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Combination Therapy in Painful Diabetic Neuropathy: A Scoping Review

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Abstract

Diabetic neuropathy is the most common microvascular complication of Diabetes Mellitus. Approximately one-third of patients with Diabetic Neuropathy experience clinical features that fit the Painful Diabetic Neuropathy spectrum. Many studies have discussed the effectiveness of monotherapy in Painful Diabetic Neuropathy. Recommendations indicate that if pain is not resolved with monotherapy, then drug combination therapy can be considered. This scoping review aimed to map the evidence on pharmacological combination therapy for Painful Diabetic Neuropathy. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews and the Population-Concept-Context framework, we searched PubMed, ScienceDirect, EBSCOhost, and ProQuest until December 2023. Seventeen studies were included and appraised using the Mixed Methods Appraisal Tool. Three clinical outcomes most studied were clinical effectiveness (pain relief, nerve function improvement, and sleep improvement), clinical safety, and cost-effectiveness. Combination therapy most commonly involved Pregabalin and Methylcobalamin. Across studies, combination therapy demonstrated greater pain relief, improved nerve function, and better sleep outcomes compared with monotherapy, while safety profiles and overall costs were similar. In conclusion, combination therapy appears to offer enhanced clinical benefits without added safety risks or cost burden, supporting its role as an alternative when monotherapy is insufficient.

Keywords: **Painful Diabetic Neuropathies, Combination, Drug Therapy, Treatment Outcome, Treatment Efficacy, Adverse Effects**

Introduction

Peripheral neuropathy (PN) is a disorder of the peripheral nerve system encompassing many symptoms. Peripheral neuropathy can impair sensory and motor nerves, resulting in various signs and clinical presentations. Sensory symptoms may include tingling sensation, numbness, tightness, and pain (burning or pins and needles). Motor symptoms may include cramps, stiffness, weakness, and wasting [(1)].

Diabetes is one of the disorders most associated with peripheral neuropathy. The global prevalence of diabetes mellitus is expected to be over 537 million in 2021, which will continue to rise to 783 million by 2045 [(2)]. Approximately half of adults with diabetes will eventually develop peripheral neuropathy. Estimates vary across studies due to factors such as age, diabetes type, disease duration, and glycaemic control [(3)].

Diabetic neuropathy clinical manifestations range from asymptomatic to painful neuropathic symptoms. The most common finding is diabetic peripheral neuropathy (DPN), a symmetrical, length-dependent sensorimotor polyneuropathy. It typically begins distally and moves proximally as the disease progresses, with lower-limb long axons being the most vulnerable, also known as the "stocking and glove" distribution. According to estimates, about one-fifth of diabetes individuals experience painful diabetic neuropathy (PDN) [(4)]. PDN is characterized by burning, tingling, and electric shock-like sensations with or without additional negative symptoms (numbness) or positive symptoms (hyperalgesia, allodynia, or paraesthesia) [(5)]. Over 70% of patients with PDN experience moderate-to-severe pain that is often debilitating and leads to general activity deficits, fatigue, distress, and ultimately reduced quality of life. It has been linked to various mental health problems, including mood instability, interpersonal issues, and various psychiatric symptoms [(6)].

Pathogenesis-oriented therapies target the underlying mechanisms of diabetic neuropathy rather than providing symptomatic relief. Hyperglycaemia and dyslipidaemia contribute to mitochondrial dysfunction and excess production of reactive oxygen species, driving oxidative stress and activation of pathways such as polyol, hexosamine, protein kinase C, and advanced glycation end-products (AGEs). Several agents have been developed to intervene in these processes, including aldose reductase inhibitors, antioxidants such as α-lipoic acid (ALA), protein kinase C inhibitors, prostacyclin analogues, and AGE inhibitors. Of these, ALA, Actovegin, Benfotiamine, and Epalrestat are currently approved for diabetic sensory polyneuropathy in selected countries—ALA and Benfotiamine in many regions, Actovegin in Russia and Eastern Europe, and Epalrestat in Japan and India [(7)]. These therapies highlight the potential of mechanism-based approaches and open opportunities for synergistic use alongside symptomatic treatments.No single drug reverses neuropathic changes or provides complete analgesia (8). Many first-line agents like Amitriptyline, Duloxetine, Gabapentin, and Pregabalin have been studied, but most can only provide 50% pain relief at best, with less than half of PDN sufferers achieving this outcome. With the emergence of pathogenesis-oriented therapies and the limitations of monotherapies, numerous trials of combination therapy in PDN management have been conducted. Despite the growing number of clinical trials and observational studies investigating pharmacological combinations for PDN, the evidence base remains fragmented and heterogeneous. While systematic reviews exist for monotherapies, there is no comprehensive, systematic mapping of the range, outcomes, and quality of evidence for pharmacological combinations specifically in PDN. Combination therapy is further complicated by drug–drug interactions, which may increase adverse effects or toxicity, or reduce drug efficacy (9). Current guidelines acknowledge combination therapy as a potential option when monotherapy fails, yet they provide little consensus on which combinations are most effective, safest, or cost-efficient. At the same time, the global burden of diabetes is rising sharply, with PDN contributing substantially to disability, reduced quality of life, and healthcare costs. This creates an urgent need to systematically map and synthesise the available evidence to clarify where combination therapy offers genuine clinical advantage, where uncertainties remain, and how future research can be directed. This scoping review aims to systematically map the available studies, evidence, and current guidelines on combination therapy in the management of PDN, and to identify existing gaps in knowledge to inform future research and clinical practice.

Materials and Methods

Literature search

We did a systematic search method for this scoping review following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) statement guideline. The present scoping review was conducted using Arksey and O'Malley's methodological framework. It included the following steps: identifying research questions, identifying relevant studies, selecting relevant studies, charting the data, collating, summarizing, and reporting the results. We also reviewed each article's references to find other relevant studies not identified by the search [(10)].

Research question and definitions

Although many guidelines have addressed the usage of monotherapies, from effective doses to side effects, the data on combination therapies is still limited. For this review, "combination therapy" refers to the concurrent use of two or more pharmacological drugs to achieve a more pronounced therapeutic effect [(11)]. It could be a combination of first-line, second-line, or other symptomatic/pathogenesis-oriented medications. Therefore, the research question addressed for the present review was, "What is empirically known from the existing literature about combination therapies among patients with painful diabetic neuropathy?". This question served as guidance throughout the writing of this research. **Table 1** summarizes the underlying research questions and objectives following the PCC (Population-Concept-Context) framework.

Table 1. Research questions were formed based on the PCC model.

Research Questions		Specific Objectives	
1.	What are the characteristics and distribution of study populations in combination therapy research for PDN?	1.	Explore the baseline characteristics of the study population on combination therapy.
2.	What are the design types of the studies related to combination therapy in PDN?	2.	To identify the main types of study designs used in studies on combination therapy in PDN.

Continued table 1.

