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UPDATED DIAGNOSIS AND TREATMENT OF DIABETIC PERIPHERAL NEUROPATHY

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ABSTRACT

Diabetic peripheral neuropathy comprises several distinct forms. It is frequently overlooked, yet its consequences include chronic pain, loss of protective sensation, foot ulceration and reduced quality of life. This structured narrative review first outlines the classification of these forms, together with their identifying features and management principles, and then updates the diagnosis and treatment of distal symmetric sensorimotor polyneuropathy (DSPN) and its painful phenotype, which account for most of the clinical burden. PubMed/MEDLINE, the Cochrane Library and official national and international guidance were searched up to 31 July 2026. The diagnosis of DSPN remains primarily clinical and combines the history with assessment of small-fiber function, large-fiber function and ankle reflexes. Screening for DSPN, identifying loss of protective sensation and stratifying ulcer risk are three distinct objectives: the 10-g monofilament serves the second of these and, given its low sensitivity in early disease, must not be used to exclude DSPN; nerve conduction studies are required only for atypical presentations or when diagnostic confirmation is needed. Management combines multifactorial risk-factor control and foot protection with individualized use of gabapentinoids, serotonin-norepinephrine reuptake inhibitors or tricyclic antidepressants, starting low, titrating slowly and adjusting the dose for age and renal function. When the response is incomplete, switching drug class or combining agents rationally is usually more useful than prolonged dose escalation, and long-term opioid therapy should be avoided. Alpha-lipoic acid and benfotiamine should be regarded as adjunctive only, since a 2024 Cochrane review found that alpha-lipoic acid probably has little or no effect on neuropathy symptoms at six months. Reliable early markers of small-fiber damage and disease-modifying therapies remain open research questions.

Keywords: diabetic peripheral neuropathy; distal symmetric polyneuropathy; neuropathic pain; diagnosis; treatment; diabetic foot.

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1. INTRODUCTION

Nerve injury in diabetes takes several forms and affects both the peripheral and the autonomic nervous systems. Three terms used in this review need to be distinguished from the outset. Diabetic peripheral neuropathy is the umbrella concept and includes distal symmetric sensorimotor polyneuropathy (DSPN), predominantly small-fiber neuropathy, entrapment mononeuropathies, radiculoplexus neuropathies and several focal or multifocal forms. DSPN is the most common form: it is symmetric, progresses in a length-dependent manner, is predominantly sensory, and begins in the toes before spreading proximally in a stocking distribution. The painful form is a symptomatic phenotype within DSPN rather than a separate disease: a patient may have DSPN with no pain at all and, conversely, pain in a person with diabetes is not necessarily due to DSPN. Both the 2025 Vietnamese Ministry of Health guideline and the 2026 Standards of Care in Diabetes of the American Diabetes Association (ADA) regard DSPN as a clinical diagnosis, to be made only after other causes of neuropathy have been considered [1,2].

The clinical picture varies with the fiber population involved. When small fibers are affected, patients report burning pain, paresthesia and hyperalgesia; large-fiber damage instead causes numbness, reduced vibration sense, imbalance and loss of protective sensation. A substantial proportion of patients are entirely asymptomatic, whereas in the painful form sleep, mood, capacity for work and quality of life are all clearly affected [2,3]. A 2025 systematic review pooling 41 studies estimated that, among people who already have diabetic peripheral neuropathy, about 46.7% (95% CI 41.8-51.7) have pain; this is not the prevalence in the whole diabetic population, and heterogeneity between diagnostic methods was substantial [4]. In the longer term, falls, foot ulceration, infection and amputation are the most serious consequences. For this reason, detection of loss of protective sensation and prevention of foot injury must be built into the management of neuropathy from the outset [2,5].

The approach to this condition has changed considerably over the past decade. Diagnosis now requires combined assessment of small-fiber function, large-fiber function and ankle reflexes, rather than reliance on the monofilament alone. Pain management is likewise directed by drug class, comorbidity and the individual patient's functional goals, with a strategy of switching class or combining agents when monotherapy is insufficient. At the same time, multifactorial risk-factor control and foot care are placed on an equal footing with symptomatic treatment. In Vietnam, Decision 3510/QD-BYT of 2025 has provided a unified practice framework, but it still needs to be read alongside recent international evidence, particularly ADA 2026, the American Academy of Neurology guideline and head-to-head trials [1,2,6,7]. This review opens with a classification of the forms of diabetic peripheral neuropathy, setting out the identifying features and management principles of each, and then examines in detail the screening, diagnosis, differential diagnosis and treatment of DSPN and its painful form, from which a practice algorithm suited to Vietnamese clinical conditions is proposed. This emphasis reflects the fact that DSPN is the most common form and the subject of most of the available evidence.

2. REVIEW METHODS

This article was prepared as a structured narrative review. The literature was searched in PubMed/MEDLINE, the Cochrane Library and repositories of official guidance, including the websites of the Vietnamese Ministry of Health, the American Diabetes Association, the American Academy of Neurology and the International Working Group on the Diabetic Foot (IWGDF); the last search date was 31 July 2026. The search string combined MeSH terms with free-text keywords as follows: (“diabetic neuropathies”[MeSH] OR “distal symmetric polyneuropathy” OR “painful diabetic neuropathy”) AND (diagnosis OR screening OR “nerve conduction” OR monofilament OR treatment OR “neuropathic pain” OR “diabetic foot”). The corresponding Vietnamese search terms were “bệnh thần kinh ngoại biên do đái tháo đường”, “đau thần kinh”, “bàn chân đái tháo đường” and “sàng lọc”.

Publications from 2010 to July 2026, in English or Vietnamese, were prioritized. Evidence was ranked in the following order: practice guidelines and professional consensus statements, then systematic reviews and meta-analyses, then randomized controlled trials, and finally observational studies where the preceding sources were insufficient. Screening and selection of the literature were performed by the corresponding author

and reviewed by the whole group. Figures 2 and 3 are algorithms synthesized by the authors from several sources of guidance and are not reproduced verbatim from any single guideline.

