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REVIEW

Diabetes: how to manage diabetic peripheral neuropathy

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Abstract

Diabetic peripheral neuropathy (DPN) is a major complication of diabetes mellitus. Tight glycaemic management focused on lowering haemoglobin A1C and increasing time in the target glucose range along with metabolic risk factor management form the cornerstone of DPN prevention. However, there is limited evidence supporting the efficacy of glycaemic and metabolic control in reducing the symptoms and complications of DPN, including pain once painful DPN develops. DPN treatments include pharmacological agents and non-pharmacological interventions such as foot care and lifestyle modifications. Pharmacological agents primarily address pain symptoms, which affect 25–35% of people with DPN. First-line agents include the anticonvulsants pregabalin and gabapentin, the serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine, and secondary amine tricyclic antidepressants, including nortriptyline and desipramine. All agents have unique pharmacological, safety and clinical profiles, and agent selection should be guided by the presence of comorbidities, potential for adverse effects, drug interactions and costs. Even with the current treatment options, people are commonly prescribed less than the recommended dose of medications, leading to poor management of DPN symptoms and treatment discontinuation. By keeping up with the latest therapy algorithms and treatment options, healthcare professionals can improve the care for people with DPN.

Keywords: anticonvulsants, antidepressants, diabetes, hyperglycaemia, neuropathy, pain.

Citation

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Introduction

An estimated 537 million people currently have diabetes worldwide, which makes it the largest global epidemic of the 21st century.[1] Diabetes mellitus is a chronic condition that requires lifelong management through lifestyle interventions, medication use, and diabetes self-management education and support.[2] Diabetic peripheral neuropathy (DPN) is a potential complication of diabetes mellitus. If inadequately treated, DPN can lead to debilitating complications that reduce the quality of life, including ulcerations and lower extremity amputation, as well as pain, which can negatively impact sleep and cause comorbid mood disorders.[3,4] The incidence of DPN is higher in people with type 2 diabetes than in those with type 1 diabetes whilst the prevalence is similar in both groups: 8–51% in type 2 diabetes compared to 11–50% in type 1 diabetes. Data show that people with type 2 diabetes are more likely to have DPN at diagnosis or earlier in the course of their diagnosis as compared to people with type 1 diabetes. Overall risk factors include the duration of diabetes, higher A1c levels, older age, metabolic syndrome, obesity and hyperlipidaemia.[3]

Glycaemic and metabolic risk factor management is key to preventing or delaying DPN. Although there are no treatments available to reverse DPN once it develops, there are treatments to help with the symptoms, including anticonvulsants, antidepressants, opioids or topical agents. However, people are commonly prescribed less than the recommended dose of medications, leading to poor management of DPN symptoms and treatment discontinuation.[5] This narrative review discusses the pathophysiological mechanisms that are currently believed to lead to DPN, DPN screening and diagnosis, methods of prevention, and treatment options to address DPN symptoms and complications. Information was gathered from clinical guidelines, PubMed and Cochrane reviews. Articles were searched through February 2022. Clinical trials, meta-analyses and systematic reviews available in English were included. Animal studies and peripheral neuropathy not associated with diabetes were excluded.

Review

Pathophysiology of peripheral neuropathy in diabetes

There are several pathophysiological mechanisms believed to contribute to DPN (Figure 1).[6–12] Evidence suggests that cellular injury due to hyperglycaemia is the most important contributing factor. Other factors, such as obesity, dyslipidaemia, impaired neurotrophic support and insulin signalling, and microvascular disease, contribute to oxidative stress, mitochondrial dysfunction and inflammation.[4]

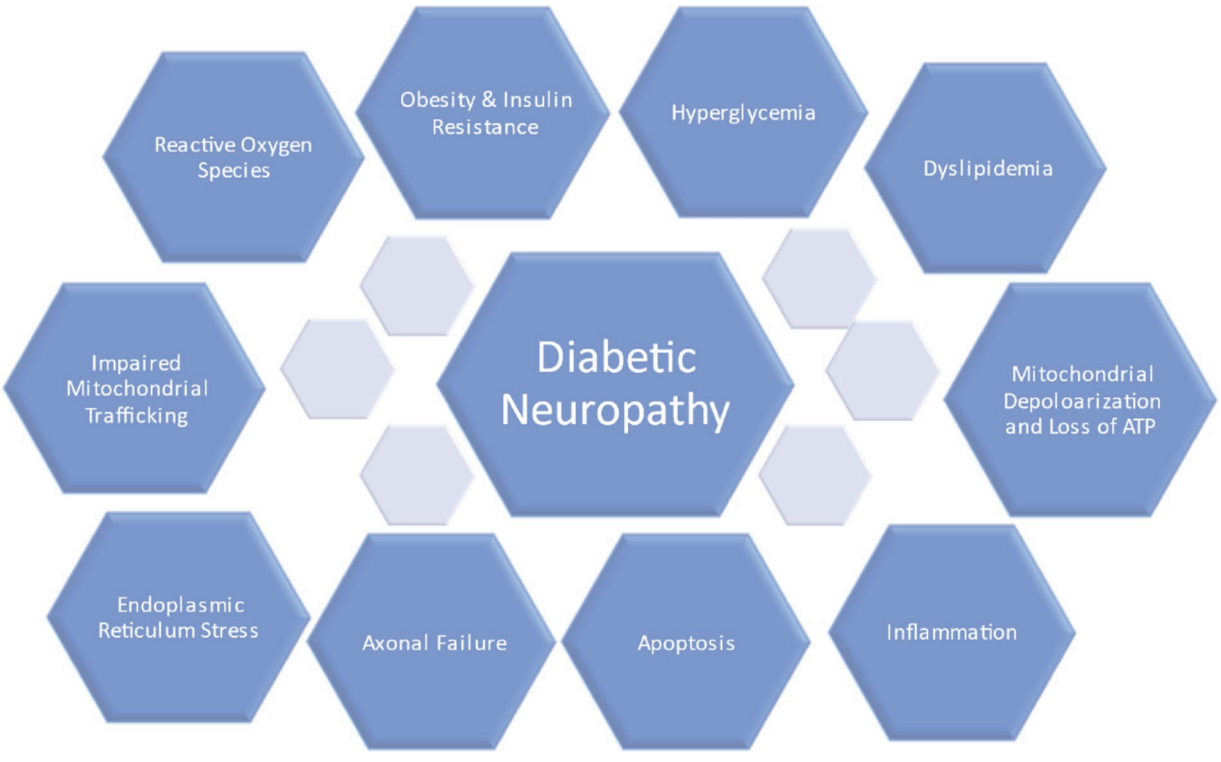
The peripheral nervous system includes small unmyelinated neurons known as C-fibres or small fibres. These fibres carry nociceptive information associated with heat and pain. There are also large fibres, which are myelinated and relay information on touch, pressure, cold, vibratory, and position sense.[7]

