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Diabetic Peripheral Neuropathy: Epidemiology, Diagnosis, and Pharmacotherapy

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ABSTRACT

Purpose: Diabetic peripheral neuropathy (DPN) is the commonest cause of neuropathy worldwide, and its prevalence increases with the duration of diabetes. It affects approximately half of patients with diabetes. DPN is symmetric and predominantly sensory, starting distally and gradually spreading proximally in a glove-and-stocking distribution. It causes substantial morbidity and is associated with increased mortality. The unrelenting nature of pain in this condition can negatively affect a patient's sleep, mood, and functionality and result in a poor quality of life. The purpose of this review was to critically review the current literature on the diagnosis and treatment of DPN, with a focus on the treatment of neuropathic pain in DPN.

Methods: A comprehensive literature review was undertaken, incorporating article searches in electronic databases (EMBASE, PubMed, OVID) and reference lists of relevant articles with the authors' expertise in DPN. This review considers seminal and novel research in epidemiology; diagnosis, especially in relation to novel surrogate end points; and the treatment of neuropathic pain in DPN. We also consider potential new pharmacotherapies for painful DPN.

Findings: DPN is often misdiagnosed and inadequately treated. Other than improving glycemic control, there is no licensed pathogenetic treatment for diabetic neuropathy. Management of painful DPN remains challenging due to difficulties in personalizing therapy and ascertaining the best dosing strategy, choice of initial pharmacotherapy, consideration of combination therapy, and deciding on defining treatment for poor analgesic responders. Duloxetine and pregabalin remain first-line therapy for neuropathic pain in DPN in all 5 of the major published guidelines by the American Association of Clinical Endocrinologists, American Academy of Neurology, European Federation of Neurological Societies, National Institute of Clinical Excellence (United Kingdom), and the American Diabetes Association, and their use has been approved by the US Food and Drug Administration.

Implications: Clinical recognition of DPN is imperative for allowing timely symptom management to reduce the morbidity associated with this condition. (*Clin Ther*. 2018;∎:∎∎–∎∎∎) © 2018 Elsevier HS Journals, Inc. All rights reserved.

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INTRODUCTION

Diabetes has reached epidemic proportions worldwide, with International Diabetes Federation estimates suggesting a prevalence of 425 million people worldwide in 2017, rising to 628 million by 2045.[1] This rise will be accompanied by an increase in the prevalence of the complications of diabetes.[2] DPN is the most common cause of neuropathy worldwide, and is estimated to affect around half of people with diabetes.[3,4] It causes considerable morbidity, impairs quality of life, and increases mortality.[5,6] Indeed, approximately one fourth of the US health care expenditure on diabetes is spent on DPN.[7]

Diabetic neuropathy refers to a collection of clinically diverse disorders affecting the nervous system, with differing anatomic features, clinical courses, and phenotypes. The common underlying pathophysiology is a consequence of hyperglycemia and microangiopathy.[8] The commonest form is distal symmetric sensorimotor polyneuropathy[9]; however, most body systems can be affected through involvement of the autonomic nerves. Despite the considerable, health care–related economic burden and effect on quality of life in DPN, treatment options are limited and prevention remains the key goal.[10] The purpose of this review was to critically review the current literature on the diagnosis and treatment of DPN, with a focus on the treatment of neuropathic pain in DPN.

MATERIALS AND METHODS

A comprehensive literature review was undertaken, incorporating article searches in electronic databases (EMBASE, PubMed, OVID) and reference lists of relevant articles with the authors' expertise in DPN. Articles published from inception of databases to December 2017 were identified. Data from articles that were felt not relevant by authors with the guidance of the senior reviewers (R.A.M., U.A.) were excluded from the review.

RESULTS

Databases searches were undertaken and 188 papers were cited in the final manuscript. Authors excluded studies that were not considered relevant to the aims of this article. Further appraisal of selected articles were undertaken and any relevant explanatory data from said articles were included in the present review as descriptive prose.

Epidemiology

Epidemiologic studies of diabetic neuropathy have provided heterogeneous results, owing to different patient populations, definitions of *neuropathy* used, and methods of assessments. Prediabetes is also associated with neuropathy.[11] In the San Luis Valley cohort,[12] the prevalence of peripheral neuropathy in patients with diabetes was 25.8%, as compared to 11.2% in subjects with impaired glucose tolerance (IGT) and 3.9% in control subjects. The MonItoring trends and determinants in CArdiovascular/Cooperative Research in the Region of Augsburg (MONICA/KORA)[13] investigators found the prevalence of neuropathic pain to be 13.3% in patients with diabetes versus 8.7%, 4.2%, and 1.2% in subjects with IGT, impaired fasting glucose, and controls, respectively. PROMISE (Prospective Metabolism and Islet Cell Evaluation)[14] followed up patients longitudinally who were at risk for developing diabetes. At 3 years, the prevalence of neuropathy (as assessed using the Michigan Neuropathy Screening Instrument) was 50% in patients who developed diabetes, 49% in those with prediabetes, and 29% in controls.[15]

In a Spanish study, the reported prevalence of DPN in primary care was 21% compared to 27% in-hospital.[16] The Rochester Neuropathy Study evaluated data from 380 participants[16]; DPN, diagnosed using a multifaceted approach, including the neuropathy symptom score, neuropathy disability score, and nerve conduction studies, was found in 66% and 59% of patients with type 1 and 2 diabetes, respectively. Importantly, approximately 10% of participants had a nondiabetic etiology of the neuropathy.[16]

A large-scale, multicenter study (N = 6500) revealed DPN (based on questionnaire and examination) in 28.5%.[4] A community-based study in ~15,000 patients with diabetes showed that 34% of patients had symptoms of painful neuropathy, with an increased risk in patients with type 2 diabetes, women, and people of South Asian origin.[17]