3. REVIEW

3.1. Classification of the forms of diabetic peripheral neuropathy

DSPN is the most common form of peripheral neuropathy in people with diabetes. It is symmetric and length-dependent and is predominantly sensory in its early stages. The term “diabetic peripheral neuropathy” should be used only once other plausible causes have been reasonably excluded, since the presence of diabetes does not in itself establish causation [5,6]. Management of DSPN rests on multifactorial risk-factor control, foot care and treatment of pain where present, as set out in the sections below. When onset is asymmetric, when motor weakness is prominent or when progression is rapid, the phenotype has departed from typical DSPN and the diagnostic work-up must be broadened.

Predominantly small-fiber neuropathy presents chiefly with burning pain, paresthesia and impaired thermal sensation, while vibration sense, proprioception and ankle reflexes remain relatively preserved. Nerve conduction studies are usually normal because the technique interrogates only large fibers, so the diagnosis relies on skin biopsy with quantification of intraepidermal nerve fiber density. Management focuses on control of metabolic risk factors and on pain relief; regular foot surveillance is still required, since small-fiber damage may precede loss of protective sensation [5,6,9].

The focal and multifocal forms have a phenotype quite unlike DSPN. Entrapment mononeuropathies occur more frequently in people with diabetes, most often carpal tunnel syndrome, followed by ulnar neuropathy at the elbow and common peroneal neuropathy at the fibular head; the presentation is localized to the territory of a single nerve, and management includes splinting, postural modification, local corticosteroid injection or surgical decompression where indicated. Cranial mononeuropathies, most often of the third, fourth, sixth and seventh nerves, typically begin abruptly, are painful and resolve spontaneously over several months, so treatment is largely supportive once vascular or compressive causes have been excluded. Lumbosacral radiculoplexus neuropathy, also known as diabetic amyotrophy, presents with severe unilateral thigh pain together with quadriceps weakness and wasting, often accompanied by weight loss; it is largely self-limiting but requires pain control, early rehabilitation and neurology referral [3,5,6].

Autonomic neuropathy may occur independently or alongside DSPN, affecting the cardiovascular system (resting tachycardia, orthostatic hypotension, silent myocardial ischemia), the gastrointestinal tract (gastroparesis, diarrhea or constipation), the genitourinary system and sudomotor function; management is chiefly symptomatic for each organ system, together with prevention of events related to orthostatic hypotension. Chronic inflammatory demyelinating polyradiculoneuropathy occurs more frequently in people with diabetes and must not be missed, since it responds to immunotherapy; features that should raise suspicion include prominent motor weakness, rapid or relapsing progression, generalized areflexia and demyelinating abnormalities on nerve conduction studies [3,6]. The general principle is that any phenotype departing from typical DSPN warrants a broader diagnostic work-up before being attributed to diabetes. From this point onwards, the review focuses on DSPN and its painful form.

3.2. Pathophysiology of distal symmetric polyneuropathy

The pathogenesis reflects the interaction of chronic hyperglycemia, dyslipidemia, insulin resistance, oxidative stress, mitochondrial dysfunction, polyol pathway activation, advanced glycation end products, low-grade inflammation and ischemia of the endoneurial microvasculature (Figure 1) [3]. Injury to Schwann cells, axons and the microvascular supply reduces the capacity for nerve regeneration, and the long fibers of the lower limbs are affected earliest. In type 1 diabetes, cumulative exposure to hyperglycemia plays the dominant role. In type 2 diabetes, obesity, hypertriglyceridemia, hypertension, smoking, chronic kidney disease and other components of the metabolic syndrome contribute substantially, which is why glycemic control alone is not sufficient to prevent progression in every patient. A cross-sectional study using nerve conduction studies in patients with type 2 diabetes found a high prevalence of abnormalities in the lower-limb nerves, together with an association with poor glycemic control and declining renal function [8]. This finding reinforces the need for active screening, but does not imply that every patient requires routine nerve conduction studies.

