Journal of Pain Research

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REVIEW

Update on Treating Painful Diabetic Peripheral Neuropathy: A Review of Current US Guidelines with a Focus on the Most Recently Approved Management Options

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Abstract: Painful diabetic peripheral neuropathy (DPN) is a highly prevalent and disabling complication of diabetes that is often misdiagnosed and undertreated. The management of painful DPN involves treating its underlying cause via lifestyle modifications and intensive glucose control, targeting its pathogenesis, and providing symptomatic pain relief, thereby improving patient function and health-related quality of life. Four pharmacologic options are currently approved by the US Food and Drug Administration (FDA) to treat painful DPN. These include three oral medications (duloxetine, pregabalin, and tapentadol extended release) and one topical agent (capsaicin 8% topical system). More recently, the FDA approved several spinal cord stimulation (SCS) devices to treat refractory painful DPN. Although not FDA-approved specifically to treat painful DPN, tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors, gabapentinoids, and sodium channel blockers are common first-line oral options in clinical practice. Other strategies may be used as part of individualized comprehensive pain management plans. This article provides an overview of the most recent US guidelines for managing painful DPN, with a focus on the two most recently approved treatment options (SCS and capsaicin 8% topical system), as well as evidence for using FDA-approved and guideline-supported drugs and devices. Also discussed are unmet needs for this patient population, and evidence for potential future treatments for painful DPN, including drugs with novel mechanisms of action, electrical stimulation devices, and nutraceuticals.

Keywords: neuropathic, pain, painful diabetic peripheral neuropathy, treatment, guidelines, diabetic nerve pain

Introduction

Diabetic peripheral neuropathy (DPN) is among the most common complications of type 1 diabetes (T1D) and type 2 diabetes (T2D)[1,2] in the United States (US), approximately 37 million individuals have diabetes, predominantly (90–95%) T2D, with an additional 96 million adults having prediabetes.[3] An estimated 50% of diabetic patients and 10–30% of prediabetic patients will develop neuropathy.[4,5] Neuropathy is accompanied by pain in approximately 20–40% of afflicted patients, many of whom continue to have unresolved pain even with treatment.[2,6–10] Diabetic neuropathic pain is associated with a high prevalence of anxiety, depression and sleep disorders which can amplify the disease burden and increase the complexity of management,[11] particularly with respect to treatment selection and potential for drug–drug interactions (DDIs) and adverse drug reactions (ADRs) in the presence of polypharmacy.

Major risk factors for DPN are hyperglycemia in T1D and metabolic syndrome in T2D.[12] Although glycemic control helps to prevent DPN in patients with T1D, it provides modest or no benefits in preventing DPN in patients with T2D, likely due to the presence of co-morbidities.[12] The development of painful DPN has been associated with numerous factors including poorly controlled glucose levels, worsening glucose tolerance, T2D (relative to T1D), insulin resistance, tobacco smoking,

Received: 29 September 2023
Accepted: 26 February 2024
Published: 13 March 2024

excessive alcohol consumption, advanced age and duration of diabetes, diabetic vessel disease, abdominal obesity, hypertension, elevated triglyceride levels, and low high-density lipoprotein levels.[8,10]

Typically, DPN presents initially as distal neuropathy without pain in the feet, followed by a gradual and symmetric progression of predominantly sensory symptoms including, paradoxically, numbness with exquisite sensitivity, allodynia and hyperalgesia.[6,13,14] Neuropathy symptoms arise from damage to the peripheral sensory nerves, accompanied by a gradual decrease in epidermal nerve fiber density, resulting in a worsening of sensory loss and an increase in responsiveness to painful stimuli.[15] The pathophysiological processes involved in the development of painful DPN are complex and appear to involve sustained hyperglycemia, dyslipidemia, and altered insulin signaling.[8,16] These lead to several possible pathological alterations (eg, DNA and macrophage activation damage, endoplasmic reticulum stress, mitochondrial dysfunction, neurodegeneration, and loss of neurotrophic signaling) in neurons and other cells critical to normal functioning. Disruptions to the intracellular processes of neurons, some of which are directly related to the effects of the metabolic syndrome, may lead to nerve dysfunction and, ultimately, neuropathy.[8]

The pathogenesis of pain related to DPN is not fully understood, although several theories have been proposed.[17] These include changes in blood vessels that supply the peripheral nerves; metabolic and autoimmune disorders accompanied by glial cell activation; alterations in sodium and calcium channel expression; and, more recently, central pain mechanisms, such as increased thalamic vascularity and imbalance of the facilitatory/inhibitory descending pathways.[17]

The management of painful DPN involves treating the underlying causes via lifestyle modifications and pharmacological control of risk factors, targeting its pathogenesis, and providing symptomatic pain relief, thereby improving patient function and health-related quality of life (HR-QoL).[8–10,18–24] Despite the substantial morbidity of painful DPN, its negative impact on HR-QoL, and immense healthcare burden, the condition is often misdiagnosed and inadequately treated.[8,14,25]

Since 2020, the US Food and Drug Administration (FDA) has approved two novel options to manage painful DPN, namely the capsaicin 8% topical system and spinal cord stimulation devices. As such, we considered it timely to examine the evidence supporting the use of these newer options and their positioning within current US guidelines. We also present evidence for three FDA-approved oral pharmacological treatments and other guideline-supported oral treatments commonly used as first-line options in clinical practice; explore potential future options to manage painful DPN; and discuss the unmet needs of this increasingly complex and rapidly growing patient population.

Guidelines for Managing Painful Diabetic Peripheral Neuropathy (DPN)

The management of painful DPN involves controlling the underlying diabetic condition and symptomatically treating the associated pain, as recommended in multiple clinical practice guidelines and expert reviews.[8–10,18–24,26–29] Given their influence and importance in determining recommendations in other relevant expert opinions and reviews,[8–10,22–24,28,29] we have focused on evidence-based guidelines and recommended treatment algorithms from the following US organizations:

- American Academy of Neurology (AAN): Published in December 2021, the Oral and Topical Treatment of Painful Diabetic Neuropathy: Practice Guideline Update Summary[18] provides updated recommendations on the treatment of painful DPN. Graded recommendations for the use of numerous drug classes and individual agents are based on a systematic and statistical analysis of the results of 133 relevant peer-reviewed randomized, controlled trials (RCTs).
- American Diabetes Association (ADA): Three publications guiding the treatment of painful DPN are available from the ADA. Diabetic Neuropathy: A Position Statement[19] was published in 2017 and provides graded recommendations on all aspects of DPN management—including prevention, diagnosis, and treatment—based on several technical reviews and associated supporting references. The clinical compendium on the Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy[20] and Standards of Medical Care in Diabetes–2022[26,27] were published in 2022. The clinical compendium focuses on the screening, diagnosis and treatment of painful DPN in routine clinical practice, and summarizes the latest guidance on effective therapies, including pharmacological agents, nutraceutical products, and non-pharmacological therapies.[20] Guidance on treating painful DPN is also provided in Chapter 12: Retinopathy, Neuropathy, and Foot Care[27] of the updated Standard of Medical Care in Diabetes –2022.[26]

- American Association of Clinical Endocrinology (AACE). Published in 2022, the AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan–2022 Update[21] provides graded recommendations for the care of diabetic patients, including diagnosis and management of DPN, based on a comprehensive search and appraisal of the current literature.

Several other international and national clinical practice guidelines on the management of neuropathy are available, including those from the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain,[30,31] the European Federation of Neurological Societies,[32] the European Association for the Study of Diabetes,[33] the UK National Institute for Health and Care Excellence,[34] the Canadian Pain Society,[35] the German Society for Neurology,[36] and the German National Disease Management Guideline for Diabetic Neuropathy.[37] However, in light of their publication date (before 2016)[30–35,37] and/or focus on the management of neuropathic pain in general,[30,32,34–36] any guidance specific to painful DPN may be incomplete, especially as it relates to newer treatment options.

