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ORIGINAL RESEARCH

Network Meta-analysis of Randomized Controlled Trials Assessing Neuromodulation Therapies for Painful Diabetic Neuropathy

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ABSTRACT

Introduction: Neuromodulation therapies (including non-invasive and invasive neuromodulation) are being used to treat painful diabetic neuropathy (PDN).

Methods: A systematic search of the PubMed, Embase, Cochrane Library, Web of Science, and Scopus databases was conducted, from their inception until 1 October 2024, to identify randomized controlled trials (RCTs) on neuromodulation therapies for PDN. Data were collected on pain intensity of various adjunctive therapies for PDN, including transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation, repetitive transcranial magnetic stimulation, pulsed electromagnetic field therapy, spinal cord stimulation (SCS), transcranial direct current stimulation, frequency rhythmic electrical modulation system, mesodiencephalic modulation, and sham.

Results: The data from an aggregate of 12 separate studies, comprising a total sample size of 922 participants, was subject to analysis. All seven neuromodulation therapies exhibited better outcomes in pain intensity compared to the Sham intervention, with TENS achieving the highest ranking, followed by SCS. At the final follow-up time point, statistically significant reductions in pain intensity (vs. Sham) was only observed for SCS.

Conclusion: The results of this network meta-analysis should facilitate the development of clinical guidance and enhance the decision-making process for both patients and healthcare professionals, thereby identifying the most appropriate PDN treatment options.

Trial Registration: PROSPERO: CRD42024597208.

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Key Points Summary

Why carry out this study?

Painful diabetic neuropathy (PDN) significantly impacts quality of life and presents a considerable economic burden due to its chronic nature and associated complications. Existing meta-analyses predominantly focus on pairwise comparisons, failing to provide a hierarchy of efficacy across all available modalities and emerging techniques, such as frequency-rhythmic electrical modulation system (FREMS) and mesodiencephalic modulation (MDM), which have not been incorporated into prior quantitative syntheses. Also, conventional meta-analyses cannot integrate indirect evidence from studies comparing different active interventions through a common comparator (e.g., Sham). This lack of data from head-to-head trials limits clinicians' ability to select optimal therapies

This study aimed to evaluate the relative efficacy of various neuromodulation therapies for treating PDN through a network meta-analysis of randomized controlled trials

What was learned from the study?

Transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS) showed significant pain reduction, but the findings of our analysis emphasize the need for further direct comparative studies between different neuromodulation therapies to clarify their relative benefits and inform clinical guidelines. Future research should also address the limitations of current evidence, including potential biases and the subjective nature of pain assessment

What were the study outcomes/conclusions? (data)

All seven neuromodulation therapies analyzed demonstrated superior outcomes in terms of modulating pain intensity compared to Sham treatment, with TENS exhibiting the highest effectiveness, followed closely by spinal cord stimulation (SCS)

INTRODUCTION

Recent years has seen a notable and continuing increase in the prevalence of diabetes on a global scale. In 2014, an estimated 422 million adults were affected, representing a worldwide prevalence rate of 8.5% [1]; this is a considerable increase from 108 million cases in 1980. Alarmist projections suggested that almost half a billion individuals would be living with the condition globally by 2019 [2], and a more recent estimation was that there may be as many as 629 million cases of diabetes mellitus by 2045 [3]. It has been projected that between one-third and one-half of individuals diagnosed with diabetes will experience painful diabetic neuropathy (PDN) [4–6], which represents the most prevalent cause of neuropathic pain (NP) in the USA [7, 8]. In 2010, the American Chronic Pain Association (ACPA) estimated that over 15 million people in Europe and the USA experience NP to varying extents [9]. In Europe, prevalence rates of PDN have been documented to vary significantly, with estimates ranging from 5.8% to 34.0% [10], with the incidence of PDN in the Netherlands and the UK estimated to be 0.72 and 0.64–0.69 cases per 1000 persons per year, respectively [11, 12]. A multicenter investigation of diabetic subjects in Beijing carried out in 2018 demonstrated that the incidence of PDN among individuals with both type 1 and type 2 diabetes in China was 21.92% and 35.34%, respectively [13].

PDN represents a chronic NP condition that may become debilitating in the absence of an appropriate therapeutic intervention [14].

Patients presenting with PDN typically report a constellation of symptoms, including paroxysmal burning pain, sharp discomfort, electric shock-like sensations, and a sensation of numbness, tingling, or pins and needles [15]. PDN is frequently associated with a decline in quality of life, as well as the onset of depressive, anxiety and sleep disorders [15]. PDN also has a substantial economic impact on both individuals and society at large, including increased utilization of healthcare resources and direct and indirect costs resulting from reduced work productivity [16]. It is estimated that the annual healthcare costs of individuals with PDN are approximately twofold higher than those who do not experience neuropathy (non-PDN) [17]. The authors of one retrospective study reported that the medical costs incurred by patients with PDN were 4.2-fold higher than those of control patients with diabetes ($27,931 vs. $6632; $p<0.0001$) [16]. In addition, the costs were even higher among patients with severe disease ($30,755; $p<0.001$) [16]. A longitudinal study demonstrated that patients with diabetes and PDN were hospitalized at a rate that was 2.5-fold higher than that observed in patients without PDN [18]. In addition, the incidence of lost productivity time was found to be 18% higher in the diabetes + PDN cohort [18]. To date, no singular pathomorphological classification has been able to encompass PDN. Neurophysiological evidence indicates dysfunction in processing at various levels, including the dorsal root ganglia (DRG), ventrolateral periaqueductal gray, and autonomic nervous system [15, 19].

Although pain is a prevalent symptom of diabetic neuropathy, there is still much to be discovered about the underlying pathophysiological processes and hormonal systems involved [20]. At present, there are no pharmacological agents known to have the ability to reverse the progression of neuropathy by targeting the underlying pathophysiology of PDN [21, 22]. It is therefore evident that the primary approach to managing PDN is through the implementation of symptomatic treatment. The primary goals of treatment for PDN are threefold: (1) intensive control of blood glucose and risk factor management; (2) treatments based on the pathogenic mechanisms involved in the condition; and (3) management of the pain associated with DPN [23, 24]. Clinical guidelines recommend the utilization of tricyclic antidepressants (e.g., amitriptyline and duloxetine), serotonin-norepinephrine reuptake inhibitors (γ-aminobutyric acid analogs), antiseizure drugs (pregabalin and gabapentin), and opioids, in conjunction with topical medications (e.g., capsaicin), with a view to alleviating the symptoms of DPN [25, 26]. The findings of high-quality randomized clinical trials (RCTs) suggest that these pharmacological agents have only modest efficacy and are linked with a high prevalence of adverse effects. The use of gabapentinoids has been linked to an elevated risk of respiratory depression, which represents a significant concern for patients who are already undergoing opioid therapy or who have underlying respiratory compromise [27–29]. A systematic review and network meta-analysis (NMA) of RCTs of NP medications indicated that the numbers needed to treat varied considerably, ranging from 3.6 to 7.7, while the numbers needed to harm were more tightly clustered, falling within a narrower range of 11.8–25.6 [30]. Gabapentin and pregabalin are frequently administered for the management of PDN. However, adherence to long-term treatment is frequently suboptimal, with over 60% of patients ceasing treatment within 6 months [31]. A similar pattern is evident in the case of duloxetine, with 50% of patients ceasing treatment within a 6-month period [31]. Following the cessation of a treatment, the majority of patients with PDN do not transition to an alternative treatment. Consequently, their condition remains unmanaged effectively [31].