The prevalence of DPN is considered to be low in patients with early type 1 diabetes; however, among participants in the Diabetes Control and Complications Trial (DCCT), the prevalences of abnormal neurologic exam results were almost 20% in those on conventional treatment and almost 10% in those on intensive treatment, after ~5 years of follow-up.[18] In the EURODIAB IDDM complications study,[19] which evaluated over 3000 patients across 16

countries, there was a 28% baseline neuropathy prevalence, which rose by 23.5% after 7 years. The risk factors for the development of neuropathy included age, duration of diabetes, poor glycemic control, elevated low-density lipoprotein cholesterol and triglycerides, hypertension, obesity, and smoking.[19] The EDIC (Epidemiology of Diabetes Interventions and Complications) study, following up patients up for 13 years after the initial 6.5 years of the DCCT,[8] showed an initial 64% reduction in the risk for DPN in those on intensive compared to conventional treatment during the DCCT period and a 30% risk reduction was maintained in the follow-up EDIC study period.[8]

More recently, the prevalence of DPN in youth with a shorter duration of diabetes has been reevaluated. In SEARCH (the Search for Diabetes in Youth Study),[20] a cohort of young people (aged <20 years) who had a duration of diabetes of over 5 years were evaluated using the Michigan Neuropathy Screening Instrument.[21] Data from 1374 patients with type 1 diabetes and 258 with type 2 diabetes were studied, revealing prevalence rates of DPN of 7% and 22%, respectively,[21] suggesting an excessive burden of DPN even in adolescents.

Pathogenetic Treatments

Numerous pathogenetic treatments that target the underlying molecular and cellular mechanisms involved in DPN, including aldose reductase inhibitors, benfotiamine, and protein kinase C inhibitors, have undergone clinical trials over the past 4 decades.[10] All have failed in Phase III clinical trials, and none have been approved by the US Food and Drug Administration (FDA) as disease-modifying treatments for DPN.[22,23] Multiple reasons have been cited for this failure. In part, the end points selected, including composite clinical scores and quantitative sensory testing (QST), which relies on patients' responses, are deemed to be subjective[24] and prone to high variability, and even objective measures such as neurophysiology have been shown to have high interobserver variability.[25–28] It is now also evident that the rate of DPN progression is slower than predicted,[23] in part due to concomitant use of routine therapies such as angiotensin-converting enzyme inhibitors,[29] and therefore trials need to be of longer duration.

Glycemic Control

Glycemic control has been shown to prevent or delay the progression of neuropathy in patients with type 1 diabetes.[30] The Pittsburgh Epidemiology of Diabetes Complications Study suggested that duration of diabetes, HbA_{1c}, smoking status, and high-density lipoprotein cholesterol are associated with neuropathy.[31,32] The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported a 20% decrease in the prevalence of DPN for a 2% decrease in HbA_{1c} over 4 years of follow-up.[33] In DCCT, HbA_{1c} values were 7.4% in the intensive group and 9.1% in the conventional group, and the risk reduction for incident DPN with intensive glucose control was 64% after 6.5 years of follow-up.[8] By the 5th year of the EDIC study, despite HbA_{1c} values in the 2 groups being similar (8.1% vs 8.2%), the prevalences of DPN and cardiac autonomic neuropathy remained significantly lower in patients who had been on intensive therapy compared to standard therapy during DCCT.[34] This phenomenon has been termed *metabolic memory*.

In type 2 diabetes, the evidence for the role of improved glycemic control in slowing the progression of neuropathy in patients is limited.[35–37] ACCORD (Action to Control Cardiovascular Risk in Diabetes)[36] showed a significant reduction in loss of sensation to light touch, which was only 1 of 4 neuropathy end points after a follow-up of 5 years. It should be noted that the intensive glucose-lowering regimen was associated with increased mortality (hazard ratio = 1.22; 95% CI, 1.01–1.46; $P = 0.04$), suggesting harm associated with tight glycemic control,[6] and self-reported DPN conferred a higher risk for mortality in the intensive glycemic control group than in those with a higher HbA_{1c} and those on aspirin.[38]

Lipids

There is an association between plasma triglycerides/remnant lipoproteins and the risk for DPN.[19] In animal models, treatment with specific fatty acids, such as docosahexaenoic acid, have been shown to exhibit a protective effect and potentially even can reverse DPN.[39] It has been suggested that cholesterol-lowering treatments (statins and ezetimibe)[40,41] and triglyceride-lowering treatments (fibrates)[40] may reduce the progression and severity of DPN. Well-planned randomized trials are needed to evaluate the impact of intensive plasma lipid normalization on DPN.

Diet and Lifestyle Interventions

In patients with IGT, lifestyle intervention could arrest the underlying process that leads to neuropathy.

The Diabetes Prevention Program study[42] demonstrated that lifestyle changes and treatment with metformin reduced the prevalence of diabetes in those with IGT. Lifestyle intervention may also be effective in preventing DPN, as shown in the IGT Causes Neuropathy study,[43] in which diet and exercise counselling in subjects with IGT resulted in increased intraepidermal nerve fiber density (IENFD) and an improvement in neuropathic pain.

Weight Loss

Experimental studies have shown that incretin-based therapies have valuable effects on diabetic complications, independent of their glucose-lowering abilities, mainly mediated by their antiinflammatory and antioxidative stress properties.[44] However, in a pilot study in patients with type 2 diabetes and mild to moderate DPN, 18 months of treatment with exenatide, compared with glargine, had no effect on neuropathy.[45]

In a meta-analysis of data from 10 studies, there was greater remission and lower risks for microvascular and macrovascular disease and mortality in the bariatric surgery group as compared to a non-surgical treatment group in patients with type 2 diabetes after at least 5 years of follow-up.[46] In a study of bariatric surgery in patients with and without diabetes, there were improvements in body mass index, systemic inflammation, metabolic parameters, and small nerve fibers, as measured by corneal confocal microscopy (CCM).[47]

Micronutrient deficiencies after bariatric surgery are associated with an acute neuropathy,[48,49] and longer longitudinal studies that accurately phenotype neuropathy are required to delineate potential risk factors for this condition.

Diagnosis of DPN

The American Diabetes Association's position statement on diabetic neuropathy (2017) advises that the early recognition of neuropathy and initiation of appropriate management are essential to the management of patients with diabetes.[50] Alternative etiologies of neuropathy should be actively diagnosed and treated. These include chronic inflammatory demyelinating polyneuropathy, B_{12} deficiency, hypothyroidism, and uremia, which may concomitantly occur in diabetes.[51] The tests frequently used to diagnose DPN have been listed in Table I, along with their advantages & disadvantages and type of nerve fiber they assess.