Previous research has demonstrated that DPN is caused by more than just glucose dysregulation alone, and this may help explain why rates are higher in people with type 2 diabetes than in people with type 1 diabetes. The metabolic syndrome includes hyperglycaemia, obesity and dyslipidaemia, and the risk of developing neuropathy increases with the presence of each of these conditions.[8] Mitochondria are the energy-producing organelles in cells. In the peripheral nervous system, mitochondria of the small and large fibres use glucose and lipids to produce adenosine triphosphatase, which supplies the needed energy for nerve impulses.[9] In people with diabetes, excess lipids and glucose disrupt the normal pathways for breakdown and produce excess electron donors that mitochondria are unable to process.[10] This can result in inflammation, endoplasmic reticulum stress, apoptosis of neurons and axonal failure.[11]

Additionally, increased glucose metabolism in diabetes mellitus leads to excessive activation of the polyol, hexosamine and protein kinase C pathways and advanced glycation end-product formation and/or receptor activation. Dyslipidaemia and hyperglycaemia further induce the release of proinflammatory cytokines and chemokines, which results in inflammatory-mediated and immune-mediated neurotoxicity. Microvascular dysfunction and downstream DNA degradation, endoplasmic reticulum stress, and mitochondrial dysfunction ultimately cause neuronal cell death.[4]

Initially, DPN often causes degeneration and loss of small fibres, which can cause new-onset pain and dysesthesia, especially in the feet, which is called painful DPN (PDPN). As the disease progresses, larger fibre loss often occurs leading to numbness and loss of proprioception in the feet that travels upward over time.[12] The hallmark of DPN is a distal-to-proximal axonal loss.[2]

Figure 1. Contributing factors to the pathophysiology of diabetic neuropathy. ATP, adenine triphosphatase. Adapted from refs.[6–12]



Clinical presentation

The clinical presentation of DPN varies.[13] It is estimated that only 25–30% of people with DPN experience pain[14] and up to 50% of people may be completely asymptomatic.[15] People with painful DPN may experience a range of symptoms, including a tingling sensation, numbness, allodynia, and stabbing pain in the feet or hands.[16] The hallmark clinical features of DPN are the progressive damage of large and small nerve fibres. In DPN, this process usually occurs in a specific symmetrical, distal-to-proximal pattern, starting at the tip of the toes and progressing proximally. Specific symptoms will vary depending on whether large *versus* small fibres are affected. The small fibres tend to produce burning, electric shocks, stabbing, hyperalgesia and allodynia whilst the large fibres cause numbness, tingling and poor balance.[3] These symptoms may often be exacerbated at night, which can disrupt sleep.[6]

Lower extremity sensory loss puts people with DPN at higher risk of foot and leg injury, ulcers, and infections, which in turn, increases the risk of amputation for people with DPN.[3] Those without pain are particularly at risk for foot infections and ulcers due to the lack of sensation and pain.[13]

Altered proprioception can result in imbalance that increases the risk of falls for people with DPN. In fact, people with DPN are two to three times more likely to fall than people with diabetes who do not have peripheral neuropathy.[14] As DPN progresses, it can affect the quality of life and the ability to perform daily activities.

Screening and diagnosis

Early identification of DPN in clinical practice allows for optimal therapeutic management to minimize disease progression and complications, including foot ulcerations and amputations.[17] Therefore, it is imperative to screen people with diabetes for DPN to ensure optimal treatment options for the management of DPN.

