Aus dem Institut für Biometrie und Epidemiologie des Deutschen Diabetes-Zentrums
Leibniz Zentrum für Diabetes-Forschung an der Heinrich-Heine-Universität Düsseldorf
Direktor: Univ.-Prof. Dr. sc. hum. Oliver Kuß

Pharmacological treatment for painful and symptomatic diabetic neuropathy - a systematic review and network meta-analysis

Dissertation

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Velina Shishkova-Stoev 2026

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gez.:
Dekan: Prof. Dr. med. Nikolaj Klöcker
Erstgutachterin: PD Dr. Sabrina Schlesinger
Zweitgutachterin: PD Dr. Brenda Bongaerts

Summary:

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes, affecting about 30% of individuals. It manifests as limb pain and abnormal sensations such as burning, stabbing and paresthesia, significantly reducing quality of life. DPN represents a significant therapeutic challenge requiring pharmacological management. Although many drugs are used, neuropathic pain is difficult to treat, and many individuals experience insufficient relief. The evidence-based guidance remains inconclusive.

Aim: The aim of this project was to conduct a systematic and comprehensive comparison of pharmacological treatments for painful DPN and to identify the most effective options using a network meta-analysis (NMA).

Methods: A systematic review was conducted by searching PubMed, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov for randomized controlled trials published up to June 2024. Studies included adults (≥18 years) with type 1 or type 2 diabetes and diagnosed painful DPN, in which pharmacological interventions were evaluated. Pain was assessed as the outcome. Risk of bias was assessed using the RoB 2.0. The treatments were grouped by pharmacological class. Pairwise meta-analyses were conducted. Random-effects NMA calculated standardized mean differences (SMDs) with 95% confidence intervals (95% CI).

Results: Of 7,619 articles identified, 892 were assessed in full text and 130 in the NMA included; 113 of them were included in the pairwise meta-analyses. The mean age of participants was 58 years. Treatments included antidepressants (SNRIs, TCAs), anticonvulsants, ion channel and receptor modulators, cannabinoids, opioids, metabolic/vascular agents, antioxidants/supplements, vitamin D, B vitamins, phytopharmaceuticals, and topical treatments. Risk-of-bias was low in 27 studies, high in 43, and moderate in 60, mainly due to deviations from intended interventions and missing outcome data or selective outcome reporting (domains 2 and 3). All interventions were superior to placebo. The most effective were herbal/ adjunctive treatments (SMD [95% CI]: −1.26 [−1.78, −0.74]), opioids (−0.99 [−1.37, −0.60]), and antioxidants/ supplements (−0.91 [−1.27, −0.54]). In direct comparison of first-line treatments, antidepressants reduced pain more than anticonvulsants (−0.40 [−0.68, −0.12]).

Conclusion: A wide range of pharmacological treatments is available for pain reduction in painful DPN. All interventions were superior to placebo with small differences. Antidepressants were more effective than anticonvulsants.

Zusammenfassung

Die diabetische periphere Neuropathie (DPN) ist eine häufige Komplikation des Diabetes und betrifft etwa 30 % der Betroffenen. Sie äußert sich durch Schmerzen der Extremitäten sowie abnorme Missempfindungen wie Brennen, Stechen, was die Lebensqualität stark beeinträchtigt. Die DPN stellt eine bedeutende therapeutische Herausforderung dar und erfordert eine medikamentöse Behandlung. Obwohl zahlreiche Medikamente eingesetzt werden, ist neuropathischer Schmerz schwer zu behandeln, und viele Betroffene erfahren keine ausreichende Linderung. Die evidenzbasierte Leitlinienlage bleibt uneinheitlich.

Ziel: Ziel dieses Projekts war es, pharmakologische Behandlungen der schmerzhaften DPN systematisch und umfassend zu vergleichen und mittels einer Netzwerk-Metaanalyse (NMA) die wirksamsten Therapieoptionen zu identifizieren.

Methoden: Es wurde eine systematische Literatursuche in *PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews* sowie *clinicaltrials.gov* nach randomisierten kontrollierten Studien bis Juni 2024 durchgeführt. Eingeschlossene wurden Studien mit Erwachsenen (≥ 18 Jahren) mit Typ-1- oder Typ-2-Diabetes mit diagnostizierter schmerzhafter DPN. Der Schmerz wurde als Endpunkt bewertet. Das Verzerrungsrisiko wurde mit RoB 2.0 beurteilt. Alle Medikamente wurden nach pharmakologischen Klassen gruppiert. Paarweise Metaanalysen wurden durchgeführt. *Random-Effects NMA* berechneten standardisierte Mittelwertdifferenzen (SMD) und 95% Konfidenzintervalle (95% KI).

Ergebnisse: Von 7619 identifizierten Artikeln wurden 919 im Volltext geprüft und 130 eingeschlossen. Das Durchschnittsalter betrug 58 Jahre. Die untersuchten Medikamente umfassten Antidepressiva (SNRI, TZA), Antikonvulsiva, Iodkanal- und -rezeptor-Modulatoren, Cannabinoide, Opioide, metabolische/ vaskuläre Substanzen, Antioxidantien / Supplemente, Vitamin D, B-Vitamine, Phytopharmaka und topische Medikamente. Das Verzerrungsrisiko war in 27 Studien niedrig Verzerrungsrisiko, in 43 hoch und in 60 moderat, hauptsächlich aufgrund von Abweichungen von den vorgesehenen Interventionen und fehlenden Ergebnisdaten (Domäne 2 und 3). Alle Interventionen waren dem Placebo überlegen. Am wirksamsten waren Phytopharmaka (SMD [95% KI]:-1,26 [-1,78, -0,74]), Opioide (-0,99 [-1,37, -0,6]) und Antioxidantien/Nahrungsergänzungsmittel (-0,91 [-1,27, -0,54]). In direkten Vergleichen der beiden Erstlinientherapie reduzierten Antidepressiva die Schmerzen stärker als Antikonvulsiva (-0.40 [-0,68, -0,12]).

Schlussfolgerung: Es existieren viele heterogene Medikamente zur Schmerzreduktion bei der neuropathischen Neuropathie. Alle Interventionen waren dem Placebo überlegen und wiesen kleine Unterschiede zwischen den Gruppen auf. Antidepressiva waren wirksamer als Antikonvulsiva.

Abbreviation	Definition
ACE	Angotensine Converting Enzyme
ALA	Alpha-Lipoic Acid
ALC	Acetyl-L-Carnitine
AMPA receptor	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor
ATP	Adenosine Triphosphate
AWMF	Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissens
CB1	Cannabinoid Receptor type 1
CB2	Cannabinoid Receptor type 2
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
CoA	Coenzyme A
CYP (1A2)	Cytochrome P450
BPI	Brief Pain Inventory
DDZ	*Deutsches Diabetes- Zentrum*
DN4	Douleur Neuropathique 4
DPN	diabetic distal symmetric sensorimotor polyneuropathy
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GABA	Gamma-aminobutyric Acid
HbA1c	Hemoglobin A1c
IQR	Interquartile Range
MAOI	Monoamine Oxidase Inhibitor
NaSSA	Noradrenergic and Specific Serotonergic Antidepressants
NCV	Nerve Conduction Velocity
NF-kB	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NMA	Network Meta-Analysis
NMDA	N-Methyl-D-aspartate
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NSS	Neuropathic Symptom Score
PENS	Peripheral Percutaneous Electrical Nerve Stimulation
PPI	Present Pain Intensity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RKI	Robert Koch Institut

RoB 2.0	Cochrane Tool of risk of bias
ROS	reactive oxygen species
SF-MPQ	Short-form McGill Pain
SMD	standardized mean difference
SNARE	N-ethylmaleimide complex, SNAP receptor
SNRI	serotonin norepinephrine reuptake inhibitor
SSNRI	selective serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressants
TENS	Transcutaneous Electrical Nerve Stimulation
THC	tetrahydrocannabinol
TRPV1	transient receptor-potential-cation channel of vanilloid receptors, subtype 1
TSS	Total Symptom Score
VAS	Visual Analogue Scale
WHO	World Health Organization

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1 Introduction

Diabetes is a metabolic disease characterized by chronic hyperglycemia. It is a consequence of either a lack of insulin secretion, impaired insulin action, or both (1). Diabetes is associated with long-term micro- and macrovascular complications (2). Microvascular complications include diabetic retinopathy, nephropathy, and DPN, affecting the small blood vessels. Macrovascular complications cause cardiovascular disease, peripheral arterial disease, and cerebrovascular disease by affecting the large arteries (3).

Diabetic neuropathy comprises a heterogeneous group of nerve disorders caused by diabetes (4). Diabetic peripheral neuropathy (DPN), most commonly distal symmetric polyneuropathy, is the predominant form (5). DPN is typically defined as peripheral nerve dysfunction in people with diabetes after exclusion of other causes (6). It usually manifests with a length-dependent pattern of neuropathic pain, sensory loss, and/or paresthesia, often starting in the feet and progressing proximally. Common pain qualities include burning, electric shock-like, sharp and evoked pain (7). Chronic peripheral neuropathic pain refers to pain that persists or recurs for at least three months and arises because of a disorder of the peripheral somatosensory nervous system. Painful DPN affects up to 25% of people with diabetes, and its frequency rises with diabetes duration and cumulative metabolic and vascular injury (8). Existing reviews report that 10–15% of individuals with newly diagnosed type 2 diabetes may already have DPN, whereas prevalence may exceed 50% after more than 10 years of diabetes (7). This condition is widely considered underdiagnosed and undertreated (9).

Complete pain relief is uncommon in individuals with neuropathic pain, and a reduction in pain intensity of approximately 30–50% is generally regarded as a clinically meaningful treatment response (10). However, commonly used pharmacological therapies are often associated with modest efficacy and substantial adverse effects, requiring careful consideration of comorbidities, potential contraindications, and tolerability. A considerable proportion of people with DPN fail to respond adequately to first-line treatments and frequently undergo a trial-and-error approach to pharmacological management. Consequently, there is a growing need for further research into mechanism-based therapeutic strategies, with future clinical trials incorporating detailed pain phenotyping to support the development of more individualized approaches to pain management(9).

The burden of painful DPN is particularly profound and extends beyond pain intensity. Contemporary clinical guidance highlights associations with reduced daily functioning, sleep disorders, depressive symptoms, and reduced quality of life, underscoring that neuropathic pain is not only a sensory phenomenon but also a multidimensional condition affecting psychosocial well-being (9). In addition to its human burden, painful DPN generates substantial healthcare utilization and economic impact. Recent health-economic analyses indicate that painful DPN contributes to increased healthcare

expenditures and resource use, reflecting higher outpatient care needs, medical use, and management of complications (11). In conclusion, diabetic neuropathy, particularly painful DPN, presents a common, disabling, and costly complication of diabetes and there is a need for a rigorous comparative evaluation of available therapeutic options (9).

1.1 Epidemiology of DPN

Diabetes has become a global epidemic disease, and it represents an enormous public health challenge for every country. Diabetes prevalence has increased over the last decades worldwide (12). The latest International Diabetes Federation (IDF) Diabetes Atlas (2025) states that 11% of the global adult population is living with diabetes, and over 4 in 10 people are unaware of their condition. In 2014, more than 380 million people were living with diabetes worldwide; by 2024, approximately 589 million adults (13) . Projections indicate that by 2050, approximately one in eight adults worldwide will be affected by diabetes, representing an increase of about 46% compared with current prevalence. More than 90% of individuals with diabetes are diagnosed with type 2 diabetes, a condition influenced by a complex interplay of socio-economic, demographic, environmental, and genetic factors (13).
In Germany, a considerable increase in the prevalence of diabetes has also been observed (4). A review carried out within the context of the diabetes surveillance framework, performed by the Robert Koch Institute (RKI) in 2025, shows higher prevalence estimates compared with previous decades: 10.3% (population aged 18 to 79 years) (14, 15).
DPN represents a frequent complication of diabetes, with a prevalence of about 30% to 50% (16),(17). DPN is the most common neuropathy in developed countries, and diabetic symmetric sensorimotor peripheral neuropathy is the most prevalent form of DPN (18, 19). However, the prevalence of DPN has not been precisely established due to poor quality and quantity of epidemiological data, mainly because of poor ascertainment and a lack of population-based studies (14, 17). The increasing global prevalence of diabetes is accompanied by a rising incidence of diabetes-related complications, including DPN, peripheral artery disease, nephropathy, and diabetic foot disease (2). A recent meta-analysis found that the presence of chronic kidney disease was linked to an increased prevalence of DPN (2). Additionally, DPN contributes substantially to morbidity through painful neuropathic symptoms, impaired balance, and an increased risk of ulceration, while foot ulcers remain a major cause of non-traumatic amputation and are associated with increased mortality and health-care costs (20). Diabetic retinopathy and nephropathy are also well-recognized microvascular sequelae that further amplify the clinical burden of diabetes and complicate management (21).
Overall, DPN is a common complication of diabetes, impacting approximately 30% to 50% of individuals with diabetes. DPN is the most common neuropathy in developed countries (21),(22).

1.2 Etiology, Symptoms, Burden of DPN

1.2.1 Etiology of DPN

The determinants of type 2 diabetes involve an interplay of genetic susceptibility, epigenetic modifications, and lifestyle factors that are dynamic and interact with one another (23). Environmental exposures and behavioral factors such as diet, physical activity, smoking, and alcohol consumption may modulate genetic risk through epigenetic alterations and contribute to disease onset and progression through metabolic and inflammatory pathways (23). As diabetes progresses, DPN emerges as one of the most frequent and severe chronic complications (23, 24).

Other risk factors associated with DPN include older age, more severe hyperglycemia, progressively impaired glucose tolerance, and longer diabetes duration (25, 26). The established risk factors for metabolic syndrome are also relevant to the development and progression of DPN. This association between metabolic syndrome and DPN is not limited to type 2 diabetes (25). The EURODIAB study showed that 24% of the participants with type 1 diabetes developed DPN over an average follow-up period of 7.3 years. The incidence of DPN was linked not only to the duration of diabetes and glycated hemoglobin levels but also with elevated triglycerides, high body mass index, and baseline hypertension, which are key components of the metabolic syndrome (27).

1.2.2 Symptoms of DPN

DPN comprises painful and non-painful forms and predominantly affects the distal lower and/or upper extremities. DPN is typically symmetric and affects peripheral sensory nerves. Symptoms start distally in the feet and/or hands and spread proximally in a stocking-and-glove distribution (28). Foot ulceration and neuropathic pain are among the most clinically relevant consequences of DPN and contribute to higher morbidity and mortality (28).

Painful DPN is characterized by neuropathic pain: spontaneous burning, prickling, shooting, or electric-shock–like sensations, frequently accompanied by paresthesia, hyperalgesia, and allodynia; symptoms typically begin distally and symmetrically in the feet and may progress proximally over time (27). Pain intensity, spatial distribution, and the presence of stimulus-evoked pain vary considerably between patients and are key determinants of functional impairment and disability (29). Painful DPN is associated with a marked reduction in health-related quality of life, significant sleep disturbance and an increased prevalence of anxiety and depressive symptoms (30). Compared with individuals with painless DPN and the broader population of individuals with diabetes, those with painful DPN have higher healthcare utilization and substantially greater direct and indirect costs. These psychosocial and functional consequences further compound the burden of multimorbidity in people with diabetes, making effective pain control a major priority for both patients and healthcare systems (31).

1.2.3 Burden of DPN

Despite its high prevalence and substantial clinical burden, therapeutic outcomes in DPN remain unsatisfactory. Although several pharmacological agents are available, current guidelines primarily

focus on symptomatic pain relief rather than disease modification (27, 32, 33). Their overall efficacy is modest and inconsistent, which is commonly attributed to the complex and multifactorial pathogenesis of DPN (34). Consequently, a substantial therapeutic gap remains in the pharmacological management of painful DPN (18, 35).

Commonly used pharmacological agents in clinical practice, including anticonvulsants and antidepressants, have demonstrated only modest efficacy, with a significant proportion of individuals with DPN failing to achieve clinically meaningful pain reduction (36),(35). The limited efficacy of symptomatic treatments is further compounded by poor tolerability, drug–drug interactions, and high discontinuation rates, particularly in elderly patients with multimorbidity (35). As a result, many individuals with DPN continue to experience persistent pain and functional impairment despite ongoing treatment, contributing to psychological comorbidity (30).

Overall, the substantial burden of DPN, together with the lack of robust evidence for durable benefits of symptomatic pharmacotherapy, underscores a critical unmet medical need for therapeutic strategies that target the underlying pathophysiological mechanisms of nerve injury and promote functional recovery rather than transient symptom suppression (18), (32).

1.3 Pathogenesis of DPN

DPN is a multifactorial complication defined by progressive damage to peripheral nerves, resulting from metabolic, vascular, and neuroinflammatory mechanisms. Chronic hyperglycemia represents the central factor, triggering this complex cascade of biochemical pathways that lead to neuronal dysfunction and impairment (18).

The pathogenesis of DPN is highly complex and involves several interrelated metabolic, vascular, and neuroinflammatory mechanisms. Among the most significant are the toxic effects of chronic hyperglycemia and oxidative stress; impaired cellular metabolism resulting in the overproduction of adenosine triphosphate (ATP) and reactive oxygen species (ROS); nerve ischemia due to microvascular changes; altered expression of sodium and calcium channels; glial cell activation; and central sensitization of pain mechanisms (18, 26, 37).

In summary, these mechanisms illustrate the complex pathophysiology of DPN and help explain why treatment responses are often limited. At the same time, they highlight several potential therapeutic targets for the development of new treatments for painful DPN (26).

1.4 Therapy for DPN

1.4.1 Conventional First-line Therapies and Agents From the Same Interventional Groups for DPN

Several European guidelines address the pharmacological treatment of painful DPN. There is currently a general agreement on first-line drugs (38, 39). The guidelines generally consist generally of three therapeutic approaches: optimization of glycemic control, symptomatic pain treatment, and pathogenesis-related treatment (38, 40).

Optimal glycemic control is essential for the prevention and the delayed onset of DPN (38). Additionally, optimal glycemic control is also relevant for slowing the progression in the absence of therapies that directly reverse nerve damage (18). However, the effect of glycemic control differs between type 1 and type 2 diabetes. In individuals with type 1 diabetes, high-quality evidence recommends aiming for intensive glycemic control in the prevention and management of DPN (35). Long-term follow-up of the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glycemic control not only delayed the onset of neuropathy but also reduced the progression of electrophysiological indicators, including nerve conduction velocity and vibration perception thresholds (41).

In type 2 diabetes, glycemic control appears to have a more limited effect on the progression of neuropathy (42). The meta-analysis "Enhanced glucose control for preventing and treating diabetic neuropathy" (Callaghan et al.), which analyzed four trials with 6669 patients with type 2 diabetes, found a non-significant trend towards a small reduction in risk of DPN with enhanced glucose control (risk difference RD -0.58%, 95% CI -1.4 to 0.01) (43). The lack of a major effect of glucose control suggests that additional factors beyond hyperglycemia, including components of metabolic syndrome, are crucial in the pathophysiological mechanisms underlying DPN in type 2 diabetes (44). Therefore, the treatment strategy in this population should also focus on lipid control, blood pressure management, and weight reduction. Additionally, lifestyle modifications aimed at a balanced diet and regular exercise are recommended (45). On the other hand, glucose-lowering agents may have different effects on DPN incidence and progression. As a post-hoc analysis of the BARI 2D clinical trial showed, participants receiving insulin sensitizers had a lower incidence of DPN after four years compared with those receiving insulin or sulphonylureas (39, 46).

Symptomatic treatment focuses mainly on pain management. Pain is often described as stabbing, burning, electric shock-like. Many individuals with DPN experience persistent pain and associated disability. First-line pharmacological treatment options address pain. However, they are not effective for non-painful symptoms of DPN, such as numbness and paresthesia. These agents mainly include anticonvulsants and antidepressants, particularly serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs).

Anticonvulsants are included in the guidelines as a first-line treatment option and the leading agents are gabapentin and pregabalin. They are $\alpha 2$-δ calcium channel subunit binders of central and peripheral nociceptive neurons. They have been approved by both EMA and FDA for the treatment of neuropathic pain. Guidelines of the American Academy of Neurology state that gabapentin is a second-line therapy after pregabalin, whereas European guidelines, for instance the Association of the Scientific Medical Societies in Germany *(Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF) consider both agents as equivalent first-line therapies (39). Clinical studies, particularly of pregabalin, have reported more than 30-50% reduction in pain (47). However, not all trials have shown significant pain improvement compared to placebo. Additionally, both agents

are associated with adverse effects, such as dizziness, vertigo, peripheral edema, ataxia, visual disturbances, and drowsiness (48). Gabapentin has also been reported to reduce pain. However, it has been associated with dizziness and suicidal behavior (49). These adverse effects may present a therapeutic limitation. In addition, dose adjustment is required in individuals with renal impairment, which is highly relevant in a population with frequent diabetic kidney disease (50).

Other anticonvulsants, including sodium channel inhibitors such as carbamazepine, oxcarbazepine, eslicarbazepine, and topiramate, have also been studied in the treatment of painful DPN. These agents reduce neuronal excitability by blocking sodium channels, AMPA receptors, and activating GABA receptors (51). However, their evidence in painful DPN is limited, and their use is complicated by severe adverse effects, such as cognitive disorders, drowsiness, vertigo, ataxia, and gastrointestinal disorders. Moreover, hyponatremia, leukopenia, and liver damage can occur (51). Because of insufficient evidence and tolerability concerns, sodium channel inhibitors have not been routinely recommended in current guidelines, although they may be considered in individual cases (52). Evidence for other anticonvulsants such as lamotrigine, lacosamide, phenytoin, levetiracetam, and sodium valproate is also insufficient for routine recommendations (36, 53-55).

TCAs are also established first-line treatments in painful DPN (52). This pharmacological group includes amitriptyline, nortriptyline, clomipramine, imipramine, protriptyline. Amitriptyline is the most commonly used agent and has shown efficacy that appears non-inferior to that of pregabalin and gabapentin (56, 57). TCAs are thought to exert analgesic effects primarily through inhibition of noradrenaline- and serotonin reuptake at the presynaptic level, thereby enhancing descending inhibitory pathways, although additional sodium channel effects have also been proposed (58). Despite their potential efficacy, their use is limited by contraindications, anticholinergic adverse effects, cardiac safety concerns, and frequent drug interactions due to CYP metabolism (59, 60), (52, 60).

Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) and is also recommended as first-line therapy in both Europe and the USA (44). By inhibiting serotonin and norepinephrine reuptake, duloxetine increases the effectiveness of descending inhibitory pain pathways in the spinal cord (51). Duloxetine is also associated with improvement in the quality of life of individuals with painful DPN (52). However, duloxetine is contraindicated in liver failure, severe renal dysfunction, and uncontrolled hypertension. Common adverse effects include nausea and vomitting in the first weeks of treatment, dry mouth, decreased appetite, sleepiness, sweating, hyponatremia, and gastrointestinal disorders (39, 61). Furthermore, duloxetine may impair glycemic control by increasing glycated hemoglobin A1c (47). Duloxetine is a substrate of CYP1A2 enzymes and should not be prescribed along with monoamine oxidase inhibitors (MAOI), Saint John´s wort, as well as CYP1A2 inhibitors such as ciprofloxacin (52). Evidence for other SNRIs, such as venlafaxine, desvenlafaxine, milnacipran, and doxepin, remains limited and insufficient for routine recommendation in European guidelines, although some may be used off-label (62).

