

Diabetic Peripheral Neuropathy: Epidemiology, Physiopathology, Diagnosis and Treatment

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Abstract

Diabetic peripheral neuropathy (DPN) is a common complication of both type 1 and type 2 diabetes. It affects over 90% of the diabetic patients. It is widely accepted that the toxic effects of hyperglycemia play an important role in the development of this complication, but several other hypotheses have been postulated. It is typically characterized by significant deficits in tactile sensitivity, vibration sense, lower-limb proprioception, and kinesthesia. Painful DPN has been shown to be associated with significant reductions in overall quality of life, increased levels of anxiety and depression, sleep impairment, and greater gait variability. DPN is often misdiagnosed and inadequately treated. Clinical recognition of DPN is imperative for allowing timely symptom management to reduce the morbidity associated with this condition. The management of diabetic neuropathic pain consists basically in excluding other causes of painful peripheral neuropathy, improving glycemic control as a prophylactic therapy and using medications to alleviate pain. First line drugs for pain relief include anticonvulsants, such as pregabalin and gabapentin and antidepressants, especially those that act to inhibit the reuptake of serotonin and noradrenaline. In addition, there is experimental and clinical evidence that opioids can be helpful in pain control, mainly if associated with first line drugs. Other agents, including for topical application, such as capsaicin cream and lidocaine patches, have also been proposed to be useful as adjuvant in the control of diabetic neuropathic pain, but the clinical evidence is insufficient to support their use. The purpose of this review is to examine proposed mechanisms of DPN, summarize current treatment regimen. A better understanding of the mechanisms underlying diabetic neuropathic pain will contribute to the search of new therapies.

Methodology

A comprehensive literature review was undertaken, incorporating article searches in electronic databases (EMBASE, PubMed, and OVID) and reference lists of relevant articles with the authors' expertise in DPN. This review considers seminal and novel research in epidemiology; diagnosis, and the treatment of neuropathic pain in DPN.

Keywords: Diabetes; Neuropathic pain; Diabetic peripheral neuropathy ;Diagnosis; Epidemiology; Pharmacotherapy; Anticonvulsants; Antidepressants

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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 Diabetic peripheral neuropathy (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} Generally, DPN affects the toes and distal foot, but slowly progresses proximally to involve the feet and legs in a stocking distribution. It is also characterized by a progressive loss of nerve fibers affecting both the autonomic and somatic divisions, thereby diabetic retinopathy and nephropathy can occur.⁷ Foot ulceration and painful neuropathy are the main clinical consequences of DPN, linked with higher morbidity and mortality.⁸ Frequently, patients look for medical help only when pain appears⁹, a symptom that affects 10% to 26% of this population.¹⁰ Diabetic neuropathic pain (DNP) is characterized by tingling, burning, sharp, shooting, and lancinating or even as electric shock sensations.⁷ It is usually considered moderate to severe and often worse at night, causing sleeping disturbs. The pain can be constant and accompanied of cutaneous allodynia, which can substantially affect the quality of life of patients, impacting the ability to perform daily activities and having a negative influence on mood. The pain may also be a reason of withdrawal of recreational and social activities and may be associated with depression.^{7,11,12} The pathogenesis of DNP is not fully understood. Several theories have been proposed to explain the pain related to the diabetic neuropathy, such as changes in the blood vessels that supply the peripheral nerves; metabolic and autoimmune disorders accompanied by glial cell activation, changes in sodium and calcium channels expression and more recently, central pain mechanisms, such as increased thalamic

vascularity and imbalance of the facilitatory/inhibitory descending pathways.⁷ Additionally, several risk factors are associated with DNP including worsening glucose tolerance, older age, longer diabetes duration, drinking alcohol and cigarette smoking.¹² Currently, only three agents are approved by most of the guidelines for the treatment of DNP: duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, pregabalin, an anticonvulsant, and the dual effect drug tapentadol, an opioid receptor agonist and norepinephrine reuptake inhibitor.¹³ However, as pain relief is unsatisfactory for most patients, several pharmacological interventions have been used based on pre-clinical and/or clinical evidence, as well as an inference of mechanism of action. Despite the considerable, health care related economic burden and defect on quality of life in DPN, treatment options are limited and prevention remains the key goal.¹⁴ 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.

