improvement in mean nerve conduction velocity and amplitude compared to placebo. At 12-month treatment, mean visual analog scale score were statistically significantly reduced from baseline compared with placebo group.
<i>Lifestyle modifications</i>					
Singleton et al, 2015 ¹⁵²	RCT	67	I-A	Baseline ankle intraepidermal nerve fiber density (IENFD) and 30-day cutaneous regeneration	Baseline distal leg IENFD was significantly reduced for both metabolic syndrome and diabetic groups. With exercise, participants significantly improved exercise capacity and lower extremity power. Following exercise, 30 day reinnervation rate demonstrated a statistically significant improvement.
Singleton et al, 2014 ¹⁵¹	RCT	100	I-A	Distal leg IENFD	Lifestyle intervention for the prevention of diabetic neuropathy with a program of sustained, mentored exercise resulted in a significant increase in IENFD among diabetic patients without peripheral neuropathy, whereas counseling alone resulted in stability.
Ismail-Beigi et al, 2010 ¹⁴⁵	RCT	10251	I-A	Dialysis, renal transplantation, serum creatinine, retinal photocoagulation, vitrectomy.	Intensive target hemoglobin A1c of <6.0% versus standard (7.0–7.9%) glycemic therapy. Intensive therapy did not reduce the risk of advanced measures of microvascular outcomes but delayed the onset of albuminuria and some measures of eye complications and neuropathy. Microvascular benefits of intensive therapy should be weighed against the increase in total and cardiovascular disease-related mortality, increased weight gain, and high risk for severe hypoglycemia.
Duckworth et al, 2009 ¹⁵⁰	RCT	1791	I-A	Primary outcome was the time from randomization to the first occurrence of a major cardiovascular event	Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications with the exception of progression of albuminuria.

Abbreviations: RCT, randomized controlled trial; SNAP, sensory nerve action potential; PROM, patient-reported outcome measure; VAS, visual analog scale; PRP, platelet rich plasma; QST, quantitative sensory test; IDNFD, intraepidermal nerve fiber density.

will be on the literature addressing psychological treatments aimed at reducing patients' pain severity, pain experience and levels of pain interference.

Psychological approaches commonly studied in the treatment of PDN include cognitive behavior therapy (CBT), mindfulness therapy (MT) (either mindfulness meditation (MM) or mindfulness-based stress reduction (MBSR)) and, most recently, Acceptance and Commitment Therapy (ACT).

Table 22 ASPN Recommendations for Alternative Approaches in PDN

Therapy	Statement	Evidence Level	Level of Certainty	Grade
Acupuncture	Acupuncture may be considered in patients with PDN. Some studies including RCTs indicate possible benefit with low adverse event rates.	II	Moderate	B
Lumbar Sympathetic Block and Neurolysis	Lumbar sympathetic block and neurolysis may be considered in patients with PDN. However further studies on safety are needed to validate long term outcomes in treatment patients. Therefore, use of this technique for management of PDN is on a case-by-case basis.	II	Low	C
Botulinum Toxin Injection	Botulinum toxin injection may be considered as a treatment option for patients with PDN. There are multiple studies that indicate that it may be beneficial in reducing neuropathic pain and improving quality of life. However, given the small effect size, it should only be considered adjuvant therapy to other first line treatments.	II	Low	C
Supplementations (Alpha Lipoic Acid, Acetyl-L-Carnitine, Vitamin B Complex (B1, B6, B12))	Dietary supplements may have a role in helping manage PDN. However, few high-grade studies are available to report on supplement efficacy in comparison to typical pharmacologic agents for PDN treatment. Further, no recommended dosing is available at this time for safe treatment. Therefore, it is neither advisable or inadvisable at this time.	II	Low	C
Lifestyle modification	Intensive glycemic control may delay development or progression of PDN in patients with Type 1 DM but there is little effect on PDN in patients with Type 2 DM. Further, tight glycemic control may result in increased mortality in patients with Type 2 DM. However, improved glycemic control is nonetheless important in all patients with diabetes due to increased intraepidermal nerve fiber density with improved glycemic control though further studies are needed to understand the importance of these findings.	II	Moderate	B

Abbreviations: PDN, painful diabetic neuropathy; RCT, randomized controlled trial; DM, diabetes mellitus.

