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ABSTRACT  |  Diabetic neuropathies are the most common chronic complications of diabetes, with an estimated lifetime prevalence exceeding 50% in people with diabetes. Among various forms of neuropathy, diabetic peripheral neuropathy (DPN) is the most common and has the strongest evidence base regarding therapeutic approaches. This American Diabetes Association clinical compendium summarizes the latest information about screening for, diagnosing, and treating painful DPN in routine clinical practice. It opens with an overview of the epidemiology of DPN, followed by a description of the pathophysiology of the disease and its often severely painful symptoms. The authors recommend a stepwise approach to effectively diagnose DPN and offer a novel perspective on the impact of social determinants of health on the development and management of DPN. They summarizes the latest guidance on effective therapies, including pharmacological oral and topical agents, nutraceutical products, and nonpharmacological therapies, including physical activity and dietary interventions, passive modalities, and energy or nerve stimulation techniques. Throughout the publication, the authors identify knowledge gaps that need to be addressed and advocate a personalized care approach to reduce the burden of painful DPN and optimize quality of life for individuals affected by it.

Diabetic neuropathy is one of the most prevalent chronic complications in adults with type 1 or type 2 diabetes while also affecting individuals with prediabtes and young people with diabetes, with an estimated lifetime prevalence exceeding 50% (1–4). Although the term “diabetic neuropathy” encompasses a broad spectrum of different neuropathic conditions, diabetic peripheral neuropathy (DPN) is the most common and most studied among them and has the strongest available evidence regarding therapeutic approaches (1).

A detailed epidemiological overview is beyond the scope of this monograph. However, understanding some of the key phenotypes and their associated differences in the risk of developing DPN is crucially important for busy clinicians who treat people with diabetes.

There are some epidemiological differences between DPN in type 1 versus type 2 diabetes, despite there being no major structural differences in nerve pathology. As demonstrated by the DCCT (Diabetes Control and Complications Trial) (5), the prevalence of DPN is low in individuals with newly

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Diagnosed and early type 1 diabetes (<10 years’ duration). The prevalence then increases with disease duration to up to 34% after ~25 years, as documented in the DCCT’s observational follow-up EDIC (Epidemiology of Diabetes Interventions and Complications) study (2). Similar rates were reported earlier by the EURODIAB IDDM (European Insulin–Dependent Diabetes Mellitus Prospective Complications Study) (6) in randomly selected individuals with type 1 diabetes of similar duration from 16 European countries. Furthermore, data from contemporary cohorts reflective of current standards of care on both sides of the Atlantic have found similar results. For example, the T1D Exchange clinic network (7), consisting of >25,000 people with type 1 diabetes in >80 U.S.-based pediatric and adult endocrinology practices, and the large Scottish T1D Register (8), which includes all people with type 1 diabetes in Scotland, both of which phenotyped for DPN with the Michigan Neuropathy Screening Instrument (MNSI) questionnaire (9), found prevalence rates of 11–13% for symptoms of DPN, including pain, in their real-world cohorts. Interestingly, in addition to traditional risk factors such as glycemic control, age, and diabetes duration, cardiovascular risk factors (e.g., obesity, hyperlipidemia, hypertension, and smoking) and particularly socioeconomic risk factors have emerged as very strong predictors of DPN in type 1 diabetes (2,7,8).

In contrast, more than half of all individuals with type 2 diabetes develop signs and symptoms of DPN during their lifetime, as documented in several large observational or interventional cohorts (1,10–14). In fact, the prevalence of DPN is quite high, with rates of up to ~20–30% even in newly diagnosed and early type 2 diabetes, including in contemporary cohorts such as the >1,500 individuals with screen-detected type 2 diabetes in the Danish arm of the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment of Diabetes in Primary Care) trial (15) and >5,000 individuals with early type 2 diabetes (~4 years’ duration) in the GRADE (Glucose Reduction Approaches in Diabetes–A Comparative Effectiveness) trial (3). Both of these trials phenotyped participants for DPN using the MNSI. In type 2 diabetes, in addition to traditional DPN risk factors (e.g., glycemic control, age, and diabetes duration), racial/ethnic minority status also carries a higher DPN risk, including among American Indians.

Importantly, high prevalence rates of DPN similar to those observed in adults with early type 2 diabetes also have been observed in contemporary youth cohorts, particularly those with type 2 diabetes, as reported by the SEARCH (SEARCH for Diabetes in Youth) study (4), which included ~2,000 young people with type 1 or type 2 diabetes.

Among DPN symptoms, neuropathic pain, often severe, affects up to 30% of all individuals with DPN and is challenging to manage, resulting in increased risks of associated problems such as sleep disturbances, further reduced quality of life, polypharmacy, socioeconomic consequences (e.g., higher health care costs and reduced ability to work or perform daily activities), morbidity, and mortality (1,16–18). Given the epidemic explosion of diabetes in the United States (19) and worldwide (20), the high prevalence of this complication, and its clinical and socioeconomic consequences, effective therapeutic and preventive measures for DPN and DPN-related pain are of paramount importance.

This monograph offers clinicians up-to-date, evidence-based information regarding the mechanisms involved in inducing nerve fiber damage and neuropathic pain and the spectrum of risk factors and DPN phenotypes across the life span, as well as a novel discussion of the impact of social determinants of health (SDOH) on DPN development and management. It also provides busy clinicians with a customized, stepwise approach to effectively screen for and diagnose DPN in routine care. Additionally, it summarizes the latest guidance on effective pharmacological and nonpharmacological therapeutic strategies for painful DPN, including the respective roles of nutraceutical products, dietary modification, exercise, and new technologies. Finally, this publication outlines knowledge gaps that need to be targeted to identify modifiable risk factors, develop more sensitive assessments, and produce effective therapies to either prevent the progression of or reverse neuropathic disease. It advocates a personalized care approach to ultimately reduce sequelae and the related health care burden and optimize quality of life for people with diabetes and DPN.

**PATHOPHYSIOLOGY OF DPN**

Diabetes preferentially affects the peripheral nervous system (PNS), a likely reflection of the unique anatomy of the PNS (21). PNS axons are frequently ≥3 feet long and >20,000 times the length of their supporting cell bodies. PNS sensory neurons and their receptors lie outside the blood–brain barrier and are more vulnerable to injury secondary to diabetes than motor neurons, which lie within the barrier. Among the sensory neurons, there are small unmyelinated neurons known as C-fibers but also frequently called “small fibers.” These fibers carry nociceptive information, particularly related to heat and pain, and constitute the majority of sensory axons in the PNS. The lack of myelin results in slow, continuous conduction of small fibers secondary to a uniform distribution of ion channels along the axon. In conjunction with small fibers...
are small, thinly myelinated Aβ fibers, which relay information on touch, pressure, and cold, and fully myelinated fibers of different diameters, designated Aα and Aβ, which are responsible for vibratory and position sense. Collectively, these fiber types are known as large fibers. Myelin, provided by Schwann cells, ensheathes the axons of these fibers in a highly controlled manner, forming the nodes of Ranvier and paranodes, the sites of ion channels required for rapid nerve conduction and of tight junctions that protect large fibers from toxic substances (21).

Anatomical studies from sural nerve biopsies of patients with diabetic neuropathy align with their presenting symptoms (22). Early degeneration and loss of C fibers are evident in patients experiencing new-onset pain, burning, or pricking, which are known as dysesthesias, in their feet, followed by initial demyelination/remyelination of large fibers. As the disease progresses, large fiber axonal loss eventually occurs, and patients experience numbness and loss of proprioception in the feet that travels upward over time. This distal-to-proximal axonal loss and its accompanying symptoms are the hallmark of diabetic neuropathy (23).

Between 1970 to 2010, studies aiming to understand the pathophysiology of diabetic neuropathy focused on glucose dysregulation (24). In the polyol pathway, aldose reductase converts excess glucose to sorbitol, resulting in a series of downstream reactions that decrease sodium–potassium adenosine triphosphatase (ATP) activity, deplete nicotinamide adenine dinucleotide phosphate, and produce reactive oxygen species (ROS), impairing nerve function. Aldose reductase inhibitors were tested in 32 diabetic neuropathy clinical trials but unfortunately failed to improve nerve function.

Excess glucose also enters the hexosamine pathway, producing inflammatory by-products and activating protein kinase C (PKC) secondary to the accumulation of diacylglycerol. PKC activation, in turn, enhances insulin resistance, disrupts growth factor biology, and leads to vasoconstriction of nerve blood vessels. Similar to the aldose reductase trials, clinical trials of PKC inhibitors failed in human diabetic neuropathy.

Advanced glycation end products (AGEs), which bind receptors for AGEs (RAGEs), are another by-product of excess glucose. Activation of AGEs and RAGEs leads to downstream inflammation, ROS accumulation, and decreased blood flow to peripheral nerves. Although preclinical trials targeting activation of RAGEs were promising, available compounds were too toxic for human trials and remain in therapeutic development (25).

Many of the failed clinical trials occurred at the same time multiple, newer clinical trials were suggesting that glucose control alone was insufficient to prevent neuropathy in people with type 2 diabetes (26). There is now consensus that glycemic control alone cannot prevent the progression of DPN in patients with type 2 diabetes. The metabolic syndrome has emerged as a crucial risk factor for neuropathy based on data from multiple clinical studies in the United States (4,27–29), Denmark (15), Germany (30), the Netherlands (31), India (32), and China (33,34). The metabolic syndrome encompasses hyperglycemia, obesity, and dyslipidemia, and the risk of developing neuropathy increases with the number of these components present in an individual (27,28). These clinical trials led to new thinking about the pathophysiology of diabetic neuropathy focused on the idea that disruption in whole-nerve bioenergetics (i.e., how the nerve accesses energy along its entire length) is the crucial factor leading to disease (35).

Mitochondria are the energy-producing organelles in cells and use both glucose and lipids to produce ATP. In the PNS, mitochondria are primarily made in the cell body and are trafficked down long axons to provide energy for nerve function (36). In small fibers, mitochondria are found along the length of the axons. In large fibers, they are also present along the length of the axons but are particularly present at the nodes of Ranvier and the paranodes, where they assist in salutatory nerve conduction. In both fiber types, mitochondria produce ATP from glucose and lipids (21). ATP then supplies the needed energy for nerve impulses to travel the length of the axons and reach distal nerve terminals.

Under normal conditions, glucose and lipids undergo a series of distinct, highly regulated chemical reactions, ending with the transfer of the electron donors nicotinamide adenine dinucleotide and flavin adenine dinucleotide to the mitochondrial electron transport chain. These electron donors travel across the inner mitochondrial membrane and undergo oxidative phosphorylation, with generation of ATP for energy and small amounts of ROS as a by-product of the process. However, in the diabetic environment, excess glucose and lipids not only disrupt the normal pathways used for their own breakdown, but also produce excess electron donors that the mitochondria are unable to process. The result is bioenergetic failure (37) and the loss of normal mitochondrial membrane function (mitochondrial depolarization), decreased ATP production, impaired mitochondrial trafficking, and accumulation of ROS, leading to inflammation, endoplasmic reticulum stress, apoptosis of neurons, and axonal failure (38) (Figure 1).