3.	What clinical outcomes have been investigated in studies on combination therapy for PDN?	3.	To identify the clinical outcomes that previous studies have researched.
4.	What are the findings of previous studies?	4.	To summarize the results of the previous studies on combination therapy in PDN.
5.	What recommendations do current clinical guidelines provide regarding the use of combination therapy in PDN?	5.	To summarize the current recommendations on combination therapy in PDN.
6.	What evidence exists regarding the clinical effectiveness, safety, and adverse effects of combination therapy in PDN?	6.	To summarize the effectiveness, safety, and adverse effects that are commonly found in combination therapy in PDN treatment.
7.	What is the cost-effectiveness of combination therapy over monotherapy?	7.	To summarize the cost-effectiveness of combination therapy in PDN treatment.
8.	What gaps in the literature have been identif ied regarding combination therapy in PDN management?	8.	To summarize the gaps in the current studies available on combination therapy in PDN.

Search strategy and selection criteria

We conducted a structured literature search from the beginning of the database coverage until December 2023 to identify all published articles related to combination therapy in painful diabetic neuropathy. We searched PubMed, ScienceDirect, EBSCOhost, and ProQuest using the MeSH term keywords “Drug Therapy, Combination”, “Combination Drug Therapy”, “Combination Therapy”, “Drug Combination”, “Diabetic Neuropathies”, “Painful Diabetic Neuropathy”, “Diabetic Neuralgia”, “Peripheral Neuropathy”, and “Neuralgia”. **Table 2** presents the search terms applied in this study along with the year coverage of each database and number of studies retrieved. We applied no other filters such as publication types, text availability, article types, article language, sex, age, species, and locations.

Following duplicate removal, two independent authors screened the titles and abstracts to determine eligibility. The title and abstract of these articles were reviewed based on the following criteria: (1) human studies, (2) studies included diabetic populations with painful neuropathy, and (3) combined pharmacological therapy (two or more monotherapies). **Table 3** outlines the inclusion and exclusion criteria applied in this study. We performed a backward citation tracking from review papers following the same inclusion criteria. A start date of 2003 was selected to coincide with the emergence of pivotal trials for first-line agents such as Pregabalin, which received regulatory approval in 2004–2005 and became widely adopted for neuropathic pain. We included only original research articles with a comparator group, while excluding other contexts such as clinical practice guidelines, economic models, or policy papers, since the focus of this scoping review was to map original comparative research evidence rather than secondary syntheses or non-empirical frameworks. The selected articles were then presented in a PRISMA flow chart according to the established criteria.

Table 2. Databases and search terms.

Database	Search Terms	Year Coverage	Studies
PubMed	("Drug Therapy, Combination"[MeSH] OR "Combination Drug Therapy" OR "Combination Therapy" OR "Drug Combination") AND ("Diabetic Neuropathies"[MeSH] OR "Painful Diabetic Neuropathy" OR "Diabetic Neuralgia" OR "Peripheral Neuropathy" OR "Neuralgia")	1962-2023	2876

Continued table 2.

ScienceDirect	(("Drug Combination") OR ("Combination Therapy")) AND (("Painful Diabetic Neuropathy") OR ("Painful Diabetic Neuropathies") OR ("Diabetic Neuralgia") OR ("Neuralgia"))	1995-2023	1477
EBSCOhost	TI (Drug Combination) OR AB (Drug Combination) OR TI (Combination Therapy) OR AB (Combination Therapy) AND TI (Painful Diabetic Neuropathy) OR AB (Painful Diabetic Neuropathy) OR TI (Painful Diabetic Neuropathies) OR AB (Painful Diabetic Neuropathies) OR TI (Diabetic Neuralgia) OR AB (Diabetic Neuralgia) OR TI (Neuralgia) OR AB (Neuralgia)	1960-2023	147
ProQuest	(title(Drug Combination) OR abstract(Drug Combination) OR title(Combination Therapy) OR abstract(Combination Therapy)) AND (title(Painful Diabetic Neuropathy) OR abstract(Painful Diabetic Neuropathy) OR title(Painful Diabetic Neuropathies) OR abstract(Painful Diabetic Neuropathies) OR title(Diabetic Neuralgia) OR abstract(Diabetic Neuralgia) OR title(Neuralgia) OR abstract(Neuralgia))	1960-2023	90

Table 3. Inclusion and exclusion criteria based on PCC model.

Inclusion criteria	Exclusion criteria
Population • Human participants with any age and sex • Subjects with diagnosis of diabetes and painful diabetic neuropathy (PDN)	**Population** • Animal model studies
Concept • Any pharmacological combination therapy* in diabetic populations with painful diabetic neuropathy published from 2003 to 2023	**Concept** • All studies not related to combination therapy (monotherapy only) or non-pharmacological therapy (exercise therapy, laser therapy, etc.) • Painful neuropathy of other causes (trigeminal neuralgia, multiple sclerosis post-traumatic, etc.) not including diabetes as one of the causes
Context • Eligible study designs included randomized controlled trials, cohort studies, case-control studies, and other original research with a comparator group, such as cross-sectional or quasi-experimental designs • All settings considered	**Context** • Non-scholarly articles • Single arm interventional study with no comparison group • Review articles (expert opinion, brief review, systematic review, and meta-analysis) were excluded unless used for reference mining • Full text not attained

* Combination therapy refers to the use of two or more pharmacological drugs concurrently to achieve a more pronounced therapeutic effect. Cross-over studies were still considered combination therapy as they assess the outcomes at the end of the study period.

Screening, full-text review, data extraction, and quality appraisal

All authors carried out the data mapping process independently to ensure data accuracy. For articles that met inclusion criteria after full-text review, the following information was extracted: first author, year of publication, study population, study design, combination/monotherapy used, dose/regiments, outcomes of the study, and study results.

We used the Mixed Methods Appraisal Tool (MMAT) to evaluate the study quality. MMAT is a quality assessment tool for reviews that include qualitative, quantitative, and mixed methodologies studies. It appraised each study based on their design category (qualitative, RCT, non-randomized quantitative, descriptive quantitative, or mixed methods). For each study, five questions/criteria (Q1-Q5) should be appraised. The developer discouraged computing total score, instead presenting a descriptive summary was highly encouraged. In this review, we only report the total score and the inter-reliability value. The reasoning will be supplied if the author requests it. The flexibility of this tool made it suited for this scoping review [(12)]. Each article was individually scored by two reviewers, and any discrepancies had to be resolved by a third reviewer. Inter-rater reliability was calculated using the Cohen's κ value. The MMAT score was utilized to describe the quality of the literature used in the current investigation rather than for inclusion or exclusion.

Results

Selection of Sources of Evidence

Through the primary search strategy, we have collected 4590 studies. All studies were imported into EndNote 20. From the initial search, 2876 articles were identified from PubMed, 1477 from ScienceDirect, 147 from EBSCOhost, 90 from the ProQuest database, and no additional study from other sources. 1085 articles were excluded as duplicates, leaving 3505 articles to be reviewed. After a review of titles and abstracts, 51 citations were identified as potentially relevant and proceeded to full-text review. We were unable to retrieve the complete text of two articles. We excluded 32 citations for various reasons. The most common reasons for exclusion were studies that did not focus on combination therapy (n = 15), wrong study design (n = 14), and studies with unspecified or non-diabetic populations (n = 3). The PRISMA flowchart diagram and exclusion reasons can be found in **Figure 1**.