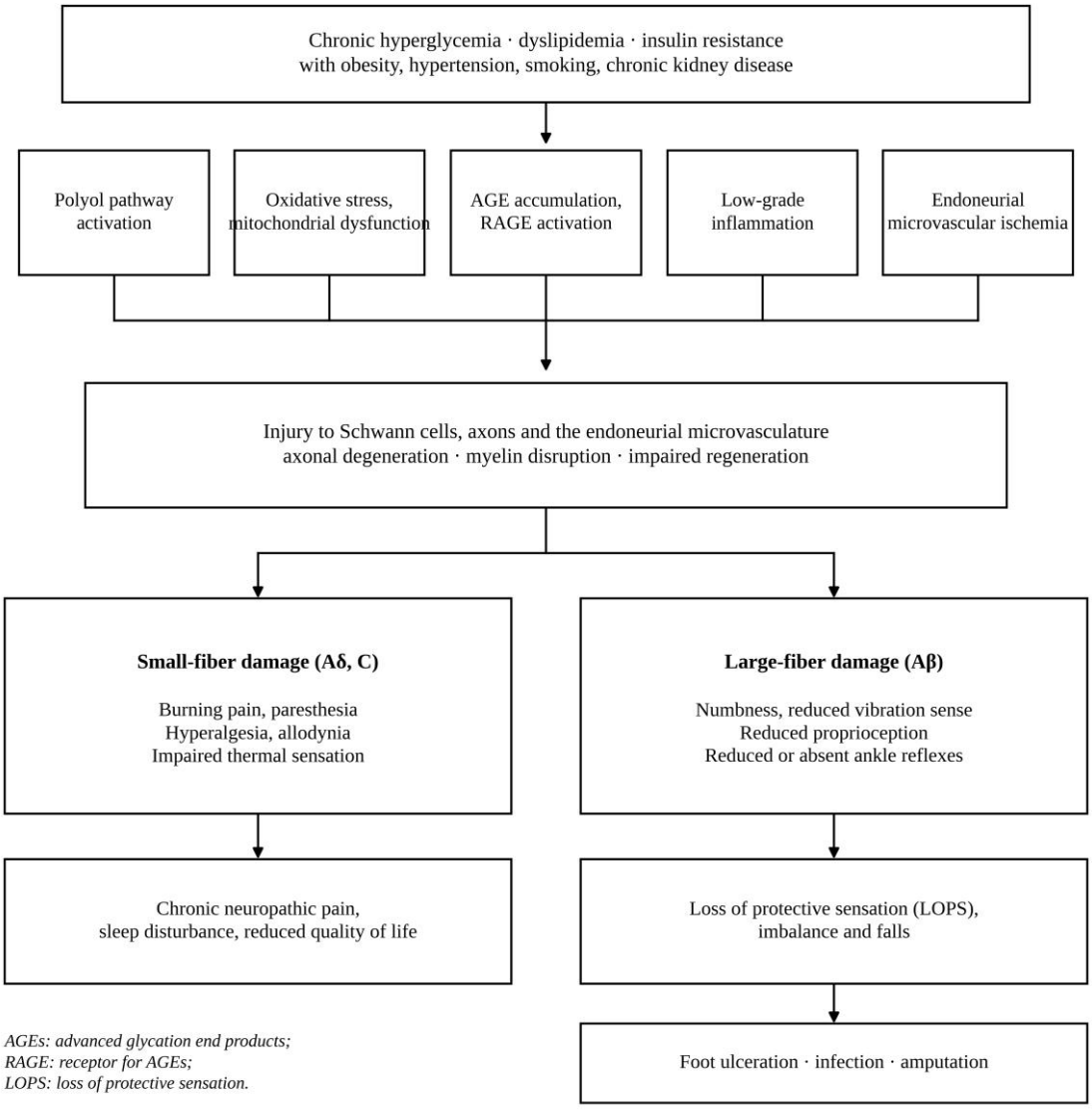


Figure 1. Pathophysiology of diabetic distal symmetric polyneuropathy [3,21]

3.3. Diagnosis of diabetic peripheral neuropathy

3.3.1. Screening and clinical examination

The ADA recommends screening for DSPN at the time of diagnosis of type 2 diabetes, five years after the diagnosis of type 1 diabetes and at least annually thereafter; people with prediabetes and suggestive symptoms should also be assessed [2]. Screening should begin with a few brief questions about numbness, burning, tingling, electric-shock-like pain, hypersensitivity to light touch, abnormal cold sensation, imbalance, stumbling and painless foot wounds. The history should also cover time of onset, distribution, symmetry, course, severity of night-time pain and the impact on sleep and function.

Neurological examinations must combine several modalities. Small-fiber function is assessed by pinprick and thermal sensation; large-fiber function by the 128 Hz tuning fork, proprioception and ankle reflexes. Within the same examination, three non-equivalent objectives need to be distinguished. Screening for DSPN aims to detect symptoms and signs of small- or large-fiber damage. Identifying loss of protective sensation (LOPS) aims to recognize the patient who cannot perceive injury to the foot. Ulcer-risk stratification requires LOPS to be combined with peripheral artery disease, foot deformity, previous ulceration, previous amputation and end-stage kidney disease. The 10-g monofilament serves the second of these objectives. According to the IWGDF, the test is applied at three plantar sites on each foot, namely the plantar surface of the hallux and the first and fifth metatarsal heads, avoiding areas of callus; three applications are made at each site interspersed with sham applications, and protective sensation is considered lost when the patient answers incorrectly on two of

three applications. Where monofilament is not available, the Ipswich Touch Test is an acceptable alternative [5,19]. Because its sensitivity in early DSPN is low, a normal monofilament result must not be interpreted as evidence excluding DSPN; conversely, a patient without pain may already have lost protective sensation and be at high risk of ulceration. During the same foot examination, dry skin, fissures, callus, deformity, limited joint mobility, inappropriate footwear, peripheral pulses and any history of ulceration or amputation should all be recorded (Figure 2).

Standardized scores improve reproducibility but do not replace direct examination. The Michigan Neuropathy Screening Instrument (MNSI) comprises a questionnaire and an examination of the foot, vibration sense and ankle reflexes; it has been used widely in both research and practice [10]. The Toronto Clinical Neuropathy Score and similar scales can be used to grade severity, monitor progression and standardize data collection. For the painful form specifically, the Douleur Neuropathique 4 (DN4) questionnaire or painDETECT helps identify a neuropathic pain component; pain intensity should be recorded on a 0-10 numeric rating scale (NRS), together with assessment of sleep, anxiety, depression and activity limitation.

3.3.2. Establishing the diagnosis, laboratory work-up and red flags

According to the Toronto consensus, DSPN is “possible” when symptoms or signs are present, and “probable” when at least two of three components are present, namely neuropathic symptoms, distal sensory loss, and reduced or absent ankle reflexes. A “confirmed” diagnosis requires an abnormal nerve conduction study together with symptoms or signs; if nerve conduction is normal but small-fiber neuropathy is still suspected, a validated small-fiber confirmatory test is needed. Subclinical disease corresponds to electrophysiological abnormalities or small-fiber markers in the absence of clear symptoms and signs [6]. This classification is useful for research and for atypical cases; in primary care, a high-probability diagnosis still rests mainly on the typical clinical phenotype.

A distinction must be drawn between diagnostic certainty as defined for research and the clinical diagnosis made in everyday practice. The Toronto classification was developed chiefly to standardize case selection in research and specialist assessment, which is why the “confirmed” category requires an abnormal nerve conduction study. This does not mean that every patient with clinically evident DSPN must undergo nerve conduction studies. In primary care, a patient with diabetes whose phenotype is symmetric, length-dependent and slowly progressive, without red flags, can reasonably be given a clinical diagnosis of DSPN and managed accordingly. Nerve conduction studies are indicated only when research-level certainty is required, when the presentation is atypical, or when the result would alter management.