The American Diabetes Association (ADA) recommends annual screening for DPN when people are first diagnosed with type 2 diabetes or 5 years after a diagnosis of type 1 diabetes and at least annually thereafter.[18]

DPN is a diagnosis of exclusion.[18] The gold standard for identifying people with DPN is through a series of simple clinical tests in the clinical setting that assess small-fibre and large-fibre functions.[15] Symptoms of small-fibre dysfunction are typically characterized by pain, burning, or tingling sensations and usually present early in DPN progression. Pinprick and temperature sensation tests are quick and easy tools to assess small-fibre function.[15] Large-fibre dysfunction symptoms often include numbness and loss of protective sensation and are generally assessed via 10-g monofilament or vibration perception tests.[18] These tests can help identify which people may be more at risk for foot ulcerations and amputations. There are numerous alternative methods that have been used to assess DPN such as corneal confocal microscopy and quantification of intraepidermal nerve fibre density; however, these tests are not commonly utilized in clinical practice.[19,20]

Prevention and treatment

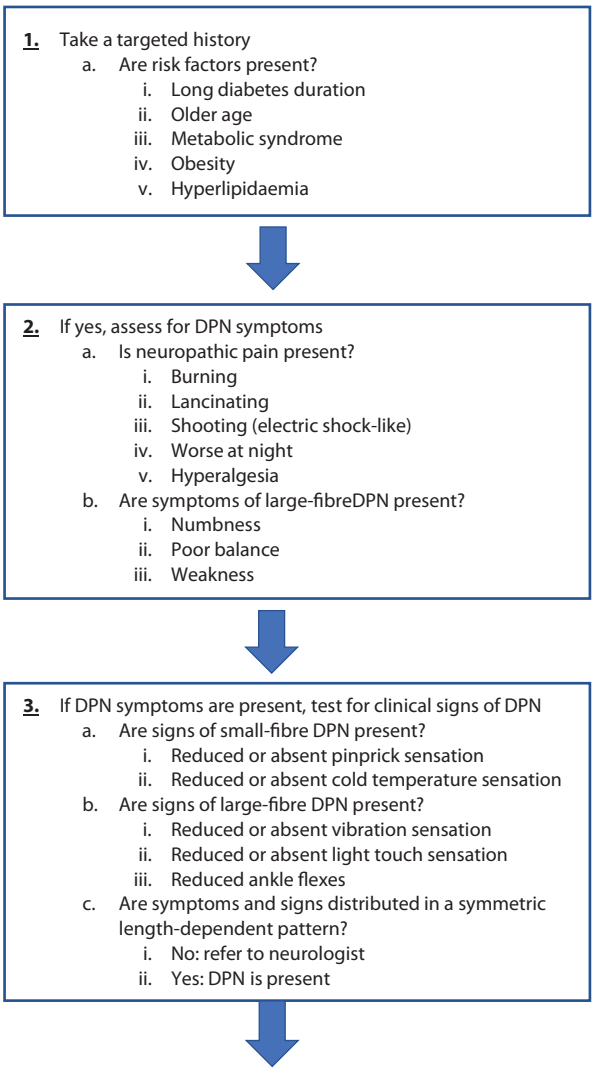
Tight glycaemic control and metabolic risk factor management is the cornerstone of DPN prevention.[15] However, there is limited evidence supporting the efficacy of glycaemic and metabolic in reducing the symptoms and complications of DPN, including pain, once DPN develops.[18] Pharmacotherapy can be employed to manage DPN symptoms (primarily pain), although non-pharmacological interventions, including counselling, exercise and radiofrequency devices, have also shown some potential.[21] Foot care is also important in managing the ulceration and infection complications associated with DPN.[3] In clinical trials, employing multidisciplinary care that includes pharmacological and non-pharmacological interventions has been shown to significantly decrease pain and improve overall functioning.[22] Unfortunately, despite a multidisciplinary approach, effective treatment of neuropathic pain continues to be challenging.[23] It is estimated that only 10–25% of people treated with the currently available pharmacological therapies will attain a clinically meaningful response in pain control compared to placebo, which is typically defined as at least a 50% reduction in pain intensity.[23] Unfortunately, undertreatment, underdiagnosis and mismanagement of DPN are well documented in the literature.[24,25]

In 2017, the ADA published a position statement that guides clinicians on the optimal approaches to the prevention and management of DPN.[18] These approaches are reiterated in the ADA 2022 Standards of Care.[15] Figure 2 outlines the ADA's treatment algorithm for DPN. In the following sections, we discuss the core components of DPN prevention and management, including management of glycaemia and other metabolic factors, pharmacological treatment options, foot care, and lifestyle modifications.

Management of glycaemia and other metabolic risk factors

Tight glycaemic management is key to preventing or slowing the progression of DPN in type 1 diabetes and can moderately slow the progression of DPN in type 2 diabetes.[15] A Cochrane Database review assessed the evidence for tight glycaemic control in the prevention of DPN in type 1 and type 2 diabetes.[26] Based on two studies with 1228 participants, enhanced glucose control (measured by A1c) was associated with a significant reduction in the risk of developing DPN in type 1 diabetes (annualized RD –1.84%).[26] However, based on four studies involving 6669 participants, there was a non-significant association between enhanced glycaemic control and a reduction in the risk of developing DPN in type 2 diabetes (annualized RD –0.58%; p=0.06).[26]

Figure 2. Algorithm for the diagnosis of DPN. Adapted from ref.[18]



DNP, diabetic peripheral neuropathy.

