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# Literature Review: Diagnosis, Classification, Clinical Manifestations, Pathophysiology, and Treatment of Diabetic Neuropathy

Susanna Halim[1*], David Rajagukguk[2]

[1] Department of Master of Dental Science, Prima Indonesia University, Medan, Indonesia
[2] Students of Master of Dentistry Science, Prima Indonesia University, Medan, Indonesia

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Corresponding Author:
Susanna Halim
sussanahalim@unprimdn.ac.id

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**Abstract:** Diabetic neuropathy (DN) is a very common and debilitating complication of Diabetes Mellitus disease that greatly affects quality of life. The literature review aims to critically summarize recent findings that examine the development of understanding of DN, from a simple complication to a complex and multifaceted disease. This study used a literature review based on articles obtained from Google Scholar and PubMed databases. All articles discussed Diabetic Neuropathy from the perspective of pathophysiology, clinical classification, diagnosis, and management. The analysis was conducted using a descriptive-qualitative approach, reported pharmacological and non-pharmacological therapy options. Based on the search, all articles that met the inclusion criteria were narrative reviews, consensus studies, and case reports. These articles outlined the complexities of Diabetic Neuropathy diagnosis, evolving pathophysiological theories, and therapeutic approaches. A multidisciplinary diagnostic approach that includes a thorough history, neurological clinical examination, and ancillary tests (e.g., HbA1c, MRI) is essential. Management involves pharmacological therapy (e.g., tricyclic antidepressants, gabapentinoid), non-pharmacological therapy (e.g., cognitive behavioral therapy, nerve blocks), and comprehensive oral health management. Interdisciplinary collaboration between clinicians, neurologists, and endocrinologists is essential for optimal patient care. Further research is needed to understand the detailed mechanisms and develop more effective therapies.

**Keywords:** Diabetes Mellitus; Neuropathy; Painful Diabetic Neuropathy.

## Introduction

Diabetes Mellitus (DM) has become one of the greatest global health challenges of the 21st century, with its prevalence continuing to increase exponentially worldwide (Santosh and Janadrdhan, 2024). As a chronic metabolic disease, DM is characterized by persistently high blood glucose levels, which over time can cause serious damage to various organ systems and body tissues. Long-term complications of DM are diverse, ranging from retinopathy, nephropathy, cardiovascular disease, to the most common, damage to the nervous system, known as diabetic neuropathy (Santosh and Janadrdhan, 2024).

The increasing global prevalence of diabetes mellitus (DM) is directly correlated with the increasing health burden associated with diabetic neuropathy. This significantly underscores the urgency for all healthcare practitioners to have a comprehensive understanding of the spectrum of these complications. Increasing numbers of patients will seek care for symptoms that may stem from diabetic neuropathy, and therefore, appropriate identification and management are increasingly vital.

Diabetic neuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in individuals with diabetes, after excluding other possible causes (Huizinga and Peltier, 2007). One of the most impactful phenotypes is painful diabetic neuropathy (PDN), which occurs in over 16% of diabetic patients (Price et al., 2022). Despite its high prevalence, pain associated with PDN is often not adequately discussed between patients and physicians, resulting in pain often going untreated (Price et al., 2022). The high

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prevalence of diabetic neuropathy (up to 50%) and PDN (>16%), coupled with the fact that pain is often untreated, indicates significant gaps in patient care and communication. This situation emphasizes the importance of identifying early symptoms of undiagnosed neuropathy or poorly controlled diabetes.

Diabetic neuropathy is one of the most common and devastating chronic complications of diabetes, with a global prevalence increasing in tandem with the worldwide diabetes epidemic (Zhu et al., 2024). Affecting various components of the nervous system, from the peripheral nerves to the cardiovascular, gastrointestinal, and genitourinary systems, DN is estimated to impact up to 50% of individuals with diabetes (Zhu et al., 2024). This prevalence is even higher in patients with type 2 diabetes (T2DM) compared to type 1 diabetes (T1DM), particularly in those with longer disease duration and a higher burden of comorbidities (Smith et al., 2022). For example, studies have found that while 10–15% of newly diagnosed T2DM patients may have diabetic peripheral neuropathy (DPN), this figure can jump to over 50% in those who have had diabetes for more than a decade (Zhu et al., 2024).