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, citalopram, sertraline, paroxetine, have also been explored for neuropathic pain but are not supported by sufficient evidence for routine use in painful DPN (44).

Noradrenergic and specific serotonergic antidepressants (NaSSA) such as mirtazapine have been tested for neuropathic cancer pain in small patient populations. Therefore, there is currently no recommendation for their use in DPN (42).

1.4.2 Second-/ Third-line and Topical Therapies for DPN

Opioids are common therapeutic agents used in patients with painful DPN. They act primarily through agonism at μ-opioid receptors in the central nervous system (CNS). Furthermore, there are weak and strong opioids (63). Weak opioids such as tramadol and dual-mechanism agents such as tapentadol have shown analgesic effects, but the evidence is still limited (64, 65). The Cochrane systematic review "Morphine for chronic neuropathic pain in adults" (Cooper et al., 2017) found insufficient evidence for the efficacy of morphine (66). Oxycodone showed a pain reduction of at least 30%. However, the evidence was still insufficient to support a recommendation for patients with DPN (49). Opioids are associated with adverse effects such as a high potential for addiction, sedation, nausea, constipation, respiratory depression, and other opioid-related adverse effects (62). For this reason, weak opioids are generally considered second-line and strong opioids third-line therapies, while some guidelines recommend opioids only as third-line treatment options (9, 36, 40, 67).

Cannabinoids have also been investigated in neuropathic pain. These are biologically active compounds used as anti-emetics, antiepileptic medications, and medications for chronic pain. Cannabinoids function by stimulating the cannabinoid receptor type 1 (CB1) and type 2 (CB2) within the endocannabinoid system and may modulate neurotransmitter release and pain processing (55). Available cannabinoid agents include dronabinol (also known as tetrahydrocannabinol or THC), nabilone, and nabiximols. Nabilone is a partial agonist of cannabinoid CB_1 and CB_2 receptors and binds with higher affinity and greater efficacy than THC (68, 69). A commonly used pharmacological agent is Sativex which contains both THC and cannabidiol in a 1:1 molecular ratio (70). A meta-analysis (Meng et al., 2017) suggested that cannabinoids provide a moderate analgesic effect in patients with neuropathic pain, yet well-designed and larger randomized studies are required to evaluate the benefit of these agents (71). In conclusion, cannabinoids are not recommended for DPN by the AWMF guidelines, although they may be considered as off-label use in cases of treatment failure (52).

Several additional pharmacological approaches have been tested in painful DPN, including NMDA receptor antagonists, NSAIDs, local capsaicin, botulinum toxin, and lidocaine (61, 72-74). While some of these interventions, particularly capsaicin 8% patch and topical lidocaine, appear promising, the evidence base is variable in quality and quantity.

Capsaicin 8% patch is recommended as a second-line option in some guidelines and may offer pain relief with fewer systemic adverse effects than oral therapies (40, 52). Capsaicin is an active extract of

chili peppers and a member of the vanilloid family (75). It acts as an agonist at vanilloid receptor subtype 1 (TRPV1) (76). Capsaicin is used as an analgesic in concentrations between 0.025% and 0.1%. However, the concentration of 8% has proven to be effective in individuals with painful DPN (44). Some studies have provided evidence for superiority compared with oral pregabalin, duloxetine, and gabapentin for pain relief among DPN patients (39, 77).

Lidocaine has also shown promising effects and appears relatively well tolerated, but further comparative trials are needed. Lidocaine is a voltage-gated sodium channel blocker of the abnormally functioning neuronal sodium channels in the dermal A-δ and C fibers. As a result, the generation of ectopic action potentials is suppressed. Studies have demonstrated pain relief in patients with DPN comparable to the efficacy of pregabalin, amitriptyline, gabapentin (78, 79).

Botulinum toxin may represent another potential option, although the current evidence is based on only a few small studies. Botulinum toxin blocks the formation of the soluble N-ethylmaleimide complex (SNARE). Consequently, the release of acetylcholine is blocked resulting in muscle paralysis (80). However, evidence has been presented that botulinum toxin also reduces the release of pro-inflammatory mediators such as prostaglandins, substance P, glutamate, calcitonin gene-related peptide (CGRP) in peripheral nerves and dorsal roots, which leads to pain relief. The meta-analysis "Botulinum Toxin-A for Painful Diabetic Neuropathy" (Lakhan et al., 2015) provided evidence of a significant pain reduction, although it includes two studies and a small population of only 58 patients (81).

The NMDA receptor antagonists include ketamine, memantine, dextromethorphan, and amantadine. A systematic review (Aiyer et al., 2017) provided evidence that ketamine infusion has a strong effect on neuropathic pain. Nevertheless, the use of ketamine for DPN is neither EMA- nor FDA-approved, and it requires an expensive setup with monitoring for clinical safety. Therefore, NMDA receptor antagonists are not recommended for the treatment of painful DPN (61).

Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the management of neuropathic pain. Nevertheless, they still lack adequate evidence. A systematic review (Moore et al., 2015) showed only third-tier evidence of very low quality, so that there is no evidence to support or refute the use of oral NSAIDs to treat neuropathic pain conditions such as DPN (82).

Alpha-lipoic acid (ALA) is an antioxidant with potential pathogenesis-oriented effects in painful DPN. It can scavenge a variety of reactive oxygen species (ROS), neutralize free radicals and regenerate other antioxidant systems such as vitamin C and E, and enhance glutathione synthesis (18, 83). ALA also has an anti-inflammatory effect by inhibiting I Kappa B kinase and thereby suppressing NF-kB-mediated cytokine activation (83). Several randomized controlled trials and meta-analyses have suggested beneficial effects of ALA on pain and other neuropathic symptoms, although certainty of evidence remains limited by incomplete reporting and study heterogeneity (84-86). ALA is recommended in the latest S2 guidelines in Germany as a second-line treatment (38, 40, 87).

Overall, current guidelines for painful DPN recommend pregabalin, gabapentin, duloxetine, and TCAs as first-line therapies; capsaicin 8% patch and ALA as a second-line option (although ALA is recommended only in Europe); and opioids as third-line treatments. Nevertheless, many pharmacological interventions remain insufficiently studied, and the available evidence is often limited by small sample sizes, short follow-up durations, and inconsistent outcome assessment.

1.4.3 Alternative Therapy Approaches for DPN

Alternative and pathogenesis-oriented pharmacological approaches have been investigated particularly for individuals with painful DPN who are unresponsive to, or intolerant of, first- and second-line symptomatic therapies. These therapeutic agents are of interest because they may target biological mechanisms underlying the neuropathic process rather than acting solely as analgesics (88).

Epalrestat, an aldolase reductase inhibitor, has been investigated in individuals with DPN and has been used particularly in Japan and India (50, 88, 89). Aldose reductase is an aldo-keto reductase that catalyzes the first step in the polyol pathway that converts glucose to sorbitol. During hyperglycemia, the flux of glucose via the polyol pathway increases significantly, resulting in the excessive formation of sorbitol (89). The inhibition of aldose reductase suppresses the polyol pathway-driven accumulation of osmotically active sorbitol, and thus delays the development of DPN. However, its availability and evidence base remain regionally limited (89).

Several nutritional and supplement-based therapies have also been studied. Vitamin E is another antioxidant, and its effect in reducing neuropathic symptoms was investigated in individuals with DPN. The VENUS study (Hor et al., 2018) indicated that oral mixed tocotrienols did not reduce neuropathic symptoms after one year of treatment. Therefore, the current evidence does not support a clear therapeutic benefit in DPN (90).

Benfotiamine, a synthetic derivative of thiamine (vitamin B1), is mainly available as an over-the-counter drug for the treatment of DPN (91). A considerable deficiency of vitamin B1 has been found among individuals with DPN, and, as in individuals with alcohol use disorder, it may also lead to polyneuropathy (92). Consequently, these symptoms may be improved by supplementation of benfotiamine (92). However, the evidence for benfotiamine in the treatment of DPN is still limited due to the limited number of high-quality studies (93).

Acetyl-L-carnitine (ALC), a derivative from the acetylation of carnitine in the mitochondria, has attracted attention because of its neuroprotective and potentially analgesic properties. ALC facilitates the function of coenzyme A (CoA) and can eliminate oxidative products (94). Its effects on the peripheral nerves include increasing nerve conduction velocity (NCV), reducing sensorineural loss, and supporting nerve regeneration (93). Several clinical trials suggest that ALC is effective and safe in treating painful DPN. However, direct comparisons with established standard-of-care treatments are lacking, and long-term evidence remains limited (93).

Herbal oils have been identified as a potentially relevant complementary treatment approach in painful DPN (95). Several herbal preparations used in DPN, including lavender, Citrullus colocynthis,

nutmeg, and green tea extract oil, have been investigated in RCTs. Their potential therapeutic effects may be mediated through modulation of oxidative stress, inflammatory pathways, local sensory stimulation associated with massage, and aromatherapy-based application (96). In addition, herbal oils may offer a favourable safety and tolerability and may therefore be promising adjunctive options, especially in older individuals with multimorbidity and polypharmacy. However, the currently available evidence remains limited due to small sample sizes and short treatment durations, so their role in the pharmacological management of painful DPN has not been clearly identified (97).
To provide a comprehensive overview, the present systematic review and network meta-analysis also includes RCTs investigating a broad range of less established pharmacological interventions, such as gamma-linolenic acid, omega-3 fatty acids, cilostazol, beraprost, cyclandelate, coenzyme Q10, folic acid, magnesium, nano curcumin, quercetin, ginkgo biloba, angiotensin converting enzyme (ACE) inhibitor, rosuvastatin, liraglutide among others (98).

1.4.4 Clinical Problem and Objective

The treatment goals in painful DPN include achieving a clinically meaningful pain reduction >30%, improving physical function, sleep, and quality of life (87). Although multiple pharmacological treatments are available, recent evidence suggests that only 38% of individuals with polyneuropathy reporting clinically relevant pain receive medical treatment (73). One possible explanation may be that treatment selection remains challenging due to inconsistent recommendations across evidence-based guidelines and variable findings from existing systematic reviews (50).
Although numerous randomized clinical trials (RCTs) have investigated pharmacological agents for painful DPN, their comparative effectiveness remains insufficiently defined (36). The available evidence is characterized by substantial heterogeneity in outcome measures, study design, intervention duration, and participant populations, impacting comparability across studies (36). As a result, clinicians face considerable uncertainty when selecting optimal pharmacotherapy (36).
Existing systematic reviews have attempted to synthesize the evidence. However, they also present important limitations. Many reviews focus on pairwise comparisons or specific drug classes rather than providing a comprehensive comparison of all relevant treatments (49, 53, 54, 65, 66, 79, 82). Furthermore, some reviews have focused generally on neuropathic pain populations rather than DPN-specific cohorts, thereby reducing applicability to clinical decision-making in DPN (36, 49, 65, 66, 79). In addition, some reviews are narrative in nature and lack a systematic methodology (97).
Methodological limitations at the trial level further reduce the quality of evidence. Previous reviews have highlighted the generally modest efficacy of available pharmacological treatments, large placebo responses, short study durations, and high dropout rates due to adverse effects (36, 59). The quality of evidence is often limited by the small number of trials for many pharmacological interventions (59). In addition, selective reporting bias may arise from incomplete reporting of unpublished or negative trials, potentially leading to an overestimation of treatment effects (36, 59, 99). Some systematic

reviews also rely on previously published reviews and reuse extracted data, which may repeat earlier errors or bias and reduce methodological independence (59).

NMA provides a methodological framework to address these limitations by integrating both direct and indirect evidence from randomized controlled trials within a single analytical model. This approach enables the simultaneous comparison and ranking of multiple interventions, including those that have not been directly compared in head-to-head trials (100). However, to date, no sufficiently comprehensive NMA has systematically included all major pharmacological classes for painful DPN using uniform inclusion criteria and standardized outcome measures, leaving an important gap in the evidence base.

This dissertation aims to provide a comprehensive comparative evaluation of pharmacological treatments for painful DPN. Its novelty lies in:

1) the inclusion of a broad range of pharmacological treatments with European Medicines Agency (EMA) or U.S. Food and Drug Administration (FDA) approval, regardless of the indication, including standardized, adjunctive, and local pharmacotherapy;

2) the evaluation of treatment efficacy in pain reduction across multiple intervention groups; and

3) the use of NMA, which enables the systematic simultaneous comparison and ranking of multiple available pharmacological interventions within a single analytical framework.

1.4.5 Aim of the Dissertation

The aim of this dissertation was to systematically evaluate the efficacy of pharmacological treatments for painful DPN systematically and comprehensively and to establish a comparative ranking using a NMA that incorporates both direct and indirect comparisons (36, 100-102). In addition, this dissertation may highlight areas in which further high-quality randomized research is needed. The findings of the present project may help guide clinicians, guideline developers, and researchers in finding appropriate therapeutic options for individuals with painful DPN (103).

2 Methods

This is a systematic review and network meta-analysis of randomized controlled trials evaluating pharmacological treatments for painful DPN, aiming to comprehensively compare available therapeutic options and estimate their relative efficacy for pain reduction in adults with type 1 or type 2 diabetes. All study procedures were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for network meta-analysis (103). A predefined protocol was followed to ensure methodological rigor and transparency, and it was registered at Prospero (https://www.crd.york.ac.uk/PROSPERO/view/CRD42024564222). A comprehensive literature search was performed in electronic databases to identify eligible studies. Study selection, data extraction, and assessment of methodological quality were carried out using standardized procedures.

2.1 Eligibility Criteria

A systematic review was conducted using comprehensive searches in relevant electronic databases to identify eligible studies.

The search included all randomized controlled trials published up to June 2024. Eligible studies enrolled adults aged 18 years or older with type 1 or type 2 diabetes and a diagnosis of painful DPN, in whom pharmacological interventions were evaluated and pain-related outcomes were reported (103). Studies that met the eligibility criteria were included. Data from the included studies were extracted (104).

The eligibility criteria were summarized in a PICOS-question (Table 1). PICOS stands for four different components of a health question. P stands for patient or population; I for intervention; C for comparison; O for outcome; and S for study design (105).

Participants: Participants in the studies had to be 18 years old or older and must have type 1 or 2 diabetes and painful DPN. Studies including pregnant women were excluded.

Intervention: Any pharmacological treatments approved by EMA or FDA for any indication, including pharmacotherapies used off-label for DPN, were included. This includes oral, intravenous, and local therapies as well as adjunctive treatment (dietary supplements). The doses and route of administration were not evaluated. The duration of the therapy had to be 3 weeks or longer.

Comparison: The pharmacological treatment had to be compared either to placebo, standard-of-care treatment, or another pharmacological treatment.

Outcome: The primary outcome of interest was pain, assessed by validated pain assessment scores. As the included RCTs used a variety of different pain scores, direct comparability of the studies was limited.

To address this heterogeneity and ensure a consistent outcome selection, a predefined ranking system was established based on the frequency with which each instrument was used across the studies. This approach prioritized the most frequently used and thus most comparable outcome measures within the included studies.

In cases where multiple pain scales were reported within a single study, the outcome corresponding to the highest-ranked instrument was selected for analysis.

The ranking system included the following pain measurement scales (in descending order of frequency of use): Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Brief Pain Inventory (BPI), Short Form McGill Pain Questionnaire (SF-MPQ), Present Pain Intensity (PPI), Douleur Neuropathique en 4 questions (DN4), Neuropathic Pain Symptom Inventory (NPSI), Likert scale, McGill Pain Index, Pain Intensity Score, Total Symptom Score (TSS), and Neuropathic Symptom Score (NSS). The last two scores assessed neuropathic pain alongside associated symptoms (e.g., paresthesia and numbness).

Study design: Only randomized controlled trials (RCTs) with parallel-group and crossover designs were included. RCTs had to provide effect estimates (mean differences with the 95% confidence interval (95% CIs). The articles must have been peer-reviewed and be available as full-text articles.

Table 1: PICOS question

Participants	≥ 18 years Type 1 or type 2 diabetes DPN No pregnant women
Interventions	Pharmacological treatment for DPN with an intervention duration of 3 weeks or longer
Comparator	Placebo Standard-of-care treatment Other pharmacotherapies
Outcome	Primary outcome: Pain
Study design	RCTs: with parallel and cross-over design

PICOS stands for: P- participants; I- intervention; C- comparison; O- outcome; S- study design.

2.2 Literature Search

A search strategy was predefined for databases and used to search for articles without any restrictions (103). The search terms included the condition "diabetic peripheral neuropathy", the types of studies of interest "randomized controlled studies", and pharmacological treatment. These three generic terms were combined with the conjunction "AND". A predefined list of relevant pharmacological treatments that were mentioned in systematic reviews and meta-analyses was created (106). All pharmacotherapies were included in the pharmacological treatment search term and were linked with "OR". The search strategy was then adapted for every database (see full electronic search strategy in Appendix) (106).

RCTs were identified through an initial literature search on 15.11.2019 using this search strategy in the databases PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and clinicaltrials.gov (107, 108). Additionally, the reference lists from the retrieved articles and systematic reviews and meta-analyses were checked to identify further relevant studies (103).

All search results were imported into EndNote and were assessed to determine whether they met the inclusion criteria. After removing duplicates, studies with irrelevant titles or abstracts were excluded. A second, more thorough check was conducted in which the full texts of the studies were assessed for eligibility (109). The excluded studies were filed in EndNote together with the reason for exclusion. All studies were screened by the doctoral student and in duplicate by a second investigator (researcher from *Deutsches Diabetes Zentrum*, DDZ). We discussed any disagreements and reached a final decision (109).

We conducted an update of the search on 08.04.2022 to identify newly published relevant studies from the period between 2019 and 2022 and continued to work in Covidence (110).

2.3 Data Extraction

Relevant data from the studies were extracted in pilot-tested Excel spreadsheets (103). The following study characteristics were of interest: the first author's name, publication year, the country where the study was conducted, study design, number of participants in the intention-to treat-analysis, number of participants in the per-protocol-analysis, follow-up duration (weeks), drop-out rate in percent, proportion of males in percent, mean baseline age, diabetes type, proportion of participants with diabetes type 2 in percent, mean baseline hemoglobin A1c (HbA1c), percent insulin-dependent patients, duration of diabetes, duration of neuropathy, trial duration in weeks, treatment arms with description pharmacological treatment, outcome measure, effect estimates for the primary outcome pain according to our ranking system- mean difference with the corresponding standard deviation and adverse effects (see Table data extraction in Appendix). The adverse effects were presented as an Excel-generated pie chart. All data were extracted by the doctoral student and a second investigator checked the data extraction to avoid mistakes (103).

2.4 Risk of Bias Assessment

The risk of bias of the studies was evaluated using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2.0), which has been developed to provide a structured, transparent, and outcome-specific assessment of potential sources of bias in randomized studies (111). The RoB 2.0 tool assesses bias at the outcome level and includes signaling questions to support domain-level judgments based on prespecified criteria (112). The tool comprises five distinct domains of bias, addressing key aspects of trial design, conduct, and reporting:

1- bias arising from the randomization process;
2- bias due to deviations from the intended interventions;
3- bias due to missing outcome data;
4- bias in the measurement of the outcome; and
5- bias in the selection of the reported result.

For crossover trials, the additional S-domain of the RoB 2.0 tool was applied to assess potential bias arising from period effects and carryover effects, which are specific methodological concerns in crossover study designs (111). For each included study, a risk-of-bias judgment (low, some concerns, or high risk of bias) was assigned for each individual domain. An overall risk-of-bias judgment for each study was subsequently derived based on the combined assessments across all relevant domains, in accordance with the RoB 2.0 guidance (111). The rating was assessed by two investigators independently (the doctoral student and a researcher from DDZ). Any disagreements were resolved through discussion, and if consensus could not be reached, a third independent reviewer was consulted

for adjudication (112). The Risk-Of-Bias VISualization (robvis) tool was used to generate graphical summaries of the risk-of-bias assessment (113)

2.5 Classification of Pharmacological Interventions

Initially, the data of each pharmacological intervention were extracted. This comprehensive approach resulted in the identification of more than 100 distinct pharmacological treatment regimens (103). In accordance with recommendations of PRISMA-NMA, the interventions were subsequently grouped according to their pharmacological class (103). By reducing excessive fragmentation of treatment nodes and improving network connectivity, this strategy enabled the conduct of a more robust and clinically relevant network meta-analysis.

The classification was based on shared or similar pharmacodynamic mechanisms of action, resulting in the merging of treatments into the following 11 pharmacological classes: antidepressants/ serotonin and noradrenaline reuptake inhibitors (SNRIs)/ tricyclic antidepressants (TCAs); anticonvulsants/ neuropathic pain medications; ion channel and receptor modulators/ other analgesics; cannabinoids; opioids; metabolic/ vascular agents; antioxidants/ supplements; vitamin D; B-vitamins; herbal and adjunctive treatments; and topical/localized pharmacological therapies (Table 2).

Table 2: Classification of pharmacological interventions

№	Pharmacological class	Medications
1	Antidepressants / SNRIs / TCAs	desvenlafaxine,duloxetine,venlafaxine, reboxetine,nortriptyline,dextrometorphan
2	Anticonvulsants/ Neuropathic pain medications	pregabalin, gabapentin, mirogabalin, lacosamide, oxcarbazepine, eslicarbazepine, lamotrigine, Topiramate, zonisamide, sodium valproate
3	Ion channel and receptor modulators / other analgesics	mexiletine, lanepitant, clonidine, baclofen
4	Cannabinoids	sativex, nabilone
5	Opioids	oxycodon, tramadol, tapentadol, buprenorphine
6	Metabolic/ vascular agents	glyceryl trinitrate spray, isosorbide dinitrate spray, nitroglycerin transdermal, pentoxifyline, beraprost, cilostazol, rosuvastatin, cytoflavin, hesperidin, empagliflozin
7	Antioxidants / supplements	alpha-lipoic acid, coenzyme Q10, resveratrol, quercetin, vitamin E, acetyl-L-carnitine, gamma-linolenic acid, palmitoylethanolamide, nano curcumin, ginkgo biloba
8	Vitamin D	
9	B-Vitamins	vitamin B12, metanx
10	Herbal/ adjunctive treatments	nutmeg oil, citrullus colocynthis oil, lavendel oil, nerve support formula, green tea extract oil
11	Topical/ localized pharmacological therapies	lidocaine, capsaicin, botulinum toxine

The pharmacological treatments were classified based on their pharmacodynamic actions.

2.6 Statistical Analysis

The quantitative synthesis was conducted using a two-step analytical approach that included pairwise meta-analysis and network meta-analysis. Since the outcomes were measured using different scales across RCTs, the measurement scales differed substantially. Therefore, a unitless effect measure was used and calculated as standardized mean differences (SMDs) and 95% confidence intervals (95% CIs) to ensure comparability of the results.