RCTs

The initial RCT on MM in PDN was a pilot published by Teixeira in 2010.¹⁶² In a small study, the author determined that subjects experienced significant improvements in QOL compared to controls, although relative changes in pain severity and pain unpleasantness were insignificant. The study's methodology was weak, with the author noting numerous limitations.

The initial RCT on CBT for PDN was published in 2013 by Otis and colleagues.¹⁶³ RCT patients reported significantly reduced pain severity and pain interference from pretreatment to 4-month follow-up, unlike treatment-as-usual controls. Interestingly, however, neither group reported a significant change in depressive symptoms. This finding is surprising, as CBT has its roots in the treatment of depression. Any minimal and insignificant decreases in pain severity and pain interference cannot be considered particularly strong evidence, as this was a pilot involving only 12 subjects in the treatment group and 8 control group subjects.

Of note regarding ACT for chronic pain is a 2020 Iranian RCT in which pain perception and pain acceptance were significantly better both immediately following a course of ACT and at 3-month follow-up when compared to control patients.¹⁶⁴ The authors, however, noted a small sample size due to a high dropout rate based on their inclusion-exclusion

criteria in discussing the study's limitations, which may have resulted in sampling bias. This is the only RCT in the extant literature that has considered ACT's impact on pain perception.

All published RCTs of psychological treatments for reduction of pain severity, pain experience and levels of pain interference are summarized in Table 23, and group recommendations are given in Table 24.

Table 23 Literature Summary for Psychological Treatment of PDN

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Teixeira, 2010 ¹⁶²	RCT	Convenience sample of 20 subjects, randomized into either the mindfulness meditation (MM) group or attention- placebo group. Size of groups was unspecified.	I-A	Patients completed the Neuropathic Pain Scale (NPS), the Neuropathy-Specific Quality of Life Questionnaire (NeuroQoL), and the Pittsburgh Sleep Quality Index (PSQI) at baseline and at week 4.	MM subjects experienced significant improvements in QOL compared to controls, although relative changes in pain severity and pain unpleasantness were insignificant.
Otis et al, 2013 ¹⁶³	RCT	12 experimental patients received cognitive behavior therapy (CBT), 8 received treatment as usual (TAU).	I-A	West Haven Yale Multidimensional Pain Inventory (WHYMPI) and Beck Depression Inventory (BDI) administered at baseline and at 4-month follow-up.	There were no significant differences between the CBT and TAU groups in pain severity or pain interference as measured by the WHYMPI at 4 months, nor in depression as measured by the BDI.
Taheri et al, 2020 ¹⁶⁴	RCT	20 experimental patients received 8 sessions of ACT, 21 control group patients, with conditions of control not specified.	I-A	McGill Pain Questionnaire (MPQ) and the Chronic Pain Acceptance Questionnaire (CPAQ) administered pre-treatment, post-treatment, and at 3-month follow-up	Pain severity as measured by the MPQ and pain acceptance as measured by the CPAQ were significantly better in the experimental group compared to the control group at post-treatment and 3-month follow-up.
Higgins et al, 2022 ¹⁶⁵	RCT	23 experimental group patients received CBT and standard pharmacological care, and 24 control group patients received diabetes education and standard pharmacological care. Both groups received 10 weekly, individual, 60-minute outpatient sessions, delivered within 14 weeks.	I-A	NRS, NPS, Interference Subscale of the WHYMPI (MPI-I), BDI, PSQI, and the Veterans Short Form Survey (SF-36V) were administered pre-treatment and at 12-weeks and 36-weeks post-baseline.	Difference in NRS scores between CBT and control groups at 12 and 36 weeks was not significant. However, NPS pain severity mean change from baseline to 12 weeks was significantly greater in the CBT group compared to the control group, with changes at 36 weeks not reported. Pain interference as measured by the MPI-I was significantly lower in the CBT group at 36 weeks. Mental health improvement as measured by the SF-36V were significantly better than in the control group at 36 weeks, although there were no between-group differences at 12 and 36 weeks on the BDI or PSQI.
Izgu et al, 2020 ¹⁶⁶	RCT	23 patients received relaxation training (RG), 21 received mindfulness meditation training (MG), 21 were in a control group (CG) that received "attention control education".	I-A	All subjects were administered the VAS, the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F), and the Neuropathic Pain Impact on Quality of Life Questionnaire (NePIQOL) at baseline, 12 weeks, and 14 weeks.	Pain severity as measured by the VAS was significantly lower in the RG and MG compared to the CG at week 12, and in the RG group at week 14. Fatigue severity as measured by the FACIT-F was significantly worse in the CG compared to the RG at 12 and 14 weeks, although there was no difference in terms of QOL between the MG and CG at both time points.