Patients with a symmetric, length-dependent, slowly progressive presentation and no red flags do not require routine nerve conduction studies. The test is indicated when the diagnosis needs confirmation, when severity is to be quantified, when axonal damage must be distinguished from demyelination, or when the presentation is atypical; needle electromyography is a separate component of the electrophysiological work-up and is added only when motor involvement, radiculopathy or myopathy is suspected, rather than being required in every case. Red flags include acute or subacute onset, rapid progression, marked asymmetry, prominent motor weakness, early upper-limb involvement, radicular pain, sphincter disturbance, disproportionate generalized areflexia, weight loss, fever or systemic features. In these situations the patient should be referred to neurology, and chronic inflammatory demyelinating polyradiculoneuropathy, vasculitis, monoclonal gammopathy, amyloidosis, toxic exposure, hereditary neuropathy or entrapment should be considered.

The laboratory work-up should be tailored to the phenotype rather than applied uniformly. In a patient with symmetric, length-dependent and slowly progressive DSPN, routine assessment need include only glycemic control, a full blood count, renal function and vitamin B12 measurement in those on long-term metformin, those with macrocytic anemia or those with impaired proprioception. An extended panel comprising liver function, electrolytes, thyroid-stimulating hormone (TSH), serum protein electrophoresis with immunofixation, and autoimmune, infectious or toxicological tests should be requested only in the presence of red flags, when the phenotype is atypical, or on the basis of the individual patient's age and history. Where small-fiber neuropathy is suspected but nerve conduction is normal, skin biopsy with quantification of intraepidermal nerve fiber density at the distal leg provides structural evidence and is a valuable confirmatory method. Quantitative

sensory testing (QST) is a psychophysical method that depends on the patient's subjective response; it therefore plays only a supporting role and is not equivalent to skin biopsy (Table 1) [9].

Table 1. Diagnostic approach to diabetic peripheral neuropathy [1], [2], [6], [9], [10], [19]

Component	Content	Role
History	Burning pain, tingling, numbness, paresthesia, imbalance; stocking distribution; impact on sleep and function	Every screening visit
Small fibers	Pinprick and thermal testing; hyperalgesia, paresthesia or reduced pain/thermal sensation	Detection of early disease and of the painful form
Large fibers	128 Hz tuning fork, proprioception, ankle reflexes	Assessment of deep sensory loss and fall risk
10-g monofilament	Applied at 3 plantar sites on each foot (plantar hallux, first and fifth metatarsal heads), avoiding callus; 3 applications per site interspersed with sham applications; protective sensation is lost when 2 of 3 responses are incorrect. Ipswich Touch Test if no monofilament is available	Identifies LOPS and ulcer risk; not used to screen for or exclude early DSPN
Scales	MNSI or Toronto Clinical Neuropathy Score; 0-10 NRS together with DN4 or painDETECT when pain is present	Standardizes screening, severity grading and follow-up
Nerve conduction studies (NCS)	Assess large fibers, distribution of injury and axonal versus demyelinating pattern; needle electromyography added only when motor involvement, radiculopathy or myopathy is suspected	Atypical features, rapid progression, weakness, asymmetry, or need for confirmation
Skin biopsy (IENFD) and QST	Skin biopsy quantifies intraepidermal nerve fiber density and provides structural evidence; QST measures sensory thresholds and depends on the patient's subjective response	Suspected small-fiber neuropathy with normal nerve conduction; QST is supportive only and does not replace skin biopsy

DN4: Douleur Neuropathique 4 questionnaire; IENFD: intraepidermal nerve fiber density; LOPS: loss of protective sensation; MNSI: Michigan Neuropathy Screening Instrument; NCS: nerve conduction studies; NRS: numeric rating scale; QST: quantitative sensory testing. Screening for DSPN, identifying LOPS and stratifying ulcer risk are three distinct objectives and do not substitute for one another.