The SMD was computed as the difference between the post-treatment means of the intervention and control groups divided by the pooled standard deviation (114). The pooled standard deviation was calculated using the following formula:

$$SD_{pooled} = \sqrt{\{[(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2]/ n_1 + n_2 - 2\}}$$

To reduce the upward bias in effect-size estimates from small RCTs, SMDs were adjusted using Hedges' correction factor, as recommended by the Cochrane Collaboration, defined as:

$$J = 1 - 3/ [4(n_1 + n_2) - 9]$$

The corrected effect size was obtained by multiplying the SMD by the factor J (114). This approach ensures comparability of effect estimates by standardizing mean differences relative to the pooled standard deviation within each study (115). Both the pairwise- and network meta-analyses aimed to include intention-to-treat data; a per-protocol analysis was conducted only for studies which did not report the outcome for the intention-to-treat population.

The proportion of adverse events for each intervention group was calculated by dividing the total number of reported side effects in that interventional group by the total number of side effects reported across all treatment arms.

2.6.1 Pairwise Meta-Analyses

The pairwise meta-analyses provided a transparent assessment of the available direct evidence and served as the empirical foundation for the subsequent network meta-analysis. All pairwise meta-analyses were conducted using STATA 14.1.

In the first step, pairwise meta-analyses were performed to compare each pharmacological intervention with placebo or control, providing pooled estimates of direct treatment effects, when direct evidence from randomized controlled trials was available. For each pharmacological class, SMDs with corresponding 95% CIs were calculated using a random-effects model to account for both within- and between-study variability (116). The SMDs were calculated based on post-treatment means, standard deviations, and sample sizes of the intervention and control groups. The pooled estimates were obtained using the DerSimonian and Laird method, which was used to estimate the between-study variance (117).

Forest plots were used to visualize the results of the included studies, displaying the SMDs with their corresponding 95% CIs (118). A negative SMD indicates that the intervention reduced pain compared with the control group, whereas a positive SMD indicates higher pain levels in the intervention group relative to the control group. An SMD of 0 indicates no difference between the intervention and

control groups (118). Statistical significance was determined based on the 95% CI: if it did not cross 0, the results were considered statistically significant (118). The diamond represents the pooled effect estimate for the corresponding intervention group. The center of the diamond indicates the overall effect size, while the left and right edges correspond to the lower and upper bounds of the 95% CI (119). Effect sizes were interpreted according to Cohen's guidelines (0.2- small, 0.5- medium, 0.8- large) (120).

Between-study heterogeneity was assessed using I^2, which quantifies the proportion of total variability attributable to heterogeneity rather than chance (121-123). I^2 values range from 0-100% and were interpreted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions meaning that 0% showed no heterogeneity and 100% indicated complete heterogeneity (123).

2.6.2 Network Meta-Analysis

A frequentist network meta-analysis (NMA) was conducted to synthesize the results across the studies. NMA is an extension of pairwise meta-analysis and allows the simultaneous comparison of direct effects within trials and indirect effects between trials (102). Treatments that have not been directly compared in head-to-head trials can be evaluated through a shared comparator (124). This approach allowed for the integration of both direct and indirect evidence across the treatment network, thereby enabling comparisons between interventions that had not been directly compared in head-to-head trials (100).

All treatment effects were estimated using a random-effects model within a frequentist framework. SMDs and their corresponding 95% CIs were estimated for each study and pooled using inverse-variance weighting (125).

The geometry of the treatment network was illustrated using network diagrams, in which node size represented the number of participants per treatment and edge thickness represented the number of studies informing each direct comparison (126).

The results of the NMA were presented using forest plots comparing each pharmacological treatment against placebo. A league table was generated to display all pairwise comparisons between the treatments, expressed as SMDs and 95% CIs (127).

To rank treatments according to their efficacy in reducing pain in DPN, p-scores were calculated. The p-scores are a frequentist ranking measure that quantifies the extent of certainty that one treatment is better than alternative treatments, ranging from 0 to 1, with higher p-scores indicating a higher probability that a treatment is among the most effective options (128).

All analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria), version 4.5.2, with the netmeta package (129, 130) .

2.6.3 Publication Bias of the Pairwise Meta-analyses

Publication bias and small-study effects were assessed in accordance with Cochrane guidelines. To evaluate them, we used funnel plots and Egger's test if the analysis included at least 10 studies (112,

131, 132). Potential publication bias could be considered if the funnel plot appeared asymmetrical or if Egger's test yielded a statistically significant small-study effect (p-value < 0.10) (132).

2.6.4 Transitivity Assessment of the NMA

Transitivity is a key assumption of network meta-analysis and implies that treatment comparisons are valid across trials provided that relevant effect modifiers are similarly distributed across treatment comparisons (126). To evaluate this assumption, we visually compared the distributions of potential effect modifiers across the available direct comparisons using boxplots (133). We considered age and trial duration as potential effect modifiers.

2.6.5 Consistency Assessment of the NMA

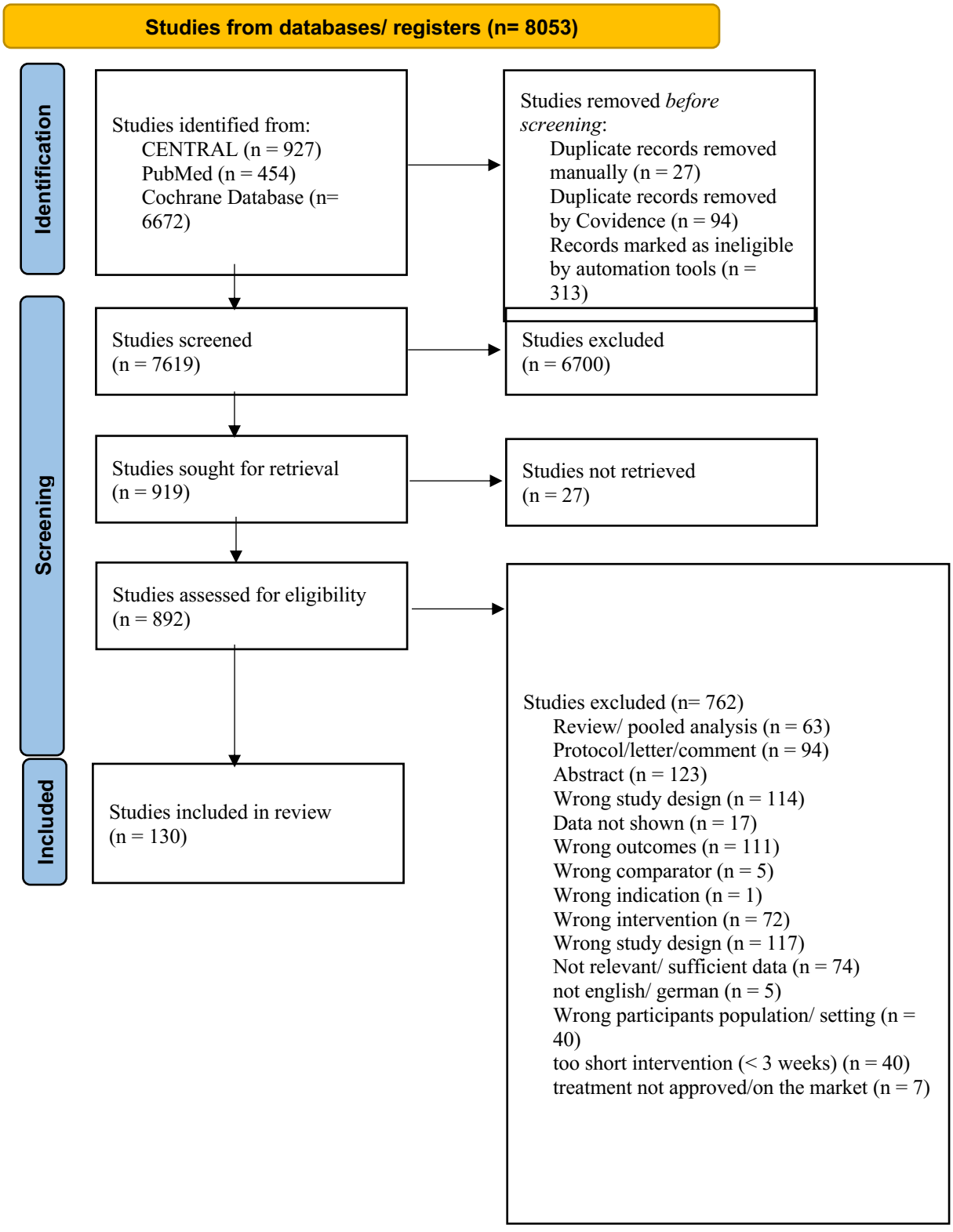
The assumption of consistency is defined as an agreement between direct and indirect evidence within the treatment network. Consistency implies that the estimated treatment effects derived from head-to-head comparisons agree with those obtained through a common comparator. Furthermore, the validity of the results depends on the assumption of consistency (126, 134). To assess this assumption, we generated forest plots which simultaneously show the direct and indirect treatment effects with 95% CIs, allowing for a comparison between direct and indirect evidence (135). Consistency was assumed when direct and indirect estimates were similar in direction and magnitude and when their 95% CIs overlapped. Substantial differences suggested potential inconsistency (134).

3 Results

3.1 Literature Search

A total of 7,619 articles were identified. After title and abstract screening, 892 potentially relevant studies were assessed in full text. Of these, 130 studies met the inclusion criteria for the network meta-analysis, and 113 of them were included in the pairwise meta-analyses. The rest (17 studies) compared the investigating medication with an active control and not with placebo. The results of the study selection process are summarized in a PRISMA 2020 flow diagram (Figure 1) (103).

Figure 1: PRISMA 2020 flow diagram of data processing and analysis



Flow chart presents the identification, screening, eligibility assessment, and inclusion of studies for the present systematic review and network meta-analysis in accordance with the PRISMA 2020 statement (103). 27 reports were not retrieved because full texts could not be obtained despite requests through library services and author contact. The complete list of excluded studies is provided in the Appendix.

3.2 Study Characteristics

Table 3 shows a summary of the main characteristics across the included studies and Table 4 presents all characteristics of each RCT. Most studies were conducted in the United States of America and Asia. Most studies had double-blind, placebo-controlled parallel study design (118 studies), followed by: double-blind, active-controlled parallel study design (22 studies); double-blind, placebo-controlled crossover study design (eleven studies); double-blind active-controlled crossover study design (six studies); single-blind, placebo-controlled parallel study design (two studies); and single-blind, active-controlled parallel study design (one study). The sample size varied considerably across the studies, ranging from 11 participants (Simpson et al., 2001) to 1269 participants (Thienel et al., 2004), according to the intent-to-treat analysis (136, 137). The study duration and follow-up varied among the studies as well- from 3 weeks (Ala et a., 2022) to 208 weeks (Ziegler et a., 2011) (38) (Table 4). The mean age of participants was 58 years (Table 3). The mean number of men study participants was 51%. A total of 86 studies included participants with both type 1 and 2 diabetes mellitus; 36 studies exclusively enrolled participants with type 2 diabetes mellitus; and eight studies included participants with diabetes without specifying the type (Table 3). The diabetes and neuropathy duration varied among the studies from 3 to 19.6 years and from 3 months to 8.8 years, respectively (Table 4).

Table 3: Main characteristics of the included studies.

Age, mean	**58 years**
Treatment duration, mean	12 weeks
Type of diabetes	Type 2 diabetes (n=36) Both (n=86) Unknown (n=8)
Diabetes duration, mean	11 years
Outcome assessment	VAS (n=61) NRS (n=29) BPI (n=16) Other (n=24)

Mean age, mean treatment duration (weeks), type of diabetes, mean diabetes duration (years), outcome assessment

Table 4: All of the characteristics of the included RCTs

Author, year	Country	Study Design	n	Drop-out (%)	Male (%)	Age	Diabetes type	t (wk)	Comparison	Pain scale
Agoons 2020	Cameroon	Db pc	22	0	54.5	57.5	2	8	Placebo Capsaicin	VAS
Agrawal 2007	India	Db pc cross-over	48	10.4	-	58	-	4	Placebo Glyceryl trinitrate spray	VAS
Agrawal 2009	India	Db pc	83	3.6	-	60	2	12	Placebo Glyceryl trinitrate spray, sodium valproate	VAS
Akbari Fakhrabadi 2014	Iran	Db pc	74	16	26	56	2	12	Placebo Coenzyme Q10	VAS
Ala 2022	Iran	Db pc	66	1	50	61	1 and 2	3	Placebo Baclofen	DN4
Allen 2014	USA	Db pc	405	25	73	60	1 and 2	13	Placebo Desvenlafaxine	NRS
Amin 2024	Iraq	Db pc	120	19	42	59.6	2	13	Placebo Resveratrol	VAS
Amini 2022	Iran	Db ac	112	10	39	59	1 and 2	8	Placebo Coenzyme Q10	NRS
Anand 2022	Iran	Db pc	50	26	45	63	1 and 2	12	Standard of care Capsaicin	NRS
Arezzo 2008	USA	Db pc	167	31	62	58	1 and 2	13	Placebo Pregabalin	NRS
Asadi 2019	Iran	Db pc	80	10	12.5	54	2	8	Placebo Nano curcumin	TSS
Astellas Pharm Europe 2014	USA	Db pc	369	8.4	58	63	1 and 2	12	Placebo Capsaicin	BPI
Atli 2005	USA	Db pc	23	30	40	59	1 and 2	12	Placebo Zonisamide	VAS
Azhar 2022	Pakistan	Db ac	150	0	51	46,2	-	6	Duloxetin Amitriptyline	VAS
Backonja 1998	USA	Db pc	165	18.5	60	53	-	8	Placebo Gabapentine	VAS
Bansal 2009	India	Db ac cross-over	44	52	43	54.5	2	5	Amitriptyline Pregabalin	VAS
Begum 2023	India	Db ac	71	15.5	47	48	2	4	Duloxetine Gabapentin e	VAS
Beydoun 2006	USA	Db pc	347	33	55	61	1 and 2	16	Placebo Oxcarbazepine	VAS

Bial Portela 2009	Europe, Russia, South Africa and America	Db pc	332	58	-	-	1 and 2	12	Placebo Eslicarbazepi-ne	NRS
Bial-Portela 2010	Europe, Russia, South Africa and America	Db pc	332	58	-	-	1 and 2	12	Placebo Eslicarbazepi-ne	NRS
Bies-brock 1995	USA, Canada	Db pc	235	10	56	60	1 and 2	8	Capasicin Amitriptyline	VAS
Bio Delivery 2014	USA	Db pc	260	11	58.5	60	1 and 2	12	Placebo Clonidine	NRS
Bio Delivery 2017	USA	Db pc	138	9.4	43.5	59.5	1 and 2	12	Placebo Clonidine	NRS
Boyle 2012	UK	Db ac	83	22	68	65	1 and 2	4	Pregabalin Duloxetine Amitriptyline	VAS
Campbell 2012	USA	Db pc	179	12	48	58.5	1 and 2	12	Placebo Clonidine	NRS
Chen 2024	China	Db ac	120	0	54	53	2	4	Amitriptyline Carbama-zepine, amitriptyline	VAS
Cohen 1990	USA	Db ac cross-over	16	0	100	63	3	4	Pentoxifylline Clonidine	Pain score
Cohen 1991	USA	Db pc	40	5	-	59.5	2	24	Placebo Pentoxifylline	VAS
Cross 2023	India	Db pc	64	22	50	53	2	6	Placebo Nerve support formula	NRS
Cruccu/ Lipone 2020	Europe	Db pc	142	27	52	62.5	-	8	Placebo Trazodone	BPI
Davoudi 2021	Iran	Db pc	90	11	52.5	55	2	12	Placebo Vitamin D	NRS
De Grandis 2002	Italy	Db pc	333	11	56.5	-	1 and 2	48	Placebo ALC	VAS
Dejgard 1988	Denmark	Db pc cross-over	19	16	62.5	50	-	10	Placebo Mexiletine	VAS
Didangelos 2020	Greece	Db pc	85	0	52	64	2	48	Placebo Superoxide Dismutase, ALA, ALC, Vit B12	Pain daily score
Dogra 2005	USA	Db pc	146	27	58	60	-	16	Placebo Oxcarbaze-pine	VAS

Eisen-berg 2001	Israel	Db pc	59	22	62	55	1 and 2	8	Placebo Lamotrigine	SF-MPQ
El-Haggar 2024	Egypt	Db pc	55	5	-	53	2	12	Placebo Empagliflo-zin	BPI
El-Nahas 2020	Egypt	Db pc	200	0	39	53	2	24	Placebo ALA	VAS
Eli Lilly 2009	Japan	Db pc	338	12	76	61	1 and 2	12	Placebo Duloxetine	NRS
Enomot o 2018	Japan	Db ac	303	11.2	72.6	59.6	1 and 2	12	Duloxetine Pregabalin	VAS
Ertas 1998	Turkey	Db pc	25	0	60	58	1 and 2	4	Placebo Levodopa	VAS
Essmat 2021	Egypt	Db pc	216	10	48.5	45	-	16	Placebo Green tea extract	VAS
Fonseca 2013	USA	Db pc	214	6.5	69	62.6	2	24	Placebo Metanx	VAS
Freeman 2007	USA	Db pc	312	24	59	56	1 and 2	9	Placebo Tramadol, acetamino-phen	VAS
Gaber 2022	Egypt	Db ac	30	0	65	60	2	12	Duloxetine Gabapentine Botulinum Toxin A	VAS
Gao 2010	China	Db pc	215	15	47	60	-	14	Placebo Duloxetine	BPI
Gao 2015	China	Db pc	405	14	45	61	1 and 2	12	Placebo Duloxetine	BPI
Gilron 2024	Canada	Db ac cross-over	20	-	-	-	-	6	ALA Pregabalin ALA, pregabalin	NRS
Gimbel 2003	USA	Db pc	159	28	52	60	1 and 2	6	Placebo Oxycodon	BPI
Goldstei n 2001	USA	Db pc	93	11	63	61	1 and 2	8	Placebo Lanepitant	Pain score
Goldstei n 2005	USA	Db pc	457	25	61.5	60	1 and 2	12	Placebo Duloxetine	BPI
Gorson 1999	USA	Db pc	40	0	77.5	62	1 and 2	6	Placebo Gabapentin	VAS
Grossko pf 2006	Europe, USA	Db pc	141	32.6	55	61	1 and 2	16	Placebo Oxcarbazepi-ne	VAS
Guo 2024	China	Db pc	393	9	54	58	1 and 2	14	Placebo Mirogabalin	VAS
Hanna 2008	Europe, Australia	Db ac	328	24	64	61	-	12	Gabapentin Oxycodon Gabapentin	BPI
Harati 1998	USA	Db pc	131	37.4	59	59	1 and 2	6	Placebo Tramadol	NRS
	Iran	Db ac	30	0	37	50	2	12	Gabapentin, clonidine	VAS

Hassenzadeh 2023									Clonidine	
Hernandez-Ojeda 2012	Mexico	Db pc	56	12.5	22	56	2	12	Placebo Ubiquinone	NSS
Hernandez-Ojeda 2014	Mexico	Db pc	34	-	15	57	2	12	Placebo Rosuvastatin	NSS
Heydari 2016	Iran	Db pc	60	8	47	55	-	12	Placebo Citrullus colocynthis	NRS
Hor 2018	Malaysia	Db pc	300	24	43	57.6	1 and 2	12	Placebo Vit E	TSS
Huffman 2015	USA, Europe, South Africa	Db pc	384	8	65	59	1 and 2	6	Placebo Pregabalin	BPI
Hussain 2021	Pakistan	Db pc	291	6	-	45	2	12	Placebo Lidocain Capsaicin	BPI
Jafar-zadeh 2023	Iran	Db ac	143	21	38	55	2	9	Gabapentine Memantine, gabapentine	DN4
Jamal 1990	UK	Db pc	22	0	45.5	54	1 and 2	24	Placebo Gamma-Linolenic acid	Symp-tom score
Jann 2020	Italy	Db ac	23	0	-	65	1 and 2	6	Placebo IVIG	VAS
Joharchi 2019	Iran	Db ac	180	20	39	54.5	2	12	Duloxetine Pregabalin	VAS
Kadiroglu 2008	Turkey	Db pc	60	0	21.6	53	2	8	Placebo Venlafaxine	SF-MPQ
Kharito-nova/ Strokov 2023	Russia	Db pc	215	9	32.6	63	2	12	Placebo SINR cytoflavin	TSS
Kiani 2015	Iran	Db ac	139	33	27	56.6	2	12	Capsaicin Clonidine	VAS
Kochar 2002	India	Db pc	60	13	55	56	2	4	Placebo Sodium valproate	MPQ
Kochar 2004	India	Db pc	43	9	54	55	2	12	Placebo Sodium valproate	MPQ
Kulkan-trakon 2013	Thailand	Db pc cross-over	33	39	48.5	58	2	8	Placebo Capsaicin	VAS
Kulkan-trakon 2019	Thailand	Db pc cross-over	42	35	45	66	2	8	Placebo Capsaicin	VAS
Lee 2006	China	Db ac	45	-	24	58	1 and 2	12	ALA i.v. ALA oral	TSS
Lesser 2004	USA	Db pc	337	10	60	60	1 and 2	5	Placebo Pregabalin	VAS

Li 2016	China	Db ac	232	12	52.6	58	1 and 2	24	Methylco-balamin ALC	NSS
Majdina-sab 2019	Iran	Db ac	104	13	43	60	-	8	Gabapentine Duloxetine	VAS
Malik 2022	Pakistan	Db pc	120	0	67.5	40.5	2	12	Placebo Vitamin D	NSS
Marton 2023	Romania	Sb pc	41	0	36	68.5	1 and 2	12	Placebo Vitamin D	TCNS
Moha-mmad 2023	Iraq	Sb ac	40	0	55	-	2	12	Gabapentine Gabapentine, taurine	TCNS
Moha-madali 2021	Iran	Db pc	66	16.6	7	58	-	5	Placebo Duloxetine Nortriptyline	NRS
Morello 1999	USA	Db ac cross-over	25	24	96	60	1 and 2	6	Gabapentine Amitriptyline	NRS
Motilal 2013	Trinidad	Db pc	74	7	32	60	1 and 2	4	Placebo Nutmeg oil	BPI
Mu 2018	China	Db pc	620	15.6	47	60.5	1 and 2	9	Placebo Pregabalin	VAS
Mujeen UI 2022	Pakistan	Db pc	92	22	56	41	-	20	Placebo Lacosamide	
Mundi-pharm 2009	Europe	Db pc	98	7	51	60.6	-	12	Placebo Oxycodone, naloxone	SF-MPQ
Mushar-raf 2017	Pakistan	Db ac	300	-	57	48	1 and 2	12	Capsaicin Turpenine oil	VAS
Niesters 2014	Nether-lands	Db pc	24	0	58	-	1 and 2	4	Placebo Tapentadol	VAS
Numan 2016	Pakistan	Db pc	152	12	-	52	2	24	Placebo Ginkgo biloba	SF-MPQ
Osama 2023	Egypt	Sb pc	131	1.5	48	50	2	12	Placebo Hesperidin Diosmin Hesperidin, diosmin	MNSI
Paul 2024	India	Db pc	100	-	65	55	-	48	Glimepiride, metformin, teneligliptin Vit E	VAS
Pfizer 2007	Europe, USA, South Africa	Db pc	124	22	57	60	1 and 2	8	Placebo Reboxetine	NRS
Pickering 2022	New Zealand	Db pc	70	6	50	63.5	1 and 2	8	Placebo PEA	BPI
Preeth 2024	India	Sb ac	165	9	63	55	1 and 2	12	Epalrestat Methylcobal-amin	VAS

