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NEUROPATHY IN DIABETIC MELLITUS: CAUSES, DIAGNOSIS AND THERAPEUTIC MODELS

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Abstract

Diabetic neuropathy (DN) is the most common and severe side effect of diabetes mellitus, associated with high morbidity and mortality rates, significantly straining diabetes care. Modern definitions describe diabetic neuropathy as a symmetric, length-dependent sensory polyneuropathy resulting from metabolic changes and microvascular damage due to prolonged hyperglycemia and cardiovascular risk factors. The management and clinical assessment of DN are complex. Patients with DN should be evaluated for autonomic neuropathy, as these conditions often coexist. Currently, duloxetine and pregabalin are the primary medications prescribed for neuropathic pain, yet neither offers complete relief, even when combined. This study reviews the available treatments and current guidelines for managing diabetic neuropathy, focusing on pain management and diabetic autonomic neuropathy. There remains a critical need to investigate medication combinations that may more effectively reduce or even reverse the progression of the disease while enhancing pain relief. Addressing these gaps could lead to improved outcomes for patients suffering from this debilitating condition.

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INTRODUCTION

The most prevalent and severe complication of diabetes mellitus (DM) is diabetic neuropathy (DN), which has the highest morbidity and mortality rates and places a significant financial strain on diabetes care. As the most prevalent type of neuropathy in affluent nations, it causes 50% to 75% of nontraumatic amputations, more hospitalizations than all other diabetic complications combined, and more hospitalizations overall. DN is a collection of clinical disorders that can impact different parts of the nervous system alone or in combination. It may manifest with clinical symptoms and generic

indications and proceed slowly but resemble those of many other diseases. It may also be silent and go unnoticed while wreaking its havoc. The diagnosis of DN is thus made via exclusion. Unfortunately, less than one-third of doctors know the cause or talk to their patients about it, and both endocrinologists and non-endocrinologists lack the training necessary to identify the illness, even when DN is symptomatic [1].

SCOPE OF THE PROBLEM:

One of the most prevalent complications of diabetes is diabetic peripheral neuropathy (DPN). There is no widely recognized classification for the range of disorders it causes. These neuropathies can be broadly classified as symmetric polyneuropathies, such as sensorimotor polyneuropathy (DSPN), and focal/multifocal neuropathies, such as diabetic amyotrophy. About 25% of diabetic patients in the community and 30% of those receiving hospital care have the latter type, which is the most prevalent. According to contemporary definitions, DPN is a symmetric, length-dependent sensorimotor polyneuropathy caused by changes in metabolism and microvascular structure brought on by long-term exposure to hyperglycemia (diabetes) and cardiovascular risk factors. It usually has a subtle beginning; if left untreated, it progresses over time [2] . Thermal and pain perception are lost when small-fiber-mediated feeling is compromised, while touch and vibration perception are lost when large-fiber impairment occurs. The involvement of sensory fibers can also produce "positive" symptoms like pain and paresthesias. However, neuropathic patients may have no symptoms in as many as 50% of cases. Although diabetic autonomic neuropathy, which seldom results in severe symptoms, can be linked to DPN's involvement in the autonomic nerve system, its cardiovascular form is unquestionably linked to at least a three-fold more significant risk of death. Cardiovascular risk has more recently been linked to diabetic autonomic neuropathy or even autonomic imbalance between the sympathetic and parasympathetic neural systems [3].

CLASSIFICATION OF DIABETIC NEUROPATHIES

It is crucial to understand that various types of DN, such as distal polyneuropathy and carpal tunnel syndrome, can coexist in the same patient. Nearly every component of the somatic peripheral and autonomic nerve systems can malfunction in the range of clinical neuropathic symptoms seen in diabetes mellitus patients [4].

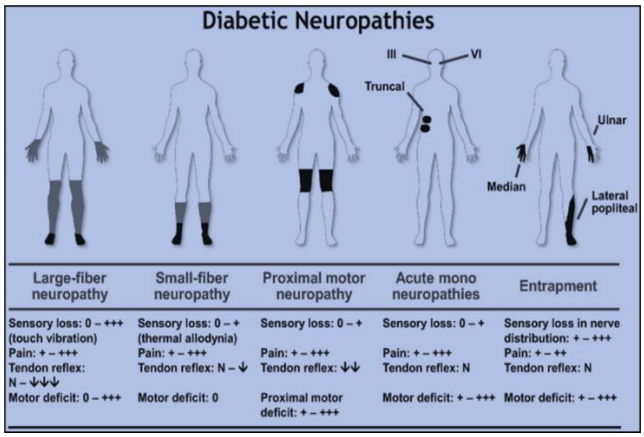

Figure 1 Clinical signs of both large-fiber and small-fiber neuropathies

Table 1 Differentiating between distal symmetric polyneuropathy, entrapment syndromes, and mononeuropathies

