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europathic pain in diabetes mellitus: a systematic review of physiopathology, treatment and hypertension management

Dolor neuropático en la diabetes mellitus: una revisión sistemática de fisiopatología, tratamiento y manejo de la hipertensión

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Abstract

Diabetic neuropathic pain (DNP) is a debilitating complication of diabetes mellitus, arising from a complex interplay of metabolic, vascular, and neuroinflammatory mechanisms. This systematic review synthesizes current evidence on the pathophysiology and treatment of DNP, with a specific focus on its intersection with cardiovascular comorbidity, particularly hypertension. The analysis reveals that the pathogenesis of DNP shares critical pathways with hypertension, including endothelial dysfunction, chronic low-grade inflammation, oxidative stress, and sympathetic dysregulation. This shared biology suggests a synergistic relationship where each condition potentiates the other, complicating clinical management. While pharmacological therapies such as gabapentinoids and serotonin-norepinephrine reuptake inhibitors (SNRIs) form the mainstay of symptomatic treatment, their efficacy is often limited, and their side-effect profiles necessitate careful consideration in patients with concomitant hypertension. The review advocates for a paradigm shift towards integrated, phenotype-informed management. This approach combines personalized analgesic strategies with aggressive, multifactorial cardiovascular risk reduction, including stringent blood pressure control, lifestyle modification, and targeted supplementation. A holistic care model that concurrently addresses neuropathic pain and systemic vascular health is essential for improving long-term outcomes and quality of life in this high-risk patient population.

Keywords: Diabetic neuropathic pain, Hypertension, Pathophysiology, Integrated management, Cardiovascular risk, Phenotype-based treatment.

Resumen

El dolor neuropático diabético (DNP) es una complicación debilitante de la diabetes mellitus, derivada de una compleja interacción de mecanismos metabólicos, vasculares y neuroinflamatorios. Esta revisión sistemática sintetiza la evidencia actual sobre la fisiopatología y el tratamiento del DNP, con especial atención a su interacción con la comorbilidad cardiovascular, en particular la hipertensión. El análisis revela que la patogénesis del DNP comparte vías críticas con la hipertensión, incluyendo disfunción endotelial, inflamación crónica leve, estrés oxidativo y disregulación simpática. Esta biología compartida sugiere una relación sinérgica donde cada condición potencia a la otra, lo que complica el manejo clínico. Si bien las terapias farmacológicas como los gabapentinoides y los inhibidores de la recaptación de serotonina y noradrenalina (IRSN) constituyen la base del tratamiento sintomático, su eficacia suele ser limitada y sus perfiles de efectos secundarios requieren una cuidadosa consideración en pacientes con hipertensión concomitante. La revisión aboga por un cambio de paradigma hacia un manejo integrado basado en el fenotipo. Este enfoque combina estrategias analgésicas personalizadas con una reducción agresiva y multifactorial del riesgo cardiovascular, que incluye un control estricto de la presión arterial, la modificación del estilo de vida y la suplementación dirigida. Un modelo de atención holística que aborde simultáneamente el dolor neuropático y la salud vascular sistémica es esencial para mejorar los resultados a largo plazo y la calidad de vida en esta población de pacientes de alto riesgo.

Palabras clave: Dolor neuropático diabético, Hipertensión, Fisiopatología, Manejo integrado, Riesgo cardiovascular, Tratamiento basado en el fenotipo.

Diabetes mellitus represents a significant and growing global chronic metabolic disorder, characterized by persistent hyperglycemia resulting from defects in insulin secretion, action, or both¹. This condition imposes a substantial burden on public health systems, with its microvascular and macrovascular complications driving considerable morbidity and mortality. Among the most prevalent and debilitating of these complications is diabetic neuropathy, a heterogeneous group of nerve disorders that affects approximately half of all diabetic patients during their lifetime². A particularly challenging subset is painful diabetic neuropathy (PDN), which manifests as chronic neuropathic pain and severely impairs quality of life, sleep, and psychological well-being³.

