

Review

Diabetic Peripheral Neuropathy: Implementing Guidelines into Practice

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Abstract

Diabetic Peripheral Neuropathy (DPN) is a common and debilitating complication of diabetes, affecting up to 50% of patients. Early identification and management of DPN are crucial to minimize complications and maintain patient quality of life. Multiple guidelines have been developed to provide evidence-based recommendations for DPN screening, diagnosis, and management. However, implementation of these guidelines in clinical practice remains a challenge. Therefore, a task force was assembled by the American Limb Preservation Society (ALPS) to summarize the recent literature in this area. This article outlines the key recommendations of DPN guidelines and discusses their implementation in a local context. The authors provide suggestions for real-world implementation in practice, focusing on documentation, stakeholder engagement, practice support, care pathways, and continuity of care. By adopting a systematic approach to DPN guideline implementation, healthcare providers can improve patient outcomes and reduce the burden of this progressive and disabling condition.

Keywords: diabetic peripheral neuropathy; guidelines; implementation; diabetic foot



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Clinical guidelines summarize the body of evidence and clinical expertise in a specific clinical area to assist practitioner and patient healthcare decisions [1,2]. However, successful implementation does not end at guideline development. To ensure adoption in the clinical setting, adequate resources, training and support for clinicians and patients in local communities are needed along with an ongoing process of evaluation and adaptation [3,4].

Several guidelines have been published specific to diabetic peripheral neuropathies [5–9]. Evidence-based recommendations with a broader focus on prevention, screening, and management for diabetic foot ulcers which address peripheral neuropathy have also been published [10]. However, the level of detail and specific recommendations vary considerably across guidance documents, in part because each was developed using the evidence available at the time. With growing clinical interest and an expanding body of

trial data in this area, practical guidance is needed to support real-world implementation of recommendations for the screening, diagnosis, and management of diabetic peripheral neuropathy. Such guidance would be relevant to both general practitioners and specialists, given the high prevalence and progressive nature of the condition [11]. Therefore, the American Limb Preservation Society (ALPS) assembled a task force to summarize key recommendations from existing diabetic peripheral neuropathy guidelines and discuss their implementation in local clinical practice.

1. Diabetic Peripheral Neuropathy Today

1.1. Prevalence of Diabetic Peripheral Neuropathy

The prevalence and impact of diabetes continue to grow. The International Diabetes Federation Diabetes Atlas reported that approximately 589 million adults aged 20–79 years were living with diabetes worldwide in 2024, representing 11.1% of the adult population, and projected this number to increase to approximately 853 million by 2050 [12]. More than 90% of people with diabetes have type 2 diabetes mellitus (T2DM) [12]. Beyond hyperglycemia itself, the burden of diabetes is intensified by its microvascular and macrovascular complications [5,7].

Diabetic neuropathies are among the most common chronic complications of diabetes [7,13]. They comprise a heterogeneous group of disorders affecting different parts of the nervous system that are attributable to diabetes [7]. Reported prevalence varies widely because of differences in populations studied, diabetes type and duration, diagnostic definitions, and the tests used to define nerve damage. Contemporary data demonstrate that DPN may be present early in the course of type 2 diabetes, is relevant in youth-onset diabetes, and may occur in association with impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, and obesity. The lower estimate observed in cohorts with shorter diabetes duration should be interpreted in this context, because prevalence generally increases with longer diabetes duration, older age, and the use of more sensitive diagnostic methods. Key epidemiologic findings are summarized in Table 1.

Table 1. Selected epidemiologic findings relevant to diabetic peripheral neuropathy.

Population or Cohort	Clinical Context or Presentation	Key Prevalence or Epidemiologic Finding
Adults aged 20–79 years worldwide	Diabetes prevalence	The International Diabetes Federation estimated that approximately 589 million adults were living with diabetes worldwide in 2024, representing 11.1% of the adult population, with a projected increase to approximately 853 million by 2050 [12].
Adults with diabetes	Diabetes type	More than 90% of people with diabetes have type 2 diabetes mellitus [12].
People with diabetes	Diabetic neuropathies broadly	Diabetic neuropathies are among the most common chronic complications of diabetes and include a heterogeneous group of disorders affecting different parts of the nervous system [7,13].
GRADE cohort	Type 2 diabetes of less than 10 years’ duration	Peripheral neuropathy assessed by the Michigan Neuropathy Screening Instrument was present in 21.5% of participants [14].
SEARCH cohort	Youth and young adults with diabetes	Peripheral neuropathy was more common in youth and young adults with type 2 diabetes than in those with type 1 diabetes after similar diabetes duration [15].

Table 1. Cont.

Population or Cohort	Clinical Context or Presentation	Key Prevalence or Epidemiologic Finding
Population-based studies	Impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, and obesity	Polyneuropathy may be present before overt diabetes and may be associated with impaired glucose metabolism, metabolic syndrome, and obesity [16,17].
Individuals with DPN	Painful DPN	Neuropathic pain affects up to approximately 30% of individuals with DPN and may be persistent or follow a fluctuating course [6,7,18].
People with diabetes after exclusion of other causes	Distal symmetric polyneuropathy	Distal symmetric polyneuropathy is the most common presentation of peripheral nerve dysfunction in people with diabetes [7].

The major clinical patterns and expected progression of DPN are summarized in Figure 1.