Feature Onset	Mononeuropathy Sudden	Entrapment Syndrome Gradual	Neuropathy Gradual
Design	One nerve, but perhaps several	Trauma to a single nerve	Polyneuropathy with distal symmetry
Nerves engaged	Peroneal, median, ulnar, CN III, VI, VII	Peroneal, medial, lateral, ulnar, and median plantar	Autonomic, sensory, motor, and mixed
History of Nature	Spontaneously resolves	Advancement	Advancement
Sensory loss distribution	A region that the nerve supplies	The area provided outside the entrapment location	The distribution of "glove and stocking" is symmetrical and distal.

Autonomic neuropathy

One of the features of diabetic neuropathy is autonomic dysfunction, which can have fatal consequences. Resting tachycardia is typically the first sign of clinical cardiovascular problems; the heart rate may eventually return to normal, but it does not show typical fluctuations in response to shifting physiological conditions. Postural hypotension, characterized as a decrease in systolic blood pressure of more than 30 mmHg following a transition from a lying to a standing posture without an increase in heart rate, is one of the most painful symptoms of autonomic neuropathy accompanying postural syncopes. Tricyclic antidepressants, which are commonly used to treat persistent pain in diabetic neuropathy and diarrhea episodes, might exacerbate postural hypotension. There appears to be a clear correlation between cardiac autonomic neuropathy and an elevated risk of silent myocardial ischemia and death [5].

Focal and multifocal neuropathy

In diabetic patients, localized and multifocal neuropathies are far less frequent than LDDP. These types of neuropathy primarily affect people with type 2 diabetes and are typically observed beyond the age of 50. Proximal diabetic neuropathy (PDN) of the lower limbs, limb and truncal neuropathies, and involvement of the cranial nerve are examples of focal neuropathies. It is uncommon for diabetic individuals to develop sensory deficits in the territories of one or more nerve trunks, roots, or plexuses. If necessary, a nerve biopsy should be performed to rule out alternative causes of neuropathy [6].

PATHOLOGY OF DIABETIC NEUROPATHIES

Distal symmetrical diabetic neuropathy

Primary demyelination brought on by Schwann cell dysfunction, secondary segmental demyelination brought on by compromised axonal regulation of myelination, remyelination, Schwann cell proliferation, atrophy of denervated bands of Schwann cells, and axonal degeneration of nerve fibers, onion-bulb formations, and hypertrophy of the basal lamina are among the abnormalities associated with diabetic neuropathy [7]. In LDDP, dying-back fibers and fibers with distal sprouting of the proximal stump after distal axon degeneration have also been found. In nerve biopsies, there is no association between axon loss and demyelination; axon loss is more common distantly. Early morphological changes include axonal regeneration and slight alterations to myelinated and unmyelinated fibers. Recent morphological and physiological studies support the idea that tiny myelinated and unmyelinated somatic sensory fibers are primarily and early involved in diabetic neuropathy. One of the main symptoms of type 2 diabetes is small-fiber sensory neuropathy, which manifests as decreased IENF density and associated rise of warm thresholds. As diabetes worsens over time, the degree of skin denervation increases. The nerve-axon reflex, used to evaluate C-nociceptive fiber function, has also demonstrated that small-fiber damage occurs early in the natural history of diabetic neuropathy. Some people with comparable levels of diabetes may have more severe polyneuropathy than others, which genetic factors could explain. Diabetic microangiopathy frequently manifests in endoneurial capillaries as a noticeable basal lamina thickening. The existence of multifocal nerve lesions and alterations in endoneurial capillaries have suggested a role for circulatory factors in symmetrical diabetic neuropathy. However, nerve ischemia alone cannot account for dissociated sensory loss, severe autonomic dysfunction, and the primary loss of unmyelinated axons [8].