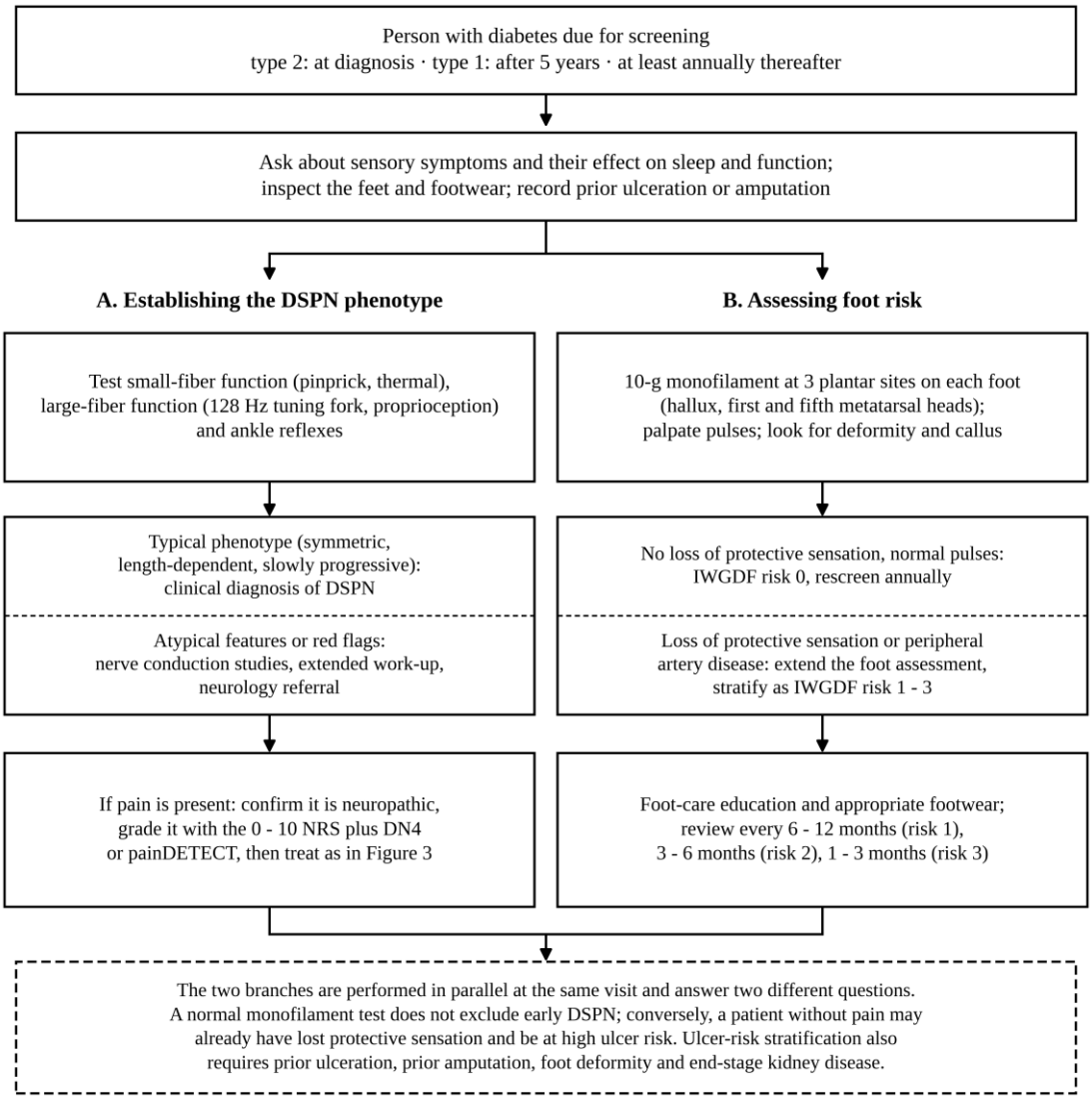


Figure 2. Algorithm for screening and diagnosis of diabetic distal symmetric polyneuropathy, with separate branches for establishing the DSPN phenotype and for assessing foot risk [1,2,6,7,19]

3.4. Treatment

3.4.1. Goals and treatment aimed at slowing progression

Treatment aims to slow disease progression, relieve pain, improve sleep and function, prevent falls, preserve the skin of the foot and reduce ulcer risk. No therapy has yet been shown to reverse established DSPN, and analgesic drugs treat symptoms only: they neither restore sensation nor alter disease progression. Explaining realistic expectations and setting goals together with the patient is therefore an essential step. A pain reduction of at least 30% is generally regarded as a clinically meaningful improvement and at least 50% as a strong response. These are conventional benchmarks used in clinical trials; they serve as a reference when discussing progress with the patient rather than as mandatory thresholds for continuing or stopping a drug. Alongside pain intensity, changes in sleep, mobility and quality of life should be assessed [1].

Glycemic control is fundamental, although its effect depends on the type of diabetes. Pooled evidence shows that intensive glycemic control clearly prevents neuropathy in type 1 diabetes, whereas the benefit in type 2 diabetes is more modest and must be balanced against the risk of hypoglycemia [11]. In type 2 diabetes, management of weight, blood pressure, lipids, smoking, physical activity and chronic kidney disease is of particular importance [1,2]. Treatment-induced neuropathy of diabetes (TIND) may appear as small-fiber pain and autonomic disturbance after a rapid fall in HbA1c. A decrease of at least 2 percentage points over three months has been used as a descriptive threshold in some observational studies, but it is neither a validated diagnostic threshold nor a mandatory limit on the rate of HbA1c reduction [12]. TIND is rare and has been

described mainly in case series from specialist centers. This knowledge is not intended to delay glycemic control; it reminds clinicians to individualize the rate of improvement, to counsel the patient in advance and to monitor symptoms closely when HbA1c falls rapidly.

3.4.2. Treatment of neuropathic pain

Before prescribing, the pain should be confirmed as neuropathic and limb ischemia, arthritis, radiculopathy, nerve entrapment, drug-induced myalgia and infected ulceration excluded. The initial assessment must record pain intensity, distribution and duration, sleep, mood, fall risk, renal and hepatic function, cardiovascular disease, edema, drug interactions and the risk of substance misuse. The general principle is to start low, titrate gradually, maintain a tolerated dose for an adequate period and then reassess after 2-4 weeks or after each dose adjustment [1,7].

The drug classes with evidence and recommended for initial use are the gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and certain sodium channel blockers [2,7,13]. In the Vietnamese setting, the choice usually lies between pregabalin or gabapentin, duloxetine or venlafaxine, and amitriptyline in suitable patients. No single drug is optimal for every patient. Pregabalin and gabapentin are convenient when pain is accompanied by insomnia, but may cause dizziness, somnolence, edema and an increased risk of falls, and require dose reduction according to the glomerular filtration rate. Duloxetine suits patients with depression or anxiety and calls for caution in liver disease and in severe renal impairment. Venlafaxine requires monitoring of blood pressure and heart rate and dose adjustment for renal and hepatic function. Amitriptyline is useful when pain is accompanied by insomnia, but its high anticholinergic burden, orthostatic hypotension and risk of conduction disturbance mean it is usually not the preferred option in older people, those prone to falls, those with cardiac disease, angle-closure glaucoma or prostatic hypertrophy. Sodium channel blockers such as lacosamide, lamotrigine and oxcarbazepine are recognized as supported by evidence in the American Academy of Neurology guideline, but they are not included in Table 2 because the observed effect size is modest, they are not licensed for diabetic neuropathic pain in Vietnam and local experience with them is limited; they should be considered only by a specialist after the options above have failed [13] (Table 2).