The pathogenesis of diabetic neuropathic pain is multifactorial and complex, involving a confluence of metabolic, vascular, inflammatory, and neurobiological mechanisms. Chronic hyperglycemia initiates a cascade of detrimental processes, including increased polyol pathway flux, accumulation of advanced glycation end-products (AGEs), and activation of protein kinase C (PKC), all of which contribute to neuronal and microvascular damage⁴. Concurrently, oxidative stress and low-grade systemic inflammation exacerbate nerve injury. These pathophysiological pathways are not isolated to the peripheral nervous system; they share significant overlap with the mechanisms driving other diabetic complications, notably cardiovascular disease and hypertension⁵. For instance, endothelial dysfunction, a hallmark of both diabetic neuropathy and hypertension, results from similar metabolic insults and inflammatory mediators⁶. Furthermore, the dysregulation of ion channels (e.g., sodium and calcium channels) in nociceptive neurons, which underpins neuronal hyperexcitability in PDN, also plays a role in vascular smooth muscle tone regulation and blood pressure control⁷.

The clinical management of PDN remains a formidable challenge. Current first-line pharmacotherapies, such as gabapentinoids (pregabalin, gabapentin) and serotonin-norepinephrine reuptake inhibitors (duloxetine), primarily offer symptomatic relief and are often limited by side effects and variable efficacy⁸. A critical gap exists between the advanced understanding of molecular mechanisms and the translation into targeted, disease-modifying therapies. Moreover, the management of diabetic patients is frequently complicated by multimorbidity, where PDN coexists with conditions like hypertension. This coexistence is not merely coincidental but may be pathophysiologically linked through shared mechanisms such as autonomic dysfunction, chronic inflammation, and sympathetic overactivity⁹. The presence of hypertension can

potentially alter pain perception and response to analgesics, while some neuropathic pain medications may influence blood pressure, necessitating an integrated treatment approach¹⁰.

This systematic review aims to synthesize current evidence on the pathophysiology and treatment of diabetic neuropathic pain. It will critically appraise the molecular and cellular mechanisms underlying PDN, evaluate the efficacy and limitations of existing therapeutic interventions, and explore the rationale for a more personalized, phenotype-based management strategy. A particular focus will be placed on elucidating the interconnected pathophysiological pathways between PDN and systemic comorbidities, especially hypertension, to advocate for a holistic clinical approach that addresses the multifaceted nature of diabetes and its complications. By integrating insights from pain neurology and cardiovascular medicine, this review seeks to inform safer and more effective management strategies for patients navigating the dual burdens of chronic pain and cardiovascular risk.

Study Design and Reporting

This study was conducted as a systematic literature review to comprehensively analyze and synthesize contemporary evidence on the pathophysiology and management of diabetic neuropathic pain (DNP). The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency¹¹.

Search Strategy and Eligibility Criteria

A systematic and comprehensive literature search was executed across four major electronic databases: MEDLINE (via PubMed), EMBASE, SCOPUS, and Web of Science. The search was designed to capture studies published within the last decade to prioritize current evidence, with the final search conducted in October 2023. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to the core concepts of the review. The primary search string included terms such as: (“diabetic neuropathy” OR “painful diabetic polyneuropathy” OR “diabetic peripheral neuropathic pain”) AND (“pathophysiology” OR “mechanism”) AND (“treatment” OR “management” OR “therapy”) AND (“neuropathic pain” OR “chronic pain”). To explore the specific link with cardiovascular comorbidity, a secondary search strand included terms like (“hypertension” OR “cardiovascular risk” OR “blood pressure”) to identify relevant intersecting literature.

Inclusion criteria were defined to select studies that: (1) specifically investigated painful diabetic neuropathy or diabetic peripheral neuropathic pain in human subjects;

(2) elucidated pathophysiological mechanisms, diagnostic approaches, or therapeutic interventions (pharmacological or non-pharmacological); (3) were published in English in peer-reviewed journals. Exclusion criteria encompassed: (1) studies focusing exclusively on animal models without human data correlation; (2) articles on non-diabetic neuropathies; (3) conference abstracts, editorials, or narrative reviews without original data; (4) studies not available in full text.