The economic and psychosocial consequences of DN are substantial. The total annual cost of treating painful DN and its associated complications, such as foot ulcers and limb amputations, is estimated to be in the billions of dollars in the United States alone, with up to 27% of direct medical costs for diabetes attributable to this condition (Zhu et al., 2024). In addition to the financial burden, DN significantly reduces patients' quality of life, leading to serious health problems, including a higher risk of falls, limb loss, and increased cardiovascular and all-cause mortality (Smith et al., 2022). The consequences of untreated DN go far beyond discomfort, becoming a major risk factor for debilitating complications (Zhu et al., 2024). This literature review aims to comprehensively examine the relationship between diabetic neuropathy and its impact on patients. It will include an in-depth discussion of pathophysiology, clinical manifestations, diagnostic challenges, and management strategies, with particular emphasis on the crucial role of the clinician within the multidisciplinary care team. It is hoped that this report will serve as a fundamental resource for clinicians, researchers, and other healthcare professionals. The ultimate goal is to foster a deeper understanding of diabetic neuropathy as a complex and heterogeneous disease, thereby bridging the gap between basic knowledge and the rapidly evolving clinical and research paradigms.

## Method

This study used a literature review based on articles obtained from Google Scholar and PubMed databases. All articles discussed Diabetic Neuropathy from the perspective of pathophysiology, clinical classification, diagnosis, and management. The analysis was conducted using a descriptive-qualitative approach, reported pharmacological and non-pharmacological therapy options.

*Result*

Based on the search, all articles meeting the inclusion criteria were narrative reviews, consensus studies, and case reports. These articles outlined the complexities of diabetic neuropathy diagnosis, evolving pathophysiological theories, and therapeutic approaches

**Table 1**. Summary of Reviewed Studies

| Reference | Focus | Key Findings |
|---|---|---|
| Alare, K., Alare, T. and Odunitan, T. (2024) | Neurological and Molecular Mechanisms of ND | NADPH (nicotinamide adenine dinucleotide phosphate) depletion has been identified as a major driver of neuronal demyelination. This deficiency is caused by increased consumption via the polyol pathway and decreased production via the hexose monophosphate shunt. |
| Bönhof, GJ et al. (2019) | Emerging Biomarkers, Diagnostic Tools, and Treatments | The development of new diagnostic tools and the identification of systemic biomarkers such as myeloperoxidase (MPO) and superoxide dismutase (SOD3) allow for earlier diagnosis. The use of multi-omics and bioinformatics technologies has the potential to lead to more personalized treatments. |
| Bodman, M.A., Dreyer, M.A. and Varacallo, M.A. (2024) | Diabetic Peripheral Neuropathy | Oxidative stress and inflammation are major etiologic factors in the initiation and progression of diabetic neuropathy. Tight glycemic control can reduce the risk of neuropathy by up to 78% in patients with early-diagnosed type 1 diabetes, but the effect is much less pronounced in long-term type 2 diabetes. |
| Dillon, B.R., Ang, L. and Pop-Busui, R. (2024) | Diagnosis and Treatment of Diabetic Neuropathy | This review demonstrates that diabetic neuropathy is a complex and multifaceted condition. The cornerstone of management is strict glycemic control. The greatest challenge is the lack of effective therapies to reverse nerve damage. |