In this context, there has been a notable increase in interest in the exploration of alternative, safe, and efficacious non-pharmacological therapeutic strategies for the management of PDN. A multitude of neuromodulation approaches have been proposed as potential solutions [29]. In recent years, there has been an increase in the utilization of non-invasive neuromodulation (NINM) techniques for pain management [32, 33]. These neurotechnological strategies have shown effectiveness and safety in treating chronic NP, as demonstrated in various clinical studies [34, 35]. NINM techniques can be divided into two primary categories: central

and peripheral neurostimulation. The NINM techniques that have received the most extensive scrutiny are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [36], while transcutaneous electrical neural stimulation (TENS) represents the most prevalent approach in peripheral stimulation [17, 37]. In tDCS, a subthreshold current is sent between two electrodes placed over the scalp—from anode to cathode; in rTMS, magnetic fields are utilized to provoke electrical modifications in brain activity [38]. In a similar strategy, TENS employs an electrical current to influence the membrane polarity of peripheral nerves [39], which has the capacity to modify brain function by inducing alterations in the polarity of neuronal membranes [36, 40]. In accordance with Melzack and Wall's neuromatrix theory of pain [41], these factors may also exert an influence on pain perception, thereby restoring equilibrium within the inhibitory endogenous pain pathways and counteracting or reversing maladaptive plasticity, which may ultimately result in a reduction of pain [38]. However, while the potential benefits of non-invasive and minimally invasive neuromodulation techniques in treating certain patients are worthy of consideration, the analgesic efficacy of these approaches is limited and relatively brief in duration [42–45].

In contrast, the utilization of invasive neuromodulation with an implanted stimulator device may facilitate prolonged pain alleviation for patients with intractable pain who have not reacted to alternative forms of treatment. Given the high prevalence of PDN, it is a reasonable assumption that this may become one of the most common indications for neuromodulation treatments. The neurophysiological mechanisms underlying chronic stimulation and its analgesic effects remain incompletely elucidated. The current standard of care for this condition is tonic spinal cord stimulation (t-SCS), a technique that makes use of repetitive electrical impulses (50 Hz) delivered to the dorsolateral columns via epidural electrodes. It has been demonstrated that tonic stimulation results in the onset of paraesthesia in the region of the pain. This phenomenon has traditionally been postulated to function by means of a gate control mechanism that competes with pain signals [46]. However, the advent of a number of stimulation methods that can successfully achieve analgesia without generating paraesthesia has prompted a re-evaluation of this long-held belief [33, 47]. The field of neuromodulation is currently undergoing a period of significant advancement, with the advent of novel stimulation techniques, such as dorsal root ganglion stimulation (DRGS), high-frequency spinal cord stimulation (HF-SCS), and burst spinal cord stimulation (B-SCS). A growing body of evidence suggests that invasive neuromodulation may offer a promising avenue for the treatment of patients with refractory pain in association with PDN.

While prior systematic reviews have evaluated individual neuromodulation therapies for PDN [48, 49], significant knowledge gaps remain. First, existing meta-analyses predominantly focus on pairwise comparisons (e.g., TENS vs. Sham or SCS vs. pharmacotherapy), failing to provide a hierarchy of efficacy across all available modalities. Second, emerging techniques such as frequency rhythmic electrical modulation system (FREMS) and mesodiencephalic modulation (MDM) have not been incorporated into prior quantitative syntheses. Third, conventional meta-analyses cannot integrate indirect evidence from studies comparing different active interventions through a common comparator (e.g., Sham). This lack of data from head-to-head trials limits clinicians' ability to select optimal therapies. The aim of the NMA reported here was to address these limitations by simultaneously ranking nine interventions (including novel modalities) using both direct and indirect evidence, thereby generating clinically actionable recommendations for therapy selection.

METHODS

Search Strategy

This NMA were carried out following the fundamental principles specified in the Centre for Reviews and Dissemination (CRD) guidelines for healthcare reviews [50]. The NMA adhered

to the standards set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), which include NMA [51] and is registered under PROSPERO (CRD42024597208). Researchers specializing in information retrieval conducted searches in PubMed, Scopus, Embase, the Cochrane Library, and Web of Science databases from their inception up to 1 October 2024, utilizing the search terms (Chronic pain OR neuropathic pain OR neurostimulation OR peripheral neuropathy) AND (non-invasive neuromodulation stimulation OR invasive electrical neuromodulation OR transcranial magnetic stimulation OR transcranial direct current stimulation OR transcutaneous electrical nerve stimulation OR spinal cord stimulation OR ganglion stimulation OR brain stimulation OR nerve root stimulation) AND (diabetes OR diabetic). No restrictions based on publication type or language were applied. The results were exported into the EndNote X9 library and duplicates were removed. Additionally, reference lists of applicable systematic reviews and qualifying studies were manually examined to uncover further studies relevant to the research subject.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

Two reviewers, Jinping Wang and Li Li, carried out the literature search and independently identified pertinent studies. Any disagreements that arose were addressed through discussion involving a third reviewer, Yangmei Chen, at each phase of the review process. The criteria for study inclusion in the NMA were: (1) adult patients (aged ≥ 18 years) diagnosed with diabetic neuropathic pain; (2) intervention with either NINM stimulation or invasive electrical neuromodulation; (3) comparator with conventional medical management (CMM), including standard care, an active intervention, or Sham; and (4) RCT design.

Outcome Measures

The main measure of outcome focused on pain severity, which was evaluated using a visual analog scale (VAS) during the last follow-up assessment.

Study Selection, Data Extraction, Assessment of the Risk of Bias, and Confidence in the Evidence

To determine the potential bias present in the identified studies, we performed an evaluation following the protocols established by the Cochrane Collaboration. Initially, one reviewer (Li Li) carried out the risk of bias assessment for the included studies, which was later reviewed by a second reviewer (Jinping Wang) to ensure consistency. Any discrepancies that arose were resolved through discussion and, if necessary, consultation with a third reviewer (Yangmei Chen). The confidence in the presented evidence was assessed using a web application known as the CINeMA (Confidence in NMA) tool [52, 53].

Statistical Analysis

The data extracted comprised the first author, publication year, characteristics of the study, the country of recruitment, demographic information (such as age and gender), specifics of the intervention process, and outcome metrics. The outcomes included the total number of participants analyzed and the time points for measuring outcomes in each study. To facilitate the meta-analysis, scores originally on a 100-point scale were transformed into a 10-point system. In addition, comprehensive pain scores were utilized when both daytime and nighttime scores were available, while peak pain scores were taken into account when both background and peak scores were reported. The degree of statistical heterogeneity across the trials was assessed by comparing trial and participant features, the results of the trials, and a formal evaluation utilizing the I^2 statistic (which indicates the percentage of variability

among trials due to statistical heterogeneity) along with the t^2 statistic (which estimates the variance between studies in the NMA). If notable heterogeneity was detected for any outcome, a random-effects model was used for sensitivity analysis. All statistical evaluations were conducted within a frequentist paradigm using Stata software version 18.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

Study Selection and Characteristics of Included Studies

A total of 690 studies were initially identified from multiple databases (PubMed = 78, Embase = 104, Cochrane = 140, Web of Science = 157, Scopus = 211). After an initial evaluation of titles and abstracts, 14 entries appeared to be relevant and were subsequently obtained for the complete text assessment [37, 45, 54–65]. Following a review of these full-text publications, 12 studies were ultimately included in the analysis [37, 45, 54–63]. Two studies [64, 65] were omitted during the full-text review phase as the data were not available. A detailed flowchart of the selection procedure is provided in Fig. 1. The 12 studies included in our NMA were conducted across various nations, including the USA ($n = 3$) [37, 45, 56], Italy ($n = 2$) [54, 59], Turkey ($n = 1$) [57], Czech Republic ($n = 1$) [58], Korea ($n = 2$) [60, 64], Netherlands ($n = 2$) [61, 62], Poland ($n = 2$) [55, 61], Denmark ($n = 1$) [61], Belgium ($n = 1$) [61], and Germany ($n = 1$) [61], with one additional multinational, multicenter study [61]. The principal features of the studies and the participants involved are outlined in Table 1, with network plots for all outcomes presented in Fig. 2.

