

EVIDENCE-BASED REVIEW

Update of evidence-based interventional pain medicine according to clinical diagnoses

4. Painful diabetic polyneuropathy

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Abstract

Introduction: Pain as a symptom of diabetic polyneuropathy (DPN) significantly lowers quality of life, increases mortality and is the main reason for patients with diabetes to seek medical attention. The number of people suffering from painful diabetic polyneuropathy (PDPN) has increased significantly over the past decades. **Methods:** The literature on the diagnosis and treatment of diabetic polyneuropathy was retrieved and summarized.

Results: The etiology of PDPN is complex, with primary damage to peripheral nociceptors and altered spinal and supra-spinal modulation. To achieve better patient outcomes, the mode of diagnosis and treatment of PDPN evolves toward more precise pain-phenotyping and genotyping based on patient-specific characteristics, new diagnostic tools, and prior response to pharmacological treatments. According to the Toronto Diabetic Neuropathy Expert Group, a presumptive diagnosis of “probable PDPN” is sufficient to initiate treatment. Proper control of plasma glucose levels, and prevention of risk factors are essential in the treatment of PDPN. Mechanism-based pharmacological treatment should be initiated as early as possible. If symptomatic pharmacologic treatment fails, spinal cord stimulation (SCS) should be considered. In isolated cases, where symptomatic pharmacologic treatment and SCS are unsuccessful or cannot be used, sympathetic lumbar chain neurolysis and/or radiofrequency ablation (SLCN/SLCRF), dorsal root ganglion stimulation (DRGs) or posterior tibial nerve stimulation (PTNS) may be considered. However, it is recommended that these treatments be applied only in a study setting in a center of expertise.

Conclusions: The diagnosis of PDPN evolves toward pheno- and genotyping and treatment should be mechanism-based.

KEY WORDS

anti-neuropathic drugs, evidence-based medicine, neuropathic pain, painful diabetic polyneuropathy, spinal cord stimulation

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INTRODUCTION

This narrative review-update on painful diabetic polyneuropathy (PDPN) is part of the series “Update of Evidence-based Interventional Pain Medicine according to clinical diagnoses.” The first review of this guideline series was published by Pluijms et al. in 2011.¹ This article adds a review of the literature from 2010 through 2023.

According to the ICD-11 systematics, PDPN is classified as chronic neuropathic pain (first level) of peripheral origin (second level) caused by polyneuropathy (third level).^{2,3} The definition of PDPN comes from an amalgamation of the definitions of chronic (neuropathic) pain and diabetic polyneuropathy.^{4–6} Consequently, PDPN can be defined as the clinical presence of symptoms and/or signs, including pain, of dysfunction in the somatosensory system attributed to diabetes mellitus.^{6,7} Recent insights into the onset of chronification of neuropathic pain in diabetes show influences of both peripheral and central mechanisms.^{6,8} Furthermore, neuropathic pain has been reported to occur between 4% and upwards of 40% in at a prediabetic stage.^{9,10} These two findings raise the question whether PDPN should be seen as a disease entity “in its own right” or exclusively as part of a diabetic peripheral polyneuropathy spectrum.¹¹ For this article, the latter view was adapted.

METHODOLOGY

This narrative review is based on the article “Diabetic polyneuropathy” published in 2011.¹ In 2015, an independent company, Kleijnen Systematic Reviews (KSR), performed a systematic review of the literature for the period 2009–2015, based on existing systematic reviews (SRs) and randomized controlled trials (RCTs).^{12,13} For the current article an updated search was conducted for the period 2015–2022, using “diabetic neuropathies” and “painful” and “diagnosis” associated with individual interventional pain management techniques, in this case “spinal cord stimulation” or “sympathetic” Additionally, the authors could select relevant missing articles based on PubMed, Google, and reference list searches.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Depending on the diagnostic criteria, estimates on the prevalence of PDPN ranges from 8% to 26%.^{6,10,11,14–17} Pain as a symptom of diabetic polyneuropathy (DPN) significantly lowers quality of life, increases 10-year mortality and is the main reason for patients to seek medical attention.^{6,10,11,18} As the prevalence of diabetes mellitus has increased dramatically worldwide over the

past decade, the number of people suffering from PDPN has increased commensurately.¹⁹

Although uncommon, poor glycemic control in type 1 diabetes can lead to PDPN within a few months.²⁰ After re-stabilization with strict glucose control, PDPN seems to be reversible in type 1 diabetes.²¹ In type 2 diabetes, optimization of glucose control does not seem to reduce pain.²² Chronification of PDPN is therefore more common in type 2 DM.^{21,22}

DPN develops in about 50% of all people with diabetes, about half of whom develop neuropathic pain. Why half develop pain and the other half do not, is not clear but almost certainly involves pathoanatomical and physiological differences as well as genetic and psychosocial reasons, similar to other chronic pain conditions.^{16,21} Cross-sectional studies shown that there are a few differences in risk factors between DPN and PDPN. The most consistent objective finding is that PDPN is associated with more profound sensory loss than DPN.⁴ Risk factors for developing PDPN include: (1) longer disease duration; (2) female gender; (3) dyslipidemia; (4) existence of other complications of DM; (5) obesity; (6) older age; (7) smoking; (8) high alcohol intake; (9) HbA1C levels; (10) sensory phenotype and severity of neuropathy; (11) genotype (tetrodotoxin sensitive sodium channels NaV1.3, NaV 1.7, NaV 1.8, and NaV1.9, elevated levels of miR-146a, miR-98, and miR-155); (12) increased serum levels of TNF-alpha and other inflammatory cytokines and chemokines; (13) increased methylglyoxal (MGO) (activation TRPA1 and NaV1.8); (14) decreased serum Vitamin D; (15) decreased blood flow (increased hypoxia-inducible factor 1-alpha (HIF 1 α) and von Willebrand factor (vWF)).^{6,21,23–27}

Although the complex pathogenesis of PDPN is not fully understood, different pathophysiological mechanisms have been hypothesized (Figures 1 and 2). Hyperglycemia has traditionally been considered a major determinant of diabetic neuropathy. A complex interaction of genetic, sensory phenotypic, psychological, and metabolic factors such as: (1) promotion of polyol metabolism, (2) promotion of production of advanced glycation end products (AGEs), (3) increase in free radicals, (4) decrease in NO levels, and (5) promotion of protein kinase C (PKC) activity, are postulated to play a crucial role.^{28,29} Preclinical studies on the pathogenesis of PDPN show that oxidative stress is consistently associated with the release of inflammatory cytokines (ie, TNF- α and IL-1 β production after p38-MAPK and PKC pathway activation). Neuropathic pain can occur because sorbitol accumulation in nerve cells causes endothelial changes, which in turn leads to a decrease in microvascular integrity at the dorsal horn and terminal axon. Damage occurs at the level of peripheral axons, associated Schwann cells, and the neuron perikarya in dorsal root ganglia (DRG). Microvascular alterations, such as structural and functional abnormalities of the

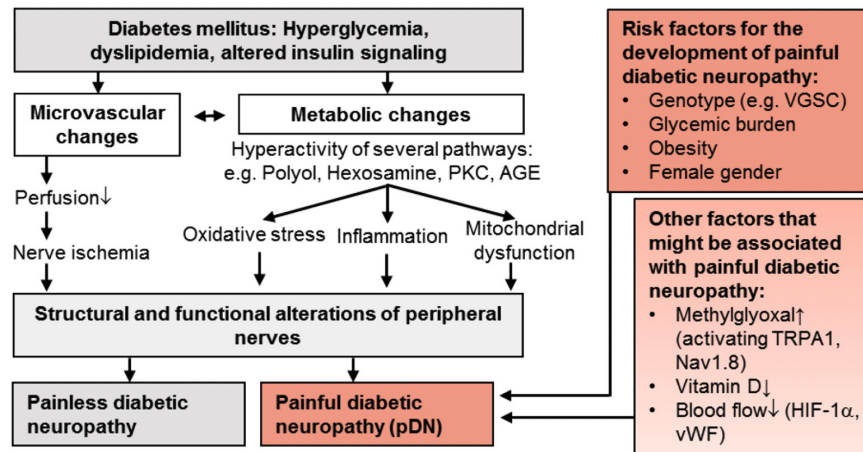


FIGURE 1 Pathophysiological mechanisms leading to painful diabetic polyneuropathy (PDPN).⁶ AGE, advanced glycation end-products; HIF-1 α , hypoxia inducible factor 1 α ; Nav1.8, voltage-gated sodium ion channel subtype 1.8; PKC, Protein kinase C; TRPA1, transient receptor potential channel ankyrin 1; VGSC, voltage-gated sodium channels; vWF, von Willebrand factor.