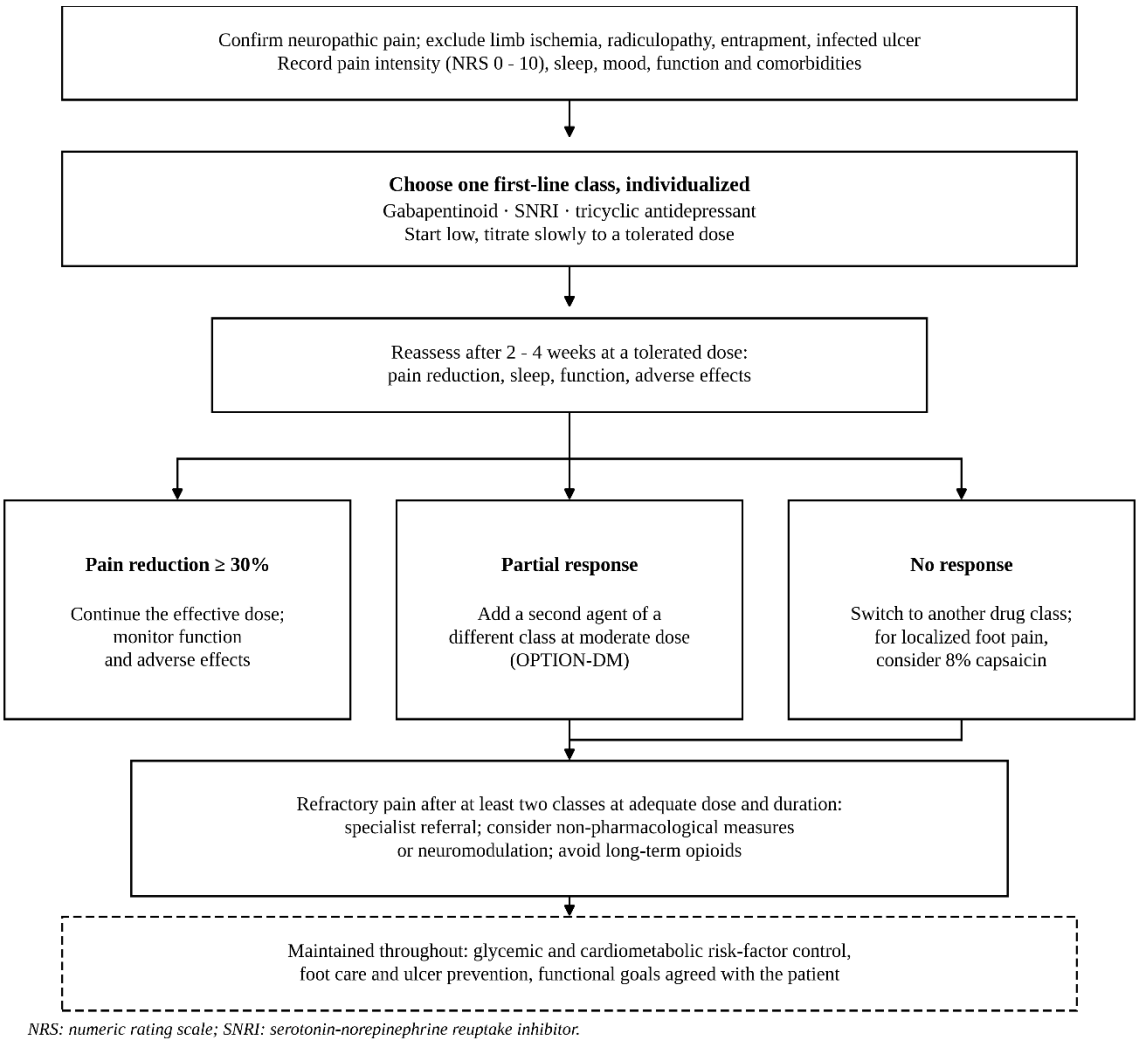
A pain reduction of less than 30% at a tolerated dose is commonly used as a prompt to consider switching to another drug class rather than escalating the dose indefinitely; the final decision must still take account of adverse effects, changes in sleep and function, and the patient's preferences. Where the response is partial, two classes may be combined at moderate doses. The OPTION-DM trial showed that three sequential strategies, amitriptyline followed by pregabalin, duloxetine followed by pregabalin, and pregabalin followed by amitriptyline, were of broadly equivalent overall efficacy, and that adding a second agent produced further improvement in patients who had not reached their target on monotherapy [15]. The choice should therefore rest on comorbidity, adverse effects, cost and patient preference rather than on any rigid ranking of a “best” drug (Figure 3).

Topical 8% capsaicin is a useful option for localized foot pain, particularly when systemic effects or drug interactions are to be avoided. A randomized trial showed that a single application can produce modest pain relief and improve sleep for several weeks without worsening protective sensation; application must follow a defined clinical protocol because it may cause local burning [16]. Topical lidocaine is sometimes used for localized pain, although the evidence specific to diabetic neuropathy is less consistent. Opioids, tramadol and tapentadol should not be used routinely or over the long term, given their limited durable efficacy and the risks of tolerance, dependence and overdose [1,2,7,14].

Table 2. Drug options for diabetic peripheral neuropathic pain [1, 2, 7, 13, 15-17]

Drug	Starting and usual dose	Preferred situations	Main cautions
Pregabalin	75 mg/day in 2 divided doses; 25 mg 2-3 times daily in older people or those prone to falls. Titrate to response, usually to a maximum of 300 mg/day in this indication	Pain with insomnia or anxiety; early onset of effect	Dizziness, somnolence, edema, weight gain, increased risk of falls; reduce the dose according to glomerular filtration rate; caution in heart failure and in older people
Gabapentin	Start at 100-300 mg at night; increase every 3-7 days as tolerated, more slowly in older people or renal impairment; usual dose 900-1,800 mg/day in 3 divided doses, maximum 3,600 mg/day with normal renal function	Flexible titration; may help when pain is accompanied by insomnia	Somnolence, dizziness, edema, ataxia, falls; reduce the dose according to glomerular filtration rate
Duloxetine	30 mg/day for the first 1-2 weeks, target 60 mg/day	Pain with depression or anxiety; little tendency to cause edema	Nausea, dry mouth, insomnia; caution in liver disease; many labels advise against use when eGFR is below 30 mL/min/1.73 m², and the locally approved label should be checked
Venlafaxine extended release	37.5 mg/day, titrated to 75-225 mg/day; reduce the total daily dose by about 25-50% in renal or hepatic impairment	Pain with depression when duloxetine is unsuitable	Monitor blood pressure and heart rate; discontinuation syndrome on abrupt withdrawal; adjust the dose for renal and hepatic function
Amitriptyline	10-12.5 mg at night in older people, 25 mg in younger patients; titrate slowly, usually to no more than 75 mg/day	Younger patients without cardiac disease, when pain is accompanied by insomnia	High anticholinergic burden (dry mouth, constipation, urinary retention, confusion), orthostatic hypotension, QT prolongation; usually not the preferred option in older people or those prone to falls
8% capsaicin	Applied in a facility with a defined protocol, usually for 30 minutes on the foot; may be repeated as indicated	Localized pain, multimorbidity or polypharmacy, intolerance of systemic drugs	Burning, erythema; the skin and protective sensation must be checked
Alpha-lipoic acid	Usually 600 mg/day orally; some regimens use a short intravenous course	Adjunctive, in line with national guidance; does not replace analgesics with stronger evidence	2024 Cochrane review: probably little or no improvement in symptoms at 6 months, and no demonstrated effect on disease progression; monitor for hypoglycemia and gastrointestinal upset
Benfotiamine	300-450 mg/day in line with national guidance	Considered only as adjunctive treatment	Limited long-term evidence and limited data on prevention of foot events; no demonstrated effect on disease progression