Study Selection Process

The initial database searches yielded a combined total of 2,347 records. After automated and manual removal of duplicates, 1,815 unique titles and abstracts were screened for relevance by two independent reviewers. This screening phase led to the exclusion of 1,562 records that did not meet the inclusion criteria. The full texts of the remaining 253 articles were retrieved and assessed in detail for eligibility. Discrepancies between reviewers at any stage were resolved through discussion or consultation with a third senior reviewer. Following the full-text assessment, 71 studies were deemed to satisfy all criteria and were included in the final qualitative synthesis.

Data Extraction and Synthesis

Data from the included studies were extracted using a standardized, piloted form. Extracted information encompassed: study characteristics (author, year, design, sample size), population details (diabetes type, neuropathy characteristics), key pathophysiological findings (e.g., metabolic pathways, ion channel dysregulation, central sensitization), diagnostic methods, and details of interventions and outcomes (efficacy, safety, impact on quality of life). Special attention was paid to extracting any data pertaining to comorbid conditions, particularly hypertension or cardiovascular parameters, and their reported interaction with DNP. Given the anticipated heterogeneity in study designs, interventions, and outcome measures across the included literature—ranging from molecular studies to large clinical trials—a meta-analysis was not feasible. Therefore, a narrative synthesis approach was employed. The extracted data were thematically organized into coherent sections: pathophysiology (metabolic, vascular, inflammatory, neuronal mechanisms), diagnosis, and therapeutic management. Within the discussion of pathophysiology and treatment, a dedicated analytical thread was woven to interpret findings through the lens of systemic comorbidity, explicitly exploring the shared pathways and clinical considerations relevant to hypertension and cardiovascular risk management in this patient population.

Results

The systematic search and selection process, culminated in the inclusion of 71 studies for qualitative synthesis. The included literature encompassed a broad spectrum of research designs, providing a multi-faceted evidence base. This comprised 18 randomized controlled trials (RCTs), 22 cohort and cross-sectional observational studies, 15 mechanistic or pathophysiological laboratory studies with human tissue or biomarker data, 10 systematic reviews or meta-analyses, and 6 clinical practice guidelines or consensus statements. The publication dates ranged from 2013 to 2023, ensuring the incorporation of contemporary evidence and evolving therapeutic paradigms.

The first domain involves hyperglycemia-induced metabolic dysfunction. Persistent hyperglycemia was consistently identified as the primary instigator, activating several deleterious pathways. The polyol pathway leads to sorbitol accumulation and redox imbalance, while the formation of advanced glycation end-products (AGEs) causes direct protein cross-linking and receptor-mediated inflammation⁴. Concurrent activation of protein kinase C (PKC) and hexosamine pathways further contributes to vascular and neuronal injury. Notably, these metabolic disturbances are not confined to neural tissue; they are central to the development of diabetic microangiopathy and macroangiopathy, establishing a direct pathophysiological link to endothelial dysfunction and hypertension⁶.

The second domain centers on microvascular compromise and hypoxia. Studies highlighted that diabetic neuropathy is fundamentally a disease of the vasa nervorum. Endothelial dysfunction, basement membrane thickening, and pericyte loss lead to reduced endoneurial blood flow, creating a state of chronic nerve ischemia and hypoxia¹². This vascular pathology mirrors the microvascular rarefaction and dysfunction observed in other diabetic end-organs, including the heart and kidneys, and is exacerbated by concurrent hypertension, which further stresses the compromised microcirculation¹³.

The third domain pertains to neurobiological alterations. This includes ion channel dysregulation, where upregulation of voltage-gated sodium channels (e.g., Nav1.7, Nav1.3) and calcium channels (e.g., Cav3.2, $\alpha_2\delta$ -1 subunit) in nociceptors leads to neuronal hyperexcitability and spontaneous ectopic discharges^{7, 14}. Additionally, peripheral nerve injury triggers a cascade of central events: microglial activation in the spinal dorsal horn releases pro-inflammatory cytokines (e.g., TNF- α , IL-1 β), promoting central sensitization—a state of heightened responsiveness of central pain-signaling neurons^{15, 16}. This central sensitization manifests clinically as allodynia and hyperalgesia.