PATHOGENESIS:

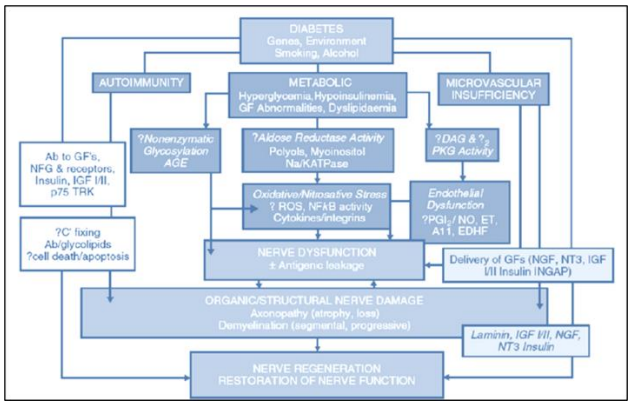

Figure 2 Diabetic neuropathy pathogenesis

Diabetic Amyotrophy, or proximal motor neuropathy, and chronic demyelinating neuropathies Proximal neuropathy has long been thought to be a part of DN. Its pathophysiology was poorly known, and therapy was disregarded in the hope that the patient would eventually

recover—albeit after experiencing significant pain, weakness, and impairment throughout one to two years.Diabetic amyotrophy and femoral neuropathy are two synonyms for the condition. These shared characteristics can be used to identify it clinically: (1) it mainly affects people with type 2 diabetes who are 50–60 years old;

(2) it can start gradually or suddenly;

(3) it starts with excruciating thigh, hip, and buttock pain, followed by severe lower limb proximal muscle weakness that makes it impossible to get out of a seated position (positive Gower maneuver)

(4) it can spread bilaterally after beginning unilaterally;

(5) distal symmetric polyneuropathy frequently coexists with it; and

(6) Its characteristic is the fasciculation of muscles, either spontaneously or in response to percussion.

While immune-mediated epineurial microvasculitis has been observed in some cases, the pathogenesis remains unknown. Diabetes patients are more likely to develop the illness than the general population, even though it is now known to be secondary to several factors unrelated to diabetes. Patients with circulating GM1 antibodies, monoclonal gammopathy, inflammatory vasculitis, and chronic inflammatory demyelinating polyneuropathy (CIDP) are included [9].

Treatment options include:

Steroids and azathioprine for vasculitis, intravenous immunoglobulin for CIDP, plasma exchange for monoclonal gammopathy of uncertain significance, and stopping medications or other substances that might have contributed to vasculitis. Since amyotrophy progresses on its own over months to years, but the CIDP variation responds dramatically to intervention, separating proximal disorders into these two groups is crucial. They should be regarded as distinct syndromes until further information is obtained [10].

Diabetic Truncal Radiculoneuropathy

Patients with diabetic truncal radiculoneuropathy range in age from middle-aged to elderly, and men are more likely to be affected than women. The most significant symptom is pain, distributed like a girdle over the abdominal or lower thoracic wall. It might be spread bilaterally or unilaterally. It is uncommon to have motor weakness. Usually, resolution takes place in four to six months.

Rapidly Reversible Hyperglycemic Neuropathy

Diabetes that is poorly managed or newly diagnosed might cause reversible impairments of nerve function. Since recovery occurs quickly after euglycemia is restored, Diabetic Neuropathy 751 structural abnormalities are unlikely to be the source of these illnesses. It is unknown if the distal sensory complaints that are typically present in rapidly reversible hyperglycaemic neuropathy increase the chance of developing chronic neuropathies in the future [11].

Diabetes-related focal and multifocal neuropathies

A patient with proximal neuropathy of the lower limbs had biopsy samples of the intermediate cutaneous nerve of the thigh, a sensory branch of the femoral nerve that transmits sensation from the anterior aspect of the thigh, a region commonly involved in PDN. The samples showed lesions typical of nerve ischemia. Inflammatory infiltrates surrounding epineurial and perineurial blood arteries were connected to these lesions (**Figure 3**).

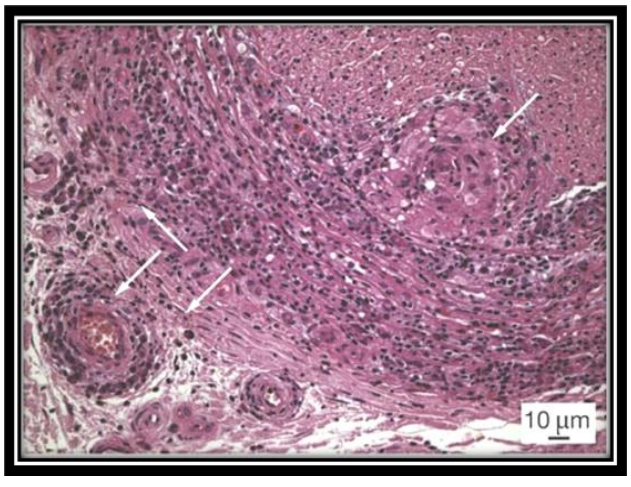

Figure 3 Multifocal diabetic neuropathy

The inflammatory lesions were composed of macrophages and B and T cells. Other people noted similar findings in biopsy specimens of the sural nerve and the thigh's intermediate cutaneous nerve. According to my group,