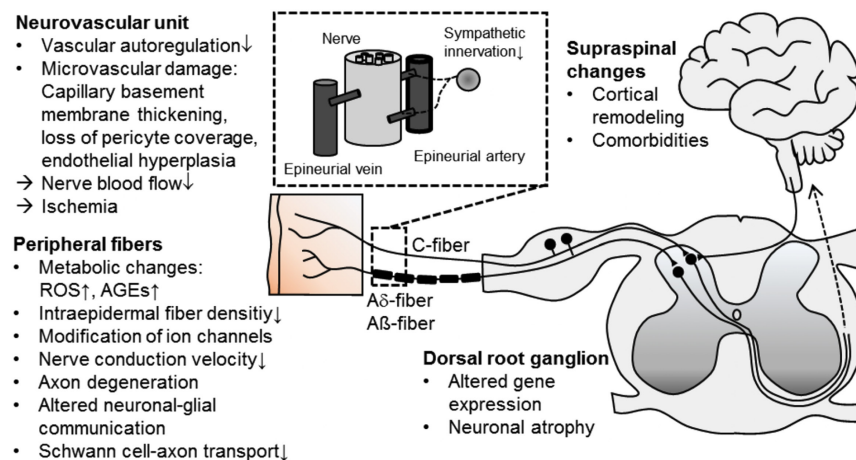


FIGURE 2 DM induced alterations in the sensory nervous system contributing to painful diabetic polyneuropathy (PDPN).⁶ AGEs, advanced glycation end products; ROS, reactive oxygen species.

vasa nervorum (in the skin) and altered regulation of peripheral blood flow (involving HIF-1 α and vWF) are associated with PDPN.^{6,21} Metabolic derangements, such as toxicity caused by elevated levels of triglycerides, cholesterol, and other compounds may also contribute to nerve damage, though the precise relationship is still being elucidated.³⁰ Diabetes structurally and functionally affects spinal, somatomotor, limbic (increased cerebral blood flow in the anterior cingulate), thalamic, ascending, and descending modulatory systems as well as higher brain centers (somatomotor cortex and insula atrophy).^{11,31,32} Peripheral neurons are damaged and show altered expression of voltage-gated sodium, potassium, and calcium channels.³³ Greater corneal nerve loss at the inferior whorl has also been observed in patients with painful compared to painless DPN.³⁴ In summary, recent research shows that the entire sensory nervous system is targeted by diabetes, leading to (P)DPN.

DIAGNOSIS

History

From a clinical point of view, a thorough history and physical examination are crucial to associate the patient's pain to an abnormality of the somatosensory nervous system, as well as to distinguish it from other pain components (nociceptive and nociplastic).^{6,35} Among the various neuropathies that can complicate diabetes, distal symmetric polyneuropathy is the most common, accounting for greater than 75% of cases.¹⁶ Motor, autonomic, inflammatory neuropathies are also seen in patients with diabetes. **Figure 3** shows other DM-related neuropathies which can also cause pain.

The symptoms of (P)DPN usually occur first in the feet and gradually spread, which can be explained by the pathophysiological phenomena in which the

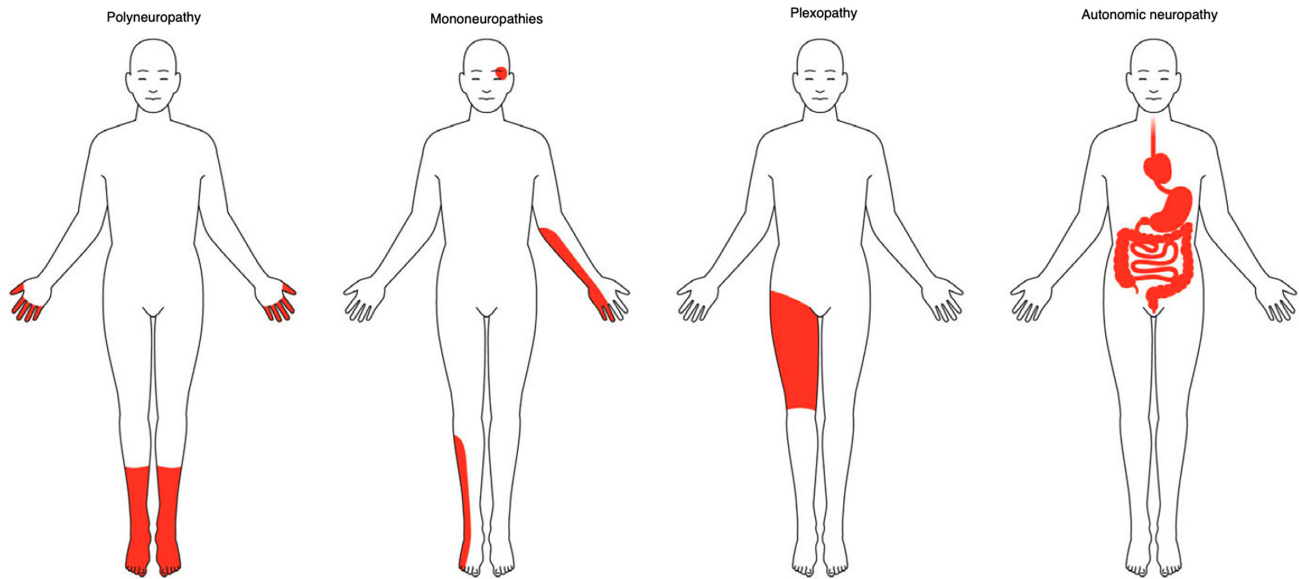


FIGURE 3 DM-related neuropathies.⁴

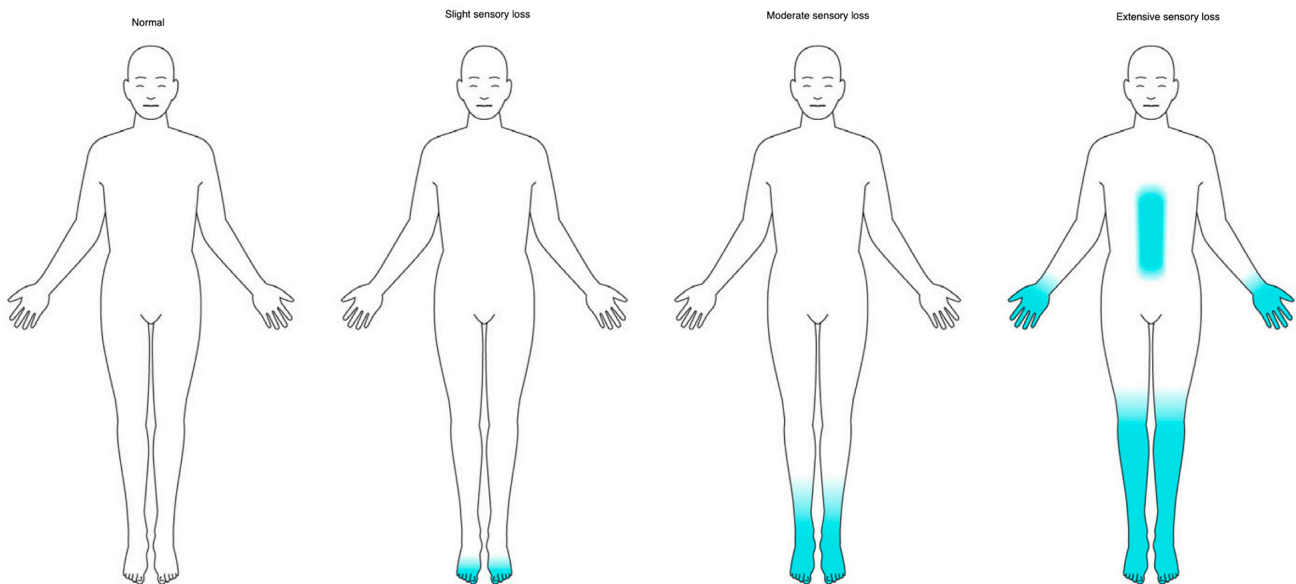


FIGURE 4 Course of PDN with increase in severity.⁴

longest, most vulnerable nerves are damaged first. This is also called length-dependent diabetic polyneuropathy (LDDP). This is followed by shorter fibers innervating the extremities, and in extreme situations, the trunk can also be affected (Figure 4).