With fewer functional mitochondria in the cell body and along the axons, energy-starved small and large nerve fibers lose their ability to function and undergo degeneration, with the axons farthest from the cell body (i.e., those in
the feet) being most vulnerable. This vulnerability occurs because fewer functional mitochondria successfully travel the long distance from the cell body along the entire length of the axons to their most distal terminals (Figure 2). Small fibers that convey pain and dysesthesias are particularly vulnerable to this energy loss. Schwann cells can provide energy-starved large, myelinated axons with some usable fuel, mitochondria, and protection from toxic substances (39), but small fibers lack this energy source and protection. This explains why small fibers are the earliest fibers to undergo injury secondary to diabetes and why pain and dysesthesias are frequently the first symptoms of DPN.

KEY POINTS

» Early injury and loss of small fibers, susceptible to energy flux, occur in people with diabetes, resulting in symptomatic pain and burning in their feet.

» As the disease progresses, larger nerve fibers also become injured by the lack of energy sources, and individuals experience numbness and loss of position sense in their feet.

» These signs and symptoms progress from the feet upward into the leg and reflect a distal-to-proximal fiber loss that is the hallmark of diabetic neuropathy.

FIGURE 1 Chain of events underlying the pathophysiology of diabetic neuropathy. Components of the metabolic syndrome contribute to diabetic neuropathy by causing energy overload from excess glucose and lipids, leading to mitochondrial bioenergetic failure, with mitochondrial depolarization, loss of adenosine triphosphatase as an energy source, and accumulation of reactive oxygen species. This process leads to impaired mitochondrial trafficking from the cell body down the length of the axons, endoplasmic reticulum stress, apoptosis of neurons, and axonal failure.

FIGURE 2 In metabolically healthy individuals (left), mitochondria produced in the neuron cell body traffic down the axons, providing energy for normal axonal function. In prediabetes and type 2 diabetes (right), the chain of injurious events leads to mitochondrial dysfunction, with adenosine triphosphatase loss and distal-to-proximal degeneration of energy-starved axons.

SCREENING AND DIAGNOSING DPN

As discussed in detail above, the hallmark clinical features of DPN are the result of progressive damage to and eventual loss of all populations of large and small myelinated and unmyelinated nerve fibers and related downstream effects. In diabetes, this process occurs in a specific symmetrical, distal-to-proximal pattern, starting at the tip of the toes and eventually progressing proximally. Thus, the entire constellation of symptoms and clinical signs associated with DPN follows the same pattern, creating the typical “stocking-and-glove” clinical presentation, which is an important diagnostic clue (Figure 3) (1).

A Customized, Stepwise Approach for Primary Care

Considering the high prevalence of DPN and the magnitude of its consequences, implementing effective screening strategies as part of routine clinical practice is key to ensuring its diagnosis at the earliest possible stage and the timely treatment of DPN pain, thereby preventing progression and the development of advanced complications, including limb amputations and death (1). All individuals should be assessed for DPN starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter.

Although the anatomy of the PNS, and hence the evaluation of the various nerve fiber populations, may be quite complex, there are several important tips that can
guide clinicians in implementing efficient and successful DPN screening and diagnosis procedures, as described in the American Diabetes Association’s position statement on diabetic neuropathy (1). Importantly, when screening for DPN, one should keep in mind that each of the specific types of nerve fibers has a specific function and role; thus, targeted evaluations can be performed easily in the clinic. A stepwise approach to screening and diagnosis is shown in Figure 4 and described below.

1. Take a Targeted History
A targeted medical history may be obtained quickly during a routine clinic visit or may be ascertained from the electronic health record (EHR) by reviewing for the presence of several risk factors known to be strongly associated with DPN, including poor glycemic control, long duration of diabetes, older age (>70 years), tall stature, hypertension, obesity, and metabolic syndrome (1,28,40,41). In addition, a history of recent falls, particularly when no other risk factors for falls are apparent, may reflect gait and balance disorders that can be a direct consequence of the large-fiber dysfunction associated with DPN (42,43). Individuals with this type of nerve dysfunction are also at increased for other complications, including fractures and hospitalizations, and thus require more specific care.

2. Assess for DPN Symptoms
The symptoms associated with DPN are dependent on the type of fibers most affected initially (Table 1), although some individuals with DPN may be completely asymptomatic and thus may first present with advanced complications such as foot ulcers (1,44).

**Small-Fiber DPN**
Neuropathic pain is the key feature associated with the damage to small nerve fibers that usually occurs in the earliest stages of DPN (1,45). Neuropathic pain is largely a clinical diagnosis. Characteristically, it is described as burning, lancinating, tingling, and/or a shooting, electric shock–like sensation, occurring in varying combinations and typically worse at night. The pain may

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**TABLE 1** Symptoms and Clinical Signs of Diabetic Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Function</th>
<th>Signs on examination (clinically diagnostic)*</th>
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</thead>
<tbody>
<tr>
<td>Large, Myelinated Nerve Fibers</td>
<td>• Numbness</td>
<td>• Pressure</td>
</tr>
<tr>
<td></td>
<td>• Tingling</td>
<td>• Balance</td>
</tr>
<tr>
<td></td>
<td>• Poor balance</td>
<td></td>
</tr>
<tr>
<td>Small Nerve Fibers</td>
<td>• Pain:</td>
<td>• Nociception</td>
</tr>
<tr>
<td></td>
<td>• Burning</td>
<td>• Protective sensation</td>
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<tr>
<td></td>
<td>• Electric shocks</td>
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<tr>
<td></td>
<td>• Stabbing</td>
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</tr>
<tr>
<td></td>
<td>• Hyperalgesia</td>
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<tr>
<td></td>
<td>• Allodynia</td>
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</table>

*Document impairment/loss in symmetrical, distal-to-proximal pattern.
be accompanied by dysesthesias such as an exaggerated response to painful stimuli (hyperalgesia) and/or pain evoked by contact with ordinarily unpainful stimuli such as socks, shoes, and bedclothes (allodynia) (1,46,47). Available evidence shows that up to 25–30% of people with diabetes will experience DPN pain, and because it heralds early disease, neuropathic pain may be present even in the absence of any neurological deficits (1,45,48). However, clinicians should also be aware that some individuals may not voluntarily report some symptoms, including pain, to their health care providers because of a variety of sociocultural factors (e.g., fear or being misunderstood or not taken seriously and misperception that treatments are unavailable or would not help) (45,49). Thus, DPN pain may be underreported.

Several other important tips may be helpful to clinicians when evaluating pain caused by DPN. Neuropathic pain may be the first symptom that prompts an individual to seek medical care, and it could be present in individuals with newly diagnosed diabetes or even prediabetes (1,46). Thus, the absence of a prior diagnosis of diabetes should not rule out the need for formal DPN screening, particularly in the presence of several of the risk factors mentioned above and with the typical clinical characteristics (Table 1) (1,46).

Women, members of some racial/ethnic minority groups, and individuals with type 2 diabetes appear to be at greater risk for developing DPN pain (45). Additionally, the direct and indirect economic burden associated with neuropathic pain is substantial. This pain may directly or indirectly interfere with daily activities or lead to loss of balance, disability, psychosocial impairment, sleep disturbances, and reduced health-related quality of life (1,46). Thus, there should be a strong suspicion of DPN in

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**FIGURE 4** A stepwise approach to screening and diagnosing diabetic peripheral neuropathy.
individuals presenting with any of these complications. Some individuals may present with sub-acute onset (over a period of days) and a clinical presentation dominated by foot and lower-limb pain, suggesting a prominent involvement of small fibers. The pain progresses over days to weeks to constant burning dysesthesias and allodynia involving the legs in a stocking distribution. Occasionally, the pain spreads to proximal sites, including the trunk, or it spreads more diffusely and is associated with several autonomic features (1). Despite the prominent pain, sensory loss may be mild or absent, there is no weakness, and reflexes are generally preserved. The sub-acute forms of DPN may be seen with acute weight loss or may be induced by diabetes treatment, developing within 2–4 weeks (occasionally up to 6 weeks) after the achievement of rapid and sustained glycemic control with insulin, oral antidiabetic agents, or dietary measures.

Large-Fiber DPN
Symptoms associated with the damage and loss of the large nerve fibers include numbness, tingling without pain, loss of protective sensation, and, in more advanced stages, poor balance (1,46), weakness, and unsteadiness that may lead to falls (1,23). Some individuals may also present with completely insensate, numb feet and may state in the clinic that their feet feel as if they are wrapped in wool or as if they are walking on thick socks (1,46).

Asymptomatic DPN
Clinicians should be also aware that up to half of all people with DPN may be either asymptomatic or, as previously mentioned, reluctant to report some symptoms (1,45). In such cases, neurological deficits may be discovered by chance during a routine clinical examination (1,46). Other individuals who are initially aware of neuropathic symptoms may become asymptomatic later in the course of the disease, as they experience severe sensory loss in all types of nerve fibers and develop insensate feet (1,46). A serious consequence of insensate feet is an increased risk for painless injury, leading to an increased risk for foot ulceration and amputation (1,50). For example, objects lodged in the shoe, including a wrinkled stocking; unrecognized, increased pressure during walking and weight bearing; or contact with very sharp or hot objects without the appropriate protection may produce blisters that erode through the skin and lead to more severe complications. It is the loss of the so-called “gift of pain” that causes people with plantar neuropathic ulcers to unknowingly walk on their lesions, inducing chronicity that is frequently complicated by infection (1).

In summary, periodic, flexible assessment for DPN risk factors and symptoms and their trajectories over time should be part of standard care for all people with diabetes.

3. Test for Clinical Signs of DPN
Similar to the DPN symptoms discussed above, the clinical signs of DPN are also characteristic of the type of nerve fiber deficits present and their progression (Table 1) (1,46).

Several well-established, effective clinical tests exist to assess small- and large-fiber function as part of routine clinical care and require only simple tools that can be carried easily in a lab coat pocket. Evaluation of DPN-associated small-fiber damage can be accomplished by testing a person’s pinprick sensation using a sharp object such as a safety pin (discarded after one use) and temperature threshold sensation, which is mostly performed with a cold metal object such as a tuning fork (1,23). Evaluation of DPN-associated large-fiber damage involves assessing vibration perception using a 128-Hz tuning fork, proprioception, light-touch pressure with a 10-g monofilament on the dorsal aspect of the great toe, and bilateral ankle reflexes.

It is important to note that there are many monofilaments available, with varying diameters. Clinicians should use a standardized 10-g instrument that has been pretested to buckle at a 10-g force when applied to the site of interest and should apply the monofilament at the dorsal aspect of the great toe to ensure standardized assessment (1,46). Although the 10-g monofilament is arguably the most often used test to screen for DPN in routine care, its use alone is not recommended for effective screening or diagnosis, as the loss of light-touch sensation occurs in advanced stages of neuropathy, and relying solely on this test could miss opportunities to implement early preventive care measures in many people with DPN (1,46). Sensation testing with pin and vibration is more sensitive. Loss of ankle reflexes and weakness of small foot muscles and dorsiflexors occur earlier in the course of DPN (23).