(Continued)

Table 23 (Continued).

Source, Year	Design	Sample Size	Level of Evidence	Outcome Measures	Results
Nathan et al 2017 ¹⁶⁷	RCT	31 study subjects received mindfulness-based stress reduction (MBSR), 32 were in a control group that received “optimized treatment as usual”, the components of which were unspecified.	I-A	All subjects were administered the Brief Pain Inventory (BPI), the Patient Health Questionnaire-9 (PHQ9), the PGIC, the Profile of Mood States-2A (POMS-2A), the Perceived Stress Scale (PSS), the PCS, and the NeuroQoL at baseline, 2 weeks post-intervention and 3 months post intervention.	MBSR patients were significantly more likely than controls to experience reductions in pain intensity and lower levels of pain interference as measured by the BPI through 12 weeks. They also reported significantly greater impression of improvement through the PGIC. MBSR patients reported significantly greater reductions in catastrophizing (PCS), depression (POMS-2A), and perceived stress (PSS) than controls, and better neuropathy-related quality of life (NeuroQoL).
Hussain & Said, 2019 ¹⁶⁸	RCT	All study subjects were females of >55 years of age with PDN. 36 were randomized to the MM group and received 16 session of mindfulness meditation training combined with unspecified “elements of cognitive therapy”. 32 subjects were randomized to the PM group and received 16 sessions of “progressive relaxation meditation”. 37 were randomized to the CM (control meditation) group and received 16 sessions involving discussion and instructions to relax as best as possible.	I-A	All subjects completed the Brief Pain Inventory modified for PDN and the PGIC at baseline and 4-week, 8-week, and 12-week follow-ups.	At 12-week follow-up, the MM and PM groups demonstrated significant reductions in pain severity and patient impression of change as measured by the PGIC. MM results were more favorable than those of the PM group. The CM group achieved significant improvement on neither measure.

Abbreviations: RCT, randomized controlled trial; MM, mindfulness meditation; NPS, Neuropathic Pain Scale; NeuroQOL, Neuropathy-Specific Quality of Life Questionnaire; PSQI, Pittsburgh Sleep Quality Index; CBT, cognitive behavior therapy; TAU, treatment as usual; WHYMPI, West Haven Yale Multidimensional Pain Inventory; BDI, Beck Depression Inventory; ACT, Acceptance and Commitment Therapy; MPQ, McGill Pain Questionnaire; CPAQ, Chronic Pain Acceptance Questionnaire; NRS, numeric rating scale; SF-36, 36-item Short Form questionnaire of health-related quality of life; MPI-I, interference subscale of the WHYMPI; RG, relaxation training group; MG, mindfulness meditation training group; CG, control group; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; NePIQOL, Neuropathic Pain Impact on Quality of Life Questionnaire; MBSR, mindfulness-based stress reduction; BPI, Brief Pain Inventory; PHQ9, Patient Health Questionnaire-9; PGIC, Patient Global Impression of Change; POMS, Profile of Mood States; PSS, Perceived Stress Scale; PCS, Pain Catastrophizing Scale; CM, control meditation.