The Toronto Diabetic Neuropathy Expert Group has defined minimal diagnostic criteria for DPN and PDPN (Figure 5).³⁶ Patients suffering from PDPN typically complain of progressive unpleasant sensory sensations that are most pronounced at night. These sensations include tingling (paresthesias), burning pain, shooting pains (like “electric shocks”) in the legs (and later in the hands / arms), “stabbing or knife-like” pains, evoked pain, often with clothing and bedding (allodynia),

sensations of heat or cold in the feet, persistent aching sensations in the feet, and spasmodic feelings in the legs. Pain exacerbated by walking is often described as “walking barefoot on marbles” or “walking barefoot on hot sand,” attacks of shooting pain also occur.¹¹ If the pain is tolerable, variations in sensitivity can often be identified making the diagnosis of diabetic polyneuropathy likely, especially when this is associated with trophic disorders and poor wound healing. Recovery of sensory disturbances cannot be expected once loss of small fibers has occurred.^{37,38}

Various general questionnaires have been developed for the qualification and quantification of neuropathic pain, including The Neuropathic Pain Questionnaire, The

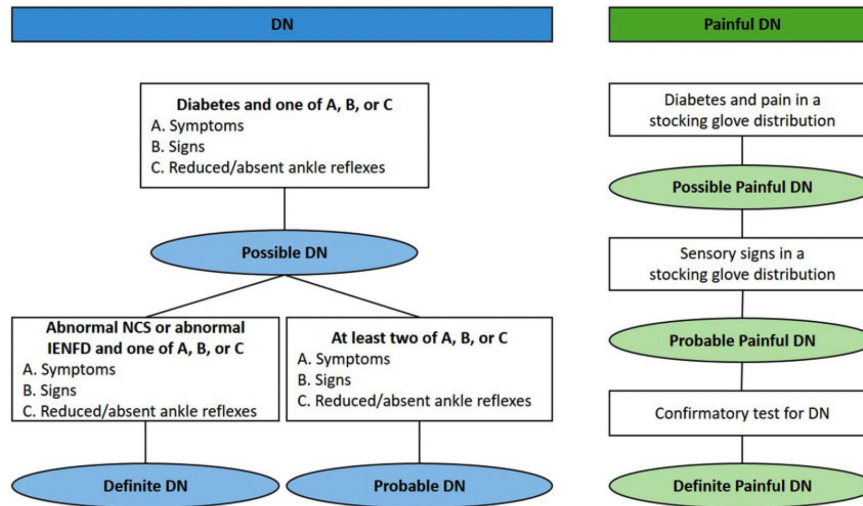


FIGURE 5 Hierarchical structure of diagnosing PDPN according to The Toronto Diabetic Neuropathy Expert Group.^{16,36} DN, diabetic neuropathy. (1) Possible DPN: symptoms or signs of DPN. (2) probable DPN: a combination of symptoms and signs including two or more of the following: neuropathic symptoms, decreased distal sensation or decreased/absent ankle tendon reflexes. (3) confirmed DPN: an abnormality of nerve conduction and symptom(s) or sign(s) of neuropathy; if nerve conduction is normal, an established attribute measure of small fiber neuropathy might be used. (4) subclinical DPN: absence of signs/symptoms with concomitant abnormal nerve conduction studies (NCS) or an established attribute of small fiber neuropathy.

McGill Pain Questionnaire, The Brief Pain Inventory, Pain Detect, The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique 4 questionnaire (DN4), and the Neuropathic Pain Symptom Inventory.^{4,39} The sensitivity and specificity of these screening tools are around 80–85% but were validated before formalization of the category of nociplastic pain which shares many overlapping variables. Such questionnaires can be used as screening tools for neuropathic pain, but since they can miss up to 20% of cases of neuropathic pain, they cannot be used to exclude PDPN and therefore cannot replace a comprehensive history and physical examination.^{4,6} In instrument validation studies, physician designation is always considered the reference standard.

Physical examination

Proper neurological evaluation is important as part of the additional clinical examination. The neurological examination should include: (1) examination of all qualities of somatosensory function, taking symmetry and a distal-proximal gradient into account; (2) reflexes; and (3) muscle strength.⁴ Acceptable reliability for the detection of nerve fiber deterioration was found with the vibration perception threshold (VPT) (performed with a biothesiometer, neurothesiometer, or maxivibrometer), ankle reflexes, and the four-site monofilament test.⁴⁰ A 128 Hz tuning fork is not considered a suitable instrument for screening and monitoring of (P)DPN because of the wide range in reported reliability and only moderate diagnostic capability.⁴⁰

Additional tests

In general, additional tests are not necessary in the diagnosis of PDPN. The level “probable PDPN” (history and physical examination) according to the Toronto Diabetic Neuropathy Expert Group is considered sufficient to initiate treatment.^{4,6}

However, in science, additional tests are often used for a better understanding of the pathophysiology of (P)DPN or to help develop diagnostic and/or prognostic tools. Potential candidates for additional tests are briefly elaborated below.

Nerve conduction and direct nerve imaging

Several diagnostic tests are available for (P)DPN and neuropathic pain in general.

These tests include skin biopsies with quantification of intra-epidermal and dermal nerve fiber density (IENFD), measurements of small nerve fibers in the cornea using corneal confocal microscopy (CCM), and assessment of neurogenic flare with laser Doppler as a measure of small nerve fiber (C-fiber) function. CCM shows greater corneal nerve loss at the inferior whorl in patients with painful compared to painless DPN.³⁴ There are also assessments of sudomotor function and quantitative sensory tests (QST). With QST, thermal and mechanical detection of pain thresholds, vibration thresholds, dynamic mechanical allodynia, wind-up ratio, and pressure pain threshold can be investigated.¹⁶ These different tests measure the function of A β , A δ (cold sensing), and C (heat sensing) fibers. It has been

suggested that alterations in the processing of nociceptive signals occur in the pain modulatory system of the central nervous system, resulting in decreased inhibition, and increased amplification in patients with PDPN. This can be evaluated with dynamic QST measures (such as conditioned pain modulation and temporal and spatial summation).³⁸ In QST, mechanical hyperalgesia and temporal summation may indicate central sensitization, while heat hyperalgesia suggests a predominance of peripheral sensitization.⁴¹ Although highly subjective and time consuming, QST may be particularly useful in patients suspected of having (P) DPN with normal nerve conduction studies (NCS) or when definitive quantitative structural assessment of small nerve fibers (skin biopsy or CCM) cannot be performed.³⁹ QST can help cluster phenotypes of neuropathic pain conditions and has been used to predict response to different treatments.^{42,43}

Small fiber impairment precedes large fiber impairment, suggesting that small fiber testing, by skin biopsy, could be appropriate for early screening and treatment. Although most studies have demonstrated a relationship between pain and morphological and functional markers IENFD, some have not.³¹ Moreover, whether loss of intraepidermal nerve fibers merely serves as a biomarker for disease burden or can actually cause pain remains unknown. Due to a lack of robust evidence on their added value, QST, CCM, and skin biopsy are not yet recommended for routine use by international guidelines but only for consideration in patients in whom the diagnosis of (P)DPN is unclear.^{21,44}