| Reference | Focus | Key Findings |
|---|---|---|
| Harati, Y. (2007) | Unanswered Questions about Diabetic Neuropathy | The lack of suitable animal models to replicate the acute and chronic events of diabetic neuropathy is a significant obstacle in preclinical research and drug development. |
| Huizinga, M.M. and Peltier, A. (2007) | Diabetic Neuropathy Pain Management | Duloxetine and venlafaxine (SNRIs), as well as gabapentin and pregabalin (gabapentinoids), are common choices for managing neuropathic pain. |
| Kang, Y. et al. (2025) | Efficacy of Moxibustion as an Adjunct Therapy | Moxibustion and acupuncture show clinical evidence supporting their efficacy in reducing pain and improving nerve function, but standardization of clinical protocols is needed. |
| Khan, S. et al. (2025) | Diabetic Peripheral Neuropathy: Controversy and Progress | Antioxidant therapy with alpha-lipoic acid (ALA) shows promise in reducing oxidative stress and improving neuronal function. There is a shift from a universal approach to a "phenotype-based treatment model." |
| Lee, J.-E. and Won, JC (2025) | Clinical Phenotype of Diabetic Peripheral Neuropathy | DPN can be categorized into painful and painless forms. Quantitative Sensory Testing (QST) is an important tool for identifying specific sensory phenotypes that can differentiate between painful and painless DPN. |
| Mallick-Searle, T. and Adler, J. A. (2024) | Diabetic Peripheral Neuropathy Treatment Guidelines Update | The FDA has approved three oral medications (duloxetine, pregabalin, tapentadol extended-release) and one topical agent (capsaicin topical system 8%) for the treatment of painful DPN. |
| Price, R. et al. (2022) | Oral and Topical Treatments for Diabetic Polyneuropathy | Painful diabetic neuropathy (PDN) occurs in more than 16% of patients with diabetes. There is evidence of efficacy for pharmacological therapies such as |
| Quiroz-Aldave, J. et al. (2023) | Diabetic Neuropathy: Past, Present, and Future | Diabetic neuropathy is classified into several types, including peripheral, autonomic, proximal, and mononeuropathy. Each type has specific symptoms. |
| Santosh, KN and Janadrdhan, MS (2024) | Diabetic Neuropathy - An Overview | Peripheral neuropathy is the most common type of diabetic neuropathy, with symptoms such as numbness, tingling, and burning sensations. Focal neuropathy, which damages a single nerve, can cause symptoms such as difficulty focusing and paralysis on one side of the face. |
| Sima, AAF and Kamiya, H. (2006) | Differences between DN in Type 1 and Type 2 DM | The pathophysiology of DN differs significantly between type 1 and type 2 diabetes. Patients with type 1 DM sometimes show better and faster improvement in clinical symptoms. |
| Shinoda, M. et al. (2021) | Orofacial Neuropathic Pain | Research is needed to understand the detailed mechanisms of persistent orofacial pain after trigeminal nerve injury and the role of non-neuronal cells. Pharmacological therapies such as SNRIs and gabapentinoids work by influencing neurotransmitter release. |
| Yang, Y. et al. (2025) | Explores the complex mechanisms underlying DN and highlights recent advances in diagnostic and therapeutic strategies. | Comprehensive overview of current understanding and future directions in DN research and management. |
| Zhou, T. et al. (2022) | Diabetic Corneal Neuropathy: Mechanisms and Therapeutic Strategies | The main pathogenic mechanisms identified in nerve damage are Advanced Glycation End-Products (AGEs), the Polyol Pathway, and Protein Kinase C (PKC) activation. Accumulation of AGEs and sorbitol causes nerve damage, while PKC activation affects nerve conduction. |
| Zhu, J. et al. (2024) | Pathogenetic Mechanisms and Treatment of Diabetic Peripheral Neuropathy | Diabetic neuropathy (DN) is estimated to affect up to 50% of individuals with diabetes. The consequences of untreated DN go far beyond discomfort, becoming a major risk factor for debilitating complications. |

*Discussion*

*Diagnosis*

*Limitations of Conventional Diagnostics*

Historically, the diagnosis of DN has relied on traditional clinical measures such as physical examination and nerve conduction studies (NCS) (Smith et al., 2022). Although NCS is considered the gold standard for assessing large-fiber neuropathy, it is not sensitive enough to detect early nerve damage that often occurs in small-fiber neuropathy, which is often the first to be affected (Lee and Won, 2025). Furthermore, many of these conventional assessments are subjective and may not accurately reflect the patient's underlying neurological health (Bönhof et al., 2019). These

limitations have prompted a significant push to develop more objective and sensitive diagnostic tools.

*Non-Invasive and Minimally Invasive Diagnostic Tools*

Recent years have seen the publication of validation and application of new tools that allow earlier detection and more precise characterization of DN. Corneal Confocal Microscopy (CCM) is a non-invasive imaging technique that allows rapid, high-resolution visualization of the sub-basal nerve plexus in the cornea. (Yang et al., 2025). Studies since 2020 have shown that CCM is a reliable and reproducible tool for detecting early nerve changes in prediabetes and diabetes, with a strong correlation between CCM parameters (such as corneal nerve fiber density) and traditional DPN measurements (Yang et al., 2025).

Quantitative Sensory Testing (QST) techniques are important tools for phenotypic characterization (Lee and Won, 2025). These techniques include thermal testing to evaluate the function of small fibers (Aδ and C fibers) and mechanical/vibration testing to assess the integrity of large fibers (Aβ fibers) (Lee and Won, 2025). QST can identify specific sensory phenotypes, such as mechanical allodynia and hyperalgesia, which can differentiate between painful and non-painful DPN (Lee and Won, 2025).

Minimally invasive procedures such as skin biopsy also provide a pathological diagnosis of DN by allowing direct visualization and analysis of intraepidermal nerve fiber density (IENFD). (Yang et al., 2025). Although useful, it is important to note that IENFD may not have a strong association with the presence or severity of neuropathic pain, thus indicating the need to identify additional pathological biomarkers (Røikjer et al., 2024).