Key AAN, ADA, and AACE recommendations for managing painful DPN are summarized in Table 1.[18–21] All three organizations advocate a customized stepwise approach, with the choice of pharmacological agent guided by factors such as comorbidities, cost, and potential for DDIs and ADRs.[18–21]

Guideline-recommended (although not necessarily FDA-approved) first-line oral options to treat painful DPN include tricyclic antidepressants (TCAs), gabapentinoids, and serotonin-norepinephrine reuptake inhibitors (SNRIs); the AAN

Table 1 Summary of Current American Academy of Neurology,[18] American Diabetes Association,[19,20] and American Association of Clinical Endocrinology[21] Guidelines for the Management of Diabetic Peripheral Neuropathy

Prevention and diagnosis	
Prevention[19–21]	Patients with T1D: tight glucose control (dramatically ↓ DPN risk) Patients with T2D/prediabetes/metabolic syndrome: patient-centered lifestyle modifications (eg, exercise, diet); intensive glucose control alone is only modestly effective in preventing DPN
Screening for DPN[19–21]	Patients with T2D: screen at diagnosis, then annually
	Patients with T1D: screen 5 years after diagnosis, then annually
	Prediabetic patients with symptoms of DPN: consider screening
Symptoms and diagnostic signs on clinical examination showing involvement of nerve fibers[19–21]	Large myelinated nerve fibers: numbness, tingling, poor balance; symmetrical distal-to-proximal pattern of ↓ vibration perception and 10 g monofilament response, ↓ ankle reflexes, impaired proprioception
	Small nerve fibers: pain, hyperalgesia, allodynia; symmetrical distal-to-proximal pattern of ↓ thermal discrimination and pinprick sensation
Pharmacological agents commonly used for pain management[a,b]	
First-line oral treatment[a]	TCA (eg, amitriptyline, nortriptyline, imipramine),[18–21] SNRI (eg, duloxetine[c], venlafaxine, desvenlafaxine),[18–21] gabapentinoid (eg, pregabalin[c], gabapentin),[18–21] sodium channel blocker (eg, carbamazepine, oxcarbazepine, lamotrigine)[18]
Topical treatment	Capsaicin 8% topical system[c].[20,21]
After treatment failure[d]	
Change or add treatments	Switch to a different first-line therapy[18,21] or try a combination of pharmacological agents belonging to different classes or a combination of pharmacological plus non-pharmacological options[18,20,21]
Chronic intractable pain[20]	Spinal cord stimulation[c] (low-frequency[20] or high-frequency[20,21])

(*Continued*)

Table 1 (Continued).

Pharmacological options that should not be used	
Opioids and dual opioid/SNRI agents (tapentadol ER[c], tramadol)	Use is not recommended due to the risk of serious ADRs, abuse and other complications, and lack of evidence of long-term efficacy[18,20,21]
	In patients currently receiving these agents, offer the option of a safe taper off and discuss alternative nonopioid strategies[18]
Adjunctive non-pharmacological options	
Lifestyle interventions[18,20,21]	Dietary modifications, improved glucose control, exercise (aerobic, resistance, strengthening, balance), less sedentary behavior
Psychologic options[18,20]	Cognitive behavioral therapy, mindfulness, meditation
Nutraceuticals[20]	α-Lipoic acid, benfotiamine (synthetic prodrug of thiamine), supplementation therapy in patients with proven deficiencies in vitamins B and D, magnesium

Notes: [a]Advise patients that the goal of therapy is to reduce (not eliminate) pain. [b]Consider factors such as potential ADRs and drug interactions, patient comorbidities/conditions (eg, sleep and mood disorders, epilepsy, pregnancy), cost, and patient preferences when selecting treatment. [c]FDA approved for the treatment of DPN. [d]A treatment has failed when a demonstrated efficacious dose for ≈12 weeks has not provided clinically significant pain reduction or when ADRs outweigh any benefit from reduced neuropathic pain.[18]

Abbreviations: *ADR*, adverse drug reaction; DPN, diabetic peripheral neuropathy; *ER*, extended release; *FDA*, US Food and Drug Administration; *SNRI*, serotonin-norepinephrine reuptake inhibitor; *TCA*, tricyclic antidepressant; *T1D*, type 1 diabetes; *T2D*, type 2 diabetes; ↓ decreased or absent.

guideline also includes sodium channel blockers.[18] Based on the results of a meta-analysis of Class I and II trials showing comparable estimated effect sizes, the AAN states that it is difficult to recommend any one drug class over another.[18] Later-line therapy involves switching first-line agents or using combinations of pharmacological agents from different classes or pharmacological plus non-pharmacological options.[18,20,21]

Capsaicin 8% topical system, the only FDA approved non-oral pharmaceutical to treat painful DPN, is a first-line treatment option in the AACE guidelines[21] and is recommended in the ADA compendium.[20] The German Diabetes Association (Deutsche Diabetes Gesellschaft, DDG) also positions capsaicin 8% topical system as a first-line treatment for painful DPN,[22] whereas an international expert consensus group considers it a third line analgesic treatment for painful DPN in clinical practice.[29]

FDA-Approved Treatments for Painful DPN

Five treatments are currently approved by the FDA to treat painful DPN based on their efficacy and safety in RCTs in this patient population. These include three oral medications (duloxetine, pregabalin, and tapentadol extended release [ER]); one topical agent (capsaicin 8% topical system); and low- and high-frequency spinal cord stimulation (SCS) devices indicated for the treatment of chronic intractable painful DPN, which is defined as constant moderate to severe pain that has no known cure and requires daily medical treatment.

Table 2 summarizes the year of approval, indication, contraindications, and most common adverse events reported with the use of FDA-approved options to treat DPN.[38–44] Although pain-related endpoints among RCTs differed to some extent, all treatments were associated with significant improvements from baseline in pain scores relative to placebo or standard therapy, as well as increases in the proportion of patients achieving a clinically meaningful pain response (ie, a ≥30% or ≥50% improvement in pain score).

In reverse chronological order of their FDA approval, the efficacy and safety of these treatments in their pivotal RCTs are examined, with emphasis on the two most recently approved options (ie, SCS devices and the capsaicin 8% topical system).

Spinal Cord Stimulation (SCS) for Intractable Painful DPN

SCS therapy involves placing wire leads within the epidural space of the spinal canal accompanied by implantation of an internal pulse generator device in the superficial tissue, usually the back or buttock.[38,39] SCS requires minor outpatient

Table 2 Current FDA-Approved Options for the Management of Painful Diabetic Peripheral Neuropathy (Trade name; Year of FDA Approval for Painful DPN)

Approved Indication	Contraindications	Application/Dosage	Most Common Adverse Events
Spinal cord stimulation devices:[38,39] Programmable low-frequency SCS (Medtronic Vanta™; 2022); Programmable high-frequency SCS (Medtronic Intellis™; 2022); Preprogrammed high-frequency (10 kHz) SCS (Nevro Senza®, Senza II™, Senza Omnia™; 2021)			
Aid in the management of chronic, intractable pain associated with unilateral or bilateral DPN of the lower extremities	Poor candidate for surgery (eg, poor glycemic control); lack of effective pain relief during trial stimulation period; inability to operate the stimulation system	Surgical implantation of SCS following a trial stimulation period	Events related to the implantation procedure (eg, wound dehiscence, infection)
Capsaicin 8% topical system (Qutenza®; 2020)[40]			
Neuropathic pain associated with DPN of the feet	None	Apply 1–4 patches to painful area for 30 min; may repeat at ≥3 month intervals	Application site: transient burning sensation and pain
Tapentadol ER (Nucynta® ER; 2012)[41]			
DPN neuropathic pain severe enough to require daily, 24-h, long-term opioid treatment; alternative treatment options are inadequate	Significant respiratory depression; acute/ severe asthma; paralytic ileus; use of MAOIs concurrently or within the last 14 days; hypersensitivity to tapentadol/other ingredients	Usual 100–250 mg/day; maximum 500 mg/day; do not abruptly discontinue in physically-dependent patients	Nausea, constipation, vomiting, dizziness, somnolence, headache
Duloxetine delayed-release (Cymbalta®, Drizalma Sprinkle™; 2004)[42,43]			
Pain associated with DPN	Use of MAOIs concurrently or within the last 14 days; current treatment with linezolid or intravenous methylene blue	Usual 60 mg/day; consider starting with ↓ doses if tolerability concerns or renal impairment	Nausea, dry mouth, somnolence, ↓ appetite, constipation, hyperhidrosis
Pregabalin (Lyrica®; 2004)[44]			
Neuropathic pain associated with DPN	Known hypersensitivity to pregabalin or any of its components	Initial 150 mg/day; ↑ based on efficacy/ tolerability; maximum 300 mg/day; use ↓ doses if renal impairment; withdraw gradually	Dizziness, dry mouth, peripheral edema, blurred vision, ↑ weight, somnolence, ↓ attention or concentration

Abbreviations: *DPN*, diabetic peripheral neuropathy; *FDA*, US Food and Drug Administration; *MAOI*, monoamine oxidase inhibitor; *SCS*, spinal cord stimulation; ↑, increase(d); ↓, lower/decreased.

surgery and, for decades, has been a component of the management of intractable pain of the torso and limbs. Use in painful DPN was only recently added to its indications. Conventional tonic SCS devices use low-frequency (40–100 Hz) SCS to induce paresthesia in painful anatomic regions.[45] High-frequency (10 kHz) SCS induces minimal to no paresthesia and is thought to act by modulating axonal activity in the superficial dorsal horn, thereby regulating chronic pain pathways.[45]

In 2022, the FDA approved the Medtronic Vanta™ and Intellis™ implantable neurostimulation systems to aid in the management of chronic intractable unilateral or bilateral pain of the lower limbs associated with DPN (Table 2).[38] These devices have options to personalize patient therapy and allow patients to adjust the intensity of the electric current as required.[38] The Vanta™ SCS device provides low-frequency SCS and does not require recharging (the battery is estimated to last 11 years). The Intellis™ SCS device provides high-frequency SCS and is transcutaneously recharged within 1 hour using a recharge antenna.

