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Review

Analgesic effect of non-invasive neuromodulation approaches among patients with diabetic peripheral neuropathy: A systematic review

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Abstract

Diabetic peripheral neuropathy (DPN), a complication of Diabetes Mellitus, is increasingly contributing to global morbidity and mortality. Non-invasive neuromodulation (NINM) approaches have become popular as safe, effective, and non-intrusive methods for managing persistent neuropathic pain. A key strategy for addressing DPN symptoms, neuromodulation modifies nerve function and encourages plastic changes in the central nervous system, aiding pain relief. This review aims to systematically assess scientific literature on the safety and effectiveness of NINM in reducing pain and improving physical function in DPN patients. Using PRISMA guidelines, searches were conducted across electronic databases such as MEDLINE (via PubMed), Web of Science, ScienceDirect, Cochrane, and PEDro, with study quality assessed using the PEDro scale. Fourteen studies with 436 participants were analyzed, revealing that NINM approaches can access deeper cortical regions without invasion, causing beneficial changes in the primary motor cortex (M1) that promote adaptive responses and activate pain control mechanisms without significant side effects. NINM shows promise in reducing neuropathic pain, evidenced by improved pain scores and physical function, leading to enhanced quality of life for patients suffering from chronic DPN-related pain.

Keywords: diabetes mellitus, diabetic peripheral neuropathy, neuromodulation, pain threshold, quality of life.

Introduction

Diabetes mellitus (DM) causes a long-term significant, profound and destructive consequence in the overall well-being of the affected population [1]. According to the International Diabetes Federation, it is predicted that 438 million people worldwide will have Diabetes by the year 2045 [2, 3]. Typical factors that increase the likelihood of complications from DM encompass blood pressure, lipid levels such as total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides, heart rate, body weight and uric acid [4]. Diabetic peripheral neuropathy (DPN) is a challenging condition resulting from DM and is emerging as a major cause of morbidity and increased mortality [5].

Approximately 50% of the population diagnosed with Diabetes are likely to develop neuropathy [6, 7]. According to recent research, risk factors such as the period a person has been with Diabetes, age, levels of HbA1c, presence of diabetic retinopathy, smoking habits, body mass index, fasting plasma glucose and blood urea nitrogen levels are associated with an increase in likelihood for DPN [8]. According to reports, the combined yearly cost of DPN and its consequences in the US ranges between 4.6 to 13.7 billion dollars, or 27% of the direct medical cost [9].

DPN is a solitary risk factor for diabetes-related foot, accounting for 50–75% of non-traumatic amputations and is characterized by axonal degeneration of both myelinated and non-myelinated fibers, affecting the sensory, motor and autonomic nerves [10]. The initial sensory symptoms observed are loss of vibratory, thermal, tactile and proprioceptive sensations, followed by musculoskeletal and autonomic symptoms. Musculoskeletal impairments presented are reduced strength of extrinsic-intrinsic muscles of the foot, increased fat proportion between the foot muscles and altered biomechanical properties of calcaneal tendon [11]. These alterations may further lead to disturbed mechanics of locomotion accompanied by a gradual decrease in range of motion (ROM) of the ankle joint and afflicting lower limb muscle activation, eventually leading to atrophic changes presenting as distal symmetrical and sensory-motor polyneuropathy. The majority of the population diagnosed with DPN exhibit pain as an associated complaint along with neuropathic involvement. The severity of pain may vary from tingling ("pins and needles" or paraesthesia) and shooting (like electric shock) to lancing (stabbing) [12–14].