									Epalrestat, methylcobalmin	
Raskin 2004	USA	Db pc	323	40.5	49.5	59	1 and 2	12	Placebo Topiramate	VAS
Raskin 2005	USA, Canada	Db pc	348	15	46.6	59	1 and 2	12	Placebo Duloxetine	SF-MPQ
Raskin 2014	USA	Db pc	294	19	53	58.5	1 and 2	6	Placebo Pregabalin	NRS
Raskin 2016	USA, Europe	Db pc cross-over	301	14	54.5	59	1 and 2	6	Placebo Pregabalin	NRS
Rauck 2007	USA	Db pc	119	21	47	55	1 and 2	10	Placebo Lacosamide	NRS
Rauck 2013	USA	Db pc	421	29	59	59	1 and 2	12	Placebo Gabapentin-enacarbil Pregabalin	NRS
Razazian 2014	Iran	Db ac	257	13	39	56	1 and 2	4	Carbazepine Pregabalin Venlafaxine	VAS
Richter 2005	USA	Db pc	246	11	60.5	57	1 and 2	6	Placebo Pregabalin	VAS
Rivaz 2021	Iran	Db pc	78	4	24	52	1 and 2	4	Placebo Lavendel oil Standard of care	VAS
Rosales 2011	Philippiness	Db pc	48	2	28	57	2	12	Placebo Cilostazol	NSS
Rosenstock 2004	USA	Db pc	146	13	56	60	1 and 2	8	Placebo Pregabalin	NRS
Rowbotham 2004	USA	Db pc	243	17	59	59	1 and 2	6	Placebo Venlafaxine	VAS
Sajedi 2024	Iran	Db ac	102	0	16	56	2	8	N-acetylcysteine Pregabalin	VAS
Sandercock 2012	USA	Db pc	147	6	54.5	58.6	1 and 2	4	Placebo Gabapentine	NRS
Satoh 2011	Japan	Db pc	314	16	25.5	61.6	1 and 2	13	Placebo Pregabalin	NRS
Scheffler 1991	USA	Db pc	54	24	35	60.6	1 and 2	8	Placebo Capsaicin	VAS
Schwartz 2011	USA	Db pc	395	33	60	60	1 and 2	12	Placebo Tapentadol	NRS
Selvarajah 2010	UK	Db pc	29	17	62	56	1 and 2	12	Placebo Sativex	VAS
Shaibani 2009	USA	Db pc	468	43	56.5	60	1 and 2	18	Placebo Lacosamide	NRS
Shaibani 2012	USA	Db pc	379	36	62	61	1 and 2	13	Placebo Dextromethorphan	NRS
	India	Db ac	100	10	48	50.5	1 and 2	12	Epalrestat SR	VAS

Shende 2018									Epalrestat IR	
Shin 2013	South Korea	Db pc	110	10	41	60	2	8	Placebo Beraprost	TSS
Shokri 2021	Iran	Db pc	103	12	31	59.5	2	8	Placebo Melatonin	NRS
Siddique 2021	Pakistan	Db pc	110	0	51	47	1 and 2	5	Standard of care ALA	TSS
Sima 2005	USA, Canada, Europe	Db pc	342	-	-	-	1 and 2	52	Placebo ALC	VAS
Simpson 2001 Study 1	USA	Db pc	60	10	60	50	1 and 2	8	Placebo Gabapentin	NRS
Simpson 2001 Study 2	USA	Db pc	11	27	60	50	1 and 2	8	Placebo Venlafaxine	NRS
Simpson 2016	USA	Db pc	181	32	67	63	1 and 2	12	Placebo Buprenorphine transdermal	NRS
Simpson 2017	USA	Db pc	369	4.6	58	63	1 and 2	12	Placebo Capsaicin	BPI
Singh 2024	India	Db ac cross-over	78	0	22	48	2	4	Duloxetine Gabapentine	VAS
Srivastava 2001	India	Db pc	57	9	55.6	56	2	4	Placebo Sodium valproate	VAS
Stracke 1992	Germany	Db pc	95	1	56	56.5	1 and 2	5	Placebo Mexiletine	MPQ
Sutiknov 2023	Romania	Db pc	34	0	44	63	2	8	Standard of care Vitamin D	VAS
Taheri 2015	Iran	Db pc cross-over	30	33	20	58	1 and 2	4	Placebo Nitroglycerin transdermal	BPI
Taheri 2020	India	Db pc	47	-	39	55	1 and 2	4	Placebo Botulinum toxine	VAS
Tandan 1992	USA	Db pc	22	0	50	54	1 and 2	8	Placebo Capsaicin	VAS
Tesfaye 2013	Europe, Australia, Canada, Mexico, South Korea	Db ac	804	70	56	62	1 and 2	8	Duloxetine Pregabalin	BPI
Tesfaye 2022	UK	Db ac cross-over	130	40	74	61	1 and 2	16	Amitriptyline Pregabalin Duloxetine	NRS
Tesfaye 2024	Europe	Db pc	240	17	53	62	1 and 2	8	Placebo Trazodone, gabapentin Gabapentin	NRS
Thienel 2004	USA, Europe	Db pc	125	49	58	58	1 and 2	22	Placebo Topiramate	VAS

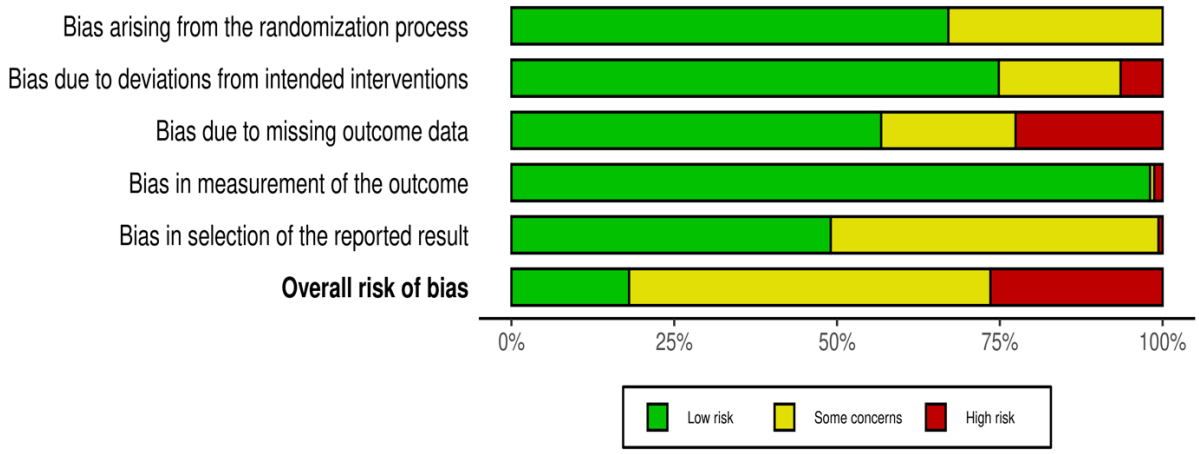
Tölle 2008	Europe, Australia, South Africa	Db pc	395	20	55.4	58.6	1 and 2	12	Placebo Pregabalin	NRS
Toth 2012	Canada	Db pc	26	4	38	61	1 and 2	5	Placebo Nabilone	VAS
Valensi 2005	France	Db pc	34	0	56	57.4	1 and 2	4	Placebo Quercetin 333	VAS
Villegas-Rivera 2015	Mexico	Db pc	74	3	39	54.6	2	15	Placebo Ezetimibe, simvastatin rosuvastatin	NSS
Vinik 2007	USA	Db pc	679	38	54	60	1 and 2	12	Placebo Lamotrigine	SF-MPQ
Vinik 2014	USA, Canada	Db pc	318	28.6	-	-	1 and 2	12	Placebo Tapentadol	NRS
Watson 2003	Canada, UK	Db pc cross-over	42	14	58	63	1 and 2	4	Placebo Oxycodon	VAS
Werni-cke 2006	USA	Db pc	334	26	61	61	1 and 2	12	Placebo Duloxetine	BPI
Won 2019	Korea	Db ac	100	27	55	61	2	12	ALA Gamma linolenic acid	VAS
Wymer 2009	USA	Db pc	365	37	55	58	1 and 2	18	Placebo Lacosamide	Likert
Yasuda 2011	Japan	Db pc	338	13	76	61	1 and 2	12	Placebo Duloxetine	BPI
Yuan 2009	Taiwan	Db ac cross-over	20	10	33	65.6	2	12	Placebo Botulinum toxine A	VAS
Yuen 2002	UK	Db pc cross-over	22	-	65	64	1 and 2	4	Placebo ISDN	VAS
Zaker-kish 2017	Iran	Db ac	134	12	42	53.4	1 and 2	6	Duloxetine Nortriptyline	VAS
Ziegler 1999	USA, Europe	Db pc	503	25	50	57	2	24	Placebo ALA	TSS
Ziegler 2006	Russia, Israel	Db pc	181	8	40	58	1 and 2	5	Placebo ALA	TSS
Ziegler 2010	Europe	Db pc	355	31	51.5	58	1 and 2	18	Placebo Lacosamide	VAS
Ziegler 2010	USA, Canada, Europe	Db pc	460	40.4	66.6	53.6	1 and 2	192	Placebo ALA	TSS

The table presents the complete extracted characteristics of the included RCTs. Proportoin of male participants and age are expressed as mean values. n= sample size of the ITT- or PP-population (ITT was preferred if available); t= treatment duration; wk= weeks; db pc= double-blinded placebo-controlled parallell RCT; db pc cross-over= double-blinded placebo-controlled cross-over RCT; ALC= acetyl-L-carnithine; ALA= alpha=lipoic=acid; epalrestat SR= sustained release; epalrestat IR= immediate release; ISDN=isosorbide dinitrate, IVIG= intravenous immunoglobulin; vit= vitamin.

3.3 Risk of Bias

Figure 2 presents the overall risk-of-bias assessment of the included studies showing the proportion of studies rated as low risk, some concerns, and high risk. The risk-of-bias assessment showed that 27 studies had a low risk of bias, 43 had a high risk of bias, and the majority (n = 60) raised some concerns. Increased risk of bias was primarily due to deviations from intended interventions and missing outcome data or selective outcome reporting (domains 2 and 3). The complete data extraction table and results are provided in the Appendix.

Figure 2: Overall risk-of-bias assessment of the included studies



The figure presents the proportion of studies rated as low risk, some concerns, or high risk across the five RoB 2 domains and the overall risk-of-bias judgement. For crossover trials, the additional S-domain (not included in this table) was applied to assess potential bias arising from period effects and carryover effects. The complete data extraction table and results are provided in the Appendix.

3.4 Pairwise Meta-Analyses

Initially, pairwise meta-analyses of 113 studies were conducted, including all studies evaluating the corresponding medications in each pharmacological group compared with placebo for pain reduction.

3.4.1 Anticonvulsants

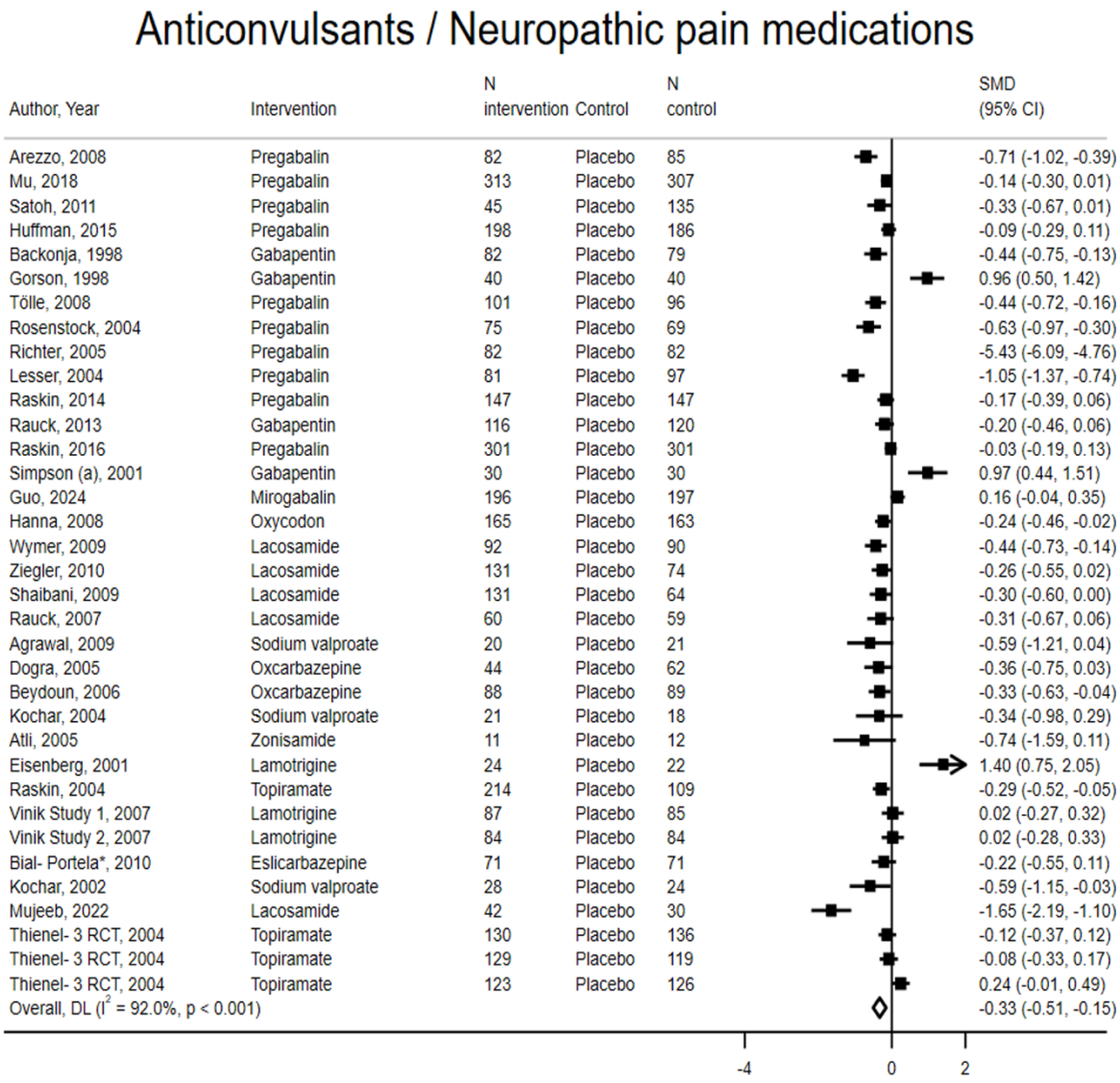
A total of 33 studies evaluated the effect of anticonvulsants on pain reduction in participants with DPN. The medications investigated in this group included pregabalin, gabapentin, mirogabalin, lacosamide, oxcarbazepine, eslicarbazepine, lamotrigine, topiramate, zonisamide, and sodium valproate (Figure 3).

Most studies showed a reduction in pain in the intervention group compared with the control group (Figure 3). The remaining four studies reported no reduction in pain or even higher pain scores in the intervention group than in the control group (136-139). Nevertheless, 21 of these studies did not reach statistical significance (137, 140-156).

The pooled effect estimate for the anticonvulsant group was -0.33 [-0.51; -0.15]. This indicates a small but statistically significant reduction in pain in the intervention group compared with the control group.

Considerable heterogeneity was observed among the included studies (I^2 = 92%, p < 0.001), indicating substantial variability in effect estimates across trials. Despite this heterogeneity, the treatment effect was largely consistent across studies, with most trials suggesting a reduction in pain (Figure 3).

Figure 3: Forest plot of pairwise meta-analysis for anticonvulsants/ neuropathic pain medications



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.2 Cannabinoid Agents

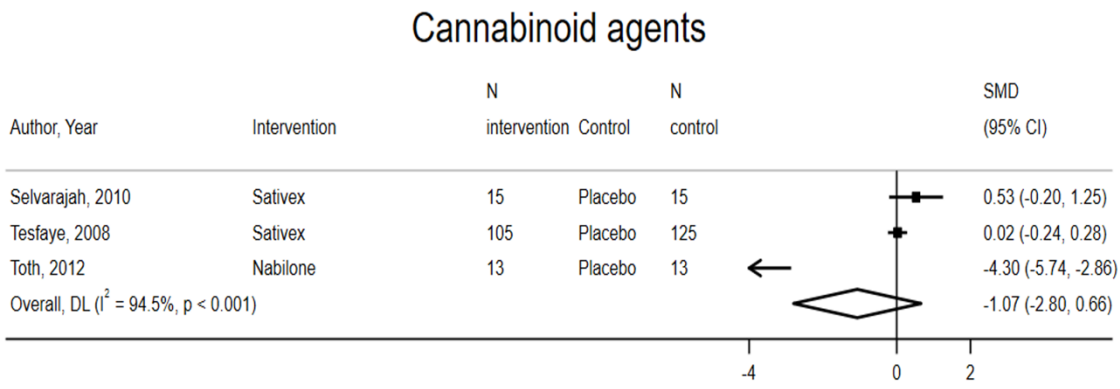
A total of three studies evaluated the effect of cannabinoid agents on pain reduction in participants with DPN. The medications investigated in this group were nabilone and Sativex.

One study investigating nabilone reported a statistically significant reduction in pain (157). The other two studies evaluated Sativex and did not report a reduction in pain compared with the control group (158, 159). These results were not statistically significant (Figure 4).

The pooled effect estimate for the cannabinoid agents' group was -1.07 [-2.8; -0.66]. This suggests a statistically significant large reduction in pain compared with the control group (Figure 4).

Considerable heterogeneity was observed among the included studies (I^2 =94 %, p<0.001), likely due to the pronounced treatment effect observed in the nabilone study.

Figure 4: Forest plot of pairwise meta-analysis for cannabinoids



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.3 Ion Channel and Receptor Modulators/ Other Analgesics

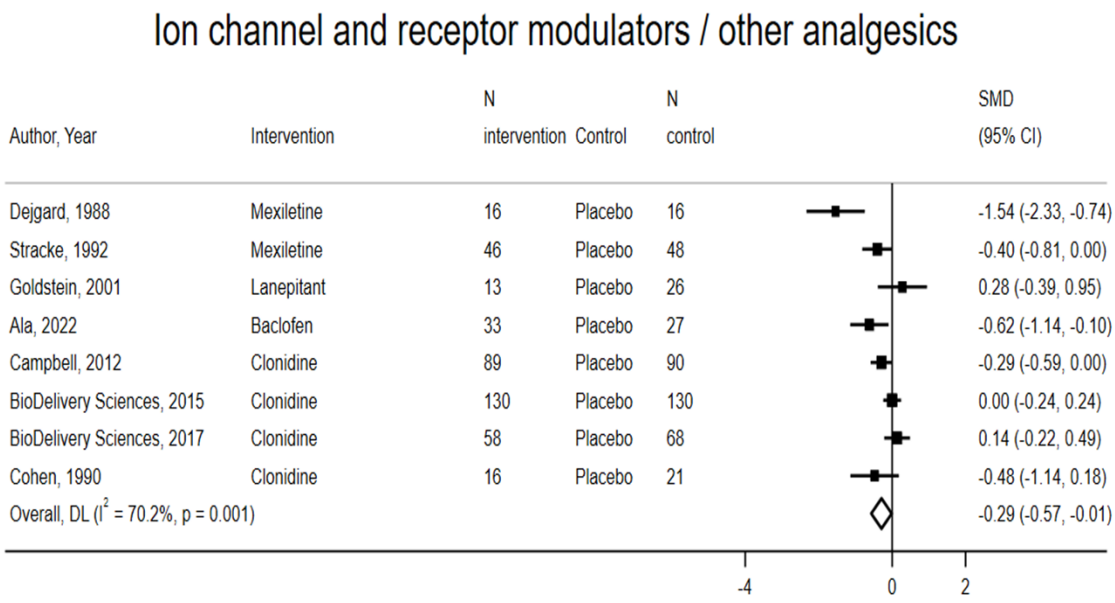
A total of eight studies evaluated the effect of ion channel and receptor modulators/other analgesics on pain reduction in participants with DPN. The medications investigated in this group included mexiletine, lanepitant, clonidine, and baclofen.

Most studies suggested a reduction in pain compared with the control group, although several trials were not statistically significant (160-162) (Figure 5). Three studies did not report a reduction in pain compared with the control group; however, these findings were also not statistically significant (163-165).

The pooled effect estimate was -0.29 [-0.57; -0.01], suggesting a small, yet statistically significant reduction in pain compared with the control group. The relatively narrow CI suggests a reasonably precise estimate of the pooled effect, likely reflecting consistent and similar results across the studies.

However, substantial heterogeneity was observed among the studies (I^2=70 %, p=0. 001).

Figure 5: Forest plot of pairwise meta-analysis for ion channel and receptor modulators/ other analgesics



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.4 Antidepressants/ SNRI/ TCA

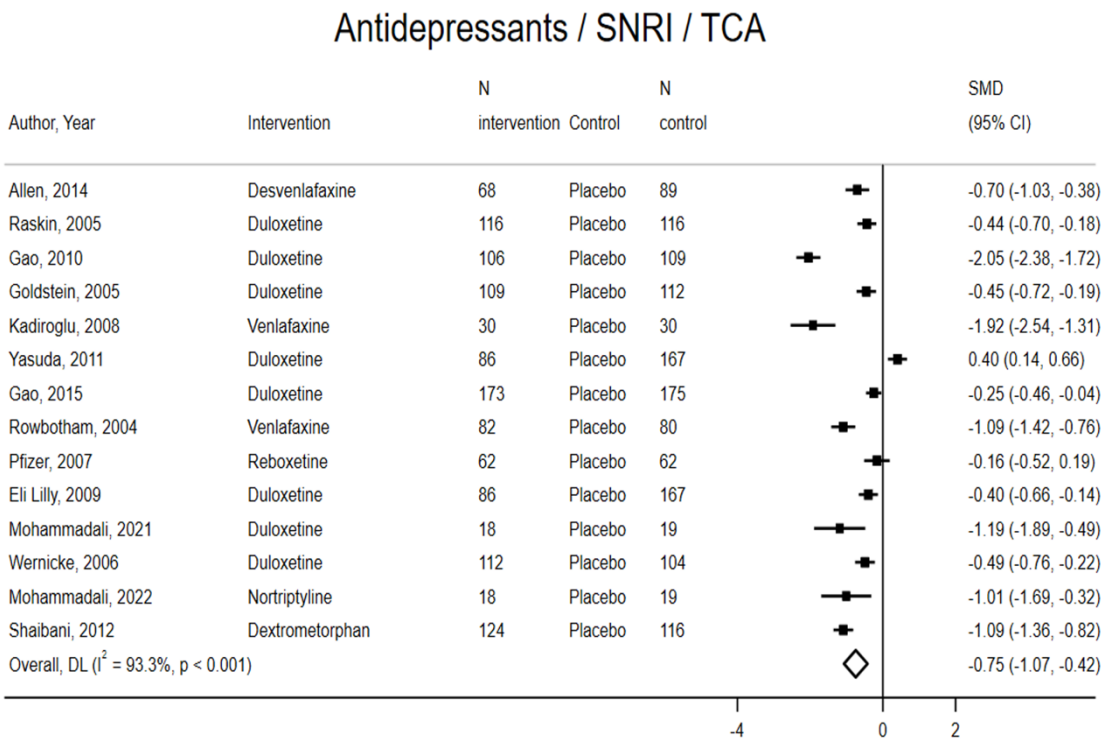
A total of 13 studies evaluated the effect of antidepressants, including SNRIs and TCAs, on pain reduction in participants with DPN (Figure 6). The medications investigated in this group included desvenlafaxine, duloxetine, venlafaxine, reboxetine, nortriptyline, and dextromethorphan.