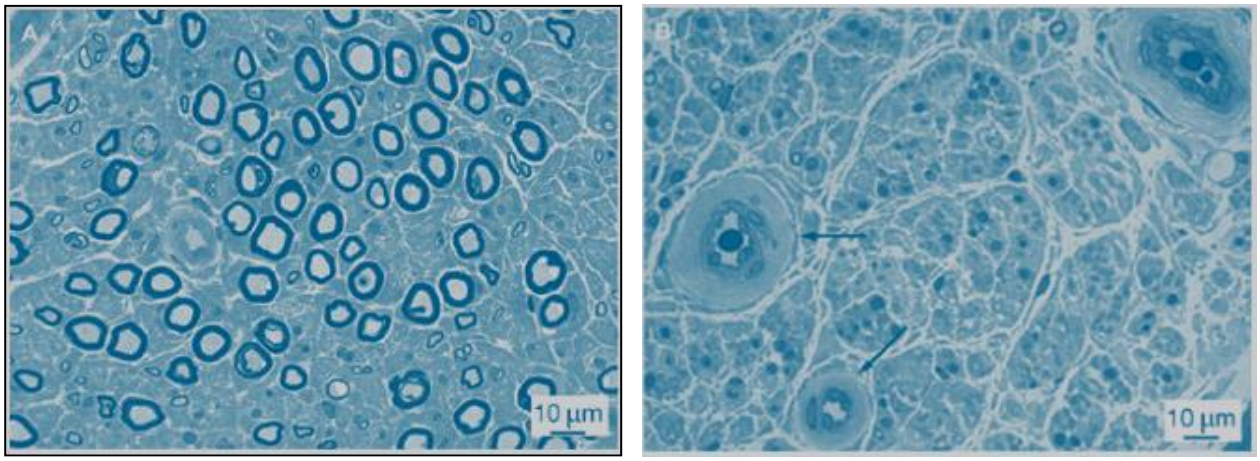

Figure 4 Diabetic polyneuropathy with length-dependent nerve biopsy findings

spontaneous healing was not hindered by inflammatory infiltrates. Perineurial and endoneurial blood vessel vasculitis was linked to asymmetric axonal lesions in nerve biopsy specimens taken from patients with MDN in an afflicted region. The endoneurial red cell is linked to perivascular mononuclear cell infiltrations in most nerve specimens. In older diabetic individuals with MDN, nerve lesions appear to be associated with precapillary blood vessel destruction, which results in a subsequent inflammatory and hemorrhagic response. The reason behind the preponderance of lesions on lower spinal roots, the lumbar plexus, and lower limb nerves in proximal and multifocal diabetic neuropathies is unknown. Although the discovery of inflammatory lesions in PDN was initially unexpected, it is now evident that type 2 diabetes and obesity have intricate relationships, with both disorders appearing to be closely linked to subcellular "inflammation," The activation of a network of inflammatory signalling pathways and abnormal cytokine production characterizes it. Damage to the vessel wall may cause further blood vessel lesions, leading to increased inflammatory responses in people with type 2 diabetes [12].

CAUSES OF NEUROPATHY IN PATIENTS WITH DIABETES

Diabetic individuals with distal sensory polyneuropathy are comparatively likely to have neuropathy caused by factors other than diabetes. According to a retrospective analysis of 100 consecutive diabetic patients with symptomatic neuropathy and frequently uncommon characteristics, 79% of patients with LDDP and 74% of all patients in the group had diabetes-related neuropathies. A neuropathy unrelated to diabetes affected one-third of the individuals. In this cohort, chronic inflammatory demyelinating neuropathy was the most common nondiabetic cause of neuropathy, occurring in 9% of the patients [13]. **Table 2** presents the comparative features of motor impairments in people with diabetes. It is essential to rule out general causes of neuropathy before attributing a polyneuropathy to diabetes, such as amyloid polyneuropathy, monoclonal gammopathy, drug-induced neuropathy, alcoholism, vitamin deficiencies, and POEMS syndrome. It appears that people with diabetes are more likely to experience pressure palsy than people without the disease; for instance, carpal tunnel syndrome was shown to affect 12% of diabetic patients, compared to 4% to 5% of the general population.