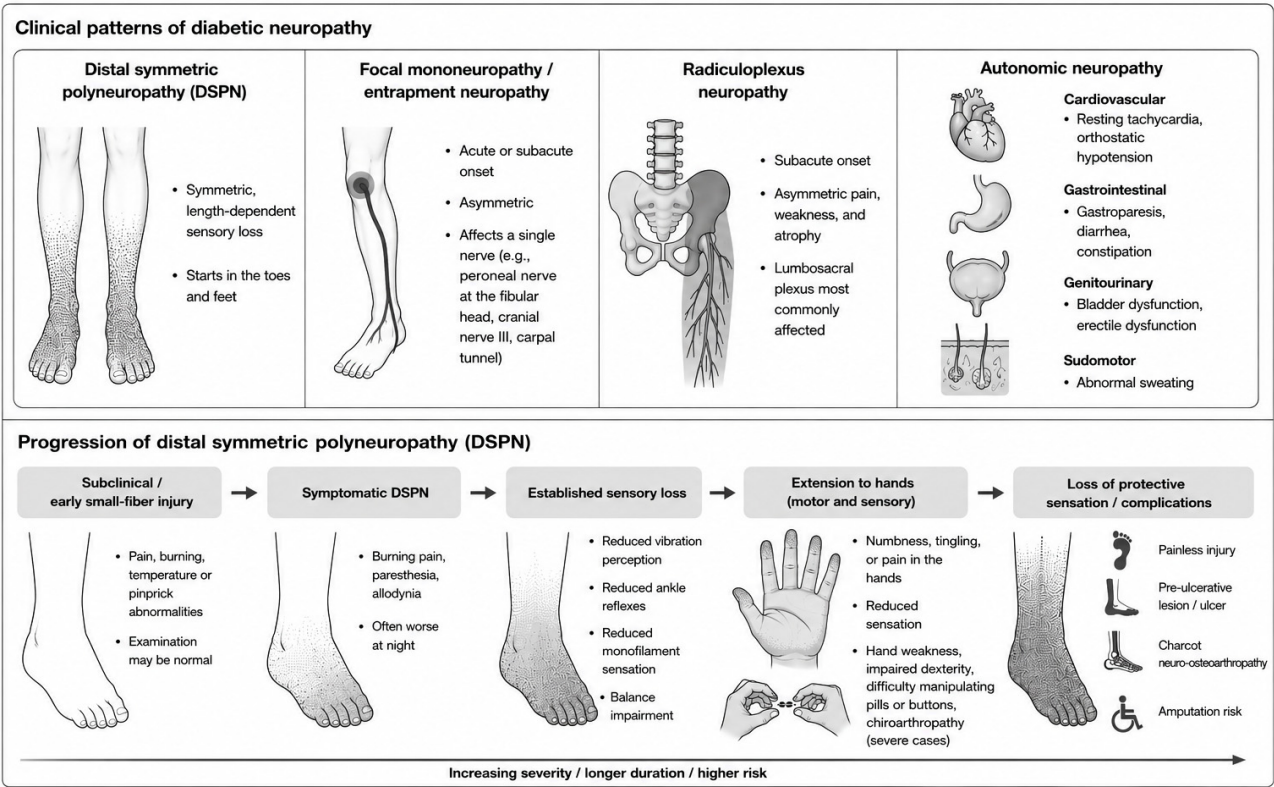


Figure 1. Clinical patterns and progression of diabetic peripheral neuropathy. DPN = diabetic peripheral neuropathy; DSPN = distal symmetric polyneuropathy.

1.2. Impact of DPN

The impact of DPN can be devastating, impairing quality of life, and potentiating risk of disability including from amputation [19,20]. Those with painful DPN were shown to have 20% higher healthcare costs and were more than 16 times more likely to have a limb amputation than diabetes-matched controls without neuropathy or pain medications [21]. The lifetime risk of developing a foot ulcer is estimated to be between 19% and 34%, with 9.1 million to 26.1 million individuals with diabetes developing foot ulcers each year [22,23]. Despite widespread guidance to avoid the use of opioids in noncancer pain, patients with

painful DPN were also 200% more likely to use opioids compared with diabetic controls, leading to other negative impacts [21,24,25].

With a lack of disease modifying therapies to address the underlying nerve damage [7], early interventions targeting established risk factors are key to prevent DPN development and progression and to minimize its impact. If preventive care is not implemented, patients may be at risk of lower-extremity complications such as loss of protective sensation, loss of balance, falls, foot ulcerations, Charcot foot (progressive weakening of bone, joint, and soft tissue of the foot), amputation, severe pain, and major psychological disorders [22,26]. Once established, the recurrence of ulceration in the foot is high, at around 40% within one year of ulcer healing [23]. More than half of ulcers develop devastating infections. Around 20% of moderate to severe infections result in amputations [27,28].

1.3. Mechanisms of DPN

A vast array of mechanisms driven by hyperglycemia and obesity associated insulin resistance, chronic inflammation, oxidative stress, mitochondrial energy deficits, autoimmune injury, metabolic dysfunction and lipotoxicity, and microvascular dysfunction lead to a progressive nerve damage in DPN [7,11,26].

DPN typically affects the longest axons first, with distal, symmetrical, length-dependent sensory loss beginning in the toes, and progressing proximally with time [26].

2. Screening and Diagnosis of DPN

A combination of tests and evaluations that capture history, symptoms, and signs for small and large fiber function, and exclusion of other causes is needed for appropriate sensitivity and specificity [29]. The American Diabetes Association (ADA) recommends all patients be assessed for DPN when type 2 diabetes is first diagnosed and after five years of type 1 diabetes, and then annually [5,7]. Symptomatic patients with impaired glucose tolerance may also be screened [7]. Assessment may be performed by primary, secondary or tertiary care [30].