*Diagnosis with Biomarkers and Precision Treatment*

The diagnostic field is undergoing a paradigm shift with a focus on identifying systemic biomarkers for screening and early diagnosis (Bönhof et al., 2019). New biomarkers related to oxidative stress and inflammation, such as myeloperoxidase (MPO) and superoxide dismutase (SOD 3), are being investigated. (Bönhof et al., 2019). A specific example of this approach is the finding that lower adiponectin levels and higher leptin levels were significantly associated with an increased risk of DN, suggesting that these adipokines may serve as potential biomarkers for identifying at-risk individuals (Basu, Prasoon and Susuki, 2025).

Furthermore, the integration of multi-omics technologies (proteomics, metabolomics) and bioinformatics analyses promises a more comprehensive understanding of the molecular alterations associated with DN (Yang et al., 2025). This approach could lead to the identification of novel diagnostic and therapeutic targets, ultimately paving the way for more personalized treatment approaches (Bönhof et al., 2019).

*Classification of Diabetic Neuropathy*

Diabetic neuropathy is a heterogeneous disorder encompassing a wide variety of clinical syndromes (Dillon, Ang and Pop-Busui, 2024). In general, diabetic neuropathy can be classified into several main types based on the pattern of nerve damage. Peripheral neuropathy (Distal Symmetric Polyneuropathy/DPN) is the most common type of diabetic neuropathy. (Santosh and Janadrdhan, 2024)Commonly reported symptoms include numbness (loss of sensation), tingling or burning sensations, sharp or cramping pain, muscle weakness, and extreme sensitivity to touch, where even the weight of a blanket can be painful (Quiroz-Aldave et al., 2023; Santosh and Janadrdhan, 2024). Painful Diabetic Neuropathy (PDN), which is a painful form of DPN, occurs in more than 16% of diabetic patients (Price et al., 2022). Autonomic neuropathy is a type of neuropathy that affects the autonomic nervous system, which controls involuntary bodily functions such as blood pressure, heart rate, sweating, pupils, bladder, digestive system, and sexual organs (Santosh and Janadrdhan, 2024).

**Table 2.** Classification of Diabetic Neuropathy.

| Classification of Diabetic Neuropathy | Symptom | Reference |
|---|---|---|
| Peripheral Neuropathy (Distal Symmetric Polyneuropathy/DPN) | Numbness, tingling, burning sensation, sharp pain, muscle weakness, extreme sensitivity to touch. | (Quiroz-Aldave *et al.*, 2023; Santosh and Janadrdhan, 2024) |
| | Painful Diabetic Neuropathy is often a form of Peripheral Neuropathy. | (Price *et al.*, 2022) |
| Autonomic Neuropathy | Hypoglycemia insensitivity, orthostatic hypotension (dizziness when standing), rapid heartbeat, bladder/bowel problems, gastroparesis, difficulty swallowing, changes in eye adaptation to light, sexual dysfunction. | (Quiroz-Aldave *et al.*, 2023; Santosh and Janadrdhan, 2024) |
| Proximal Neuropathy (Diabetic Polyradiculopathy) | Pain or weakness in the thigh, hip, buttocks, or leg. It can also affect the chest or abdomen, usually on one side of the body. | (Santosh and Janadrdhan, 2024) |

| | | |
|---|---|---|
| Mononeuropathy (Focal Neuropathy) | Damage to a specific nerve can occur in the face, trunk, arm, or leg. Symptoms may include difficulty focusing/double vision or paralysis on one side of the face. | (Santosh and Janadrdhan, 2024) |

Symptoms can include hypoglycemia insensitivity (lack of warning signs of low blood sugar), orthostatic hypotension (a drop in blood pressure upon standing, causing dizziness or fainting), rapid heartbeat at rest, bladder or bowel problems, gastroparesis (slow stomach emptying), difficulty swallowing, changes in the eye's adaptation to light, and sexual dysfunction (Quiroz-Aldave et al., 2023; Santosh and Janadrdhan, 2024). Proximal neuropathy (diabetic polyradiculopathy) is a type of neuropathy that often affects nerves in the thigh, hip, buttocks, or leg area, and can also affect the chest or abdomen area and is usually limited to one side of the body and rarely spreads to the other side (Santosh and Janadrdhan, 2024). Mononeuropathy (Focal Neuropathy) is damage to one specific nerve, which can occur in the face, trunk, arms, or legs (Santosh and Janadrdhan, 2024).