Table 24 ASPN Recommendations for Psychological Interventions in PDN

Recommendation	Grade	Level of Evidence	Level of Certainty Net Benefit
The SWEET Consensus Committee recommends consideration of psychological approaches to PDN, despite a paucity of clinical evidence for such approaches as stand-alone treatments. Emotional benefits of such treatments appear to exist, with their risk:benefit ratio extremely low. However, they should be provided as an aspect of multimodal interdisciplinary care.	C	II-B	Moderate

Abbreviations: SWEET, systematic guideline process to outline the current state of the art in treatment of painful diabetic neuropathy; PDN, painful diabetic neuropathy.

Systematic Reviews

Because of the paucity of meaningful RCTs on psychological treatments that alter PDN pain experience, the limited systematic reviews that have been attempted tell us little of value. For example, a 2015 Cochrane review on psychological treatments for chronic neuropathic pain written by esteemed authors¹⁶⁹ chose to include only 2 studies, neither of which was PDN. A 2016

systematic review from an Italian consensus conference on pain in neurorehabilitation¹⁷⁰ considered only a single study,¹⁶³ and concluded, “For the treatment of diabetic neuropathy and neuropathic pain associated with cancer or HIV [human immunodeficiency virus], CBT may be used”. The authors graded their evidence as a D [evidence level 3 or 4 or extrapolated evidence from studies rated as 2+]. (GPP [recommended best practice based on the clinical experience of the guideline development group]). The most recent systematic review and meta-analysis of CBT and MT in the treatment of PDN¹⁷¹ determined that at the conclusion of treatment, experimental groups reported significantly less pain than control group patients, although at follow-up at ≥ 2 weeks, no significant differences between groups were evident. Further, the authors determined that although there were no immediate post-treatment differences between groups in terms of pain interference, the CBT/MT groups experienced significantly less pain interference than did control group patients at 24-week follow-up. Unfortunately, this systematic review and meta-analysis was seriously flawed methodologically in a number of ways, with selection of articles for inclusion in their analysis questionable.

Section 5. Algorithmic Approach

We describe an algorithm (see [Figure 2](#)) that can be utilized to treat PDN, although treatment options should be specific and individualized to the patient, accounting for comorbidities, type and severity of diabetes, and other patient-related variables.

The initial tier of treatment modalities centers on preventive strategies and conservative treatment. The natural history of PDN in patients with diabetes is variable,¹⁷² yet studies suggest that persistent hyperglycemia may be a primary cause of nerve dysfunction, resulting in hyperexcitable painful pathways in the peripheral and central nervous system. Therefore, a reasonable first step in the treatment of PDN is to treat the major underlying cause of neuropathy – hyperglycemia. Glycemic control may not only prevent PDN, but in those who already have established PDN symptoms, glycemic control may partially reverse or modulate these painful symptoms.¹⁷² This is particularly notable in type 1 diabetes with high-quality evidence supporting that intensive glycemic control is associated with lower odds of distal symmetric polyneuropathy compared to conventional insulin therapy.^{24,173} However, intensive glycemic control in type 2 diabetes has not consistently shown benefit in preventing or treating PDN symptoms, and may increase the risk for hypoglycemia. In terms of additional conservative treatment modalities, physical therapy including long-term aerobic exercise, weight-bearing exercise, and massage therapy should be offered early in the course of PDN as these modalities may improve motor and sensory neuropathy, balance, and quality of life.^{174–176}