The presence of peripheral neuropathic pain (PNP) limits functional ability, leading to an overall decrease in quality of life [15, 16]. The current pharmacological approaches to manage DPN are centered on maintaining a level of HbA1c and administration of first-line drugs (tricyclic compounds, serotonin-norepinephrine reuptake inhibitors (*e.g.*, duloxetine) and anticonvulsants (*e.g.*, pregabalin). However, response to monotherapy drugs is usually suboptimal, and combination treatments are often needed to control pain. These regimens may be associated with serious adverse effects in the long term and might not be well tolerated by the patients [17]. Non-pharmacological interventions, when incorporated in conjunction with pharmacological treatments, are effective in dealing with symptoms of DPN [18–20]. Literature highlights the effectiveness of acupuncture, reiki, photic stimulation, electromagnetic stimulation of neural electrical stimulation and LASER therapy as non-pharmacological strategies in alleviating diabetic neuropathic pain [21]. Apart from these, in recent times, the non-invasive neuromodulation (NINM) approach has gained popularity and is widely used in practice, as it is a secure and non-intrusive technique to induce pain relief and treat persisting neuropathic pain. The neuromodulation approach alters nerve function, causing plastic changes in the central nervous system. Transcutaneous Electrical Nerve Stimulation (TENS) is the most widely used peripheral NINM approach, whereas Scrambler Therapy (ST) and Frequency Rhythmic Electrical Modulated System (FREMS) are relatively new techniques. To date, Transcranial Direct Current Stimulation (tDCS) and Repetitive Transcranial Magnetic Stimulation (rTMS) are the central NINM approaches that have been the most thoroughly researched [22].

The lack of sufficient evidence supporting the viability and safety of neuro-modulatory techniques and the rising understanding of pain as a product of supraspinal cortical processing is the most compelling justification for investigating the role of neuromodulation techniques as a treatment strategy in treating the pain associated with DPN [15, 23]. The current review aims to thoroughly and methodically assess and examine the effectiveness of various neuro-modulatory approaches (tDCS, TENS, rTMS, FREMS and ST) on perceived pain levels among DPN patients with chronic pain.

Material and methods

Registration

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [24]. The protocol was registered with PROSPERO-CRD42023475785 (International Prospective Register of Systematic Reviews). The ethical guidelines were followed while conducting this review.

Study selection criteria

The following standards were met by published studies to be included in the present review: full-text randomized controlled trials, case studies and cross-sectional studies in which participants with DPN were subjected to NINM, administered alone or as a combination. Study participants were those clinically diagnosed with

type I or type II diabetes mellitus with DPN and aged >18 years. Only original studies in English assessing interventions with a validated clinical outcome measure related to pain were included. Even with resource limitations, authors in the present review did not include studies published in other languages, book chapters, book reviews and letters to the editors. Excluded from the review were non-human trials, research involving patients with neuropathy other than DPN and interventions that predominantly fall under the purview of different professions, such as pharmacotherapies, psychotherapy and speech therapies.

Information source and search strategy

In August 2023, a search for information regarding DPN and NINM approaches among patients with DM was completed. For pertinent literature, searches were done on MEDLINE (accessible by PubMed), Web of Science, Science Direct, Cochrane, and Pedro. MeSH (Medical Subject headings) were utilized to design the search strategy. A manual search was performed by using the following keywords: DM, DPN, Pain, Pain Threshold, Transcranial direct current stimulation (tDCS), transcutaneous electrical nerve stimulation (TENS), repetitive transcranial magnetic stimulation (rTMS), Frequency Rhythmic Electrical Modulated System (FREMS) and scrambler therapy (ST). The "AND" and "OR" Boolean logical operators combined the specific phrases (Table 1).

Reviewing procedure and data extraction

Records deemed irrelevant were excluded after carefully reviewing titles and abstracts. Eligibility of full-text articles was assessed once the irrelevant research was eliminated. The authors conducted Initial screening and entered data into a templated Microsoft Excel collection form (Microsoft Corp.). Authors gathered fundamental data from each study, including the author, publication year, study type, population size, research or article location, purpose and main findings by recommendations for best practices. Data on the characteristics of the assessed results was retrieved. The same researchers extracted the data, and data consistency was examined. Discussion with a research team was used to settle any disagreements.

Table 1: Methodological quality assessment of included studies via PEDro scale.