Nevro's Senza®, Senza II™ and Senza Omnia™ neuromodulation systems were approved in 2021 to treat chronic intractable unilateral or bilateral pain of the lower limbs associated with DPN (Table 2).[39] When used in this indication,

the devices are preprogrammed to deliver high-frequency (10 kHz) paresthesia-free electrical pulses.[39] The batteries in the devices are transcutaneously recharged using hand-held portable chargers, via a schedule that fits with the patient's lifestyle and maintains a sufficient charge to deliver the desired level of stimulation. The battery has an expected life of at least 10 years using a typical 10 kHz program stimulation setting.[39]

Before implantation of SCS devices, patients undergo trial stimulation for approximately 1 week to determine whether implantation is appropriate.[38,39] If pain relief, functional enhancement, and tolerability goals are satisfied, a complete SCS system (neurostimulator and leads) is implanted. Adverse events are generally associated with the implantation procedure (Table 2). Although the minimally invasive implantation procedure is usually well tolerated, adverse events and complications, such as wound-related issues, may be more frequent and severe in diabetic patients, especially those with poor glucose control.[38,39]

At the time of manuscript development, SCS devices manufactured by Nevro and Medtronic were approved for painful DPN, but the authors have since become aware of FDA approval of devices from Abbott (Proclaim™ Plus and Proclaim™ XR) and Boston Scientific (WaveWriter Alpha™). As this therapeutic area is evolving rapidly, we might anticipate the approval of more devices in future.

Evidence for the Efficacy of SCS in Refractory Painful DPN

FDA approvals of the Medtronic and Nevro SCS devices were based on the results of three open-label multicenter RCTs of low-frequency[46,47] or high-frequency[48] SCS. To be eligible for enrollment in these RCTs, patients were required to have painful DPN for ≥1 year that was refractory to conventional pharmacological therapy.[46–48] Patients were randomized to receive open-label SCS treatment plus best/conventional medical management (CMM) or CMM alone for 6 months. Patients in the SCS plus CMM group underwent temporary trial stimulation for 5–7 days, and those who achieved a ≥50% pain reduction were eligible for device implantation.

According to an analysis conducted by Medtronic, low-frequency SCS[46,47] and high-frequency SCS[48] had similar adjusted ≥50% responder rates (55% vs 55%).[49] The findings are supported by results from a recent network meta-analysis of SCS RCTs for painful DPN.[50] In addition, a systematic review and meta-analysis of individual patient and aggregate data showed that SCS is an effective therapeutic adjunct to best medical therapy in reducing pain intensity and improving HR-QoL in patients with painful DPN.[51]

Low-Frequency SCS

In the larger (n = 60) of two clinical trials of low-frequency SCS for intractable painful DPN, trial stimulation was successful (ie, ≥50% pain reduction) in 93% of the low-frequency SCS plus CMM group.[46] This group had a significant reduction in mean visual analog score (VAS) scores at 6 months (from 7.3 cm at baseline to 3.1 cm at 6 months; $p < 0.001$), as well as improvements in other pain and HR-QoL outcomes. In contrast, the CMM group had no improvements in any outcomes. Significantly more patients in the low-frequency SCS plus CMM group than in the CMM group achieved ≥50% pain relief (60% vs 5%; $p < 0.001$). No patients required device removal due to adverse events.

Similar results were shown in the smaller (n = 36) of the two RCTs, in which trial stimulation was successful in 77% of patients.[47] At 6 months, 59% of low-frequency SCS plus CMM versus 7% of CMM alone recipients achieved treatment success, which was defined as ≥50% pain relief during daytime or nighttime or "much improved" or "very much improved" on Patient Global Impression of Change (PGIC) pain and sleep scores. In terms of safety, one case of fatal subdural hematoma due to dural puncture during trial lead implantation, and one infection of the SCS system that required removal of the device 6 weeks after implantation occurred.

Patients with DPN have been shown to gain significant long-term pain relief with low-frequency SCS plus CMM. In a 5-year follow-up of 48 patients enrolled in two identically designed studies,[47,52] 86% of patients achieved treatment success at 1 year, a rate that slowly decreased each year to 55% at 5 years.[53] Kaplan–Meier survival analysis indicated that 80% of the patients were still using their SCS device after 5 years. One patient required removal of the device 8 months after implantation due to a chronic infection of the SCS system.[53] More recently, an 8- to 10-year follow-up study of 19 patients with painful DPN who continued to use SCS treatment after at least 8 years reported that pain intensity, day

and night, was reduced significantly compared with baseline and, for >50% of patients, the pain reduction was >30% (considered to be clinically meaningful).[54]

High-Frequency SCS

Approval of the high-frequency Nevro 10-kHz SCS device to treat chronic retractable DPN was based on the results of an open-label 6-month RCT, with optional crossover at 6 months.[48] Patients with refractory painful DPN were randomized to receive 10-kHz SCS plus CMM (n = 113) or CMM alone (n = 103). In the 10-kHz SCS plus CMM group, 104 patients underwent temporary trial stimulation. This was successful in 98 patients (94%), with 90 patients opting to undergo permanent device implantation.

The primary endpoint (≥50% improvement from baseline in VAS pain without worsening of baseline neurological deficits at 3 months) was achieved by significantly more 10-kHz SCS plus CMM than CMM alone recipients (79% vs 5%; between-group difference [BGD] 73.6%; 95% CI 64.2–83.0; $p < 0.001$). At 6 months, 10-kHz SCS plus CMM was associated with significantly ($p < 0.001$) higher rates of patients with a ≥50% improvement in pain response (85% vs 5%), sustained pain remission (60% vs 1%), neurological improvement (62% vs 3%), and patient satisfaction (92% vs 6%) than CMM alone.[48] Substantial pain relief and other benefits were maintained over 12 months with 10-kHz SCS plus CMM.[55]

Over a 12-month period, procedure-related infections were reported in eight patients (5.2%), leading to surgical removal of the SCS device in five patients; infections in the remaining three patients were resolved with conservative treatment.[55] Stimulation-related ADRs were not reported.

Capsaicin 8% Topical System

Capsaicin is a highly selective agonist for the transient receptor potential vanilloid-1 (TRPV1) receptor, which is an ion channel-receptor complex expressed on nociceptive nerve fibers in the skin.[40] The 2021 Nobel prize in Physiology or Medicine was awarded jointly to Dr. David Julius and Dr. Ardem Patapoutian for their respective groundbreaking discoveries of receptors for temperature (TRPV1 receptors) and touch (Piezo2 ion channels).[56] Discovery of the TRPV1 receptor led to an understanding of its importance in pain perception. In chronic pain states, TRPV1 receptors are up-regulated on neurons, have reduced stimulation thresholds, and increase pain perception. Activation of TRPV1 receptors results in pain, burning, itching, stinging, and other physiological responses.[57,58]

The capsaicin 8% (179 mg) topical system (Qutenza®)[40] is the only topical treatment, and the only topical formulation of capsaicin, approved by the FDA to treat adults with painful DPN of the feet. Although multiple over-The-counter (OTC) products contain capsaicin, these relatively low-concentration (0.025–0.075%) formulations are not approved to treat painful DPN. Unlike the capsaicin 8% topical system, OTC topical capsaicin products require application several times each day, leading to poor compliance, and tend to have modest efficacy and generally poor tolerability.[57,58] The capsaicin 8% topical system, in contrast, provides rapid and sustained benefits due to its engineered and patented matrix delivery system, which creates a forced diffusion of high concentration capsaicin into the skin during an application period of 30 min (for painful DPN of the feet) or 60 min (for post-herpetic neuralgia), with subsequent applications at ≥3-month intervals.[40,59]

The capsaicin 8% topical system consists of a silicone adhesive matrix that contains a microreservoir of high-concentration capsaicin solubilized in diethylene glycol monomethyl ether (DGME) with a polyester backing and removable liner.[59] During application to the feet of patients with painful DPN, capsaicin is rapidly diffused into the epidermal layers of the skin via the influx of DGME and efflux of water. During the application period, and possibly for a few days afterward, the patient may feel a hot, burning sensation with hyperalgesia.[57,58,60,61] This initial reaction is triggered by activation of TRPV1 receptors on the nociceptive nerve endings and is followed by desensitization,[57,60,62,63] leading to defunctionalization and ablation of epidermal nerve fibers (ENF) via a chemoneurolytic process at the application site.[64–67] This ablation and reduction of ENF density is temporary and reversible. Reinnervation of the TRPV1 nerve fibers occurs over the course of several months and pain may gradually reemerge due to the continuous consequences of diabetes.[40] Of note, recent evidence suggests that treatment with capsaicin 8% topical systems may have an impact beyond pain relief, including the promotion of healthy nerve regeneration (see Unmet needs in the treatment of painful DPN: Disease prevention section for details).[68–71] Systemic exposure to capsaicin following application of the topical system is very transient and low, since the high-concentration capsaicin does not penetrate deep into the dermal layers of the skin.[58,72] As a result, the capsaicin 8% topical system is well

tolerated, with a general lack of systemic ADRs, no potential DDIs or contraindications to its use, and no requirements for dose titration or adjustments in any patients (Table 2).[40] This makes the capsaicin 8% topical system particularly favorable for use in complex patient populations, such as those taking multiple medications, those with co-morbid conditions, including hepatic or renal impairment, and those in whom treatment with oral medications that increase the risk of falls and fractures is considered unsuitable.