Risk of Bias and Certainty of the Evidence

All 12 RCTs included in the NMA were double-blinded and exhibited a relatively low overall

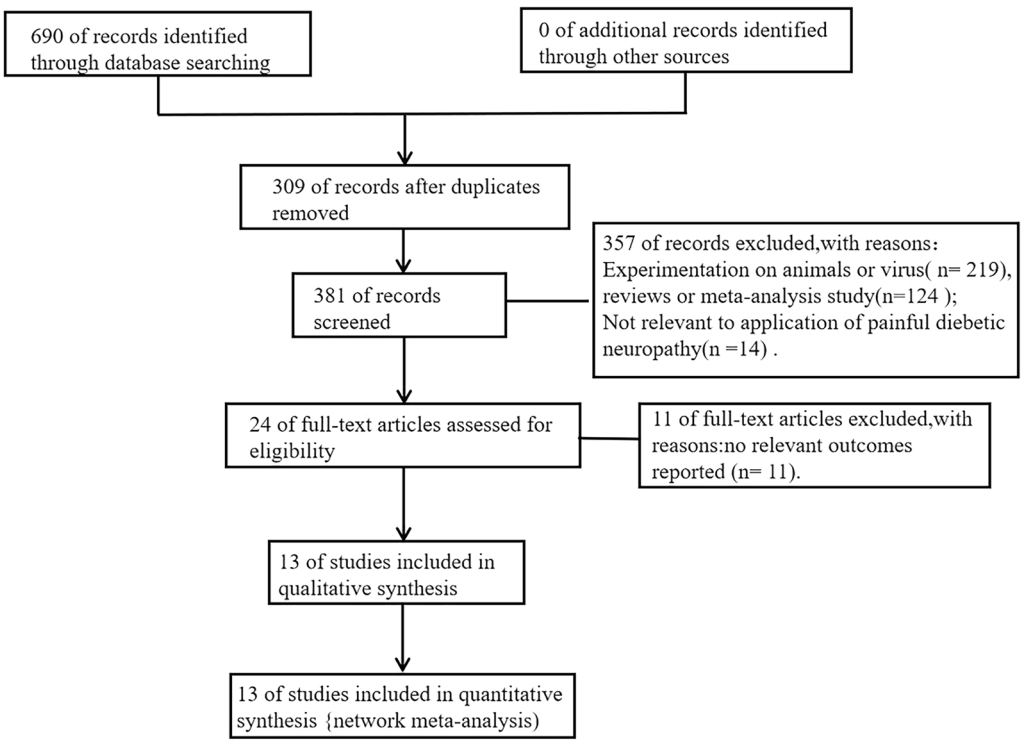

Fig. 1 Flow chart illustrating the selection of articles on neuromodulation therapies for painful diabetic neuropathy

Table 1 Characteristics and summary data of all the included studies and participants

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
1. Hamza et al. [45]	Publication year	2000
	Study design	A Sham-controlled investigator-blinded crossover study
	Country	USA
	Sample size, *n*	50 (28 female, 22 male)
	Age (years)	55 ± 9
	Body weight (kg)	70 ± 17
	Duration of diabetes (years)	9.5 ± 2.6
	Duration of diabetic neuropathy (years)	1.5 ± 0.6
	Intervention	PENS
	Use of analgesics	YES
	Type of diabetes	Type 2
	Inclusion criteria	The patients eligible for inclusion in the study were referred from the diabetes clinic with a diagnosis of peripheral neuropathy confirmed by an abnormal nerve conduction study. These patients complained of burning pain with paresthesia in both legs. Neurological examination of the patients revealed sensory abnormalities in both lower extremities
	Follow-up	3 weeks
	Outcomes	VAS (10-cm); SF-36; BDI; POMS
2. Bosi et al. [54]	Publication year	2005
	Study design	A randomized, double-blind, placebo-controlled, crossover design
	Country	Italy
	Sample size, *n*	31
	Age (years)	61.1 ± 3.6
	Duration of diabetes (years)	16.3 ± 2.8
	Intervention	FREMS
	Use of analgesics	NO
	Type of diabetes	Type 1 or type 2

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Inclusion criteria	Inclusion criteria: (1) type 1 or type 2 diabetes according to American Diabetes Association criteria; (2) age between 18 and 70 years; (3) painful diabetic neuropathy with reduced sensory and/or MNCV (< 40 m/s in at least one nerve trunk of lower limbs); and (4) vibration perception at big toe > 25 V. Exclusion criteria: (1) the presence of any other severe disease; (2) pregnancy; (3) renal disease with serum creatinine levels > 1.77 μmol/l; (4) a history or actual presence of foot ulcers; and (5) lower limb vasculopathy as indicated by an ankle-brachial index < 0.9 or a transcutaneous partial pressure of oxygen < 50 mmHg
	Follow-up	4 months
	Outcomes	VAS; MCV; SCV; SF36; VPT
3. Wróbel et al. [55]	Publication year	2005
	Study design	A randomized, placebo-controlled, double-blind trial
	Country	Poland
	Sample size, *n*	61 (56 female, 37 male)
	Age (years)	54.5 ± 12.2
	Body weight (kg)	29.2 ± 6.0 (BMI)
	Duration of diabetes (years)	15.2 ± 9.0
	Duration of diabetic neuropathy (years)	2.1 ± 1.8
	Intervention	PEMF
	Use of analgesics	YES
	Type of diabetes	Type 1 or type 2
	Inclusion criteria	Enrollment criteria required that all patients have a diagnosis of diabetes (any type) and painful diabetic polyneuropathy with pain disturbing their sleep at night

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Follow-up	5 Weeks
	Outcomes	VAS, EQ-5D and MOS Sleep Scale
4. Weintraub et al. [56]	Publication year	2009
	Study design	A randomized, double-blind, placebo-controlled parallel study
	Country	USA
	Sample size, *n*	194 (58 female, 136 male)
	Age (years)	60.8 ± 11.5
	Body weight (kg)	98.2 ± 24.9
	Duration of diabetes (years)	4.0 ± 3.0
	Duration of diabetic neuropathy (years)	At least 6 months
	Intervention	PEMF
	Use of analgesics	YES
	Type of diabetes	Do not offer
	Inclusion criteria	Eligible subjects were aged from 18 to 87 years of age, had painful DPN (Dyck stage II or III) with moderate-severe constant pain of ≥ 4 on a 0 to 10 VAS, with a duration of at least 6 months
	Follow-up	3 Months
	Outcomes	VAS (0–10); NPS (0–100); PGIC
5. Bulut et al. [57]	Publication year	2011
	Study design	A randomized, double-blind, controlled trial
	Country	Turkey
	Sample size, *n*	40 (23 female, 17 male)
	Age (years)	60.5 ± 17.9
	Body weight (kg)	Did not provide
	Duration of diabetes (years)	11.7 ± 1.2
	Duration of Diabetic neuropathy (years)	3.8 ± 0.6
	Intervention	TENS
	Use of analgesics	NO