	Criteria*											
Author/Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Score**
Abdelkader AA *et al.* [1] 2019	1	1	-	-	-	-	-	-	-	1	1	4/10
Kim YJ *et al.* [24] 2013	1	-	-	1	-	-	-	1	1	1	1	6/10
Cozma L *et al.* [26] 2018	1	1	1	1	1	-	-	1	-	1	1	8/10
Onseti E *et al.* [27] 2013	1	1	1	1	1	-	-	1	-	1	1	8/10
Rahmy AF *et al.* [28] 2018	1	1	-	-	1	1	-	1	1	1	1	8/10
Lundeberg TCM *et al.* [29] 1992	1	1	-	1	-	-	-	1	-	1	1	6/10
Shereen H *et al.* [30] 2018	1	1	-	1	-	-	-	1	-	1	1	6/10
Kumar D *et al.* [31] 1997	1	1	1	1	-	-	-	1	-	1	1	7/10
Bulut M *et al.* [32] 2010	1	1	-	1	-	-	-	1	-	1	1	6/10
Lee YS *et al.* [33] 2019	1	-	-	1	-	-	-	1	1	-	1	5/10
Serafini G *et al.* [34] 2000	1	-	-	-	-	-	-	1	1	-	1	4/10
Siudak GD *et al.* [35] 2023	1	-	-	1	-	-	-	-	1	-	1	4/10
Bosi E *et al.* [36] 2013	1	1	-	1	-	-	-	1	1	1	1	7/10
Conti M *et al.* [37] 2009	1	1	1	1	-	-	-	1	-	-	1	6/10

Note: Criteria * – 1. Specific eligibility requirements were followed; 2. Subjects were randomly divided into groups; 3. The allocation was concealed; 4. The most crucial prognostic factors were identical across the groups at inception; 5. All participants were blinded; 6. All therapists who delivered the therapy were blinded; 7. All assessors who measured at least one important outcome were blinded; 8. More than 85% of the subjects who were initially divided into groups provided measurements of at least one major outcome; 9. Analysis with the intention to treat; 10. Comparison between groups; 11. The study provides measures of variability.

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Characteristics of studies included for review

Participants

Overall, 14 studies conducted between 1997 and 2023 involving 436 participants have been included in the present review (Figure 1). The age of participants ranged from 18–60 years. The estimated sample size in the included studies varied between 1 and 75 and comprised both male and female participants in varying proportions. Details of sample size calculation were reported only in one study, where the sample size was determined using G*Power software (ver. 3.0.10; http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3) [25], whereas other studies did not specify their method for sample size estimation. (Demographic details for included studies are depicted in Table 2). The risk of bias assessment was done through review manager ver. 5.4.1, as shown in Figures 2 and 3.

Intervention

In the current review, articles using different neuromodulation modalities, such as rTMS [26–28], tDCS [25, 29, 30], TENS [29–32], ST [33, 34]and FREMS [35–37], were included. Table 3 mentions the treatment sessions and study setting for each included study.

Outcome measures

Fourteen full-text articles finalized to be included in the review; eight utilized visual analog scale (VAS), two studies employed neuropathic pain scale (NPS), whereas another relied on scores obtained by making use of a numerical rating scale (NRS) as an outcome measure. Furthermore, two studies implemented a quality of life (QOL) questionnaire, and two additional studies used the clinical global impression (CGI) [38] scores to determine the long-term impact of perceived pain on activities of daily living and quality of life among patients with DPN.