Table 1: Summary of Key Pathophysiological Domains in Diabetic Neuropathic Pain and Links to Hypertension

Pathophysiological Domain	Key Mechanisms in DNP	Shared Pathways/Links to Hypertension
Metabolic Dysfunction	Polyol pathway flux, AGE accumulation, PKC activation.	AGEs and PKC activation cause endothelial dysfunction, a primary driver of hypertension. Insulin resistance is common to both.
Microvascular Compromise	Endothelial dysfunction, reduced nerve blood flow, endoneurial hypoxia.	Identical microvascular rarefaction and endothelial dysfunction underlie essential hypertension and target organ damage.
Neurobiological Alteration	Ion channel dysregulation (NaV, CaV), central sensitization, microglial activation.	Sympathetic overactivity (from central dysregulation) contributes to both neuropathic pain maintenance and hypertension.
Systemic Inflammation & Oxidative Stress	Elevated pro-inflammatory cytokines (TNF- α , IL-6), increased ROS.	Chronic inflammation is a key mediator in the pathogenesis of arterial stiffness and hypertension.

The fourth domain encompasses systemic inflammation and oxidative stress. A state of chronic, low-grade inflammation is a hallmark of both type 2 diabetes and hypertension. In DNP, inflammatory cytokines and reactive oxygen species (ROS) directly damage neurons and

Schwann cells, while also perpetuating microvascular dysfunction⁵. This shared inflammatory milieu provides a compelling biological link between DNP, hypertension, and increased cardiovascular risk, suggesting these conditions may fuel one another in a vicious cycle.

Table 2: Phenotypic Classification of Diabetic Neuropathic Pain and Therapeutic Implications

Predominant Pain Phenotype	Clinical Description & Features	Proposed Neural Mechanism	First-Line Targeted Therapies	Considerations in Co-existing Hypertension
Burning/ Spontaneous Pain Phenotype	Constant, deep burning pain, often worse at night.	Spontaneous (ectopic) activity in C-fibers due to upregulated sodium channels (e.g., Nav1.7). May also involve microglial activation.	SNRIs (duloxetine), TCAs, Gabapentinoids.	SNRIs and TCAs can affect BP (increasing or decreasing, respectively). Regular monitoring is essential.
Shock-like/ Paresthetic Phenotype	Sharp, shooting, electric-shock-like pains, with tingling.	Ectopic activity in A β or A δ fibers. Often linked to upregulated sodium channels (Nav1.3).	Gabapentinoids (pregabalin), Topical lidocaine (if localized).	Gabapentinoids generally have less direct impact on BP, but peripheral edema can be problematic.
Allodynia/ Hyperalgesia Phenotype	Pain from non-noxious stimuli (e.g., bed sheets). Exaggerated response to painful stimuli.	Central Sensitization. Amplified pain signaling in the spinal cord and brain.	Gabapentinoids (first-line), Cannabinoids (in some protocols), Non-drug therapies (TENS, CBT).	Managing this phenotype is challenging. High-dose systemic therapies may carry side-effect burdens in CVD patients.
Ischemic/Pressure-like Pain Phenotype	Deep, cramping pain, worse with activity, may accompany autonomic symptoms.	Nerve ischemia from microangiopathy and reduced endoneurial blood flow. Strong overlap with peripheral arterial disease (PAD).	Optimize vascular risk control: stringent hypertension, dyslipidemia management, smoking cessation. Pentoxifylline (as a rheological agent).	Optimal BP control is critical in this group. Antihypertensives with endothelial benefits (e.g., some ACE inhibitors) may be beneficial.

The review of treatment studies revealed a primarily symptom-focused pharmacological arsenal, with limited disease-modifying options.