This focal neuropathy is often very painful and can occur suddenly (Santosh and Janadrdhan, 2024). When it affects nerves in the head or face, symptoms can include difficulty focusing or double vision, as well as paralysis on one side of the face (Santosh and Janadrdhan, 2024). This classification of diabetic neuropathy explicitly indicates that nerve damage is not limited to the lower extremities, as is often assumed, but also includes the cranial nerves.

*Signs and symptoms*

The clinical sign of DPN can be broadly categorized into painful and painless forms, underscoring the importance of phenotypic characterization for targeted treatment (Lee and Won, 2025). Patients may experience a variety of subjective sensory symptoms, including tingling, burning, stabbing pain, cramping, and increased sensitivity to touch (allodynia) (Bodman, Dreyer and Varacallo, 2024). Motor symptoms, such as muscle weakness, atrophy, and gait disturbances, can also significantly impact daily activities (Smith et al., 2022).

The key difference in DPN is whether the damage primarily affects small or large nerve fibers, as each presents with a unique set of symptoms and signs. The following table summarizes this important information, providing a valuable comparison for clinical assessment. Further studies are needed to identify specific risk factors and biomarkers to enable early identification and preventive interventions (Borgnakke and Poudel, 2021)

**Table 3.** Comparison of Clinical Features in Small and Large Fiber Neuropathy (Lee and Won, 2025).

| Neurons Involved | Subjective Symptoms | Objective Signs |
|---|---|---|
| Small Fiber Neuropathy | Hypersensitivity to pressure or touch; tingling, burning, freezing, stabbing, pain, and electric shock sensations; chronic or transient sensations (usually precede large fiber neuropathy) | Minimal sensory loss or motor deficit; slightly decreased tendon reflexes; abnormal autonomic nervous system function (e.g., decreased sweating, cold feet) |
| Large Fiber Neuropathy | Sensation of "walking on cotton"; floor feels "strange"; inability to perform fine motor tasks such as buttoning clothes or turning pages; pain | Sensory loss and motor deficits; decreased tendon reflexes; impaired perception of light touch and joint position; sensory ataxia; abnormal nerve conduction velocity findings |

*Current Theories of DN Pathophysiological*

*Multifactorial Cascade Initiated by Hyperglycemia*

The main pathogenic mechanisms identified in nerve damage initiated by hyperglycemia in diabetes include:

1. Advanced Glycation End -Products (AGEs):

AGEs are reactive metabolites formed through non-enzymatic glycation reactions between proteins or lipids and sugar molecules (Zhou et al., 2022). Accumulation of AGEs in peripheral nerves has been reported to cause segmental demyelination (damage to the nerve myelin sheath), impaired axonal transport, and decreased nerve regenerative activity (Zhou et al., 2022). AGEs can also cause cross-linking of collagen fibrils and alter the structure and function of the corneal epithelium, stroma, and basement membrane, which is relevant for trigeminal neuropathy affecting the eye (Zhou et al., 2022). The interaction between AGEs and their receptor (RAGE) triggers oxidative stress and inflammatory reactions, which contribute to nerve cell damage (Kang et al., 2022).

2. Polyol Pathway

Under chronic hyperglycemia, excess glucose in nerve cells is diverted to the polyol pathway when the glycolysis cycle becomes saturated (Zhou et al., 2022). In this pathway, glucose is converted to sorbitol and then fructose by the intracellular enzymes aldose reductase and sorbitol dehydrogenase (Zhou et al., 2022). The accumulation of sorbitol and fructose within nerve cells, due to the impermeability of the nerve cell membrane to

them, increases the osmotic pressure of nerve cells, causing cell swelling and damage (Zhou et al., 2022). In addition, this reduction process consumes the essential cofactor nicotinamide adenine dinucleotide phosphate (NADPH), leading to decreased reduced glutathione production, tissue antioxidant capacity, and free radical scavenging ability, thus triggering tissue damage due to oxidative stress (Zhou et al., 2022). Decreased levels of myoinositol, a sugar alcohol required for normal nerve conduction velocity, also contribute to nerve dysfunction by reducing Na+/K+ ATPase activity, which disrupts electrolyte balance and damages nerve fiber structure (Zhou et al., 2022).