Results

Effect of rTMS on chronic pain

rTMS, as a NINM technique in treating chronic pain among patients with DPN, is found to be beneficial by creating structural changes and improving pain threshold. Also, it showed a more long-lasting impact on pain than other devices. Findings from a study where patients were subjected to 5 consecutive sessions of high-frequency rTMS suggested a significant reduction in the VAS

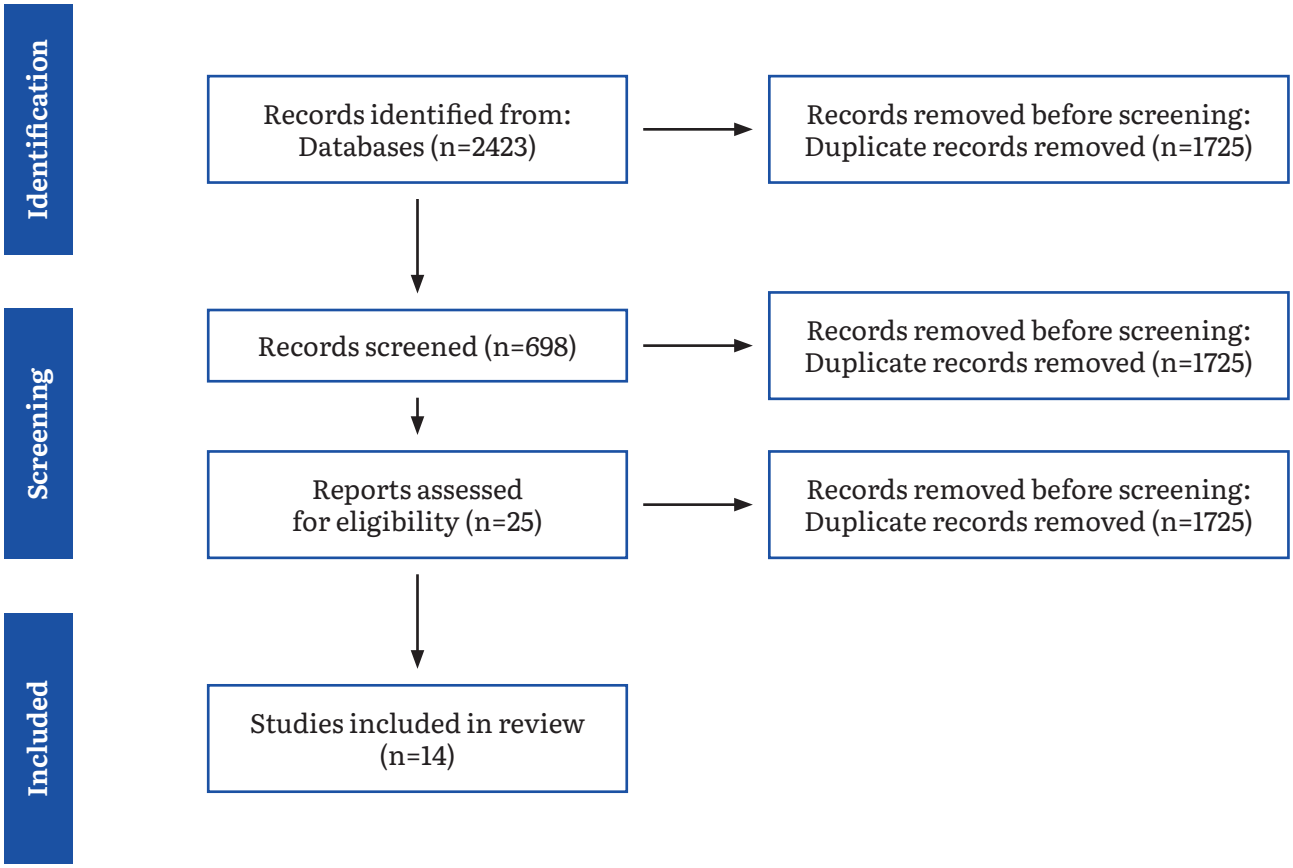

Figure 1: PRISMA flow diagram for article selection.

Table 2: Characteristics of articles included for review.