From 2003 to 2023, we gathered 17 relevant publications that met our inclusion and exclusion criteria. Five of these original studies were mined from brief review and expert opinion studies. The baseline characteristics, study designs, and study results of combination therapy presented in this scoping review are summarized in **Table 4**. Participants differed between trials; twelve (70.6%) comprised PDN participants and five (29.4%) included mixed peripheral neuropathic subjects. Mean age of each study varied from 52 to 70 years, mean diabetic onset ranging from 9.5 to 15 years, and mean PDN onset ranging from 2 to 6.1 years. All studies predominantly involving patients with moderate to severe PDN. Most studies (82.4%) were randomized clinical trials, with one non-randomized clinical trial, one pilot study, and one retrospective cohort study. Most studies evaluated Pregabalin-based combinations, often with Duloxetine or Methylcobalamin. Pregabalin has also been shown to be the most versatile drug as many drug combinations has been studied. Most of these studies evaluated the efficacy of combination therapy on pain reduction (88%), followed by adverse events on combination therapy (71%).

The Mixed Methods Appraisal Tool (MMAT) assessed 11 RCTs and six non-randomized quantitative studies. Among the 11 RCTs, ten studies were rated 100 and one studies were rated 80 due to partially complete reporting data. Among the six non-randomized quantitative studies, four studies were rated 80 and two studies were rated 60. Most of these studies had limited control for confounding variables (Q4), and some only provided incomplete outcome data (Q3). Item-level Cohen's κ indicated substantial to almost-perfect agreement for Q3 (κ = 0.62, 88.2% agreement) and Q4 (κ = 0.88, 94.1% agreement); Q1, Q2, and Q5 all showed perfect agreement (κ = 1.00, 100% agreement). Overall, the substantial inter-rater agreement and consistently high scores for RCTs suggest that the core efficacy data derive from studies of reasonably sound methodology, although non-randomized studies demonstrated important limitations, particularly in confounding control.

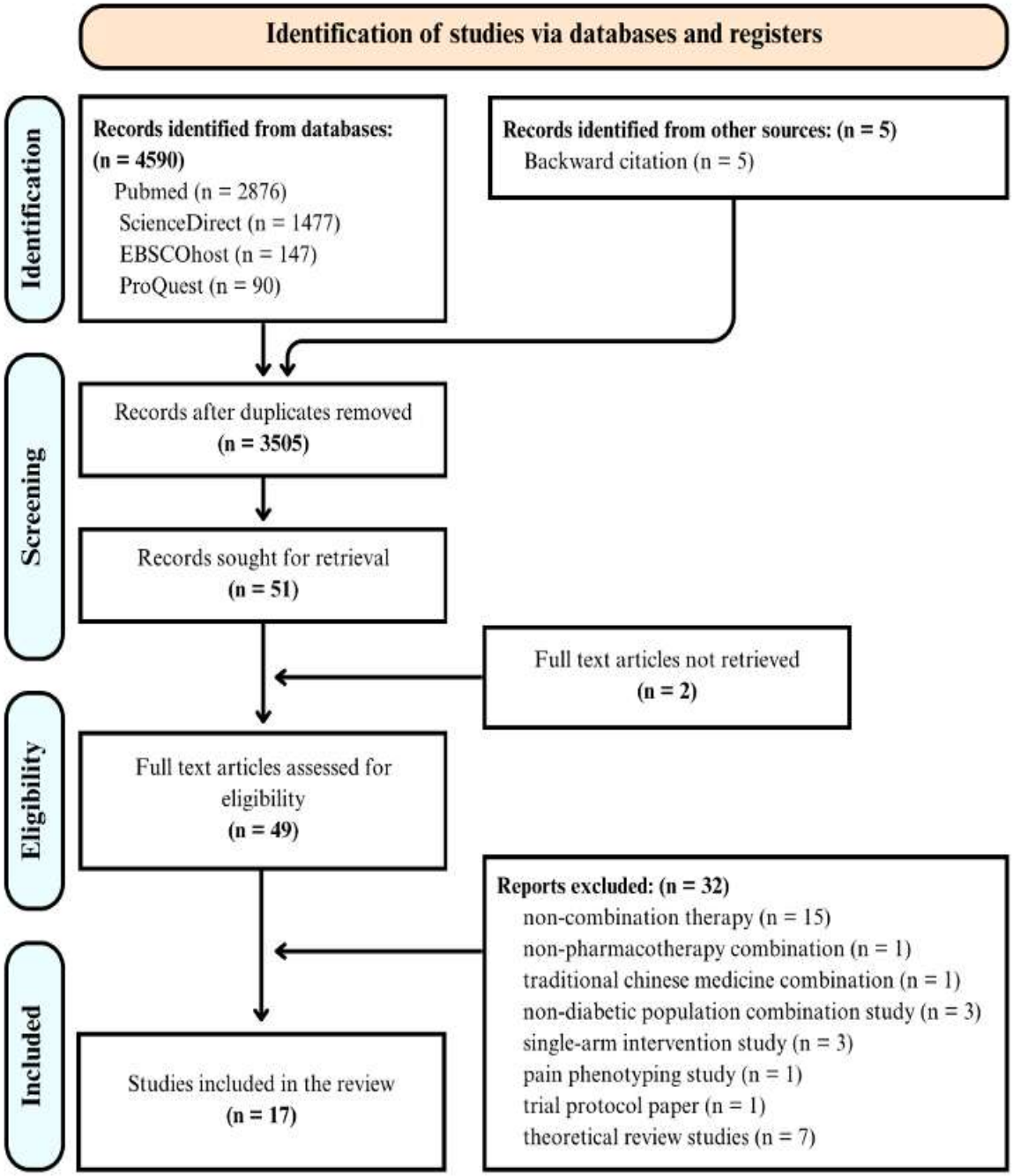

Figure 1. The PRISMA-ScR flowchart diagram depicting the study selection process.

Characteristics of Sources of Evidence

Table 4. Combination therapy in the management of painful diabetic neuropathy (PDN).

First author (year)	Population	Context	Concept			Findings/Outcomes
	Study Population; Characteristics of Combination Group	Study Design	Combination Therapy	Dose/Regiments	Clinical Outcomes Assessed	
Lynch et al. 2005 [13]	92 NP[§] subjects; Mean age 52 years, PDN onset (mean) 5.4 years, VAS (mean) 6.7/10.	Randomized, double-blind, placebo-controlled trial	● AMT + KTM vs. ● Monotherapy[**]	● AMT (2% topical) + KTM (1% topical) for three weeks	● Pain relief	= No significant advantage on pain relief
Freeman et al. 2007 [14]	313 PDN subjects; Mean age 56.2 years, Diabetic onset (mean) 10.7 years, PDN onset (mean) 3.7 years, VAS (mean) 7.1/10.	Multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial	● TRA + ACT vs. ● PCB Monotherapy[**]	● TRA (37,5 mg/day PO) + ACT (325 mg/day PO) for 66 days.	● Pain relief ● Sleep quality ● Quality of life ● Mood ● Patient's global impression of change (PGIC) ● Adverse events of combination therapy	Δ Improvement in pain relief Δ Improvement in sleep quality Δ Improvement in quality of life Δ Improvement in mood Δ Improvement in PGIC ∇ More nausea over PCB
Hanna et al. 2008 [15]	338 PDN subjects; Mean age 59.6 years, BS-11 pain score (mean) 6.4/10.	Randomized, double-blind, parallel-group comparative study	● GBP + OXY-PR vs. ● Monotherapy[**]	● GBP (100 - 18,000 mg/day PO[a]) + OXY-PR (10 mg/day PO) for 12 weeks	● Pain relief ● Escape medication ● Sleep quality ● Global pain assessment ● Adverse events of combination therapy	Δ Improvement in pain relief Δ Improvement in sleep quality Δ Less escape medication Δ Did not exacerbate opioid-induced AEs