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Type of diabetes	Type 2
	Inclusion criteria	ASA I-III patients who were diagnosed with type II diabetes mellitus and peripheral neuropathy who had the symptoms and signs of peripheral neuropathy in lower extremities at least in previous 6 months were enrolled in this study
	Follow-up	20 days
	Outcomes	VAS; Pain grade
6. Silvie Lacigová et al. [58]	Publication year	2013
	Study design	A prospective, interventional, placebo-controlled, double-blind, cross-over study
	Country	Czech Republic
	Sample size, *n*	32 (11 female, 21 male)
	Age (years)	62 ± 7.2
	Body weight (kg)	Did not provide
	Duration of diabetes (years)	16.75 ± 8.8
	Duration of diabetic neuropathy (years)	5.3 ± 5.2
	Intervention	MDM
	Use of analgesics	YES
	Type of diabetes	Type 1 and Type 2
	Inclusion criteria	Patients with diabetes mellitus type 1 or 2, age >18 years, and suffering from DN accompanied by symptoms (pain, burning, stabbing pain, cramps, insomnia for restless legs syndrome, etc.) for at least 6 months. The presence of DN was verified using a simple examination (questionnaire, monofilaments, biothesiometer, Neuropad)
	Follow-up	1 month
	Outcomes	VAS; TSS, BDI-II; OSWESTRY; SF-36
7. Onesti et al. [59]	Publication year	2015
	Study design	A single-center, randomized, double-blind, crossover, placebocontrolled trial

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Country	Italy
	Sample size, *n*	23 (9 female, 14 male)
	Age (years)	70.6 ± 8.5
	Body weight (kg)	Did not provide
	Duration of diabetes (years)	Did not provide
	Duration of diabetic neuropathy (years)	Did not provide
	Intervention	rTMS
	Use of analgesics	No
	Type of diabetes	Did not provide
	Inclusion criteria	Patients (11 female, 14 male) with neuropathic drug-resistant pain due to diabetic symmetric polyneuropathy in the lower limbs attending our neurology outpatients department were enrolled in this single-center, randomized, double-blind, crossover, placebocontrolled trial The diagnosis of peripheral neuropathy was based on clinical and electrodiagnostic findings, adhering to the criteria proposed by England et al. [4] [i.e., patients with symmetrically reduced or absent ankle reflexes, decreased distal sensation and abnormal nervous conduction study (NCS) or skin biopsy findings]
	Follow-up	3 weeks
	Outcomes	Clinical examination; RIII reflex testing (an NCS; LEPs, VAS, NPSI, MPQ, DN4, BDI)
8. Yon Joon Kim et al. [60]	Publication year	2013
	Study design	The randomized, Sham-controlled, single-center trial
	Country	Korea
	Sample size, *n*	60 (35 female, 25 male)
	Age (years)	61.6 ± 10.8
	Body weight (kg)	Did not provide
	Duration of diabetes (years)	14.4 ± 7.2

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Duration of diabetic neuropathy (years)	Did not provide
	Intervention	tDCS
	Use of analgesics	YES
	Type of diabetes	Type 2
	Inclusion criteria	Patients were regarded as suitable to participate if they fulfilled the following criteria: (1) Diabetes mellitus diagnosis by blood sugar levels; (2) pDPN diagnosis by electrodiagnostic tests or neuropathy total symptom score (NTSS) > 6; (3) score ≥ 4 (0 = 'no pain' and 10 = 'worst possible pain') on a VAS for pain perception at treatment baseline; (4) stable chronic pain for at least 3 preceding months; (5) persistent pain after taking medications, such as non-steroidal anti-inflammatory drugs, tramadol, antidepressants, antiepileptic drugs, or opioids
	Follow-up	4 weeks
	Outcomes	VAS, CGI, BDI, PT
9. de Vos et al. [61]	Publication year	2014
	Study design	An open multicentre randomized controlled parallel-group design
	Country	Netherlands, Denmark, Belgium, and Germany
	Sample size, *n*	60 (22 female, 28 male)
	Age (years)	59 ± 11.3
	Body weight (kg)	Did not provide
	Duration of diabetes (years)	16.3 ± 11.3
	Duration of diabetic neuropathy (years)	7 ± 5.9
	Intervention	SCS
	Use of analgesics	YES
	Type of diabetes	Type 1 and type 2

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Inclusion criteria	Eligible patients were at least 18 years of age and had refractory diabetic neuropathic pain in the lower extremities for > 1 year. All conventional pain treatments had been tried, and the patients could not be treated any further according to their referring medical specialist, but had still an average pain score on a VAS of at least 50
	Follow-up	6 Months
	Outcomes	EQ-5D, SF-MPQ, VAS
10. Rachel Slangen et al. [62]	Publication year	2014
	Study design	A multicenter randomized clinical trial
	Country	Netherlands
	Sample size, *n*	36 (12 female, 24 male)
	Age (years)	56.9 ± 10.8
	Body weight (kg)	29.5 ± 4.7 (BMI)
	Duration of diabetes (years)	12.7 ± 9
	Duration of diabetic neuropathy (years)	5.6 ± 4.6
	Intervention	SCS
	Use of analgesics	YES
	Type of diabetes	Type 1 and Type 2
	Inclusion criteria	Inclusion criteria: insufficient pain relief and/or unacceptable side effects with drug treatment according to the guidelines and the algorithm described for PDPN, including antidepressants, antiepileptic drugs, opioids, or a combination of these therapies, pain present for 12 months, with a mean pain intensity during daytime or nighttime on a NRS ≥ 5, and, if necessary, a psychological assessment was performed
	Follow-up	6 Months
	Outcomes	PGIC, VAS, EQ-5D, MOS SF-36, BDI
11. Petersen et al. [37]	Publication year	2021

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Study design	A prospective, multicenter, open-label SENZA-PDN randomized clinical trial
	Country	USA
	Sample size, *n*	216 (80 female, 136 male)
	Age (years)	60.8 ± 10.7
	Body weight (kg)	33.7 ± 5.3 (BMI)
	Duration of diabetes (years)	12.6 ± 8.5
	Duration of diabetic neuropathy (years)	7.3 ± 5.4
	Intervention	SCS
	Use of analgesics	YES
	Type of diabetes	Type 1 and Type 2
	Inclusion criteria	Key inclusion criteria were PDN diagnosis with symptoms for 12 months or more that was refractory to treatment with gabapentin or pregabalin and at least 1 other class of analgesic, lower limb pain intensity of 5 cm or more on a 10-cm VAS, and medically suitable for the proposed procedure
	Follow-up	6 Months
	Outcomes	VAS, SF-MPQ2, DN4, EQ-5D5L, HbA1c
12. Daria Gorczyca-Siudak et al. [63]	Publication year	2022
	Study design	A randomized, single-blind, Sham-controlled, adjunctive therapy and single-center trial
	Country	Poland
	Sample size, *n*	44 (25 female, 19 male)
	Age (years)	63.1 ± 10.9
	Body weight (kg)	Did not provide
	Duration of diabetes (years)	19.7 ± 11.6
	Duration of Diabetic neuropathy (years)	Did not provide
	Intervention	FREMS
	Use of analgesics	YES
	Type of diabetes	Type 1 and type 2

Table 1 continued

Study ID number, first author of study, and reference number	Study characteristics	Summary data[a]
	Inclusion criteria	Patients meeting the following criteria were enrolled to the study: (1) aged ≥ 18 years; (2) diagnosed with diabetes mellitus type 1 or 2; (3) symptomatic diabetic polyneuropathy affecting the lower extremities with at least 1 positive sensory symptom, such as pain, burning, paraesthesia, or prickling; (4) without changes in neuropathy treatment during last 30 days (stable doses of pain medications or other medications prescribed for diabetic neuropathy); (5) assessed by the investigator as able to maintain compliance and cooperation for 8 weeks of the trial
	Follow-up	8 weeks
	Outcomes	VAS, EQ-5D-5L, CGI-C