All of these sensory modalities should be tested initially by application of the sensory stimulus to a body site where normal responses are expected, such as the forehead. Then the stimulus is applied to the great toe and then moved proximally up the limb to the level where the sensation is felt to be normal. In addition, for many of these evaluations (e.g., vibration perception using a 128-Hz tuning fork or the 10-g monofilament) using a blinded, forced-choice testing procedure will reduce the potential for bias and increase the sensitivity of the evaluations. This procedure involves applying a stimulus (either true vibration or just a touch with the tuning fork) at one of two times while a patient’s eyes are closed and then asking
whether the patient felt the stimulus at time A or time B. Those with sensation loss may choose the incorrect time or state that they did not feel the stimulus either time. All of these assessments should follow the typical DPN pattern, starting distally (the dorsal aspect of the hallux) and moving proximally until a sensory threshold is identified, with the same evaluations being performed on both sides to confirm a symmetrical, distal-to-proximal distribution (Figure 3) (1,46).

A combination of at least two of these evaluations, with at least one targeting small fibers and one targeting large fibers, is recommended to screen for and diagnose DPN in routine clinical care (1,46). Several clinical scales combining symptoms and signs have been validated over time for the screening and diagnosis of DPN and can be used easily in routine care. These include the Toronto Clinical Neuropathy Score (51), the Utah Early Neuropathy Scale (52), the Neuropathy Disability Scale (53), or the previously mentioned MNSI (9). Similarly, there are several validated scales for neuropathic pain and its severity, including the McGill Pain Questionnaire and its more recent, shorter version known as the Douleur Neuropathique en 4 Questions (DN4) (54).

As DPN progresses, its symptoms and clinical deficits become more severe as a reflection of damage and loss of all nerve fibers, with sensory deficits also involving more proximal segments and including distal weakness with foot drop and variable degrees of autonomic dysfunction (1,55).

Although the norm in clinical care historically was to refer people with suspected DPN to a neurologist and to order electrophysiological testing to confirm the diagnosis, more recent evidence has shown that these measures are not necessary except in specific cases in which clinical features are atypical, onset is abrupt, and a different etiology is suspected, as described below (1,22,45). Indeed, specialized electrophysiological testing is usually not cost-effective, and its high associated costs and typically long waiting times would place unnecessary additional burden on both people with DPN and the health care system.

4. Develop a Differential Diagnosis

The presence of DPN is determined largely through clinical diagnosis based on the development of the symptoms and signs mentioned above (Table 1) in an individual with diabetes or prediabetes in whom other causes of neuropathy have been excluded (1,45). Therefore, a comprehensive differential (Figure 5) is needed initially in all individuals before a firm diagnosis of DPN is established, particularly given that there are many other forms of peripheral neuropathy that may either mimic or coexist with DPN and may be treatable.

![FIGURE 5](image_url) Considerations for developing a differential diagnosis for diabetic peripheral neuropathy.

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A careful medical history may unveil some of these conditions, including alcohol abuse or other toxic exposures, neoplasia with a history of chemotherapy, or amyloidosis (1,22,45). In addition, clinicians should order a comprehensive metabolic panel and screen for hypothyroidism by testing for thyroid-stimulating hormone. Consider as well the possible role of end-stage renal disease with uremia, particularly in individuals with type 1 diabetes, or perform serum immunoelectrophoresis with immunofixation to evaluate for a monoclonal gammopathy (1,22,45). Vitamin B12 deficiency is one of the most prevalent DPN mimics found in people with type 2 diabetes and can be completely reversed with treatment (1,22,45). Up to 30% of people with type 2 diabetes who are treated with metformin may develop B12 deficiency. Thus, laboratory screening for vitamin B12 levels (methylmalonic acid with or without homocysteine) is recommended at least annually in these individuals. Chronic inflammatory demyelinating polyradiculoneuropathy may also mimic or coexist with DPN, and a high level of suspicion should be raised by a sudden onset and rapid progression of symptoms and signs. Finally, more genetic forms of polyneuropathy are being discovered, and novel treatments have become available for disorders such as familial transthyretin amyloidosis. Thus, genetic testing could be also considered, although the role of routine genetic testing remains unclear.

5. Perform Confirmatory Tests as Needed
Confirmatory tests in ambiguous cases may include determining changes in nerve conduction studies to assess predominantly large-fiber dysfunction. These tests are performed with surface stimulating and recording techniques evaluating motor and sensory nerve fibers in the upper and lower limbs and usually demonstrate a decrease in sural nerve amplitude, followed by reductions in sensory and motor nerve conduction velocity (22). The gold standard for small-fiber neuropathy is assessment of intra-epidermal nerve fiber density measurements by skin punch biopsy. This test can be performed in the clinic if needed, but it is an invasive approach that is rarely necessary for routine diagnosis of DPN and is used primarily for research purposes (22). Other modalities may include quantitative sensory thermal thresholds for reduced cooling detection thresholds or elevated heat thresholds, laser Doppler flare imaging studies, or corneal confocal microscopy, although the latter, again, is largely reserved for research studies.

In summary, a thorough history and examination and routine screening laboratory testing are recommended to ensure that other etiologies, many of which may be treatable, are not contributing to the clinical presentation of DPN (1,22,45). Additionally, in atypical cases involving asymmetrical distribution of symptoms and clinical signs, a motor predominance, or an acute onset and rapid progression of signs such as severe weakness, a timely referral to a neurologist should be made, and cerebrospinal fluid examination by lumbar puncture for protein levels, genetic testing, and MRI imaging of nerve roots and peripheral nerves may be required.

KEY POINTS
» DPN assessment should be performed annually starting at diagnosis for type 2 diabetes and 5 years after the diagnosis for type 1 diabetes. People with prediabetes and young people with symptoms or signs of DPN should also be screened.
» Assessment should include a detailed history and at least two sensation and reflex tests. Electrophysiological testing is rarely needed for people with typical signs and symptoms.
» A complex differential is recommended, and ambiguous or atypical cases should be referred to a neurologist and/or have additional testing.

SOCIAL DETERMINANTS OF HEALTH AND THEIR IMPACT ON DPN
Diabetes continues to grow at an alarming pace, leading to excess morbidity and mortality in the United States and worldwide (19,56). Currently, 34.2 million Americans (10.5% of the U.S. population) have diabetes, with a disproportionate burden on racial and ethnic minorities and low-income populations (19,57). Despite an expanding arsenal of therapeutic options, only 26% of Americans are meeting combined targets for A1C, lipids, and blood pressure (58). Not unexpectedly then, DPN remains prevalent, affecting up to 50% of patients with diabetes (1). Recognizing that social factors are the root cause for health disparities, particularly for type 2 diabetes, the American Diabetes Association (ADA) in 2021 published a scientific review on SDOH and diabetes (59). This review highlighted the key social domains affecting diabetes incidence, prevalence, and outcomes (59). We seek here to complement this report with a focus on the impact of SDOH specifically on DPN.
Theoretical Frameworks: SDOH, Health Disparities, and Diabetes Risk
Health determinants historically have been classified into biological, clinical, and nonclinical factors (60). As health disparities worsen in the United States (61), research is unveiling the importance of nonclinical factors such as social, behavioral, and economic influences on both population and individual health. These factors, collectively known as SDOH, are defined by the World Health Organization (WHO) as “the conditions in which people are born, grow, live, work, and age; these circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels” (62). Recognizing that up to 50–60% of health outcomes are attributed to SDOH (63), multiple frameworks have been developed to both categorize and describe the influence of SDOH on individual and population health outcomes (59). The most comprehensive framework was developed by the WHO in 2010 and highlights the causal effects of upstream structural determinants (e.g., socioeconomic context, political context, and socioeconomic position) on intermediary determinants (e.g., biological, behavioral, and psychosocial factors, as well as the health system), leading to health inequities (64). More recently, the Centers for Disease Control and Prevention’s Healthy People 2020 (and now Healthy People 2030) framework grouped SDOH into five general domains, including the neighborhood and built environment, social and community context, economic stability, education access and quality, and health care access and quality (65), as shown in Figure 6. The common theme among all frameworks is that the inequitable distribution of SDOH is the fundamental basis for all health disparities (59).

Impact of Key SDOH on DPN
Adverse distribution of SDOH has both direct and indirect impacts on proximal diabetes outcomes such as glycemic control (67), which in turn contribute to the pathogenesis of diabetes complications, as demonstrated in Figure 7. These indirect pathways, or mediators, include adverse care processes (e.g., preventive screenings for complications), poor access to health care (e.g., patient-centered care), or inadequate self-care behaviors (e.g., medication-taking) (67). Examples of negative diabetes outcomes resulting from the specific domains of SDOH are discussed below, with a particular focus on DPN.

Economic Stability
SES is a complex construct that commonly includes measures of income and occupation, both of which are closely intertwined with education (59). As described above, people with lower SES, as determined by poverty and low education status, are more likely to have type 2 diabetes. Furthermore, those with lower SES who have diabetes are more likely to have inadequate glycemic control (68). Unsurprisingly, then, individuals with type 1 diabetes living in more socially deprived areas in Scotland were found to be 2.17 times more likely to have DPN (8).

Education
Researchers conducting an analysis of the T1D Exchange clinic registry cohort in the United States found that lower individual educational attainment predicted DPN in type 1 diabetes, even when adjusted for glycemic exposure and vascular risk factors (7). Additionally, low educational status has been shown to be associated with the development of any microvascular complication in type 2 diabetes (69).

Health Care Access and Quality
In the United States, access to quality health care is highly dependent on having health insurance. This was particularly true in the era before passage of the Affordable Care Act; prior studies using data from 2011
and 2012 demonstrated a lack of routine diabetes care measures such as assessment of glycemic control and preventive diabetes screenings, even when controlled for individual income (70). It was not surprising, then, that T1D Exchange researchers were able to demonstrate in their clinic registry cohort that DPN in type 1 diabetes was associated with having public or no insurance versus private insurance (7).

**Physical and Built Environment**

Stable housing, food security, and safe environments in which to engage in physical activity are crucial for individuals with diabetes to facilitate consistent medication use (e.g., the proper storage of insulin or noninsulin injectables) and self-care behaviors to achieve proximal glycemic outcomes (59). However, there is a lack of research evaluating the effects of the physical and built environment specifically on DPN.

**Social Environment**

Factors such as social context and social support have been shown to be important in improving glycemic control, self-care behaviors, and quality of life (59). There are also known cultural preferences in terms of support systems and interventions to improve support that include multifaceted approaches such as peer support, community health worker support, and support from the health care team, depending on the target population (59). However, there is a paucity of studies evaluating the impact of the social environment on DPN specifically.

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**Special Considerations**

**Racism as a Potential Root Cause for Health Disparities in Diabetes**

Members of racial and ethnic minority groups historically have borne a disproportionate burden of diabetes and its associated complications (19,60). Biological factors such as alterations in glucose metabolism, insulin resistance, and obesity have been found to account for some of this increased risk (71). However, studies assessing race and ethnicity have found inconsistent findings, with many of the increased risks attributable to SDOH (72). With regard to DPN specifically, there have been no consistent findings of racial or ethnic differences in DPN prevalence rates (71,73).

With an increased understanding of the importance of SDOH in diabetes prevalence, incidence, and outcomes, the upstream social and political contexts that contribute to and perpetuate health disparities have been receiving increased attention. Specifically, the concept of racism, rather than race, as the root cause of the structural and social factors leading to socioeconomic deprivation, residential segregation, and discrimination has been proposed and warrants further evaluation (74).