Trial	Research outline	Total participants	Mean age (years)	Time of assessment
Abdelkader AA *et al.* [1] 2019	Prospective, cross sectional, single-center study	20 patients	Age range: 18–60 years Insulin dependent group: 52.1±6.45 Non-Insulin dependent group: 57.9±10.22	Pre and post treatment
Kim YJ *et al.* [24] 2013	Randomized, Sham Controlled Trial	60 patients	M1 tDCS group: 59.60±13.15, Sham tDCS group: 61.60±10.27 DLPFC tDCS group: 63.50±8.75	Pain was assessed daily and other outcomes were assessed at baseline followed by 5th day, 2nd and 4th week post intervention
Cozma L *et al.* [26] 2018	Case series	3 patients	Mean: 63.33±16.62	Baseline, 2nd week and 3rd week
Onesti E *et al.* [27] 2013	Single-centered, randomized, double-blind, crossover, placebo-controlled trial	25 patients	Real-sham rTMS group: 70.7±9.5 Sham-real rTMS group: 70.6±7.9	Pre and post first intervention, 3 weeks after 1st intervention, 2 weeks after washout, pre and post second intervention
Rahmy AF *et al.* [28] 2018	Randomized clinical trial	40 patients	Age range: 50–60 years Group A: 52.8±1.88 Group B: 53.05±1.93	Pre and post treatment
Lundeberg TCM *et al.* [29] 1992	Randomized controlled trial	64 patients	Placebo ENS: 66+7.9 ENS: 67.5+8.6	Pre and 2, 4, 6, 8, 12 weeks post treatment
Shereen H *et al.* [30] 2018	Randomized clinical trial	40 patients	Group A: 52.8±1.88 Group B: 53.05±1.93	Pre and post treatment
Kumar D *et al.* [31] 1997	Randomized controlled trial	31 patients	Electrotherapy group: 53±4 Sham group: 59±3	Pre and post treatment
Bulut M *et al.* [32] 2010	Randomized controlled trial	40 patients	TENS group: 58.45±15.9 Placebo TENS group: 62.05±19.9	Pre, mid and post treatment
Lee YS *et al.* [33] 2019	Case report	1 patient	45 years	Pre and post treatment with an additional follow-up one week post intervention
Serafini G *et al.* [34] 2000	Quasi Experimental Study	18 patients	Mean: 64±12	Weekly for 6 weeks
Siudak GD *et al.* [35] 2023	Randomized, single- blind, sham-controlled trial	44 patients	FREMS Group: 64±10.5 Sham-FREMS Group: 62±11.5	Pre and post treatment, follow-up after 8 weeks
Bosi E *et al.* [36] 2013	Placebo-controlled clinical trial	75 patients	FREMS: 59.0±10.6 Placebo: 61.3±8.3.	Pre, mid and post treatment

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Table 2: Continued.

Trial	Research outline	Total participants	Mean age (years)	Time of assessment
Conti M *et al.* [37] 2009	Randomized, double-blind, placebo-controlled, cross over clinical trial	31 patients	Age range: 18–70 years Mean 63.1±3.1 years	Pre and post first intervention, pre and post second intervention and follow up after 4 weeks

Note: Values for age are presented as mean±standard deviation or number (%). tDCS – transcranial direct current stimulation; M1 – primary motor cortex; DLPFC – dorsolateral prefrontal cortex; FREMS – Frequency Rhythmic Electrical Modulated System; rTMS – repetitive transcranial magnetic stimulation.

score after receiving treatment (p>0.01). Additionally, active high-frequency rTMS, when applied to the primary motor cortex corresponding to the non-dominant hand area, decreased pain by 58% from baseline two weeks after the start of active stimulation. One week later, pain reduction improved to a 72% decrease [27]. A study following the application of real rTMS presented a notable and significant reduction in both VAS scores (p=0.01) and RI reflex area (p<0.01), whereas sham rTMS treatment did not present a substantial effect on these variables. However, changes observed in outcome measures of pain score due to rTMS were not sustained approximately three weeks after the stimulation [28].