Evidence for the Efficacy of a Single Application

In the double-blind, placebo-controlled 12-week STEP trial, adult patients with painful DPN of the feet received a single 30-min application of the capsaicin 8% topical system (n = 186) or placebo (n = 183) and were followed for 12 weeks.[73]

The capsaicin 8% topical system provided rapid and sustained (≥3-month) improvement in pain-related outcomes that were significantly greater relative to placebo.[73] The reduction from baseline in mean numeric pain rating scale (NPRS) scores for average daily pain during weeks 2–8 (primary endpoint) was significantly greater with the capsaicin 8% topical system than with placebo (BGD –6.6%; 95% CI –12.3 to –0.8; p = 0.025); and improvement was maintained during weeks 2–12 (BGD –7.1%; 95% CI –12.9 to –1.2; p = 0.02). Significantly more patients treated with the capsaicin 8% topical system than placebo achieved a clinically meaningful ≥30% reduction in pain during weeks 2–12 (40.9% vs 31.7%; p = 0.05). Compared with placebo, capsaicin 8% topical system recipients had a shorter median time to treatment response (defined as the first of three consecutive days on which the patient reported ≥30% decrease from baseline in average daily pain score; 19 vs 72 days), modest improvements from baseline in sleep interference scores during weeks 2–8 and weeks 2–12 (p ≤ 0.03 vs placebo), and no changes in sensory perception and reflex testing.[73]

In the capsaicin 8% topical system group, headache (in 2.2% of patients) was the only systemic ADR reported. Application-site reactions were reported by 33.9% of patients, and no patients discontinued treatment due to ADRs.[73]

Evidence for Safety and Efficacy After Repeated Applications

Due to the progressive nature of diabetes, patients with DPN have reduced ENF density,[15] underscoring the need to investigate the potential consequences of repeated nerve fiber ablation on peripheral nerve sensory function. The open-label PACE RCT was designed primarily to evaluate the long-term (52-week) safety of repeated applications of the capsaicin 8% topical system plus standard of care (SoC) consisting of optimized treatment with antidepressants, anticonvulsants, and/or opioids.[74,75] Adult patients with painful DPN of the feet were randomized to receive the capsaicin 8% topical system applied for 30 min plus SoC (n = 156), capsaicin 8% topical system applied for 60 min plus SoC (n = 157), or SoC alone (n = 155). Results are presented for the group treated with the capsaicin 8% topical system (30 min) plus SoC, as 30 min is the application duration approved for treatment of painful DPN of the feet.

The capsaicin 8% topical system was applied 1–7 times at intervals of ≥8 weeks. The mean between-treatment interval was 68.4 days, and 53.8% of patients in the capsaicin 8% topical system 30-min group received seven applications.[74]

The primary endpoint was the change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) scores. This validated patient-reported outcome measure captures the entire impact of nerve fiber dysfunction on QoL in DPN; score reductions correspond with functional improvement.[74] Repeated treatment with the capsaicin 8% topical system was not associated with any deterioration of functional or neurological sensation. Improvements from baseline in Norfolk QoL-DN scores were −27.6% with capsaicin 8% topical system 30-min plus SoC in the total group, slightly higher (−31.2%) in the subgroup which received seven applications, and lower (−6.7%) in the SoC alone group. Norfolk subscale scores (small fiber, symptoms, autonomic, physical function, activities of daily living) and Utah Early Neuropathy Scale total and sharp sensation subscale scores also improved from baseline to a greater extent with the capsaicin 8% topical system plus SoC than SoC alone. The capsaicin 8% topical system had no negative effect on sharp, warm, cold, and vibration perception and reflex function relative to SoC alone.[74]

Compared with SoC alone, the capsaicin 8% topical system 30-min plus SoC led to numerically greater improvements in NPRS pain scores (average daily pain, pain intensity and pain interference) and EQ-5D utility index and VAS scores, higher rates of ≥30% and ≥50% pain responses (67.3% vs 40.6% and 44.8% vs 23.8%, respectively), higher rates of being "very much, much or minimally improved" on the PGIC scale (67.3% vs 38.5%), and lower rates of new prescriptions for

concomitant opioids, antidepressants and anticonvulsants (increase from baseline of 0.1–1.3% vs 3.2–10.9%) at week 52.[75] Formal statistical testing of these secondary efficacy endpoints was not performed, as PACE was primarily a safety study.

Repeated treatment with the capsaicin 8% topical system may result in progressive improvements in pain and other outcomes. A post-hoc analysis of PACE investigated the efficacy of repeated applications of the capsaicin 8% topical system in patients who failed to achieve a ≥30% pain response following the first application.[76] Among 313 recipients of the capsaicin 8% topical system (pooled 30- and 60-min application times) plus SoC, 96 (30.7%) achieved a ≥30% response following the first application. Among non-responders at 3 months, 28.1% achieved a ≥30% reduction at 6 months, increasing to 42.5% and 45.7% at 9 and 12 months, respectively. By month 12, progressive improvements in pain, sleep, QoL, and patient satisfaction achieved by slower responders were similar to those in early responders.[76] According to the investigators, a progressive pattern of response in some patients after repeated applications of the capsaicin 8% topical system may arise from a "pruning" effect on abnormal nerve fibers followed by regeneration of more normal fibers and/or a gradual effect of peripheral therapy on central sensitization leading to decreased pain perception over time.[76]

Efficacy and Tolerability Compared with Oral Medications

A network analysis has provided indirect evidence of the relative efficacy of the capsaicin 8% topical system versus placebo and oral pregabalin, gabapentin, and duloxetine in treating painful DPN,[77] as no head-to-head studies have been conducted. Twenty-five RCTs were included in an analysis of the odds of achieving a ≥30% response at 12-weeks. STEP was the only RCT of the capsaicin 8% topical system to be included.

The likelihood of achieving a ≥30% response with the capsaicin 8% topical system was significantly greater relative to placebo (odds ratio 2.28; 95% CI 1.19–4.03), and similar to that of pregabalin, gabapentin and duloxetine (odds ratio 0.99–1.83, with non-significant 95% CIs). Importantly, the capsaicin 8% topical system offered tolerability benefits since, unlike oral medications, it was not associated with reports of systemic ADRs such as somnolence, dizziness, nausea, diarrhea, constipation, and fatigue, or with discontinuations due to ADRs.[77] The only ADR of interest was the capsaicin 8% topical system had in common with oral pregabalin, gabapentin, and duloxetine was headache. The odds ratio for headache did not differ significantly between the capsaicin 8% topical system and placebo, and the mean probability of headache was lower with the capsaicin 8% topical system than with pregabalin, gabapentin, and duloxetine (10.6% vs 83.3%, 60.4%, and 28.8%, respectively).[77]

Tapentadol Extended-Release Tablets

Tapentadol ER (Nucynta® ER) is a dual μ-opioid receptor agonist and norepinephrine reuptake inhibitor (Table 2),[41] which was approved to treat painful DPN based on its efficacy in two 12-week RCTs.[78,79] Optimized dosages of tapentadol ER 100–250 mg twice daily significantly improved pain scores and other outcomes.[78,79] In a pooled analysis of these key RCTs, the mean pain intensity score of 7.29 at the beginning of the initial open-label phase decreased to 4.15 following 3 weeks of treatment.[80] In the double-blind phase limited to tapentadol responders, mean pain intensity scores at week 12 were lower with tapentadol ER than with placebo (3.77 vs 4.76), indicating that pain levels remained consistent with continued use of tapentadol ER, but worsened when placebo replaced tapentadol ER. Significantly more tapentadol ER than placebo recipients had a ≥50% reduction in pain intensity (38.9% vs 28.4%) and reported that their painful DPN was "very much improved" or "much improved" using the PGIC assessment (65.5% vs 41.7%).[80]

Despite regulatory approval of tapentadol ER to treat painful DPN, current AAN,[18] ADA,[20] and AACE[21] guidelines do not recommend its use due to general concerns about opioid therapy (Table 1). In addition to more common ADRs (Table 2), tapentadol is associated with several potentially serious ADRs and DDIs. According to black-box warnings required by the FDA in the US prescribing information,[41] tapentadol may cause serious, life-threatening or fatal respiratory depression; is associated with a risk of addiction, abuse, and misuse that can lead to overdose and death; and may result in profound sedation, respiratory depression, coma, and death if used concomitantly with benzodiazepines or other central nervous system depressants, including alcohol.