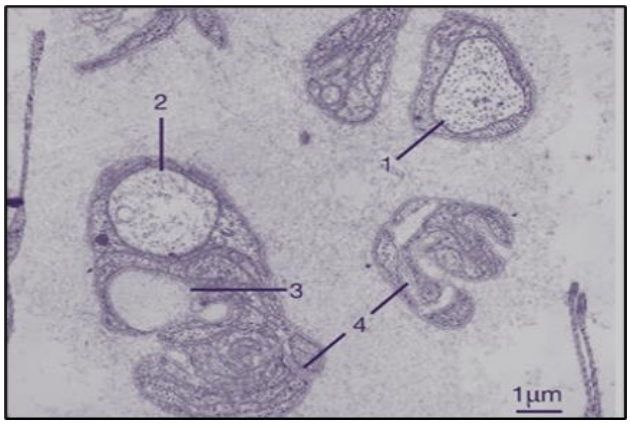

Figure 5 Unmyelinated fiber abnormalities in severe length-dependent diabetic polyneuropathy

DIABETIC NEUROPATHY DIAGNOSIS:

STUDIES OF NERVE CONDUCTION

Diabetic neuropathy symptoms include decreased nerve action potentials due to axon loss, demyelination, and loss of giant myelinated fibers, which slow down nerve conduction velocity. In diabetic patients, pure demyelinating neuropathy is uncommon and more indicative of an inflammatory or cryoglobulinemic demyelinating neuropathy. Patients with diabetes who have typical peripheral neuropathy do not require systematic electrophysiological testing. Although asymptomatic patients may exhibit changes in conduction velocity, the onset of symptomatic neuropathy is not predicted by the existence of these changes. The most objective, noninvasive way to assess nerve function is through nerve conduction studies (NCS) [14]. They help determine neuropathy in extensive epidemiological and clinical research [15]. However, due to its various limitations and the need to interpret results in light of clinical data, NCS should not replace a thorough clinical examination in clinical practice. The primary disadvantage of NCS in the case of LDDP, as in many small-fiber poly neuropathies, is that the sensory action potential picked up by standard NCS does not originate from tiny myelinated and unmyelinated nerve fibers, which are impacted early in the course of diabetic neuropathy. Only when more giant myelinated fibers are involved—which is frequently a late event in diabetic patients- does the sensory action potential change. As a result, electrophysiological data must continually be assessed in a clinical setting.

DIABETIC NEUROPATHY TREATMENT

Preventive treatment:

The best course of action is still to prevent diabetic neuropathy and its sequelae. Maintaining optimal glycaemic control increases the risk of hypoglycemia but reduces the risk of acquiring debilitating peripheral neuropathy. Four. To minimize the danger of bone infection and avoid uncomfortable ulcers, diabetic patients also require guidance on foot care and footwear and how to protect pressure points and hypersensitive

Table 2 The primary characteristics of various patterns of disabling neuropathies in diabetic patients

Feature	Length-dependent polyneuropathy	CIDP (chronic inflammatory demyelinating polyneuropathy) in diabetic patients	Diabetes-related focal and multifocal neuropathy
Pain	frequent in the limbs' distal regions	Occasionally	In most situations
Weakness	Minor, distal symmetrical	Frequently severe, both proximal and distal	Asymmetrical joint, nerve, or root region
Symmetric sensory loss at the distal end	Minor, distal symmetrical	Frequently severe, both proximal and distal	Asymmetrical joint, nerve, or root region
Results of electrophysiological tests	Distal symmetrical axonal pattern	Mixed demyelination and axonal	Axonal pattern, multifocal
Sensory ataxia	Rare	Common	Rare
Cerebro Spinal Fluid protein	Variable	Increased	Increased
Nerve biopsy findings	Significant loss of axons	Variable demyelination and axon loss	Axon loss, vasculopathy, and inflammation
Response to corticosteroids	No	Good	Good

areas. The best places to prevent and treat "diabetic foot" are specialty foot clinics. Transplanting the pancreas, which could stabilize neuropathy, is not standard [16], [17].