Twelve studies demonstrated a reduction in pain compared with the control group, with statistically significant results in all but one trial (166). Only one study reported no reduction in pain, and this finding was statistically significant (167), (Figure 6).

The pooled effect estimate was -0.75 [-1.07; -0.42], indicating a moderate to large reduction in pain compared with placebo.

Considerable heterogeneity was observed among the studies (I^2=93.3%, p< 0.001), which is likely due to several studies reporting particularly large reductions in pain (168-170) with SMDs -1.19; -2.05; -1.92, respectively (Figure 6).

Figure 6: Forest plot of pairwise meta-analysis for antidepressants/ SNRIs/ TCAs



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.5 Metabolic/ Vascular Agents

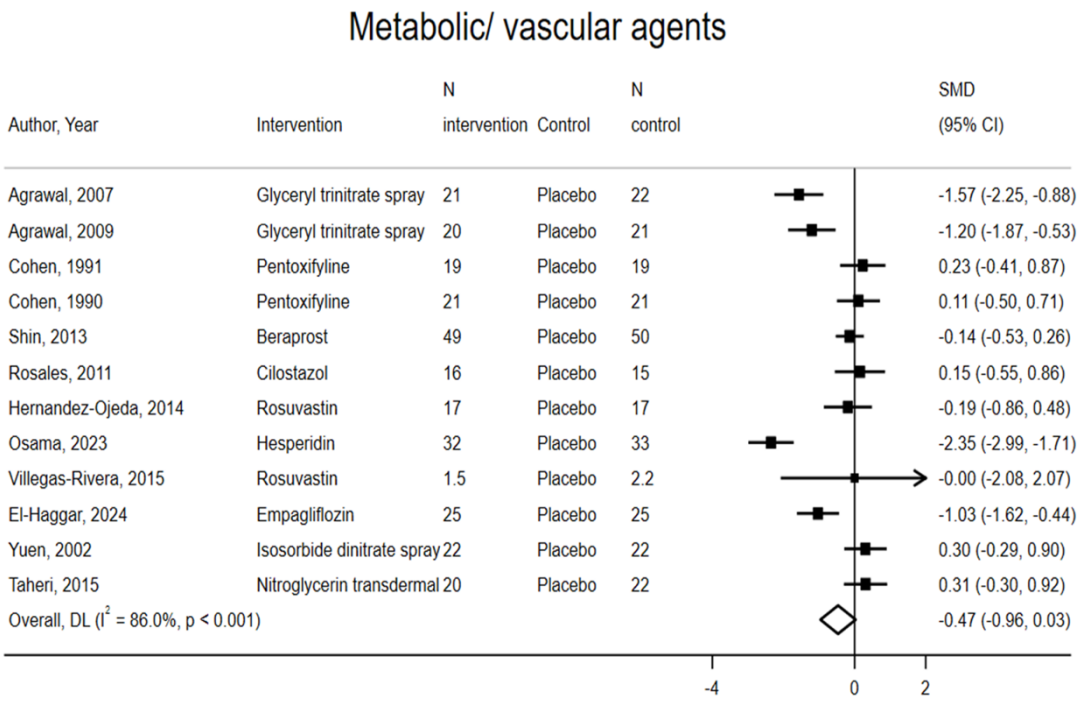
A total of twelve studies evaluated the effect of metabolic and vascular agents on pain reduction in participants with DPN. The medications investigated in this group included glyceryl trinitrate spray, isosorbide dinitrate spray, nitroglycerin transdermal therapy, pentoxifylline, beraprost, cilostazol, rosuvastatin, cytoflavin, hesperidin, and empagliflozin.

Results were mixed, with half of the studies suggesting a reduction in pain compared with the control group (150, 171-175). Most of these studies reported statistically significant results. The remaining six studies did not demonstrate a reduction in pain and did not reach statistical significance (Figure 7).

The pooled effect estimate was -0.47 [-0.96; 0.03], indicating a small to medium reduction of pain compared with the control group; however, this result was not statistically significant.

Substantial heterogeneity was observed among the studies (I^2=86%, p< 0.001).

Figure 7: Forest plot of pairwise meta-analysis for metabolic/ vascular agents



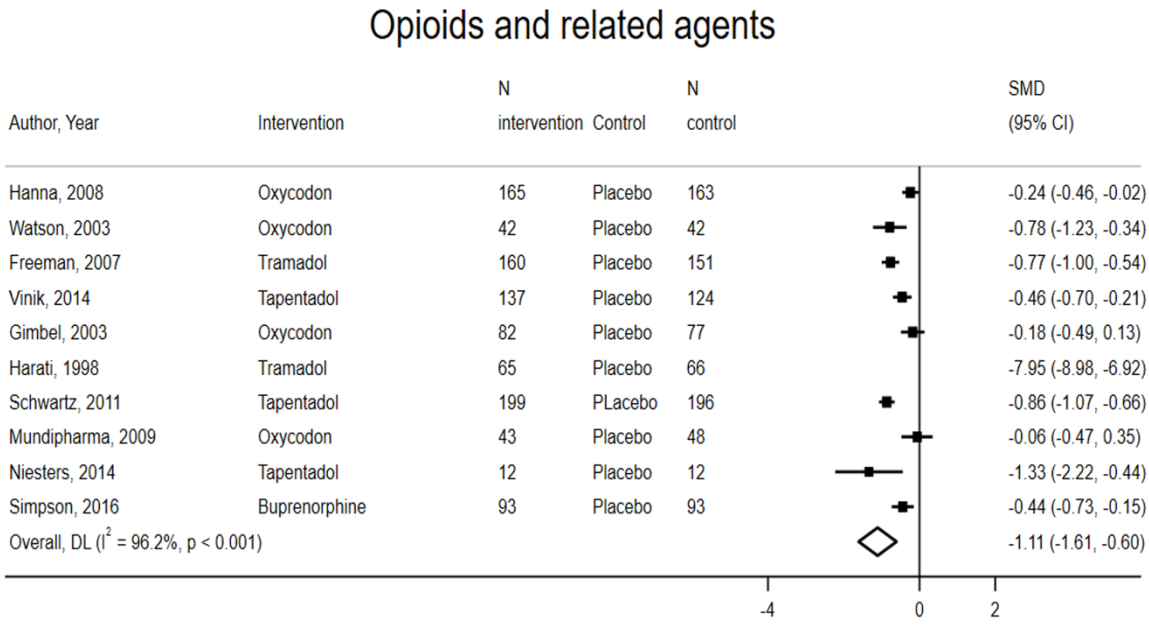
The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.6 Opioids and Related Agents

A total of ten studies evaluated the effect of opioids and related agents on pain reduction in participants with DPN. The medications investigated in this group included oxycodone, tramadol, tapentadol, and buprenorphine.

All studies reported a reduction in pain compared with the control group, although two trials did not reach statistical significance (176, 177) (Figure 8). The pooled effect estimate was -1.11 [-1.61; -0.6], indicating a large and statistically significant reduction in pain compared with the control group. Considerable heterogeneity was observed among the included studies (I^2 = 96.5%, p < 0.001).

Figure 8: Forest plot of pairwise meta-analysis for opioids and related agents



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.7 Topical/ Localized Pharmacological Therapies

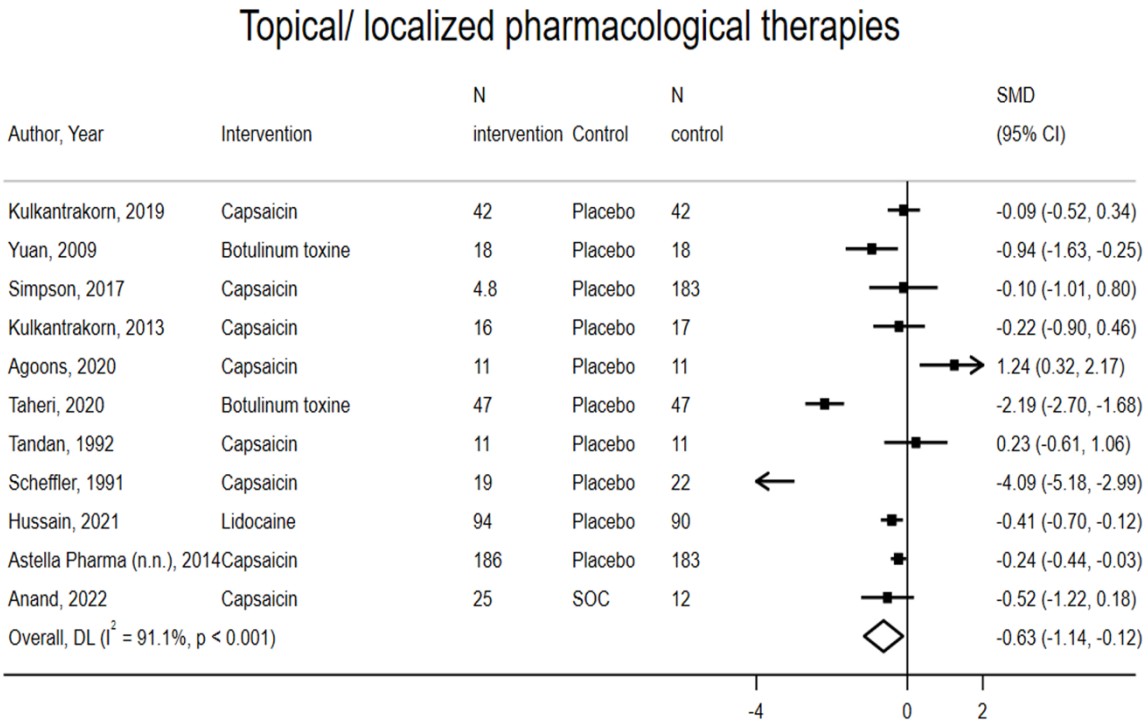
A total of eleven studies evaluated the effect of topical/localized pharmacological therapies on pain reduction in participants with DPN (Figure 9). The medications investigated in this group included lidocaine, capsaicin, and botulinum toxin.

Most studies reported a reduction in pain compared with the control group. Agoons et al. (2020) and Tandan et al. (1992) did not demonstrate a reduction in pain; however, the findings of Tandan et al. (1992) were not statistically significant (178, 179). Four additional studies did not report statistically significant effects (180-183).

The pooled effect estimate was -0.63 [-1.14; -0.12], indicating a moderate and statistically significant reduction in pain compared with the control group.

Considerable heterogeneity was observed among the studies (I^2=91.1%, p< 0.001), indicating substantial variety in effect estimates across the trials.

Figure 9: Forest plot of pairwise meta-analysis for topical/ localized pharmacological therapies



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

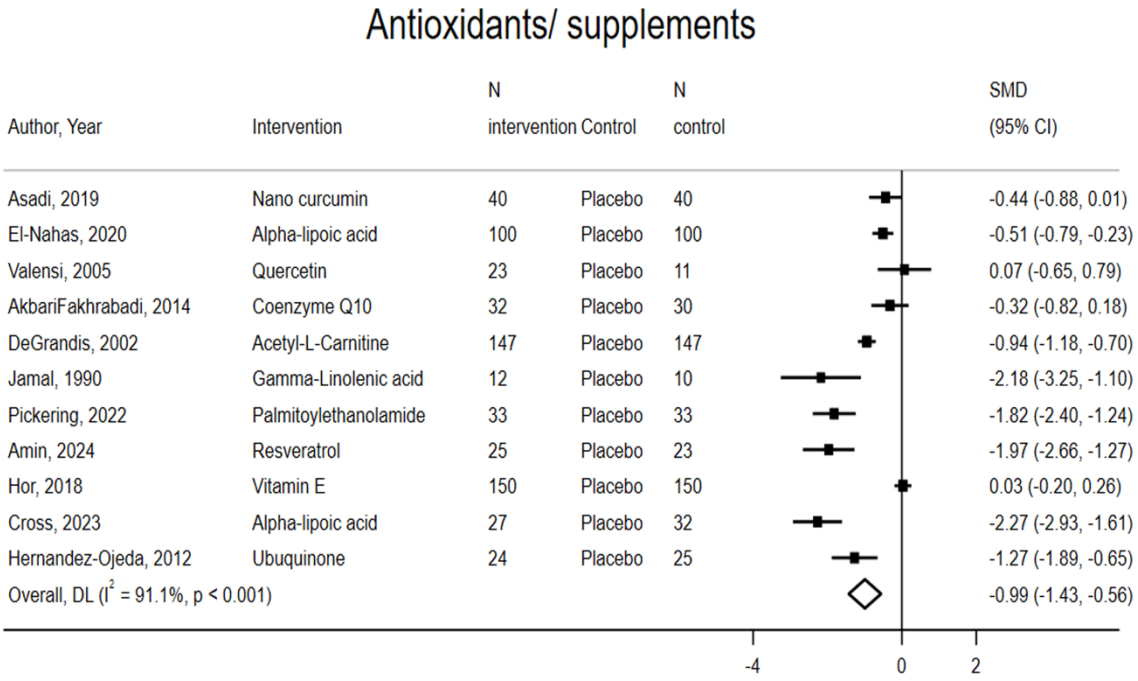
3.4.8 Antioxidants/ Supplements

A total of eleven studies evaluated the effect of antioxidants and supplements on pain reduction in participants with DPN (Figure 10). The medications investigated in this group included alpha-lipoic acid, coenzyme Q10, resveratrol, quercetin, vitamin E, acetyl-L-carnitine, gamma-linolenic acid, palmitoylethanolamide, nano curcumin, and ginkgo biloba.

Most studies demonstrated a reduction in pain compared with the control group. The corresponding effect estimates were statistically significant in all but two studies (184, 185). Two additional studies did not demonstrate a reduction in pain; their findings were not statistically significant (186, 187). The pooled effect estimate was -0.94 [-1.43; -0.56], indicating a large, statistically significant reduction in pain compared with the control group.

Considerable heterogeneity was observed across the studies (I^2=91.1%, p< 0.001) (Figure 10).

Figure 10: Forest plot of pairwise meta-analysis for antioxidants/ supplements



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.9 B- Vitamins

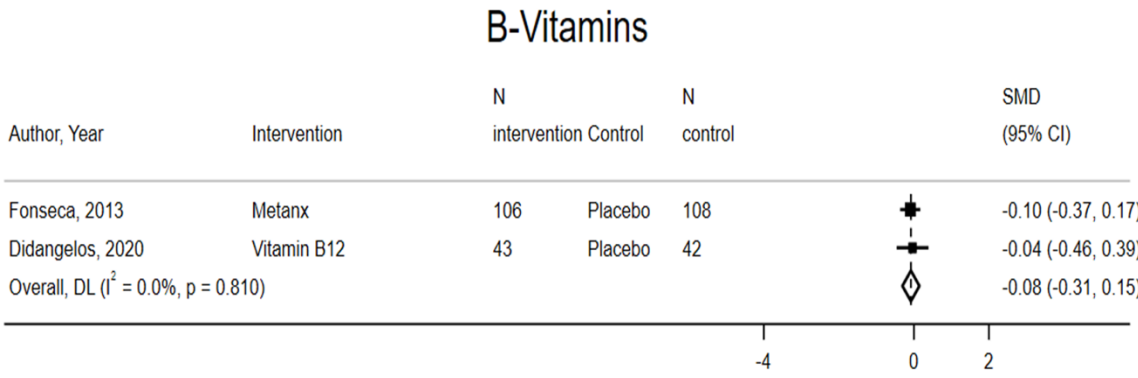
A total of two studies evaluated the effect of B-vitamins on pain reduction in participants with DPN (Figure 11). The medications investigated in this group included vitamin B12 and Metanx, which contains L-methylfolate, pyridoxal 5'-phosphate, and methylcobalamin (188).

Both studies reported a small reduction in pain compared with the control group, although neither of the findings was statistically significant (189, 190).

The pooled effect estimate was -0.08 [-0.31; 0.15], suggesting no meaningful reduction in pain compared with the control group. However, the limited number of included trials restricts the strength of the evidence.

There was no indication of heterogeneity (I^2= 0%, p= 0,810). The absence of heterogeneity should be interpreted cautiously, as the detection of heterogeneity is limited when only a small number of studies are included.

Figure 11: Forest plot of pairwise meta-analysis for B-vitamins



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.10 Herbal/ Adjunctive Treatment

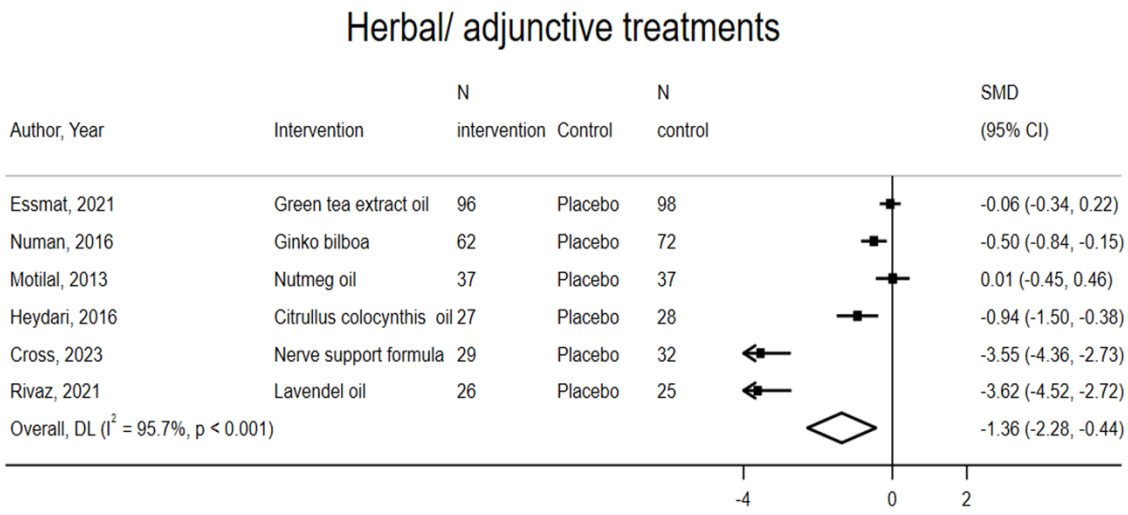
A total of five studies evaluated the effect of herbal and adjunctive treatments on pain reduction in participants with DPN. The medications investigated in this group included nutmeg oil, citrullus colocynthis oil, lavender oil, nerve support formula, and green tea extract oil.

All but one study reported a reduction in pain compared with the control group, and this finding was not statistically significant (191) (Figure 12). Among the studies showing a reduction in pain, only one trial did not reach statistical significance (192). Three studies demonstrated a particularly large reduction in pain compared with the control group (193-195).

The pooled effect estimate was -1.58 [-2.83; -0.32], indicating a large reduction in pain compared with the control group.

Considerable heterogeneity was observed among the included studies ($I^2 = 95.7\%$, $p < 0.001$), likely driven by the exceptionally large effect estimates reported in the previously mentioned trials.

Figure 12: Forest plot of pairwise meta-analysis for herbal/ adjunctive treatments



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

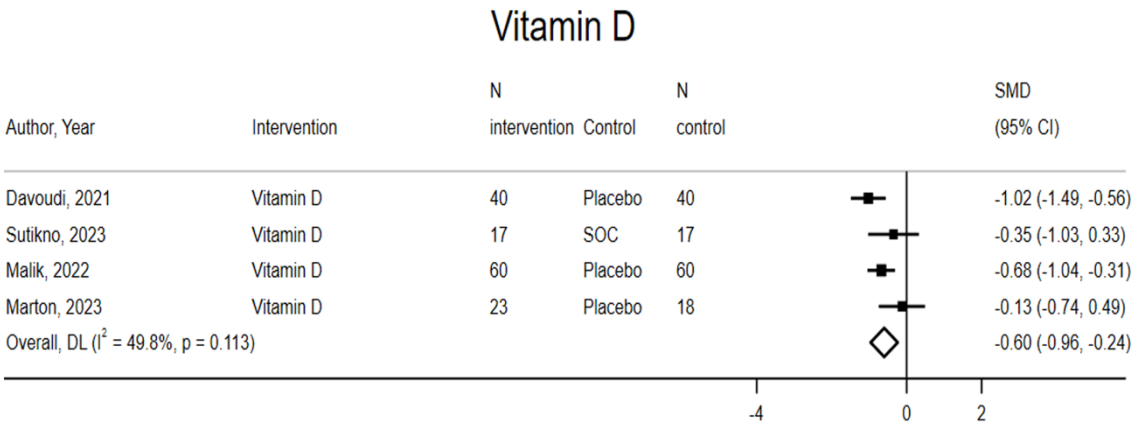
3.4.11 Vitamin D

A total of four studies evaluated the effect of vitamin D on pain reduction in participants with DPN. All studies reported a reduction in pain compared with the control group. However, only two trials demonstrated statistically significant effects (196, 197) (Figure 13).

The pooled effect estimate was -0.6 [-0.96; -0.24], showing a medium and statistically significant reduction in pain compared with the control group.

Moderate heterogeneity was observed among the included studies (I^2=49.8%, p= 0.0), indicating relatively consistent findings across the trials.

Figure 13: Forest plot of pairwise meta-analysis for vitamin D



The squares represent the study effect estimate SMD for the intervention group with its corresponding 95% CI (horizontal line). The diamond shows the pooled SMD.