Screening

Patients with type 2 diabetes mellitus should be screened annually from diagnosis, and those with type 1 diabetes, after 5 years of diagnosis.[50] People with

Table I. A summary of the common tests used to assess neuropathy.

Test	Advantage	Disadvantage	Type of Nerve
NCS	Sensitive, specific, and reproducible and easily standardized gold standard technique	Must be done by trained professional. Only assesses large fiber damage.	Large fiber
NDS	Good predictor for risk for ulceration	Does not detect sub-clinical large fiber damage.	Large and small fiber
QST	Reproducible and reliable	Subjective	Large and small fiber
Skin biopsy	Gold Standard, reliable and reproducible	Invasive procedure. Needs specialized laboratory service.	Small fiber
CCM	Rapid, reproducible, non-invasive. Can detect small fiber damage and track progression.	Must be done by trained professional.	Small fiber

CCM = corneal confocal microscopy; NCS = nerve conduction studies; NDS = neuropathy disability score; QST = quantitative sensory testing.

prediabetes should also undergo an assessment for neuropathy if symptoms are present.[50]

Assessment

The assessment of patients for DPN should include a careful and focused history. Symptomology of neuropathy will differ according to the type of nerve fiber involvement. Patients with large fiber dysfunction may experience numbness, tingling, or poor balance. Small fiber neuropathy (SFN) may present with neuropathic pain described as burning, stabbing, or electric shocks. Pain is the trigger for patients to seek medical care in 25% of patients diagnosed with DPN.[13,52]

Many patients may be asymptomatic, and thus examination is key to the diagnosis. A bedside test should be employed for both small and large fiber neuropathy, such as the neuropathy disability score (NDS), which is a validated reliable and reproducible screening tool that can also assess the severity of neuropathy. The NDS consists of testing sensory modalities, which include pain sensation (pinprick), temperature perception (using hot and cold rods), and vibration (128-Hz tuning fork), all scored as either normal (0) or reduced/absent (1). Abbott et al[53] showed that a neuropathy disability score of $>6/10$ was an independent risk factor for new foot ulcers. All patients should undergo annual 10-g monofilament and pedal pulse evaluation to assess the risk for foot ulcers.[50] The key is that the 10-g monofilament should not be used to diagnose or exclude DPN as it detects only advanced neuropathy. Indeed, in a recent systematic review it was shown to have a very poor diagnostic utility, with a sensitivity of 88% but a specificity of only 55%, when nerve conduction was used to diagnose DPN.[54] The alternative 1-g monofilament may, however, be better for detecting earlier neuropathy.[55] The assessment of SNF remains a particular challenge, especially in diabetic neuropathy.[56]

DPN is common, and the diagnosis of DPN begins with a careful history and examination of sensory and motor symptoms and signs. The quality and severity of neuropathic pain, if present, should be assessed using a validated method that is reproducible, such as the Michigan Neuropathy Screening Instrument. Examination within a clinic setting should include inspection of the feet and evaluation of reflexes and sensory responses to vibration, light touch, pinprick, and the 10g monofilament. The exact pathophysiologic mechanisms of DPN remain to be elucidated, and treatments targeted at the natural history and pathophysiologic mechanisms of DPN are urgently required.

Diagnostic Definition

The Toronto Diabetic Neuropathy Expert group[57] classifies DPN as:

1. Confirmed DPN—abnormal nerve conduction and a symptom or sign of neuropathy;
2. Probable DPN—2 or more of the following signs or symptoms: neuropathic symptoms, decreased distal sensation, or decreased/absent ankle reflexes; or
3. Possible DPN—any of the following symptoms: decreased sensation, positive neuropathic sensory symptoms (eg "asleep numbness," prickling/stabbing, burning, or aching pain), predominantly in the toes, feet, or legs; OR signs, including symmetric decrease of distal sensation or decreased/absent ankle reflexes.

The ADA's position statement does not recommend the use of neurophysiology for the diagnosis of typical DPN, and this testing modality should be reserved for patients in whom atypical features are present or the diagnosis is unclear.

Neuropathy Symptoms

Questionnaires are a subjective method to assess and quantify the severity of neuropathic symptoms and pain. The McGill Pain Questionnaire[58] is widely used to evaluate neuropathic pain. Other questionnaires specifically developed for neuropathic pain quantification are the Brief Pain Inventory,[59] Neuropathic Pain Questionnaire,[60] Neuropathic Pain Symptom Inventory,[61] and the Doleur Neuropathique 4.[62] The Neuropathic Symptom Profile has been validated to detect and stage the severity of neuropathy.[63] The Brief Pain Inventory, Neuropathic Pain Questionnaire, Neuropathic Pain Symptom Inventory and NSP are all validated self-administered questionnaires.

Quantitative Sensory Testing

QST, which includes a thermal threshold assessment for cold sensation (A-δ fibers) and warm sensation (c fibers), assesses small fiber dysfunction and

therefore can detect early neuropathy, but is highly subjective. However, QST is a sensitive method of detecting SFN, particularly in those patients with normal nerve conduction study results,[64] and may be used where no definitive quantitative structural assessment of small nerve fibers (skin biopsy or CCM) can be undertaken.

Also, vibration perception threshold, assessed using a biothesiometer, correlates with the severity of DPN, and a vibration perception threshold of >25 V is a strong predictor of foot ulceration.[65]

Nerve Conduction Studies

Nerve conduction studies (NCSs) are commonly used to assess the severity of DPN and are considered to be sensitive and specific for DPN.[66] Interestingly, Dyck et al[24] compared NCS to individual physicians' clinical diagnosis of DPN and found that clinician's diagnoses were excessively variable and frequently inaccurate, with an overestimation of DPN. Vinik et al[67] conducted a study in 205 patients with both type 1 and 2 diabetes and mild DPN and showed that sural nerve conductivity correlated well with the severity of DPN. However, NCSs evaluate only large myelinated nerve fibers and cannot detect an early SFN as commonly seen in prediabetes and short-duration diabetes. The ADA's position statement does not advocate the routine use of NCS, and it should be reserved for patients with atypical features in whom the diagnosis is unclear.[50]