Clinical symptoms and signs may reflect involvement of both small and large nerve fibers. Early small-fiber dysfunction may contribute to “positive” neuropathic symptoms, including burning pain, lancinating pain, electric shock-like sensations, allodynia, hyperalgesia, and pins and needles [7,26]. These neuropathic symptoms may be induced or continuous and are typically worse at night [22]. Large-fiber dysfunction is associated with numbness, a dead or asleep feeling, impaired vibration or proprioception, loss of balance, and painless injury or ulceration [7,22,26]. However, DPN is frequently a mixed-fiber neuropathy, symptoms may be absent, and clinical progression does not always follow a predictable sequence from small-fiber to large-fiber involvement [7]. At present, there are no defining pathological features which distinguish painful from non-painful DPN [31–33].

The co-development of peripheral autonomic neuropathy, causes loss of sweating, leading to dry skin that may be complicated by fissures [29]. Loss of protective sensation secondary to advanced symmetrical sensory neuropathy is a risk factor for ulceration and amputation [22].

A clear and thorough history is important to reveal inconsistencies in the timeline of neuropathy in a patient with diabetes, which may be suggestive of an alternate cause [7,34]. At present, the diagnosis of DPN remains one of exclusion [7,29,35]. A targeted differential diagnosis is needed because other forms of peripheral neuropathy may mimic DPN in people with diabetes, and some alternative etiologies may be treatable [7,26,34,36].

In patients with atypical clinical features (motor deficit greater than sensory deficit, rapid onset or asymmetrical presentation) or where the diagnosis is unclear or suggests a

different etiology, patients are commonly referred to a neurologist for electrophysiological testing (see Figure 2) [7].

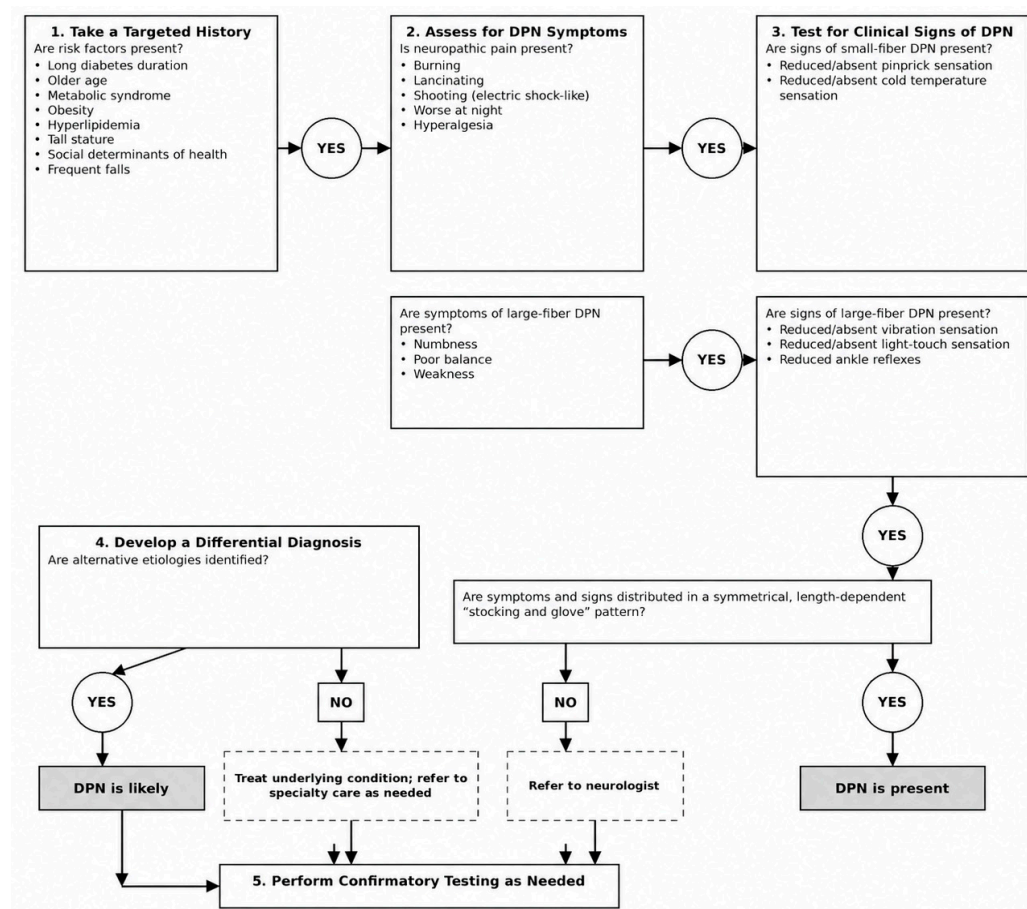


Figure 2. DPN diagnostic flowchart.

It is important to rule out other causes of distal symmetric polyneuropathy which may mimic diabetic neuropathy (see Table 2). A thorough history should be taken to ascertain prior ulcerations, amputation, Charcot foot, angioplasty or vascular surgery, tobacco smoking, retinopathy, renal disease and current symptoms of neuropathy or peripheral artery disease (PAD) [5]. Since PAD is common in diabetes and may present with painful symptoms that may be mistaken for DPN, it should be excluded as a cause. Initial screening recommendations for PAD include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation and handheld Doppler sounds [5]. Patients with a history of leg fatigue, claudication and rest pain relieved with dependence (symptoms which may be blunted in the presence of DPN) or decreased or absent pedal pulses for ankle-brachial index should be referred for further assessment [5]. Also note any symptoms which interfere with daily activities and/or sleep [8].

Table 2. Peripheral neuropathies which may have a similar presentation to diabetic peripheral neuropathy. Adapted from Rogers et al. [34].