Duloxetine Capsules

Duloxetine (Cymbalta®, Drizalma Sprinkle™, Irenka®) acts as an SNRI (Table 2).[42,43] Its analgesic effects in the treatment of DPN are thought to be associated with preferential blockade of late Na_v 1.7 sodium ion channels,[81] with increases in norepinephrine and, to a lesser extent, serotonin and dopamine in the CNS also appearing to play a role in the inhibition of neuropathic pain.[82]

Approval for the use of duloxetine 60 mg once daily to treat painful DPN was based on the results of two 12-week RCTs.[83,84] Relative to placebo, duloxetine 60 mg once or twice daily significantly improved mean NPRS scores by an additional 1–1.7 points. Significantly more duloxetine than placebo recipients achieved a ≥50% pain response (40–45% vs 20–22%). There were no significant differences between duloxetine 60 mg once or twice daily. Pain relief was recorded as early as the first week in some patients and persisted throughout the study duration.[83,84]

In addition to common ADRs (Table 2), duloxetine has been associated with potentially fatal hepatotoxicity, serotonin syndrome (when taken alone or in combination with other serotonergic agents), severe skin reactions, increased risk of bleeding, increased blood pressure, sexual dysfunction, and other potentially serious ADRs and DDIs that require caution.[42,43]

Pregabalin Capsules and Solution

Pregabalin (Lyrica®)[44] is a gabapentinoid with a complex mechanism of action (MoA) that involves inhibiting the calcium-mediated release of various neurotransmitters at neuronal synapses, as well as other activities, including influencing affective components of pain.[85]

In two RCTs pivotal to its approval for treating painful DPN, patients received pregabalin 100 mg three times daily (maximum dosage) for 5 weeks[86] or 8 weeks.[87] Pregabalin 300 mg/day significantly improved pain scores compared with placebo (mean change from baseline in VAS score 2.5 vs 0.8 cm) and increased the proportion of ≥50% pain responders (45% vs 18%). In both trials, pain decreased in some patients during the first week, with improvements persisting throughout the study period. A meta-analysis of 11 placebo-controlled RCTs found that pregabalin was effective in the treatment of both moderate and severe DPN-related pain, with greater improvement in those with severe than moderate pain.[88]

In addition to common ADRs (Table 2), pregabalin is associated with a risk of angioedema leading to life-threatening respiratory compromise, hypersensitivity reactions, and an increased risk of suicidal thoughts and behaviors, as well as other warnings and precautions.[44] As the misuse and abuse of pregabalin appears to be growing, its use requires caution in high-risk patients, such as those with a history of opioid abuse.[89]

Other Guideline-Supported First-Line Oral Options

Guideline-supported first-line oral options for the treatment of painful DPN in clinical practice include TCAs, gabapentinoids, SNRIs, and sodium channel blockers,[18–21] which are considered to modulate pain.[90] Table 3 summarizes the MoA and clinical efficacy of these drug classes in treating painful DPN.[18–21,77,82,85,91–114]

Tricyclic Antidepressants

TCAs (eg, amitriptyline (Elavil®, Vanatrip®),[92–97] nortriptyline (Aventyl®, Pamelor®),[98] desipramine (Norpramin®),[99] and imipramine (Tofranil®)[100] are frequently used to treat painful DPN and other types of neuropathic pain. Most evidence for the efficacy of TCAs in treating painful DPN relates to the use of amitriptyline, with little evidence for other TCAs (Table 3).[18,19]

The well-known ADRs of TCAs (eg, gastrointestinal issues, orthostatic hypotension, dry mouth, and urinary retention) are likely due to their activity on histaminic, adrenergic, and cholinergic receptors,[10] and may be problematic in patients with pre-existing constipation, urinary retention, or orthostatic hypotension.[18] Nortriptyline and desipramine[98,99] are generally better tolerated than amitriptyline and imipramine and may be a safer option, especially in older patients.[8]

Table 3 Mechanism of Action and Efficacy of Oral Pharmacological Agents Recommended as First-Line treatment[18–20] in Patients with Painful Diabetic Peripheral Neuropathy

MoA in DPN	Efficacy in RCTs
TCAs	
Involves balanced inhibition of reuptake of noradrenaline and serotonin by presynaptic neurons and blocking of peripheral nerve sodium channels[81,91]	*Amitriptyline*: in small RCTs, amitriptyline ↓ DPN pain vs placebo;[92–94] however, meta-analyses have generally found little evidence that amitriptyline is more effective than placebo or other treatments, while being associated with an ↑ risk of ADRs[18,77,95–97]
	Nortriptyline,[98] *desipramine*,[99] and *imipramine*:[100] Cochrane reviews found little evidence to support the use of these TCAs in DPN; some improvements in pain-related outcomes were shown vs placebo in low-quality RCTs, but all ↑ the risk of ADRs[98–100]
SNRIs	
Inhibit sodium channels, which blocks abnormal neural firing associated with neuropathic pain, and ↑ norepinephrine levels in the CNS; ↑ serotonin and dopamine levels play an auxiliary role[82]	*Duloxetine*: FDA approved to treat painful DPN
	Desvenlafaxine: in a 13-week RCT,[101] desvenlafaxine 200 and 400 mg significantly ↑ pain relief vs placebo (mean BGD in NPRS score 1.10 and 0.91, respectively)
	Venlafaxine: ↓ from baseline in VAS pain intensity was significantly greater with venlafaxine ER 150–225 mg/day than placebo (50% vs 27%; $p < 0.001$) in a 6-week RCT[102]
Gabapentinoids	
Complex mechanism of action; blocks calcium-mediated release of various neurotransmitters at neuronal synapses and influences the affective components of pain[85]	*Pregabalin*: FDA approved to treat painful DPN
	Gabapentin: in an 8-week RCT, gabapentin 900–3600 mg/day provided significant, but small, ↑ in pain relief vs placebo (mean BGD in NPRS score 1.2 points);[103] however, gabapentin 900 mg/day had no significant effect on pain in a 6-week crossover RCT (mean BDG in VAS 0.4 cm)[104]
Sodium channel blockers	
Inhibit the abnormal neural firing associated with neuropathic pain by blocking the activation of voltage-sensitive sodium channels, as well as providing secondary effects on other ion channels and the release of glutamate[105,106]	*Lacosamide*: lacosamide 400 mg/day significantly ↑ pain relief vs placebo in two 18-week RCTs;[107,108] however, ↑ pain relief was significant with lacosamide 600 mg/day in only one of these RCTs[107] (probably due to relatively high numbers of patients withdrawing due to ADRs)[108]
	Lamotrigine: lamotrigine 400 and 600 mg/day significantly ↑ pain relief vs placebo in a 6-week RCT[109] and two pooled 19-week RCTs[110]
	Oxcarbazepine: significant ↑ in pain relief with oxcarbazepine 300–1800 mg/day vs placebo in a 16-week RCT,[111] but not with oxcarbazepine 1200 mg/day in another RCT[112]
	Valproic acid: significant ↑ in pain relief with valproic acid 500 mg/day vs placebo at the end of 1 month in two RCTs,[113,114] with the benefits being maintained to the end of 3 months in the longer RCTs[114]

Notes: Unless otherwise indicated, these drugs are not specifically approved by the FDA to treat DPN.

Abbreviations: *ADR*, adverse drug reaction; *BGD*, between-group difference; *DPN*, diabetic peripheral neuropathy; *ER*, extended release; *FDA*, US Food and Drug Administration; *MoA*, mechanism of action; *NPRS*, Numeric Pain Rating Scale; *RCT*, randomized controlled trial; *SNRIs*, serotonin/norepinephrine reuptake inhibitors; *TCAs*, tricyclic antidepressants; *VAS*, visual analog scale; ↑ increase (d/s); ↓ decreased.

Serotonin/Norepinephrine Reuptake Inhibitors

In addition to FDA-approved duloxetine, ADA[18] and AAN[19] guidelines also recommend venlafaxine (Effexor®)[102] and desvenlafaxine (Pristiq®),[101] the only active metabolite of venlafaxine, as oral options for treating painful DPN (Table 3). These SNRIs have greater selectivity for inhibiting serotonin reuptake than norepinephrine reuptake, which occurs in a dose-related and sequential manner, and weakly inhibit dopamine reuptake.[115]

The tolerability profiles of desvenlafaxine and venlafaxine are comparable to that of duloxetine, with nausea and dizziness being the most common ADRs.[101,102] The sequential effects of SNRIs on serotonin and norepinephrine results in an initial onset of serotonergic ADRs (eg, headaches, nausea, fatigue, sexual dysfunction) followed by ADRs at higher dosages that relate to both serotonin and norepinephrine (eg, activation effects, dry mouth, night sweats).[115] Venlafaxine and duloxetine are metabolized by CYP isoenzymes leading to potential DDIs, whereas desvenlafaxine bypasses such metabolism, limiting the possibility of DDIs.[115]

Gabapentin

Gabapentin (Neurontin®, Gabarone®), the only gabapentinoid other than pregabalin currently available in the US, is FDA approved to treat post-herpetic neuralgia[116] but not DPN. Two recent formulations of gabapentin, gabapentin gastro-retentive tablets (Gralise®) and gabapentin enacarbil ER (Horizant®), are also approved to treat post-herpetic neuralgia, but not painful DPN. Nevertheless, gabapentin has shown some efficacy in treating painful DPN (Table 3).[103,104] In comparison to pregabalin, gabapentin has a much lower oral bioavailability (30–60% vs 90%) and is less rapidly absorbed (time to peak plasma concentrations 1 vs 3 hours).