Biomarkers

Biomarkers may be used to facilitate diagnosis, as surrogate outcome measures, and to identify treatment responders. For (P)DPN, biomarkers can be roughly divided into four groups: (1) AGE-related molecules (methylglyoxal and glyoxalase I) as causative agents of (P)DPN, (2) molecules that participate in the progression of inflammation (e.g. Toll-like receptors, TNF- α , miR-146a, adiponectin) (3) molecules associated with nerve damage (nerve-specific enolase and semaphorin) and (4) molecules involved in nerve protection (nerve growth factor and HSP27).²⁸ Biomarkers from groups 2–4 manifest at a later stage of disease progression. Of all biomarkers, TNF- α might be the most promising.^{26,45} Indeed, higher serum TNF- α levels have been found in patients with DPN as compared to patients without DPN, as well as in patients with PDPN as compared to those with painless DPN.²⁶ Although promising, biomarkers are not routinely used in the diagnosis of PDPN.²⁸

Radiological diagnostics

MRI studies show that people with PDPN in combination with sensory function loss have a reduced volume of spinal cord neurons and primary somatosensory cortical gray matter compared with patients with painless DPN. Furthermore, patients with PDPN at rest appear to have greater vascularity in the posterolateral nucleus of the thalamus (VPL) with increased cerebral blood flow compared to diabetic patients without DPN and painless DPN.^{11,38} This suggests that hypervascularity in the VPL is present in patients with painful DPN, whereas hypovascularity in the thalamus is a feature in patients with painless DPN.¹¹

fMRI studies have reported an increased blood-oxygen-level dependent (BOLD) response in PDPN compared with painless DPN.³¹ Areas identified included the anterior cingulate cortex (ACC), medial thalamus, anterior insula, sensory cortices, and lentiform nucleus.

(f)MRI and spectroscopic studies show (1) differences in the cross-sectional area of the spinal cord, particularly in subclinical DPN; (2) volumetric differences and spectroscopic density of sections differences indicative of parenchymal atrophy in the primary sensory cortex; (3) hyperperfusion in painful DPN and hypoperfusion in painless DPN in the thalamus; (4) neurochemical changes indicative of abnormal neuronal thalamic function; (5) changes in GABA-Glx spectral resonances and the excitatory-inhibitory neurotransmitter balance; and (6) complex variability in the BOLD response to an external painful stimulus in DPN. Although (f)MRI and spectroscopy techniques have great potential in revealing the nature of CNS involvement in PDPN, current use is limited to research settings.¹¹

Differential diagnosis

The diagnosis of PDPN is usually made based on sensory, motor, and autonomic clinical symptoms. There is much clinical overlap between different causes of painful polyneuropathy.⁴⁶ The presence of diabetes makes the diagnosis of polyneuropathy resulting from diabetes very likely.

However, painful polyneuropathy has many other etiologies including alcohol abuse, uremia, hypothyroidism, monoclonal gammopathy, vitamin B12 deficiency, peripheral arterial disease, cancer, inflammatory or infectious diseases, neurotoxic drugs, and others. More than one etiology can be present in a person with painful polyneuropathy. Additional laboratory testing to establish differential diagnosis and rule out non-diabetic causes should include a complete blood count, serum creatinine, C-reactive protein,

thyroid-stimulating hormone, vitamin B12, folic acid, and liver enzymes.⁴⁷ Specific differentiation from toxic forms of painful polyneuropathy is important, because of potential reversibility upon cessation of exposure to the causative toxin.

TREATMENT OPTIONS

Conservative management

Non-pharmacological treatment

Of the non-pharmacological symptomatic pain treatments, cognitive behavioral therapy (GBT), transcutaneous electrical nerve stimulation (TENS), frequency-modulated electromagnetic stimulation (FMES), exercise and physiotherapy (EPT) have been systematically investigated. TENS and FMES were found to be ineffective. No or insufficient evidence could be found on GBT and EPT.⁴⁸

Pharmacological treatment

PDPN mechanism-directed treatment

In general, optimal glucose control is essential for the prevention of all microvascular complications of diabetes, including (P)DPN. As secondary prevention, interventions to reduce risk factors for (P)DPN are recommended, including lifestyle modification and multifactorial measures to reduce cardiovascular risk, as hypertension and cardiovascular disease have been shown to be independent risk factors for (P)DPN.^{10,49} Spontaneous recovery of PDPN cannot be expected once symptoms have developed.

The efficacy of agents related to the pathogenesis have been investigated in several randomized clinical trials. These agents target the underlying causal pathways. Of these, α -lipoic acid (an antioxidant), benfotiamine (an advanced glycation end product (AGE) inhibitor), and actovegin (a poly adenosine diphosphate-ribose polymerase (PADRP) inhibitor) have been approved in some countries for the treatment of (P)DPN. In one multicenter, randomized, placebo-controlled study, oral treatment with α -lipoic acid (600–1800 mg/day) for 5 weeks reduced pain, paresthesia, and numbness compared to placebo in 181 patients with PDPN, with no difference between doses.^{10,48,50} Other non-registered examples include aldose reductase inhibitors (alrestatin, sorbinil, ponalrestat, tolrestat, epalrestat, zopolrestat, zenarestat, fidarestat, and ranirestat), antioxidants (vitamin E), protein kinase C (PKC) inhibitors (ruboxistaurin), prostacyclin (PGI₂) analogues (iloprost, beraprost), prostaglandin derivatives (PGE₁CD), c-linolenic acid, trandolapril, nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and C-peptide.

Symptomatic pain treatment

The goal of pharmacological treatment of neuropathic pain in general, and thus also in PDPN, is to reduce peripheral sensitization, ectopic activity, and central sensitization to include brain and spinal cord amplification of nociceptive signaling and enhanced descending modulation.

Systematic review studies show that selective norepinephrine reuptake inhibitors (SNRI: duloxetine, venlafaxine), α 2 δ -subunit calcium channel blockers (α 2 δ -sCCB: pregabalin, gabapentin), sodium channel blockers (oxcarbazepine), tricyclic antidepressants (TCA: amitriptylin, nortriptylin), various opioids, and botulinum toxin are more effective in relieving pain intensity than placebo.^{10,51,52} However, other patient-reported outcome measures (PROMS) are often incompletely or not included in analyses at all. Follow-up of these studies is often short (a few weeks), whereas the therapy is intended to last for years. In addition, the number of patients who discontinue their medication during short follow-ups due to side effects is significant (around 10%).^{10,52} In a study comparing combination therapy of duloxetine 60 mg plus pregabalin 300 mg daily to high-dose (pregabalin 600 mg or duloxetine 120 mg monotherapy (COMBO-DN), the researchers found no difference between groups in the percentage who experienced 2-point reduction in the Brief Pain Inventory (BPI) score, the primary endpoint. However, in a secondary analysis, duloxetine 60 mg/day was found to be more effective than pregabalin 300 mg/day in the first 8-week run-in phase.⁵³ An exploratory post hoc analysis showed that high-dose monotherapy was more effective in patients with severe pain, while combination therapy was more favorable in patients with mild to moderate pain. Patients who received duloxetine (60 mg/day) as initial therapy compared with pregabalin (300 mg/day) also had a better response to combination therapy.⁵⁴ PDPN patients with dysesthetic paresthesia benefited more from high-dose duloxetine (120 mg/day) compared to high-dose pregabalin (600 mg/day).³⁹

In a randomized, double-blind, active-control, crossover clinical trial, low-dose naltrexone (1.5–4.5 mg/day) was found to be as effective and safer than amitriptyline.⁵⁵ Low-dose naltrexone antagonizes opioid receptors and Toll-like receptor 4 (found on macrophages, including microglia), which may increase the body's production of endorphins and have an anti-inflammatory effect.⁵⁶

Beneficial effects of opioid agonists in PDPN have also been demonstrated.^{57–59} Opioids are often used as supplementary therapy in combination with another pharmacological approach. If indicated, we recommend using opioids only for refractory patients at the lowest possible dose, for a limited duration of time or with serial evaluations for continued effectiveness, and under universal precautions.⁶⁰