Note: The doses in this table are indicative only and must be individualized on a start-low, go-slow basis according to age, glomerular filtration rate, frailty, comorbidity and concomitant medication; the locally approved product label should be checked. For pregabalin, the total daily dose is usually halved when creatinine clearance is 30-60 mL/min and reduced further below 30 mL/min. For gabapentin, the usual dose range falls to 400-1,400 mg/day at a creatinine clearance of 30-59 mL/min, 200-700 mg/day at 15-29 mL/min and 100-300 mg/day below 15 mL/min. ALA: alpha-lipoic acid; eGFR: estimated glomerular filtration rate; SNRI: serotonin-norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant.



NRS: numeric rating scale; SNRI: serotonin-norepinephrine reuptake inhibitor.

Figure 3. Algorithm for the treatment of diabetic peripheral neuropathic pain [1,2,13,15]

3.4.3. Mechanism-based and non-pharmacological treatment

The 2025 Vietnamese Ministry of Health guideline permits the use of alpha-lipoic acid (ALA) and benfotiamine as mechanism-based treatment, either alone in the painless form or in combination with analgesics [1]. ADA 2026 and the American Academy of Neurology guideline do not place these two agents among the standard first-line analgesics [2,7]. The evidence on ALA remains inconsistent. A 2023 meta-analysis found that oral ALA improved the Total Symptom Score with a dose-dependent trend, but showed no benefit on the visual analogue scale, the vibration perception threshold, the NIS-LL score or nerve conduction [17]. By contrast, the 2024 Cochrane review, which included only trials using ALA for at least six months, concluded that ALA probably has little or no effect on neuropathy symptoms at six months and may have little or no effect on the degree of neurological impairment, with the certainty of evidence rated moderate to low [18]. When ALA is described as mechanism-based treatment, it must therefore be made clear that a mechanistic rationale is not the same as demonstrated efficacy in modifying disease progression. ALA 600 mg/day should be considered only as adjunctive treatment, after the certainty of the evidence has been discussed with the patient, and it does not replace risk-factor control, foot care or analgesics supported by stronger evidence. Benfotiamine 300-450 mg/day should likewise be regarded as adjunctive only, since data on clinically meaningful outcomes remain limited.

B vitamins should not be given as a matter of habit in the absence of deficiency or a specific indication. Vitamin B12 should be measured and replaced when deficient, particularly in patients taking metformin. Conversely, prolonged high-dose pyridoxine can cause sensory neuropathy. Among non-pharmacological measures, patient education, appropriate aerobic and strength training, balance exercises, physiotherapy, sleep hygiene and psychological support all have a place. Transcutaneous electrical nerve stimulation,

acupuncture and neuromodulation techniques may be tried in selected patients, although the quality of evidence is uneven. Spinal cord stimulation relieves pain in selected refractory cases, after specialist assessment and failure of standard treatment [1,14].

3.4.4. Ulcer prevention and foot care

Every patient with DSPN requires foot-risk stratification. According to the IWGDF, risk category 0 is assessed at least annually, category 1 every 6-12 months, category 2 every 3-6 months and category 3 every 1-3 months [19]. Patients and their families should be taught to inspect the feet daily, never to walk barefoot, to wash and dry between the toes, to moisturize dry skin but not between the toes, to cut the nails correctly and to report blisters, cracked callus, discoloration or wounds promptly. Footwear must fit well, be sufficiently deep and offload areas at risk; callus, deformity, pre-ulcerative lesions and peripheral artery disease all require active management. The Vietnamese Ministry of Health guideline on diabetic foot ulcers provides a framework for coordination between endocrinology, vascular medicine, surgery, infectious diseases and rehabilitation that is well suited to national practice [20].

Drawing on the evidence above, a five-step practical process can be implemented. The first step is to screen at the appropriate time and to establish the symmetric, length-dependent distribution. The second is combined testing of small-fiber function, large-fiber function and ankle reflexes for the purpose of diagnosing DSPN, together with the 10-g monofilament, palpation of peripheral pulses and foot examination for the purpose of identifying LOPS and stratifying ulcer risk. The third step is the search for atypical features and for reversible causes, in particular vitamin B12 deficiency, hypothyroidism, alcohol and neurotoxic drugs; monoclonal gammopathy is sought only when there are suggestive features. Chronic kidney disease also affects the peripheral nerves, but uremic neuropathy improves only partly after renal replacement therapy, so advanced chronic kidney disease does not belong among the reversible causes in the same sense as vitamin B12 deficiency or hypothyroidism. If the patient has pain, the fourth step is to grade the pain and its functional impact, select a drug according to comorbidity, age and renal function, reassess after 2-4 weeks, consider switching class when the response is poor and combining agents when it is partial. In the final step, multifactorial risk-factor control and ulcer prevention are maintained regardless of whether the pain improves.