Autoimmune Diseases
Monoclonal gammopathy
Multiple myeloma

Table 2. *Cont.*

Autoimmune Diseases
Amyloidosis
Sjögren’s syndrome
Genetic Diseases
Hereditary motor and sensory neuropathy
Hereditary sensory and autonomic neuropathy
Fabry’s disease
Infectious diseases
Human immunodeficiency virus (and antiretroviral therapy)
Hepatitis C virus
Tabes dorsalis
Lyme disease
Inflammatory causes
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Paraneoplastic neuropathy
Metabolic diseases
Uremia (chronic kidney disease)
Hypothyroidism
Nutritional deficiencies
Alcoholism (B1 deficiency)
Vitamin B deficiencies (B6 and B12)
Toxic causes
Alcoholism (direct toxic effects)
Heavy metal poisoning
Chemotherapy (platinum drugs, taxanes, vinca alkaloids)
Other drugs (fluoroquinolones, isoniazid)
Vasculitis
Polyarteritis nodosa (including Churg-Strauss variant)
Wegener’s granulomatosis

2.1. DPN Clinical Instruments

Pain is often an initial presenting symptom, but signs of autonomic neuropathy including orthostatic dizziness, syncope or dry cracked skin in the extremities should be investigated (see Table 3) [5,30]. Damage to large fibers may elicit numbness, tingling and poor balance [7]. Damage to small fibers may elicit pain, electric shocks, or stabbing sensations [7]. In terms of monitoring the emergence and severity of neuropathic pain, guidance on the optimal frequency to assess neuropathic pain is currently not well defined in current guidelines [6]. Like non-painful symptoms, the tools available to screen for neuropathic pain are not comprehensive [6]. General numerical rating scales and visual analog scales are insufficient to measure the impact of pain [6]. Therefore, a number of clinical instruments that included a combinations of symptoms and signs have been developed and validated to diagnose DPN in large cohorts or clinical care. The Toronto Clinical Neuropathy Score (TCNS) and Michigan Neuropathy Screening Instrument (MNSI)

are able to diagnose and stage disease [37,38]. The MNSI involves both a questionnaire and physical examination [30]. A score of ≥ 7 in the questionnaire and ≥ 2 in the physical examination is suggestive of DPN in T2DM [28,38]. An alternative tool is the simplified Neuropathy Disability Score (NDS), where a score of ≥ 6 signals established neuropathy. NDS is also able to stratify mild (3–4), moderate (5–6) or severe neuropathy (7–10) [30,39].

Table 3. Symptoms and signs of diabetic autonomic neuropathy.

Resting tachycardia
Orthostatic hypotension
Orthostatic tachycardia
Exercise intolerance
Gastroparesis
Esophageal dysfunction
Intestinal immotility (diarrhea or constipation)
Sexual dysfunction
Skin xerosis

2.2. Sensory Testing

Sensory assessments should include either a temperature or pinprick sensation to assess small fiber function and vibration sensation using a 128 Hz tuning fork and ankle reflexes for large fiber function testing [7]. Recommended approaches are listed in Table 4. Protective sensation may be assessed using 10 g monofilament testing, though due to its limited sensitivity early in the disease course, it is not recommended as the sole test to diagnose DPN [40–42].

Table 4. Sensory testing modalities for peripheral neuropathy.

Temperature:
Tested using a Tiptherm [®] or cold tuning fork on the dorsal surface of the foot and great toe. Impairment is considered if ≥ 2 out of 3 contacts per foot are incorrectly discriminated.
Sharp/touch:
Tested using a Neurotip [®] , Neuropen [®] or pinprick to the dorsum of the foot and great toe. Impairment is considered if ≥ 2 out of 3 contacts per foot are not perceived as painful.
Pressure/touch:
Tested using a 10 g Semmes-Weinstein monofilament applied to the plantar hallux and the first, third, and fifth metatarsal heads on each foot; loss of protective sensation is present if the patient cannot perceive the monofilament at one or more tested sites [43]. The examiner should avoid callused areas which can result in a false positive result. Alternatively, in resource-limited situations, the Ipswich Touch Test or light pressure with a cotton-tipped applicator to the dorsum of the great toe may be used.
Vibration:
Tested using a 128 Hz tuning fork or quantitative electronic tuning fork (ETF), while considering age-dependent normative values can assess vibratory perception, or by using a biothesiometer.

2.3. Advanced Testing Methods

Point-of-care tests are available and may be used to assist in efficiently determining nerve functioning. However, robust data regarding their diagnostic and prognostic abilities is currently lacking. NC-Stat DPNCheck[®] is a Food and Drug Administration (FDA)-cleared point-of-care nerve conduction device that evaluates sural nerve function at the lateral malleolus, providing information on large fiber function [30]. SUDOSCAN is a point-of-care device that is FDA-cleared for sudomotor dysfunction [30], that quantifies electrochemical skin conductance (ECS) of the hands and feet as a measure of postganglionic sympathetic integrity [30]. The Neuropad[®] test identifies sudomotor dysfunction using adhesive plasters containing cobalt-II-chloride, which changes color from blue to pink upon exposure to sweat [30].

Skin biopsy with quantification of intra-epidermal nerve fiber density (IENFD) is considered the gold standard to diagnose small fiber neuropathy. However, this method is expensive, requires specialist facilities and experience for reliable, reproducible results [30].