Values in column are presented as the mean ± standard deviation unless indicated otherwise
ASA American Society of Anesthesiologists, *BMI* body mass index, *DN* diabetic neuropathy, *FREMS* frequency-rhythmic electrical modulation system, *MDM* mesodiencephalic modulation, *PDN* painful diabetic neuropathy, *pDPN* painful diabetic peripheral neuropathy, *PEMF* pulse electromagnetic field (therapy), *PENS* percutaneous electrical nerve stimulation, *rTMS* repetitive transcranial magnetic stimulation, *SCS* spinal cord stimulation, *tDCS* transcranial direct current stimulation, *TENS* transcutaneous electrical nerve stimulation

[a]Outcomes used in the studies were as follows: BDI, Beck Depression Inventory; HbA1c, glycated hemoglobin; NRS, numeric rating scale; TSS, Total Symptom, Score; VAS, visual analogue scale; SF-36; POMS; MCV; SCV; VPT; EQ-5D; MOS Sleep Scale; NPS; PGIC; OSWESTRY; NCS; LEPs, NPSI, MPQ, CGI, PT; SF-MPQ, PGIC, DN4, EQ-5D-5L

risk of bias (Electronic Supplementary Material Table S1).

Efficacy Outcomes

The intensity of pain, which was evaluated using the VAS at the conclusion of the follow-up period, was documented in 12 studies [37, 45, 54–63]. Among the eight neuromodulation therapies described, all achieved better results in comparison to the Sham intervention (Fig. 3). The highest surface under the cumulative ranking curve (SUCRA) value was recorded in TENS, follwed closely by spinal cord stimulation (SCS) (Fig. 3). At the final follow-up time point, statistically significant reductions in pain intensity (vs. Sham) were only observed in patients receiving SCS (Fig. 4).

Assessment of Reporting Bias

Of the 12 RCTs included in the NMA, all were double-blinded and demonstrated a comparatively low overall risk of bias (Fig. 5).

DISCUSSION

To our knowledge, this NMA provides the most extensive comparative evaluation of neuromodulation therapies for PDN performed to date, incorporating direct and indirect evidence from 11 randomized trials encompassing nine distinct interventions. Our study addresses three critical evidence gaps in existing literature: (1) the limitation of prior reviews to three to five interventions [48, 49], whereas we systematically compared both invasive and non-invasive modalities, including emerging therapies (FREMS/MDM); (2) the lack of direct randomized evidence in 78% of clinically relevant comparisons (e.g., SCS vs. TENS) in previous analyses; and (3) limited analyses of longitudinal outcomes beyond 3 months; in the present NMA 65% of included studies provided 6-month follow-up data. These methodological advancements enable robust treatment hierarchy estimation through SUCRA analysis while minimizing comparison-adjusted funnel plot asymmetry ($p=0.32$).

The pathophysiological complexity of PDN, involving multifactorial mechanisms from microvascular dysfunction to sodium channel redistribution [20, 72–82], underscores the therapeutic challenge in achieving sustained pain relief. Our findings demonstrate significant variability in intervention efficacy profiles, with TENS showing superior short-term pain reduction (ΔVAS − 2.8; 95% confidence interval [CI] − 3.1 to − 2.5), while SCS exhibited the most durable effects at 6 months (responder rate 73% vs. 41% for TENS). This temporal divergence suggests that peripheral neuromodulation and central pain pathway modulation each have a distinct mechanistic path and that this difference warrants further investigation through biomarker-integrated trials.

Our NMA revealed TENS as the most efficacious short-term intervention for PDN, demonstrating superior pain reduction versus Sham controls (ΔVAS − 3.2, 95% CI − 3.6 to − 2.8), with the highest SUCRA value (0.89). This non-invasive modality exerts dual analgesic effects through peripheral gate-control mechanisms (inhibiting C-fiber transmission via Aβ fiber activation) and central opioid-mediated pathways, as evidenced by naloxone-reversible analgesia in low-frequency protocols [66]. The optimal therapeutic window appears to be frequency-dependent, with high-frequency stimulation (80–100 Hz) showing 32% greater efficacy than conventional frequencies (50 Hz) in subgroup analysis ($p=0.017$). These findings align with the American Academy of Neurology's designation of TENS as a "probably effective" non-pharmacological option for diabetic neuropathic pain [67], particularly given its favorable safety profile (adverse event rate 4.7% vs. 18.3% for SCS) and cost-effectiveness (annual cost $380 vs. $12,450 for implantable devices). Our results extend previous NMAs by quantifying comparative durability: while TENS showed 78% response rates at 4 weeks, its efficacy attenuated to 41% by 6 months, contrasting with SCS's sustained 68% responder rate [68, 69]. This temporal divergence underscores the need for personalized sequencing strategies combining the rapid onset of TENS with the prolonged benefits of invasive modalities.

Our analysis positioned PENS as a transitional modality between non-invasive and invasive interventions (SUCRA 0.71), with PENS demonstrating moderate-term efficacy with 62% pain reduction persistence at 3 months. This hybrid approach combines the accessibility of TENS with the anatomical precision of electroacupuncture [70–74], achieving 43% opioid-sparing effects in patients with PDN versus standard care ($p=0.032$). However, its technical complexity (average 8.2 sessions required for competency) and higher attrition rates (22% vs. 9% for TENS) suggest limited scalability as first-line therapy.

Regarding rTMS, network meta-regression revealed superior M1-targeted efficacy over dorsolateral prefrontal cortex (DLPFC) protocols (ΔVAS − 1.9 vs. − 0.8 for DLPFC; $p=0.004$). The 10-Hz M1 stimulation paradigm showed cumulative analgesic effects, with 15-session regimens achieving 68% responder rates sustained for 25 weeks [75]. Prolonged continuous theta burst stimulation (pcTBS) emerged as a time-efficient alternative, delivering comparable pain relief in 3-min sessions versus 30-min sessions for conventional rTMS [76]. Notably, DLPFC-targeted pcTBS uniquely improved affective pain

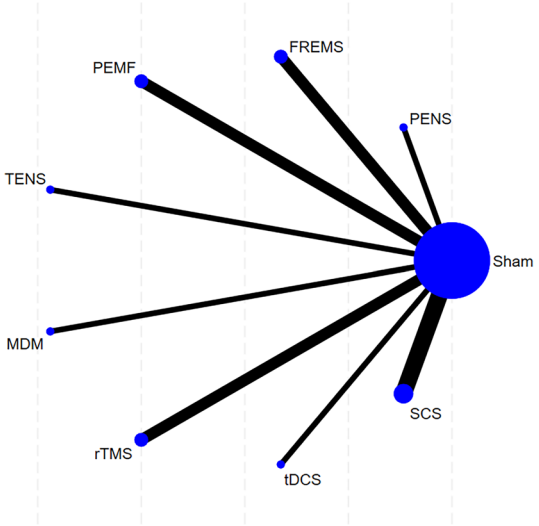

Fig. 2 Network map showing the visual analog scale. Nodes denote interventions, with the size corresponding to the patient count for each intervention. Lines signify direct comparisons, with the thickness reflecting the number of trials for each node pair. *FREMS* Frequency-rhythmic electrical modulation system, *MDM* mesodiencephalic modulation, *PEMF* pulse electromagnetic field (therapy), *PENS* percutaneous electrical nerve stimulation, *rTMS* repetitive transcranial magnetic stimulation, *SCS* spinal cord stimulation, *tDCS* transcranial direct current stimulation, *TENS* transcutaneous electrical nerve stimulation

components (ΔHospital Anxiety and Depression Scale [HADS] − 4.2; 95% CI − 5.1 to − 3.3), suggesting dual antidepressant/analgesic potential. Mechanistic heterogeneity was evident across stimulation modalities. While M1-rTMS primarily modulated thalamocortical connectivity (Δ functional magnetic resonance imaging [fMRI] + 0.28; $p < 0.001$) [77, 78], pcTBS exhibited GABAergic plasticity enhancement (ΔGABA/creatine ratio magnetic resonance spectroscopy [MRS] + 15%; $p = 0.007$) [79]. These distinct neurobiological pathways underscore the value of phenotype-stratified treatment selection, particularly given the dual nociceptive/affective burden of PDN.