Symptomatic treatment:

The course of focal neuropathy, which includes truncal neuropathy, PDN, and cranial nerve palsy, is self-limited and typically resolves on its own in a few months. Both focal neuropathies and LDDP might make pain management challenging. When used with codeine phosphate, carbamazepine, phenytoin, clonazepam, or paracetamol may be helpful. The typical dosage of tricyclic antidepressants, like amitriptyline or imipramine, ranges from 30 to 150 mg daily; they are frequently beneficial. Tricyclic antidepressants may exacerbate postural hypotension. Pregabalin and duloxetine, two newly approved medications, are also helpful. Treatment is only necessary for symptomatic cases of postural hypotension. Before employing 9-α-fluorohydrocortisone, the most effective treatment for postural hypotension, it is worthwhile to attempt midodrine (where licensed) as it bears a risk of hypertension [16] , [17].

Treatment for diabetic neuropathies, both focal and multifocal:

PDN typically causes excruciating pain that is often unresponsive to standard therapies. In certain situations, corticosteroid treatment may be explored for a few weeks or months, along with glycaemic control adjustments. It is crucial to remember that focal diabetic neuropathies have a favorable overall spontaneous outcome [16] , [17].

Diabetic Neuropathic Pain: Medicinal Therapeutic Methods

Therapy based on Pathogenic Theories of Pain:

The odds ratio (OR), relative risk, or relative risk reduction are commonly used to represent the relative benefit of an active treatment over a control in clinical studies. However, to determine the degree of a therapeutic impact (pain reduction, for example) that may be applied in clinical practice, utilizing a straightforward metric helps the doctor choose the best course of action for each patient. The number needed to treat (NNT) is a valuable metric that quantifies the number of patients who must receive a specific therapy to notice a clinically significant impact or adverse event in a single patient. **Table 3** lists the OR, NNT, and number needed to harm (NNH) for each medicine used to treat painful DN. For 50% or more pain alleviation, medications with NNTs larger than six are often considered to have limited efficacy. However, the lack of uniformity in treatment treatments, mechanisms of action, pain syndromes, and outcome measures has led some researchers to warn against the use of NNT estimates. Developing and improving a symptom-/mechanism-based approach to neuropathic pain, new therapy techniques employing the more current antiepileptic drugs may target the underlying neurophysiologic abnormalities in neuropathic pain, increasing the likelihood of effective management. These developments in understanding the neural and pharmacologic basis of neuropathic pain are likely to have significant treatment significance.

Adrenergic blockers

The patient first suffers blistering, lancinating, and dysesthetic pain when there is continuous nerve injury; hyperalgesia and allodynia are frequently present as well. Sympathetic blocking medications

Table 3 Efficacy and withdrawal odds ratios, numbers needed to treat (NNT), and numbers needed to harm (NNH)

Drug Class	Odds Ratio: Effectiveness	Withdrawal is the odds ratio (secondary to adverse event)	Numbers Needed to Treat	Numbers Needed to Harm
Tricyclics	22.1 (5.7–83.6)	2.2 (0.5–9.6)	1.4–3.4	2.8–16.0
Duloxetine	2.5 (1.5–4.7)	2.3 (1.2–5.3)	5.6–5.7	14.0
Conventional Anticonvulsants	5.2 (1.7–15.0)	1.4 (0.2–7.1)	2.2–3.3	2.6–3.1
A new class of anticonvulsants	3.2 (2.2–4.6)	3.1 (1.74–5.2)	2.8–4.4	25.2
Opioids	4.2 (2.2–7.7)	4.2 (1.3–14.3)	2.5–3.8	8.0

like clonidine may alleviate pain because peripheral sympathetic nerve fibers are tiny, unmyelinated C fibers.

Topical capsaicin

The neuropeptide substance P is the neurotransmitter used by C fibers, and pain is frequently reduced when axonal substance P is depleted (by taking capsaicin). When capsaicin is applied for an extended period, sensory nerve terminals lose their stocks of substance P and possibly other neurotransmitters. This procedure reduces or eliminates the passage of painful stimuli from the peripheral nerve filaments to the higher centers. Numerous studies have shown that after 8 weeks of treatment with 0.075% capsaicin cream, diabetic individuals with severe neuropathy have significant pain reduction and an improvement in their quality of life.