First-line pharmacotherapy includes anticonvulsants (pregabalin, gabapentin) and serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine. Their mechanisms involve modulating calcium channel subunits ($\alpha 2\delta$ -1) and enhancing descending inhibitory pathways, respectively. RCT evidence supports their superiority over placebo, though the average pain reduction is often modest (30-50%), and side effects (dizziness, somnolence, edema) are common⁸. Tricyclic antidepressants

(amitriptyline, nortriptyline) are also effective but are limited by anticholinergic side effects and cardiac risks.

Second-line options include topical agents (capsaicin 8% patch, lidocaine patches) for localized pain and the opioid tapentadol, which has a dual mechanism. Strong opioids are discouraged due to poor risk-benefit profiles. Several adjuvant and investigational therapies were reviewed, including alpha-lipoic acid (antioxidant), benfotiamine (blocks AGE formation), and vitamin D supplementation, which showed inconsistent but promising results in subsets of patients.

Table 3: Overview of Pharmacological Treatments for DNP and Considerations in Hypertensive Patients

Drug Class	Examples	Primary Mechanism	Efficacy in DNP	Special Considerations in Hypertension/CVD
Gabapentinoids	Pregabalin, Gabapentin	Bind $\alpha 2\delta$ -1 subunit of voltage-gated Ca^{2+} channels.	First-line; moderate efficacy.	May cause peripheral edema; use with caution in heart failure.
SNRIs	Duloxetine, Venlafaxine	Inhibit reuptake of 5-HT & NE, enhancing descending inhibition.	First-line; moderate efficacy.	Can increase BP and heart rate; monitor BP regularly.
TCAs	Amitriptyline, Nortriptyline	Inhibit NE/5-HT reuptake; sodium channel blockade.	Effective but 2nd-line due to side effects.	Anticholinergic effects (tachycardia); risk of orthostatic hypotension; QTc prolongation.
Topical Agents	Capsaicin 8% patch, Lidocaine 5% patch	Depletes substance P; local sodium channel blockade.	Effective for localized neuropathic pain.	Minimal systemic absorption; generally safe in CVD.
Opioid (Atypical)	Tapentadol	μ -opioid receptor agonist & NE reuptake inhibitor.	2nd/3rd-line for severe pain.	NE action may increase BP; general opioid risks (constipation, sedation).

A critical finding across therapeutic studies was the impact of comorbidities on treatment. For instance, the edema associated with gabapentinoids can exacerbate heart failure or poorly controlled hypertension. Conversely, the norepinephrine reuptake inhibition by SNRIs

can lead to increases in blood pressure, necessitating careful monitoring in hypertensive patients¹⁰. This underscores the necessity of an integrated treatment plan that considers the patient's full cardiovascular risk profile.

Table 4: Evidence Assessment of Adjunctive Therapies and Their Role in Integrated Management

Adjunctive Therapy	Proposed Mechanism of Action	Level of Evidence for DNP Pain Reduction	Potential Impact on CV/ BP Parameters	Role in Integrated Management
Alpha-Lipoic Acid (ALA)	Potent antioxidant, improves endothelial function, reduces oxidative stress.	Meta-analyses show moderate improvement in neuropathy symptoms.	May positively impact vascular resistance indirectly via improved endothelial function. Generally safe.	A promising adjunct, especially in patients with high oxidative stress or poor glycemic control.
Benfotiamine	Inhibits AGEs and hexosamine pathways. Vascular protection.	Studies with conflicting results. Some show improvement in symptoms and nerve conduction velocity.	By inhibiting AGEs, may play a role in reducing vascular stiffness (a factor in hypertension).	May be useful in early-stage neuropathy or as part of a combined approach.
Vitamin D	Immune regulation, anti-inflammatory effects, role in neural health.	Vitamin D deficiency is associated with neuropathy severity. Supplementation may improve symptoms in deficient individuals.	Strong inverse association between vitamin D deficiency and hypertension/CVD risk. Supplementation may modestly lower BP.	Screening vitamin D levels in all DNP patients is rational. Correcting deficiency can be a dual-benefit intervention (pain & CVD).
Regular Aerobic Exercise	Improves endoneurial blood flow, increases neurotrophic factors, reduces systemic inflammation, central desensitization.	Strong evidence for improving neuropathy symptoms, physical function, and quality of life.	Cornerstone of hypertension and diabetes management. Lowers BP and improves insulin sensitivity.	First-line non-pharmacologic intervention. Most effective single intervention for improving multiple outcomes simultaneously.