2.4. Foot Complications

Complications associated with DPN, such as foot ulceration are caused by a cascade of factors. These include neuropathy, peripheral vascular disease, trauma and infection; however, neuropathy is considered to have the most clinically important impact [44]. People with diabetes should have a comprehensive foot evaluation completed at least annually to identify risk factors for ulcers and amputations. Patients with a history of ulceration or amputation should be evaluated at every clinic visit [5]. Evaluation includes:

- Inspection of the skin integrity, turgor, color, temperature and sweat function;
- Active or past foot ulcer locations, extent and any associated infection should be noted;
- The foot structure should be assessed for hyperkeratosis and callus formation and deformities such as hammer toes or claw toes;
- Neurological function should be assessed as described above;
- Pulse and vascular health of the legs and feet should also be assessed;
- Assess patient gait and examine footwear for appropriate size, style, and wear and tear.

A 3 min diabetic foot examination has been proposed that allows screening, and advice on preventive foot self-care to be delivered in a 15 min consultation [7,45].

3. Foot Risk Classification

Risk classification translates findings from the foot examination into a practical prevention and surveillance plan. Its purpose is not simply to label disease severity, but to identify the likelihood of future ulceration or amputation, determine the appropriate frequency of foot examination, guide patient education and footwear recommendations, and identify when referral to foot care specialists, vascular specialists, or an interdisciplinary limb preservation team is needed.

Several risk classification systems have been proposed for diabetes-related foot complications, and they differ slightly in terminology, risk thresholds, and recommended follow-up intervals (Table 5) [5,46–49]. However, most systems escalate risk based on the presence of loss of protective sensation (LOPS), peripheral artery disease (PAD), foot deformity, pre-ulcerative lesions or callus, previous ulceration, previous amputation, kidney failure or renal replacement therapy, Charcot neuro-osteoarthropathy, and active pathology such as ulceration, infection, gangrene, chronic limb-threatening ischemia, or suspected acute Charcot neuro-osteoarthropathy.

Table 5. Diabetic foot risk categorization schemes.

Risk Level	UT Foot Risk Category [46]	International Diabetes Federation [47]	International Working Group on the Diabetic Foot [48]	American Diabetes Association [5]	National Institute for Health and Care Excellence [49]
Very low	Absence of LOPS or PAD		Absence of LOPS or PAD	Absence of LOPS or PAD	
Low	LOPS	Normal plantar sensation	LOPS or PAD	LOPS +/– deformity	Callus alone
Moderate	PAD, or LOPS + Deformity	LOPS	Presence of LOPS + PAD, or PAD + deformity	PAD +/– LOPS, diminished dorsalis pedis or posterior tibial pulse	Deformity, neuropathy, or PAD
High	History of ulceration, amputation, or Charcot foot	LOPS + PAD, deformity, or onychomycosis	LOPS or PAD + one or more of the following: Previous foot ulceration, lower-extremity amputation, or end-stage renal disease	History of ulceration, amputation	History of ulceration, amputation, end-stage renal disease, neuropathy + PAD, neuropathy + callus, PAD + callus.
Very high		History of ulceration, amputation, or neuropathic fracture		Active foot pathology, ulceration, Charcot foot deformity, vascular compromise	Ulceration or foot infection, CLTI, or gangrene, acute Charcot foot

LOPS, loss of protective sensation; PAD, peripheral arterial disease.

In clinical practice, risk status should be considered dynamic. A person without LOPS or PAD may generally be evaluated annually, whereas the presence of LOPS, PAD, deformity, prior ulceration or amputation, kidney failure, or active foot pathology should prompt more frequent reassessment and a more intensive prevention strategy. These strategies may include reinforced self-care education, professional foot care, treatment of pre-ulcerative lesions, vascular evaluation when indicated, therapeutic footwear or orthoses, and referral to foot protection or interdisciplinary limb preservation services. The selected risk classification system should be applied consistently within a practice or health system so that risk status, follow-up frequency, and referral pathways are clear to both clinicians and patients.

In addition to assigning risk, clinicians should use risk category to trigger prevention interventions, including education on avoiding barefoot walking, daily foot inspection, professional treatment of pre-ulcerative lesions, appropriate footwear, and consideration of skin temperature monitoring for selected moderate-to-high-risk patients [48].

4. Management of DPN

There are no treatments proven to reverse established nerve damage in DPN; therefore, prevention, early identification, risk-factor modification, and management of symptoms are central to care [7,50]. Optimization of glycemia and cardiovascular risk factors may reduce the incidence or progression of neuropathy, particularly when instituted early [50,51]. For patients with LOPS, deformity, pre-ulcerative lesions, or a history of ulceration, management should

also include strategies to reduce repetitive mechanical stress and identify early signs of inflammation before skin breakdown occurs [5,48].

4.1. Footwear

Appropriate footwear is a core prevention strategy for patients with DPN, particularly when LOPS, deformity, prior ulceration, callus, or other pre-ulcerative lesions are present [48]. Patients with DPN may be unable to perceive excessive pressure, shear, poor fit, foreign bodies, or minor trauma within the shoe; therefore, footwear should be evaluated with the patient standing and should accommodate foot length, width, depth, deformity, and areas of increased plantar pressure.

For patients at risk of ulceration without significant deformity or prior plantar ulceration, footwear should fit properly and accommodate the shape of the foot. For patients with deformity, elevated plantar pressure, callus, or pre-ulcerative lesions, extra-depth shoes, custom-made footwear, custom insoles, or toe orthoses may be needed. For patients with a healed plantar foot ulcer, therapeutic footwear should have a demonstrated plantar pressure-relieving effect during walking and should be worn consistently, indoors and outdoors. When plantar pressure measurement is available, pressure-relieving footwear or insoles should aim for a $\geq 30\%$ reduction in in-shoe peak pressure at high-pressure locations or an in-shoe peak pressure < 200 kPa. Because benefit depends on actual use, adherence to prescribed footwear should be assessed at follow-up visits and barriers such as comfort, appearance, cost, indoor shoe use, and cultural practices should be addressed [48,52–54].