**Importance of Psychological Determinants of Health in Painful DPN**

There is increasing evidence that psychological determinants such as emotional distress (75) and depression (76) significantly affect sleep and quality of life in painful DPN (77). It is recognized that there is a complex interplay...
between SDOH, psychological determinants, and glycemic control (67). Further investigation to is needed to learn how these complex relationships extend to DPN, and particularly painful DPN.

**The Way Forward**
The writing group for the ADA’s SDOH scientific review emphasized the need to evaluate the impacts of SDOH pathways on different populations with diabetes (59). Data specific to the effects of SDOH on DPN are limited but crucial to provide a comprehensive understanding of the contributors to this debilitating and common complication of diabetes. Because there are no clearly effective, disease-modifying agents for DPN (1), targeting proximal diabetes outcomes such as glycemic control, blood pressure control, and adequate treatment of lipid pathways remains the mainstay of therapy for prevention of DPN. Additional research on the impacts of SDOH on DPN risk and outcomes can provide clarification on potential high-yield intervention targets. Historically, our treatment strategies for DPN have focused on improving symptoms such as pain in individuals but are limited in terms of their effectiveness, with only 50% of people with DPN responding to such interventions (1). Ultimately, interventions that target more upstream social, political, and psychological causes of DPN may be more effective for a larger population.

In summary, DPN remains a common complication of both type 1 and type 2 diabetes, and early investigation in observational studies of large cohorts suggest that socioeconomic factors and health care accessibility are risk factors for DPN. A more comprehensive assessment of the impacts of social and psychological determinants of health on DPN is needed to better our understanding of potential therapeutic targets. It is likely that interventions that address more upstream causes of health disparities at structural and societal levels will be more effective for a larger population of patients at risk for DPN.

**KEY POINTS**

- Discrepancies in SDOH are the basis for health disparities, particularly in diabetes, leading to an increased disease prevalence and incidence.
- Inequitable distribution of SDOH has both direct and indirect effects on diabetes outcomes, including glycemic control and cardiovascular outcomes.
- Social deprivation, lower educational status, and limited health care access are risk factors for DPN. Future exploration of other SDOH domains on DPN risk and progression should be pursued.

**TREATING PAINFUL DPN**
As mentioned previously, ~30% of all individuals with DPN will experience painful symptoms that will require pharmacological and other treatments (78). Although painful DPN may occur in all age-groups, it is more common in older patients. Additionally, there are specific differences in pain phenotypes. For instance, in younger individuals with poorly controlled type 1 diabetes, pain may be present with no or very few other clinical signs (78,79), whereas older individuals are also likely to have large-fiber dysfunction, resulting in unsteadiness and gait disturbances, which can adversely affect activities of daily living (80). In a large, community-based study in the United Kingdom, painful DPN was more common in individuals with type 2 diabetes, and there was a weak association with older age (79). Given that the mean age of the 15,000 patients in this study was 61 years, this finding suggests that the management of painful DPN in the elderly requires special attention.

**Pain Assessment**
Successfully treating painful DPN requires the means to evaluate the effectiveness of each patient’s therapeutic regimen. A large number of scales to assess pain severity have been proposed (81,82), including a visual analog scale (VAS) or a series of simple, orienting questions such as found in the DN4 (54), and these approaches may be useful in clinical practice. More detailed assessment of neuropathic symptoms can be accomplished with tools such as the Neuropathy Total Symptom Score–6 or the modified Toronto Clinical Neuropathy Score instruments (82–84).

**Role of Glycemic Control**
As described earlier, chronic hyperglycemia is a major contributory factor in the etiopathogenesis of the diabetic neuropathies; however, the importance of glycemic control in the management of painful symptoms is less clear. Early studies suggested that stable glycemic control with few excursions into hyperglycemia or hypoglycemia was associated with reduced pain scores as assessed on a VAS (78). Later, with the advent of continuous glucose monitoring, a small study confirmed that people with painful DPN have greater fluctuations in glucose and poorer overall glycemic control than matched subjects with painless neuropathy (85). Although there has not been, nor will there ever be, a randomized trial to test the hypothesis, an early step in the management of painful DPN should be to achieve optimal and stable glycemic control (86). Thus, the stability of glycemic control may
be more important than the actual level of control, as indicated by A1C, in the management of painful DPN.

Acute Painful Diabetic Neuropathy
Acute painful diabetic neuropathy is a rare but well-recognized and distinct variety of the sensory neuropathies. It is characterized by very severe neuropathic symptoms, as described earlier, that typically occur after a sudden change in glycemic control and has been described as occurring after normalization of blood glucose levels after simultaneous pancreas and kidney transplantation. It can also follow an episode of ketoacidosis, and in young people, particularly females, it may be associated with eating disorders (87). The prognosis of this acute form of painful neuropathy is good, typically with resolution of symptoms within 12 months. However, pharmacological treatment of the severe symptoms, as described below, is invariably required. This variety of neuropathy was originally called “insulin neuritis,” but a more recent review by Gibbons and Freeman (88) suggested the term “treatment-induced neuropathy of diabetes,” as insulin is not the only cause.

Chronic Painful Diabetic Neuropathy
This chronic painful neuropathy is common among people of all ages with either type 1 or type 2 diabetes. Many of these individuals will require treatment, and the commonly used therapeutic approaches are described below. It is important to remember that the natural history of this condition is usually characterized by the resolution of severe symptoms over a period of years (78), although data from reliable, long-term studies are lacking. Thus, regular review and adjustment of the therapeutic approach in each patient is essential.

Therapeutic Approaches
Because there are no pathogenetically oriented pharmacological treatments approved by the U.S. Food and Drug Administration (FDA), the treatment approaches described below target the symptoms but do not alter the natural history of neuropathy, which is one of progressive loss of nerve fibers in a distal-to-proximal manner. The following sections briefly describe the commonly used pharmacological agents, topical treatments, and physical therapies, as summarized in Figure 8. Limited space prevents us from including discussion of the many

![FIGURE 8](image-url) Recommended therapeutic approaches to painful diabetic peripheral neuropathy. Pharmacological therapy selection should be individualized based on factors such as comorbidities, cost, potential drug-drug interactions, and potential for adverse effects. Opioids are not recommended because of their high risk of addiction, abuse, and adverse effects. Topical capsaicin and a variety of nonpharmacological approaches are also available, and combination therapy may be needed. Not depicted are the neutraceuticals α-lipoic acid and benfotiamine, which are used in some countries but not approved in the United States. Individuals with severe pain that is refractory to other therapies should be referred to a specialist pain clinic. *U.S. Food and Drug Administration–approved for the treatment of painful diabetic peripheral neuropathy. SNSRI, selective norepinephrine and serotonin reuptake inhibitor.)
other agents that have been proposed for the treatment of painful DPN. For a detailed discussion of this topic, readers are referred to recent systematic reviews and meta-analyses, position statements, and review articles (1,45,81,82,89).

**FDA-Approved Pharmacological Treatments**

There are three FDA-approved therapies for painful DPN: pregabalin, duloxetine, and tapentadol (1). However, the last is an opioid, and a systematic review after its approval questioned its effectiveness (90). This issue will be addressed in a separate section below.

**Pregabalin**

Pregabalin is a calcium channel α2-δ subunit ligand, the efficacy of which has been confirmed in a large number of studies (1,45,81,82,89,91). It has been extensively studied in painful DPN (1,82,91), and evidence suggests a dose-dependent response, with weaker effect at lower doses (92). It can be given twice, or, on occasion, three times daily, and most patients require 300–600 mg/day for symptomatic relief. However, because it is excreted virtually unchanged in the urine, great caution must be taken in individuals with renal impairment, especially those with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m². Adverse effects, which commonly include somnolence, dizziness, and peripheral edema, are more likely with higher dosages and also in the elderly.

As recommended by Freynhagen et al. (91), a low-and-slow dosing approach can limit these adverse effects. These authors also recommend starting with asymmetric dosing, with a larger dose being given in the evening. Up-titration should be based on pain relief. Thus, in a middle-aged patient with normal renal function, it is common to start with 75 mg twice daily and gradually increase the dose every 3–7 days to a maximum of 600 mg/day. Greater caution is required in elderly patients, who are more likely to have renal dysfunction and in whom side effects are more common; in these individuals, starting at 25 mg daily may be required.

Because pregabalin additionally has anxiolytic activity, it may be particularly helpful in individuals with marked anxiety, which is not uncommon among people experiencing neuropathic pain.

**Duloxetine**

Duloxetine is a selective norepinephrine and serotonin reuptake inhibitor and can be given once daily at a dose of either 60 or 120 mg. Its efficacy has been proven in a number of randomized controlled trials (RCTs), and it has been shown in head-to-head trials to have similar efficacy to other agents, including pregabalin and gabapentin (45). Its adverse effects are well recognized and include nausea, somnolence, and dizziness, among others (1,45,82).

Because duloxetine and pregabalin have different modes of action, the combination of these agents has been used with good effect in clinical practice. However, the largest comparative trial (93) did not show a significant difference between high-dose monotherapy with either agent and a standard-dose combination of both. However, there was a trend consistently favoring combination therapy over monotherapy.

Because duloxetine is also an antidepressant, it may be particularly helpful in people with painful DPN who also have depressive symptomatology.

**Other Pharmacological Therapies**

**Amitriptyline**

Amitriptyline and other tricyclic antidepressant agents have been used for many years in the management of neuropathic pain (1,45,81,82,89). However, adverse effects are common, especially in the elderly, and include anticholinergic effects such as dry mouth, urinary retention, and drowsiness. There are also warnings to use these agents with caution in the presence of ischemic heart disease or glaucoma.

Up to one in three patients cannot tolerate even the lowest dose of amitriptyline because of these predictable side effects. It can be given once daily, usually in the early evening, and the usual starting dose is 25 mg, increasing as necessary to a maximum of 150 mg. However, much lower doses must be used in older patients, and because of potential cardiovascular adverse effects, great caution should be taken in those with known ischemic heart disease.

**Gabapentin**

Gabapentin, similar to pregabalin, was first used as an anti-epileptic drug but has been shown to have efficacy in the management of painful DPN. However, it has a shorter half-life and therefore must be dosed three times daily. As with pregabalin, up-titration is recommended, but trials have shown that most patients require 1,800 mg daily in divided doses for pain relief, and, occasionally, patients need the maximum daily dose of 3,600 mg. Lower doses are recommended for individuals with a reduced eGFR (45).

The adverse effects of gabapentin are similar to those of pregabalin and include dizziness, somnolence, and, on occasion, gait disturbances. A recent systematic review comparing the efficacy and safety of gabapentin and duloxetine in painful DPN found no significant differences between the two drugs (94).
**Opioids**

Although several opioids have been shown to have some efficacy in the management of neuropathic pain in general, their associated high risks of addiction, abuse, sedation, and other complications such as somnolence, headache, and impaired gastrointestinal motility even in the short term are major barriers to their use. Additionally, it has been revealed recently that even the weak synthetic opioid agonists tramadol and the extended-release tapentadol pose the same risks with only modest evidence of efficacy in relieving severe neuropathic pain. Thus, given the evidence on risks versus potential benefits, none of these agents should be used in the treatment of painful DPN, and they should be avoided especially in the elderly.