As regards future research, the technologies currently attracting interest serve different purposes and should not be grouped together. Corneal confocal microscopy and quantification of intraepidermal nerve fiber density are directed at the diagnosis and monitoring of small-fiber damage. Temperature sensors and plantar pressure sensors are directed at predicting or detecting foot injury early. Metabolic and inflammatory markers mainly serve mechanistic research, while machine-learning models may support risk stratification but depend on the quality of the input data and require external validation [21]. To date, no simple marker allows small-fiber damage to be detected before protective sensation is lost; there are likewise no clear criteria for predicting which analgesic will suit an individual patient, and no disease-modifying therapy has emerged. A marker sensitive to biological change is not necessarily a valid surrogate for the outcomes that matter to patients: these technologies must demonstrate that improving an intermediate marker translates into fewer ulcers, fewer falls or less pain. For Vietnam specifically, what is most needed are multicenter studies using uniform diagnostic criteria, reporting the painful and painless forms separately, and assessing the feasibility and cost-effectiveness of an integrated screening and management algorithm.

4. CONCLUSION

Diabetic peripheral neuropathy should be identified actively, before pain appears. The diagnosis of DSPN is primarily clinical and rests on the typical distribution together with combined assessment of small-fiber function, large-fiber function and ankle reflexes. Screening for DSPN, identifying loss of protective sensation and stratifying ulcer risk are three separate objectives; the 10-g monofilament serves the second of these and is not used to exclude early disease. Nerve conduction studies and small-fiber tests are reserved for atypical presentations or when the diagnosis must be confirmed to research standards. Effective treatment requires control of glycemia and cardiometabolic risk factors, foot care, agreed functional goals and analgesic therapy individualized for age, renal function and comorbidity. Gabapentinoids, SNRIs and tricyclic antidepressants remain the mainstays, applied on a start-low, go-slow basis; when the response is insufficient, the class should be switched or agents combined rationally, while long-term opioid therapy is avoided. ALA and benfotiamine should be regarded as adjunctive only, since evidence that they modify disease progression remains limited.

Future research should separate diagnostic markers, monitoring markers and markers predicting ulceration, and should demonstrate benefit on the outcomes that matter to patients.

List of abbreviations

Abbreviation	Definition
ALA	Alpha-lipoic acid
ADA	American Diabetes Association
DSPN	Distal symmetric sensorimotor polyneuropathy
IWGDF	International Working Group on the Diabetic Foot
LOPS	Loss of protective sensation
MNSI	Michigan Neuropathy Screening Instrument
SNRI	Serotonin-norepinephrine reuptake inhibitor
TIND	Treatment-induced neuropathy of diabetes
DN4	Douleur Neuropathique 4 questionnaire
IENFD	Intraepidermal nerve fiber density
NCS	Nerve conduction studies
NRS	Numeric rating scale
QST	Quantitative sensory testing
TCA	Tricyclic antidepressant

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Declaration of Competing Interest

The authors declare no financial conflict of interest and no personal relationship that could have influenced the work reported in this article.

Declaration of Generative AI and AI-Assisted Technologies

The authors did not use artificial intelligence software in the writing of this article.

Author contributions

All authors read and revised the manuscript and approved its final version; Tran Dang Dang Khoa is responsible for correspondence.

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CẬP NHẬT CHẨN ĐOÁN VÀ ĐIỀU TRỊ BỆNH THẦN KINH NGOẠI BIÊN DO ĐÁI THÁO ĐƯỜNG

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Bệnh thần kinh ngoại biên do đái tháo đường là một nhóm bệnh gồm nhiều thể, thường bị bỏ sót trên lâm sàng trong khi hậu quả để lại khá nặng nề: đau mạn tính, mất cảm giác bảo vệ, loét bàn chân và suy giảm chất lượng sống. Bài tổng quan tường thuật có cấu trúc này trình bày cách phân loại các thể bệnh cùng đặc điểm nhận diện và nguyên tắc xử trí của từng thể, sau đó tập trung cập nhật chẩn đoán và điều trị bệnh đa dây thần kinh cảm giác - vận động đối xứng đoạn xa (distal symmetric polyneuropathy - DSPN) và thể có đau, vốn chiếm phần lớn gánh nặng lâm sàng. Tài liệu được tìm trên PubMed/MEDLINE, Cochrane Library cùng các hướng dẫn chính thức trong nước và quốc tế đến ngày 31/7/2026. Chẩn đoán DSPN trước hết là chẩn đoán lâm sàng, dựa vào bệnh sử kết hợp thăm khám sợi nhỏ, sợi lớn và phản xạ gân gót. Sàng lọc DSPN, xác định mất cảm giác bảo vệ và phân tầng nguy cơ loét bàn chân là ba mục tiêu khác nhau: monofilament 10 g phục vụ mục tiêu thứ hai và có độ nhạy thấp với bệnh giai đoạn sớm nên không dùng để loại trừ DSPN; điện dẫn truyền thần kinh chỉ cần thiết khi biểu hiện không điển hình hoặc khi cần khẳng định chẩn đoán. Về điều trị, kiểm soát đa yếu tố nguy cơ và chăm sóc bàn chân đi song song với việc lựa chọn cá thể hóa gabapentinoid, thuốc ức chế tái hấp thu chọn lọc serotonin - norepinephrine hoặc thuốc chống trầm cảm ba vòng, theo nguyên tắc khởi liều thấp, tăng chậm và chỉnh liều theo tuổi cùng chức năng thận. Khi đáp ứng chưa đủ, đổi nhóm cơ chế hoặc phối hợp thuốc hợp lý thường tốt hơn việc tăng liều kéo dài; opioid dùng dài ngày nên tránh. Acid alpha-lipoic và benfotiamine chỉ nên xem là điều trị bổ trợ, vì tổng quan Cochrane năm 2024 cho thấy acid alpha-lipoic có lẽ ít hoặc không cải thiện triệu chứng thần kinh sau sáu tháng. Phát hiện sớm tổn thương sợi nhỏ và các liệu pháp làm thay đổi tiến triển bệnh vẫn là những hướng nghiên cứu còn bỏ ngỏ.

Từ khóa: bệnh thần kinh ngoại biên; đái tháo đường; bệnh đa dây thần kinh đối xứng đoạn xa; đau thần kinh; chẩn đoán; điều trị; bàn chân đái tháo đường.