Agrawal et al. 2009 [16]	83 PDN subjects; Mean age 58.4 years, Diabetic onset (mean) 9.1 years, VAS (mean) 7.6/10.	Randomized, double-blind, placebo-controlled trial	● GTN + SV vs. ● Monotherapy**	● GTN (spray; 0,4mg/actuation) + SV (20 mg/kg/day PO) for twelve weeks	● Pain relief ● Nerve conduction study ● Number needed to treat (NNT)	Δ Improvement in pain relief Δ Improvement in median motor nerve distal latency and mean amplitude related to distal Δ lower number needed to treat (NNT)
Gatti et al. 2009 [17]	409 NP§ subjects; Mean age 62 years, NRS (mean) 7.4/10.	Multicenter, open-label, prospective study	● PGB + OXY-CR [17] vs. ● Monotherapy*	● PGB (108.1 mg/day PO) + OXY-CR (19.4 mg/day PO) for 90 days ● OXY (24,1 mg/day PO) for 90 days ● PGB (85,6 mg/day PO) for 90 days	● Pain relief ● Quality of life ● Effective dose ● Adverse events of combination therapy	Δ Greater pain relief (versus PGB monotherapy) = No significant advantage on pain relief (versus OXY-CR monotherapy) Δ Improvement in quality of life Δ Allowed dose reduction on both agents (22% for OXY-CR and 51% for PGB) Δ Superior safety profile
Baron et al. 2009 [18]	229 NP§ subjects; Mean age 61.5 years, PDN onset (mean) 4.6 years, NRS (mean) 5.8/10.	Multicenter, randomized, open-label study	● LDO + PGB vs. ● Monotherapy**	● LDO (5% topical plaster) + PGB (150 – 600 mg/day PO[a]) for 8 weeks[c]	● Pain relief	Δ Greater pain relief
Zin et al. 2010 [19]	62 NP§ subjects; Mean age 70.3 years, PDN onset (mean) 4.5 years, VAS (mean) 6.9/10.	Randomized double-blind, placebo-controlled, parallel-group clinical trial	● OXY + PGB vs. ● Monotherapy**	● OXY (10 mg/day P.O.) + PGB (75 / 150 / 300 / 600 mg/day P.O.) for four weeks	● Pain relief ● Sleep interference	= No significant advantage in pain relief; trend favored combination therapy = No significant difference in sleep interference score; trend favored combination therapy
Tesfaye et al. 2013 [20]	343 PDN subjects; Mean age 61 years, Diabetic onset (median) 11 years, PDN onset (median) 2 years, NRS (mean) 5.8/10.	Multinational, randomized, double-blind, parallel-group study*	● PGB + DLX vs. ● High-dose monotherapy*	● PGB (150 – 300 mg/day PO[a]) + DLX (30 – 60 mg/day PO[a]) for 20 weeks[b]. ● PGB (300 – 600 mg/day PO[a]) for 20 weeks. ● DLX (60 – 120 mg/day PO[a]) for 20 weeks.	● Pain relief ● Adverse events of combination therapy	= No significant advantage on pain relief; trend favored combination therapy = No significant advantage on TEAEs

Irving et al. 2014 [21]	407 PDN subjects; Mean age 61.9 years, Diabetic onset (mean) 10 years, PDN onset (mean) 4.2 years, NRS (mean) ≥4/10.	Multi-center, randomized, open-label, parallel non-inferiority study	● DLX + PGB vs. ● Monotherapy**	● DLX (30 – 60 mg/day PO[a]) + PGB (150 – ≥900 mg/day PO[a]) for 12 weeks ● DLX (60 mg/day PO) for 12 weeks ● PGBB (300 mg/day PO) for 12 weeks	● Safety ● Adverse effect of combination therapy	= No significant between-group differences in the incidence of severe adverse effect Δ Lower diastolic blood pressure and less weight loss Δ Less insomnia (versus DLX monotherapy) Δ Less peripheral edema (versus PGB monotherapy) ∇ More nausea, hyperhidrosis, decreased appetite, and vomiting (versus PGB monotherapy).
Vasudevan et al. 2014 [22]	29 PDN subjects; Mean age 56.9 years, moderate-severe (BPI-MSF ≥4), NRS (mean) 7/10.	Open-label, randomized, controlled parallel-group pilot study	● PGB + MC + ALA vs. ● PGB monotherapy**	● PGB (75 mg/day PO) + B12 (750 µg/day PO) + ALA (100 mg/day) for 12 weeks.	● Pain relief ● Sleep quality ● Global assessment ● Nerve conduction study ● Adverse effect of combination therapy	= No significant advantage on pain relief = No significant advantage on sleep quality improvement Δ Improvement in the mean nerve conduction velocity bilaterally = No significant global assessment difference; trend favored combination therapy = No adverse events were reported by any subjects
Gilron et al. 2015 [23]	51 NP[§] subjects; Mean age 66 years, Diabetic onset (mean) 10 years, PDN onset (mean) 6.1 years, NRS (mean) 5.3/10.	Single center, randomized, double-blind, crossover trial	● NOR + MOR vs. ● Monotherapy**	● NOR (10 mg/day PO) + MOR (10 mg/day PO) for 18 weeks	● Pain relief ● Mood ● Quality of life ● Adverse effect of combination therapy	Δ Greater pain relief = No significant improvement in mood and = No significant improvement in quality of life = No significant advantage on TEAEs; trend favored combination therapy
Alvarado et al. 2016 [24]	270 PDN subjects; Mean age 52.5 years, Diabetic onset (mean) 9.5 years, PDN onset (mean) 2.8 years, NPRS (mean) 7/10.	Phase IV, multicenter, randomized, open-label, parallel-group, noninferiority study	● B Complex (B1/B12) + GBP vs. ● PGB monotherapy***	● B Complex (100 mg B1; 0,2 mg B12) + GBP (300 – 3600 mg/day PO[a]) for 12 weeks ● PGB (150 – 600 mg/day PO[a]) for 12 weeks	● Pain relief ● Sleep quality ● Patient's global impression of change (PGIC)	= No significant advantage on pain relief = No significant advantage on sleep quality improvement = No significant advantage on IGCP score Δ Significantly less dizziness