Effect of tDCS on chronic pain

tDCS aids pain reduction by facilitating non-intrusive plasticity of the cortex and polarizing nerve membranes with continuous weak direct currents at subthreshold levels. The direction of tDCS-induced plastic changes is determined by stimulation polarity; anodal stimulation increases excitability, whereas cathodal stimulation decreases it. According to a study, the M1 group exhibited a significantly larger decrease in pain and PT, as indicated by the VAS scores, compared to the sham and DLPFC groups (p<0.001). This reduction in pain intensity was maintained in the M1 group even after 2 and 4 weeks of follow-up, in contrast to the sham group (p<0.001, p=0.007). Over time, there were significant variations among the three groups in terms of VAS scores for pain (p<0.001), CGI scores (p=0.01), and PT (p<0.001) [24]. In a study of participants receiving stimulation via tDCS for 3 times per week for 2 months (current density: 0.04 mA/cm^2) showed a noticeable decrease in pain score along with improvement in quality of life [30, 39].

Effect of TENS on chronic pain

A group of participants receiving TENS as an intervention presented a decline in pain scores from 3.17±0.12 to 1.44±0.25 (P<0.01), and post-treatment pain scores were considerably lower (P<0.03). DPN patients with diabetic foot ulcers receiving 15-minute sessions from TENS with electrodes placed in the path of nerve pain around the wound effectively decreased pain levels post-intervention [29, 31].

Effect of ST on chronic pain

A 45-minute treatment session of ST, performed once weekly for 10 weeks, led to a significant decrease in bilateral plant foot pain, as assessed via the NRS scale and the effect of the intervention lasted for more than 6 months [33]. In another study, DPN patients with chronic pain underwent ST stimulation for 12 weeks. Pain intensity was evaluated using VAS before and after each treatment session (lasting 20 minutes), and pain scores were noted using a pain diary provided to the patients. On comparing weekly mean VAS values between the first and last week, a significant reduction in pain scores was observed from the first week, with patients reporting more than a 50% decrease in pain scores [34].

Effect of FREMS on chronic pain

A study's findings depicted decreased pain intensity approximately following 3.9 days of FREMS treatment. The duration required to reduce pain perception level did not show a significant statistical difference (p>0.05) compared to the sham group. However, after an 8-week follow-up period, there was a statistically significant difference in effectiveness between the FREMS therapy and sham-FREMS groups (p<0.05) [35].

Discussion

Articles included in the present systematic review focused on NINM approaches as a strategy for managing pain associated with DPN. However, more studies

Table 3: Main findings of the studies included for review.

Author/year	Intervention	Treatment parameters	Outcome measures	Findings
Abdelkader AA *et al.* [1] 2019	Both Insulin dependent (group A) and non-insulin dependent (group B) groups were subjected to a high frequency rTMS for 5 consecutive days. Electrode placement: Over motor cortex of the lower limbs which was localized on the scalp at Cz (point of tibialis anterior muscle)	Duration of session: 40 minutes 15 consecutive trains (2 seconds duration) of 50 stimuli were delivered at 100% motor threshold (MT) Intertrain intervals: 30 seconds Frequency: 10 Hertz	Visual analogue scale (VAS) Nerve conduction studies (NCS): tested for motor function for ulnar, peroneal, and tibial nerves and sensory functions of the ulnar and sural nerves Neuropathic pain: assessed via Douleur Neuropathique (DN4) diagnostic questionnaire	Highly significant improvements in VAS and nerve conduction studies ($p>0.01$) were seen post administration of rTMS indicating its role in producing analgesia and inducing plastic changes in motor cortex
Kim YJ *et al.* [24] 2013	Primary motor (M1) group: The anode (saline-soaked electrodes, 5×5 cm) was placed over C3 (as per EEG 10/20 system) and the cathode over the contra-lateral supraorbital area Dorsolateral prefrontal cortex (DLPFC group): The anode was placed over F3 (as per EEG 10/20 system) and cathode over the contralateral supraorbital area Sham group: Electrode positions were the same as used in anodal M1 stimulation, with the stimulator turned on for only 30 seconds	Mode of current: Constant Intensity: 2 mA Duration: Single 20-minute session for 5 consecutive days	VAS Clinical global impression (GCI) Beck's depression index (BDI) Pain threshold (PT), Anxiety Sleep quality	After the tDCS sessions, the M1 group showed significant decrease in VAS for pain and PT *versus* the sham and DLPFC groups ($p<0.001$) and the results of VAS for pain sustained after 2 and 4 weeks of follow-up in the M1 group) Significant differences were observed in all groups for pain score ($p<0.001$) while other parameters did not show any significant changes
Cozma L *et al.* [26] 2018	Intervention group: Active high frequency rTMS was applied to the primary motor cortex corresponding to the non- dominant hand area A pulse at 60% of the maximum power of device was produced until a muscle contraction was seen in the contralateral hand Control group: Stimulation strength was decreased to 20% of the motor threshold, and electrode placement was in the scalp area corresponding to the non- dominant primary motor hand	Duration: 4 sham sessions of rTMS stimulation, followed by 3 days of washout and ending again with 4 sessions of active stimulation Dosage: ten trains of 200 pulses Frequency: 10 Hertz Interbrain interval: 40 seconds	Numeric pain rating scale (NPRS) DN4 diagnostic questionnaire Patients' Global Impression of Change (PGIC) Quality and duration of sleep	Pain decreased by 72%, post 3 weeks of intervention and 61% from baseline after two weeks of active stimulation, indicating a persistent and significant improvement in pain post active stimulation