3.4.12 Publication Bias of the Pairwise Meta-Analyses

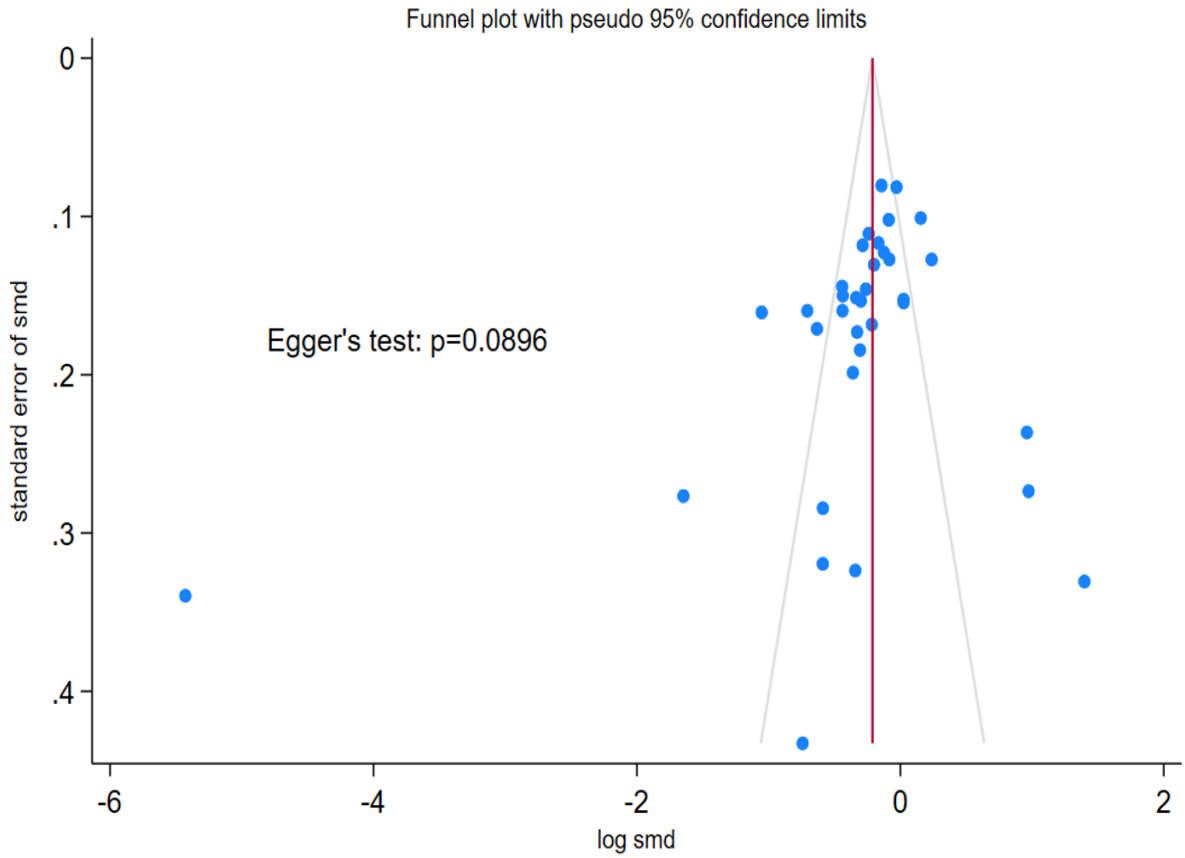
Figures 14 to 19 present the funnel plots assessing publication bias for the following pharmacological treatment groups: Figure 14 for anticonvulsants/ neuropathic pain; Figure 15 for antidepressants/ SNRIs/TCAs; Figure 16 for opioids and related agents; Figure 17 for topical/ localized pharmacological therapies; Figure 18 for metabolic/ vascular agents; and Figure 19 for antioxidants. Each blue dot represents an individual RCT. The x-axis displays the logarithm of the SMD (log SMD), whereas the y-axis represents the standard error of the effect estimate. The vertical red line shows the pooled effect estimate, and the grey diagonal lines show the pseudo 95% confidence limits. Symmetry of the funnel plot suggests the absence of publication bias, and asymmetry may indicate potential small-study effects or publication bias.

Egger's test indicated potential small-study effects for anticonvulsants/ neuropathic pain medications, antidepressants/ SNRIs/ TCAs, opioids and related agents, and antioxidants ($p < 0.1$). In contrast, no evidence of publication bias was observed for topical/ localized pharmacological therapies and metabolic/ vascular agents.

These findings were consistent with the funnel plots. For anticonvulsants/ neuropathic pain medications, antidepressants/ SNRIs/ TCAs, opioids and related agents, and antioxidants, the funnel plots appeared asymmetric. They showed a relative lack of smaller studies reporting null effects. Furthermore, a wide dispersion of studies beyond the 95% CI was observed, suggesting substantial between-study heterogeneity.

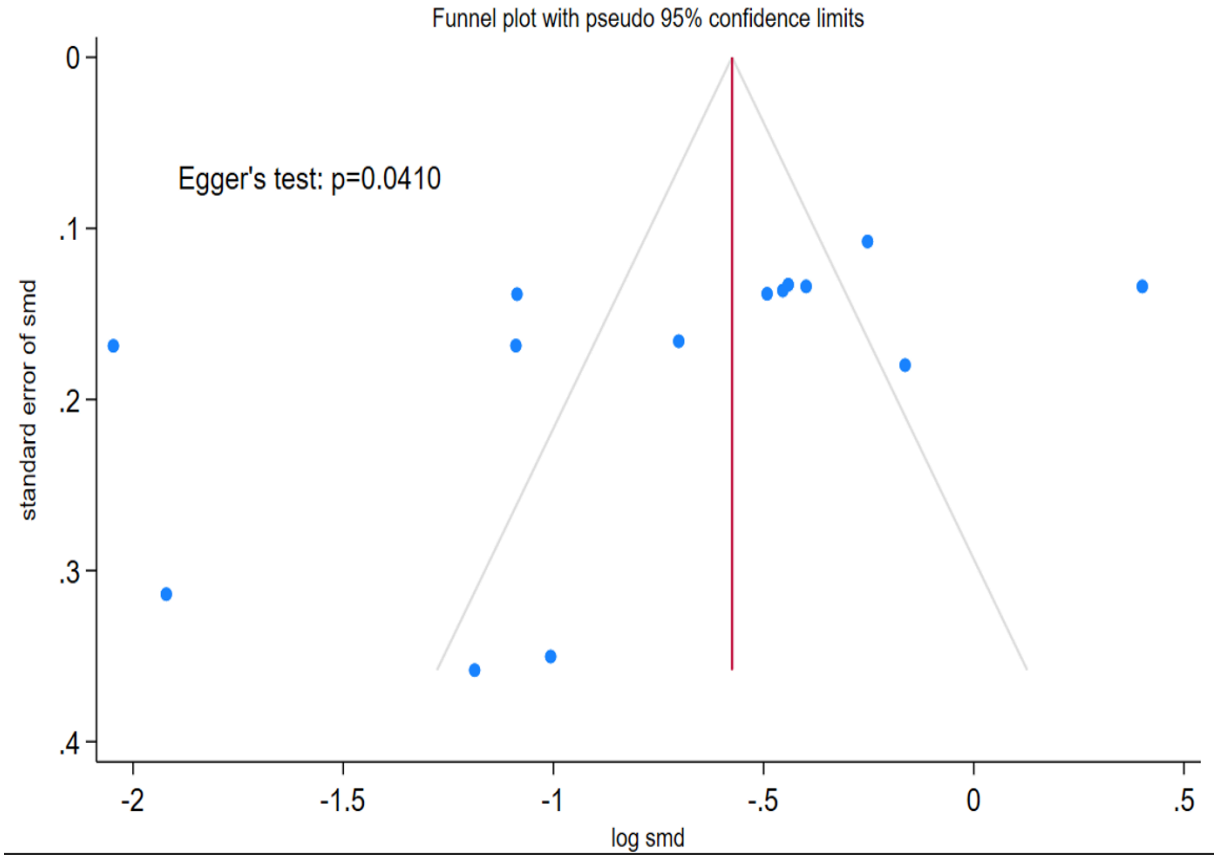
Overall, these findings suggest potential publication bias or small-study effects in several treatment groups, which should be considered when interpreting the results.

Figure 14: Funnel plot assessing publication bias for anticonvulsants/ neuropathic pain medication



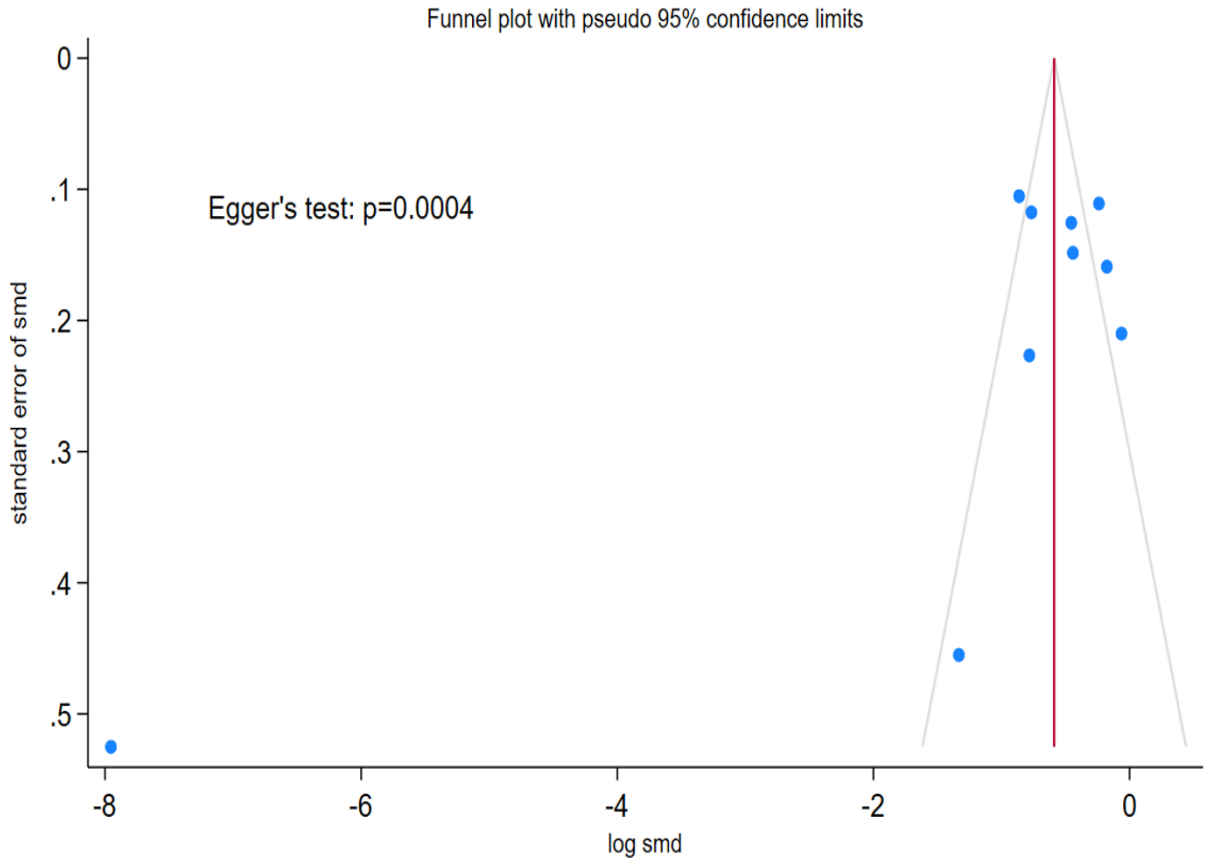
Each dot represents an individual RCT. The vertical red line shows the pooled effect estimate, and the grey diagonal lines show the pseudo 95% confidence limits.

Figure 15: Funnel plot assessing publication bias for antidepressants/ SNRIs/ TCAs.



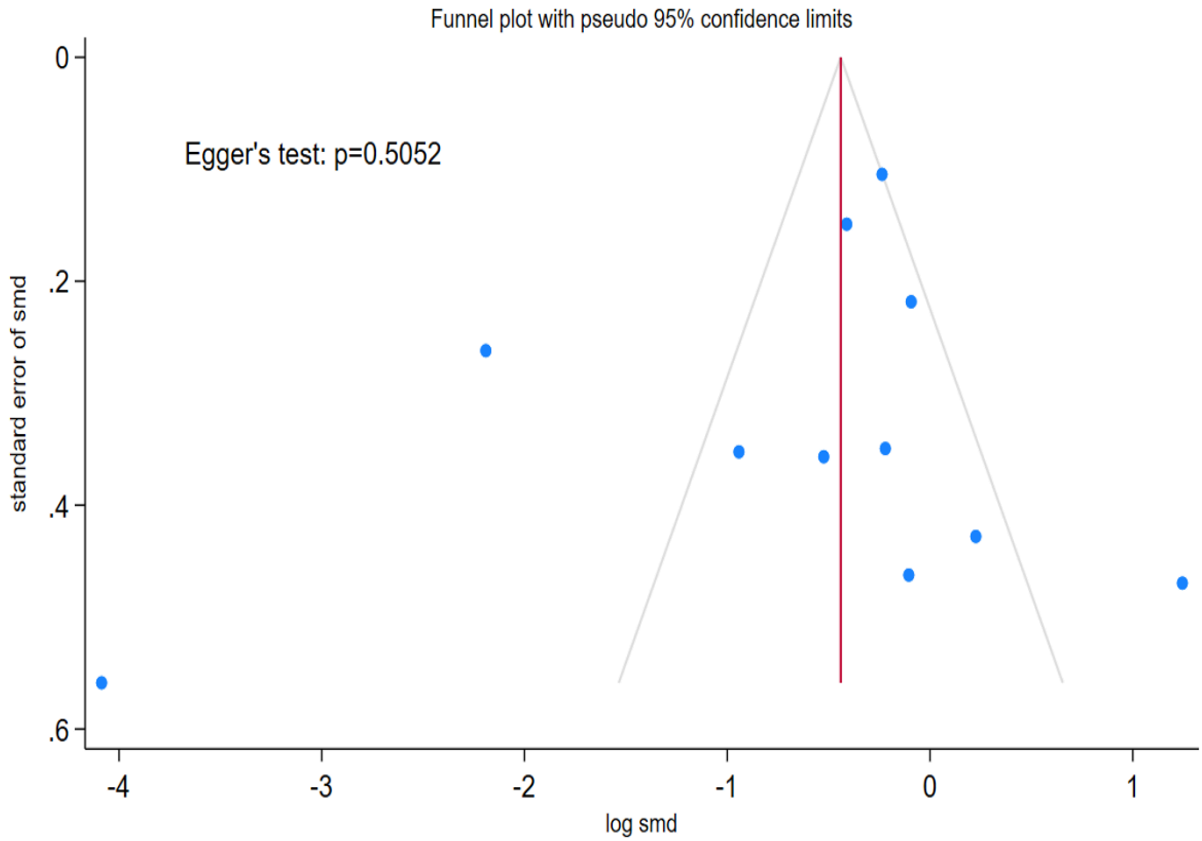
Each dot represents an individual RCT. The vertical red line shows the pooled effect estimate, and the grey diagonal lines show the pseudo 95% confidence limits.

Figure 16: Funnel plot assessing publication bias for opioid and related agents



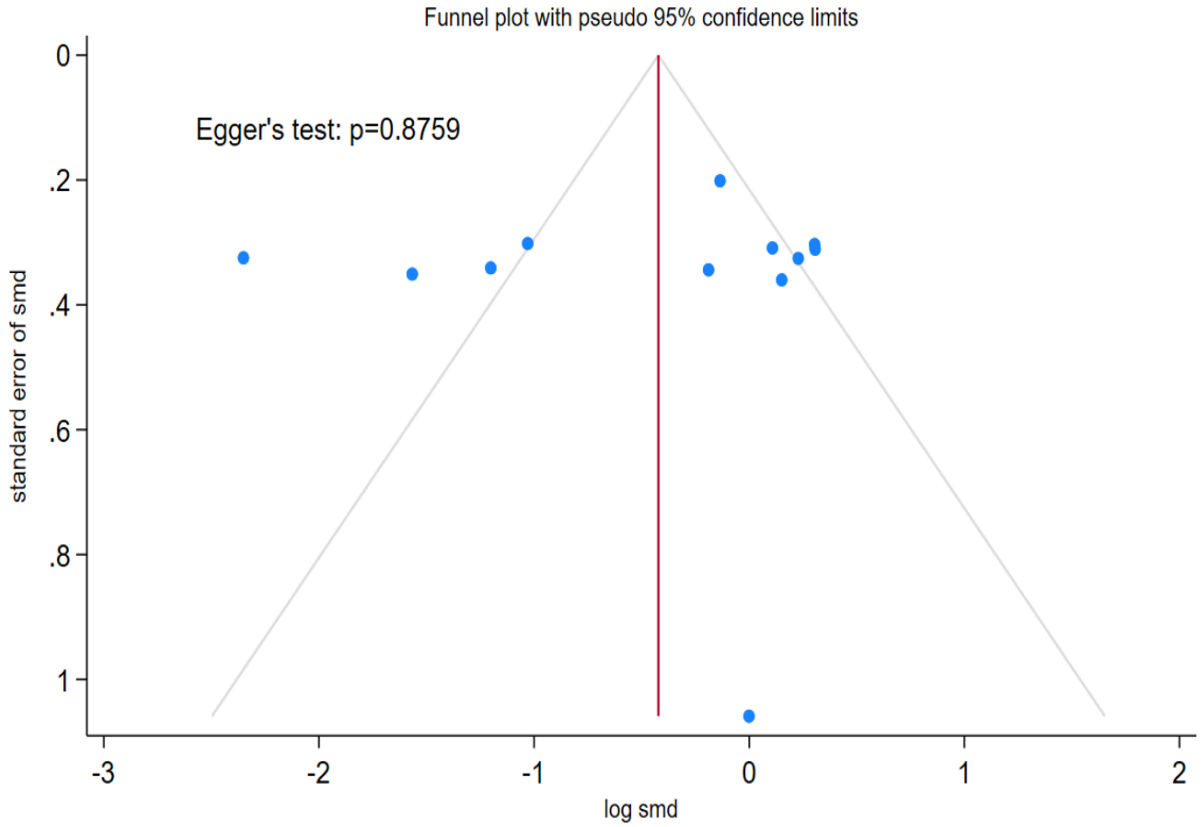
Each dot represents an individual RCT. The vertical red line shows the pooled effect estimate, and the grey diagonal lines show the pseudo 95% confidence limits.

Figure 17: Funnel plot assessing publication bias for topical/ localized pharmacological therapies



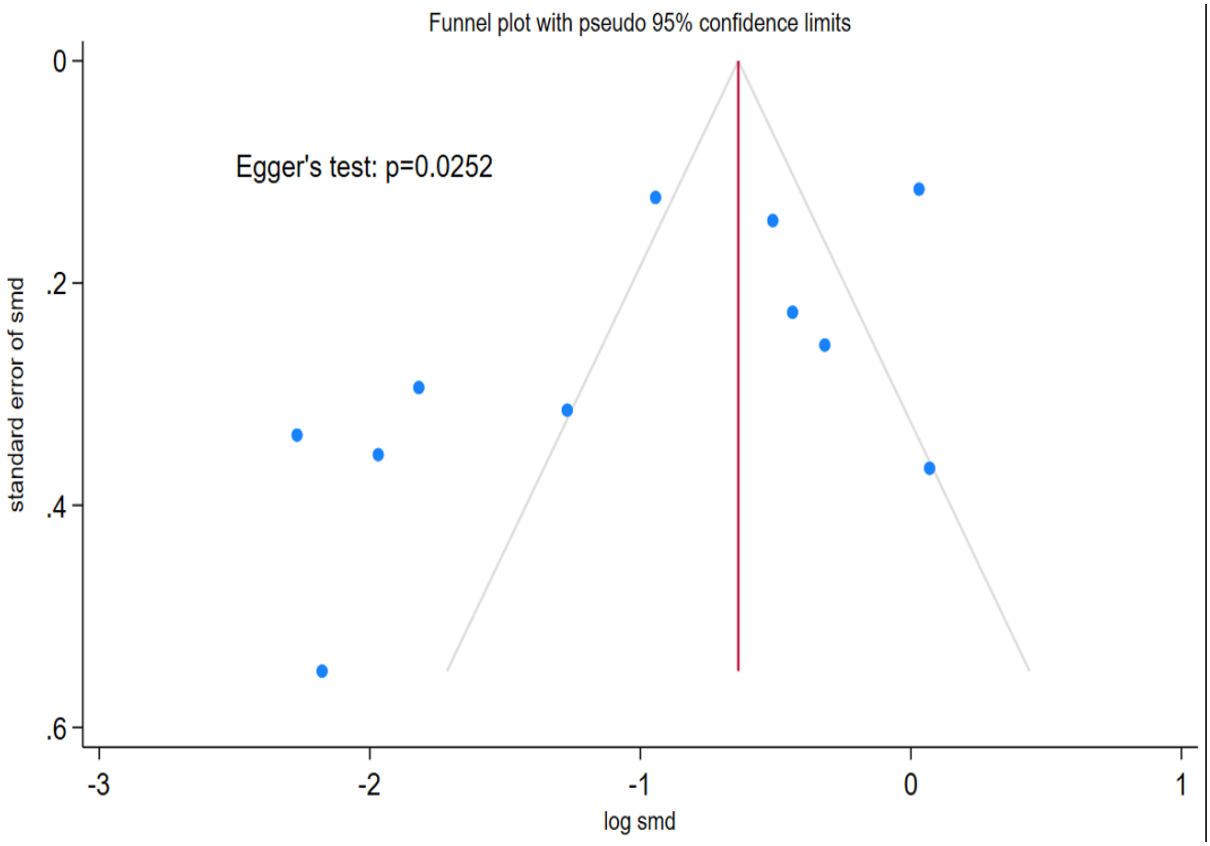
Each dot represents an individual RCT. The vertical red line shows the pooled effect estimate, and the grey diagonal lines show the pseudo 95% confidence limits.

Figure 18: Funnel plot assessing publication bias for metabolic/ vascular agents



Each dot represents an individual RCT. The vertical red line shows the pooled effect estimate, and the grey diagonal lines show the pseudo 95% confidence limits.

Figure 19: Funnel plot assessing publication bias for antioxidants



Each dot represents an individual RCT. The vertical red line shows the pooled effect estimate, and the grey diagonal lines show the pseudo 95% confidence limits.