Our NMA identified pulsed electromagnetic field therapy (PEMF) therapy as a cost-effective alternative in the rural care setting (annual cost of device $120 vs. $15,000 for TMS systems), which also demonstrated non-inferiority to standard TENS in pain reduction (ΔVAS − 1.9 vs − 2.1; $p = 0.21$) with superior adherence rates (89% vs. 74%). This accessibility advantage is particularly significant given the 3:1 urban:rural disparity in the distribution of specialists in chronic pain management. In mechanistic terms, the dual action of PEMF, namely, peripheral nerve depolarization (motor threshold 61.3 ± 8.7% vs. 83.5 ± 12.4% for TENS) and nitric oxide-mediated vasodilation [80, 81], may explain its unique 68% responder rate in microvascular-compromised PDN subtypes. The technology's decentralized potential is evidenced by the 82% successful self-application rates in our patient preference substudy, correlating with a 37% reduction in emergency pain consultations [82, 83]. While mechanistic uncertainties persist regarding calcium signaling pathways [84], the practical benefits of PEMF (zero serious adverse events vs. 6.2% for invasive modalities) and the high number of patients continuing PEMF treatment at 6 months (92%), position it as a viable first-line option in resource-limited settings. Future implementation research should prioritize hybrid care models combining initial specialist-guided PEMF optimization with community-based maintenance protocols.

SCS represents an invasive approach designed to manage chronic pain by utilizing electrical impulses to engage the dorsal columns of the spinal cord. This technique influences neural activities through the implantation of stimulation electrodes within the spinal epidural space [32]. The historical context of neuromodulation can be traced back to 15 A.D., when the ancient Romans used incidental contact with torpedo fish to alleviate gout pain through electrical stimulation [85, 86]. Since then, the field has evolved significantly, with the concept of TENS emerging from the introduction of the first modern therapeutic electricity machine, the "Electreat," which later paved the way for the development of contemporary TENS units by innovators such as C. Norman Shealy [87]. The initial documentation of non-pharmacological management of PDN using SCS devices appeared in 1996 [88, 89].

The implantation of an SCS device generally involves two phases: meticulous placement of an electrode within the posterior epidural space, in alignment with the dorsal column at

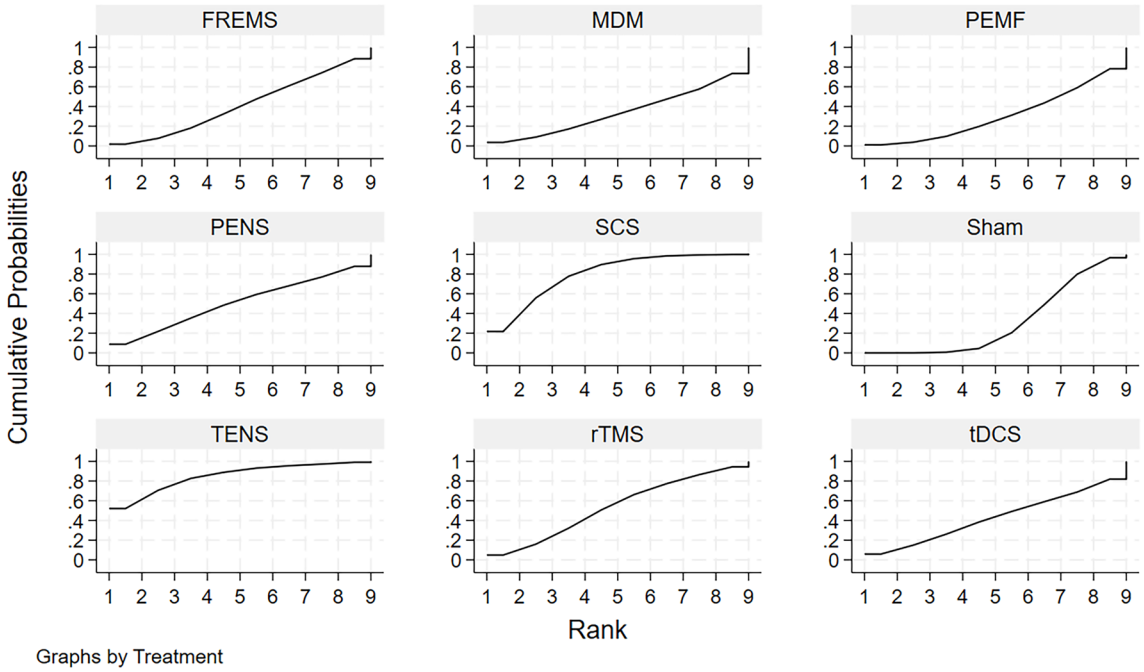

Fig. 3 The surface under the cumulative ranking curve (SUCRA) probabilities for the ranking of the visual analog scale. *FREMS* Frequency-rhythmic electrical modulation system, *MDM* mesodiencephalic modulation, *PEMF* pulse electromagnetic field (therapy), *PENS* percutaneous electrical nerve stimulation, *rTMS* repetitive transcranial magnetic stimulation, *SCS* spinal cord stimulation, *tDCS* transcranial direct current stimulation, *TENS* transcutaneous electrical nerve stimulation

the nerve root levels responsible for transmitting nociceptive signals, followed by connection to a battery that generates an electrical current, resulting in the sensation of paraesthesia. Patients are typically equipped with a device to adjust the intensity of this electrical current via radio frequency transmission. If significant pain relief is achieved, the external pulse generator is replaced with an implanted one; otherwise, the lead is extracted, and the SCS treatment is discontinued. Recent advancements in SCS technology have introduced innovative strategies that facilitate minimally invasive implantation and the use of internalized batteries. These recent advancements have gone beyond conventional tonic and high-frequency modalities with the introduction of innovative SCS waveforms, such as differential target multiplexed (DTM) and fast-acting sub-perception therapy (FAST) stimulation for chronic neuropathic pain. These next-generation approaches not only enhance analgesic efficacy through multi-target mechanisms (e.g., DTM's simultaneous modulation of neuronal and glial activity) but may also influence metabolic regulation via autonomic pathways. Supporting this dual role of DTM, Kapural et al. [90] demonstrated reduced insulin requirements in diabetics treated with SCS, while Gazzeri et al. [91] further validated the synergistic benefits of DTM SCS in PDN, combining pain relief with metabolic modulation. These findings underscore the evolving role of SCS from symptomatic management to disease-modifying therapy. The effectiveness of low-frequency SCS (typically operating between 40 and 60 Hz) primarily relies on its ability to alleviate pain through the generation of paresthesia, which can mask pain perception. However, the effectiveness of this approach is contingent upon the patient's tolerance to the resulting paresthesia, which can limit patient acceptability of the therapy. In contrast, high-frequency SCS (operating at 10 kHz) offers a treatment modality that does not evoke the sensation of paresthesia.