Interestingly, a recently published randomized, double-blind, crossover clinical trial (95) paradoxically suggested that the opioid receptor antagonist naltrexone 2–4 mg daily might be effective in the treatment of painful DPN. Naltrexone showed comparable efficacy but greater safety and tolerability than amitriptyline in this trial. However, these preliminary results, although interesting, will need to be confirmed in larger trials.

**Topical Therapies**

A number of topical therapies have been proposed for the treatment of painful DPN over the years but are not widely used because the area of neuropathic pain can be quite extensive, involving not only both feet, but also the lower limbs, generally below knee level. The most studied of these products has been capsaicin, but its use has been restricted because of the need for frequent application and also the burning pain patients often experience when a capsaicin-containing patch is applied topically.

More recently, an 8% long-acting capsaicin patch has been developed and is now approved by the FDA for painful DPN based on data from two multicenter trials demonstrating effective pain reduction. Initial results are promising (96,97), and it is associated with fewer central adverse effects than the oral medications. However, its use may cause significant pain at the application site, it should be avoided in patients with active skin lesions, and its application requires suitable infrastructure to be available and must be performed in a physician’s office.

**Physical Therapies**

Data from RCTs support the use of spinal cord stimulation (SCS) in the management of severe painful DPN. This and other energy or nerve stimulation treatments are discussed in detail in the section on nonpharmacological approaches to DPN and pain management.

**Management of Painful DPN in the Elderly**

As alluded to above, particular care is required in the management of painful DPN in elderly patients. Polypharmacy is common in the elderly, and this is especially true in those with diabetes, who may be on multiple therapies, including several oral antidiabetic agents, a statin, aspirin, and multiple treatments for other common comorbidities such as hypertension and cardiovascular disease. Indeed, an article published in 2016 by Jansen et al. (98) addressed the problem of inappropriate polypharmacy in older patients and proposed “deprescribing,” a process of planned and supervised tapering of inappropriate medications.

As noted above, painful DPN is common in elderly patients with diabetes, and, in addition to painful symptoms, these patients may also have significant loss of large-fiber nerve function, which leads to unsteadiness and motor dysfunction, leading in turn to alterations in gait (78). These patients are therefore more prone to adverse effects of some of the drugs discussed above, particularly the tricyclic antidepressants, but also anticonvulsants and duloxetine at higher doses.

Moreover, older patients are also more likely to have other complications, including diabetic nephropathy, kidney disease, and cardiovascular complications. Therefore, marked caution must be taken when dosing drugs such as pregabalin and gabapentin, which should be started at lower doses than usual and with very careful up-titration. It is also well recognized that eGFR falls with age (99); thus, although a patient who is 80 years of age and has an eGFR of 50 ml/min/1.73 m2 may be considered as having “normal” renal function, extra care must still be taken when setting dosages for the drugs discussed above. Older patients with severe painful DPN not responsive to these drugs might benefit from referral to a pain clinic for possible SCS therapy (100).

**Combination Treatment**

Given the complexity of DPN-associated pain and the high risks for side effects of available pharmacological agents, particularly when higher effective doses are needed and in a patient population with multiple other comorbidities, consideration of combination therapy may be advisable. Combining two or three of the pharmacological agents discussed above that have a strong track record of benefit may enable better pain resolution at lower doses and with better tolerance, as shown in Figure 8 (1). Similarly, combining pharmacological with nonpharmacological treatment options may be more effective in a broader number of individuals (Figure 8).
Duration of Treatment
As noted previously, the natural history of painful DPN is not well studied, but it is clinically recognized that painful symptoms rarely persist for more than a few years. Thus, periodic review of pharmacological therapy is needed, and these agents must not be regarded as lifetime medications. It is recommended that, after 6 months of symptom relief, a slow and gradual reduction of drug treatment should be attempted. If symptoms reappear during this gradual reduction, a lower dose may be required for the next few months, when further review and attempted reduction should take place.

Future of Painful DPN Treatment
As summarized in recent reviews (45,81,89), a number of new agents are currently under investigation for the management of painful DPN. Moreover, phenotyping of patients with painful DPN may well lead to the development of more and better treatments for this condition. Many of the current pharmacological therapies are unsatisfactory, not only because of their adverse effects profile, but also because of their general poor efficacy and high numbers needed to treat to improve outcomes (81). Thus, more precise phenotyping of individuals with painful DPN might help to identify subgroups of patients who are more likely to respond to a given therapy.

ROLE OF NUTRACEUTICALS IN DPN AND PAIN MANAGEMENT
As discussed earlier, DPN remains the most relevant and prevalent clinical manifestation of diabetic neuropathy and predicts the development of neuropathic foot ulcers, all-cause mortality, and cardiovascular morbidity and mortality (1,101). Despite its major clinical impact, the condition still remains underdiagnosed and undertreated (102). Given that the efficacy of causal treatments of DPN and neuropathic pain is limited, there is an unmet need for adjunct treatments.

The term “nutraceutical” was coined in 1989 (103) as a portmanteau of “nutrition” and “pharmaceutical.” However, to date, there are no internationally accepted definitions of the term or of related terms such as “functional food,” “health food,” or “herbal therapy” (104). It has been proposed that, unlike dietary supplements, nutraceuticals should not only supplement the diet, but also aid in the prevention and/or treatment of disease and/or disorder (105). However, nutraceuticals are not defined by U.S. law and usually would be categorized as dietary supplements and regulated by the FDA under the provisions of the Dietary Supplement Health and Education Act. According to that law, “Dietary supplements include a large, heterogeneous group of products intended to supplement the diet that are not better described as drugs, foods, or food additives. Supplements may contain, in whole or as a concentrate, metabolite, constituent, or extract, any combination of 1 or more vitamins, minerals, amino acids, herbs or other botanicals, and other substances used to increase total dietary intake, including enzymes, organ tissues, and oils. They must be intended for ingestion; sold in the form of capsules, tablets, soft gels, gel caps, powders, or liquids; and not be marketed as food items” (105).

Several nutraceuticals represent biofactors required by the body for its normal physiological functioning and may exert health-beneficial or disease-preventive biological activities. Essential biofactors are those that the organism cannot produce or cannot produce in sufficient quantity, thus requiring supplementation from external sources. Examples include vitamins (A, B1, B6, B9, B12, C, D, E, and K), minerals (selenium, magnesium, and zinc), fatty acids (α-lipoic acid [ALA], polyunsaturated fatty acids [PUFAs]), and amino acids (acetyl-L-carnitine) (106). Dietary supplementation with certain biofactors could be useful as a complement to established therapies for preventing and treating DPN because diabetes is associated with systemic deficits in several biofactors, but favorable effects have also been reported in the absence of such deficiencies (107).
Therapeutic Role of Nutraceuticals

In general, the management of DPN includes three cornerstones: 1) causal treatment, including lifestyle modification, intensive diabetes therapy aimed at near-normoglycemia, and multifactorial cardiovascular risk intervention, 2) pathogenetically oriented pharmacotherapy using specific nutraceuticals, and 3) symptomatic treatment of neuropathic pain (102). The available evidence for the second pillar is outlined here. For this discussion, only RCTs of single compounds (monotherapy) were considered because use of combination nutraceuticals does not allow for separate assessment of their constituent parts, and uncontrolled studies are difficult to interpret given the lower quality of the evidence they yield.

The rationale for using nutraceuticals in DPN is primarily to favorably influence the underlying neuropathic process and its clinical consequences rather than only relieving symptomatic pain, which is usually the goal of analgesic therapy. The RCT results described below are also summarized in Table 2.

\textbf{α-Lipoic Acid}

Because oxidative stress plays a major role in the pathogenesis of diabetic neuropathy, the rationale for treatment using antioxidants such as ALA to diminish enhanced oxidative stress and thereby favorably influence DPN is obvious (108). Among the nutraceuticals reviewed herein, ALA has the best evidence in DPN. In summary, intravenous infusions of ALA (600 mg/day) ameliorated neuropathic symptoms and deficits (i.e., signs or impairments) after 3 weeks (108). Moreover, treatment for 5 weeks and 6 months using oral ALA 600 mg daily and twice daily, respectively, reduced the main symptoms of DPN, including pain, paresthesias, and numbness, to a clinically meaningful degree (108,109). Several meta-analyses confirmed the efficacy of ALA in symptomatic DPN (108). In the NATHAN (Neurological Assessment of Thiocetic Acid in Diabetic Neuropathy) 1 trial, which included 460 patients with diabetes and mild to moderate, largely asymptomatic DPN, after 4 years of ALA treatment using 600 mg daily, neuropathic deficits (i.e., signs) were improved, suggesting a potential to favorably influence the underlying neuropathy, and the drug was well tolerated throughout the trial (108). Clinical and post-marketing surveillance studies have revealed a highly favorable safety profile (108).

ALA is approved and recommended by guidelines (101) as pharmacotherapy for the treatment of DPN in several countries, but not in the United States or Canada. The primary indication for ALA is symptomatic DPN, including not only neuropathic pain but also nonpainful symptoms such as paresthesias and numbness, particularly if these interfere with a patient’s quality of life. On the other hand, based on the results of the NATHAN 1 trial (108), ALA (600 mg daily) can also be considered for long-term use ≥4 years in asymptomatic DPN to improve neuropathic signs (i.e., the underlying neuropathy) (108).

The usual dose is 600 mg daily, but higher doses (600 mg twice or three times daily) may occasionally be useful if symptom relief is only partial (≤30% reduction). The duration of RCTs using ALA in symptomatic DPN has been limited to ≤6 months, similar to those using analgesic drugs in painful DPN, which lasted ≤3 months. Nonetheless, these pharmacological therapies are being used for considerably longer periods in clinical practice if residual neuropathic symptoms or pain persist.

Theoretically, there is a rationale for using ALA and other nutraceuticals in combination with analgesic drugs to enhance efficacy and synergistically target the underlying neuropathy, but there are no RCTs to support this strategy.

\textbf{Benfotiamine}

Thiamine (vitamin B1) is a water-soluble vitamin that constitutes an essential cofactor of several enzymes involved in carbohydrate metabolism. Benfotiamine, a lipid-soluble allithiamine homolog, is a synthetic S-acyl derivative (prodrug) of thiamine and has been shown to inhibit the formation of AGEs (106). The BENDIP (Benfotiamine in Diabetic Polyneuropathy) study showed that neuropathic symptoms, with Neuropathy Symptom Score as the primary endpoint, were improved after 6 weeks of treatment using a benfotiamine dose of 300 mg twice daily but not 300 mg daily (102), while the smaller and shorter BEDIP (Benfotiamine in the Treatment of Diabetic Polyneuropathy: a Three-Week Randomized, Controlled Pilot Study) study found improvement in a score combining neuropathic symptoms and signs after 3 weeks of treatment with benfotiamine 400 mg daily (102). The incidence of adverse events did not differ between active and placebo treatment.