Non-pharmacological strategies, such as transcutaneous electrical nerve stimulation (TENS), aerobic exercise, and cognitive-behavioral therapy (CBT), were supported by evidence showing benefits in pain modulation, improving function, and addressing pain-related distress. Crucially, intensive glycemic control was reaffirmed as a cornerstone for preventing and slowing the progression of neuropathy in type 1 diabetes, though its

effect is more attenuated in type 2 diabetes, where multifactorial risk factor intervention—including blood pressure and lipid management—becomes paramount^{17,18}. This highlights that the most effective long-term strategy for DNP may be comprehensive cardiovascular risk reduction, treating hypertension and dyslipidemia with the same urgency as hyperglycemia.

Table 5: Proposed Framework for Integrated Assessment and Management of Patients with Co-existing DNP and Hypertension

Management Phase	Key Actions	Goals
1. Comprehensive Initial Assessment	<p>Confirm DNP Diagnosis: Neurological exam, validated tools (e.g., DN4).</p> <p>Assess Pain Severity & Phenotype: Pain questionnaires, identify dominant symptoms.</p> <p>Full Cardiovascular Profiling: BP measurement, CVD history, assess all risk factors (lipids, smoking).</p> <p>Review Current Medications: Identify potential interactions.</p>	<ul style="list-style-type: none"> - Accurate DNP diagnosis. - Understand dominant pain mechanism. - Determine overall CV risk level.
2. Optimize Foundational Therapy & Lifestyle	<p>Stringent Glycemic Control: Personalized HbA1c target.</p> <p>Optimal Blood Pressure Control: Target typically <130/80 mmHg (per guidelines).</p> <p>Lifestyle Modification: Prescribe regular exercise (walking, swimming), DASH/Mediterranean diet, smoking cessation, weight management.</p> <p>Supplementation if deficient: Vitamin D, consider ALA.</p>	<ul style="list-style-type: none"> - Slow neuropathy progression. - Reduce overall inflammatory and oxidative burden. - Establish a solid foundation for symptomatic therapy.
3. Initiate Pain Pharmacotherapy with CV Consideration	<p>Select First-line Analgesic: Based on pain phenotype, side effects, and patient's CV profile.</p> <ul style="list-style-type: none"> - Controlled hypertensive: Gabapentinoid or duloxetine with monitoring. - Resistant HTN or heart failure: Gabapentinoids likely preferred. <p>Start low, go slow.</p> <p>Educate patient on side effects and monitoring.</p>	<ul style="list-style-type: none"> - Meaningful pain reduction and functional improvement. - Minimize CV adverse effects and interactions.
4. Monitoring, Titration, and Referral	<p>Monitor Pain Response: Every 2-4 weeks initially.</p> <p>Monitor BP and CV Symptoms: Especially with initiation of SNRIs/TCAs.</p> <p>Therapy Adjustment: Dose titration, drug switching, or combination therapy for inadequate response.</p> <p>Specialist Referral: For refractory pain, uncontrolled hypertension, or complex heart disease.</p>	<ul style="list-style-type: none"> - Achieve and maintain adequate pain control. - Preserve cardiovascular stability. - Provide multidisciplinary care for complex cases.

Discussion

This systematic review synthesizes the complex pathophysiology and management landscape of diabetic neuropathic pain (DNP), with a deliberate focus on its intersection with systemic cardiovascular comorbidity, particularly hypertension. The findings underscore that DNP is not an isolated complication but rather a manifestation of widespread metabolic and vascular derangements intrinsic to diabetes mellitus. The pathophysiological overlap between DNP and hypertension—encompassing endothelial dysfunction, chronic inflammation, oxidative stress, and sympathetic nervous system dysregulation—is striking and clinically consequential^{4,5,6}. This shared biology suggests that the presence of one condition likely exacerbates the other, creating a synergistic burden that complicates management and worsens overall prognosis.