					● Adverse events of combination therapy	
Kuo et al. 2016 [25]	7566 PDN subjects; Mean age 60.6 years.	Retrospective cohort study	● Various Combination Therapy vs. ● Monotherapy**	● NOR ● DLX ● PGB ● GBP ● TCA ● Opioid ● Lidocaine	● Safety ● Cost-effectiveness	∇ More discontinuation (130%) = No differences in the total cost of care
Didangelos et al. 2020 [26]	85 PDN subjects; Mean age 65.1 years, Diabetic onset (mean) 15 years, PainDETECT (mean) 19.5/38.	Prospective, randomized, double-blind, placebo-controlled study	● SOD + ALA + MC + Carnitine vs. ● PCB Monotherapy**	● SOD (10 mg/day PO) + ALA (570 mg/day PO) + MC (250 mcg/day PO) + Carnitine (300 mg/day PO) combined in one tablet for 12 months.	● Pain relief ● Quality of life ● Nerve conduction study	Δ Greater improvement in pain relief Δ Improvement in quality of life Δ Improvement in sural SNCV and sural SNAP
Sharma et al. 2021 [27]	100 PDN subjects; Mean age 57.8 years	Prospective, randomized, open-label, interventional, and parallel-group study	● DLX + MC ● PGB + MC vs. ● MC Monotherapy**	● DLX (60 mg/day PO) + MC (1500 mg/day PO) ● PGB (150 mg/day PO) + MC (1500 mg/day PO)	● Pain relief ● Nerve function (vibration, touch/light pressure sensation, and thermal sensitivity) ● Adverse events of combination therapy	Δ Duloxetine combination showed greatest pain relief Δ Duloxetine combination greatest recovery of vibration and touch/light pressure sensation Δ Pregabalin combination showed least adverse effects.

Shokri et al. 2021 [28]	103 PDN subjects; Mean age 60.6 years, Diabetic onset (mean) 13.6 years, PDN onset (mean) 2.5 years, NRS (mean) 8.2/10.	Randomized, double-blind, placebo-controlled trial	● PGB + MLT vs. ● Monotherapy**	● PGB (150 mg/day PO) + MLT (3 – 6 mg/day PO[a]) for 8 weeks	● Pain control ● Sleep interference ● Patient's global impression of change (PGIC) ● Adverse events of combination therapy	Δ Greater pain relief Δ Lower sleep interference score Δ Improvement in PGIC = No significant advantage on TEAEs
Tesfaye et al. 2022 [29]	130 PDN subjects; Mean age 61 years, Diabetic onset (mean) 14.9 years, PDN onset (mean) 4.8 years, NRS (mean) 6.7/10.	Multicenter, randomized, double-blind, center-stratified, multi-period crossover trial	● AMT + PGB ● DLX + PGB ● PGB + AMT vs. ● Each other**	● AMT (25 – 75 mg/day PO) + PGB (75 – 300 mg/day PO[a]) + DLX (30 – 60 mg/day PO[a]) for 16 weeks[d] (six weeks of monotherapy, ten weeks of combination therapy)	● Pain relief ● Adverse events of combination therapy	Δ All three combination therapies showed significantly greater pain relief (versus AMT / DLX / PGB) = No significant advantage on TEAEs

Abbreviations: ACT, acetaminophen; ALA, alpha-lipoic acid; AMT, amitriptyline; BPI-MSF, brief pain inventory modified short form; CPN, common peroneal nerve; DLX, duloxetine; GBP, gabapentin; GTN, glyceryl trinitrate; H3RIA, histamine-3-receptor inverse agonist; KTM, ketamine; LA, lipoic-acid; LDO, lidocaine; MC, methylcobalamin; MLT, melatonin; MOR, morphine; NOR, nortriptyline; NPRS, numerical pain rating scale; NRS, numerical rating scale; NTSS-6, neuropathy total symptom score-6; OLM, oral L-methyl folate; OXY, oxycodone; P5P, pyridoxal-5-phosphate; PCB, placebo; PDN, painful diabetic neuropathy; PGB, pregabalin; PGE1, prostaglandin E-1; PO, orally; PR, prolonged release; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; SOD, superoxide dismutase; SF-BPI, short-form brief pain inventory; SV, sodium valproate; TCM, traditional Chinese medicine; TRA, tramadol; TEAEs, treatment-emergent adverse event; IM, intramuscular; IV, intravenous; IVR, interactive voice response; VAS, 10-cm visual analogue scale.

The following icons indicate study outcomes: "Δ" = Favors combination therapy; "=" = No significant difference; "∇" = Favors monotherapy/placebo.

* Studies comparing combination therapy with every single agent used in the combination regimen but with higher doses.

** Studies comparing combination therapy with placebo or with every single agent used in the combination regimen.

*** Studies comparing combination therapy with other monotherapy not used in the combination regimen.

**** Review studies with pooled population, comparing combination therapy with non-combination therapy.

§ Mixed neuropathy subjects including painful diabetic neuropathy, postherpetic neuralgia, and post-traumatic pain.

[a] Indicates flexible dosing or titrated dosing (see reference for details on dose adjustment).

[b] Subjects started with initial therapy for ten weeks, followed by another ten weeks of high-dose monotherapy or combination therapy.

[c] Subjects started with monotherapy for four weeks, then continued to either combination therapy (insufficient response) or stay in monotherapy (sufficient response) for another four weeks.

[d] Subjects started with monotherapy for six weeks (with the first two weeks for titration), then continued to the second treatment phase for eight weeks (with the first two weeks for titration. After completing these two phases, the subject would move to other pathways/combination therapy.

Table 5. Clinical outcomes studied on previous studies.

Clinical Outcomes	n (%)
Pain relief	15/17 (88%)
Sleep quality or sleep interference	6/17 (36%)
Quality of life	4/17 (24%)
Mood	2/17 (12%)
Patient's global impression of change (PGIC)	3/17 (18%)
Global pain assessment	2/17 (12%)
Effective dose	1/17 (6%)
Nerve conduction study or nerve function	4/17 (24%)
Safety or adverse events	12/17 (71%)
Cost-effectiveness	1/17 (6%)
Escape medication	1/17 (6%)
Number needed to treat	1/17 (6%)

Clinical outcomes

Common clinical outcomes included significant pain relief in combination therapy over monotherapy (n = 15) [13–20,22–24,26–29], followed by nerve function improvement (n = 4) [16,22,26,27] and sleep improvement (n = 6) [14,15,19,22,24,28]. Additionally, some studies also reported improvement in quality of life [14,17,23,26], mood [14,23], and global impression of change [14,24,28] (**Table 5**).

Pain relief reported in these studies was measured using a variety of assessment tools including the numeric pain rating scale (NPRS), visual analog scale (VAS), BS-11, and pain DETECT questionnaire. Among the 15 studies that reported pain, ten studies reported improvement, and five studies reported no significant advantage over monotherapy. Pain improvement in combination was mostly observed by using Pregabalin (n = 5) [17,18,27–29], followed by Duloxetine (n = 2) [27,29]. Some medications like Tramadol, Acetaminophen, Glyceryl trinitrate, Sodium valproate, and Melatonin were not included as first or second-line therapy in the current guidelines (**Table 6**), but were still used in the studies and showed good efficacy in pain relief [14,16]. Note that Tramadol and Acetaminophen combination were superior to placebo only [14].