Benfotiamine is approved and recommended by guidelines (101) as pharmacotherapy for treatment of DPN in several countries, but not in the United States or Canada. Similar to ALA, the primary indication for benfotiamine is symptomatic DPN, including not only neuropathic pain but also nonpainful symptoms. However, the number of available RCTs is lower and their durations have been shorter than for ALA.

Based on the results of the BENDIP study (102), the appropriate dose of benfotiamine over the first 6
<table>
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<td>65‡</td>
<td>600/1,200/placebo</td>
<td>2 years PO</td>
<td>NCS +</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ALADIN III (108)†</td>
<td>0/508</td>
<td>600 IV/1,800 PO/placebo</td>
<td>3 weeks IV/6 months PO</td>
<td>Symptoms + Signs + QoL +</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ORPIL (108)†</td>
<td>0/24</td>
<td>1,800/placebo</td>
<td>3 weeks PO</td>
<td>Symptoms + QoL (+) Signs +</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>SYDNEY (108)†</td>
<td>30/90</td>
<td>600/placebo</td>
<td>3 weeks IV</td>
<td>Symptoms + NSC + Signs +</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>SYDNEY 2 (108)†</td>
<td>30/151</td>
<td>600/1,200/1,800/placebo</td>
<td>5 weeks PO</td>
<td>Symptoms + NSC + Signs +</td>
<td>Dose-dependent GI symptoms</td>
</tr>
<tr>
<td></td>
<td>NATHAN 1 (108)†</td>
<td>110/344</td>
<td>600/placebo</td>
<td>4 years PO</td>
<td>Signs + NCS −</td>
<td>SAEs slightly increased§</td>
</tr>
<tr>
<td></td>
<td>El-Nahas et al. (109)</td>
<td>0/200</td>
<td>1,200/placebo</td>
<td>6 months PO</td>
<td>Symptoms + VPT +</td>
<td>Mild nausea</td>
</tr>
<tr>
<td>Benfotiamine</td>
<td>BENDIP (102)†</td>
<td>16/117</td>
<td>300/600/placebo</td>
<td>6 weeks</td>
<td>Symptoms + (PP) Signs −</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>BEDIP (102)†</td>
<td>8/32</td>
<td>400/placebo</td>
<td>3 weeks</td>
<td>Symptoms/signs + Pain +</td>
<td>None</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Didangelos et al. (112)</td>
<td>0/90</td>
<td>1/placebo</td>
<td>1 year</td>
<td>Symptoms + Signs − Pain +VPT + NCS +</td>
<td>None</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Karonova et al. (114)</td>
<td>0/67</td>
<td>40,000 IU/5,000 IU per week</td>
<td>24 weeks</td>
<td>Pain + Symptoms + Signs +</td>
<td>None</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>VENUS (116)</td>
<td>300‡</td>
<td>400/placebo</td>
<td>1 year</td>
<td>Symptoms – Lancinating pain (+)</td>
<td>None</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>Sima et al. (118)</td>
<td>1,257‡</td>
<td>3,000/placebo</td>
<td>1 year</td>
<td>Pain + VPT + NCS −</td>
<td>None</td>
</tr>
<tr>
<td>γ-Linolenic acid (GLA)</td>
<td>Keen et al. (119)</td>
<td>57/51</td>
<td>480/placebo</td>
<td>1 year</td>
<td>NCS + Signs +</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Won et al. (120)</td>
<td>0/100</td>
<td>320 GLA/600 ALA</td>
<td>12 weeks</td>
<td>Symptoms, pain noninferior</td>
<td>None</td>
</tr>
<tr>
<td>Magnesium</td>
<td>de Leeuw et al. (122)</td>
<td>110/0</td>
<td>300/ no supplement</td>
<td>5 years</td>
<td>DPN stage + NCS +</td>
<td>GI symptoms</td>
</tr>
</tbody>
</table>

*Doses are mg/day except for Vitamin D, which is IU/week. †Summarized in review article. ‡Diabetes type not available. §Incidence: 38% (ALA) versus 28% (placebo), including cardiovascular and cerebrovascular disorders, infections, inflicted injuries, and fractures; deaths: 1.3% (ALA) versus 2.7% (placebo). ††For GLA versus ALA. †‡Versus no supplement. + Indicates improvement compared to placebo. (+) Indicates trend toward improvement compared to placebo. − Indicates no difference compared to placebo. ALADIN, Alpha-Lipoic Acid in Diabetic Neuropathy; BENDIP, Benfotiamine in the Treatment of Diabetic Polyneuropathy; BEDIP, Benfotiamine in Diabetic Polyneuropathy; DPN, diabetic peripheral neuropathy; GI, gastrointestinal; IV, intravenous; NATHAN, Neurological Assessment of Thioctic Acid in Diabetic Neuropathy; NSC, nerve conduction studies; ORPIL, Oral Pilot; PO, oral administration; PP, per protocol analysis; QoL, quality of life; SAEs, severe adverse events; SYDNEY, Symptomatic Diabetic Neuropathy; T1D, type 1 diabetes; T2D, type 2 diabetes; VENUS, Vitamin E in Neuroprotection Study; VPT, vibration perception threshold.
weeks is 300 mg twice daily. Whether this dose should be maintained during long-term treatment is currently being examined by the BOND study (110) assessing the effects of 1-year treatment with benfotiamine 300 mg twice daily on morphometric, neurophysiological, and clinical measures in individuals with type 2 diabetes and symptomatic DPN.

**Vitamin B12**

Vitamin B12 deficiency can have hematological or neurological consequences, including polyneuropathies (1). Because of the increased risk of a vitamin B12 deficiency associated with metformin treatment, the ADA recommends periodic measurement of vitamin B12 levels for metformin-treated patients (111). A recent 12-month RCT assessed the effects of oral vitamin B12 supplementation with 1,000 µg per day in metformin-treated people with type 2 diabetes and DPN who had low vitamin B12 levels (<400 pmol/L). Oral vitamin B12 treatment improved neurophysiological measures, pain score, sudomotor function, and quality of life, but not MNSI score (112). Vitamin B12 deficiency should be supplemented with oral vitamin B12 1,000 µg daily. The duration of supplementation depends on the cause and may be lifelong (e.g., in pernicious anemia or after bariatric surgery). Treatment of DPN with vitamin B12 in the absence of vitamin B12 deficiency is not indicated.

**Vitamin D**

Obesity, prediabetes, and type 2 diabetes constitute important risk factors for vitamin D deficiency. There is also accumulating evidence suggesting a link between low systemic vitamin D levels and DPN (113). In a randomized, open-label study in participants with type 2 diabetes and DPN, the majority of whom were vitamin D deficient, improvements in neuropathic symptoms and deficits were observed after 24 weeks of high-dose vitamin D treatment (40,000 IU/week) compared to a control group supplemented with vitamin D 5,000 IU/week (114). Thus, further studies are needed to define the exact role of vitamin D supplementation specifically in vitamin D–deficient people with DPN.

In general, vitamin D deficiency (<50 nmol/L (20 ng/mL)) is associated with fractures and bone loss. Severe vitamin D deficiency (<30 nmol/L (12 ng/mL)) dramatically increases the risk of excess mortality, infections, and many other diseases and should be avoided whenever possible (115). However, there is no international consensus on the optimal level for vitamin D supplementation, and recommendations range from 400 to 2,000 IU daily (115).

**Vitamin E**

Vitamin E is the most abundant liposoluble antioxidant, comprising eight fat-soluble compounds (four tocopherols and four tocotrienols) protecting cell membranes from oxidative stress. In a large clinical trial, vitamin E (200 mg of mixed tocotrienols twice daily) did not improve neuropathic symptoms over 1 year in people with DPN. However, in post hoc subgroup analyses, tocotrienols reduced lancinating pain among people with A1C levels >8% and normohomocysteinemia after 1 year (116). Based on these data, vitamin E cannot be recommended for DPN treatment.

**Acetyl-L-carnitine**

In humans, the metabolic pool of carnitine comprises nonesterified levo-carnitine (L-carnitine) and acyl carnitine esters, among which the amino acid acetyl-L-carnitine represents the greatest component. A Cochrane review analyzed four studies in participants with DPN (117). Although some favorable effects on pain and vibration perception threshold were reported (118), the evidence was rated as being of low certainty as to whether acetyl-L-carnitine causes a reduction in pain after 6 to 12 months of treatment in people with DPN (117).

**Polyunsaturated Fatty Acids**

An early RCT reported favorable effects of treatment with the PUFA γ-linolenic acid (GLA) for 1 year on multiple neurophysiological and clinical parameters in individuals with DPN (119). In a recent 12-week, multicenter, noninferiority RCT trial comparing the efficacy of GLA (320 mg/day) and ALA (600 mg/day) in participants with type 2 diabetes and painful DPN, both neuropathic symptoms and pain improved after 12 weeks, and GLA was noninferior to ALA in reducing pain intensity (120). Further studies are required before PUFAs can be recommended for DPN treatment.

**Magnesium**

Magnesium is the second most abundant intracellular divalent cation and is involved in several hundred metabolic reactions, in which it mainly serves as a cofactor and plays an important role in carbohydrate metabolism and cellular bioenergetics. Magnesium deficiency (serum levels <0.75 mmol/L) can lead to an enhanced neuromuscular excitability, including symptoms such as nervousness or cramps of both smooth and skeletal muscle (121). Reduced magnesium intake and systemic magnesium levels are associated with both prediabetes and diabetes (121). However, there is no evidence from placebo-controlled RCTs assessing the efficacy of
magnesium supplementation in DPN. In an open, low-quality RCT, individuals with type 1 diabetes, with or without DPN, were supplemented with magnesium (Group A), while another group did not receive magnesium (Group B). Magnesium in red blood cells increased to normal levels in Group A but remained low in Group B. After 5 years, DPN stages improved more often in Group A than in Group B (39 vs. 8%, respectively) and worsened more often in Group B than in Group A (12 vs. 61%, respectively) (122).

Magnesium supplementation has been recommended for people with diabetes and hypomagnesemia if other dietary approaches fail to balance magnesium status (121). Oral magnesium supplementation is safe in adults when used in dosages below the upper intake level of 350 mg daily, but because of its renal secretion, magnesium should be used with caution in individuals with kidney disease (123).

In summary, given that the efficacy of both causal therapies for DPN and symptomatic treatments for neuropathic pain is limited, there is an unmet need for adjunctive therapies. Experimental studies have indicated that diabetic neuropathy can be prevented or ameliorated by various nutraceuticals in animal models by interfering with the pathophysiology of the underlying condition. Some of these findings could be translated successfully into the clinical arena and confirmed in clinical trials of DPN.

The efficacy and safety of several nutraceuticals, including ALA, benfotiamine, vitamin B12, acetyl-L-carnitine, vitamin D, vitamin E, and the PUFA GLA have been studied in RCTs, some better designed than others. For clinical use, ALA and benfotiamine are licensed as drugs and approved for the treatment of DPN in several countries worldwide; however, they have not been approved for this use in the United States or Canada. ALA has the best evidence as therapy for symptom relief, highlighted by several meta-analyses. People with proven deficiencies in vitamins B and D and magnesium should receive supplementation to prevent worsening of DPN and other disorders.