The analysis of therapeutic evidence reveals a persistent translational gap. While first-line agents like gabapentinoids and duloxetine provide meaningful symptomatic relief for many, their efficacy is often partial, and their side-effect profiles introduce significant complexity in a population frequently burdened by multimorbidity^{8,10}.

The phenotyping approach outlined in Table 2 represents a promising step toward personalization, moving beyond a one-size-fits-all model. For instance, a patient with predominant “ischemic” pain phenotypes may derive greater benefit from aggressive vascular risk factor control than from escalating doses of neuromodulatory drugs. Conversely, the potential for drug-disease interactions, as detailed in Table 3 and Table 5, cannot be overstated. The initiation of an SNRI in a patient with borderline or uncontrolled hypertension requires vigilant monitoring, as the therapeutic goal of pain relief must not come at the expense of cardiovascular stability.

A central argument emerging from this synthesis is the imperative for integrated care. The conventional siloed approach, where neuropathic pain is managed separately from hypertension and other cardiovascular risks, is physiologically misaligned and potentially harmful. The most effective long-term strategy for mitigating DNP progression, as evidenced by the attenuated benefit of glycemic control alone in type 2 diabetes, is comprehensive cardiovascular risk reduction¹⁵. This includes stringent blood pressure control, lipid management, smoking ces-

sation, and the promotion of physical activity. As shown in Table 4, interventions like aerobic exercise and vitamin D repletion offer dual benefits, simultaneously targeting pain pathways and improving cardiovascular health. The management framework proposed in Table 6 provides a practical roadmap for clinicians to implement this holistic approach, emphasizing initial comprehensive profiling, foundational lifestyle and risk factor optimization, and careful, monitored pharmacotherapy.

This review also highlights critical gaps in the current evidence base. First, there is a paucity of large-scale clinical trials that specifically enroll patients with DNP and significant cardiovascular comorbidity, limiting our understanding of optimal treatment sequences and long-term outcomes in this high-risk group. Second, while phenotyping is conceptually appealing, validated and readily applicable clinical tools to reliably identify these phenotypes in routine practice are still needed. Future research must prioritize the development of such tools and the design of trials that test integrated care models against standard fragmented care, with co-primary endpoints encompassing pain reduction, functional improvement, and cardiovascular event rates.

Conclusions

In conclusion, diabetic neuropathic pain is a debilitating condition rooted in multifaceted pathophysiological processes that extend far beyond the peripheral nerve. Its strong mechanistic and clinical ties to hypertension and cardiovascular disease necessitate a fundamental shift in management philosophy. Effective care requires a dual focus: providing personalized, mechanism-informed symptomatic relief while concurrently executing aggressive, multifaceted management of systemic cardiovascular risk factors.

Key takeaways for clinical practice include: (1) Routine cardiovascular risk assessment is essential in every patient presenting with DNP; (2) Pharmacological choices must be guided by the patient's cardiovascular profile, carefully weighing efficacy against risks such as blood pressure elevation, edema, or orthostatic hypotension; and (3) Non-pharmacological interventions, particularly structured exercise, should be championed as foundational therapy with proven benefits for both neuropathic pain and hypertension.

The proposed integrated management framework advocates for a collaborative, patient-centered model involving endocrinologists, pain specialists, cardiologists, and primary care physicians. By treating the patient as a whole rather than a collection of discrete diagnoses, clinicians can break the cycle of mutual exacerbation be-

tween neuropathic pain and cardiovascular dysfunction. Future efforts should concentrate on validating phenotypic classification systems, developing novel therapies that target shared pathways (such as inflammation or endothelial health), and implementing integrated care pathways that demonstrably improve the long-term quality of life and cardiovascular outcomes for this vulnerable population.

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