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Table 3: Continued.

Author/year	Intervention	Treatment parameters	Outcome measures	Findings
Onesti E *et al.* [27] 2013	Sham and real rTMS sessions lasted 20 minutes and were delivered for 5 consecutive days for both groups, Real-sham rTMS group and sham-Real rTMS group After a 5-week washout period, they switched over to the alternative treatment for additional 5 days Active rTMS group: Active RTMS coil was placed on the scalp for stimulation Sham Rtms group: stimulation was delivered with a sham coil producing negligible electric current	Active rTMS sessions consisted of 30 consecutive trains of 50 stimuli (intertrain interval lasting 30 seconds) Frequency: 20 Hz Resting motor Threshold (RMT): 100%	100-step VAS for pain Motor and sensory NCS testing RIII reflex: Nociceptive flexion reflex	rTMS group showed a significant reduction in the VAS score ($p=0.01$) and RIII reflex area as compared to sham group ($p<0.01$). However, the results did not sustain until 3 weeks post intervention
Rahmy AF *et al.* [28] 2018	Both groups received stimulation 3 times per week for 2 months Group A: Transcranial Direct Current Stimulation (tDCS) Anode electrode was placed over primary motor cortex while cathode was placed over the supraorbital area. Group B: Transcutaneous Electrical Nerve Stimulation (TENS) Electrodes were placed at or around the painful area and at least one pad width apart	TENS: Intensity: As tolerated by the patient Duration: 20 minutes/session, three times a week tDCS: DC current with intensity increased gradually over several seconds until reaching 1mA Current density: 0.04 mA/cm^2 Duration: Weekly 3 sessions, with each session lasting for 20 minutes	Neuropathy pain scale (NPS)	tDCS and TENS showed significantly decreased pain scores and an overall improvement in quality of life among patients in both groups
Lundeberg TCM *et al.* [29] 1992	ENS group: subjected to electrical stimulation Standard treatment+ placebo ENS: paste impregnated bandage and self adhesive elastic bandage along with placebo ENS	ENS: applied outside ulcer area with an intensity evoking parasthesias 20 mins a day/twice daily, with polarity of treatment electrode changed after every treatment (4 cm×6 cm) Standard treatment+ Placebo ENS: electrodes were applied but had no output	Healing of the ulcers	Findings were suggestive of significant improvement in ulcer area and healed ulcer in the ENS group as compared to the placebo group.

Table 3: Continued.