Although enhanced glycaemic control was associated with DPN risk reduction in type 1 diabetes and potentially associated with a DPN risk reduction in type 2 diabetes, the review also found that enhanced glycaemic control was associated with increased risks of severe hypoglycaemia episodes in both type 1 and type 2 diabetes. The authors noted that this risk 'needs to be taken into account when evaluating its risk/benefit ratio'.[26]

To address these concerns surrounding hypoglycaemia, the novel metric 'time in range' might be a suitable supplemental glycaemic metric to evaluate and address the risk of developing DPN. Time in range is a measure of the percentage of readings and time spent within a target glucose range. In general adult type 1 and type 2 populations, 70–180 mg/dL is the consensus target range.[27,28] Time in range is most accurately measured via continuous glucose monitoring but can also be expressed as 'results in range' or 'fingerstick-derived time in range' based on blood glucose monitoring data.[27] The benefits of time in range relative to A1c are well documented. In particular, time in range is valuable because it does not conflate increased hypoglycaemia with improved glycaemic control, as can be the case with A1c. In 2019, an international consensus was reached on the targets for time in range (>70% of time) as well as for time below range (<4% of time) and time above range (<25% of time).[28] Table 1 includes the full list of consensus targets. Using these time in range targets, effective and safe glucose control can be achieved by increasing time in range and reducing time below range.[28]

Two studies validate the correlation between time in range and DPN in type 2 diabetes. Using two 6-day periods of out-patient continuous glucose monitoring data from 105 participants with type 2 diabetes on insulin or sulfonylurea, Mayeda et al. found that the prevalence and severity of DPN were inversely correlated with time in range: with every 10% decrease in time in range, there was a 25% higher risk of DPN, independent of age, sex or race.[29] The study also validated the goal for 70% time in range: 74% of those who did not achieve the target had DPN whilst only 43% of those achieving the target had DPN. Similar trends were seen when stratified by chronic kidney disease (CKD) status. Notably, the researchers found no association between DPN and A1c, in line with previous mixed data on the correlation between A1c and DPN risk in type 2 diabetes. In the second study, using 3 days of in-patient seven-point fingerstick-derived time in range data (n=1296 patients with type 2 diabetes), Sheng et al. found that a time in range value below 70% is a significant risk factor for developing DPN in people with type 2 diabetes, further validating the 70% standardized target for time in range.[30] Whilst future studies are necessary to correlate time in range with DPN risk in type 1 diabetes and larger studies in type 2 diabetes might be needed, these early findings suggest that time in range may be effectively used to reduce the risk of DPN without the risk of increased severe hypoglycaemia.

Whilst glycaemic control is important in preventing or slowing DPN, other metabolic factors must also be addressed to prevent or slow the progression of DPN, particularly in those with type 2 diabetes. The pathogenesis of DPN in type 1 and type 2 diabetes is intrinsically different, and those with type 2 diabetes have a greater response to interventions aimed at improving metabolic syndrome rather than just focusing on hyperglycaemia.[31] A study by Callaghan et al. demonstrated that symptomatic DPN is more common in people with metabolic syndrome independent of glycaemic status and suggested that a larger waist circumference and lower HDL levels were associated with DPN.[32] Research shows that dyslipidaemia can cause oxidative and inflammatory stress that damages nerves and can contribute to disease progression.[33] One study reported that elevated triglyceride levels can increase nerve damage independent of diabetes disease duration, age, diabetes, control or other variables.[34] Therefore, managing hyperlipidaemia and overweight/obesity in addition

Table 1. Glycaemic goals for non-pregnant patients.[27]

Parameter	Target
A1C	<7.0% (53 mmol/mol
Standard	
Preprandial capillary plasma glucose	80–130 mg/dL (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose	<180 mg/dL (10.0 mmol/L)
14-day percent sensor time	
Glycaemic variability (% coefficient of variation)	≤36%
TAR: % of readings and time >250 mg/dL	<5%
TAR: % of readings and time 181–250 mg/dL	<25%
TIR: % of readings and time 70–180 mg/dL	>70%
TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	<4%
TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	<1%

TAR, time above range; TBR, time below range; TIR, time in range.

Box 1. Oral pharmacological agents for the management of diabetic peripheral neuropathy.[18,21]

- Anticonvulsants
  - Pregabalin
  - Gabapentin
- Tricyclic Antidepressants
  - Nortriptyline
  - Amitriptyline
  - Desipramine
  - Imipramine
- Serotonin-norepinephrine reuptake inhibitors
  - Desvenlafaxine
  - Duloxetine
  - Venlafaxine
- Tramadol
- Tapentadol
- Opioid agonists
  - Oxycodone
  - Methadone

to hyperglycaemia is important to the prevention and management of DPN.

Although addressing these risk factors is important to preventing and slowing the progression of DPN, there is limited evidence available to show that improved glycaemic and metabolic management reduces the symptoms and complications of DPN, including pain.[2] It is also worth noting that, as Freeman et al. stated in 2009, 'not all neuropathy in diabetes is of diabetic aetiology', and it is important to attend to the other risk factors for peripheral neuropathy in people with diabetes, including kidney health, alcohol abuse and vitamin B12 deficiency.[35]

Pharmacological treatment options

Several medications have been investigated for use in the management of DPN, including antidepressants, anticonvulsants, topical treatments and opioids. Most of these pharmacological agents address the pain sometimes associated with DPN although some may also improve motor function and paraesthesia. In the United States, four agents are currently approved by the FDA for the management of neuropathic pain: duloxetine and pregabalin, both of which are considered first-line options, and tapentadol and 8% capsaicin; all other agents are utilized off-label.[18] Box 1 lists the agents that are used for DPN. There is a paucity of data on the comparative efficacy of these agents, and instead much of the data on these agents are based upon anecdotal use or placebo-controlled trials.