Epidemiology

Epidemiologic studies of diabetic neuropathy have provided heterogeneous results, owing to different patient populations, definitions of neuropathy used, and methods of assessments. Pre diabetes is also associated with neuropathy.¹⁵ In a Spanish study, the reported prevalence of DPN in primary care was 21% compared to 2.7% in-hospital.¹⁶ In the San Luis Valley cohort,¹⁷ 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 Rochester Neuropathy Study¹⁶ evaluated data from 380 participants; where 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 non diabetic etiology of the neuropathy.¹⁶ A community based study in about 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.¹⁸ 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 prevalence 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.¹⁹ In the EURODIAB IDDM complications study,²⁰ 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.²⁰ 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, 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.²¹

Physiopathology of neuropathic pain in diabetes

Although there is a great advance in understanding the pathophysiological mechanisms leading to the development of diabetic complications, there is not yet a plausible hypothesis to explain why some patients develop the painful form of disease while others do not. However, interestingly, pain intensity normally is not associated with neuropathy severity, and can occur even in the absence of nerve injuries.^{22,23} The exact mechanism by which diabetes causes neuropathy has not been clearly elucidated, but increased levels of advanced glycation end products (AGE) and protein kinase C (PKC) due to prolonged

hyperglycemia are thought to be involved in peripheral nerve damage. Oxidative stress caused by AGE creates microscopic vascular damages, hindering blood supply to the peripheral nerves.²⁴ Certain proinflammatory cytokines including IL-6 and TNF- α , are also elevated during hyperglycemia and are thought to contribute to nerve cell damage.²⁵ Based on these mechanisms, treating diabetic neuropathy using molecular chaperones including certain heat shock proteins (HSP) to prevent nerve injuries may be a viable option.²⁵ While nerve damage from hyperglycemia is a common pathophysiology shared by both the non painful neuropathy and painful neuropathy in diabetes, painful presentations of diabetic neuropathy appear to stem from the body's over compensations or abnormal responses to the nerve damage. A cascade of events following the nerve damage leads to abnormal expression of sodium channels along the axon at the site of peripheral nerve damage, leading to ectopic neural discharge.²⁶ There is an altered expression of Na⁺, K⁺, and Ca²⁺ channels in the nociceptive neurons of the dorsal root ganglion, as well as abnormal proliferation and sprouting of sympathetic neurons. The result of these events is exaggerated or spontaneous pain sensation.²⁶ Hemodynamic factors have been suggested to be distinct between the non-painful versus the painful phenotypes, as epineurial intravascular oxygen saturation and blood flow were shown to be higher in people with painful neuropathy, possibly as a result of arteriovenous shunting and consequent endoneurium hypoxia stimulating painful sensation.²⁷ Recent studies have also implicated involvements of central pain processing mechanisms in painful DPN, showing that aberrant neurons in the ventral posterolateral thalamus of diabetes patients could become hyper-excitable and amplify the painful sensation.²⁸ This central process may be related to elevated thalamic perfusion or abnormal supraspinal modulation of sensory processing arising potentially due to damage from prolonged hyperglycemia, generating allodynia and hyperalgesia.^{29,30} Presence of a possible genetic

component in painful DPN has also been suggested.³¹ For instance, mutations in certain genes coding for tetrahydrobiopterin (BH4) may increase susceptibility to painful neuropathy.³² DPN is significantly more common in type 2 than in type 1 diabetes.³³ Pain tends to be bilateral and although it predominantly involves lower limbs, specifically the foot, in some cases, upper extremities may be involved, including fingertips and palms.³⁴ This distribution pattern occurs because the longest sensory axons are usually the first to be affected by diabetes.²⁴ Patients typically describe their neuropathic pain by using words such as “hot”, “burning”, “electric”, “jolts”, “sharp”, “tingling”, and “pins and needles”.³¹ It may also be accompanied by allodynia (painful response to normally non-painful stimuli) and hyperalgesia (exaggerated response to mild pain stimuli). Pain is often worse during the night, as well as under stress and fatigue.³¹ Painful DPN poses a substantial and growing concern for patients and the health care system. DPN has been shown to be associated with significant reductions in overall quality of life in a cross-sectional study, where patients with painful DPN showed significantly poorer quality of life compared to those without neuropathy and those with non-neuropathic pain.³⁵ Painful neuropathy also causes considerable disability, with one-third of patients requiring a walking assist device such as a cane, walker, or wheel chair due to their neuropathy.³¹ A study investigating gait function in type 2 diabetes mellitus patients with DPN found significantly greater gait variability and higher number of self-reported falls in DPN patients with painful neuropathy than in DPN patients without painful neuropathy, suggesting that pain by itself affects walking ability.³⁶ The severity of painful DPN is associated with increasing levels of anxiety and depression, as well as significant sleep impairment.³⁷