Nerve conduction studies employing electromyography (EMG) to determine nerve velocities and many other subjective tests (128 Hz tuning fork test, Semmes-Weinsten monofilament test, and thermo-tube test) were used to assess nerve function improvement. All studies [16,22,26,27] reported nerve function improvement in combination therapy. Nerve function improvement was mostly observed involving Methylcobalamin (n = 3) [22,26,27] and Alpha-Lipoic Acid (ALA) (n = 2) [22,26], with Pregabalin as the first line therapy. Other medications like Superoxide dismutase and carnitine in combination with Methylcobalamin also showed significant improvement, but they were compared to placebo [26].

A sleep questionnaire and a sleep-interference score (SIS) were used to assess sleep improvement. Three [14,15,28] of the six studies that used combination therapy to measure sleep quality/interference found improvements, while the other three found no significant changes. The three studies that demonstrated significant improvement used a combination of Gabapentin plus Oxycodone, Pregabalin plus Melatonin, and Tramadol plus Acetaminophen. It should be noted that the Tramadol and Acetaminophen combination performed better than placebo alone [14]. The addition of Methylcobalamin, ALA, and vitamin B complex did not affect sleep improvement [22,24].

Other clinical outcomes like mood (n = 2) [14,23], effective dose (n = 1) [17], and number needed to treat (NNT) (n = 1) [16] were assessed. Tramadol plus Acetaminophen considerably improved mood, however, Morphine plus Nortriptyline showed no significant improvement over monotherapy. This should be interpreted with caution because the first study was compared to placebo and the second study compared combination therapy with Nortriptyline (antidepressant) as a comparator. The effective dose in combination therapy was lower than in monotherapy as seen in the Oxycodone and Pregabalin trial. The Oxycodone dose was reduced by 22%, and the Pregabalin dose was reduced by

51%. The study found that combining Glyceryl Trinitrate with Sodium Valproate reduced the NNT, even though the combination group did not report significant pain relief.

Clinical safety outcomes

Many studies (n = 12) [14,15,17,20–25,27–29] examined the frequency of adverse events to assess the safety of combination therapy. Four studies [15,17,24,27] found significant improvement in the safety profiles of combination therapy, one study [21] reported mixed results, five studies [20,22,23,28,29] found no significant treatment-emergent adverse effect on either combination therapy or monotherapy, and two studies reported more nausea [14] and discontinuation [25] using the combination therapy. The combination of Oxycodone with Pregabalin/Gabapentin was found to be safer than monotherapy [15,17]. Gabapentin side effects were also minimized with the addition of B complex [24]. Pregabalin plus Duloxetine proved effective in some cases (patients with peripheral edema or insomnia), although it may raise the risk of nausea, vomiting, and hyperhidrosis [21].

Cost-effectiveness outcomes

Cost-effectiveness was measured in one study [25] with 7566 PDN subjects. This study included PDN population prescribed with one or more of the following: Duloxetine, Pregabalin, Gabapentin, TCAs (Amitriptyline, Desipramine, Nortriptyline), Opioids (Tramadol, Oxycodone, Morphine, Oxymorphone, Methadone, Levorphanol, Hydrocodone, Hydromorphone), or Lidocaine. This study had a significant population size and demographic differences between the monotherapy and combination therapy groups. The author concluded that the overall cost of monotherapy and combination therapy did not differ significantly ($818 vs $1425; $P = 0.63$).

Existing guidelines on neuropathic pain

The latest international guidelines recommend tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or γ-aminobutyric acid (GABA) analogs like Gabapentin and Pregabalin as the first-line treatment in managing PDN. Much evidence exists on the efficacy of these monotherapy drugs, but many have limited efficacy in providing adequate pain control. Currently, there is no head-to-head evidence on which first-line agents were to be used and which agents can be added in combination [29]. The primary objectives in managing diabetic patients with PDN are intensive glycemic control, managing risk factors, and pharmacotherapy. There are two approaches in pharmacological treatment: symptomatic treatments that aim to relieve painful symptoms of PDN to normalize physical and psychological distress and pathogenesis-oriented treatments that target the underlying pathophysiological mechanism causing nerve fiber loss [8,30].

Table 6. Comparison of selected guideline recommendations for drugs used in symptomatic treatment of PDN.

Drug	NNT*	EFNS (2010) [31]	AAN (2011) [32]	NeuPSIG IASP (2015) [33]	NICE (2020) [34]	AAN (2022) [35]
TCAs		First line				
Amitriptyline	1.3		Second line		First line	Second line
Desipramine	2.6			First line		
SNRIs		First line	Second line	First line		Second line
Duloxetine	6.0				First line	
Venlafaxine	3.1					
GABA analogs		First line		First line		
Gabapentin	5.8				First line	
Pregabalin	5.0		First line		First line	First line
Opioids		Second line	Second line	Second line		Second line

Tramadol	3.8				Second line	
Topical						
Capsaicin cream (0,075%)	6.6			Second line		

Abbreviations: AAN, American Academy of Neurology; EFNS, European Federation of Neurological Societies; NeuPSIG IASP, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; NICE, National Institute for Health and Care Excellence.
*The number needed to treat (NNT) was collected from Cochrane collaboration reviews for at least 50% pain relief compared to baseline.

Current gaps in the literature

Despite a growing number of trials, important gaps remain that limit confident guidance on combination therapy for PDN. Existing studies are heterogeneous in drug pairings, dosing regimens, and outcome measures, which prevents meaningful synthesis and head-to-head comparisons; many trials are small, short-term, or open-label, reducing power to detect durable benefits or rare harms. Long-term data on sustained pain control, nerve-function recovery, and functional outcomes are scarce, as are robust cost-effectiveness analyses in real-world settings. Safety reporting is often inconsistent, with limited evaluation of clinically relevant drug–drug interactions, polypharmacy effects, and adherence in older or multimorbid patients who represent much of the PDN population. There is also underrepresentation of diverse ethnic groups and of patients with varying diabetes duration and severity, and few mechanistic or biomarker studies that could identify which subgroups benefit most from specific combinations. Addressing these gaps will require larger, well-powered randomized trials with standardized endpoints, longer follow-up, pragmatic effectiveness studies, and integrated safety and pharmacoeconomic assessments.

Discussion

This scoping review synthesized evidence from 17 studies and found that pharmacological combination therapy for PDN generally provided greater pain reduction, improved nerve function, and better sleep outcomes compared with monotherapy. The most frequently studied and effective regimens involved Pregabalin-based combinations and Methylcobalamin-containing therapies. While study quality was generally high, with substantial to almost perfect inter-rater reliability, the evidence base remains heterogeneous, and many trials were constrained by short follow-up, small sample sizes, or open-label designs.

Clinical outcomes resulted in a consistent signal for superior analgesia with certain combinations, suggesting additive or complementary mechanisms of action. These findings suggest potential clinical benefit for patients who do not achieve adequate relief with a single agent. The American Academy of Neurology (AAN), the American Academy of Physical Medicine and Rehabilitation (AAPM&R), and the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) all recommend Pregabalin 300 to 600 mg/day as the first-line therapy for managing PDN [(32)]. Methylcobalamin-containing combinations were notable for nerve conduction improvements, supporting a potential disease-modifying or neurotrophic contribution beyond symptomatic relief [(36)].