The ADA neuropathy algorithm recommends three classes of agents as first-line agents, including the anticonvulsants pregabalin and gabapentin, the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine, and secondary amine tricyclic antidepressants (TCAs) nortriptyline and desipramine.[18] Although the FDA approved tapentadol as a treatment for DPN, it is associated with opioid-like adverse effects and mixed efficacy support, so it is not considered a first-line agent.[21] All of these medications have unique pharmacological, safety and clinical profiles, and agent selection should be guided by the presence of comorbidities, potential for adverse effects, drug interactions and costs.[18] If there is a lack of pain control after an adequate trial of an agent (typically considered 3–8 weeks), another first-line or second-line option can be trialled.[18,21]

Anticonvulsants

Pregabalin and gabapentin are both anticonvulsants that exert their mechanism in neuropathic pain by binding to the calcium channel-α2 subunit and ultimately inhibiting neurotransmitter release, thereby reducing excitatory cells.[21,36] Whilst pregabalin has an FDA indication for the management of PDPN, gabapentin is only approved for postherpetic neuralgia in the United States.[18] Nonetheless, both agents are frequently used for PDPN management in clinical practice.

Both agents have been evaluated in Cochrane reviews and have demonstrated efficacy in reducing the intensity of

neuropathic pain. A Cochrane review of pregabalin was conducted in 2018 to determine the analgesic efficacy and adverse effect profiles of pregabalin when utilized for the management of neuropathic pain.[37] Forty-five studies of almost 12,000 participants were included. When utilized for PDPN, more participants treated with both doses of pregabalin (300 and 600 mg) had at least a 30% pain intensity reduction when compared to placebo (number needed to treat [NNT] 22 with 300 mg and NNT 9.6 with 600 mg). When assessed for a 50% pain intensity reduction, more participants treated with pregabalin achieved pain control compared to those treated with placebo (NNT 22 and 7.8 for 300 and 600 mg, respectively). Common adverse effects included somnolence and dizziness and occurred to a higher degree in participants treated with pregabalin over placebo. This study demonstrated that pregabalin provides a safe and effective method for pain reduction in DPN.[37] Similarly, a Cochrane review was also conducted on the effectiveness of gabapentin in a variety of neuropathic pain syndromes.[38] The review included 37 studies with almost 6000 participants who were followed for 4–12 weeks. More participants treated with gabapentin (38%) reported a substantial reduction in their pain of at least 50% when compared to placebo (23%) with an NNT of 6.6 (RR 1.7, 95% CI 1.4–2.0). When assessing for moderate benefit of at least a 30% reduction in baseline pain, over 52% of participants treated with gabapentin reported control, in comparison to 37% treated with placebo (RR 1.4, 95% CI 1.3–1.6; NNT 6.6 (4.9–9.9)). The most common adverse effects associated with gabapentin usage were as expected and included dizziness, somnolence, peripheral oedema and gait disturbances.

Clinicians must be cognizant of dosing considerations for both gabapentin and pregabalin. Both agents undergo renal excretion and thus must be dose adjusted. Initial doses of pregabalin begin at 25 mg daily titrated to a goal dose of 600 mg daily, whilst gabapentin is typically initiated at a dose of 100–300 mg daily, with a maximum dose of 3600 mg daily.[18] Whilst it is unknown if there is a dose-related response with doses >1800 mg daily of gabapentin, it is suspected that doses less than 1200 mg daily are more likely to be ineffective for DPN. Therefore, clinicians must overcome clinical inertia and titrate doses appropriately to ensure proper pain relief.[38]

Antidepressants

Antidepressants were amongst the first pharmacotherapeutic agents utilized to treat neuropathic pain. Of the many classes that have been tried, SNRIs and TCAs appear to be effective, whilst selective serotonin reuptake inhibitors appear to be ineffective agents for nociceptive pain.

Tricyclic antidepressants

Although no TCA has an FDA indication for neuropathic pain, they are frequently prescribed for DPN.[39] All TCAs have been shown to be effective at reducing intensity of neuropathic pain although, clinically, amitriptyline is most often utilized.[18] TCAs have numerous mechanisms through which they exert their effects in neuropathic pain. However, their largest impact is believed to be through the inhibition of serotonin and noradrenaline, which ultimately affects descending neuron activity.[18,21] TCAs are also known to interact with other neurotransmitters and receptors, including histamine, adrenaline, acetylcholine, NMDA and GABA, which may be responsible for both their pain-modulating effects and side effect profile.[40] Several studies have been conducted analysing the benefit of TCAs on neuropathic pain. In a meta-analysis that evaluated TCAs and their effectiveness in neuropathic pain in 18 placebo-controlled trials, the use of TCAs was associated with a moderate benefit.[41] The NNT to witness a treatment benefit with TCAs was 3.6 (3.0–4.4), whilst the number needed to harm was 13.4 (9.3–24.4). Interestingly, separate Cochrane reviews performed on amitriptyline, desipramine, nortriptyline and imipramine have found little evidence to support a benefit in neuropathic pain; however, there also was no strong evidence in any of these reviews of a lack of treatment benefit.[42–45]