The advantage of nutraceuticals is their excellent safety profile, but longer, well-designed, well-conducted confirmatory RCTs should be performed to establish the value of their use in DPN over the long term. Overall, nutraceuticals have the potential to favorably modify the natural history of DPN, and there is hope that, ultimately, they will contribute to expanding our therapeutic armamentarium against this common, debilitating, and potentially even life-threatening complication of diabetes.

**KEY POINTS**

- Because the efficacy of both causal therapies for DPN and symptomatic treatments for neuropathic pain is limited, there is an unmet need for a holistic approach considering pathogenetically oriented adjunctive therapies.
- Based on evidence for efficacy in reduction of symptoms and excellent safety from RCTs, ALA and benfotiamine (currently approved in some countries, although not FDA-approved in the United States) may be added for the management of persistent neuropathic symptoms, including pain in DPN.
- Confirmatory RCTs should clarify the value of using nutraceuticals in DPN over the long term.

**NONPHARMACOLOGICAL APPROACHES TO DPN AND PAIN MANAGEMENT**

The DCCT (124) showed in 1993 that tight glucose control reduces the risk of developing DPN in type 1 diabetes by >60%. The same has not proved true in type 2 diabetes, and, 30 years after the DCCT, no medication has been convincingly shown to retard the incidence of DPN or slow its progression (1). In this setting, nonpharmacological approaches that might alter the natural history of DPN or ameliorate neuropathic pain have received increasingly sophisticated evaluation. Treatments reviewed here fall broadly into three categories: health behavior interventions (HBIs), including exercise, dietary counseling, and their combination (Table 3); passive modalities, including massage and biofeedback; and nonpharmacological energy or nerve stimulation treatments.

**Health Behavior Interventions**

The DPP (Diabetes Prevention Program) and similar large, prospective RCTs demonstrated that a curriculum-based behavioral treatment combining dietary and exercise counseling delays the onset of type 2 diabetes (125,126). Physical activity has been shown to delay the onset and progression of DPN in individuals with type 2 diabetes or prediabetic metabolic syndrome, even in the absence of significant weight loss or improved glucose control (127). It is no surprise, then, that the most recent ADA position statement on the treatment of DPN (1) recommends lifestyle modifications that include supervised aerobic and/or resistance training, alone or in combination with dietary modifications based on those used in the DPP trial or based on a predominantly plant-based
Physical Activity and Exercise
Physical activity is defined as any movement that increases energy use. Exercise, a more structured form of physical activity, should be regarded as medical therapy and concurrently inhibits multiple established pathways in the pathogenesis of DPN. Animal models of neuropathy in diabetes and prediabetic metabolic syndrome demonstrate that sustained exercise reduces hyperglycemia and consequent excess oxidative and nitrosative stress; improves mitochondrial bioenergetics in both the nerve cell body and the distal axon; enhances microvascular vasoreactivity and reduces nerve ischemia; increases axonal transport; opposes the inflammatory effects of obesity, lipotoxicity, and hyperlipidemia; and enhances nerve regeneration after metabolic injury. Broadly, outcomes in human DPN exercise trials can be placed in three categories: neuropathy progression (e.g., exam, nerve conduction studies, and cutaneous nerve fiber density); mobility, balance, and gait; and neuropathic pain and quality of life.

Neuropathy Progression Outcomes
High-quality evidence is lacking on the specific effects of exercise on objective measures of neuropathy progression in individuals with DPN. Exercise is perhaps the only intervention shown to improve the regenerative capacity of small-diameter cutaneous sensory axons in people with metabolic syndrome and those with diabetes. Using change in intraepidermal nerve fiber density from a 3-mm skin biopsy, either alone or obtained before and 1–3 months after experimental capsaicin axotomy, sustained mentored exercise has been shown to increase nerve fiber density and regenerative capacity in people with metabolic syndrome or early type 2 diabetes (128). Participants who show improvement in the greatest number of metabolic syndrome features demonstrate the greatest improvement in reinnervation rate.

Mobility, Balance, and Gait Outcomes
Exercise convincingly improves measures of mobility, balance, and gait and reduces fall risk in DPN (129). These improvements have been demonstrated with different modes of exercise training, including aerobic, resistance, balance, Tai Chi, and whole body vibration, as

<table>
<thead>
<tr>
<th>TABLE 3  Lifestyle Interventions for Diabetic Peripheral Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention Type</strong></td>
</tr>
<tr>
<td>Aerobic exercise</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Resistance or strengthening exercise</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Balance exercise</td>
</tr>
<tr>
<td>Anti-sedentary behavior</td>
</tr>
<tr>
<td>Diet modification</td>
</tr>
</tbody>
</table>

*MET, or metabolic equivalent, refers to the energy expenditure required to carry out a specific activity, with 1 MET equal to the rate of energy expenditure while sitting at rest.
well as combinations of these modalities (130). Generally, training improves function specific to the training discipline (e.g., therapy focused on balance improves measures of balance). However, aerobic training has also been shown to improve mobility, balance, and gait outcomes in DPN. In a controlled trial of multimodal aerobic training, moderate-intensity (50% heart rate reserve) or vigorous (75% heart rate reserve) exercise yielded equivalent benefits, suggesting that both training intensities promoted these improvements (131). Current exercise intensity and frequency recommendations for people with DPN mirror the U.S. Department of Health and Human Services’ physical activity guidelines for Americans (132), although lower-intensity activity has also shown benefit and may be especially attractive for individuals unaccustomed to regular exercise.

**Neuropathic Pain and Quality-of-Life Outcomes**

Reduction of neuropathic pain is perhaps the most important outcome of interest to individuals with DPN. Randomized trials of scheduled aerobic exercise using modes such as cycling, treadmill, and progressive walking programs have reported significant improvement in pain scale scores, pain interference measures, and/or quality-of-life metrics over intervention periods ranging from 12 weeks to 4 years (133,134).

Less-intensive exercise modes may also show benefit in neuropathic pain. Passive whole body vibration is a new exercise mode in which participants stand on a vibrating platform and resist its effect to maintain an upright posture. It has been shown in small, sham-controlled, randomized trials to significantly improve neuropathic symptoms, pain, and health-related quality of life (135). Similarly, a Tai Chi regimen significantly improved DPN total symptom score, pain, and quality of life over the 12-week intervention, albeit with a 34% attrition rate (136).

**Exercise Prescription and Safety**

The potential benefits of exercise among people with DPN are increasingly clear. Clinically, a formal exercise prescription can stress the therapeutic value of exercise, encourage increased activity, and regulate progression to allow tissue adaptation without causing injury. Exercise prescriptions for individuals with DPN should include information on exercise type, mode, goal intensity, frequency, and duration (Table 3). Participation in weight-bearing exercise in individuals without severe foot deformity or peripheral vascular disease has been found to be safe. Individuals with DPN should seek medical clearance for cardiovascular risk before starting a formal exercise program.

Complications of exercise, including joint and muscle pain, hypoglycemia, orthostasis associated with autonomic dysfunction, and skin irritation, occur in more than one-third of mentored exercise participants with DPN and should be expected (137). Ongoing monitoring of neuropathic symptoms, glucose, heart rate, and blood pressure, as well as musculoskeletal and integumentary status, is recommended. Supervision by a physical therapist or exercise specialist is ideal to regulate progression and surveil for injury risks.

**Reducing Sedentary Behaviors**

Simply reducing sedentary behaviors (those that do not increase energy expenditure beyond the resting level) is another strategy that might improve DPN outcomes. The average awake sedentary time of adults >50 years of age is 8.3 hours (>500 minutes) daily. Restricted contraction of postural support muscles alters lipid metabolism and increases free fatty acid and adipokine release. Prolonged sitting also worsens insulin resistance.

Well-designed studies investigating the impact of reduced sedentary time on DPN outcomes are lacking, but epidemiological evidence linking inactivity to cardiovascular risk and poor health outcomes, independent of time spent in aerobic exercise, makes anti-sedentary behavioral modification an alluring future research direction (138). Wearable devices such as fitness trackers and smartphone applications, as well as research-grade accelerometers, make accurate measurement of sedentary behavior possible to provide feedback and facilitate goal-setting.

**Dietary Counseling and Modifications**

Dietary counseling as an isolated intervention for DPN has received only sparse investigation, but eating pattern modifications may prove effective as part of a more comprehensive lifestyle treatment regimen. Components of a healthy eating pattern ameliorate insulin resistance, improve glucose control, and promote anti-inflammatory effects in individuals with type 2 diabetes (139). Key components of a healthy eating pattern in the setting of DPN include calorie restriction, processed carbohydrate restriction, and emphasis on polyunsaturated fats and antioxidant foods.

Obesity, and especially abdominal adiposity, generate a potent pro-inflammatory state. Pro-inflammatory cytokines and free fatty acids released from enlarged adipocytes are neurotoxic to axons. Calorie restriction was more important than exercise for weight loss in the DPP and similar curriculum-driven HBI trials (125,126). Lipid metabolites and chronic cellular hyperglycemia activate pro-inflammatory cellular injury response pathways and contribute to oxidative stress, which inhibits mitochondrial function in distal axons.
Concentrated carbohydrates should be avoided, while emphasizing dietary sources of antioxidants such as green, leafy vegetables, berries, citrus fruits, and salmon. These dietary precepts are embodied in the low-fat and low-sugar eating pattern outlined in the DPP curriculum (125) and in predominantly plant-based diets such as the Mediterranean eating pattern (45% carbohydrate, 35–40% fat, and <10% of saturated fat) (139).

Passive Modalities
Thai massage (140) and other passive physical treatments and alternative medicine modalities have been reported in prospective studies to provide pain reduction or symptom improvement in DPN, but without the size and/or rigor of trial design or trial confirmation necessary to adequately evaluate their efficacy. These modalities include neuro-biofeedback (141), foot bath techniques (142), and static magnetic fields (143). None have been shown to alter the natural history of DPN progression.

Energy or Nerve Stimulation Treatments
In addition to HBIs and passive modalities, other nonpharmacological approaches to painful DPN that have received prospective evaluation include decompressive surgery and various forms of electrical modulation of nerve or other tissues, including transcutaneous electrical nerve stimulation (TENS), frequency-modulated electromagnetic stimulation, transcranial magnetic stimulation (TMS), and the previously mentioned SCS. These modalities have been extensively reviewed in practice guidelines, structured reviews (144), and detailed reports from the Agency for Healthcare Research and Quality (136). None of these treatments has been clearly shown to prevent or delay onset of DPN symptoms or to alter the natural history of DPN.

Electromagnetic Stimulation Modalities
In DPN, spontaneous ephaptic transmission from metabolically injured peripheral sensory afferent fibers generates sensation of neuropathic pain that often develops a chronic quality through central spinal sensitization. Various modes of intermittent electrical stimulation have been trialed to interrupt pain sensation. TENS and similar cutaneous nerve stimulation modes offer a competing sensory experience, whereas TMS and SCS modalities interrupt central processing of peripheral afferents. Although trial evidence for all of these modes is considered weak, centrally acting modes (i.e., TMS and SCS) appear more efficacious than peripherally acting modes. Several trials of electromagnetic stimulation have included change in exam or other measures of neuropathy severity as secondary or exploratory endpoints, but none has convincingly demonstrated neuropathy improvement with these therapies.