Specifically, Pregabalin (inhibiting presynaptic voltage-gated calcium channels in dorsal horn neurons) combined with Duloxetine (enhancing synaptic norepinephrine and serotonin to augment descending inhibition) [(37)] may provide complementary inhibition of pain pathways at pre- and post-synaptic levels. Pregabalin supplemented with Amitriptyline (blocking sodium channels and inhibiting reuptake of norepinephrine/serotonin) [(38)] similarly targets peripheral excitability and central modulation, while Pregabalin plus topical Lidocaine (sodium-channel blockade) [(39)] adds localized peripheral silencing to central neuromodulation. Opioid–TCA pairings such as Morphine plus Nortriptyline combine μ-opioid receptor–mediated analgesia with noradrenergic enhancement of descending inhibitory control [(40)]. The addition of Methylcobalamin enhances nerve function by increasing the synthesis of neuronal lipids (myelin sheath), and nerve regeneration, and also acts as a neuroprotector [(36)]. Melatonin's antioxidant and anti-inflammatory actions may synergize with Pregabalin's central effects to improve sleep and pain interference. These mechanistic complementarities help explain the reproducible benefits observed for Pregabalin-based and Methylcobalamin-containing combinations in PDN [(41)].

Several other uncommon combinations have shown some benefits involving Prostaglandin E-1 (PGE1) and Melatonin. PGE1 is a vasoactive substance that produces constriction of the vascular wall followed by dilatation, resulting in increased arterial blood flow. This was demonstrated by a study that found that administering Lipo PGE1 improved peripheral nerve conduction velocity and increased mean dermal temperature [(42)]. Melatonin's high antioxidant capacity also serves as a neuroprotector. It effectively reduces free radicals, increases antioxidant enzyme expression, and decreases inflammatory protein expression in all cells [(43)]. Both medications, when paired with their respective safety profiles, have been demonstrated to be effective when used in conjunction with the other first-line prescribed drug in PDN.

Safety analysis showed most trials reported no significant increase in treatment-emergent adverse events with combination therapy compared with monotherapy, and some studies even reported fewer dose-related adverse effects due to the ability to reduce individual drug doses. However, adverse event profiles varied by agent class (e.g., increased nausea with some antidepressant combinations, opioid-related effects with opioid-containing regimens), even though the majority were neither serious nor life-threatening. This emphasizes the importance of individualized risk assessment when selecting combinations.

Cost-effectiveness analysis showed that combination therapy did not appear to significantly cut treatment costs. Although the combination method allows physicians to reduce the dose, and duration, and improve the safety profile of a certain drug, several circumstances may hinder efficacy, resulting in increased treatment duration. A study by Kuo *et al.* showed that once patients are on combination therapy, receiving new medications, or switching drugs, they are more likely to discontinue their index medications. When patients failed their first treatment, both mono- and combination therapy were likely to fail as well. Some older patients with polypharmacy (hypertension, diabetes, or other chronic conditions) also tend to not adhere to combination therapy because they experience drug-drug interactions [((25))]. The evidence base for cost-effectiveness remains sparse and context dependent.

This scoping review highlights several major limitations in the collected studies: (1) Heterogeneity and methodological limitations. Included studies differed widely in design (randomized, open-label, crossover, retrospective), sample size, duration (weeks to months), outcome measures (various pain scales, nerve conduction studies, sleep and quality-of-life instruments), and comparator strategies. Although the majority are randomized trials, several trials lacked adequate blinding or used open-label designs, increasing the risk of performance and detection bias. Short treatment durations in many studies limit conclusions about long-term efficacy, tolerability, and sustained nerve function changes. This heterogeneity precluded meta-analysis and limits our ability to make strong, quantitative comparative statements about the superiority of any specific combination; (2) Population and external validity limitations. Most trials enrolled patients with moderate to severe PDN and relatively long diabetes duration; therefore, findings may not generalize to patients with early or mild neuropathy, different comorbidity profiles, or diverse demographic groups. Retrospective and registry data introduced confounding by indication and treatment selection bias in observational analyses; (3) Outcome measurement gaps. There was inconsistent use of standardized, patient-centered outcome measures (e.g., responder rates, minimal clinically important difference, functional outcomes). Objective measures of nerve structure and function were included in only a subset of studies, limiting the ability to determine whether symptomatic improvements reflect true neurophysiological recovery. (5) Lastly, our search was limited to published studies and may not capture negative or ongoing trials, potentially overestimating the positive effects of combination therapy. Despite these limitations, the aggregated evidence supports considering combination therapy for patients with PDN who have inadequate pain control on monotherapy, particularly when the combination targets complementary mechanisms (e.g., neuromodulation plus neurotrophic support). Clinicians should weigh potential benefits against individual patient risk factors, drug–drug interactions, and tolerability, and should aim to use the lowest effective doses to minimize adverse effects.

CONCLUSIONS

This scoping review found that pharmacological combination therapy for PDN, particularly Pregabalin-based and Methylcobalamin-containing regimens, offers superior pain relief, improved nerve function, and better sleep compared with monotherapy, without added safety or cost concerns. Evidence remains limited by heterogeneity, short follow-up, and small samples. Future research should prioritize head-to-head RCTs of guideline-recommended combinations (e.g., Pregabalin + Duloxetine) versus high-dose monotherapy, with ≥6 months follow-up to assess durability and safety. Pragmatic trials incorporating patient-centered outcomes and cost-utility analyses are also needed to guide clinical practice and policy.

Conflicts of Interest

The authors declare no conflict of interest.

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Ethics Statements

The study does not need ethical approval from an ethics committee.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: J.F.A.B., H.S., Y.O.H., R.T.P., I.P.E.W.; data collection: J.F.A.B., H.S., Y.O.H.; analysis and interpretation of results: J.F.A.B., H.S., R.T.P., I.P.E.W.; draft manuscript preparation: J.F.A.B., H.S., Y.O.H., R.T.P., I.P.E.W. All authors have reviewed the results and approved the final version of the manuscript.

References

1. Girach A, Julian TH, Varrassi G, Paladini A, Vadalouka A, Zis P. Quality of Life in Painful Peripheral Neuropathies: A Systematic Review. *Pain Res Manag*. 2019;2019:2091960.

2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, *et al*. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119.

3. Hicks CW, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. *Curr Diab Rep*. 2019;19(10):86.

4. Preston FG, Riley DR, Azmi S, Alam U. Painful Diabetic Peripheral Neuropathy: Practical Guidance and Challenges for Clinical Management. *Diabetes Metab Syndr Obes*. 2023;16:1595–612.

5. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, *et al*. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care*. 2017;40(1):136–54.

6. Davoudi M, Rezaei P, Rajaeiramsheh F, Ahmadi SM, Taheri AA. Predicting the quality of life based on pain dimensions and psychiatric symptoms in patients with Painful diabetic neuropathy: a cross-sectional prevalence study in Iranian patients. *Health Qual Life Outcomes*. 2021;19(1):49.

7. Ziegler D, Papanas N, Schnell O, Nguyen BDT, Nguyen KT, Kulkantrakorn K, *et al*. Current concepts in the management of diabetic polyneuropathy. *J Diabetes Investig*. 2021;12(4):464–75.