The pain-relieving effects of TCAs can be observed within just a few days, significantly faster compared to their clinical effects when utilized for depression treatment.[39] Furthermore, doses required for the management of neuropathy are significantly smaller than those needed for the management of depression, with effective pain modulation occurring at 20–30% of the dose needed for the antidepressant effect.[21]

Although secondary amines (nortriptyline and desipramine) have improved tolerability when compared to tertiary amines (amitriptyline and imipramine), the adverse effect profile of all TCAs continues to limit their use.[18] TCAs are associated with an increased risk of anticholinergic effects, including urinary retention, constipation, glaucoma, dry mouth, orthostatic hypotension and, most concerning, cardiotoxicity.[18,46] Clinician discretion should be utilized when initiating these agents for those who are elderly or in those with a history of cardiac disease.[18]

Serotonin-norepinephrine reuptake inhibitors

SNRIs exert their effects in DPN by inhibiting reuptake of serotonin and norepinephrine, thereby enhancing descending inhibition and modulating pain control.[21] Of the available SNRIs, duloxetine has the greatest level of evidence supporting its use for DPN and is currently FDA approved although venlafaxine is also used in the clinical setting.[18] In a Cochrane review of eight studies, doses of duloxetine 60–120 mg daily were shown to be effective in reducing pain intensity.[47] Duloxetine dosed at 60 mg daily was associated with a risk ratio (RR) for ≥50% pain reduction at 12 weeks of 1.73 (95% CI 1.44–2.08), with an NNT of 5. Concerning adverse effects include insomnia, hypertension and cardiac toxicity.[4] Like TCAs, adverse effect profiles may be more troublesome in the elderly; thus, clinician discretion is encouraged.[18]

Tapentadol and other agents

Several other anticonvulsants, antidepressants and analgesics have been studied for DPN with varying results.[48] For people who do not obtain adequate relief from a first-line agent, consideration can be given to tapentadol, which does possess an FDA indication for DPN, or tramadol.[18] The ADA endorses tapentadol as an alternative in people who do not achieve pain control with first-line options, although its clinical efficacy is questionable, and data appear to be conflicting on its therapeutic benefit. Tapentadol is a central-acting opioid agonist that exhibits inhibition of norepinephrine. Coupled with the high risk of opioid-like adverse effects, its use should be reserved as a second-line or even third-line option.[21] Similarly, tramadol exhibits a multimodal mechanism of action, including agonism at the opioid μ-receptor, inhibition of serotonin and norepinephrine reuptake and, in some reports, antagonism at the NMDA receptor.[21] It has been shown to be effective in the treatment of DPN, although the same opioid-like adverse effects limit its use. Lastly, whilst some opioid agonists, like oxycodone and methadone, have shown moderate efficacy in clinical trials for DPN, their concerns about long-term safety and sustained efficacy limit their overall use for DPN.[18,21]

Combination therapy

Many people with painful DPN will not achieve adequate pain control with a single first-line agent.[21] In fact, almost 90% of people with painful DPN will require multiple medications to achieve pain control.[49] The ADA endorses a combination approach utilizing combinations of first-line medications for people requiring intensification of pain control, although there is a paucity of data on the best combination regimen to initiate.[18]

Topical therapies

Topical therapies may be considered in people with DPN who do not respond to first-line oral agents or as add-on therapies. Most of the evidence is for capsaicin and lidocaine although there is some literature suggesting clonidine and isosorbide dinitrate may have some symptomatic benefit in reducing neuropathic pain in people with diabetes. A list of topical agents for DPN is provided in Box 2.

Box 2. Topical agents for the management of diabetic peripheral neuropathy.

- Capsaicin
- Lidocaine
- Clonidine gel
- Isosorbide dinitrate spray

Capsaicin

The evidence supporting use of topical capsaicin products is mixed. A Cochrane review from 2012 found that applying capsaicin 0.075% cream for ≥6 weeks may reduce neuropathic pain but is poorly tolerated.[50] Another systematic review of 2017 concluded that capsaicin 0.075% cream might not reduce pain in people with DPN.[51] There are various formulations of capsaicin such as creams, lotions, gels and liquids. These products are typically applied up to four times daily and are recommended for scheduled use rather than on an as-needed basis. Side effects, including a burning sensation to the skin that can be exacerbated by hot weather or contact with warm or hot water, often limit capsaicin use.

In 2020, the FDA approved a high concentration topical capsaicin patch for the treatment of neuropathic pain associated with DPN of the feet in adults. This patch, known as Qutenza®, is only to be administered by a healthcare professional under close supervision of a physician in a well-ventilated treatment area due to the risk of unintended exposure causing severe irritation to the eyes, mucus membranes, respiratory tract and skin.[42] Clinical trial results demonstrated a change in average pain from baseline of –22% *versus* –30% for placebo *versus* Qutenza®, respectively, when used for 12 weeks.[52]

Lidocaine

The 2012 American Academy of Neurology guideline on the treatment of painful DPN stated that lidocaine 5% patches may possibly be effective for reducing neuropathic pain based on the findings of several studies that showed they improved pain scores by 20–30% from baseline.[53,54] One to three lidocaine patches can be applied topically once daily and left on for up to 12 hours per 24-hour period.[53] A separate trial demonstrated that a lidocaine 5% plaster of one application daily for 4 weeks may work as well as systemic pregabalin to reduce pain and is associated with fewer side effects.[54] Topical lidocaine patches are generally considered to be very safe and well tolerated.[41]