4.2. Skin Temperature Monitoring

Skin temperature monitoring is an adjunctive self-management strategy intended to identify inflammation before ulceration develops. Patients with DPN, especially those with prior ulceration, deformity, or other moderate-to-high-risk features, may develop repetitive tissue stress without pain. A localized increase in temperature can serve as an early warning sign of impending tissue injury [48,55,56].

Patients selected for this strategy may be coached to measure plantar foot temperatures once daily at corresponding sites on the left and right foot. A temperature difference greater than 2.2°C (4.0°F) between corresponding sites on two consecutive days should prompt reduction in ambulatory activity and contact with a trained member of the foot-care team for further evaluation. The evidence supporting temperature monitoring is strongest when monitoring is paired with a clear action plan, particularly activity reduction when a hotspot is identified. Newer remote temperature-monitoring platforms, including smart mats, may improve ease of use and adherence, but clinical benefit still depends on timely recognition of abnormal findings and appropriate preventive action [48,57,58].

4.3. Non-FDA Regulated Supplements

Several nutritional supplements and nonpharmacologic modalities have been promoted for DPN, including α -lipoic acid, the thiamine precursor benfotiamine, L-methylfolate/methylcobalamin/pyridoxal-5'-phosphate combinations, and photobiomodulation or low-level laser therapy [6,11,50]. Some studies suggest potential improvement in neuropathic symptoms, pain, or selected measures of nerve function; however, results are heterogeneous, many studies are small or short term, and these interventions have not established consistent, guideline-level evidence as disease-modifying therapies that restore nerve function. When considered, these approaches should be discussed as adjunctive or investigational options rather than substitutes for glycemic optimization, cardiovascular risk reduction, foot-risk management, offloading, and evidence-based pain management.

4.4. Pain Management

Pain management is appropriate when pain is severe or interferes with the patient's daily activities and sleep [8,59,60]. In painful DPN clinical trials, few patients achieve 100% pain relief, with expectations historically set at 50% relief of pain considered success and 70% relief considered exceptional [26]. However, the latest American Academy of Neurology (AAN) guideline suggests more conservative pain relief expectations should be set. With the goal of therapy to reduce, not eliminate pain, there may be merit in lowering the expected efficacy of interventions to 30% pain relief as realistic [6]. AAN highlighted it is likely that patients will need a series of medications to achieve adequate pain relief [6].

Like screening and diagnosis, trialing treatment options for DPN in practice is a process. The minimum duration treatments should be trialed before deeming unsuccessful is 12 weeks (unless the patient is unable to tolerate treatment) [6]. Following failure of one treatment to produce an acceptable response, if the medication was otherwise well tolerated, another agent from the same class may be considered [6]. However, choosing from a different class is expected to increase the likelihood of pain relief success [6]. Combining treatments from different classes may be appropriate to achieve pain relief success, although data on combination therapy beyond 16 weeks is currently lacking [6]. A practical approach to treatment selection and escalation for painful DPN is summarized in Figure 3.

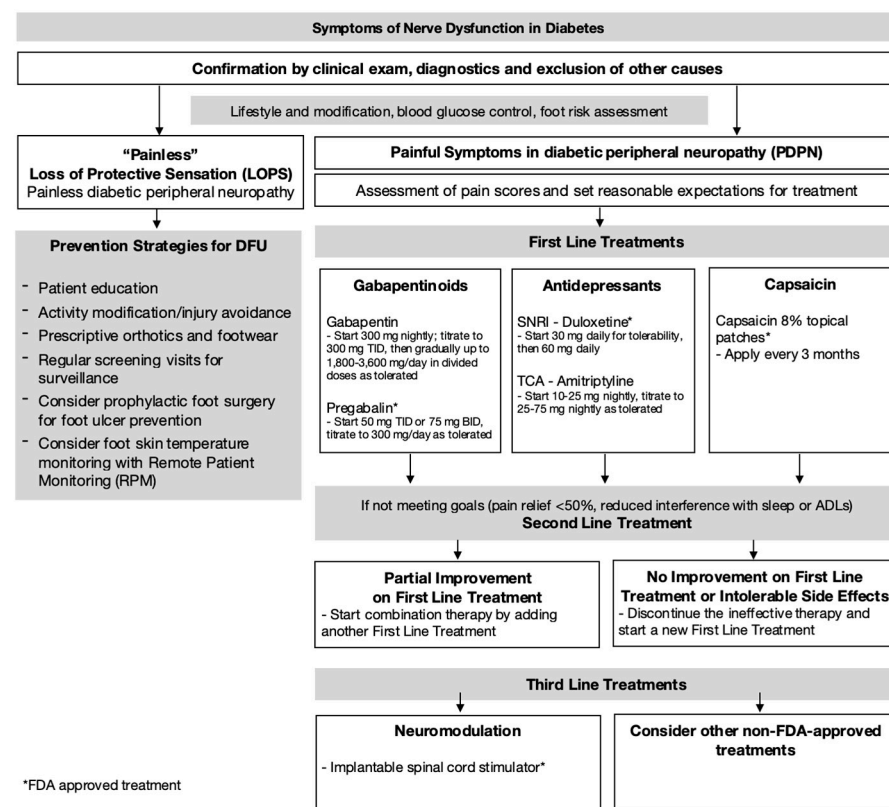


Figure 3. Management approach and escalation in diabetic peripheral neuropathy. * FDA-approved for painful diabetic peripheral neuropathy.