Spinal Cord Stimulation
SCS, in which stimulating electrodes are surgically implanted in the epidural space, is extensively used for pain reduction in failed back surgery syndrome and has been compared in clinical trials against best medical care (but not sham procedures) for treatment of painful DPN (145). These trials found large effect sizes favoring pain reduction with SCS over a 6-month follow-up period. Modest pain reduction appears durable. In longitudinal follow-up from a multicenter RCT of SCS, about one-third of recipients reported at least a 50% reduction in pain compared to baseline at 60 months (146).

Small, single-arm trials and RCTs of high-frequency (e.g., 10 kHz) SCS have reported 60–80% reduction in pain compared to best medical management, but also subjective improvements in sensory function. The strongest evidence for 10-kHz SCS comes from a recent multicenter RCT that randomized 216 patients with painful DPN who had not experienced improvement with at least one gabapentinoid and had a VAS score >50 mm to medical management alone or with 10-kHz SCS (100,147). Of the 104 participants assigned to SCS, 98 responded to temporary stimulation; 90 were implanted; 5 experienced implantation-related adverse events, with 2 requiring explants; and 74 reported a 50% reduction in baseline VAS pain at 6 months and 72 participants at 12 months, compared to 5 of 95 participants randomized to medical management alone. Control participants were allowed to cross over to 10-kHz SCS after 6 months of follow-up and showed similar significant improvement in pain measures as participants randomized to SCS at baseline. Quality-of-life measures improved significantly after 10-kHz SCS. Reported improvements in foot sensation on standardized exam for SCS participants suggest improved neurological function, but also raise concern about possible examiner and participant bias in a study that was not blinded or sham-controlled.

Risks for perioperative and long-term complications limit the appeal of SCS. Surgical and long-term complications of SCS specific to DPN have not been reported except in the context of clinical trials. However, a meta-analysis of 32 peer-reviewed longitudinal studies examining SCS for other indications found a complication rate of 21%, with chronic lead migration or infection requiring surgical revision or removal in 10% of recipients (148).

Transcranial Magnetic Stimulation
TMS using deep cortical stimulation has been reported in a 5-day, sham-controlled, crossover trial to provide significant short-term reduction in perceived neuropathic pain in people with DPN, with a return to baseline pain over 3 weeks (149).
Transcutaneous Electrical Nerve Stimulation

TENS in various forms, including via dermal pads, as an adjunct to amitriptyline, with electrode stockings, via percutaneous needles, and as frequency-modulated or pulsed stimulation (150) have been compared to sham treatment in short-duration randomized or crossover trials of up to 225 participants. A report by the Agency for Healthcare Research and Quality (136) and other structured reviews of these therapies concluded that TENS treatment was not clearly superior to sham for either pain or quality of life, with more rigorous and longer-duration trials yielding less apparent benefit (150).

Systematic Surgical Decompression

Systematic surgical decompression, in which individuals undergo surgery at multiple nerve sites in the leg that are considered common sites for compressive injury (e.g., the tibial nerve at tarsal tunnel and peroneal nerve at fibular head), has been reported prospectively in a small uncontrolled series (11 individuals with DPN) and a single-limb trial using the opposite leg as a control (42 individuals) (151). These studies reported improvement in neuropathic pain measures, with large effect sizes in the surgical subject or limb. However, poor design, treatment bias, lack of sham controls, lack of follow-up data on perioperative or long-term complications of surgery, and lack of confirmation from other trials substantially limit the ability to interpret these results.

Acupuncture

A 10-week RCT in 45 individuals with DPN and neuropathic pain compared acupuncture at traditional meridian-based sites to sham needling, using a VAS for neuropathic pain and the 36-Item Short-Form Health Survey as a measure of quality of life. It found only nonsignificant trends toward improvement in both measures over the treatment period (152).

Photon Stimulation

Photon stimulation describes a group of therapies in which pulsed infrared light or near-infrared laser energy is applied transcutaneously to neuropathy-affected skin with the goal of increasing blood flow and cellular and mitochondrial metabolism. Small, short-duration, sham-controlled, single-blind RCTs of the use of these technologies in DPN have shown a nonsignificant trend toward improved pain and quality-of-life measures (153).

In summary, clinical trial evidence for the efficacy of nonpharmacological therapies in DPN remains rudimentary. No energy or physical treatment modality has demonstrated the ability to sustainably alter the natural history of DPN. SCS and high-frequency SCS provide long-lasting reduction in neuropathic pain in people with DPN pain refractory to medical therapy and may be recommended in these situations. This potential benefit must be balanced against serious wound, infection, and equipment complications that affect 8–22% of people with SCS implants. Among modalities considered to be primary pain therapy, TMS consistently provides pain reduction, but there is no evidence that this improvement can be sustained. Other energy or physical treatment modalities have low-quality trial evidence and/or have not shown consistent neuropathic pain improvement and are not recommended.

HBIs that include a combination of regular aerobic, strengthening, and balance exercise; reduction of sedentary behavior; and dietary modification aimed at reducing calorie intake and increasing plant-based foods and polyunsaturated fats are recommended for every person with DPN. Intervention should be tailored to each patient’s preferences and degree of physical conditioning to optimize adherence. Provision of exercise prescriptions and supervision by an exercise specialist to assess patients’ baseline fitness and risk factors, regulate progression, and provide active encouragement can improve exercise behaviors and reduce the risk for exercise-associated injury, especially in people naive to exercise or with physical disabilities that increase their risk for falls.

**KEY POINTS**

- Regular aerobic, strengthening, and balance exercise, alone or in combination; reduction of sedentary behavior; and dietary modification aimed at reducing calorie intake and increasing plant-based foods and polyunsaturated fats have all demonstrated positive outcomes for individuals with DPN.

- Exercise participation, guided by exercise prescription and supervision by an exercise specialist, is safe and can improve exercise behaviors and reduce the risk for exercise-associated injury.

- SCS and high-frequency SCS provide long-lasting reduction in neuropathic pain in people with DPN pain refractory to medical therapy but must be balanced against serious potential complications in this population.
SUMMARY AND CONCLUSION

Our main objective in writing this monograph was to provide up-to-date information regarding painful DPN, including novel mechanisms and risk factors contributing to the contemporary prevalence trends for this serious and common complication of diabetes. Additionally, we sought to offer clear guidance to the greater diabetes care community on the best approaches for screening and diagnosis of DPN in individuals with type 1 diabetes, type 2 diabetes, or prediabetes, as well as on a broad spectrum of management strategies, with the ultimate goal of ensuring access to optimal, evidence-based DPN management for all people with this condition.

The symptoms associated with DPN are dependent on the type of fibers most affected initially, although some individuals with DPN may be completely asymptomatic and thus may first present with advanced complications such as foot ulcers. The small fibers that convey pain and dysesthesias are particularly vulnerable to the energy-starved environment of diabetes, which explains why small fibers are the earliest fibers to undergo injury secondary to diabetes. Thus, burning pain and dysesthesias are frequently the first symptoms of DPN. Both type 1 and type 2 diabetes increase the risk of developing painful DPN. Women, members of some racial/ethnic minority groups, and individuals with type 2 diabetes appear to be at greater risk for developing DPN pain.

Periodic, flexible assessment for DPN risk factors and symptoms and their trajectories over time should be part of standard care for all people with diabetes. Although earlier diagnosis of DPN could enable targeted treatment to prevent progression of the disease and other adverse outcomes, it remains underdiagnosed in many individuals with diabetes today. Thus, DPN assessment, including a detailed history and at least two sensation and reflex tests, should be performed annually starting at diagnosis of type 2 diabetes and 5 years after diagnosis of type 1 diabetes, including in young people. Electrophysiological testing is rarely needed for people with typical signs and symptoms of DPN. A complex differential is recommended, as nondiabetic neuropathies may coexist in individuals with diabetes and may be treatable. Additionally, more recent evidence from large cohorts has revealed that socioeconomic factors and health care accessibility are risk factors for DPN. Therefore, clinicians are encouraged to incorporate comprehensive assessment of the impacts of social and psychological determinants of health on DPN and to address these impacts as part of overall DPN management.

Because there are no FDA-approved, pathogenetically oriented pharmacological treatments to reverse DPN, current treatment approaches target prevention of DPN and relief of its symptoms. Prevention and management decisions should be individualized and might include intensively controlling blood glucose, as well as targeting other risk factors such as dyslipidemia, obesity, hypertension, and smoking, with both lifestyle and pharmacological interventions.

We have provided here a targeted DPN management strategy that includes the currently available oral (e.g., anticonvulsants and tricyclic antidepressants) and topical pharmacological agents with evidence of clinically meaningful pain reduction, as well as HBIs specifically for painful DPN (Figure 8). Dosing regimens should take into account individuals’ age and comorbidities, and efforts should be made to use the lowest effective dose for a given agent alone or in combination to mitigate side effects, while avoiding opioid therapies entirely. Importantly, none of these agents should be regarded as lifetime medications, and periodic review of pharmacological therapy is recommended, with gradual reduction of drug treatment in response to symptom abatement over time. Particular care is required in the management of painful DPN in elderly patients, in whom polypharmacy is common and the risk of adverse effects is amplified.

Given their excellent safety profile, many nutraceuticals have been developed, some with proven benefit for relief of DPN pain symptoms, although the potential of these products to favorably modify the natural history of DPN remains to be proven in well-designed, well-conducted confirmatory RCTs. Several nonpharmacological approaches also might alter the natural history of DPN or ameliorate neuropathic pain. These include HBIs such as exercise, dietary modification, or their combination; passive modalities such as massage and biofeedback; and nonpharmacological energy or nerve stimulation treatments. These, too, deserve more study.

In conclusion, we encourage all clinicians who treat people with diabetes to strive for early recognition of DPN using the algorithms and tools we have described here and to bring to bear the requisite thoughtful clinical evaluation and implementation of a multilevel management strategy to ensure that all individuals with painful DPN benefit from optimal personalized care.

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Duality of Interest
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D.Z. has served as a consultant to Allergan, Bayer, Berlin-Chemie, Biogen, Cannaxan, Clexio, Grünenthal, Mitsubishi Tanabe, Mundipharma, Novo, Novaremed, Novartis, Pathways Public Health, Pfizer, Procter & Gamble, Stada, Takeda, Viatris, and Wörwag; he has been a speaker for Astellas, AstraZeneca, Berlin-Chemie, Mundipharma, Pfizer, Sanofi, Takeda, Viatris, and Wörwag; and he has received research support from Mitsubishi Tanabe, Novartis, and Wörwag.
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Author Contributions
Lead author R.P.-B. reviewed all content, wrote the introduction and conclusion, and co-wrote with L.A. the section titled “Screening and Diagnosing DPN.” A.J.M.B. wrote the section titled “Treating Painful DPN.” E.L.F. wrote the section titled “Pathophysiology of DPN.” R.L.M. and J.R.S. co-wrote the section titled “Nonpharmacological Approaches to DPN and Pain Management.” K.M.-S. wrote the section titled “Social Determinants of Health and Their Impact on DPN.” D.Z. wrote the section titled “Role of Neutraceuticals in DPN and Pain Management.” All authors reviewed and edited the manuscript and approved the final version for publication. R.P.-B. is the guarantor of this work.

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