Oral analgesics are commonly trialed thereafter, or concomitantly with, conservative therapy. First-line oral analgesics include gabapentinoids (pregabalin and gabapentin) and serotonin-norepinephrine reuptake inhibitors (duloxetine).²⁴ Careful titration and monitoring for side effects (eg, dizziness, sedation) are warranted. If the patient does not obtain meaningful pain relief or experiences intolerable side effects, other second-line and third-line oral analgesics may be trialed. For instance, tapentadol is approved by the FDA for treatment of PDN, although it is an opioid analgesic with risk for opioid-related side effects. Tricyclic anti-depressants such as amitriptyline and nortriptyline may also provide analgesia, although they commonly manifest with neurologic and cardiac side effects. Opioids are generally not recommended¹⁷⁷ due to modest short-term analgesia and an unfavorable safety profile consisting of respiratory depression, sedation, opioid use disorder, and constipation.^{24,178} When conservative treatment options and oral analgesics fail, clinicians may consider offering topical therapy. Eight percent capsaicin patch is approved by the FDA for treatment of PDN of the feet.⁵¹ The risk of application site reactions is substantial and may impact over 30% of patients, although strategies exist to improve patient tolerability. Given its non-invasiveness and safety profile, 8% topical capsaicin is a very reasonable first-line option after the failure of at least two proven oral pharmacological agents.

If the patient continues to experience refractory pain that is unresponsive to conservative modalities and pharmacologic agents (eg, trial of at least 1–2 analgesics) and topicals, consideration of interventional options is warranted.⁷⁹

Neuromodulation interventions may alleviate symptoms of PDN by intervening within the ascending pathways that lead to perception, cognition, and awareness of the symptoms. Therapeutic disruption of this pathway may be in the periphery, the dorsal root ganglion, and in the dorsal columns of the spinal cord. These interventions can be categorized into traditional spinal cord stimulation (t-SCS), 10-kHz spinal cord stimulation (10-kHz SCS) and target-based neuromodulation (brain, dorsal root ganglion, and peripheral).