4.4.1. Pharmacotherapy

Several guidelines have published recommendations on pharmacological and non-pharmacological management of pain in DPN. In 2022, the AAN recommended that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders based on the increased frequency of these problems in individuals with DPN [6]. Some treatments for pain may have beneficial effects on sleep and mood

(e.g., serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs)) [6].

The AAN, ADA, Canadian and German guidelines have endorsed the use of gabapentinoids, SNRIs, sodium channel blockers and TCAs first-line for the treatment of pain in DPN [6–9]. However, the AAN guidelines identified gaps in current knowledge regarding painful DPN management including the following: few studies alone have investigated the effect of interventions on quality of life, patient functioning, mood, or sleep; there are few comparator studies of first-line drugs and their combinations; and scarce data is available on which patients respond to a specific intervention [6]. OPTION-DM, a multicentre, randomized, double-blind, crossover trial in patients with painful DPN, tried to address all these limitations [61]. This longest ever crossover neuropathic pain trial compared: amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin, with each pathway lasting 16 weeks. The primary outcome was the difference in 7-day average daily pain during the final week of each pathway. The study showed that all three treatment pathways and monotherapies had similar analgesic efficacy. Moreover, combination treatment was well tolerated and led to 37% improved pain relief in patients with suboptimal pain control with a monotherapy [61]. Thus, the most recent guidelines recommend combination treatment when there is suboptimal pain relief with a first line monotherapy [11].

There are differences in recommendations around SNRI/opioid dual-mechanism agents, with the ADA discouraging the use of tapentadol or tramadol due to risk of addiction and other complications [5–7]. Recognizing the gap opioid avoidance leaves in the pain management toolbox, the AAN explored other pain management recommendations, including non-oral and alternative therapies [6]. In addition to pharmacological interventions, cognitive behavioral therapy (CBT), exercise, Tai Chi and mindfulness may be suitable non-pharmacological interventions to include in the patient's treatment regimen [6]. The ADA emphasized the appropriateness of referring a patient to a neurologist or pain specialist if adequate pain relief is not achieved within the practitioner's scope of practice [5].

Other pharmacological agents available for pain management via pain management specialists include intravenous therapies such as lidocaine and ketamine, and intrathecal pain therapy, although evidence of use in DPN is limited, and the risks of treatment must be weighed against the benefits in the context of comorbidities [50]. Similarly, there is limited evidence for the use of topical compounded medications, however, intended to minimize systemic side effects and reduce utilization of oral medications [62,63].

Future pharmacologic options for painful DPN may include novel non-opioid agents targeting peripheral pain signaling pathways. Suzetrigine, a selective NaV1.8 inhibitor, has demonstrated positive Phase 2 results in painful DPN and is being evaluated in Phase 3 trials. Pilavapadin, an oral AAK1 inhibitor, has also shown encouraging Phase 2 data and is advancing toward Phase 3 development. NRD.E1, an investigational oral non-opioid agent with a novel mechanism of action, has shown proof-of-concept Phase 2a data and is undergoing further Phase 2b evaluation. These agents remain investigational for painful DPN pending peer-reviewed confirmatory efficacy and safety data [64–68].

Warnings on All Opioids

The ADA Position Statement on Diabetic Neuropathy emphasized that despite the demonstrated effectiveness of opioids in the treatment of neuropathic pain, there is a high risk of addiction, abuse, sedation, and other complications and psychosocial issues even with short-term opioid use. For these reasons, opioids are not recommended in the

treatment of painful DSPN before failure of other agents that do not have these associated concerns [7].

4.4.2. Topical Treatments

While used in neuropathic pain, topical lidocaine for pain in DPN has not been examined in guidelines to date [11]. Capsaicin 8% topical system (Qutenza) is FDA-approved in adults for the treatment of neuropathic pain associated with DPN of the feet and is administered by a healthcare professional as a single 30 min application to painful areas of the feet, with repeat treatment permitted no more frequently than every three months [69]. In a randomized, double-blind, placebo-controlled trial of 369 patients with painful DPN, a single 30 min capsaicin 8% patch application produced modest but statistically significant improvement in average daily pain compared with placebo, with improvements observed from week 2 onward, shorter median time to treatment response, modest improvement in sleep interference, and no evidence of deterioration in sensory perception [70]. A 52-week open-label randomized safety study of repeat capsaicin 8% patch treatment plus standard of care found that repeat treatment was generally well tolerated, without negative functional or neurological effects compared with standard care alone [71]. Therefore, capsaicin 8% topical system may be considered as a localized, non-systemic option for painful DPN of the feet, particularly when avoidance of systemic adverse effects, drug–drug interactions, or additional oral medications is desirable.

4.4.3. Neuromodulation

Another opportunity for clinicians and patients to consider is spinal cord stimulation (SCS) [72]. Only one guideline published in 2022 has included neuromodulation, with earlier guidelines only covering the evidence up to September 2018 [6,7,73]. Over the last few years, a growing body of evidence is emerging. An 8–10 year prospective cohort study reported sustained pain relief in patients with diabetic neuropathy treated with conventional spinal cord stimulation [74]. A prospective randomized controlled trial (RCT) and real-world evidence using paresthesia-free, high frequency SCS (10 kHz) has demonstrated pain relief, improved health-related quality-of-life and sleep, and neurological improvements in painful DPN refractory to conventional medical management which may reduce overall healthcare resource utilization [75–79]. Patient selection for high-frequency SCS can be performed using a temporary, 5- to 14-day percutaneous trial, which aids in predicting response to therapy [80].

4.5. Surgery

Reconstructive foot surgery to address deformities may be an option to help reduce the risk of ulceration [44]. However, there is a lack of evidence comparing surgery to relieve pain with other medical interventions [44].