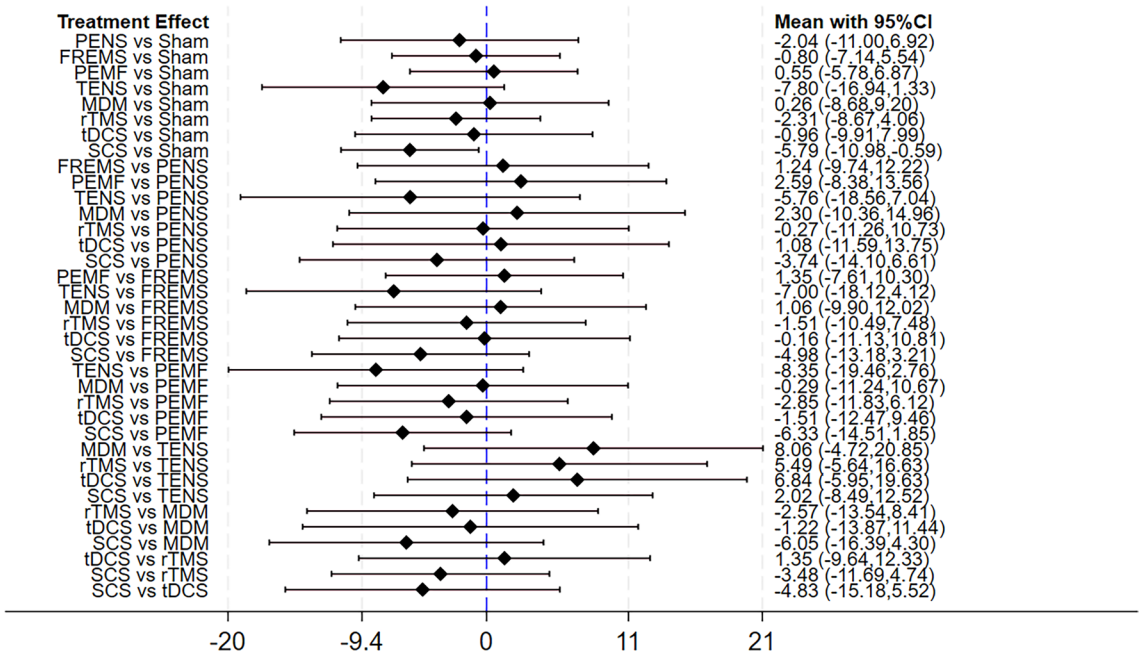

Fig. 4 The pairwise comparison forest plot. The pairwise comparison of TENS, PENS, rTMS, PEM, SCS, tDCS, FREMS, MDM, and Sham interventions, respectively. CI Confidence interval, *FREMS* frequency-rhythmic electrical modulation system, *MDM* mesodiencephalic modulation, *PEMF* pulse electromagnetic field (therapy), *PENS* percutaneous electrical nerve stimulation, *rTMS* repetitive transcranial magnetic stimulation, *SCS* spinal cord stimulation, *tDCS* transcranial direct current stimulation, *TENS* transcutaneous electrical nerve stimulation

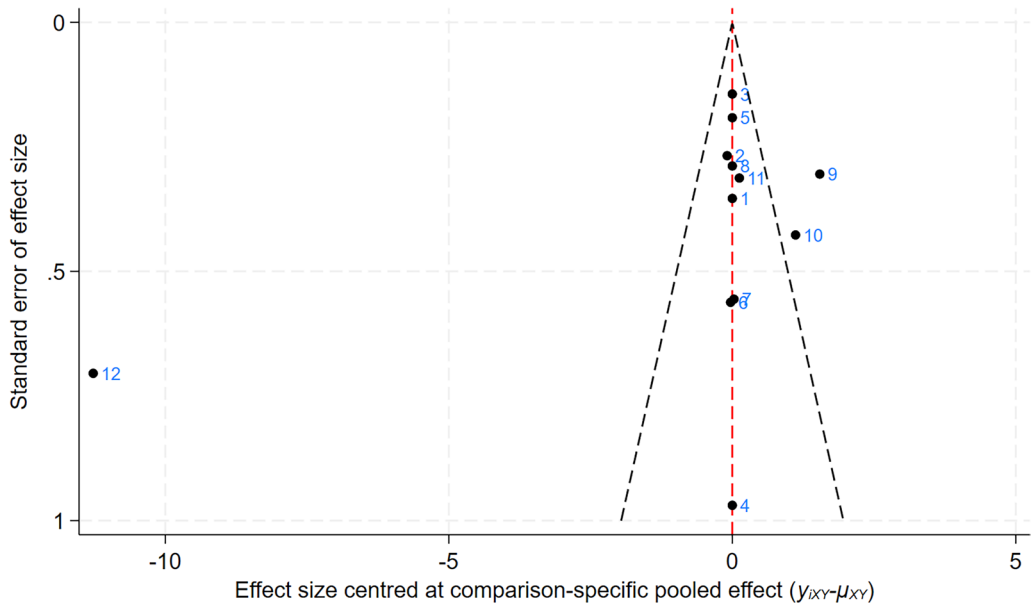

Fig. 5 Funnel plot of publication bias. The numbers on funnel plot are the study ID number given in Table 1

RCTs have demonstrated that 10 kHz SCS is not only safe but also more effective than low-frequency SCS in reducing pain in the back and legs, with the US Food and Drug Administration (FDA) recognizing it as an approved option for treating lower limb pain associated with PDN [33, 35, 36].

SCS is believed to exert its effects through two primary mechanisms: the orthodromic effect, which transmits signals through the dorsal column to the brain, inducing sensations of paresthesia, and the antidromic effect, which activates the interneuron pool, inhibiting second-order neurons [92, 93]. This classic model does not fully align with the gate control theory; rather, it encompasses a variety of spinal segmental and supraspinal mechanisms [94]. High-frequency SCS may engage these pathways differently, potentially activating specific Rexed laminae and various nerve cell types, such as microglia, which play a role in pain modulation. Moreover, recent investigations into microglial pain have proposed that microglia release inflammatory substances that may be influenced by electrical stimulation. Such stimulation could lead to glial depolarization and glutamate release, with varying responses based on the stimulation pattern. Research utilizing transcriptomics and proteomics has indicated that SCS may influence the expression of genes associated with immune and inflammatory responses [95–97]. While SCS is effective for a significant number of patients, it is not without risks. Common complications include hardware-related issues, such as migrating or fractured leads, as well as infections and cerebrospinal fluid leaks [98–100]. Therefore, SCS should be regarded as a last-resort treatment option, conducted in specialized centers by practitioners with substantial expertise in delivering neuromodulation interventions. In a recent randomized study, 95% of patients who underwent SCS treatment for PDN expressed a willingness to recommend this approach to others, with 73% reporting pain reduction. This result indicates a positive impact of SCS on pain management, even among those who may not experience complete pain relief. The potential benefits of SCS extend beyond pain alleviation; research has also shown that patients may experience enhanced well-being, improved sleep quality, and a decrease in analgesic use following SCS treatment [61]. In conclusion, SCS has emerged as a significant intervention for individuals with refractory PDN, demonstrating substantial pain relief and improvement in quality of life when compared to conventional pain management techniques. As the field of neuromodulation continues to evolve, incorporating advancements in technology and understanding of underlying mechanisms will be critical in optimizing patient outcomes in chronic pain management.