Capsaicin is a selective agonist for the “transient receptor potential vanilloid 1” (TRPV1). Initially, capsaicin

activates cutaneous nociceptors with TRPV1 expression, leading to burning and erythema due to the release of vasoactive neuropeptides. Subsequently, there is a decrease in cutaneous nociceptors and pain-transmitting neuropeptides such as substance P, which reduces sensitivity to various stimuli, a phenomenon known as defunctionalization.⁶¹ It is believed that this process of peripheral desensitization underlies the analgesic effect. Topical capsaicin 0.075% cream, applied to the painful areas for approximately 8 weeks, has been shown to reduce pain, which may lead to clinical improvements in walking, working, and sleeping in patients with PDPN.⁶²

In a randomized, placebo-controlled study, capsaicin 8% patch has been shown to be effective in relieving pain up to 24 weeks after application.⁶³ It has also been shown to provide pain relief in a disease-modifying manner via nerve regeneration and restoration of function in PDPN.⁶⁴ A recent publication notes that some patients treated with the capsaicin patch may require two or three treatments before an initial response is observed.⁶⁵

Studies have evaluated the application of local anesthetics in PDPN. The efficacy of lidocaine 5% patch compared to pregabalin was investigated in a two-phase, adaptive, randomized, controlled, open-label, multi-center study.⁶⁶ After 4 weeks of treatment, 65.3% of patients treated with lidocaine 5% patch and 62.0% receiving pregabalin responded with a reduction in pain intensity from baseline of ≥ 2 points on the 11-item numerical rating scale (NRS). Both treatments improved secondary endpoints: $\geq 30\%$ and $\geq 50\%$ pain reduction, changes in neuropathic pain symptom inventory (NPSI) scores and allodynia severity. Patients administered lidocaine 5% patch experienced fewer drug-related adverse events (3.9% vs. 39.2%) and there were significantly fewer discontinuations due to drug-related adverse events (1.3% vs. 20.3%).

The effectiveness of intravenous lidocaine 5 and 7.5 mg/kg infused in 4 h (vs. saline) in PDPN was investigated in a small double-blind, placebo-controlled crossover study of two doses of intravenous lidocaine (5 and 7.5 mg/kg).⁶⁷ Both doses of lidocaine significantly reduced the severity of pain compared to placebo (saline) at 14 and 28 days. The qualitative nature of pain was also significantly altered by lidocaine compared with placebo for up to 28 days. Studies suggest that patients with an irritable nociceptor phenotype may be more likely to respond to both intravenous and topical lidocaine.^{68,69}

The use of detailed phenotyping has been proposed to identify dysfunction of descending inhibitory pathways to enable "precision medicine".^{70,71}

As alluded to above, studies suggest that more accurate phenotyping and genotyping of PDPN may identify subgroups of patients likely to respond better to existing pharmacological treatments. Using QST for phenotyping, it has been shown that patients with an excitable nociceptor (IN) phenotype have a better response to

oxcarbazepine, expressed as a lower number needed to treat (NNT), than patients with a non-IN phenotype (NNT, 3.9 vs. 6.9).^{72–75} In a subgroup of patients with preserved nociceptive function (screened with 0.1% capsaicin), clonidine significantly reduced foot pain in PDPN.⁷⁶ Furthermore, PDPN patients with Nav 1.7 variants exhibited more severe pain in diabetes, at shorter durations.⁷⁷ This could have clinical implications because carriers of Nav1.7 genetic variants may respond better to the antiepileptic drug lacosamid.²⁹

PDPN patients with less efficient conditioned pain modulation (CPM), indicative of impaired pain modulation by the monoaminergic descending pathway—a key feature of central sensitization—demonstrated a better effect from duloxetine treatment.⁷⁸ Genetic variations might even suggest differential responses to medication stratified by gender.⁷⁹ Thus, more precise pain-phenotyping and genotyping using specific patient characteristics, incorporating new diagnostic tools, and considering a patient's response to previous pharmacological treatments, are becoming increasingly important to optimize treatment outcomes.

Current guidelines on the pharmacological approach of symptomatic pain treatment in PDPN recommend roughly the same treatment strategy for all patients.³⁹ SNRI's or TCA's and $\alpha 2\delta$ -sCCB's (or in combination) as first- and second-line treatments, and capsaicin 8% and lidocaine 5% patch or IV lidocaine as third-line treatments.³⁹ There are now numerous controlled studies that demonstrate increased effectiveness in diabetic neuropathy and other neuropathic pain conditions for combination therapy with drugs that have complementary mechanisms of action compared to unimodal therapy (antidepressants, membrane stabilizers, opioids).^{80,81} However, initiating combination therapy may also result in more adverse effects and limit a clinician's ability to assess the effectiveness of individual agents. In the future, the diagnosis precision treatment of PDPN will continue to evolve toward more accurate pheno- and genotyping.

Interventional management

Minimal invasive treatment

A systematic review found short-term (up to 18 months) benefits for pain relief from acupuncture compared to standard treatment. Acupuncture can be considered a complementary or alternative therapy with minimal side effects for patients with PDPN.⁸²

Sympathetic lumbar chain neurolysis and/or radiofrequency ablation (SLCN, SLCRF) ablation can provide pain relief up to 12 months after treatment in refractory cases of PDPN.^{83,84} Although the evidence is based on small, uncontrolled studies, SLCN and/or SLCRF can be considered in refractory cases with proven sympathetically maintained pain (eg, demonstrated by controlled

diagnostic blocks) when no other treatment options are available.^{13,82}

Electrical stimulation of neural structures

Spinal cord stimulation (SCS) was first reported as a treatment for pain by Shealy and Tazlitz in 1967.⁸⁵ Up to now, the efficacy and safety of electrical stimulation of the dorsal column of the spinal cord in PDPN has been investigated in multiple RCTs in patients, refractory to conservative treatment.^{86–88}

SCS is a medical procedure that involves the use of an implanted device to deliver electrical current to the dorsal part of the spinal cord for the management of chronic pain.

Paresthesia and non-paresthesia-based stimulation paradigms are effective in terms of pain relief and PROMS measuring functionality and quality of life. In paresthesia-based SCS, 65% of responders are likely to still benefit from this therapy even after 8–10 years of treatment.⁷ Long-term treatment failure was associated with greater severity of neuropathy.⁸⁹ In 10 kilohertz SCS (HF-10) stimulation, 63.6% and 85% of patients experienced $\geq 50\%$ pain reduction after 1 year of treatment in intention to treat (ITT) and modified intention to treat (mITT) analyses, respectively.⁹⁰ Guidelines recommend SCS in PDPN patients refractory to pharmacological treatment.^{44,82,91,92} Although the initial cost of SCS is high, its pain relief is clinically relevant in a significant proportion of patients with PDPN.⁹³ Future research on SCS for PDPN should focus on pheno- and genotyping to optimize long-term prediction of SCS responders and conducting post-marketing multi-center studies devoid of bias, as significant differences in outcomes have been reported between industry-sponsored and non-industry-sponsored studies.⁹⁴

Dorsal root ganglion stimulation (DRGS) was studied in a small retrospective cohort study and several case studies.^{91,95} Patients with good paresthesia capture of the painful area responded well for up to 12 months of therapy.⁹⁵ Stimulation of the posterior tibial nerve (PTNS) has not been studied in a homogeneous population of PDPN patients yet.⁹¹ An observational study in a heterogeneous population of peripheral neuropathic pain treated with PTNS showed promising results.⁹⁶ More robust research is needed to investigate the use of DRGS and PTNS for PDPN as most cases of diabetic neuropathy involve bilateral pain in a stocking-like distribution which may not be covered by focal nerve or nerve root stimulation.