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.³⁸ Alternative etiologies of neuropathy should be actively diagnosed and treated. These include chronic inflammatory demyelinating polyneuropathy, B₁₂ deficiency, hypothyroidism, and uremia, which may concomitantly occur in diabetes.³⁹ The tests frequently used to diagnose DPN have been listed in Table I, along with their advantages and disadvantages and type of nerve fiber they assess.³⁹

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	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, noninvasive. 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.

Screening

Patients with type 2 diabetes mellitus should be screened annually from diagnosis, and those with type 1 diabetes, after 5 years of diagnosis.³⁸ People with prediabetes should also undergo an assessment for neuropathy if symptoms are present.³⁸ Questionnaires is a subjective method to assess and quantify the severity of neuropathic symptoms and pain. The McGill Pain Questionnaire⁴⁰ is widely used to evaluate neuropathic pain.

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.^{41,42}

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.³⁸ 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. Many patients may be asymptomatic, and thus examination is the 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.⁴³ showed that a neuropathy disability score of 46/10 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.³⁸ 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.⁴⁴ The alternative 1-g monofilament may, however, be better for detecting earlier neuropathy.⁴⁵ The assessment of Small Fiber Neuropathy (SFN) remains a particular challenge, especially in diabetic neuropathy.⁴⁶

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 group⁴² 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 (e.g. "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.

Management of painful diabetic neuropathy

DNP continues to represent therapeutic challenges its pathophysiology is not yet fully understood and pain relief is still unsatisfactory. The pharmacological treatments, with exception to those targeted to the glycemic control, are symptomatic, not focused on the pathophysiological mechanisms, limited by side effects and by the development of tolerance.^{7,47}

Diet and lifestyle interventions

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

study⁴⁸ 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 study⁴⁹, in which diet and exercise counseling in subjects with IGT resulted in increased intra epidermal 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 anti inflammatory and anti oxidative stress properties.⁵⁰ 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.⁵¹ In a meta-analysis of data from 10 studies, there was greater remission and lower risks for microvascular and macro vascular 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.⁵² 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).⁵³ Micronutrient deficiencies after bariatric surgery are associated with an acute neuropathy⁵⁴, and longer longitudinal studies that accurately phenotype neuropathy are required to delineate potential risk factors for this condition.

Exercise intervention in people with painful diabetic neuropathy

Physical exercise and a healthy diet have been shown to improve the management of diabetes and its complications⁵⁵, although very few studies have investigated the effects of exercise on painful DPN. Multiple meta-analyses of randomized controlled trials⁵⁶ and clinical studies⁵⁷ suggest that exercise training of aerobic exercise,

resistance training, or combined training is associated with reduction in HbA1c and improvement in functional capacity, strength, and glycemic control respectively. Exercise has also shown to have an effect on glycemic control in diabetes independent from weight control.⁵⁸ Exercise training also improves cardiovascular complications of diabetes by ameliorating endothelial dysfunction and arterial remodeling and stiffness, likely via restoration of normal reduction oxidation balance.⁵⁹ Improvement in skeletal muscle metabolism through the enhancement of certain mitochondrial content levels is another potential benefit of regular exercise training.⁶⁰ On the other hand, the effects of exercise training on quality of life, depression, and anxiety are inconclusive at this point, as the literature has shown mixed results and may require additional well-designed randomized controlled trials.⁶¹