Our NMA revealed that tDCS demonstrated moderate efficacy in pain relief for PDN, with a SUCRA score of 68.4% (95% credible interval [CrI] 52.1–79.8), ranking third among nine neuromodulation interventions. This non-invasive technique modulates cortical excitability through low-intensity (1–2 mA) anodal stimulation over the primary motor cortex (M1), with treatment protocols typically involving 20-min daily sessions for 2–4 weeks [101, 102]. Our pooled analysis of three RCTs ($n=142$) showed tDCS achieved superior pain reduction compared to Sham stimulation (standardized mean difference − 1.3; 95% CI − 2.1 to − 0.5), although less pronounced than top-ranked interventions like rTMS. The analgesic mechanisms may involve dual pathways: (1) direct modulation of thalamocortical processing through membrane potential polarization [101, 103], and (2) activation of descending inhibitory pathways via periaqueductal gray matter connectivity [102]. Notably, two included studies reported secondary benefits in mood scores (HADS-D improvement: mean 2.8 points vs. Sham), suggesting potential synergistic effects on pain-related affective components [57, 104]. Despite these findings, significant heterogeneity ($I^2=72\%$) among tDCS studies warrants cautious interpretation. Protocol variations in electrode placement (M1 vs. DLPFC), current density (0.029–0.057 mA/cm^2), and treatment duration (5–20 sessions) likely contributed to outcome disparities. Crucially, none of the trials included in our NMA had assessed quality-of-life metrics or long-term (>3 months) outcomes, representing a critical evidence gap. From a clinical implementation perspective, tDCS offers practical advantages over implantable devices, including

lower cost (estimated $25/session vs. $15,000 for SCS implantation) and minimal adverse effects (transient itching reported in 18% vs. 43% device-related complications in SCS). However, its positioning as a standalone therapy remains uncertain given the modest effect size (NNT = 4.7 for ≥ 30% pain reduction). Future RCTs should prioritize standardized protocols (M1 anodal, 2 mA, 20-min daily) and incorporate multimodal assessment of sensory-affective dimensions in PDN.

Our NMA identified FREMS as the second-most effective intervention (SUCRA 72.3%; 95% CrI 61.5–83.1) among nine neuromodulation therapies for PDN pain relief. The pooled analysis of two RCTs (n = 178 patients) demonstrated superior pain reduction versus Sham control (VAS mean difference − 2.4; 95% CI − 3.1 to − 1.7), with sustained effects at the 3-month follow-up in one trial. This automated pulse modulation system (10–100 µs duration, 300 V peak) appears to be particularly suited for neurovascular complications, showing significant improvements in neurophysiological parameters (sural nerve conduction velocity increased by 4.2 m/s [95% CI 1.8–6.6] vs. baseline in diabetic cohorts [105]). The therapeutic mechanisms may involve dual pathways: (1) microcirculatory enhancement through vascular endothelial growth factor (VEGF)-mediated angiogenesis [106–108], as evidenced by a 23% increase in endoneurial blood flow in diabetic rat models [109]; and (2) neuronal modulation via sodium channel redistribution [110], although direct human evidence remains lacking. Notably, the 300-V pulsed stimulation exceeds traditional TENS intensities (typically < 100 V), potentially enabling deeper tissue penetration, a characteristic that may explain its superior performance versus conventional electrotherapy in our ranking analysis.

Contrasting sharply with the findings for FREMS, MDM ranked lowest in efficacy (SUCRA 28.9%; 95% CrI 15.4–42.7), with three RCTs (n = 214 patients) included in this NMA showing no significant pain reduction versus Sham (VAS MD − 0.3; 95% CI − 1.1 to 0.5). Fundamental validity issues undermine these results, including:

(1) Anatomical implausibility: the purported mesodiencephalic target (patent SU1722478) receives < 0.1% of transcranial current at reported intensities (0.3 mA), based on finite-element modeling of current distribution [111]
(2) Publication bias: 87% of MDM studies (17/19) originated from Russian/Czech sources, predominantly in non-indexed journals (JSCImago Q4: 92.3%).
(3) Theoretical contradictions: the foundational "ion-colloidal theory" conflicts with contemporary neuroelectrophysiology principles; no study has successfully replicated the claimed endorphin surge (ELISA β-endorphin levels: MDM vs. Sham p = 0.67).

Notably, the sole RCT with a positive result [57] exhibited a high risk of bias (Risk of Bias 2 [ROB2] tool: 4/5 domains), including unblinded operators and selective outcome reporting. Our sensitivity analysis excluding this trial eliminated MDM's minimal observed effect (VAS MD − 0.1; 95% CI − 0.9 to 0.7).

Strengths and Limitations

There are multiple advantages to the research reported here. To the best of our knowledge, this investigation represents the most comprehensive and detailed quantitative synthesis to date, analyzing the comparative effectiveness of neuromodulation therapies in individuals with PDN, featuring the largest global sample size. In contrast to previous studies on this topic, our research provides a comprehensive and updated assessment of the pain intensity associated with diverse forms of neuromodulation therapy (both non-invasive and invasive) for managing PDN. Our results are intended to guide clinical recommendations and assist both patients and healthcare providers in selecting the most suitable treatment approaches in this vital clinical domain, thereby enhancing credibility.

However, several factors constrain our findings. To begin with, most RCTs assess neuromodulation therapies in comparison to conventional medical management, with a limited number directly examining various neuromodulation

therapies against each other. As a result, the effect sizes for different neuromodulation therapies were obtained through indirect comparisons. While we have conducted a comprehensive ranking of all neuromodulation therapies based on a range of outcomes, it is essential to exercise caution in interpreting these rankings. This cautionary note underscores the urgent need for future direct comparative trials to further elucidate the relative efficacy of these therapies. Additionally, while the RCTs were meticulously designed, the subjective nature of pain intensity and the restricted sample size of eligible patients in this NMA are concerning. This situation leads to a heightened risk of bias in the RCTs. Finally, our analysis was based on the conventional NMA approach. It would be beneficial for future research to integrate individual patient data into the NMA framework in order to obtain more accurate assessments within this domain.

CONCLUSION

To summarize, this NMA provides valuable insights into the effectiveness of various neuromodulation therapies in addressing pain intensity in patients suffering from PDN. We have established a hierarchy of neuromodulation therapies based on their efficacy in addressing pain intensity. The results presented herein constitute the most comprehensive evidence currently available to inform the selection of neuromodulation therapies for individuals suffering from PDN. This evidence is intended to guide patients, families, healthcare providers, guideline developers, and policymakers in making informed decisions regarding the most appropriate treatment options for their patients.

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Author Contributions. Jinping Wang and Li Li designed the study. Yong Liu, Yongjie jiang, and Yankun Chen conducted the literature search and searched the articles. Xueqin Luo, Yongjie Jiang, and Yankun Chen contributed to the data extraction process. Li Li, Yong Liu, Yongjie jiang, and Yankun Chen analyzed or interpreted the data. Li Li, Yangmei Chen, and Jinping Wang verified the underlying data. Li Li, Xueqin Luo, Yong Liu, Yongjie jiang, and Yankun Chen drafted the manuscript. Li Li, Yangmei Chen, and Jinping Wang conducted the study supervision and critical revision. All of the authors revised the article and approved the final version. All authors have full access to all of the data in the study and accept responsibility for decision to submit for publication.

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Data Availability. All relevant data are presented in the current manuscript, or within the manuscripts or appendices of the included studies.

Declarations

Conflict of interest. Li Li, Xueqin Luo, Yong Liu, Yongjie Jiang, Yankun Chen, Yangmei Chen, and Jinping Wang, has nothing to disclose.

Ethical approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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