Implantation technique for SCS

The procedure is usually performed under local anesthesia with sedation or under general anesthesia, with

the patient lying in prone position. The first step in the procedure is to place an epidural lead containing multiple electrodes via a small incision in the back. The number and position of the electrodes used can vary depending on the patient's specific pain condition. The lead is positioned in such a way that the target area of the dorsal columns is precisely stimulated. The next step is to connect the lead to the pulse generator (PG), which provides the electrical stimulation. Usually, the lead is connected to an external PG via an extension cable to provide a trial phase of at least 1 week to evaluate the patient's response to the treatment. In case of a positive treatment response, the electrode is disconnected from the extension lead and an internal PG is placed. The internal PG is implanted under the skin in a subcutaneous pocket, usually paramedian to the spine, the buttock, or the abdomen. The PG is programmed to deliver the optimal stimulation parameters for the patient. This involves adjusting the frequency, amplitude, and pulse width of the electrical current delivered to the spinal cord. The programming is done using an external programmer that communicates with the pulse generator via a wireless connection.^{97–100}

Complications of interventional management

Serious adverse events with acupuncture are very rare. In hands of qualified persons, it is considered a safe intervention.¹⁰¹

Common complications of SLCN, SLCRF include bleeding, bruising, swelling, and soreness at the site of injection. These are usually self-limited and resolves within hours to days after the procedure. Some patients have also reported transient dizziness, headache, hypotension, numbness, and weakness of the leg on the side that was injected due to extravasation to somatic nerves. More serious complications include infection, visceral injury, intravascular injection, intralymphatic injection, ureteral injury, kidney damage, Horner's syndrome, and allergic reaction to the medication, although these are exceedingly rare. Anterior thigh pain, presumably due to damage to the genitofemoral nerve and lateral femoral cutaneous nerve, may occur in some patients.¹⁰²

Hardware failure (eg, lead fractures, implanted pulse generator (IPG), and lead migrations), pocket pain, and loss of therapeutic effect are frequently reported complications related to SCS treatment and have been reported up to 10 years of follow-up.^{7,103} Infection at the IPG site occurs in around 5–10% of cases and can usually be treated with antibiotics and removal of the implant.¹ Technical adverse events can be solved by lead replacement, repositioning of the pulse generator, or reprogramming of stimulation parameters. Serious adverse events after SCS implantation, like meningitis, spinal hemorrhage leading to spinal cord compression, or

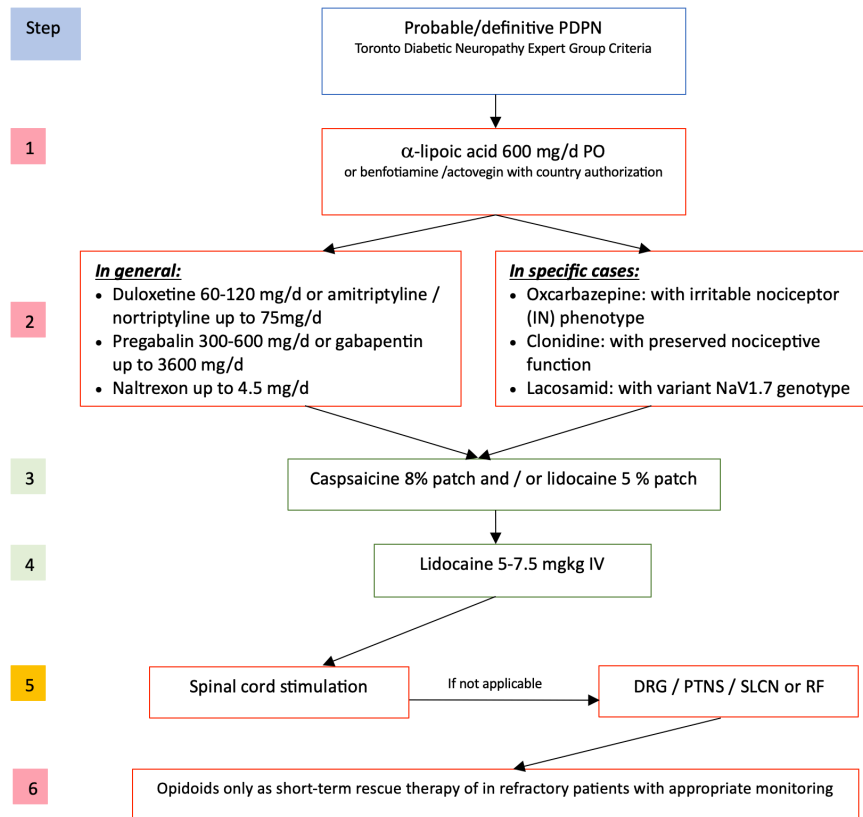


FIGURE 6 Represents the treatment algorithm for PDPN based on the available evidence. DRG, dorsal root ganglion stimulation; PTNS, posterior tibial nerve stimulation; SLCN or RF, sympathetic lumbar chain neurolysis or radiofrequency ablation.

spinal cord damage are very rare. Developing hardware that is more robust and software that improves capture rate and reduces “tolerance” are important focuses for optimizing SCS therapy.

SUMMARY OF THE INFORMATION

Proper monitoring and control of blood glucose levels, and mitigation of risk factors are essential components in the treatment of PDPN. Mechanism-based pharmacological treatment should be initiated as early as possible. If symptomatic pharmacologic treatment fails, SCS should be considered for the treatment of PDPN. In isolated cases, when these interventions do not result in sufficient pain relief or cannot be applied for other reasons, SLCN / SLCRF, DRGS, or PTNS may be considered. It is recommended that these treatments be applied only in a center of expertise (Figure 6).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

- Pluijms W, Huygen F, Cheng J, Mekhail N, van Kleef M, van Zundert J, et al. Evidence-based interventional pain medicine according to clinical diagnoses. 18. Painful diabetic polyneuropathy. *Pain Pract.* 2011;11:191–8.
- Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain.* 2019;160:53–9.
- Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). *Pain.* 2019;160:19–27.
- Gylfadottir SS, Weerachoenkul D, Andersen ST, Niruthisard S, Suwanwalaikorn S, Jensen TS. Painful and non-painful diabetic polyneuropathy: clinical characteristics and diagnostic issues. *J Diabetes Investig.* 2019;10:1148–57.
- Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain.* 2020;161:1976–82.