Skin Biopsy

Skin biopsy enables direct visualization of thinly myelinated and nonmyelinated nerve fibers that are the earliest to be affected in DPN. Skin biopsy can be used to diagnose SFN.[68] The European Federation for Neurological Societies' guidance recommends a punch skin biopsy at the distal leg or proximal thigh for the diagnosis of SFN.[69] The assessments of intraepidermal nerve fibers and IENFD are currently advocated in clinical practice in the United States[43] and are recommended as an end point in clinical trials.[23]

Pittenger et al[70] showed a reduction in IENFD in patients with SFN, with a sensitivity between 74% and 87.5%, and that IENFD was inversely correlated with QST. An inverse correlation has also been shown between IENFD and the duration of diabetes, neurologic impairment score, and results of sensory evaluation.[70,71]

Novel Surrogate Imaging Markers of DPN

Corneal Confocal Microscopy

Over the past 2 decades, the significance of evaluating corneal nerve morphology as a surrogate marker for peripheral neuropathies has been established. CCM has been suggested as a surrogate end point for the assessment of DPN, as it allows direct visualization of peripheral nerves and is a rapid, noninvasive, and objective technique,[72,73] with high sensitivity and specificity to diagnose early nerve fiber damage[23] and repair.[74] Several studies have shown that CCM is highly correlated with IENFD loss[23] and is comparable to the diagnostic ability of skin biopsy.[75,76] A number of parameters are used to quantify the corneal sub-basal nerve plexus and include corneal nerve fiber length, corneal nerve branch density, and corneal nerve fiber density. CCM has been extensively used to identify small nerve fiber damage in a range of peripheral neuropathies, including DPN,[77,78] HIV neuropathy,[79] chemotherapy-induced peripheral neuropathy,[80] CIDP,[81] Fabry disease,[82] and idiopathic SFN.[83] CCM can detect subclinical small nerve fiber damage in patients with IGT[84] and has been shown to predict the development of DPN[85] and the end points of foot ulceration and Charcot foot.[86] CCM may be an ideal technique to monitor the progression of DPN, as it is noninvasive and hence reiterative.[87]

Optical Coherence Tomography

Optical coherence tomography is a noninvasive, reproducible ophthalmic imaging technique that was recently introduced as a surrogate end point for the assessment of retinal nerve fiber loss in neurologic conditions.[88,89] Retinal nerve fiber layer (RNFL) thinning is reported in patients with DPN associated with the severity of neuropathy, particularly in patients with a higher risk for foot ulceration.[90] Previous studies have suggested that RNFL loss in patients with diabetes may be independent of diabetic retinopathy and represents a distinct type of neuropathy.[91,92] Measuring RNFL thickness has also been suggested as a potentially useful means to assess and monitor axonal loss in patients with DPN, as RNFL thinning was greater in patients with DPN compared to those without DPN over the course of 4 years.[93] However, larger-scale, longitudinal prognostic and interventional studies using optical coherence tomography as

a surrogate marker are required before routine use of this modality can be recommended.

The use of optical coherence tomography as a possible diagnostic modality is still in its infancy and requires longitudinal studies alongside established biomarkers, such as electrophysiology and skin biopsy. CCM has a wealth of research, particularly in DPN. However, the availability of CCM as a diagnostic modality is limited due to a lack of expertise in its use as a surrogate marker in peripheral neuropathies.

Symptomatic Treatment of DPN

Neuropathic pain is a debilitating feature of DPN resulting in significant morbidity.[94] Current guidelines advocate the use of therapies targeting the symptoms of painful DPN, particularly as there is a lack of treatments targeting the pathogenetic mechanisms. Although measures such as tight glycemic control may prevent the progression of diabetic neuropathy, there is no evidence that improved glycemic control improves pain in DPN. Moderate improvements in pain are considered to be ~30% to 50% pain relief, whereas >50% pain relief is considered a good outcome.[95] A recent systematic review concluded that duloxetine, venlafaxine, pregabalin, oxcarbazepine, tricyclic antidepressants (TCAs), atypical opioids, and botulinum toxin were more effective than placebo for relieving neuropathic pain, but quality of life was poorly reported. Studies were however short term and drugs had substantial discontinuation rates of ~10%.[96]

The limited benefit of any one agent alone reflects the complex etiologic basis of neuropathic pain. Thus, there is an increasing recognition that "one size does not fit all," and rather than having an agnostic approach (ie, blindly trying different therapies until one works), we should consider better clinical phenotyping and targeted therapies.[97] However, superficial clinical phenotyping in relation to symptomatology has not been shown to improve the response to therapy.[98] More detailed phenotyping using QST has shown that patients with an irritable nociceptor (IN) phenotype (n = 31) compared to a non-IN phenotype (n = 52) had a significantly greater response to oxcarbazepine and a reduced overall number needed to treat (NNT) (6.9 vs 3.9).[99] In a smaller-scale study, the relative efficacy of 5% lignocaine was assessed in 15 patients with IN and 25 patients with non-IN, a greater effect on pain paroxysms and deep aching pain was found in those with IN.[100] We have also demonstrated preclinical evidence on the physiology and pharmacology of rate-dependent depression of the spinal H-reflex as a marker for spinal disinhibition in painful diabetic neuropathy,[101] and recently translated the use of rate-dependent depression as a biomarker of spinally mediated pain to a personalized-medicine approach in the treatment of painful DPN.[102] In this section, we consider the current pharmacologic treatments for alleviating pain in DPN, the most frequently used of which are highlighted in Table II.

Antidepressants

Neurologic pathways implicated in mood disorders share neurotransmitters with pathways associated with pain processing.[103] It is therefore not surprising that there is a dual utility in alleviating neuropathic pain.

Tricyclic Antidepressants

The precise mechanism of action of TCAs in analgesic efficacy is unclear, but they are thought to indirectly modulate the opioid system in the brain via serotonergic and norepinephrine neuromodulation, among other properties.[104–106] TCAs require up-titration to effective doses, often over a period of 6 to 8 weeks before reasonable effects are noted; hence, compliance may sometimes be compromised.[107] A meta-analysis by Rudroju et al[108] concluded that amitriptyline was the least effective but a well-tolerated agent compared to other antidepressant agents used to treat painful DPN. In a joint report on painful DPN from the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation, published in 2011, it was concluded that amitriptyline has the greatest efficacy among the TCAs.[109] Despite studies showing the efficacy of imipramine,[110] it was also concluded that there is currently insufficient evidence for the routine use of imipramine.