Clonidine

A 2013 randomized controlled trial evaluated the use of 0.1% topical clonidine gel compared to placebo after sensitization with topical capsaicin.[55] The study was designed based on the knowledge that α2-receptors are present on nociceptors in the epidermis and may play a role in pain transmission.[56] Results showed a trend towards decreased foot pain with the clonidine group although the findings were not statistically significant. There is currently no topical clonidine gel available in the United States market. The American Academy of Neurology guideline does not recommend clonidine for the treatment of DPN.[57] There has been limited research on clonidine for the treatment of DPN; however, there is currently a clinical trial underway evaluating the effect of topical clonidine combined with pentoxifylline on post-traumatic neuropathic pain, and thus perhaps new information will come forth in the future.[58]

Isosorbide dinitrate

In 2002, a pilot study was performed to test isosorbide dinitrate in spray form in the management of DPN.[59] The researchers hypothesized that the vasodilating properties of isosorbide dinitrate could aid in pain management based on previous data suggesting the presence of impaired nitric oxide generation in the pathogenesis of DPN. Results of the study were statistically significant and showed that isosorbide dinitrate spray reduced overall neuropathic pain and burning sensation. The findings support the need for further research; however, there is currently no FDA-approved isosorbide dinitrate spray available in the United States market.

Dietary supplements

Alpha-lipoic acid

Alpha-lipoic acid (ALA) is an antioxidant that may improve neuropathic pain from DPN by reducing oxidative stress in the body, thereby improving the underlying pathophysiology of neuropathy. In a randomized control trial, oral ALA 600 mg daily for 4 years was superior to placebo in improving and preventing the progression of DPN.[60]

Acetyl-l-carnitine

Many people with diabetes are deficient in a form of amino acid known as acetyl-L-carnitine (ALC).[61] ALC is involved with different cellular processes that can result in neuroprotective effects and neurotrophic effects in the peripheral nervous system.[62] A meta-analysis from 2005 evaluated two studies testing the impacts of ALC 500 mg three times daily and 1000 mg three times daily on DPN. Results of the study demonstrated that supplementation with ALC was effective in reducing pain and improving nerve fibre regeneration in people with DPN. However, a Cochrane review from 2019 concluded that, based on paucity of data and low quality of evidence, there is still great uncertainty on whether ALC results in pain reduction or is safe to use.[63]

Coenzyme Q-10

Ubiquinone (coenzyme Q-10) is important in cellular function and undergoes different metabolic processes that are redistributed into lipoproteins, possibly protecting them from oxidation.[64,65] Because a major aetiology of DPN is oxidative stress, a 2012 study sought to evaluate the impact of coenzyme Q-10 on people with DPN.[66] Participants were randomized to 400 mg of ubiquinone or placebo daily for 12 weeks. Results of the study showed improved nerve conduction parameters and reduced oxidative stress with the ubiquinone study group; however, pain reduction was not assessed. Additional studies are needed to evaluate the impact of ubiquinone on pain reduction for DPN.

B vitamins

Even though vitamin B is often recommended, evidence is inconsistent regarding its benefit in the treatment of DPN. A 2008 Cochrane review assessed 13 studies involving 741 participants with alcoholic neuropathy or DPN.[67] Overall, it was determined that evidence is insufficient to determine if vitamin B is efficacious, and further studies are warranted. Some evidence suggested that vitamin B was less effective than ALA for short-term improvement but it was noted that these studies had small sample sizes. A more recent study sought to assess the efficacy and safety of mecobalamin on peripheral neuropathy, but results show that only mecobalamin combination treatment was effective for improving nerve conduction velocities, although there was no clinical benefit for mecobalamin combination or monotherapy on pain scores or symptom outcomes.[68] Vitamin B is generally considered safe and well tolerated.

Non-pharmacological treatment options

Foot care

As discussed earlier, lower extremity sensory loss puts people with DPN at higher risk of foot and leg injury, ulcers, and infections, which in turn increases the risk of amputation for people with DPN.[2] The 2022 ADA Standards of Care recommends that people with diabetes with 'evidence of sensory loss or prior ulceration or amputation' have a comprehensive foot check at every provider visit, a recommendation that would apply to all people with DPN.[15] The ADA also recommends that people with DPN who have lost foot sensation, who smoke, or who have a history of prior lower-extremity complications are referred to foot care specialists for preventative care and regular foot observation. Evidence also supports the efficacy of therapeutic footwear with pressure relief in preventing plantar foot ulcer recurrence or worsening. However, there is not enough evidence to support the use of therapeutic footwear as a preventative measure in people without a history of foot ulcers.[69] Based on this, the ADA recommends that people with severe DPN or a history of ulcers or amputations wear 'specialized therapeutic footwear' to prevent or limit the worsening of subsequent ulcers and infections.