Proposed PDN Treatment Algorithm

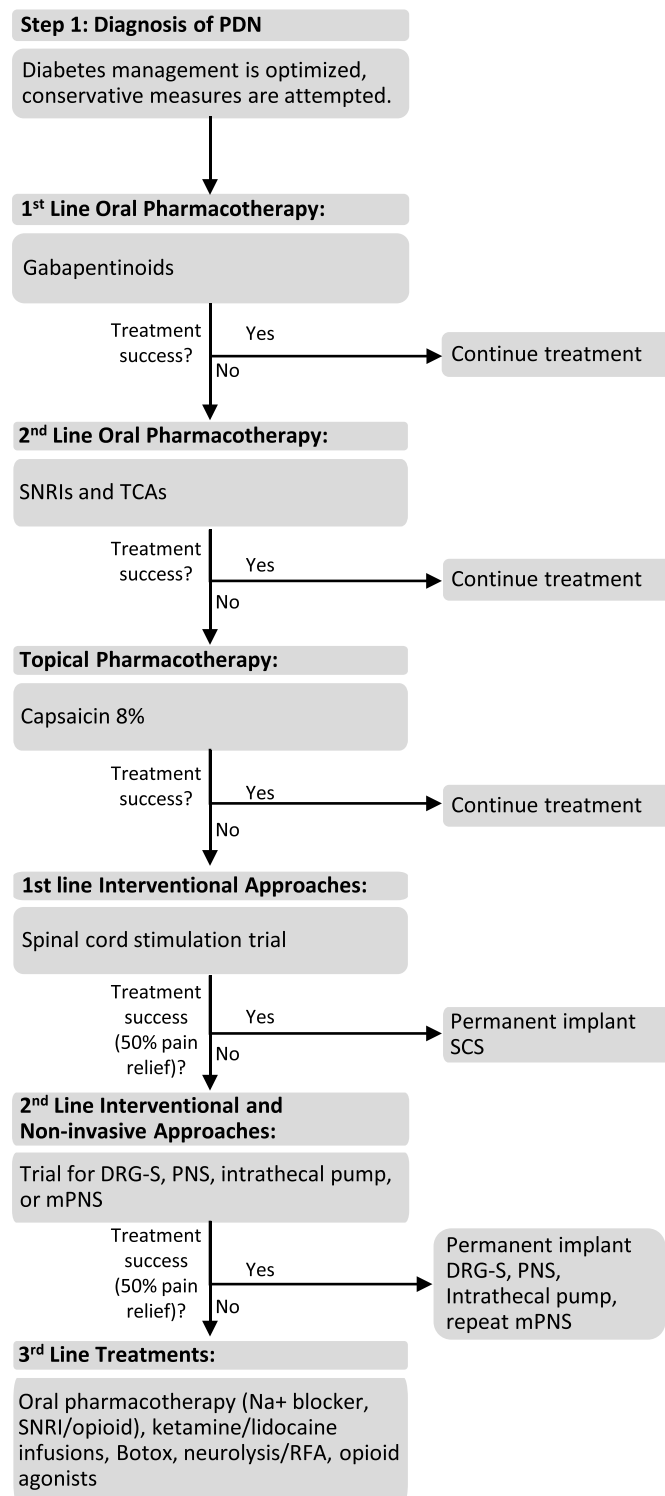


Figure 2 Algorithmic approach to management of PDN.

t-SCS, synonymous with tonic spinal cord stimulation, intrinsically refers to stimulation cycle frequency that is considered “low” and above the threshold of perception. The data to support t-SCS for PDN suggests modest to moderate efficacy.^{59,60} Subthreshold spinal cord stimulation signifies stimulation which is not cognitively perceived, and these include 10-kHz SCS and burst spinal cord stimulation (burst-SCS), among others. Recent level 1 evidence highlights significant efficacy of 10-kHz SCS in the treatment of patients with PDN when compared to CMM alone.⁶³ When compared to CMM, test subjects demonstrated substantial improvement in secondary outcomes as well as an overall health-related quality of life to 12 months.⁶⁴

Burst-SCS (with passive recharge) is known in the literature as proprietary high-frequency spike trains cycled at a specific frequency, and this pattern is designed to replicate Theta burst patterning in the thalamus. In a crossover comparative study, De Vos demonstrated that burst-SCS is more effective than t-SCS in a subset of test subjects who received burst stimulation after at least six months of continuous treatment with t-SCS,⁶¹ although this has not been investigated extensively in patients with PDN.

Similarly, limited evidence exists for dorsal root ganglion stimulation (DRG-S). Eldabe and colleagues reported a series of 10 patients who received DRG-S for PDN. Overall pain reduction was followed at one month and six months, each showing a decline of 48 and 49 on the VAS scale, respectively. This study was subject to significant attrition among the test subjects.⁷⁶

Noninvasive stimulation (NIS) or mPNS has been examined to improve symptoms and function related to PDN. However, to date, there is still only limited data to support the use of exogenous stimulation or magnetism for the treatment of this syndrome.¹⁷⁹ Current and ongoing studies on mPNS may lead to this therapy option becoming a more frontline treatment option given its favorable safety profile and noninvasive nature.

Intrathecal drug delivery (IDD) is a well-established treatment for chronic intractable pain. Ziconotide and morphine are currently the only FDA-approved agents for the treatment of chronic intractable pain. There is no existing evidence supporting the use of IDD for the treatment of PDN, however there are well-supported guidelines for the care of patients experiencing chronic intractable pain of the axial spine and legs.⁹³

In summary, spinal cord stimulation is superior to conventional medical management alone for the treatment of PDN. Studies have demonstrated modest to substantial efficacy of 10-kHz SCS and t-SCS, and this therapy may be considered when conventional medical management has failed to achieve benefit. The ability to subject patients to a temporary trial of approximately 7 days prior to surgical implantation of the permanent implant to gauge efficacy, is another considerable advantage of SCS as a treatment option for PDN.

Conclusion

The ASPN SWEET Guideline provides the first comprehensive clinical tool encompassing both pharmacological, interventional, and alternative approaches to PDN. As PDN continues to be a difficult and under-treated condition, the SWEET Guideline is intended to improve appropriate and safe treatment of patients suffering from PDN. Many recent interventional and pharmacological agents have significantly improved the ability to improve pain and suffering in PDN. Further research continues to be developed, which should only help in further identifying the optimal treatment of patients with PDN. In addition to global open access to this guideline for all clinicians involved in the care of those suffering from PDN, ASPN aims to disseminate the awareness of these important guidelines via social media, webinars, annual conferences, and other media forms. The ASPN SWEET guideline is intended to be a living document and will be updated at appropriate intervals as the research and science around PDN continues to evolve. The ASPN guidelines will be shared on the society’s website at aspnpain.com. The guidelines will be updated at a minimum of every 12 months and as impactful evidence is published relevant to the content of the SWEET guideline.