Lidocaine

A multicenter, randomized, open-label, parallel-group research that included a 2-week drug washout phase and a 4-week comparative phase of 5% lidocaine (n5 99) vs. pregabalin (n5 94) revealed that lidocaine was just as effective as pregabalin in relieving pain and that it had no side effects. The Toronto Consensus Panel on Diabetic Neuropathy claims this type of therapy customizes care for each patient. Comorbidities Contraindication Glaucoma TCAs Hypotension in orthostatic conditions TCAs Heart-related conditions Hepatic disease with TCAs Duloxetine Oedema Gabapentin and pregabalin Falls and unsteadiness Weight increase from TCAs TCAs, gabapentin, and pregabalin. Diagnosis, evaluation, and treatment guidelines for painful diabetic peripheral neuropathy.

Opioids and NMDA-receptor antagonists:

A mild opioid analgesic with central action, Tramadol is used to treat moderate to severe pain. Tramadol was superior to a placebo in a randomized controlled trial that lasted only six weeks; however, a follow-up investigation indicated that symptomatic alleviation could last for at least six months. Long-term tramadol drug typically results in tolerance and dependency, and there appears to be little chance of abuse even though side effects are somewhat prevalent and comparable to those of other opioid-like medications. Another spinal cord target for pain relief is the excitatory glutaminergic N-methyl-D-aspartate (NMDA) receptor. One theory for how dextromethorphan works as an analgesic is that it blocks NMDA receptors. NMDA receptors significantly influence the central sensitization of neuropathic pain. However, their dose-limiting side effects (Ia/A) have contributed to their limited usage.

Antidepressants

In the treatment of chronic neuropathic pain, antidepressants are increasingly being used as the first line of treatment. Antidepressant medications that block the reuptake of serotonin or norepinephrine have been used in clinical studies to stop the transmission of pain. The impacts of these neurotransmitters on the brain's endogenous pain-inhibitory systems, which alter spinal cord pain-transmission cells, are highlighted by this central activity. NMDA receptors that mediate hyperalgesia and allodynia are antagonistic, and central descending pain control systems' synapses block norepinephrine or serotonin reuptake, which are hypothesized mechanisms of antidepressant-induced pain alleviation.

Tricyclic antidepressants

A balanced reuptake inhibition of norepinephrine and serotonin is induced by imipramine, amitriptyline, and clomipramine, while desipramine is a selective norepinephrine inhibitor. In painful neuropathies, 2.1 (1.9–2.6) is the NNT (CI) for tricyclic antidepressants (TCAs) to relieve pain at least 50%. The NNH for a single study dropout resulting from adverse events in neuropathic pain patients is 16. Amitriptyline should be administered as a single nocturnal dose one hour before bedtime at a beginning dose of 25 mg (10 mg in frail patients). Weekly increases of 25 mg should be made until pain is relieved or side effects appear. 150 mg daily is typically the maximum dosage. Numerous contraindications and comparatively high rates of adverse events restrict the use of TCAs (**Table 4**).

Antiepileptic Drugs

Antiepileptic drugs (AEDs) have long been used to treat neuropathic pain. 770 GABA activity potentiation (tiagabine, topiramate), sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate, zonisamide), calcium

Table 4 Diabetic polyneuropathy symptoms, treatment options, dosage, and adverse effects

Drug Class	Drug	Dose	Side Effects
Tricyclics (mg)	Amitriptyline Nortriptyline Imipramine Desipramine	50–150 QHS 50–150 QHS 25–150 QHS 25–150 QHS	sleepiness, light headedness, dry mouth, tachycardia, constipation, retention of urine, blurred vision, and confusion.
Anticonvulsants (mg)	Gabapentin Pregabalin Carbamazepine/ oxcarbazepine Topiramate	300–1200 TID 50–150 TID Up to 200 QID p to 400 QD	Fatigue, lightheadedness, disorientation, and ataxia Weight gain, oedema, disorientation, and somnolence Lightheadedness, drowsiness, nausea, and leukopenia Ataxia, tremor, dizziness, and drowsiness
Opioids (mg)	Tramadol Oxycodone CR	50 to 100 BID 10 to 30 BID	Constipation, HA, sleepiness, and nausea Constipation, nausea, somnolence, and HA
Topical	Capsaicin Lidocaine	0.075% QID 0.04% QD	Irritation in the area Irritation in the area

channel blockade (felbamate, lamotrigine, topiramate, zonisamide), glutamate antagonism at NMDA receptors (felbamate) or AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (felbamate, topiramate), and mechanisms of action that are still unknown (gabapentin, pregabalin, levetiracetam) are the main mechanisms of action. Understanding how the different medications work gives rise to "rational polytherapy." Multiple drugs with other modes of action can work together to produce a synergistic impact. For instance, a glutamate antagonist like felbamate may be taken alongside a sodium-channel blocker like lamotrigine. Additionally, a single medication may have several modes of action, which could improve its chances of effectiveness (e.g., topiramate). Different forms of pain should respond to varying therapies if they are classified based on whether they originate from the spinal cord, the cortex, or other types of nerve fibers (e.g., Ad vs. C fiber).