3. Protein Kinase C (PKC) Activation

Excess glucose is metabolized to diacylglycerol (DAG), which activates Protein Kinase C (PKC). This activation alters gene expression and cellular function, contributing to microvascular and nerve damage (Bodman, Dreyer and Varacallo, 2024). Increased intracellular glucose levels in diabetes play a role in the synthesis of DAG, a PKC activator (Zhou et al., 2022). PKC activation has been shown to inhibit $Na^+/K^+$-ATPase activity, which in turn affects nerve conduction and nerve regeneration (Zhou et al., 2022). Studies have shown that the use of PKC inhibitors can improve microvascular blood flow and nerve conduction, thereby alleviating the symptoms of diabetic neuropathy (Zhou et al., 2022).

4. Hexosamine Pathway

Excess glucose is also diverted into the hexosamine pathway. This pathway produces uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), which modifies various proteins, affecting processes such as insulin signaling and transcription, thus contributing to neurodegeneration.

The intricate interactions and cascading effects of these molecular pathways demonstrate that diabetic neuropathy is a complex and multifaceted process. A deeper understanding of these pathophysiological pathways (AGEs, the Polyol Pathway, and PKC Activation) not only explains the root causes of nerve damage in diabetic neuropathy but also fundamentally underscores why tight glycemic control is the most important foundation of management. This is because good glycemic control directly addresses the underlying causes of this pathological process. For clinicians, this means that while they manage symptoms, they must also act as advocates for tight glycemic control. Educating patients about the systemic impact of uncontrolled blood sugar. This knowledge also paves the way for future collaborative research on targeted therapies that may complement traditional pain management.

*The Central Role of Oxidative Stress and Inflammation*

Oxidative stress and inflammation play a crucial role as primary etiologic factors in the initiation and progression of DN (Bodman, Dreyer and Varacallo, 2024). All of the metabolic pathways described above lead to the formation of reactive oxygen species (ROS), which overcome the body's antioxidant defenses and cause cell damage (Bodman, Dreyer and Varacallo, 2024). Recent findings highlight the role of systemic inflammation and immune-mediated processes in shaping the DN phenotype. Macrophages infiltrating peripheral nerve cells trigger the production of cytokines and chemokines, which trigger nerve fiber damage and contribute to pain and other symptoms (Bodman, Dreyer and Varacallo, 2024).

*Causal Relationship Between NADPH Depletion and Demyelination*

Beyond the general understanding of metabolic dysfunction, more specific pathophysiological mechanisms are emerging from recent research, centering on the depletion of the essential cofactor, nicotinamide adenine dinucleotide phosphate (NADPH) (Alare, Alare and Odunitan, 2024). This deficiency is not simply a side effect of hyperglycemia, but has been identified as a major driver of neuronal demyelination.

This process begins with the activation of the polyol pathway, which consumes significant amounts of NADPH (Khan et al., 2025). At the same time, a second mechanism comes into play: excess glucose directly inhibits the hexose monophosphate shunt, which is the main generator of NADPH in the body (Alare, Alare and Odunitan, 2024). This combination of increased consumption and decreased production creates a state of severe NADPH deficiency and is very detrimental to neuronal health (Alare, Alare and Odunitan, 2024). The consequences of this deficiency are directly related to the structural integrity of nerves. The de novo synthesis of sphingomyelin, a crucial lipid component of the protective myelin sheath, is completely dependent on the availability of NADPH. (Alare, Alare and Odunitan, 2024). When NADPH is depleted, sphingomyelin production is inhibited, which directly disrupts the remyelination process and causes massive demyelination of nerve cells (Alare, Alare and Odunitan, 2024). This provides a precise and actionable explanation for the neuronal damage seen in DN, going beyond the general concept of “metabolic injury” to specific molecular mechanisms. These insights suggest a clear therapeutic pathway: the golden standard of care could involve combined therapy with aldose reductase inhibitors to control the polyol pathway and supplementation with NADPH-generating compounds

such as citrate to support myelination. (Alare, Alare and Odunitan, 2024). Such a multi-pronged strategy could address several downstream effects of hyperglycemia simultaneously, including osmotic stress, oxidative stress, and demyelination.

*Pathophysiological Differences in DN in Type 1 DM and Type 2 DM*

The pathophysiology of DN is not a uniform process among all patients; instead, it is thought to differ significantly between diabetes subtypes, a critical nuance with important implications for treatment and prognosis (Sima and Kamiya, 2006). While hyperglycemia is a common determinant, research suggests that the specific mechanisms and long-term structural damage vary.

Studies have identified distinct molecular and morphometric abnormalities in animal models of DN (Sima and Kamiya, 2006). For example, the type 1 diabetes model exhibits more severe atrophy and axon loss, as well as unique paranodal degenerative changes not observed in the type 2 model. (Sima and Kamiya, 2006). These physiological differences may explain why patients with T1DM sometimes experience greater and more rapid improvement in clinical symptoms compared to those with T2DM (Sima and Kamiya, 2006).