As with pregabalin, gabapentin requires dose titration, tapered withdrawal, lower dosages in patients with renal impairment,[116] and caution with use in patients at high-risk of misuse and abuse.[89] The most common ADRs with gabapentin include CNS effects, weight gain, gastrointestinal effects, and peripheral edema. Due to risk of the latter, gabapentinoids should be used cautiously in patients with peripheral edema from comorbid cardiac, renal, liver, or other diseases.[18]

Sodium Channel Blockers

Sodium channel blockers (eg, carbamazepine [Tegretol®, Carbatrol®, Epitol®]), oxcarbazepine (Trileptal®), lamotrigine (Lamictal®), lacosamide (Vimpat®), and valproic acid (Depakote®, Depakene®) are also recommended for the treatment of painful DPN.[8–10,18] As a class, sodium channel blockers appear to be more effective in reducing pain associated with DPN than placebo based on limited evidence from generally small RCTs (Table 3).[107–114]

Sodium channel blockers have wide structural diversity and may block other sodium channels, such as those in the CNS and skeletal muscle. As a result, they are associated with a variety of ADRs, which differ between individual drugs depending on their specificity for certain sodium channels.[117]

Future Research in Painful DPN

At the heart of research into painful DPN is the need for a better understanding of the correlation between diabetes severity and its impact on painful DPN; as well as cardiometabolic risk factors for painful DPN and their link to cardiovascular mortality. Genetic studies are needed to clarify disease mechanisms which differentiate painful and non-painful DPN.[2,7] The increased focus on the patient has been paralleled by research into diagnostic tests using novel biomarkers, although more effort in this area is required, and assessment of more effective therapies for symptom management and ultimately disease modification.

Drugs in Phase 2 or 3 Clinical Trials

Many drugs with novel MoAs are being evaluated for the treatment of painful DPN.[118] At the time of manuscript development, drugs that had successfully completed phase 2 or 3 RCTs were VM202, a gene therapy that provided pain relief in a patient subgroup and was well tolerated;[119] and NRD135S.E1, a Lyn tyrosine kinase inhibitor that showed consistent pain relief benefits and was well tolerated.[120] Details are in Table 4.[118–122]

Table 4 Drugs in Development for Painful Diabetic Peripheral Neuropathy in Completed Phase 2 or 3 Randomized Controlled Trials as Reported in the Clinicaltrials.gov Database

Drug Name/ Code [Manufacturer]	Mechanism of Action in DPN	Clinicaltrials.gov Identifier Number: Results or Study Description[118]
Completed Phase 3 RCTs		
VM202 (Engensis) [Helximith]	Gene therapy; plasma DNA encoding two isoforms of hepatocyte growth factor, a multi-functional protein with potent neurotrophic and angiogenic activities[119]	NCT02427464:VM202 (IM to calf muscles on days 0, 14, 90, 104) provided conflicting pain relief results (not effective vs placebo at 9 months, but provided clinically meaningful pain relief in a subgroup of patients at 9 months) and was well-tolerated in patients with painful DPN[119]
Completed phase 2 RCTs		
EMA401 (Empadine) [Novartis]	Highly selective angiotensin II type 2 receptor antagonist; ↓ neuropathic pain signaling at peripheral nerve terminals[121]	NCT03297294: oral EMA401 consistently ↓ pain intensity in patients with painful DPN,[122] but the study was terminated early due to animal toxicity data
NRD135S.E1 [Novaremed]	Lyn tyrosine kinase inhibitor; modulates the phosphorylation of Lyn tyrosine kinase, a critical step in the mediation of nerve injury- induced P2X4 receptor upregulation in neuropathic pain[120]	NCT02345291: oral NRD135S.E1 was more effective than placebo in ↓ mean pain intensity at dosage of 40 mg/day but not at 150 mg/day, with secondary and post hoc analyses of pain data showed consistent beneficial effects; headache was the only ADR reported more frequently with NRD.E1 than placebo[120]

Abbreviations: *ADR*, adverse drug reaction; *DPN*, diabetic peripheral neuropathy; *IM*, intramuscular; *RCT*, randomized, controlled trial; ↓, decrease (s/d).

Numerous other drugs are in development to treat painful DPN and under evaluation in phase 2 or 3 RCTs (Table 5).[118,123–134] AT-001, an aldose reductase inhibitor, targets the pathogenesis of neuropathic pain by inhibiting glucose metabolism by the polyol pathway.[123] Other agents generally target the pathogenesis, transmission, activation, or

Table 5 Drugs in Development for Painful Diabetic Peripheral Neuropathy in Phase 2 or 3 Randomized Controlled Trials Currently Underway as Reported in the Clinicaltrials.gov Database

Drug Name/Code [Manufacturer]	Mechanism of Action in DPN	Clinicaltrials.gov Identifier Number: Results or Study Description[118]
Phase 3 RCTs being conducted		
AT-001 [Applied Therapeutics]	Aldose reductase inhibitor; targets the pathogenesis of neuropathic pain by inhibiting glucose metabolism by the polyol pathway[109]	NCT04083339: safety/efficacy of oral AT-001 vs placebo in adults with diabetic cardiomyopathy at high risk of progression to overt heart failure[118]
Phase 2 RCTs being conducted or results not yet available		
BAY-2395840 [Bayer/ Evotec]	BDKRB1 antagonist; ↓ microglia activation by BDKRB1 in diabetic pain[100]	NCT05219812: safety/efficacy of oral BAY-2395840 vs placebo in diabetic nerve pain[118]
Cannabidiol (PG-DN -20WS) [Pure Green]	TRPV1 antagonist; ↓ TRPV1 modulation of neuropathic pain[101]	NCT04679545: safety/efficacy of sublingual cannabidiol 20 mg vs placebo in DPN pain[118]
Desmetramadol (O-DMST, Omnitram) [Syntrix Biosystems]	MOR agonist/SNRI; MOR activation and ↓ norepinephrine reuptake[102]	NCT03664921: safety/efficacy of oral desmetramadol 30 mg/day vs placebo in painful DPN[118]
Elismetrep (MT 8554) [Mitsubishi Tanabe]	TRPM8 inhibitor; ↓ amplification of neuropathic pain[103]	NCT05123196: efficacy/safety/PK of oral elismetrep vs placebo in DPN pain[118]

(*Continued*)

Table 5 (Continued).

Drug Name/Code [Manufacturer]	Mechanism of Action in DPN	Clinicaltrials.gov Identifier Number: Results or Study Description[118]
LX-9211 [LexiconP/ BMS]	AAK1 inhibitor; ↓ transmission of neuropathic pain[104]	NCT04455633: efficacy/safety/PK of oral LX-9211 in DPN pain[118]
LY-3526318 [Eli Lilly]	TRPA1 antagonist; ↓ activation of sensory neurons[105]	NCT05177094: safety/efficacy of oral LY-3526318 in DPN pain[118]
LY-3016859 [Eli Lilly]	Monoclonal antibody that binds epiregulin and TGR-α; ↓ pain expression[106,107]	NCT04476108: safety/efficacy of intravenous LY-3016859 in DPN pain[118]
MEDI-7352 [AstraZeneca]	Bi-specific fusion protein that binds NGF to TNFR2; ↓ NGF levels[108]	NCT03755934: efficacy/ safety of subcutaneous MEDI-7352 vs placebo in chronic DPN pain[118]
Ricolinostat (ACY-1215) [Regency; Acetylon; Celgene]	Selective HDAC6 inhibitor; ↓ removal of acetyl groups from proteins; stabilizes nerve supply network[110]	NCT03176472: safety/efficacy of oral ricolinostat in DPN pain[118]
Naltrexone (low-dose)	μ-opioid and κ-opioid receptor antagonist (glial cell modulator); ↓ activation of microglial cells[111]	NCT04678895: low-dose naltrexone for the treatment of painful diabetic neuropathy, a small, randomized, double-blind, placebo-controlled crossover trial[118]

Abbreviations: *AAKI*, adaptor associated kinase 1; *BDKRB1*, bradykinin receptor B1; *DPN*, diabetic peripheral neuropathy; *HDAC6*, histone deacetylase 6; *MOR*, μ-opioid receptor; *NGF*, nerve growth factor; *PK*, pharmacokinetics; *RCT*, randomized controlled trial; *SNRI*, serotonin/norepinephrine reuptake inhibitor; *TGR-α*, transforming growth factor-α; *TNFR2*, tumor necrosis factor receptor-2; *TRPM8*, transient receptor potential melastatin 8; *TRPA1*, transient receptor potential A1; *TRPV1*, transient receptor potential vanilloid type 1; ↓, decreases/prevents.