3.5 Network Meta-Analysis

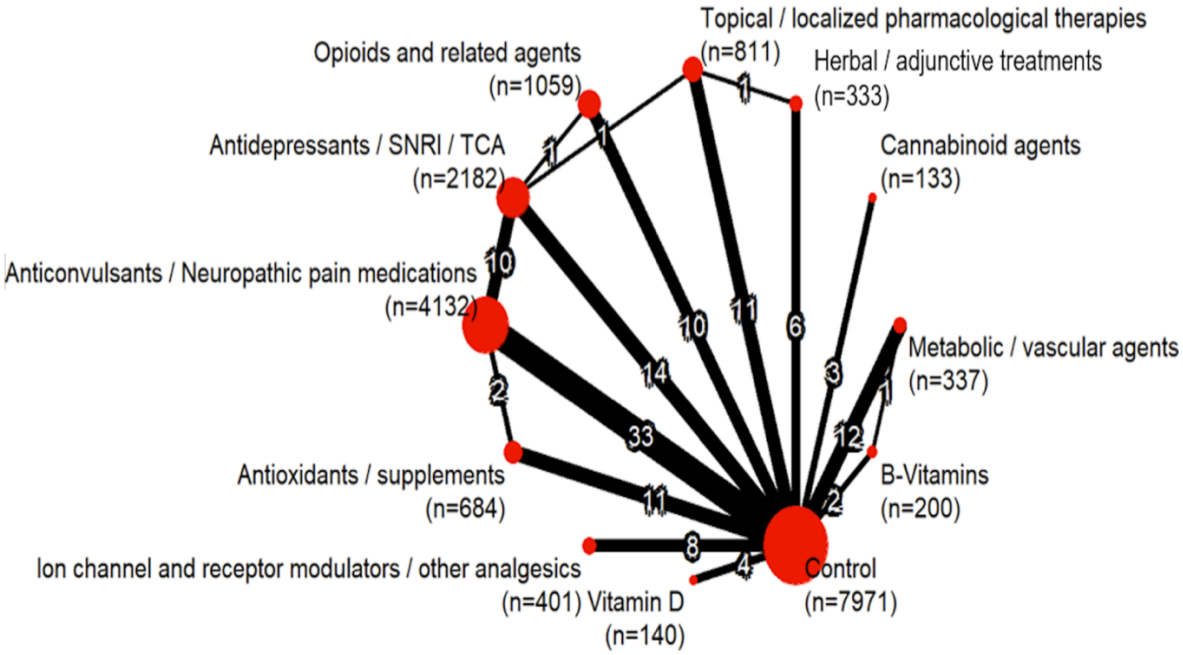
3.5.1 Network Diagram

Figure 20 illustrates the network plot of the included pharmacological interventions. The red nodes represent the intervention groups, and their size reflects the number of participants receiving each intervention across the trials. The size of each node is proportional to the total number of participants allocated to the respective intervention (198). The black edges represent direct comparisons between the intervention groups. The thickness of each edge corresponds to the number of trials providing that comparison, with thicker edges indicating a greater number of trials (198).

The network plot visualizes the structure of the available evidence and highlights the most frequently investigated comparisons. The most common comparisons were between anticonvulsants and the control group (33 vs. 14 comparisons), followed by antidepressants and the control group. Additionally, anticonvulsants and antidepressants were directly compared in 10 trials. These findings demonstrate that both intervention groups constitute the most extensively studied pharmacological treatment classes for DPN in the included literature. Both treatment classes are also among the medications recommended in current clinical guidelines for the management of DPN (grade B recommendation) (40).

Overall, the network was well connected, allowing both direct and indirect comparisons between the included pharmacological interventions in the analysis.

Figure 20: Network plot of the included direct treatment comparisons



Node size is proportional to the number of participants receiving each intervention, and edge thickness corresponds to the number of studies contributing to each direct comparison.

3.5.2 Main Findings From the NMA

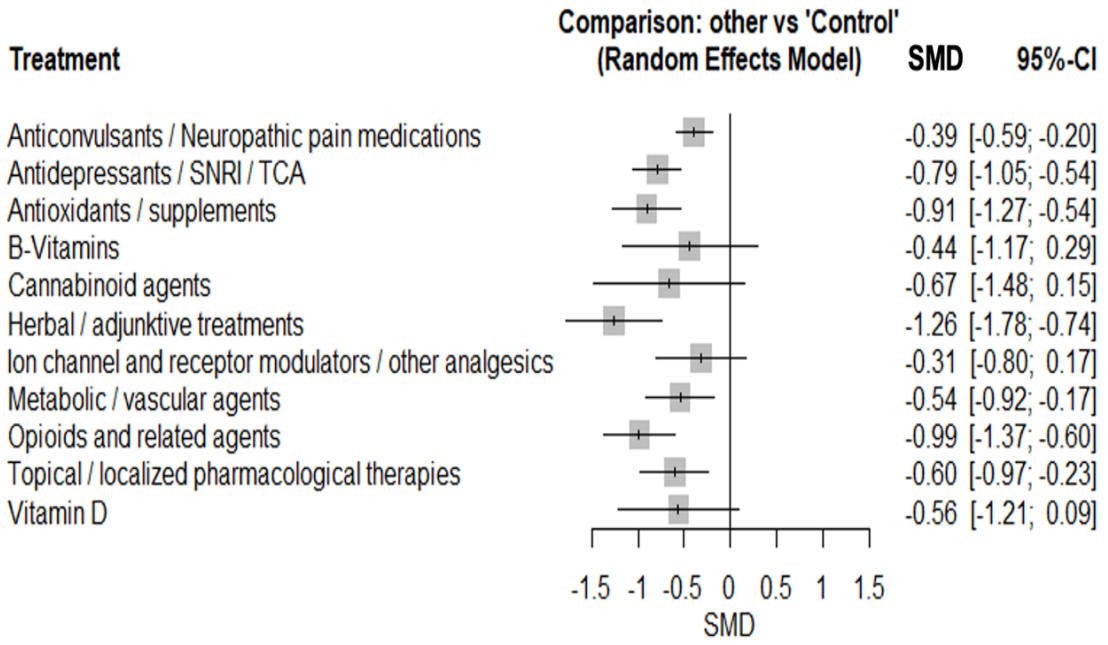
Figure 21 shows the pooled treatment effects of the investigated intervention groups compared with the control group, estimated using a random-effects model. Effect sizes are expressed as SMDs with corresponding 95% CI. The vertical line represents the line of no effect, where values to the left indicate a reduction in pain in favour of the intervention compared with the control group.

All the pharmacological treatments show a reduction in pain compared to placebo and most of these findings were statistically significant (anticonvulsants/neuropathic pain medications -0.39 [-0.59; -0.2]; antidepressants/ SNRIs/ TCAs -0.79 [-1.05; -0.54]; antioxidants/ supplements -0.91 [-1.27; -0.54]; herbal/ adjunctive treatments -1.26 [-1.78; -0.74]; metabolic/ vascular agents -0.54 [-0.92; -0.17]; opioids and related agents -0.99 [-1.37; -0.6]; topical/ localized pharmacological therapies -0.6 [-0.97; -0.23]).

Four of the interventions did not reach statistical significance (B-vitamins -0.44 [-1.17; 0.29]; cannabinoid agents -0.67 [-1.48; 0.15]; ion channel and receptor modulators and other analgesics -0.31

[-0.8; 0.17]; and vitamin D -0.56 [-1.21; 0.09]), which is likely due to the small number of trials and cohorts across the studies.

Figure 21: Forest plot of NMA treatment effects



Squares represent the pooled SMD of the investigated interventions compared with the placebo, and horizontal lines indicate the corresponding 95% CIs.

3.5.3 League Table of Treatment Comparisons

Table 5 shows the league table of treatment comparisons. The league table presents the treatment effects provided by the network meta-analysis. The table summarizes the estimated SMD with corresponding 95% CI for all direct and indirect pairwise comparisons between the investigated intervention groups. The values represent the SMD with the corresponding 95% CI between the treatment listed in the column and the treatment listed in the row. Negative SMD values indicate a greater reduction in pain in favour of the treatment listed in the column, whereas positive values indicate a greater reduction in pain in favour of the treatment listed in the row (the table should be read from left to the right).

The league table shows that all interventions were more effective in reducing pain compared with placebo. However, there is no single treatment class that is consistently superior across all comparisons.

Some pairwise comparisons suggested differences between active treatment. In particular, the comparison between the anticonvulsants and antidepressants presented a greater reduction in pain in favor of the antidepressants (-0.4 [-0.68; -0.12]). Other comparisons indicated small numerical differences between treatments, such as between antidepressants, topical treatments, and anticonvulsants. However, these differences were not statistically significant.

Although certain treatments classes showed larger effect estimates compared with other interventions, including herbal/ adjunctive therapies and opioids, these findings were often accompanied by wide 95% CIs, indicating uncertainty.

On the contrary, B-vitamins, cannabinoid agents, and ion channel/ receptor modulators tended to show smaller or less consistent effects compared with other interventions. However, these findings were also not statistically significant.

Overall, the league table indicates that while some treatments may present relative advantages in specific comparisons, most differences between active pharmacological treatments are small or uncertain.

Table 5: League Table of treatment comparisons

Antidepressants/ SNRI/ TCA											
0.19 (-0.26;0.64)	**Opioids and related agents**										
0.46 (-0.11;1.05)	0.27 (-0.37;0.92)	**Herbal/ adjunctive treatments**									
-0.25 (-0.71;0.21)	-0.44 (-0.98;0.09)	-0.72 (-1.36;-0.07)	**Metabolic/ vasular agents**								
-0.40 (-0.68; -0.12)	-0.59 (-1.02;-0.17)	-0.87 (-1.42;-0.31)	-0.15 (-0.58;0.27)	**Anticonvulsants/ neuropathic pain medications**							
-0.19 (-0.63;0.24)	-0.38 (-0.91;0.15)	-0.66 (-1.26;-0.06)	0.06 (-0.47;0.58)	0.21 (-0.63;0.20)	**Topical/ localized pharmacological therapies**						
-0.48 (-1.03;0.07)	-0.67 (-1.29;-0.05)	-1.13 (-1.95;-0.31)	-0.23 (-0.84;0.38)	-0.08 (-0.60;0.44)	-0.20 (-0.90;0.32)	**Ion channel/ receptor modulators/ other analgesics**					
-0.13 (-0.99;0.73)	-0.32 (-1.22;0.58)	-0.59 (-1.57;0.38)	0.12 (-0.78;1.02)	0.27 (-0.57;1.12)	0.06 (-0.84;0.96)	0.35 (-0.60;1.30)	**Cannaboid agents**				
0.11 (-0.33;0.55)	-0.08 (-0.61;0.45)	-0.35 (-0.99;0.28)	0.36 (-0.16;0.89)	0.51 (0.12;0.91)	0.30 (-0.21;0.82)	0.59 (-0.01;1.20)	0.24 (-0.66;1.14)	**Antioxidants/ supplements**			
-0.35 (-1.13;0.42)	-0.55 (-1.37;0.28)	-0.82 (-1.72,0.08)	-0.10 (-0.87;0.66)	0.05 (-0.71;0.80)	-0.16 (-0.98;0.65)	0.13 (-0.75;1.00)	-0.23 (-1.32;0.87)	-0.47 (-1.28;0.35)	**B-vitamins**		
-0.23 (-0.93;0.47)	-0.42 (-1.18;0.33)	-0.70 (-1.53;0.14)	0.02 (-0.73;0.77)	0.17 (-0.51;0.85)	-0.04 (-0.79;0.71)	0.25 (-0.56;1.06)	-0.10 (-1.15;0.94)	-0.34 (-1.09;0.40)	0.12 (-0.85;1.10)	**Vitamin D**	
-0.79 (-1.05;-0.54)	-0.99 (-1.37;-0.60)	-1.26 (-1.78;-0.74)	-0.54 (-0.92;-0.17)	-0.39 (-0.59;-0.20)	-0.60 (-0.97;-0.23)	-0.31 (-0.80;0.17)	-0.67 (-1.48;0.15)	-0.91 (-1.27;-0.54)	-0.44 (-1.17;0.29)	-0.56 (-1.21;0.09)	**Placebo**

The values represent the SMD with the corresponding 95% CI between the treatment listed in the column and the treatment listed in the row. Negative SMD values indicate a greater reduction in pain in favor of the treatment listed in the column, whereas positive values indicate a greater reduction in pain in favor of the treatment listed in the row (the table should be read from left to the right).

3.5.4 Ranking (P-Scores)

Table 6 presents the ultimate ranking of the intervention groups based on their p-scores, generated by the results of the league table. Based on the league table, herbal and adjunctive treatments reached the highest p-score (0.94), followed by opioids and related agents (0.82), antioxidants and supplements (0.76), and antidepressants/SNRIs/TCAs (0.67). Lower p-scores were observed for anticonvulsants (0.28) and ion channel/receptor modulators (0.24). Nevertheless, the league table indicates that differences between active therapies were generally small and often not statistically significant. Many pairwise comparisons showed overlapping 95% CIs, suggesting substantial uncertainty in the relative ranking of interventions. Furthermore, some interventions with high p-scores were associated with wide 95% CIs in the league table, indicating limited precision of the treatment effects. In contrast, treatments with lower p-scores, for instance anticonvulsants, showed more consistent but smaller treatment effects across multiple comparisons.

Table 6: P-score for each intervention group

Pharmacological treatment	P-score
Herbal/ adjunctive treatments	0.94
Opioids/ related agents	0.82
Antioxidants/ supplements	0.76
Antidepressants/ SNRI/ TCA	0.67
Cannabinoid agents	0.53
Topical/ localized pharmacological therapies	0.48
Vitamin D	0.45
Metabolic/ vascular agents	0.43
B-vitamins	0.36
Anticonvulsants/ neuropathic pain medications	0.28
Ion channel and receptor modulators/ other analgesics	0.24
Control/ placebo	0.03

P-scores range from 0 to 1. Higher p-scores suggest a higher relative ranking of the intervention regarding pain reduction.

3.5.5 Adverse Effects

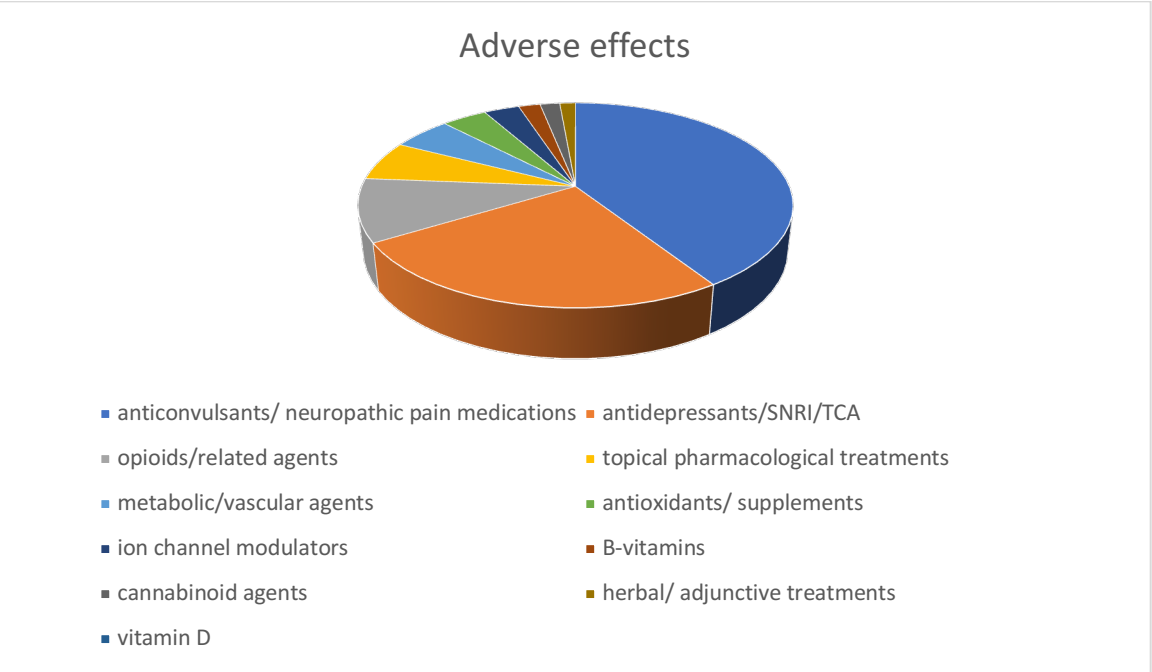
Reported adverse effects were extracted across the included studies. The most common adverse effects were nausea, dizziness, somnolence, headache, and diarrhea.

Figure 22 is a pie chart representing an exploratory overview of safety reporting showing the percentage of reported adverse effects of each interventional group. Anticonvulsants/neuropathic pain medications showed the largest proportion of adverse effects with 23.4%, followed by antidepressants and opioids. In contrast, herbal/adjunctive treatments and vitamin D presented a small proportion of

reported adverse events (0.8% and 0.0%, respectively). The complete table can be seen in the Appendix.

However, the reporting of adverse effects varied between the studies, and not all trials systematically reported the same side effects. Therefore, the observed frequencies should be interpreted with caution.

Figure 22: Adverse effects: distribution among the interventional groups



Anticonvulsants 23.4%, antidepressants 14.6%, opioids 5.7%, topicals 3.6%, metabolic/ vascular agents 3%, antioxidants/ supplements 2.3%, ion channel receptor modulators 1.8%, B-vitamins 1.1%, cannabinoid agents 1%, herbal/ adjunctive treatments 0.8%, vitamin D 0%.

3.5.6 Transitivity of the NMA

Figure 23 and Figure 24 show the transitivity of mean age and treatment duration, stratified by direct comparisons.

Each comparison is represented by a numerical code corresponding to the compared treatment. The numeric system for the treatments is: 1- control; 2- anticonvulsants/neuropathic pain medications; 3- cannabinoid agents; 4- ion channel and receptor modulators; 5- antidepressants/ SNRIs/TCAs; 6- metabolic and vascular agents; 7- opioids and related agents; 8- topical and localized pharmacological therapies; 9- antioxidants and supplements; 10- B-vitamins; 11- herbal and adjunctive treatment; and 12- vitamin D (e.g. 1:2 presents the direct comparison between control and anticonvulsants).

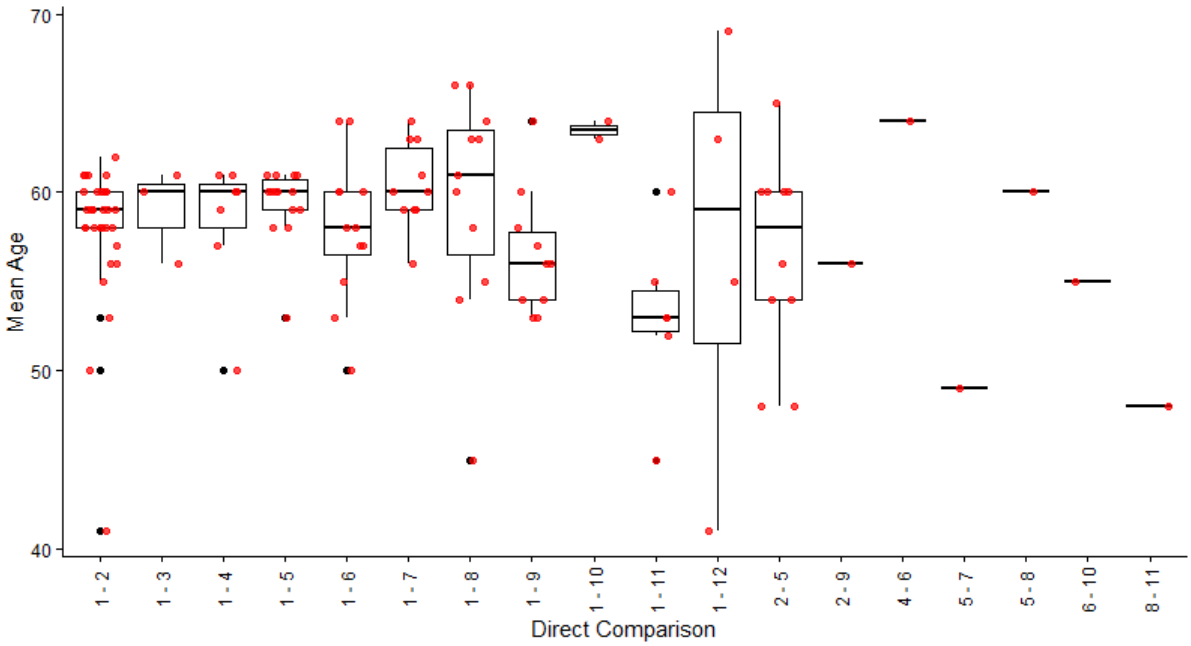
Boxplots were used to visualize the distribution of study characteristics within each comparison. The central line represents the median value, while the box indicates the interquartile range (IQR), reflecting the middle 50% of the data. Whiskers extend to the minimum and maximum observed values, and data points represent the mean values reported in each study. Wider boxes and longer whiskers indicate greater variability in the distribution of study characteristics across trials within a given comparison.

3.5.6.1 *Transitivity of Age*

The distribution of mean age across the trials is presented in Figure 23.

Overall, the median age of the participants among the studies ranged approximately between 55 and 65 years, suggesting that the populations included in the trials were comparable in terms of age. Most studies showed similar median ages and overlapping IQR, showing that the age was relatively balanced across the network. However, some variability was observed in some comparisons, for instance 1-12 and 2-5, where wider ranges were reported. These findings indicate a greater variability in participants' age. Despite this finding, the overall distribution of mean age across comparisons appeared consistent.

Figure 23: Distribution of mean age among the direct treatment comparisons for transitivity assessment



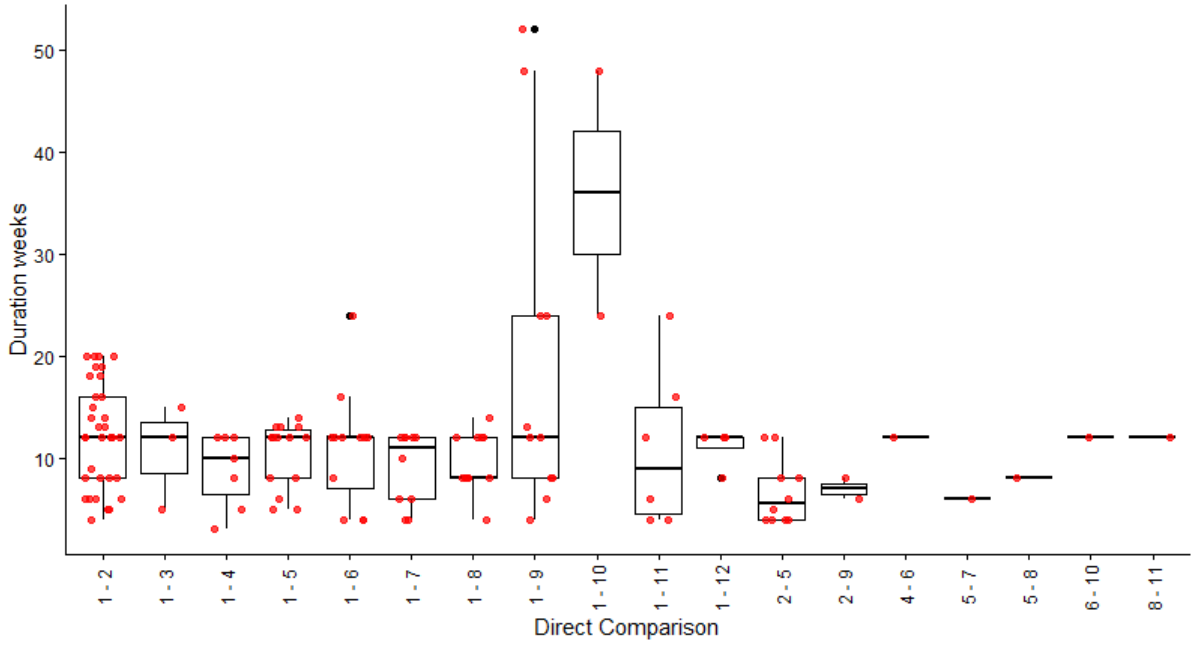
Boxplots present the distribution of study-level mean age across the direct comparisons in the NMA. Red dots represent the individual study values.