8. Javed S, Petropoulos IN, Alam U, Malik RA. Treatment of painful diabetic neuropathy. *Ther Adv Chronic Dis*. 2015;6(1):15–28.

9. Sun W, Sanderson P, Zheng W. Drug combination therapy increases successful drug repositioning. *Drug Discov Today*. 2016;21(7):1189–95.

10. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Inj J Soc Res Methodol*. 2005;8(1):19–32.

11. Xie X, Wu C, Hao Y, Wang T, Yang Y, Cai P, *et al*. Benefits and risks of drug combination therapy for diabetes mellitus and its complications: a comprehensive review. *Front Endocrinol*. 2023;14:1301093.

12. Hong QN, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, *et al*. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. Education for Information. *Edu Info*. 2018;34(4):285–91.

13. Lynch ME, Clark AJ, Sawynok J, Sullivan MJL. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. *Anesthesiology*. 2005;103(1):140–6.

14. Freeman R, Raskin P, Hewitt DJ, Vorsanger GJ, Jordan DM, CAPSS-237 Study Group, *et al*. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Curr Med Res Opin*. 2007;23(1):147–61.

15. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *Eur J Pain*. 2008;12(6):804–13.

16. Agrawal RP, Goswami J, Jain S, Kochar DK. Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: a prospective double-blind randomized placebo-controlled study. *Diabetes Res Clin Pract*. 2009;83(3):371–8.

17. Gatti A, Sabato AF, Occhioni R, Colini Baldeschi G, Reale C. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. *Eur Neurol*. 2009;61(3):129–37.

18. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in post-herpetic neuralgia and diabetic polyneuropathy. *Curr Med Res Opin*. 2009;25(7):1677–87.

19. Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful

diabetic neuropathy treated with pregabalin. *J Pain*. 2010;11(5):462–71.

20. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, *et al*. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain*. 2013;154(12):2616–25.

21. Irving G, Tanenberg RJ, Raskin J, Risser RC, Malcolm S. Comparative safety and tolerability of duloxetine vs. pregabalin vs. duloxetine plus gabapentin in patients with diabetic peripheral neuropathic pain. *Int J Clin Pract*. 2014;68(9):1130–40.

22. Vasudevan D, Naik MM, Mukaddam QI. Efficacy and safety of methylcobalamin, alpha lipoic acid and pregabalin combination versus pregabalin monotherapy in improving pain and nerve conduction velocity in type 2 diabetes associated impaired peripheral neuropathic condition. [MAINTAIN]: Results of a pilot study. *Ann Indian Acad Neurol*. 2014;17(1):19–24.

23. Gilron I, Tu D, Holden RR, Jackson AC, DuMerton-Shore D. Combination of morphine with nortriptyline for neuropathic pain. *Pain*. 2015;156(8):1440–8.

24. Alvarado AM, Navarro SA. Clinical Trial Assessing the Efficacy of Gabapentin Plus B Complex (B1/B12) versus Pregabalin for Treating Painful Diabetic Neuropathy. *J Diabetes Res*. 2016;2016:4078695.

25. Kuo K-L, Brixner D, Lipman AG, Goodman M, Hung M, Oderda GM. Single- Versus Multiple-Drug Pharmacotherapy in the Management of Diabetic Painful Neuropathy. *J Pain Palliat Care Pharmacother*. 2016;30(3):184–94.

26. Didangelos T, Karlafti E, Kotzakioulafi E, Kontoninas Z, Margaritidis C, Giannoulaki P, *et al*. Efficacy and Safety of the Combination of Superoxide Dismutase, Alpha Lipoic Acid, Vitamin B12, and Carnitine for 12 Months in Patients with Diabetic Neuropathy. *Nutrients*. 2020;12(11):3254.

27. Sharma C, Kaur I, Singh H, Grover IS, Singh J. A randomized comparative study of methylcobalamin, methylcobalamin plus pregabalin and methylcobalamin plus duloxetine in patients of painful diabetic neuropathy. *Indian J Pharmacol*. 2021; 53(5) : 358 – 63.

28. Shokri M, Sajedi F, Mohammadi Y, Mehrpooya M. Adjuvant use of melatonin for relieving symptoms of painful diabetic neuropathy: results of a randomized, double-blinded, controlled trial. *Eur J Clin Pharmacol*. 2021; 77(11) \:1649–63.

29. Tesfaye S, Sloan G, Petrie J, White D, Bradburn M, Julious S, *et al*. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *The Lancet*. 2022;400(10353):680–90.

30. Ardeleanu V, Toma A, Pafili K, Papanas N, Motofei I, Diaconu CC, *et al*. Current Pharmacological Treatment of Painful Diabetic Neuropathy: A Narrative Review. *Medicina (Kaunas)*. 2020;56(1):25.

31. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, *et al*. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113-e88.

32. Bril V, England J, Franklin GM, American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation, *et al*. Evidence-based guideline: Treatment of painful diabetic neuropathy [RETIRED]: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76(20):1758–65.

33. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–73.

34. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings (CG173). *NICE*. 2013.

35. Price R, Smith D, Franklin G, Gronseth G, Pignone M, David WS, *et al*. Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary. *Neurology*. 2022;98(1):31–43.

36. Jk G, Sana QS. Potential Benefits of Methylcobalamin: A Review. *Austin J Pharmacol Ther*. 2015;3(3).1076.

37. Baldacara L. Duloxetine: An Update. *Res Soc Dev*. 2024;13(3):e7313345331

38. Pereira CdS, Cruz JN, Ferreira MKM, Baia-da-Silva DC, Fontes-Junior EA, Lima RR. Global Research Trends and Hotspots Analysis of the Scientific Production of Amitriptyline: A Bibliometric Approach. *Pharmaceuticals*. 2023;16(7):1047.

39. Haryalchi K, Olangian-Tehrani S, Kasmaei P, Eghbal SB, Heidarzadeh A, Mehrabian F, *et al*. The Importance of Intravenous Perioperative Lidocaine as an Adjuvant to Acute Postoperative Pain Control: A Narrative Review Article. *Arch Anesthesiol Crit Care*. 2025;11(4):567-572.
40. Mi W, Wang S, You Z, Lim G, McCabe MF, Kim H, *et al*. Nortriptyline Enhances Morphine-Conditioned Place Preference in Neuropathic Rats: Role of the Central Noradrenergic System. *Anesth Analg*. 2017;125(3):1032-1041.
41. Ajayi AF, Borisade MS, Oyedokun P, Akano OP, Ajayi LO, Oluwole DT, *et al*. Melatonin protect against pregabalin-induced gonadotoxicity via anti-oxidative, anti-inflammatory, anti-apoptotic, enzymatic and hormonal regulatory mechanisms in rats. *BMC Pharmacol Toxicol*. 2025;26(1):30.
42. Li Y, Tian H, Wu T. Prostaglandin E1 for diabetic neuropathy. *Cochrane Database Syst Rev*. 2017;2017(1):CD006051.
43. Hosseini A, Samadi M, Baeeri M, Rahimifard M, Haghi-Aminjan H. The neuroprotective effects of melatonin against diabetic neuropathy: A systematic review of non-clinical studies. *Front Pharmacol*. 2022;13:984499.