TCAs remain as the first- or second-line recommendations in all 5 international guidelines on pain management in DPN, with most citing amitriptyline as the drug of choice among the TCAs (Table III). The 2017 position statement from the ADA stated that, although effective for the treatment of neuropathic

Table II. Commonly used therapies for painful diabetic peripheral neuropathy.

Drug Class	Agent	Initial Dose	Maintenance Dose	Common Adverse Reactions	Common Drug Interactions
Anticonvulsants	Pregabalin	25–75 mg TID	300–600 mg daily	Dizziness Somnolence Headache Weight gain Nausea Vomiting Dry mouth	Respiratory depression when combined with opioids. Additive effects on cognition and motor function may occur when combined with benzodiazepines, alcohol, or opioids.
	Gabapentin	100–300 mg TID	900– 3600 mg daily	Dizziness Somnolence Ataxia Fatigue	
Antidepressants	Duloxetine	20–30 mg once daily	60–120 mg once daily	Somnolence Dizziness Headache Nausea Dry mouth Reduced appetite	Avoid concurrent use with irreversible MAOIs due to increased risk for serotonin syndrome. Combination with tramadol may lower seizure threshold. Avoid use with ciprofloxacin.
	Venlafaxine	37.5 mg once daily	75–225 mg once daily	Nausea Dizziness Constipation Dry mouth Weight loss Constipation	Avoid use with MAOIs due to increased risk for serotonin syndrome. Avoid use with linezolid (a weak MAOI). Concurrent use with other SNRIs, SSRIs or serotonin receptor agonists (eg, triptans) increases risk for serotonin syndrome. Potential use is advised with caution.
	Amitriptyline	10–25 mg once daily	25–100 mg once daily	Abdominal pain Fatigue Headache Dizziness Insomnia Orthostatic hypotension	Avoid MAOIs due to risk for serotonin syndrome. Concurrent use with drugs prolonging QT interval may predispose to ventricular arrhythmias. Concurrent use with tramadol may precipitate development of the serotonin syndrome and should be done with caution. Concurrent use with anticholinergic drugs may potentiate their effects, thus increasing the risk for paralytic ileus.

(continued)

Table II. (continued).

Drug Class	Agent	Initial Dose	Maintenance Dose	Common Adverse Reactions	Common Drug Interactions
				Anorexia Nausea Urinary retention Constipation Blurred vision Mydriasis Weight gain Xerostomia Somnolence	
Opioids	Tramadol	50 mg QID	200– 400 mg QID	Constipation	Concurrent use with MAOIs and linezolid increases risk for serotonin syndrome.
				Somnolence Nausea Headache Dizziness	Combination therapy with SSRIs, SNRIs, TCAs, or antipsychotics can lower seizure threshold, leading to convulsions. Combination use with caution is advised.
	Tapentadol (immediate release)	50–100 mg 4–6 times per day Can take 700 mg on first day	600 mg daily	Same as above	Concurrent use with SSRIs or SNRIs may increase risk for serotonin syndrome. Use with caution is advised. Concurrent use with MAOIs can result in hypertensive crisis. Use with enzyme inducers such as rifampicin or St John's wort may reduce efficacy.

MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin norepinephrine re-uptake inhibitors; SSRIs = selective serotonin re-uptake inhibitors; TCAs = tricyclic antidepressants.

pain, TCAs should be used with caution given their higher-risk profile, particularly in elderly populations.[50]

Serotonin–Norepinephrine Reuptake Inhibitors

Two serotonin–norepinephrine reuptake inhibitors are used in painful DPN, duloxetine and, to a lesser extent, venlafaxine, which does not have FDA approval for use in the treatment of painful DPN. A third serotonin–norepinephrine reuptake inhibitor is desvenlafaxine, which was evaluated in a single randomized, controlled trial and showed some efficacy.[114] These drugs primarily exert their effect via inhibiting serotonin and norepinephrine reuptake, resulting in the excitation of inhibitory descending pathways with alleviation of neuropathic pain.[115]

Duloxetine at both 40 mg and 60 mg has shown efficacy in treating painful DPN.[116] A Cochrane review including 8 trials (n = 2728) showed that 60 mg of duloxetine daily was more efficacious compared with placebo, with a 50% pain reduction by 12 weeks (NNT = 5; 95% CI, 4–9).[117] Tanenberg et al[118]

Table III. Current guidelines for painful diabetic peripheral neuropathy.

Line of Treatment	EFNS (2010)[111]	AAN (2011)[109]	NICE (2013)[112]	AACE (2015)[113]	ADA (2017)[50]
1st line	Amitriptyline Duloxetine Pregabalin Venlafaxine Sodium valproate Gabapentin	Pregabalin	Amitriptyline Duloxetine Pregabalin Gabapentin	Amitriptyline SNRI Pregabalin Gabapentin Clonidine	Duloxetine Pregabalin
2nd line	Tramadol Opioids	Amitriptyline Duloxetine Sodium Valproate Venlafaxine Gabapentin Tramadol Opioids Capsaicin	Amitriptyline Duloxetine Pregabalin Gabapentin	Tramadol Tapentadol Topiramate Oxcarbazepine Lidocaine 5% Capsaicin	TCA Gabapentin
3rd line			Capsaicin Tramadol		

AACE = American Association of Clinical Endocrinologists; AAN = American Academy of Neurology; ADA = American Diabetes Association; EFNS = European Federation of Neurological Societies; NICE = National Institute of Clinical Excellence (UK); SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

showed that duloxetine was noninferior to pregabalin in treating painful DPN in patients exhibiting an inadequate response to gabapentin. Duloxetine has a superior safety profile compared to amitriptyline, owing to the comparably lower rates of anticholinergic side effects. However, one study found a 20% and 14% respective prevalence of somnolence and constipation in a cohort of patients treated with 60 mg of duloxetine daily.[119] A post hoc analysis of 3 pooled, double-blind, placebo-controlled trials evaluating the use of duloxetine in older patients (aged >65 years) advocated the tolerability and efficacy of this drug in the older population.[120]

Venlafaxine showed efficacy in treating painful DPN in a double-blind placebo controlled trial in which pain-intensity visual analog scale (VAS) scores were used as the primary outcome measure.[121] A Cochrane Collaboration systematic review[122] of venlafaxine for the treatment of neuropathic pain reported an NNT of 3.1 (95% CI, 2.2–5.1), which is comparable to that of amitriptyline.[123] Venlafaxine has shown superiority to duloxetine in some studies; however, there is a lack of larger-scale trials showing this effect.[124] Additionally, it is important to note that venlafaxine must be slowly weaned to reduce the potential for adverse events,[124] and it has not been approved by the FDA for use in treating neuropathic pain.