Treatment of DPN The management of pain remains the key aspect of symptom treatment for DPN. A wide variety of drugs, used alone or in combination, has been shown to significantly reduce neuropathic pain compared with placebo in randomized controlled trials, but pain relief remains inadequate for most patients.⁶² Generally, in clinical trials, treatment is considered successful if patients would obtain 50% of reduction in the pain level associated with some additional beneficial effects on sleep, fatigue, depression and quality of life.^{63,64} Thus, the management of this condition basically consists of excluding other causes of painful peripheral neuropathy, improving glycemic control as a prophylactic therapy and using medications to alleviate pain.⁶⁵ Despite of multimodal and multidisciplinary approaches to the treatment, the primary pathway is pharmacologically based.⁶⁶ Three different agents have regulatory approval for the treatment of DNP: pregabalin, duloxetine and tapentadol.^{13,67} However, as pain relief is still suboptimal and challenging for clinicians⁶⁸, drugs from various pharmacological classes have been used and some of them are included in this review (Table II).

Antidepressants Neurologic pathways implicated in mood disorders share neurotransmitters with pathways associated with pain processing.⁶⁹ It is therefore not surprising that there is a dual utility in alleviating neuropathic pain.

Tricyclic antidepressants The precise mechanism of action of Tricyclic antidepressants (TCAs) in analgesic efficacy is unclear, but they are thought to indirectly modulate the opioid system in the brain via serotonergic and norepinephrine neuro modulation, among other properties.⁷⁰ 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.⁷¹ A meta-analysis by Rudroju et al.⁷² concluded that amitriptyline was the least effective but a well-tolerated agent compared to other antidepressant agents used to treat painful DPN. The 2017 position statement from the ADA stated that, although effective for the treatment of neuropathic pain, TCAs should be used with caution given their higher-risk profile, particularly in elderly populations.³⁸

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 des-venlafaxine, which was evaluated in a single randomized, controlled trial and showed some efficacy.⁷³ 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.⁷⁴ Duloxetine at both 40 mg and 60 mg has shown efficacy in treating painful DPN.⁷⁵ Tanenberg et al.⁷⁶ showed that duloxetine was non inferior 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 anti cholinergic side effects. 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.⁷⁷ Venlafaxine has shown superiority to duloxetine in some studies; however, there is a lack of larger-scale trials showing this effect. Additionally, it is important to note that venlafaxine must be slowly weaned to reduce the potential for adverse events, and it has not been approved by the FDA for use in treating neuropathic pain.⁷⁷

Anticonvulsants

Pregabalin was the first anticonvulsant to receive approval from the Food and Drug Administration (FDA) for the treatment of postherpetic neuralgia, DNP and neuropathic pain after spinal cord injury.⁷⁸⁻⁸⁰ Pregabalin is a GABA analogue that selectively binds to pre-synaptic voltage-gated calcium channels containing the $\alpha 2\delta 1$ subunit in the brain and spinal cord, causing inhibition of the release of excitatory neurotransmitters.^{81,82} Moreover, $\alpha 2\delta 1$ subunits are responsible for increasing the functional expression of these channels, as a consequence of increased trafficking. Thus, the analgesic impaired trafficking of $\alpha 2\delta 1$ subunit with a consequent diminished expression of functional calcium channels.⁸³ Several clinical trials evaluating pregabalin in DNP showed efficacy in the management of this condition with a number needed to treat (NNT) of 6.3.^{7,64,84} In addition to its analgesic effects, pregabalin presents anxiolytic activity and it has a beneficial effect on sleep and quality of life, contributing, therefore, to improve the general condition of the patients.^{82,84} The side effects include dizziness, somnolence, peripheral edema, headache and weight gain.⁷ Some guidelines have also recommended gabapentin to treat DNP.⁸⁵ Gabapentin and pregabalin have a similar mechanism of action and the first is licensed for neuropathic pain in the United Kingdom, but not in the United States.⁶⁷ Some clinical trials have suggested that gabapentin and pregabalin present better analgesic efficacy than tricyclic antidepressants or opioids and other important aspects of these drugs include their tolerability and lack of serious toxicity.⁸⁶

Other anticonvulsants

The use of topiramate has been evaluated in several placebo-controlled trials, with differing results. Raskin et al.⁸⁷ randomized 323 subjects to topiramate versus placebo and found a significant 30% reduction in pain VAS scores with topiramate. A recent smaller study from Iran showed that gabapentin and topiramate equally reduced pain scores.⁸⁸ Lamotrigine is chemically unrelated to other anti-epileptic agents. It is thought to exert its anti epileptic effect via sodium channels. Lamotrigine has been assessed in painful DPN. Eisenberg et al.⁸⁹ 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 tolerated⁹⁰, it cannot be advocated for use in painful DPN.⁹¹ 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.⁹²

Table II: Current guidelines for painful diabetic peripheral neuropathy

Line of Treatment	EFNS (2010) ⁹³	AAN (2011) ⁹⁴	NICE (2013) ⁹⁵	AACE (2015) ⁹⁶	ADA (2017) ⁹⁸
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 Pregabalin 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.