Surgical Nerve Decompression

Non-specific decompression (triple nerve release) of peripheral nerves has been proposed as a treatment for positive and negative symptoms and even suggested to reduce the risk of ulceration. However, only low-quality studies have been done to support this invasive treatment [81]. The American Academy of Neurology has issued a practice advisory recommending against the routine use of the procedure [82]. There is currently a randomized controlled trial underway to evaluate the results of the surgical decompression for DPN [83]. Until the results of well-designed studies are published, surgical decompression of peripheral nerves should be performed only in the presence of verified compression of the nerve, with positive electrodiagnostic studies.

5. Implementing Guidance into Practice

The following steps outline a systematic approach to implement the strategies detailed in published best practice statements for managing DPN and are simplified in Table 6.

Table 6. Implementation checklist for systematic approach for best practices in diabetic peripheral neuropathy.

Phase	Steps
Pre-Implementation	Stakeholder Engagement
	Setting Key Performance Indicators (KPIs)
	Training and Education
Implementation	Clinical Documentation
	Screening and Risk Stratification
	Patient Education and Counseling
	Referral Pathways
Continuity of Care	Follow-up and Monitoring
	Practice Support
	Care Pathways
Quality Assurance and Performance Improvement	Performance Evaluation
	Patient Outcomes
	Continuous Improvement

5.1. Pre-Implementation Phase

1. Stakeholder Engagement

- Identify and engage key stakeholders including healthcare providers, practice managers, clinical staff, and patients.
- Organize meetings to discuss the objectives, expected outcomes, and roles of each stakeholder in the implementation process.

2. Setting Key Performance Indicators (KPIs)

- Define clear KPIs around stakeholder engagement, practice support, care pathways, and continuity of care.
- Establish measurable goals for the successful implementation of the guidelines.

3. Training and Education

- Develop and provide comprehensive training programs for all involved healthcare providers and staff.
- Focus on the specifics of DPN screening, diagnosis, and management protocols.

5.2. Implementation Processes

1. Clinical Documentation

- Standardize documentation practices to ensure consistent and comprehensive recording of patient data.
- Implement templates and electronic health record (EHR) prompts for documenting DPN-related assessments and interventions.

2. Screening and Risk Stratification

- Integrate routine DPN screening into standard care protocols for diabetic patients.

- Use validated tools such as the Michigan Neuropathy Screening Instrument (MNSI) and the Toronto Clinical Neuropathy Score (TCNS) for initial and follow-up assessments.
- 3. Patient Education and Counseling
 - Develop educational materials and programs to inform patients about DPN, its risks, and preventive measures.
 - Encourage patient self-management practices, such as daily foot inspections and proper footwear use.
- 4. Referral Pathways
 - Establish clear referral pathways to ensure timely consultations with specialists (e.g., neurologists, pain management experts) when necessary.
 - Facilitate communication between primary care providers and specialists to coordinate patient care effectively.

5.3. Continuity of Care

1. Follow-Up and Monitoring
 - Schedule regular follow-up appointments to monitor patient progress and adherence to treatment plans.
 - Use EHR systems to set reminders for annual DPN screenings and check-ups for high-risk patients.
2. Practice Support
 - Provide ongoing support to healthcare providers through regular updates on best practices and new evidence in DPN management.
 - Implement feedback mechanisms to address challenges and improve the implementation process continuously.

Implementation tools should also be adapted to local resources. EHR prompts, risk-stratification templates, and referral pathways may fail if they are not linked to clear staff responsibilities, available appointment capacity, patient education materials, and mechanisms for follow-up. In low-resource settings, practical solutions may include simplified screening tools, standing rooming protocols, use of medical assistants or nursing staff for annual foot-screening prompts, referral agreements with available foot-care or vascular services, telehealth or community health worker follow-up when feasible, and periodic audit-and-feedback reports to identify missed screening or delayed referral. The goal is to embed DPN screening and risk-based referral into the existing clinical workflow rather than create a parallel process that is difficult to sustain.

3. Care Pathways
 - Develop and implement care pathways that outline the step-by-step process for managing DPN from screening to treatment.
 - Ensure these pathways are easily accessible and understood by all members of the healthcare team.

5.4. Evaluation and Adaptation

1. Performance Evaluation
 - Conduct regular audits to evaluate the adherence to guidelines and the effectiveness of the implementation process.
 - Use the collected data to identify areas for improvement and adjust strategies as necessary.
2. Patient Outcomes

- Monitor patient outcomes, including the incidence of DPN complications, quality of life measures, and satisfaction with care.
 - Adjust treatment plans based on patient feedback and clinical outcomes to enhance care quality.
3. Continuous Improvement
- Maintain a cycle of continuous improvement by incorporating new research findings and clinical evidence into practice.
 - Engage in ongoing education and training to keep healthcare providers updated on the latest advancements in DPN management.

6. Conclusions

By adopting this systematic approach to implementing DPN guidelines, healthcare practitioners can significantly improve patient outcomes and reduce the burden of this progressive and disabling condition. Guidelines provide evidence-based recommendations intended to optimize patient care [84]. However, their implementation can be hindered by individual-, organizational-, and system-level barriers, with a systematic lack of adherence to guidelines across the world for many conditions [2,84].

As there are no robust disease-modifying therapies available for established DPN, prevention strategies, early identification, ulcer risk modification, and evidence-based management of associated pain are critical to minimize complications and maintain patient quality of life. Multiple guidelines have been developed that provide best practice recommendations in these areas; however, guidance on implementation at the local practice level has been lacking. Here we summarized the critical steps and provide suggestions for realistic implementation in practice, which allows physicians to objectively assess adherence and outcomes.

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