Anticonvulsants

Similarities in the mechanisms of neuropathic pain and epilepsy led to the use of anticonvulsant medications in the treatment of painful DPN.[125] Carbamazepine has been used efficaciously in the management of trigeminal neuralgia for many years; however, a Cochrane Collaboration review found that it had limited utility in the treatment of painful DPN,[126] and it is not recommend for painful DPN. Similarly, in a recent Cochrane review, oxcarbazepine showed little evidence for efficacy in painful diabetic neuropathy.[127]

α2δ Ligands

Gabapentin is a lipophilic analogue of γ-aminobutyric acid that binds to the $\alpha 2\delta_1$ subunit of the voltage-gated calcium channel on the presynaptic membranes and reduces excitability of chiefly glutaminergic neurones.[128]

Backonja et al[129] investigated its use in neuropathic pain in a double-blind, placebo-controlled trial of patients randomized to either gabapentin or placebo. Significant improvement in pain scores were seen 8 weeks after the start of treatment.[129] A systematic review of 35 studies (n = 727) in patients with unselected neuropathic pain concluded that gabapentin was an effective agent in alleviating pain; however, its effectiveness may be reduced if administered at low doses.[130] Rudroju et al[108] compared the efficacy and tolerability of 6 agents used in the management of painful DPN in a meta-analysis of data from 21 trials and concluded that gabapentin provided a good balance between tolerability and efficacy for the treatment of painful DPN.

Pregabalin, another analogue of γ-aminobutyric acid has higher potency and has been approved by the FDA for use in treating painful DPN based on several robust randomized, controlled trials that have shown its efficacy in the treatment of painful DPN.[131–133] Snedecor et al[134] undertook a comparative meta-analysis of data from studies of a number of agents in the treatment of painful DPN and found pregabalin to be the most efficacious in reducing pain VAS scores.

Somnolence is listed as a common side effect of pregabalin, as studies in healthy volunteers have shown that it enhances slow-wave sleep. A placebo-controlled trial evaluated the efficacy of pregabalin, amitriptyline, and duloxetine in pain relief and the effects on sleep.[135] Duloxetine increased sleep fragmentation, while pregabalin promoted sleep.[135] These findings are in agreement with those from previous studies showing that pregabalin improves subjective sleep and quality of life in patients with painful DPN.[136,137] Side effects include edema and mood disturbance, and it is important to warn patients not to abruptly discontinue its use, as this has been linked to the development of seizures, cerebral edema, and encephalopathy.[138] Both gabapentin and pregabalin are commonly prescribed as first-line agents for treating painful DPN, and this is indeed a reflection of the current recommendations.

COMBO-DN Study

The only 2 medications with both FDA and European Medicines Agency approval for use in the treatment of painful DPN are pregabalin and duloxetine. The COMBO-DN study was designed to compare the efficacy and tolerability between high-dose monotherapy and standard-dose combination therapy with both pregabalin and duloxetine.[139] This multinational, randomized, double-blind, parallel-group trial was conducted in patients with painful DPN resistant to standard-dose monotherapy. After randomization and elimination of noneligible patients, 173 received high-dose monotherapy with either duloxetine 120 mg daily or pregabalin 600 mg daily, and 170 patients received combination therapy with duloxetine 60 mg daily and pregabalin 300 mg daily.[139] A 2-point reduction in the Brief Pain Inventory score was the primary outcome measure; no significant difference was shown when comparing the standard-dose combination therapy to the high-dose monotherapy therapy in those who did not achieve adequate pain relief on standard-dose duloxetine or pregabalin.[139]

In a secondary analysis, duloxetine 60 mg was found to be more efficacious compared with pregabalin 300 mg/day in the initial 8-week run in phase. To date, this is the only head to head trial of duloxetine and pregabalin. A further exploratory post hoc analysis of data from Combination vs. Monotherapy of pregaBalin and duloxetine in Diabetic Neuropathy (COMBO-DN) showed that high-dose monotherapy was favorable in patients with severe pain, whereas combination therapy was more beneficial in patients with moderate and mild pain.[140] Also, patients who received duloxetine (60 mg/d) as initial therapy had a better response to combined duloxetine and pregabalin for evoked or severe tightness and a greater benefit with high-dose duloxetine (120 mg/d) for paresthesia–dysaesthesia.[140,141]

Other Anticonvulsants

The use of topiramate has been evaluated in several placebo-controlled trials, with differing results. Raskin et al[142] randomized 323 subjects to topiramate versus placebo and found a significant 30% reduction in pain VAS scores with topiramate.[142] A recent smaller study from Iran[143] showed that gabapentin and topiramate equally reduced pain scores.[143] However, a Cochrane Collaboration review of data from 3 placebo-controlled, parallel-group trials showed that topiramate lacks evidence of efficacy in painful DPN.[144]

Lamotrigine is chemically unrelated to other antiepileptic agents. It is thought to exert its antiepileptic effect via sodium channels. Lamotrigine has been

assessed in painful DPN. Eisenberg et al[145] observed a significant reduction in the numeric pain scale in 83% of patients randomized to lamotrigine compared to 73% receiving placebo, but this study was relatively small-scale (n = 59). In an analysis of data from 2 randomized trials, lamotrigine (300 and 400 mg daily) showed inconsistent effects in DPN, and while it was well tolerated,[146] it cannot be advocated for use in painful DPN.[147]

A double-blind, placebo-controlled trial of lacosamide found it to be efficacious compared to placebo; however, the cohort receiving 600 mg daily had a much higher withdrawal rate due to adverse reactions, such as nausea, tremor, headache, and fatigue.[148] The efficacy of lacosamide over placebo was also marginal, and it is therefore currently not recommended for use in painful DPN.[147]