High-frequency spinal cord stimulation

There is some evidence suggesting that high-frequency spinal cord stimulation (SCS) may be an effective and safe treatment for painful DPN. SCS is conducted via a small device implanted near the lower spine through a minimally invasive, non-pharmacological, reversible process.[70] SCS is not a new pain treatment as it has been used as a safe and effective pain treatment for chronic pain for 50 years, including in back and leg pain in recent years.[71] However, it has only recently been studied for use in painful DPN. A small (n=7) post hoc study found that, after 12 months of 10 kHz SCS, 6 of 7 participants achieved >50% pain relief and had pain remission, and 5 of 7 saw improvements in sensory testing and/or reflexes.[72] Building on these preliminary results, a larger randomized controlled trial (n=187) compared standard DPN care to

standard care plus 10 kHz SCS.[73] At 6 months, 79% of the 10-kHz SCS plus standard care arm achieved >50% pain reduction, compared to 5% of the standard care arm. Likewise, 62% of the 10-kHz SCS plus standard care arm saw improvements in motor, sensory or reflex testing, compared to 3% of the standard care arm. The 10-kHz SCS plus standard care arm also saw significant improvements in quality of life and impact of pain on sleep quality whilst the standard care arm saw worsening quality of life and a greater impact of pain on sleep quality at 6 months compared to baseline. Despite being only one study, which was industry sponsored, these results suggest that high-frequency SCS may be an effective treatment to address pain, sensory and motor symptoms. More research is needed to confirm the overall place in therapy for DPN.

Lifestyle modifications

In addition to tight glucose management, lifestyle interventions are recommended to help prevent and delay the progression of DPN.[15] There is no recommendation for a specific dietary plan that improves DPN as multiple eating patterns and approaches can be used to treat diabetes.[15] Several studies have shown benefit with moderate-intensity aerobic exercise and cognitive behavioural therapy (CBT).

Exercise

One study by a university-based physical therapy research clinic randomly assigned people with DPN to separate exercise groups.[74] Both groups incorporated exercises for balance, flexibility, strengthening, and aerobic exercise and met three times a week for 12 weeks. One group's exercises were completed sitting or lying down (non-weight bearing) and the other group's exercises were completed standing or walking (weight bearing). Results of the study showed that the weight-bearing group had greater increases in 6-minute walk distance and daily step counts compared to participants in the non-weight-bearing exercise group. There was still benefit found in people in the non-weight-bearing group, suggesting that moderate-intensity exercise may improve symptoms of DPN. Another study conducted at the University of Utah reported nerve fibre regeneration in people who were enrolled in a 12-week exercise programme along with lifestyle counselling compared to participants who only received lifestyle counselling.[75] However, this study excluded people with symptomatic DPN. Therefore, it is unknown if exercise aids in nerve regeneration in people with symptomatic DPN.

Cognitive behavioural therapy

A Veterans Affairs medical centre conducted a non-blinded study that randomized 12 participants with painful DPN to receive CBT and 8 participants to usual care.[76] After 4 months, the CBT group reported reduced pain severity and pain interference whilst the non-CBT group showed no change. The study concluded that CBT may reduce pain severity and interference with activities of daily living in people with painful DPN.

Conclusion

DPN is a fairly common complication in people with long-standing type 1 or type 2 diabetes. There are multiple proposed mechanisms of action. Tight glycaemic control and metabolic risk factor management is the cornerstone of DPN prevention.[15] However, there is limited evidence supporting the efficacy of glycaemic and metabolic control in reducing the symptoms and complications of DPN, including pain, once PDPN develops.[2] DPN treatments include pharmacological agents and non-pharmacological interventions such as foot care and lifestyle modifications. Pharmacological agents, including orals and topical agents, primarily address pain symptoms, which affect 25–35% of people with DPN. Lifestyle modifications along with other approaches like CBT have also shown benefit. In clinical trials, some people respond very well to therapies whilst others do not. This could be due to different mechanisms of pain, perceptions of pain, and risk factors, and these differences warrant further research and exploration. Even with the current treatment options, people with DPN are commonly prescribed less than the recommended dose of medications, leading to poor management for symptom reduction of PDPN and treatment discontinuation. By keeping up with the latest treatment algorithms and treatment options, healthcare professionals can improve the care for their patients with DPN.

Key practice points

- All patients should be assessed for diabetic peripheral neuropathy (DPN) at diagnosis of type 2 diabetes and at least annually thereafter. People with type 1 diabetes should be assessed for DPN annually beginning 5 years after diagnosis.
- Optimize glycaemic management early on in diabetes diagnosis to prevent or delay the development of DPN. Particularly in type 2 diabetes, other metabolic risk factors (e.g. obesity, hyperlipidaemia) should be addressed. As larger waist circumference and lower HDL levels were associated with DPN, managing hyperlipidaemia and weight may be beneficial in DPN prevention.
- The goals for management of DPN include achieving glucose targets, reducing symptoms, improving quality of life and avoiding further complications (foot non-healing ulcerations and amputation).

- People with DPN should receive a comprehensive foot check at every provider visit. Those with severe DPN or a history of ulcers or amputation should be referred to foot-care specialists and may benefit from therapeutic footwear.
- For first-line symptomatic treatment of DPN, initiate pregabalin/gabapentin or duloxetine.
- Tricyclic antidepressants have shown effectiveness for DPN; however, their adverse effect profile limits their use.
- Whilst tapentadol does have an FDA indication for DPN, its questionable efficacy and concerning adverse effect profiles limit its clinical use and are therefore not considered a first-line option according to the American Diabetes Association.
- Opioids are associated with high risks of addiction; therefore, tramadol, methadone and oxycodone are not first-line or second-line medications used for the management of DPN.
- Topical agents, such as capsaicin or lidocaine, can be used in those patients who do not respond to first-line agents or as add-on therapy.
- There is overall more limited evidence regarding dietary supplements, yet alpha-lipoic acid may improve symptoms of DPN.

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