expression of neuropathic pain by blocking or binding to a specific pain-related receptor (eg, bradykinin receptor B,[124] TRPV1,[125] μ-opioid receptor,[126] transient receptor potential melastatin 8,[127] adaptor associated kinase 1,[128] transient receptor potential A1,[129] transforming growth factor-α,[131] or tumor necrosis factor receptor-2.[132] The selective histone deacetylase 6 (HDAC6) inhibitor ricolinostat acts by stabilizing the nerve supply network.[133] Low-dose naltrexone acts by suppressing microglial cell activation in the CNS,[134] and was shown to have similar efficacy but better tolerability than amitriptyline in a 6-week crossover trial in 67 patients with painful DPN.[135] A further study comparing low-dose naltrexone with placebo is underway.[118]

Electrical Stimulation Devices

In addition to implantable SCS devices, several noninvasive electrical stimulation devices have been evaluated in RCTs in patients with painful DPN. Table 6 summarizes their effectiveness in treating painful DPN as reported in phase 3 or 4 RCTs and meta-analyses.[136–139] Electrical stimulation devices are thought to produce analgesic effects in painful DPN by improving the microcirculation associated with neuropathy, thereby reducing symptoms and improving nerve function, stimulating cutaneous afferent fibers and limiting the central transmission of pain signals via nociceptive inhibition at the presynaptic level in the dorsal horn.[136,140]

To date, consistent, albeit generally small and transient, benefits have been shown only with transcutaneous electrical nerve stimulation (TENS). The use of electrical stimulation devices is generally well tolerated, without the DDIs and ADRs associated with the use of oral pharmacological treatments. Study results have been limited to small patient populations and significant effects in placebo groups.[136,140]

Unmet Needs in the Treatment of Painful DPN

Unmet needs with regard to the treatment of painful DPN can be categorized at three levels, which should form the basis for a personalized approach to the management of this frequently debilitating and progressive condition.[10,20,141]

Table 6 Effectiveness of Electrical Stimulation Devices in the Treatment of Painful Diabetic Peripheral Neuropathy in Phase 3 or 4 Randomized Clinical Trials or Meta-Analyses

Device	Effectiveness
Transcutaneous electrical nerve stimulation (TENS)	Meta-analysis of 5 RCTs of TENS treatment for 2–12 weeks: TENS significantly ↓ mean pain scores vs placebo (BGD–0.44 points; 95% CI: –0.79 to – 0.09)[136]
	Meta-analysis of 5 RCTs of TENS treatment for 2, 4 or 6 weeks: TENS significantly ↓ mean pain scores vs placebo (BGD –0.54 points; 95% CI: –1.02 to –0.06)[136]
	Meta-analysis of 2 RCTs of TENS treatment for 12 weeks: TENS did not significantly ↓ mean pain scores vs placebo (BGD –0.4; 95% CI: –1.10 to 0.16)[136]
Pulsed electromagnetic field	Meta-analysis of 4 RCTs: pulsed electromagnetic field therapy did not significantly ↓ mean pain scores vs placebo (BGD –0.69; 95% CI –1.86 to 0.48)[136]
Frequency-modulated electromagnetic neural stimulation (FREMS)	In a 51-week RCT, three series of FREMS treatment, each series consisting of 10 FREMS sessions administered within 3 weeks every 3 months, did not change NCV (primary endpoint); pain scores significantly ↓ but only during the first 3 months of treatment[137]
	In a crossover RCT, a series of 10 FREMS sessions significantly ↓ daytime and night-time pain scores, sensory and vibration perception, and NCV vs baseline at the end of series, and ↑ health-related QoL scores at follow-up at 4 months; no significant changes in any endpoint were shown with placebo[138]
Anodyne monochromatic infrared photo energy (MIRE)	In a 3-month RCT, once-daily anodyne MIRE therapy was no more effective than sham therapy in improving neuropathy-related QoL scores, pain scores, NCV, and sensory and vibration perception[139]

Abbreviations: *BGD*, between-group difference; *NCV*, nerve conduction velocity; *QoL* quality of life; *RCT*, randomized controlled trial; ↑, increased; ↓ decreased.

- In the absence of any approved effective pharmacological disease-modifying therapy, preventative approaches that delay the development of nerve damage and slow disease progression would be highly beneficial. This should involve educating healthcare professionals and patients about diabetes and DPN, implementing effective targeted screening strategies as part of routine clinical practice, encouraging patients to undertake lifestyle modifications, and optimizing the use of medications. Early diagnosis and timely treatment of painful DPN is vital to prevent progression, avoid the development of advanced complications, and improve HR-QoL, economic and other outcomes.
- A vital goal should be to develop pathogenetically oriented disease-modifying treatments designed to prevent/reverse the nerve damage associated with painful DPN.
- Since approximately 30% of patients with DPN experience painful episodes, optimal approaches to minimize pain are an essential goal for a relevant proportion of patients.

Disease Prevention

To ensure that DPN is diagnosed and managed as early as possible, screening for DPN should be conducted regularly and routinely in all diabetic patients (Table 1).[18–20] Healthcare professionals should be educated in patient assessment, which involves obtaining a careful clinical history and conducting a targeted physical exam. A patient-centered approach may require referral to specialists in other disciplines including but not limited to endocrinology, pain management, and podiatry. Patients should also be educated about the risk of DPN and its early signs and symptoms.

Management decisions pertaining to DPN prevention should be individualized to the patient's needs. These include appropriate foot care and a range of initiatives to reduce DPN risk factors. To prevent the onset of DPN in patients with T1D, intensive glucose control should be implemented when possible.[18–20] In patients with T2D, controlling features of the metabolic syndrome, such as hyperglycemia, hypertension and hyperlipidemia, together with educational strategies to improve lifestyle measures, including weight loss, increased physical activity, and smoking cessation, are recommended

to prevent DPN. Education about lifestyle interventions is also important to prevent DPN in individuals with prediabetes/metabolic syndrome.[18–20]

Disease Modification

In the US, no pharmacological treatment is currently approved to modify the progression of DPN.

The loss of ENF density over time in patients with DPN is a natural consequence of disease progression and a major contributor to diabetic foot ulcers.[142] Preliminary evidence suggests that the capsaicin 8% topical system may modify peripheral neuropathic pain, as it has been shown to regenerate and restore sensory nerve fibers.[68–71] In a RCT assessing the mechanism of pain relief of the capsaicin 8% topical system, skin biopsies at 3 months in patients with painful DPN showed a significant increase in the density of intra-ENFs and sub-ENFs in those treated with the capsaicin 8% topical system plus SOC (n = 25) but not in those receiving SOC alone (n = 12).[68] Patients with painful DPN who had pain reduction at 3 months with the capsaicin 8% topical system plus SoC (n = 18) had correlating increases in nerve fiber density, whereas non-responders without pain reduction (n = 7) did not. Importantly, the increase in ENF density did not correlate with an increase in pain, suggesting that nerve fibers were restored in a healthier state compared with baseline. Although the increases in vasodilation and improvements in warm perception sensory testing observed with the capsaicin 8% topical system require further investigation, they may signal restoration of sensory function which, in turn, can lead to improvement in the overall health of the diabetic foot.[68] In similar exploratory studies, patients with peripheral neuropathic pain (n = 23),[69] painful chemotherapy-induced peripheral neuropathy (CIPN; n = 16),[70] or non-freezing cold injury (n = 16),[71] were treated with a single application of the capsaicin 8% topical system. Heat-evoked neurogenic vasodilatation showed improvement in half of the patients with peripheral neuropathic pain 4 weeks after application, indicating that nerve fibers had regenerated.[69] Intra- and sub-ENF regeneration and restoration were also shown when skin biopsies were performed 3 months post-application in patients with painful CIPN[70] or non-freezing cold injury.[71] These studies suggest that the benefits of high-concentration capsaicin may extend beyond pain relief for patients with painful DPN, although more research is needed to better understand the impact of capsaicin on the diabetic foot.

Epalrestat (an aldose reductase inhibitor which targets activation of the polyol pathway to reduce glucose metabolism) and actovegin (a poly adenosine diphosphate-ribose polymerase inhibitor with pleiotropic neuroprotective and metabolic effects) are licensed to treat DPN in various countries outside of the US based on limited evidence of their efficacy in modifying neurological signs and symptoms.[143]

Two nutraceuticals, α-lipoic acid and benfotiamine, are also licensed to treat DPN in various countries outside of the US[143] and, according to the ADA, may be used as a pathogenetic adjunct to established pharmacological and non-pharmacological interventions for the management of persistent neuropathic symptoms.[20] Of the nutraceuticals that have been evaluated in phase 3 RCTs (Table 7),[144–150] α-lipoic acid and benfotiamine have the best evidence of neuropathic benefits. α-Lipoic acid, a naturally occurring fatty acid, provides neuroprotective effects by acting as an antioxidant.[144,145] Benfotiamine, a fat-soluble derivative of thiamine, acts by inhibiting the formation of advanced glycation end products,[146] thereby improving neuropathic symptoms in patients with DPN.[147,151] These nutraceuticals are well tolerated, with adverse event profiles similar to those with placebo.

Supplementation with vitamin B, vitamin D, and magnesium should currently be limited to patients with proven deficiencies to help prevent the worsening of DPN and other diabetes-related disorders.[20] Additional evidence is needed before the use of other nutraceuticals (eg, vitamin E, acetyl-L-carnitine, polyunsaturated fatty acids) can be recommended to modify the pathogenesis of DPN.