This divergence in disease pathology challenges the traditional "one-size-fits-all" approach to DN research and clinical trial design. This reinforces the rapidly evolving field of personalized medicine, suggesting that future therapeutic strategies must be tailored not only to patient symptoms but also to specific diabetes subtypes and underlying pathology (Sima and Kamiya, 2006).

*Treatment*

Pain management in patients with diabetic neuropathy often requires a multidisciplinary approach that combines pharmacological, non-pharmacological therapies, and multidisiplinary approach.

*Fundamental and Symptomatic Management*

The cornerstone of DN management remains prevention or delay of onset through tight glycemic control (Dillon, Ang and Pop-Busui, 2024). However, crucial differences in the efficacy of these approaches are evident in recent studies. While tight glycemic control can reduce the risk of DN by up to 78% in individuals with early-diagnosed T1DM, the effect is much lower in long-term T2DM, where the risk is reduced by only 5-9% (Bodman, Dreyer and Varacallo, 2024). These crucial differences in therapeutic response highlight the need to set realistic expectations for patients and tailor treatment plans based on the type and duration of their diabetes. In addition to glycemic management, lifestyle modifications such as a healthy diet, regular exercise, and weight loss are universally recommended as core interventions (Bodman, Dreyer and Varacallo, 2024).

A critical paradigm shift is underway in the management of DN, moving from a universal symptomatic approach toward a "phenotype-based treatment model of DPN" (Khan et al., 2025). The recognition of DN as a heterogeneous condition with distinct painful, painless, small-fiber, and large-fiber phenotypes, coupled with the development of advanced diagnostic tools such as QST and biomarkers, is enabling a more precise and individualized treatment approach (Bönhof et al., 2019). This shift in clinical approach is driven by the understanding that a single therapy is unlikely to be effective for all forms of DN. Instead, clinicians can leverage new diagnostic insights to tailor treatment plans that specifically target a patient's specific sensory phenotype and underlying molecular mechanisms. This represents a major advancement that promises to optimize patient care, improve outcomes, and alleviate the substantial burden of this disease. (Lee and Won, 2025).

*Pharmacological Management for Pain Management*

For painful DPN, pharmacological interventions primarily aim to relieve symptoms. The following table summarizes efficacy data from recent clinical trials, providing a quantitative, evidence-based summary of the most common treatment options.

**Table 4.** Efficacy of Pharmacological Treatment of Painful Diabetic Neuropathy (Price et al., 2022)

| Drug Class | Specific Agent | Std. Mean Diff. (SMD) | 95% Conf. Int (CI) | Effect Size | Trust Level |
|---|---|---|---|---|---|
| Gabapentinoid | Gabapentin | 0.53 | 0.22–0.84 | Moderate | Moderate |
| | Pregabalin | 0.29 | 0.13–0.45 | Small | Low |
| | Class Effects | 0.44 | 0.25–0.63 | Small | Moderate |
| SNRI | Duloxetine | 0.50 | 0.26–0.74 | Moderate | Moderate |
| | Desvenlafaxine | 0.25 | 0.07–0.43 | Small | Low |
| | Class Effects | 0.47 | 0.34–0.60 | Small | Moderate |
| Tricyclic | Amitriptyline | 0.95 | 0.15–1.8 | Big | Low |
| Antidepressants | Class Effects | 0.95 | 0.15–1.8 | Big | Low |
| Sodium Channel | Valproic acid | 0.86 | 0.38–1.33 | Big | Low |
| Blockers | Class Effects | 0.56 | 0.25–0.87 | Moderate | Moderate |

In addition, the United States Food and Drug Administration (FDA) has approved three oral medications—duloxetine, pregabalin, and extended-release tapentadol—and one topical agent, capsaicin topical system 8%, for the treatment of painful DPN (Mallick-Searle and Adler, 2024).