Opioid Analgesia

Partial μ-Receptor Agonists

Tramadol is a centrally acting synthetic opioid that is a nonselective agonist with affinity at the μ-, δ-, and κ-opioid receptors, with preferential affinity for the μ-receptor, and also inhibits norepinephrine and serotonin reuptake.[149] A Cochrane Collaboration review found that the efficacy of tramadol in neuropathic pain was determined in small-scale, largely inadequate studies with a potential risk for bias.[149] Although data from 3 of these trials were further analyzed in a meta-analysis and showed an NNT for 50% pain reduction of 4.4 (95% CI, 2.9–8.9),[149] it still concluded that there were insufficient data of adequate quality to provide convincing evidence that tramadol is effective in relieving neuropathic pain.[149] Anecdotally, tramadol may be used to treat breakthrough pain in combination with other neuropathic pain agents, although its use in combination with TCAs and serotonin–norepinephrine reuptake inhibitors is cautioned due to the increased risk for serotonin syndrome, with increased risks for confusion, seizures, labile blood pressure, and, in extreme cases, coma and death.

Tapentadol is similar to tramadol in its mechanism of action. Schwartz et al[150] conducted a 12-week open-label study in 396 patients with DPN, which demonstrated a 30% pain reduction in 65% of patients and a 50% pain reduction in 34.9% of patients.[150] A subsequent 12-week study confirmed these earlier data, and in 2012 the FDA approved the use of modified-release tapentadol for the treatment of neuropathic pain.[151]

Opioid Agonists

There is increasing concern for opioid dependency, especially during long-term use, despite the efficacy of opioids in treating neuropathic pain.[152] A Cochrane Collaboration review[153] evaluated the use of oxycodone modified release, morphine, levorphanol, and methadone in the treatment of neuropathic pain and found that, in studies lasting 12 weeks or less, opioids exhibited a significant analgesic effect compared to placebo, but the results were subject to bias due to relatively small sample sizes and short duration of studies.[153] Additional data are needed to characterize long-term efficacy and the safety profile of opioids in neuropathic pain.

Topical Medications

Topical treatments for painful DPN may be particularly useful for patients not tolerating conventional systemic therapies, as there is a reduced prevalence of adverse effects.[154] Furthermore, the risk for drug–drug interactions is also significantly reduced, making topical therapies more attractive for a growing number of patients with multiple comorbidities and polypharmacy.

Capsaicin is a naturally occurring alkaloid found in red chili peppers. It works by selectively agonizing the transient receptor potential vanilloid 1 (TRPV1) receptor, which is expressed on small nerve fibers. Downstream signals from the TRPV1 receptor result in the release of substance P and its subsequent depletion, which causes a reduction of painful stimuli conveyed to the CNS.[155,156] The Capsaicin Study Group conducted a double-blind, placebo-controlled trial (n = 277) of 0.0075% topical capsaicin and found a significant reduction in pain, as measured by physicians' global evaluation and a VAS scale.[157] Capsaicin is currently recommended as third-line therapy in the United Kingdom's National Institute of Clinical Excellence guidelines and second-line by the American Academy of Neurology for the treatment of neuropathic pain. Its use is severely limited by the frequency of application (4 times daily) and burning pain frequently induced on application. Of concern, capsaicin has been shown to lead to a reduction in thermal nociception and total denervation, with a putative increased risk for diabetic

foot ulceration, and is not recommended in the treatment of painful DPN.[158]

Furthermore, currently not included in any published guidance for painful DPN is the 8% capsaicin patch, which was initially tested in patients with postherpetic neuralgia. A recent review reported its efficacy in a number of neuropathies of varying etiology and included data from a 12-week double-blind trial in patients with painful DPN, in whom it improved both pain and sleep quality significantly; yet the review, despite including a study on the use of capsaicin in skin biopsies, failed to report on the outcomes.[159]

Lidocaine plaster 5% applied for 18 h/d has been shown to effectively provide relief in painful DPN and has been extensively used in postherpetic neuralgia. A systematic review of data from 38 studies found a significant pain reduction using the 5% lidocaine patch that was comparable to those with amitriptyline, capsaicin, gabapentin, and pregabalin.[154] The lidocaine patch was also found to be associated with fewer and less clinically significant side effects compared to systemic agents.[154] A meta-analysis reported that the 5% lidocaine patch was as efficacious as pregabalin in treating painful DPN.[134]

Topical isosorbide dinitrate has been evaluated in the treatment of painful DPN. Impaired nitric oxide synthesis has been found to play a role in DPN pathogenesis. The vasodilatory response to nitroglycerin directly releases nitric oxide, suggesting a potential role for its use in patients with DPN.[160] Alterations of neuronal nitric oxide synthase in the dorsal root ganglion cells and in the spinal cord may contribute to spinal sensory processing, as well as to the development of neuronal plasticity phenomena in the dorsal horn of the spinal cord, as previously described in experimental studies.[160] Yuen et al[161] found significant reductions in pain and intensity in a double-blind trial recruiting 22 patients. Later, Rayman et al[162] described a case series of 18 patients treated with glyceryl-trinitrate patches with localized pain showing a reduction in pain scores. Topical lidocaine and glyceryl-trinitrate patches may be used in combination to provide 24-hour pain cover with alternating 12-hour applications of each therapy.