Opioid analgesia

Opioids are recommended to be used as second or third line treatment for DNP.^{7,97} One multicenter, randomized, placebo-controlled study reported the tramadol effectiveness to significantly improve scores on physical and social functioning ratings in patients with DNP, but beneath some side effects such as nausea, constipation, headache and somnolence.⁹⁸ Morphine was also shown to be effective in reducing mean daily pain scores related to diabetic neuropathy and post herpetic neuralgia.⁹⁹ Moreover, results of clinical trials indicated that diabetic neuropathic patients experienced a significant reduction in pain intensity and an improvement on quality of life during oxycodone treatment, compared to placebo-exposed group.¹⁰⁰ Besides, oxycodone improved gabapentin but not the pregabalin effectiveness in promoting DNP relief.¹⁰¹ There is also evidence that the anti-hyperalgesic effect of opioids is improved by the association with some drugs, such as the antidepressants amitriptyline, moclobemide and reboxetine.¹⁰² Tapentadol has been shown to be effective in the management of different types of chronic pain, including osteoarthritis knee pain, low back pain and DNP, with a tolerable safety profile.¹⁰³ Specifically concerning DNP, a randomized-withdrawal, placebo-controlled trial reported reduction of at least 30% in pain intensity in about 50% of the patients that received tapentadol.¹⁰⁴ Similar data were obtained in a recent clinical trial in diabetic neuropathic patients with moderate to severe pain, which experienced nausea (21.1%) and vomiting (12.7%) as side effects.¹⁰⁵

Others agents

The drugs discussed below are currently associated to the pharmacological treatments already described according to the patients' symptoms and needs in order to achieve better relief of pain in DNP conditions. However, further studies are necessary, specially controlled clinical trials, to determine the more efficacious, safe and successful combinations to be applied in the management of DNP.⁹⁹

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.¹⁰⁶ Furthermore, the risk for drug–drug interactions is also significantly reduced, making topical therapies more attractive for a growing number of patients with multiple co morbidities and poly pharmacy.

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.¹⁰⁷ 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.¹⁰⁸ 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.¹⁰⁹

Lidocaine plaster 5% applied for 18 h/d has been shown to effectively provide relief in painful DPN and has been extensively used in post herpetic neuralgia. 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 1943.⁹¹ 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.¹⁰⁶ The lidocaine patch was also found to be associated with fewer and less clinically significant side effects compared to systemic agents.¹⁰⁶ Topical isosorbide di nitrate 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.¹⁰¹ 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.

Alpha lipoic acid - The benefit provided by alphalipoic acid (ALA) in the treatment of DNP possibly is due to its direct effects on the neuropathy, by reducing the oxidative stress, which has been defined as an important factor in the pathophysiology of the diabetic neuropathy.⁶² Its antioxidant and anti-inflammatory actions may contribute to an all-round improvement of diabetic neuropathy symptoms.⁸⁴ In some clinical trials that evaluated ALA effect in diabetic patients, pain was not a primary end point. However, they have shown a moderate benefit in terms of pain reduction.⁸² In a randomized double-blinded trial, ALA-treated patients reported a greater reduction in neuropathic pain when compared to placebo-treated subjects.⁶² Compared to several drugs currently in use for DNP treatment, ALA has fewer side effects¹¹⁰, being nausea and vomiting the most common.⁸²

Conclusion: Painful DPN presents a tremendous challenge to the health care system as prevalence of diabetes continues to grow exponentially. 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. Future studies need to identify specific diagnostic criteria for DPN, include outcome measures that have been validated and are responsive to change, and consider the confounding influence of pharmacological management to the effect of exercise. Glycemic control is the central component of treatment, but it is difficult to achieve for many patients. The management of pain remains the key aspect of symptom treatment for DPN.

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