6. Rosenberger DC, Blechschmidt V, Timmerman H, Wolff A, Treede RD. Challenges of neuropathic pain: focus on diabetic neuropathy. *J Neural Transm (Vienna)*. 2020;127:589–624.
7. Zuidema X, van Daal E, van Geel I, de Geus TJ, van Kuijk SMJ, de Galan BE, et al. Long-term evaluation of spinal cord stimulation in patients with painful diabetic polyneuropathy: an eight-to-ten-year prospective cohort study. *Neuromodulation*. 2022;26:1074–80.
8. Ye D, Fairchild TJ, Vo L, Drummond PD. Painful diabetic peripheral neuropathy: role of oxidative stress and central sensitization. *Diabet Med*. 2022;39:e14729.
9. Stino AM, Smith AG. Peripheral neuropathy in prediabetes and the metabolic syndrome. *J Diabetes Investig*. 2017;8:646–55.
10. Ziegler D, Papanas N, Schnell O, Nguyen BDT, Nguyen KT, Kulkantrakorn K, et al. Current concepts in the management of diabetic polyneuropathy. *J Diabetes Investig*. 2021;12:464–75.
11. Tesfaye S, Selvarajah D, Gandhi R, Greig M, Shillo P, Fang F, et al. Diabetic peripheral neuropathy may not be as its name suggests: evidence from magnetic resonance imaging. *Pain*. 2016;157(Suppl 1):S72–80.
12. Huygen F, Kallewaard JW, van Kleef M, Van Boxem K, Vissers K, van Kleef M, et al. Evidence based interventional pain practice: according to clinical diagnoses. In: NVA, editor. Evidence based interventional pain practice: according to clinical diagnoses. Volume 2019. Utrecht: Nederlandse Vereniging van Medisch Specialisten; 2018. p. 664–75.
13. Huygen F, Kallewaard JW, van Tulder M, van Boxem K, Vissers K, van Kleef M, et al. "evidence-based interventional pain medicine according to clinical diagnoses": update 2018. *Pain Pract*. 2019;19:664–75.
14. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med*. 2004;21:976–82.
15. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*. 2006;29:1518–22.
16. Jensen TS, Karlsson P, Gylfadottir SS, Andersen ST, Bennett DL, Tankisi H, et al. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management. *Brain*. 2021;144:1632–45.
17. Nawroth PP, Bendszus M, Pham M, Jende J, Heiland S, Ries S, et al. The quest for more research on painful diabetic neuropathy. *Neuroscience*. 2018;387:28–37.
18. Torrance N, Elliott AM, Lee AJ, Smith BH. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. *Eur J Pain*. 2010;14:380–6.
19. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. *Nat Rev Endocrinol*. 2016;12:616–22.
20. Said G. Diabetic neuropathy—a review. *Nat Clin Pract Neurol*. 2007;3:331–40.
21. Galosi E, Hu X, Michael N, Nyengaard JR, Truini A, Karlsson P. Redefining distal symmetrical polyneuropathy features in type 1 diabetes: a systematic review. *Acta Diabetol*. 2022;59:1–19.
22. Franceschi R, Mozzillo E, Di Candia F, Rosanio FM, Leonardi L, Liguori A, et al. A systematic review of the prevalence, risk factors and screening tools for autonomic and diabetic peripheral neuropathy in children, adolescents and young adults with type 1 diabetes. *Acta Diabetol*. 2022;59:293–308.
23. Bierhaus A, Fleming T, Stoyanov S, Leffler A, Babes A, Neacsu C, et al. Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. *Nat Med*. 2012;18:926–33.
24. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. *Chest*. 2006;129:174–81.
25. Meydan C, Uceyler N, Soreq H. Non-coding RNA regulators of diabetic polyneuropathy. *Neurosci Lett*. 2020;731:135058.
26. Mu ZP, Wang YG, Li CQ, Lv WS, Wang B, Jing ZH, et al. Association between tumor necrosis factor-alpha and diabetic peripheral neuropathy in patients with type 2 diabetes: a meta-analysis. *Mol Neurobiol*. 2017;54:983–96.
27. Shillo P, Selvarajah D, Greig M, Gandhi R, Rao G, Wilkinson ID, et al. Reduced vitamin D levels in painful diabetic peripheral neuropathy. *Diabet Med*. 2019;36:44–51.
28. Fujita Y, Murakami T, Nakamura A. Recent advances in biomarkers and regenerative medicine for diabetic neuropathy. *Int J Mol Sci*. 2021;22:2301.
29. Jankovic M, Novakovic I, Nikolic D, Mitrovic Maksic J, Brankovic S, Petronic I, et al. Genetic and epigenomic modifiers of diabetic neuropathy. *Int J Mol Sci*. 2021;22:4887.
30. Yagihashi S, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: where are we now and where to go? *J Diabetes Investig*. 2011;2:18–32.
31. Shillo P, Sloan G, Greig M, Hunt L, Selvarajah D, Elliott J, et al. Painful and painless diabetic neuropathies: what is the difference? *Curr Diab Rep*. 2019;19:32.
32. Sloan G, Shillo P, Selvarajah D, Wu J, Wilkinson ID, Tracey I, et al. A new look at painful diabetic neuropathy. *Diabetes Res Clin Pract*. 2018;144:177–91.
33. Jensen TS, Backonja MM, Hernandez Jimenez S, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. *Diab Vasc Dis Res*. 2006;3:108–19.
34. Kalteniece A, Ferdousi M, Petropoulos I, Azmi S, Adam S, Fadavi H, et al. Greater corneal nerve loss at the inferior whorl is related to the presence of diabetic neuropathy and painful diabetic neuropathy. *Sci Rep*. 2018;8:3283.
35. Baskozos G, Themistocleous AC, Hebert HL, Pascal MMV, John J, Callaghan BC, et al. Classification of painful or painless diabetic peripheral neuropathy and identification of the most powerful predictors using machine learning models in large cross-sectional cohorts. *BMC Med Inform Decis Mak*. 2022;22:144.
36. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. 2010;33:2285–93.
37. Carmichael J, Fadavi H, Ishibashi F, Shore AC, Tavakoli M. Advances in screening, early diagnosis and accurate staging of diabetic neuropathy. *Front Endocrinol*. 2021;12:671257.
38. Sierra-Silvestre E, Somerville M, Bisset L, Coppeters MW. Altered pain processing in patients with type 1 and 2 diabetes: systematic review and meta-analysis of pain detection thresholds and pain modulation mechanisms. *BMJ Open Diabetes Res Care*. 2020;8:e001566.
39. Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M, Cuthbertson DJ, et al. Diabetic peripheral neuropathy: Epidemiology, diagnosis, and pharmacotherapy. *Clin Ther*. 2018;40:828–49.
40. McIlhatton A, Lanting S, Lambkin D, Leigh L, Casey S, Chuter V. Reliability of recommended non-invasive chairside screening tests for diabetes-related peripheral neuropathy: a systematic review with meta-analyses. *BMJ Open Diabetes Res Care*. 2021;9:e002528.
41. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10:895–926.
42. Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G, et al. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158:261–72.

43. Cruz-Almeida Y, Fillingim RB. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Med.* 2014;15:61–72.
44. Blonde L, Umpierrez GE, Reddy SS, McGill JB, Berga SL, Bush M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: developing a diabetes mellitus comprehensive care Plan-2022 update. *Endocr Pract.* 2022;28:923–1049.
45. Jin HY, Park TS. Role of inflammatory biomarkers in diabetic peripheral neuropathy. *J Diabetes Investig.* 2018;9:1016–8.
46. Gewandter JS, Burke L, Cavaletti G, Dworkin RH, Gibbons C, Gover TD, et al. Content validity of symptom-based measures for diabetic, chemotherapy, and HIV peripheral neuropathy. *Muscle Nerve.* 2017;55:366–72.
47. Ziegler D, Keller J, Maier C, Pannek J, German DA. Diabetic neuropathy. *Exp Clin Endocrinol Diabetes.* 2014;122:406–15.
48. Amato Nesbit S, Sharma R, Waldfogel JM, Zhang A, Bennett WL, Yeh HC, et al. Non-pharmacologic treatments for symptoms of diabetic peripheral neuropathy: a systematic review. *Curr Med Res Opin.* 2019;35:15–25.
49. Hebert HL, Veluchamy A, Torrance N, Smith BH. Risk factors for neuropathic pain in diabetes mellitus. *Pain.* 2017;158:560–8.
50. Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care.* 2006;29:2365–70.
51. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14:162–73.
52. Waldfogel JM, Nesbit SA, Dy SM, Sharma R, Zhang A, Wilson LM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review. *Neurology.* 2017;88:1958–67.
53. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The “COMBO-DN study” – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain.* 2013;154:2616–25.
54. Bouhassira D, Wilhelm S, Schacht A, Perrot S, Kosek E, Cruccu G, et al. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. *Pain.* 2014;155:2171–9.
55. Srinivasan A, Dutta P, Bansal D, Chakrabarti A, Bhansali AK, Hota D. Efficacy and safety of low-dose naltrexone in painful diabetic neuropathy: a randomized, double-blind, active-control, crossover clinical trial. *J Diabetes.* 2021;13:770–8.
56. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol.* 2014;33:451–9.
57. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA.* 2005;293:3043–52.
58. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology.* 2003;60:927–34.
59. Harati Y, Gooch C, Swenson M, Edelman S, Greene D, Raskin P, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology.* 1998;50:1842–6.
60. Ballantyne JC. Breakthrough pain: just pain? *Pain.* 2016;157:2621–2.
61. Arora V, Campbell JN, Chung MK. Fight fire with fire: neurobiology of capsaicin-induced analgesia for chronic pain. *Pharmacol Ther.* 2021;220:107743.
62. Djudla PV, Nkambule BB, Cirilli I, Marcheggiani F, Mabhidia SE, Ziqubu K, et al. Capsaicin, its clinical significance in patients with painful diabetic neuropathy. *Biomed Pharmacother.* 2022;153:113439.
63. Hussain N, Said ASA, Javaid FA, al Haddad AHI, Anwar M, Khan Z, et al. The efficacy and safety profile of capsaicin 8% patch versus 5% lidocaine patch in patients with diabetic peripheral neuropathic pain: a randomized, placebo-controlled study of south Asian male patients. *J Diabetes Metab Disord.* 2021;20:271–8.
64. Anand P, Privitera R, Donatien P, Fadavi H, Tesfaye S, Bravis V, et al. Reversing painful and non-painful diabetic neuropathy with the capsaicin 8% patch: clinical evidence for pain relief and restoration of function via nerve fiber regeneration. *Front Neurol.* 2022;13:998904.
65. Freynhagen R, Argoff C, Eerdeken M, Engelen S, Perrot S. Progressive response to repeat application of capsaicin 179 mg (8% w/w) cutaneous patch in peripheral neuropathic pain: comprehensive new analysis and clinical implications. *Pain Med.* 2021;22:2324–36.
66. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. *Clin Drug Investig.* 2009;29:231–41.
67. Viola V, Newnham HH, Simpson RW. Treatment of intractable painful diabetic neuropathy with intravenous lignocaine. *J Diabetes Complications.* 2006;20:34–9.
68. Demant DT, Lund K, Finnerup NB, Vollert J, Maier C, Segerdahl MS, et al. Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: a randomised, double-blind, and placebo-controlled, phenotype panel study. *Pain.* 2015;156:2234–44.
69. Wilkinson ID, Teh K, Heiberg-Gibbons F, Awadh M, Kelsall A, Shillo P, et al. Determinants of treatment response in painful diabetic peripheral neuropathy: a combined deep sensory phenotyping and multimodal brain MRI study. *Diabetes.* 2020;69:1804–14.
70. Javed S, Hayat T, Menon L, Alam U, Malik RA. Diabetic peripheral neuropathy in people with type 2 diabetes: too little too late. *Diabet Med.* 2020;37:573–9.
71. Marshall AG, Lee-Kubli C, Azmi S, Zhang M, Ferdousi M, Mixcoatl-Zecuatl T, et al. Spinal disinhibition in experimental and clinical painful diabetic neuropathy. *Diabetes.* 2017;66:1380–90.
72. de Greef BTA, Hoeijmakers JGJ, Geerts M, Oakes M, Church TJE, Waxman SG, et al. Lacosamide in patients with Nav1.7 mutations-related small fibre neuropathy: a randomized controlled trial. *Brain.* 2019;142:263–75.
73. Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain.* 2014;155:2263–73.
74. Han C, Themistocleous AC, Estacion M, Dib-Hajj FB, Blesneac I, Macala L, et al. The novel activity of carbamazepine as an activation modulator extends from Na(V)1.7 mutations to the Na(V)1.8-S242T mutant channel from a patient with painful diabetic neuropathy. *Mol Pharmacol.* 2018;94:1256–69.
75. Ziegler D, Hidvegi T, Gurieva I, Bongardt S, Freynhagen R, Sen D, et al. Efficacy and safety of lacosamide in painful diabetic neuropathy. *Diabetes Care.* 2010;33:839–41.
76. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag.* 2012;2:219–30.
77. Blesneac I, Themistocleous AC, Fratter C, Conrad LJ, Ramirez JD, Cox JJ, et al. Rare NaV1.7 variants associated with painful diabetic peripheral neuropathy. *Pain.* 2018;159:469–80.

78. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain*. 2012;153:1193–8.
79. Inyang KE, Szabo-Pardi T, Wentworth E, McDougal TA, Dussor G, Burton MD, et al. The antidiabetic drug metformin prevents and reverses neuropathic pain and spinal cord microglial activation in male but not female mice. *Pharmacol Res*. 2019;139:1–16.
80. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012;2020:CD008943.
81. Tesfaye S, Sloan G, Petrie J, White D, Bradburn M, Julious S, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet*. 2022;400:680–90.
82. Xu L, Sun Z, Casserly E, Nasr C, Cheng J, Xu J. Advances in interventional therapies for painful diabetic neuropathy: a systematic review. *Anesth Analg*. 2022;134:1215–28.
83. Cheng J, Daftari A, Zhou L. Sympathetic blocks provided sustained pain relief in a patient with refractory painful diabetic neuropathy. *Case Rep Anesthesiol*. 2012;2012:285328.
84. Ding Y, Yao P, Li H, Zhao R, Zhao G. Evaluation of combined radiofrequency and chemical blockade of multi-segmental lumbar sympathetic ganglia in painful diabetic peripheral neuropathy. *J Pain Res*. 2018;11:1375–82.
85. Shealy CN, Taslitz N, Mortimer JT, Becker DP. Electrical inhibition of pain: experimental evaluation. *Anesth Analg*. 1967;46:299–305.
86. de Vos CC, Rajan V, Steenbergen W, van der Aa HE, Buschman HP. Effect and safety of spinal cord stimulation for treatment of chronic pain caused by diabetic neuropathy. *J Diabetes Complications*. 2009;23:40–5.
87. Petersen EA, Stauss TG, Scowcroft JA, Brooks ES, White JL, Sills SM, et al. Effect of high-frequency (10-kHz) spinal cord stimulation in patients with painful diabetic neuropathy: a randomized clinical trial. *JAMA Neurol*. 2021;78:687–98.
88. Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. *Diabetes Care*. 2014;37:3016–24.
89. van Beek M, Geurts JW, Slangen R, Schaper NC, Faber CG, Joosten EA, et al. Severity of neuropathy is associated with long-term spinal cord stimulation outcome in painful diabetic peripheral neuropathy: five-year follow-up of a prospective two-center clinical trial. *Diabetes Care*. 2018;41:32–8.
90. Petersen EA, Stauss TG, Scowcroft JA, Brooks ES, White JL, Sills SM, et al. Durability of high-frequency 10-kHz spinal cord stimulation for patients with painful diabetic neuropathy refractory to conventional treatments: 12-month results from a randomized controlled trial. *Diabetes Care*. 2022;45:e3–6.
91. D'Souza RS, Langford B, Dombovy-Johnson M, Abd-Elseyed A. Neuromodulation interventions for the treatment of painful diabetic neuropathy: a systematic review. *Curr Pain Headache Rep*. 2022;26:365–77.
92. Duarte RV, Nevitt S, Maden M, Meier K, Taylor RS, Eldabe S, et al. Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data. *Pain*. 2021;162:2635–43.
93. Slangen R, Faber CG, Schaper NC, Joosten EA, van Dongen RT, Kessels AG, et al. A trial-based economic evaluation comparing spinal cord stimulation with best medical treatment in painful diabetic peripheral neuropathy. *J Pain*. 2017;18:405–14.
94. Knotkova H, Hamani C, Sivanesan E, le Beuffe MFE, Moon JY, Cohen SP, et al. Neuromodulation for chronic pain. *Lancet*. 2021;397:2111–24.
95. Eldabe S, Espinet A, Wahlstedt A, Kang P, Liem L, Patel NK, et al. Retrospective case series on the treatment of painful diabetic peripheral neuropathy with dorsal root ganglion stimulation. *Neuromodulation*. 2018;21:787–92.
96. Dabby R, Sadeh M, Goldberg I, Finkelshtein V. Electrical stimulation of the posterior tibial nerve reduces neuropathic pain in patients with polyneuropathy. *J Pain Res*. 2017;10:2717–23.
97. Deer T, Pope J, Hayek S, Narouze S, Patil P, Foreman R, et al. Neurostimulation for the treatment of axial back pain: a review of mechanisms, techniques, outcomes, and future advances. *Neuromodulation*. 2014;17(Suppl 2):52–68.
98. Deer TR, Krames E, Mekhail N, Pope J, Leong M, Stanton-Hicks M, et al. The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. *Neuromodulation appropriateness consensus committee*. *Neuromodulation*. 2014;17:599–615; discussion 615.
99. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery*. 2006;58:481–96; discussion 481–496.
100. Kunnumpurath S, Srinivasagopalan R, Vadivelu N. Spinal cord stimulation: principles of past, present and future practice: a review. *J Clin Monit Comput*. 2009;23:333–9.
101. Wu J, Hu Y, Zhu Y, Yin P, Litscher G, Xu S. Systematic review of adverse effects: a further step towards modernization of acupuncture in China. *Evid Based Complement Alternat Med*. 2015;2015:432467.
102. Alexander CE, De Jesus O, Varacallo M. Lumbar sympathetic block. *Treasure Island (FL): StatPearls*; 2023.
103. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery*. 2008;63:762–70; discussion 770.

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