Modulators of calcium channels (pregabalin and gabapentin)

There are five different kinds of voltage-gated calcium channels, and the L and N channels are involved in the neuromodulation of the spinal cord's sensory neurons. The drugs pregabalin and gabapentin bind to the channels' a2-d subunits. In contrast to conventional calcium-channel antagonists, they alter calcium channels' activity and expression sites rather than blocking them. This category of drugs' precise mode of action on neuromodulation is yet unclear (IIb/B).

Gabapentin

GABA is a neurotransmitter involved in the transmission and modulation of pain, and gabapentin is an anticonvulsant with structural similarities.

At least considerable pain reduction was experienced by 60% of patients on gabapentin (3600 mg/d, or 67%), compared to 33 % of patients on placebo in an 8-week multicenter dose-escalation experiment involving 165 diabetic patients with severe neuropathy.

In neuropathies that cause pain, gabapentin's NNT (CI) for at least 50% pain reduction is 6.4 (4.3–12). Overall, there is little evidence supporting gabapentin in painful DSPN because of this relatively large NNT and publication bias against unpublished negative trials. An extra advantage of gabapentin is that it makes sleep better.

Pregabalin

Pregabalin has a 6-fold higher binding affinity than gabapentin, making it a more selective a2-d ligand. Pregabalin was effective in four clinical investigations, all of which reported that it reduced pain by 11% to 13% on an 11-point Likert scale. However, the effect magnitude was small when compared to a placebo. The fourth research showed a significant dose-dependent decrease in Likert pain scores (24%–50%) compared to a placebo.

According to these trials, the NNT for a 50% pain reduction at 600 mg/d was 4. Significant improvements were seen in QOL measures, social functioning, mental health, physical pain, vigor, and sleep interference [18].

Blockers of sodium channels (lancosamide, carbamazepine, and oxcarbazepine)

Voltage-gated sodium channels largely determine neuronal excitability and signaling. The lesion site and the dorsal root ganglion cell bodies experience hyperexcitability and spontaneous firing following nerve damage. At least in part, the buildup of sodium channels at the injury site causes this hyperexcitability. For "lightning" pain caused by such spontaneous neuronal activity, carbamazepine and oxcarbazepine work best. Carbamazepine has been used extensively to treat neuropathic pain; however, because of the scant data, it is not advised for painful DN. Oxcarbazepine, its successor medication, and other sodium-channel blockers such as lamotrigine, valproate, mexiletine, and topiramate have not been approved for treating painful DN due to their limited effectiveness [19].

PAINFUL DIABETIC NEUROPATHY:

NONPHARMACOLOGICAL TREATMENT

Nonpharmacologic therapeutic alternatives should always be taken into consideration because there isn't an entirely satisfactory pharmacotherapy for painful DN. A recent systematic review assessed the data from comprehensive clinical trials and meta-analyses of complementary and alternative medicines for treating neuralgia and neuropathic pain. Treatments for complementary and alternative medicine that were discovered to have data include acupuncture, electrostimulation, herbal medicine, magnets, nutritional supplements, visualization, and spiritual healing. According to the findings, the majority of complementary and alternative medicine methods do not have enough evidence to be considered effective in treating neuropathic pain. Regarding electrostimulation (III/C), carnitine, magnets, and cannabis extract, the evidence is positive and merits more research [20].

CONCLUSION:

Diabetic neuropathy is a significant problem. The complex nature of pathogenesis necessitates careful treatment if one is to succeed. Even when used together, pregabalin and duloxetine, two medications that have been approved for neuropathic pain, have not provided total relief. Understanding pathogenic pathways in greater detail is crucial, especially the distinctions between the origins of central and peripheral pain. Even with the available pharmaceutical options, there is still a great demand for more focused and efficient treatments. Research into the pathophysiology of DN (Diabetic Neuropathy) is still ongoing, which gives the potential for the creation of novel therapies that may modify the course of the disease and enhance the lives of those impacted.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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