Abbreviation

A1c/ HbA1c, Glycated hemoglobin; AAN, American Academy of Neurology; ACCORD, Action to Control Cardiovascular Disease in Diabetes (study); ACT, Acceptance and Commitment Therapy; ACUDPN, Acupuncture in diabetic peripheral neuropathy; ASPN, American Society of Pain and Neuroscience; BDI, Beck Depression Inventory; BMT, Best medical therapy; BPI, Brief Pain Inventory; CBT, Cognitive behavior therapy; CDC, Centers for Disease Control and Prevention; CGRP, Calcitonin gene-related peptide; CI, Confidence interval; CMM, Conventional medical

management; CPAQ, Chronic Pain Acceptance Questionnaire; CRPS, Complex regional pain syndrome; DCCT, Diabetes Control and Complications Trial (study); DM, Diabetes mellitus; DRAE, Drug-related adverse event; DRG-S, Dorsal root ganglion stimulation; ePNS, Electrical peripheral nerve stimulation; EQ-5D, EuroQOL 5-dimension questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FBSS, Failed back surgery syndrome; FDA, Food and Drug Administration (United States); HF, High frequency; HIV, Human immunodeficiency virus; IDD, IDT, Intrathecal drug delivery, intrathecal drug therapy; IENFD, Intraepidermal nerve fiber density; IT, Intrathecal; LOS, Length of stay; LPN, Lateral plantar nerve; MBSR, Mindfulness-based stress reduction; MCN, Medial calcaneal nerve; MDNS, Michigan Diabetic Neuropathy Score; MM, Mindfulness meditation; MPN, Medial plantar nerve; mPNS, Magnetic peripheral nerve stimulation; MRI, Magnetic resonance imaging; MT, Mindfulness therapy; NCV, Nerve conduction velocity; NePIQOL, Neuropathic Pain Impact on Quality of Life Questionnaire; NeuroQoL, Neuropathy-Specific Quality of Life Questionnaire; NIS, Noninvasive stimulation; NMDA, N-methyl-D-aspartate (glutamate receptor); NNT, Number-needed-to-treat; NPS, Neuropathic Pain Scale; NRS, Numeric rating scale; NPRS, Numeric pain rating scale; ODI, Oswestry Disability Index; PACC, Polyanalgesic Consensus Conference; PCS, Pain Catastrophizing Scale; PDN, Painful diabetic neuropathy; PENS, Percutaneous electrical nerve stimulation; PGIC, Patient Global Impression of Change; PHQ9, Patient Health Questionnaire-9; PJI, Periprosthetic joint infection; PN, Peripheral neuropathy; PNS, Peripheral nerve stimulation; POMS, Profile of Mood States; PROM, Patient-reported outcome measure; PRP, Platelet rich plasma; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; QOL, Quality of life; QST, Quantitative sensory test; RCT, Randomized controlled trial; SCS, Spinal cord stimulation; SD, Standard deviation; SF-12/ SF-36, Short Form questionnaire; health-related quality of life (12-/ 36-item); SF-MPQ, Short form McGill Pain Questionnaire; SNAP, Sensory nerve action potential; SNRI, Serotonin-norepinephrine reuptake inhibitor; SOC, Standard of care; SSI, Surgical site infection; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SWEET, Systematic guideline process to outline the current state of the art in treatment of painful diabetic neuropathy; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; TAU, Treatment as usual; TCA, Tricyclic antidepressant; TRPV1, Transient receptor potential vanilloid 1; USPSTF, United States Preventative Services Task Force; VADT, Veterans Affairs Diabetes Trial (study); VAS, Visual analog scale; VASPI, Visual analog scale of pain intensity; WHYMPI, West Haven Yale Multidimensional Pain Inventory.

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