Various medications are available to help manage neuropathic pain, although response to oral or topical treatments for PDN is often limited and discontinuation rates are high. (Argoff, 2022)

*First Line Drugs:*

1. Tricyclic antidepressants (TCAs): Such as amitriptyline or nortriptyline, are often recommended to reduce neuropathic pain (Price et al., 2022). Nortriptyline is often chosen because it has fewer sedative and anticholinergic side effects (Veerapaneni et al., 2024). TCAs work by blocking the reuptake of norepinephrine and serotonin, enhancing the pain-inhibiting system (Shinoda et al., 2021).
2. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): Duloxetine and venlafaxine are effective options (Huizinga and Peltier, 2007). Duloxetine has the strongest evidence for neuropathic pain among SNRIs. (Veerapaneni et al., 2024). SNRIs also work by blocking the reuptake of norepinephrine and serotonin (Shinoda et al., 2021).
3. Gabapentinoids: Gabapentin and pregabalin are commonly used options for neuropathic pain (Huizinga and Peltier, 2007). These drugs work by inhibiting the release of excitatory neurotransmitters (Shinoda et al., 2021). Mirogabalin is a newer gabapentinoid that has been approved for peripheral neuropathic pain (Shinoda et al., 2021). Sodium Channel Blockers: Valproic acid may be effective (Price et al., 2022). For classic trigeminal neuralgia, carbamazepine (Level A) or oxcarbazepine (Level B) are first-line medications (Pantazopoulos et al., 2025).

*Second Line and Additional Drugs:*

1. Topical: Topical lidocaine or capsaicin can be used as adjunctive therapy to reduce pain (Veerapaneni et al., 2024). Topical lidocaine can desensitize the painful area (Shinoda et al., 2021). Capsaicin can reduce pain by depleting Substance P in primary afferent C-fibers (Shinoda et al., 2021).
2. Opioids: Opioids and opioid combinations may be an alternative if other strategies fail, although they should be used with great caution due to the risk of abuse and mortality (Price et al., 2022).

*Latest Therapy Management*

The field is actively moving towards innovative pharmacological and non-pharmacological approaches that target the underlying pathophysiology rather than simply managing symptoms (Yang et al., 2025).

1. Pharmacological and Molecular Targets:

Studies on alpha-lipoic acid (ALA) as a promising first-line antioxidant therapy that can reduce oxidative stress and improve nerve function (Khan et al., 2025). New pharmacological agents, including sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have shown promising neuroprotective effects (Yang et al., 2025). Future research is exploring neuroprotective agents, gene and stem cell therapy, and targeted interventions against inflammatory pathways (such as TNF-α and IL-6) and the nuclear factor kappa B (NF-κB) pathway (Yang et al., 2025).

2. Non-Pharmacological:

Neuromodulation or 10 kHz high-frequency spinal cord stimulation (SCS) has shown promising results for patients with PDN refractory to conventional treatments, with high response rates (Argoff, 2022). Since 2020, spinal cord stimulation (SCS) devices have received FDA approval for painful DPN, offering a promising and novel option for patients who do not respond to traditional therapies (Mallick-Searle and Adler, 2024).

Studies of alternative therapies such as acupuncture and moxibustion have clinical evidence supporting their efficacy in reducing pain and improving nerve function. However, significant research gaps remain, including the lack of standardized clinical protocols for these treatments, which hinders their wider adoption and optimization (Kang et al., 2025). More high-quality randomized controlled trials (RCTAs) evaluating the efficacy of specific treatments for neuropathic pain are needed This is essential for developing more holistic management strategies that consider the physical, affective, and social aspects of chronic pain (Borgnakke and Poudel, 2021).

3. Non-Pharmacological Therapy with a Multidisciplinary Approach

Cognitive Behavioral Therapy (CBT) is particularly beneficial when combined with medical and surgical therapies. CBT helps patients cope with pain and its impact on their lives, as well as manage psychosocial aspects such as anxiety and depression that often accompany chronic pain (Veerapaneni et al., 2024). A multidisciplinary team approach involving clinicians, neurologists, endocrinologists, and other healthcare professionals is essential for timely and accurate evaluation and treatment (Veerapaneni et al., 2024). Open communication and collaboration among team members are vital to ensure all aspects of the patient's health are considered in a comprehensive care plan.

## Conclusions

Diabetic neuropathy is a common and serious complication of diabetes that has evolved in understanding from a simple consequence of hyperglycemia into a complex disease involving multiple molecular and clinical mechanisms, particularly the role of NADPH depletion in nerve demyelination. Current advances emphasize phenotype-based diagnosis supported by non-invasive technologies and biomarker development, as well as a shift toward personalized therapeutic approaches. However, despite these developments, effective disease-modifying therapies that can halt or reverse nerve damage are still lacking, and major challenges remain in preclinical modeling and the standardization of emerging treatments.

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**Author Contributions**
Susanna Halim conceptualized the research idea, while David conducted the analysis, research process, and literature review. Both authors read and approved the final manuscript.

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**Conflicts of Interest**
The authors declare no conflicts of interest.

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