Intravenous Lidocaine

IV lidocaine has been used in the treatment of pain produced by nerve injury for many years. Major Gordon of the Royal Canadian Army Medical Corps used IV procaine to successfully provide analgesia to burn patients as early as 1943.[163] Viola et al[164] was the first group to evaluate the effectiveness of IV lidocaine infusion, in a double-blind, placebo-controlled trial in patients with intractable painful DPN refractory to standard treatment. A randomized, placebo-controlled trial of IV lidocaine infusion in 15 patients showed a significant analgesic effect, which persisted for up to 28 days.[164] There were no significant side effects of this treatment, although this cohort was small. The efficacy of lidocaine seems to be due to several independent modes of action targeting neuropathic pain. Lidocaine modifies sodium channel expression, reducing peripheral nociceptive sensitization,[165] and it also has anti-inflammatory properties similar to those of conventional anti-inflammatory drugs.[166] Inflammatory cytokines are thought to play a role in secondary hyperalgesia and the sensitization of the CNS to inappropriate pain signals.[167]

Emerging Therapies for Painful DPN

Virtually no new novel analgesics have been approved by the FDA for the treatment of neuropathic pain over the past 20 years. There are several emerging treatments that may potentially shift the pharmacologic paradigm in the treatment of neuropathic pain (Table IV). Such targets include suppression of glutaminergic neurotransmission,[168] *N*-methyl-D-aspartate receptor antagonism,[169] angiotensin II receptor type 2 antagonism, and presynaptic modulation of cannabinoids[170] and humanized anti–nerve growth factor monoclonal antibodies.[171]

Dextromethorphan is an *N*-methyl-D-aspartate receptor antagonist that has been evaluated in Phase III clinical trials for the treatment of painful DPN. In addition, it also has properties of serotonin reuptake inhibition. Administered as monotherapy, dextromethorphan has limited bioavailability due to rapid catabolism by hepatic cytochrome P-450 2D6. It must therefore be administered with a potent P-450 2D6 inhibitor such as quinidine. Shaibani et al[172] evaluated 2 doses of dextromethorphan/quinidine, 45/30 mg and 30/30 mg, in a double-blind, placebo-controlled trial (n = 379) and showed that dextromethorphan/quinidine was significantly more efficacious compared with placebo, with a reasonable safety profile.

Desvenlafaxine is the most potent metabolite of the parent compound venlafaxine and has been evaluated

Table IV. Emerging therapies for the treatment of painful diabetic peripheral neuropathy.

Drug	Drug Class	Developer
Dextromethorphan/quinidine combination	Glutamate antagonist	Avanir, New York, New York
EMA401	Angiotensin II type 2 receptor antagonist	Novartis, East Hanover, New Jersey
Capsaicin, dermal patch (NGX-4010)	Vanilloid-receptor agonist	NeurogesX, San Mateo, California
Desvenlafaxine SR	SNRI	Wyeth, Madison, New Jersey
Lacosamide (SPM-927)	Amino acid anticonvulsant	Schwarz Pharma, Mequon, Wisconsin
Lamotrigine once daily	Anticonvulsant	GlaxoSmithKline, Research Triangle Park, North Carolina
Oravescent fentanyl	Opioid agonist	Cephalon, Frazer, Pennsylvania
Tramadol ER	Mu-opioid antagonist and SNRI	TheraQuest Biosciences, Blue Bell, Pennsylvania
GW-406381	COX-2 inhibitor	GlaxoSmithKline
Cibinetide (ARA290)	Peptide of erythropoietin Innate repair receptor and TRPV1 antagonist	Araim, Tarrytown, New York

COX = cyclooxygenase; ER = extended release; SNRI = serotonin–norepinephrine reuptake inhibitor; SR = sustained release; TRPV1 = transient receptor potential vanilloid 1.

in patients with painful DPN.[114,173] In a Phase III multicenter, randomized placebo-controlled trial (n = 412), graduated doses of 200 and 400 mg/d desvenlafaxine were found to be effective in relieving pain and improving activity.[114]

EMA401 is an angiotensin II type 2 receptor antagonist that was evaluated in a multicenter, randomized, placebo-controlled trial in 183 patients with postherpetic neuralgia over 28 days and showed benefit.[174] Anand et al[175] showed angiotensin 2 immunostaining in 75% of small- to medium-diameter human dorsal root ganglia neurons and that this was the major ligand for angiotensin II type 2 receptor.[175] Angiotensin 2–mediated angiotensin II type 2 receptor signaling was reversed by EMA401, establishing a mechanism for its action in neuropathic pain.[175]

Cibinetide (ARA290), a nonhematopoietic peptide of erythropoietin, interacts selectively with the innate repair receptor–mediating tissue protection[176] and also antagonizes the transient receptor potential vanilloid 1 receptor,[177] mediating disease-modifying and analgesic effects, respectively. It has shown significantly increased small nerve fiber abundances in the cornea and skin, with improved neuropathic pain in patients with DPN[178] and sarcoid neuropathy.[179]

Tanezumab is a fully humanized anti–nerve growth factor monoclonal antibody. However, this class of drugs has a long and checkered history, with the FDA placing a clinical hold on clinical studies of anti–nerve growth factor monoclonal antibody in late 2010, because of reports of serious joint-related adverse events and sympathetic nerve damage tolerability concerns. However, the FDA lifted its hold in March 2015, and in 2017 granted fast-track status as a nonopioid pain medication,[180] particularly for hip and knee osteoarthritis.[181] In the only reported study in DPN, 20 mg of SC tanezumab was administered on day 1 and week 8 and showed a reduction in DPN pain but no improvement in patients' global assessment of pain.[182]

Vitamin D deficiency is associated with paresthesia and parasympathetic dysfunction[183,184] and is highly prevalent in diabetic populations.[185] Shebab et al[186] showed that vitamin D deficiency is a risk factor for

DPN. Furthermore, a meta-analysis in type 2 diabetes (n = 1484) confirmed a significant correlation between serum vitamin D_3 levels and the risk for DPN.[187] An open-label, prospective study conducted in Pakistan found a single IM-administered dose of 600,000 IU of vitamin D_3 provided significant pain relief in painful DPN.[188] More data are required before the role of vitamin D supplementation in painful DPN is established.

International Guidelines for Painful DPN

Five professional bodies have produced expert guidance on the management of painful diabetic neuropathy (**Table III**).[50,109,111–113] Pregabalin is recommended as first-line therapy in all 5 guidelines, and duloxetine is recommended as first-line in all of the guidelines except that from the American Academy of Neurology, based on only 1 duloxetine trial being graded as class 1 evidence, due to completion rates being <80% of those in other trials.[50]

CONCLUSIONS

DPN is common, often misdiagnosed, and inadequately treated. DPN accounts for considerable morbidity and mortality and reduced quality of life. Clinical recognition is required for allowing timely symptomatic management to reduce the morbidity associated with this condition. Glycemic control is the central component of treatment, but it is difficult to achieve for many patients. Cardiovascular risk factors play a major role in the pathogenesis of DPN and should be intensively controlled with a personalized approach to the patient. The management of pain remains the key aspect of symptom treatment for DPN.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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