Pain Management

Overall, it is estimated that more than half of patients with T2D develop signs and symptoms of peripheral neuropathy during their lifetime, with rates of 20–30% in newly diagnosed and early-stage (first few years) disease.[20] Neuropathic pain is a cardinal symptom of DPN and is often severe, poorly diagnosed and difficult to treat.[20,152] From the patient's perspective, painful DPN has a marked negative impact on daily functioning (sleeping, walking, driving, exercising, working, and performing other daily activities) and HR-QoL which, in turn, increases the social and economic burden of the disease.[20,152]

Table 7 Mechanism of Action and Efficacy of Nutraceuticals in Treating Diabetic Peripheral Neuropathy in Phase 3 Randomized Controlled Trials

Nutraceutical	MoA in DPN	Efficacy in RCTs
α-Lipoic acid	↓ oxidative stress which prevents neuronal damage, modulates protein levels, and ↑ levels of neurotransmitters and anti-oxidants[144]	Intravenous and/or oral α-lipoic acid × 3 weeks to 4 years ↓ neuropathic signs, symptoms, and deficits in patients with symptomatic or asymptomatic DPN[145]
Benfotiamine (thiamine prodrug)	Inhibits the formation of advanced glycation end products, which prevents macro- and microvascular endothelial dysfunction in patients with diabetes[146]	Oral benfotiamine 600 mg/day × 6 weeks improved neuropathic symptoms[147]
Complex of methylfolate, methylcobalamin, and pyridoxal (metabolically active B vitamins; Metanx®)	Prevents deficiencies in folic acid and vitamins B_6 and B_{12}; ↓ homocysteine levels[148]	Oral once-daily complex of methylfolate 3mg + methylcobalamin 2 mg + pyridoxal 35 mg × 6 months consistently provided symptomatic relief, with clinically significant improvement in neuropathic symptoms[149]
Mixed tocotrienols (members of the vitamin E family)	↓ oxidative stress which modulates the neuropathy pathway, and provides anti-inflammatory effects[150]	Mixed tocotrienols 400 mg/day × 1 year did not improve overall patient-reported neuropathic symptoms or sensory nerve conduction[150]

Abbreviations: *DPN*, diabetic peripheral neuropathy, *MoA*, mechanism of action; *RCTs*, randomized controlled trials; ↓, decreases; ↑, increases.

Successful treatment of painful DPN requires a personalized approach balancing pain relief with improvements in daily functioning and HR-QoL. To achieve this, it is likely that more sophisticated tools beyond simple pain scores (eg, VAS or NPRS) will provide better feedback about neuropathic symptoms.[20] The Neuropathy Total Symptom Score-6 evaluates the frequency and intensity of individual neuropathy sensory symptoms frequently identified by DPN patients (ie, numbness and/or insensitivity, prickling and/or tingling sensation, burning sensation, aching pain and/or tightness, sharp, shooting, lancinating pain, and allodynia and/or hyperalgesia).[153] The modified Toronto Clinical Neuropathy Score evaluates the presence of symptoms (ie, foot pain, numbness, tingling, weakness, ataxia and upper limb symptoms) and clinical signs (ie sensory pinprick, temperature, light touch, vibration, and position sense) associated with DPN.[154]

At present, there is a significant need for more effective and better-tolerated treatment options for painful DPN, as many affected patients continue to experience pain despite treatment. While initial responses to current guideline-recommended oral treatments (eg, antiepileptics and antidepressants) may be good, pharmacological tolerance often occurs and higher dosages may be needed to achieve the same level of pain relief. This increases the likelihood of ADRs.[20,141] Such patients may benefit from treatment choices that are better tolerated, such as lower-dose combination therapy (pharmacological and non-pharmacological), topical agents (eg, capsaicin 8% topical systems), nutraceuticals, and non-pharmacological approaches (eg, nerve stimulation).

Discussion

Despite multiple FDA-approved, guideline-recommended, and other available options to treat painful DPN, many patients continue to experience uncontrolled pain. An individualized and comprehensive approach, considering pharmacological, neuromodulatory, and non-pharmacological therapies, is often necessary to improve pain outcomes. Since complete resolution of symptoms is not always achievable, patients, caregivers and healthcare providers should have realistic expectations regarding the efficacy of available treatment options, understand that pain reduction (not necessarily pain elimination) and improved HR-QoL are the goals of therapy and that it may be necessary to try a series of treatments in order to identify the most beneficial option.[18]

Current US evidence-based guidelines on the treatment of painful DPN focus primarily on pharmacological treatments.[18–20] Careful consideration is required when selecting pharmacological agents as affected patients are generally already receiving polypharmacy to treat diabetes and other health conditions, which increases the risk of

DDIs and ADRs. Diabetic patients in the US take an average of 5.9 medications,[155] with an even higher pill burden for those with painful DPN (83% take one or more pain medications solely to treat this condition).[156] Treatment selection should consider the potential for systemic ADRs and DDIs, contraindications and precautions in special populations, the presence of comorbid mood and sleep disorders supporting the use of one option over another, costs, and individual patient preferences.[157]

Of the oral drug classes regarded as first-line therapy in US guidelines and recommendations,[18–21] TCAs (eg, amitriptyline, nortriptyline, imipramine), SNRIs (eg, duloxetine, venlafaxine, desvenlafaxine), gabapentinoids (eg, pregabalin, gabapentin), and sodium channel blockers (eg, carbamazepine, oxcarbazepine, lamotrigine) are considered to have comparable efficacy with limited data to support one therapeutic intervention over another.[18] Use of oral opioids, including those with a dual MoA such as tapentadol ER, is not recommended. Among topical pharmacological options (which include lignocaine and glyceryl trinitrate), the capsaicin 8% topical system has the most robust evidence and is the only topical agent currently approved by the FDA to treat painful DPN. The capsaicin 8% topical system can be used in combination with oral pharmacotherapy and is not associated with any contraindications, DDIs, systemic ADRs, or need for dose titration/adjustment.

In patients with painful DPN refractory to conventional treatment, neuromodulation with low- or high-frequency SCS is an FDA-approved option.[20,21] Intrathecal drug delivery may also improve pain management.[158,159] Although its FDA approval is not specific to painful DPN, intrathecal drug delivery using either ziconotide or morphine is recommended and is FDA-approved for chronic neuropathic pain. Use of these neuromodulating options requires careful consideration of individual patient characteristics (eg, pain location and intensity, stage of progression of DPN, response to previous pain therapies, comorbid medical conditions, and concomitant drug treatment), as well as their advantages and disadvantages from a patient-centric perspective.[158,159]

Future clinical studies in patients with painful DPN are needed to address gaps in current knowledge and provide guidance as to which patients will best respond to various interventions. A better understanding of the pathological mechanistic changes that occur in patients with painful DPN would not only lead to newer therapeutic targets but also would facilitate the discovery of biomarkers to identify responders versus non-responders. To support the use of one agent over another, comparative studies are needed to evaluate the efficacy of two or more active interventions (including oral medications, topical treatments, non-traditional therapies, non-pharmacologic interventions, and combination therapy). The long-term effectiveness of interventions on pain, as well as on other outcomes (eg, HR-QoL, patient functioning, mood, sleep) should be investigated.

Conclusion

Painful DPN, a highly prevalent and disabling complication of diabetes, impacts negatively on patient function and HR-QoL and is associated with significant morbidity, mortality, and healthcare costs. A variety of pharmacological and non-pharmacological options are available to treat painful DPN which may be combined as part of an individualized, comprehensive pain management plan. Healthcare providers are encouraged to increase their familiarity with the available options and to incorporate a comprehensive understanding of the clinical evidence substantiating their efficacy. In recognition of the needs of this fast-growing segment of the diabetic population, research into painful DPN has become increasingly active. Numerous studies are underway evaluating drugs with novel mechanisms of action and various noninvasive electrical stimulation devices. Beyond providing more effective pain relief, identifying disease-modifying interventions that can prevent or reverse the nerve damage associated with DPN should be a research priority. Pharmacoeconomic evaluations should be conducted to determine whether the enormous healthcare burden associated with painful DPN might be mitigated to some extent through the use of modern treatments with greater efficacy and improved tolerability relative to conventional oral agents, despite their higher acquisition costs.

Acknowledgments

The authors did not receive compensation or funding for the development and writing of the manuscript. Writing assistance was provided by Katherine Ann Lyseng-Williamson and Kerry Dechant, ISMPP CMPP™, on behalf of Content Ed Net and was funded by Averitas Pharma USA.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Funded by Averitas Pharma USA.

Disclosure

Jeremy A Adler and Theresa Mallick-Searle are members of the Speakers Bureau for Averitas Pharma USA. Dr Jeremy A Adler also reports personal fees from Collegium Pharma/BioDelivery Biosciences, Averitas Pharm, Neuromatrix, and Redhill Pharma, outside the submitted work. The authors report no other conflicts of interest in this work.

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