3.5.6.2 *Transitivity of Treatment Duration*

The distribution of treatment duration (weeks) is illustrated in Figure 24. The duration of treatment varied more than age across the included studies. Most trials reported treatment durations between 6 and 16 weeks, with median values around 10-12 weeks. However, some comparisons demonstrated longer treatment durations, for instance 1-10, where treatment duration extended up to approximately 50 weeks. This resulted in a wider IQR compared with other trials.

Overall, these findings indicate that while some effects modifiers appear relatively balanced across treatment comparisons, variability in certain comparisons, particularly for treatment duration, may be present.

Figure 24: Distribution of mean treatment duration (weeks) among the direct treatment comparisons for transitivity assessment



Boxplots present the distribution of study-level mean age across the direct comparisons in the NMA. Red dots represent the individual study values.

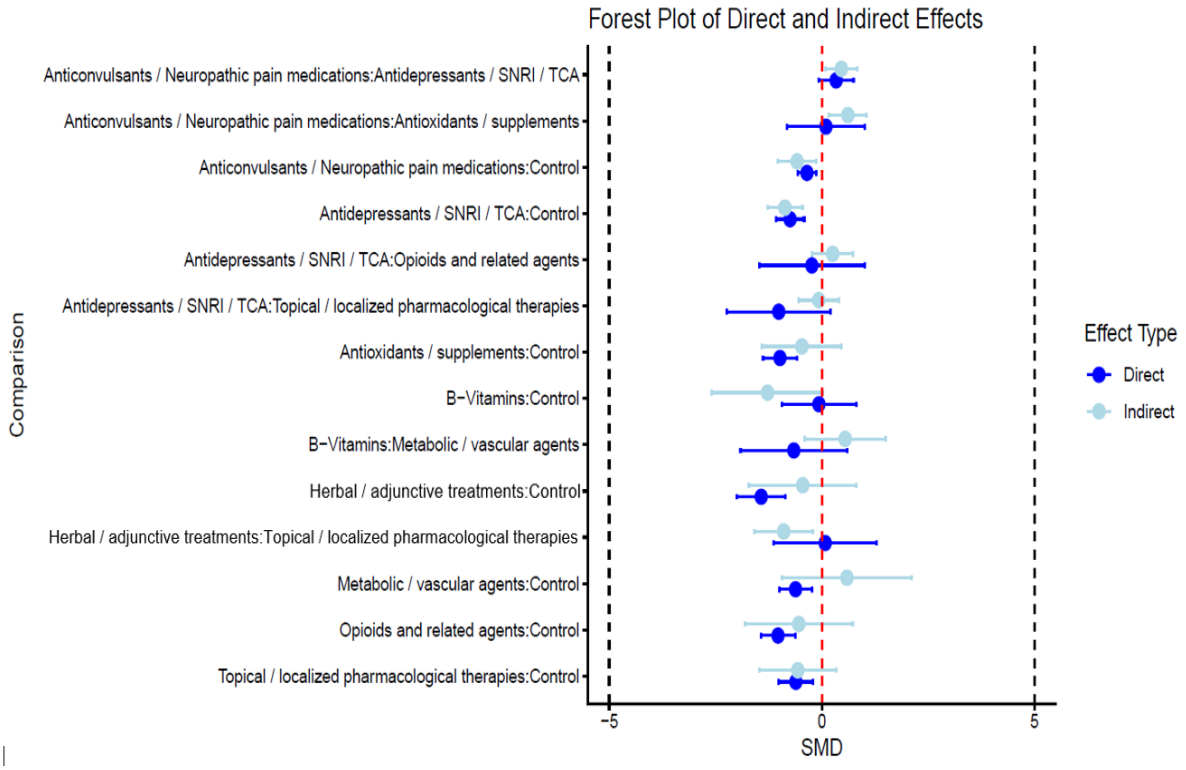
3.5.7 Consistency of the NMA

Consistency between direct and indirect comparisons was assessed by comparing the direction of effects estimates and their corresponding 95% CIs across the treatment comparisons. Figure 25 shows a forest plot of the direct and indirect comparisons. The dark blue points represent the effect estimates obtained from direct evidence, whereas the light blue points represent the indirect evidence from the treatment network. Horizontal lines show the corresponding 95% confidence intervals for each comparison. The vertical dashed line represents the line of no effect, where values to the left indicate a reduction in pain in favor of the first- listed intervention.

In general, most direct, and indirect effects were similar in direction and showed overlapping 95% CIs. This suggests a general agreement between the sources of evidence. For several comparisons, both direct and indirect effects presented a reduction in pain with comparable effect sizes and 95% CIs (e.g., antidepressants: control; anticonvulsants: antioxidants). However, some discrepancies between direct and indirect comparisons were identified. In some comparisons, differences in effect size and direction were present, although the corresponding 95% CIs overlapped, suggesting uncertainty rather than clear inconsistency (e.g., opioids: control; herbal treatment: topical treatment).

Overall, the comparison of direct and indirect evidence suggests that the assumption of consistency is largely met across the studies, although some variability between estimates cannot be excluded.

Figure 25: Forest plot of the direct and indirect effects



The dark blue points represent the effect estimates obtained from direct evidence, whereas the light blue points represent the indirect evidence from the treatment network. Horizontal lines show the corresponding 95% confidence intervals for each comparison. The vertical dashed line represents the line of no effect, where values to the left indicate a reduction in pain in favor of the first- listed intervention.

4 Discussion

4.1 Key Findings

We identified 130 articles of RCTs which were included in the NMA, and 113 of them were included in the pairwise meta-analyses. The evidence published up to June 2024 was synthesized to evaluate the comparative efficacy of pharmacological treatments for pain reduction in individuals with DPN. The risk-of-bias assessment showed that 27 studies raised a low risk of bias, 43 - high risk of bias, and the majority (n = 60)- some concerns. Increased risk of bias was primarily due to deviations from intended interventions and missing outcome data or selective outcome reporting (domains 2 and 3). Overall, most interventions demonstrated a reduction in pain compared with placebo, although the impact and statistical significance of these effects varied across treatment classes.

Among all interventions, herbal and adjunctive treatments, opioids and related agents, and antioxidants/ supplements were associated with the largest reduction in pain. Herbal and adjunctive treatments showed the highest effect size (−1.26 [−1.78, −0.74]), followed by opioids (−0.99 [−1.37, −0.60]), and antioxidants/ supplements (−0.91 [−1.27, −0.54]). These findings were further supported by a treatment ranking calculating the p-score.

Antidepressants, SNRI and TCA also demonstrated a reduction in pain and showed a statistically significant advantage over anticonvulsants (−0.40 [−0.68, −0.12]).

Other treatment classes, including topical therapies, metabolic/ vascular agents, and vitamin D, showed small effects with some variability in statistical significance. On the contrary, B-vitamins, cannabinoid agents, and ion channel/ receptor modulators did not demonstrate statistically significant effects.

Despite the generally favorable effects observed across most intervention, the NMA did not identify a single treatment class that was consistently superior across all comparisons. This is reflected in the league table results, where differences between treatments were often small and not statistically significant.

There was some heterogeneity across many pairwise meta-analyses, indicating variability in study results. However, the comparison between direct and indirect evidence suggested overall consistency within the network, supporting the validity of the findings.

In summary, all investigated pharmacological options appear effective for pain reduction in DPN. However, a clear hierarchy could not be established because of mostly comparable effects of the treatments.

4.2 Interpretation of the Findings

The group of herbal and adjunctive treatments included herbal oils such as nutmeg, Citrullus colocynths, lavender, green tea extract oil, as well as nerve support formula. These pharmacological treatments primarily target key pathophysiological mechanisms involved in DPN. Existing evidence has indicated that some herbal compounds have the potential to reduce oxidative stress and free radicals, moreover, they have many advantages over traditional medicine in preventing diabetic complications (95).

The largest pain reduction showed Rivaz 2021, which investigated the use of lavender oil. Lavender essential oil is widely used in aromatherapy for its anti-inflammatory, analgesic, and sedative effects (199). Heydari et al. (2016) also reported a significant reduction in pain using Citrullus colocynthis (bitter apple extract) oil (193). Citrullus colocynthis is a medicinal desert plant traditionally used in Africa and Asia for the treatment of nerve-originating pain (200). Citrullus colocynthis contains alkaloids and flavonoids that are reported to exert anesthetic and antioxidant effects (200). In contrast, the studies investigating nutmeg oil and green tea extract oil did not show a statistically significant or clinically meaningful reduction in pain.

However, the application of the oils, primarily through massage and/or aromatherapy, may represent potential confounding factors. The analgesic effects of massage are thought to arise from the interaction of touch with sensory fiber nerves in the skin, as well as from the absorption of essential oils into the bloodstream (96). Additionally, inhaled aroma molecules which are absorbed through the nasal mucosa, convert to neural signals in the olfactory bulb and limbic system. This process

contributes to therapeutic effects by releasing neurotransmitters such as endorphins and serotonin (199).

Nerve support formula, administered in tablet form, consists of a combination of mixed ingredients, most likely B- and D-vitamins, antioxidants like alpha-lipoic acid, and herbal ingredients such as turmeric and gingko biloba (201). Nerve support formula was investigated in one study, Cross et. al 2023, which reported exceptionally strong effects in the reduction in pain (194).

Overall, these findings should be interpreted with caution for now and require further investigation regarding their robustness. Nevertheless, the herb compounds discussed generally present a good profile of adverse effects (Figure 22). A meta-regression may help to explore potential confounding factors. However, the currently available evidence is limited, as is based on a small number of studies with relatively small sample sizes.

The group of opioids and related agents showed a statistically significant reduction in pain. The medications investigated in this group included oxycodone, tramadol, tapentadol, and buprenorphine. Their analgesic efficacy can be explained by their interaction with opioid receptors in the central and peripheral nervous system, which modulates nociceptive transmission and contributes to analgesia. Opioids are known for their strong analgesic properties and are classified as step-3 medications in the World Health Organization (WHO) analgesic ladder for management of severe pain. However, these agents are associated with several adverse events, including somnolence, constipation, and nausea, as well as the potential for dependence and addiction-related comorbidities (87). Therefore, they may be considered as a reserve, non-first line therapeutic option (36, 40, 202).

The third highest- ranking group comprised the antioxidants and supplements. The medications investigated in this group included ALA, coenzyme Q10, resveratrol, quercetin, vitamin E, ALC, gamma-linolenic acid, palmitoylethanolamide, nano curcumin, and gingko biloba. These pharmacological interventions act through several biological mechanisms, of which reduction of oxidative stress appears to be relevant (18, 35). The findings of the NMA are consistent and robust, suggesting a large reduction in pain. Particularly strong effects were observed for ALA, gamma-linoleic acid, and ALC. Alpha-lipoic acid has been extensively studied in randomized controlled trials and has demonstrated clinically meaningful improvements in neuropathic symptoms and pain (85, 203). Similarly, acetyl-L-carnitine presented beneficial effects on neuropathic pain in DPN, including in studies with relatively large sample sizes (Sima et al., 2005) (204). These findings are consistent with previous evidence and support the potential role of antioxidants as a treatment option for DPN. Nevertheless, ranking results based on the p-score should be interpreted with caution, as high rankings do not necessarily imply clinically meaningful superiority, particularly when based on limited evidence.

Furthermore, differences between individual agents within the same pharmacological class may have contributed to heterogeneity. Subgroup analyses may be important to illustrate the differences between the different medications in the same pharmacological group. For instance, pregabalin was associated

with greater pain reduction compared with gabapentin in the present analysis, which is consistent with previous evidence (205). Similarly, nabilone was associated with greater pain reduction compared with Sativex in the present analysis, contributing to heterogeneity within the cannabinoid subgroup (157). However, such comparisons should be interpreted cautiously due to indirect comparisons and potential differences in study characteristics.

Safety outcomes also require careful interpretation, as adverse event reporting varied across the studies. This is particularly relevant for herbal oils, which appeared promising regarding both pain reduction and adverse event profiles, although the available evidence remains limited.

Finally, secondary outcomes such as sleep quality, mobility, and quality of life should also be evaluated and considered in the NMA. These outcomes are clinically important, as painful DPN is associated with impaired daily functioning, sleep disturbances, and reduced quality of life (206).

To place these findings into a broader clinical context, a comparison with current guideline recommendations is essential.

4.3 Comparison with the Existing Evidence

The findings of the present NMA are broadly consistent with previous literature on the pharmacological management of neuropathic pain and DPN. For instance, earlier high-quality systematic reviews and meta-analysis have identified antidepressants, TCAs, SNRIs and anticonvulsants as first-line treatment options, although their efficacy is generally modest (36, 59). This is consistent with our results, where both antidepressants and anticonvulsants demonstrated statistically significant reduction in pain, with antidepressants showing a slightly greater effect compared with anticonvulsants.

The landmark systematic review by Finnerup et al. (2015) highlighted that pharmacological treatments for neuropathic pain typically provide only small to moderate pain relief and are often limited in tolerability and incomplete response (36). Our findings support this observation, as most treatment effects were small to moderate, and no single pharmacological class demonstrated clear superiority across all comparisons.

More recent evidence further emphasizes the increased use of NMA to establish hierarchies in the treatment of DPN. These studies similarly report that multiple medications show efficacy compared with placebo. Nevertheless, differences between active treatments are often small and associated with uncertainty, particularly when based on indirect comparisons (207). This is consistent with our results of the league table, which showed overlapping 95% CIs for many comparisons and no consistently dominated treatment class.

Remarkably, our analysis identified herbal and adjunctive therapies, opioids, and antioxidants/ supplements as the highest-ranking interventions in terms of effect size. These are currently not included in existing clinical guidelines for the treatment of painful DPN (98). While these findings might suggest potentially strong analgesic effects, they should be interpreted with caution. Previous literature has highlighted that larger effect sizes in smaller RCTs may reflect bias or heterogeneity

rather than superiority (36). This is relevant given the high heterogeneity observed in these treatment groups in the present work.

In contrast, established first-line treatments such as antidepressants and anticonvulsants presented more consistent effects across a large number of trials, supporting their crucial role in clinical guidelines (208). Current recommendations still prioritize these medications due to their balance of efficacy and evidence robustness, rather than effect size alone (209).

Overall, the present findings support the existing evidence suggesting that the pharmacological treatment of DPN is defined by multiple moderate effective options rather than a clearly hierarchical treatment, highlighting the need for individualized treatment strategies and further high-quality comparative trials.

4.4 Strengths of the Study

In addition to the clinical relevance of the findings, several methodological strengths of this work should be acknowledged. One of the main strengths of this NMA is the integration of evidence from many RCTs, resulting in a comparatively broad evidence base for indirect and direct treatment comparisons. The literature search has been very thorough and identified many treatments with available evidence which were included in the NMA. This increases the statistical power and improves the reliability of the findings. By including only randomized controlled trials, the analysis is based on high-level evidence and reduces the risk of bias compared with observational studies (210).

Furthermore, the study was conducted in accordance with PRISMA recommendations, which supports transparency and reproducibility of the analytical process (103). A crucial strength is the use of a comprehensive network meta-analysis approach, which allows the simultaneous comparison of multiple interventions, including treatments that have not been directly compared in head-to-head trials (211). The statistical analyses were conducted using robust methods, assembling both direct and indirect comparisons across the treatment groups (211). As a result, the analysis identified several statistically significant effects and generated a comprehensive ranking of the intervention groups. These methodological strengths enhance the validity and interpretability of the results (211).

4.5 Limitations

Despite these strengths, several limitations should be considered when interpreting the results of the current NMA.

Many of the included RCTs had relatively small sample sizes (e.g., the studies investigating B-vitamins, vitamin D, and cannabinoids), which may reduce the precision and robustness of the treatment effect estimates. Furthermore, considerable heterogeneity was observed across the studies, which may have influenced the findings (121). Differences in interventional protocols, sample sizes and outcome assessment may have contributed to the observed variability.

Another important limitation is the relatively short duration of treatment and follow-up, which in most studies did not exceed twelve weeks. This limits the ability to draw conclusions regarding the long-

term efficacy and sustainability of treatment effects, which is particularly relevant for a chronic disease such as painful DPN.

Furthermore, the outcome of interest was pain, reported by the patients and assessed by validated pain scales. However, pain remains a subjective outcome that is difficult to measure objectively and may be influenced by psychological factors such as mood, expectations, and communication skills of the participants (212). Additionally, depression represents a potentially substantial confounder in painful DPN, as affected participants often report higher baseline pain scores and were more likely to respond to any intervention, including placebo (213). Furthermore, concomitant antidepressant therapy may further confound treatment effects since both pain perception and treatment response can be influenced by psychological comorbidities. This may either mask or amplify the apparent analgesic effects of the investigated interventions (213, 214).

Importantly, the present analysis focused on SMDs as a measure of treatment effects. However, clinically meaningful pain reduction, commonly defined as >30% reduction in pain intensity, was not directly assessed. As a result, the clinical relevance of the observed effect sizes may be difficult to interpret.

In addition, the exact dosage of the treatments was not evaluated. Differences in dosing regimens across studies may have influenced the observed treatment effects, as efficacy and tolerability depend often on the dose. This may have introduced additional variability and limits the ability to draw conclusions about optimal dosing strategies.

A formal safety analysis was not conducted. Given the heterogeneity and inconsistent reporting of adverse events across studies, a quantitative comparison of safety outcomes would be valuable.

Another limitation relates to the quality of the included studies. A total of 43 from 130 studies with a high risk of bias were identified, which may affect the reliability of the results. Whether studies with high risk of bias should be excluded from the NMA remains debated. While exclusion may improve internal validity, it may also introduce selection bias at the review level and result in loss of potentially relevant information (215, 216). The current Cochrane Guidelines therefore recommend including such studies but addressing their impact through sensitivity analyses and assessment of the certainty of evidence using approaches such as GRADE adapted for NMA (105).

Finally, although the assumption of transitivity was assessed for crucial clinical effect modifiers, it could not be fully evaluated for all potential sources of heterogeneity. Differences in the size of the intention-to-treat populations across studies were not formally examined. This may be relevant, as smaller studies may be more prone to imprecision and small-study effects, potentially influencing the estimated treatment effects. Furthermore, the impact of small-study effects cannot be excluded, which may further influence the estimated treatment effects.

4.6 Clinical Implications

The findings of these meta-analyses have several important implications for clinical practice.

Overall, the results suggest that differences in efficacy between most active pharmacological treatments for painful DPN are small to moderate. Consequently, treatment decisions should not be driven primarily by small differences in effect size or ranking positions.

Antidepressants, SNRIs, TCAs and anticonvulsants demonstrated the most consistent evidence base across studies and should therefore remain key pharmacological options in the management of painful DPN. Their established role in current guidelines is supported not only by their efficacy but also by the robustness and consistency of the available evidence in various populations with chronic pain syndromes.

In contrast, supplement, vitamins, and many adjunctive or alternative therapies showed more variable and less consistent effects. While some interventions demonstrated potentially large effect sizes, their overall evidence base remains limited and heterogeneous. These treatments may therefore be considered as complementary or individualized options rather than equivalent alternatives to established pharmacological therapies.

Similarly, opioids did not demonstrate a consistent advantage over other medications within the network. Given their high-risk profile, including dependency and adverse effects, their use should remain restricted to carefully selected patients and considered primarily as a second- or third-line therapy (66).

Taken together, these findings support a patient-centered treatment approach. Factors such as comorbidities, side effect profiles, and underlying pain mechanisms should be considered in treatment selection rather than small differences in effect sizes between the drug classes.

Finally, although p-scores provide a useful framework for ranking treatments within the network, they should not be interpreted as a strict clinical hierarchy. Rather, they should be considered alongside the broader clinical context and the overall quality and consistency of the evidence.

4.7 Outlook

Future research should focus on conducting adequately powered randomized controlled trials with longer follow-up durations exceeding 12 weeks to better assess the long-term efficacy and safety of pharmacological treatments for DPN (97). Many currently available trials are limited by small sample sizes and short treatment durations, which reduces the robustness of conclusions regarding treatment effects (97).

Moreover, larger high-quality RCTs are needed to evaluate the effectiveness of herbal oils, as the currently available evidence remains limited despite promising results regarding pain reduction and safety. Additionally, priority should be given to head-to-head trials comparing promising emerging therapies (herbal oils, antioxidants, opioids) with established first-line treatments (anticonvulsants, antidepressants). Further trials are required for interventional groups such as vitamin D, cannabinoids, and B-vitamins, which did not reach statistical significance in the current NMA. This lack of significance may reflect insufficient statistical evidence rather than true lack of efficacy (213).

Future studies should evaluate the effectiveness of combination therapies. Given the complex pathophysiology of neuropathic pain, combination treatment may provide superior pain control compared with monotherapy (36). Herbal oils may represent promising adjunctive therapies to established first-line treatments such as anticonvulsants and antidepressants, potentially improving pain reduction without requiring dose escalation of systemic therapies (32).

Moreover, future research should further investigate multimodal treatment approaches integrating pharmacological and non-pharmacological treatments (36). Current evidence suggests that comprehensive management strategies including psychological interventions, physiotherapy, neuromodulation techniques, transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), and acupuncture may provide additional benefits when combined with pharmacological agents, although high-quality evidence remains limited (35).

Future RCTs should also investigate clinically relevant secondary outcomes such as sleep quality, physical functioning, mobility, and quality of life. These outcomes are important given the considerable impact of painful DPN on daily functioning and mental health. Standardized reporting of these outcomes would improve comparability across trials and strengthen future evidence synthesis (206).

Finally, future NMAs would benefit from improved reporting of study characteristics and potential effect modifiers to strengthen the assessment of transitivity and consistency. More standardized outcome reporting and longer follow-up periods would further improve the reliability of indirect treatment comparisons. Moreover, future trials should aim to use standardized outcome measures and core outcome sets to improve the comparability between studies. Another aim should be to minimize risk of bias through adequate randomization and blinding processes and thorough reporting of the results. Including more representative participants, including older patients with multimorbidity and higher baseline pain scores, may improve external validity.

4.8 Conclusion

In conclusion, this systematic review and pairwise and network meta-analyses present that multiple pharmacological therapies are effective in reducing pain in individuals with painful DPN, with overall small to moderate differences in efficacy between most active interventions. No single treatment class emerged as consistently superior across all comparisons.

Antidepressants and anticonvulsants remain the most reliable treatment options, supported by robust and consistent evidence base, while other treatments such as antioxidants/ supplements, herbal oils/ adjunctive therapies, and opioids should be considered with caution and in specific clinical contexts. These findings highlight the importance of an individualized, patient-centered approach to treatment selection, where factors such as comorbidities, tolerability, and preference of the individuals may outweigh small differences in effect sizes.

Future research should focus on high-quality, head-to-head trials with longer follow-up periods and clinically meaningful outcomes to improve long-term management of painful DPN.

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6 Appendix

6.1 Full Electronic Search Strategy

See Appendix.

6.2 Excluded Studies with Reasons

See Appendix.

6.3 Complete Risk of Bias Tables

See Appendix.

6.4 References (of Excluded Studies)

See Appendix.