Author/year	Intervention	Treatment parameters	Outcome measures	Findings
Shereen H *et al.* [30] 2018	Group A were treated Transcranial Direct Current Stimulation (tDCS) Group B were treated with Transcutaneous Electrical Nerve Stimulation (TENS)	Group A: 20min, 3 sessions/week for 2 successive months Group B: 20min, 3 sessions/week for 2 successive months	Neuropathy pain scale (NPS)	Transcutaneous electrical nerve stimulation and transcranial direct current stimulation were both effective equally in alleviating pain associated with diabetic painful neuropathy
Kumar D *et al.* [31] 1997	TENS group: Participants were subjected to treatment session daily for 4 weeks Sham stimulation group: Received treatment via machines with inactive electrodes	TENS parameters: Biphasic, exponentially decaying waveforms Duration: 30 minutes Pulse width: 4 ms and Voltage: 35 V Intensity: Up to 35 mA Pulse frequency: 2–70 Hz	Pain scores: assessed via self-developed scale, scoring symptoms on a grade of 0 to 5 Analog scale: for pain	The group mean pain score declined from 3.17±0.12 to 1.44±0.25, and these changes were highly significant. Post-treatment pain scores were lower for the sham group, indicating a substantial impact of TENS on pain relief
Bulut M *et al.* [32] 2010	TENS group: The electrodes of the TENS were bilaterally placed on the lumbosacral region, 3 cm lateral of the vertebral column. Placebo TENS group: No electrostimulation was given in this group	Duration: 30 minutes daily for 20 days Frequency: 80 Hz Amplitude: Set high enough to create paresthesia	VAS	VAS scores on 10^{th} and 20^{th} days of the procedure in Group A were significantly lower than Group B ($p<0.001$). Also, pain grades in Group A were significantly lower than Group B when evaluated at the end of the study ($p<0.001$)
Lee YS *et al.* [33] 2019	Scrambler Therapy (ST) stimulation: Electrodes with 5 channels were positioned in areas without pain, attaching them to normal sensory areas around the ankle	45 minutes treatment session performed once a week for 10 weeks Intensity: As per patient's tolerance level	Numerical rating scale pain score (NRS)	NRS score decreased from 6 to 3 after the first ST session. After 10 treatment sessions, the patient reported an NRS score of 2 for bilateral plantar foot pain and the effects of therapy sustained for 6 months
Serafini G *et al.* [34] 2000	ST stimulation: Participants were subjected to treatment with ST stimulation for 12 weeks	2 sessions of 20 minutes each were performed weekly. A total of 12 sessions were given	VAS pain intensity difference (PID) summatory PID (SPID)	A significant reduction in the pain scores was observed from first to last week of treatment. On comparing weekly mean VAS values between the first and last week and the 6^{th} and the 12^{th}, considerable values of $p<0.01$ and $p<0.05$ respectively become evident

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Table 3: Continued.

Author/year	Intervention	Treatment parameters	Outcome measures	Findings
Siudak GD *et al.* [35] 2023	FREMS group: Received 10 sessions of Frequency Rhythmic Electrical Modulated System (FREMS) stimulation for 5 days Sham-FREMS group: Electrodes were connected, but no stimulation was given	Asymmetric, biphasic pulses with a duration of 35 minutes (25 minutes active phase followed by 10-minute recharging phase) were given Electrode placement: on both legs and feet (tibial muscles, lateral surface of calf, below each malleolus, on feet	VAS EuroQol 5-Dimension 5- Level (EQ-5D-5L) Clinical global impression of change (GCI-C)	FREMS treatment, when incorporated among patients with DSPN (distal symmetrical polyneuropathy) induced significant enhancement in quality of life along with a decrease in severity of pain
Bosi E *et al.* [36] 2013	Patients received three series of FREMS or placebo treatment at intervals of three months, delivered 24 hours apart and not more than 21 days apart FREMS group: Four pairs of electrodes were applied to both lower extremities, and a hand-held remote was provided to patients to modulate the voltage of electrical stimulation Placebo group: Electrodes were placed without generation of electrical impulses	Biphasic (negative and positive), asymmetric and electrically balanced pulses were used, composed of: Active phase: Extra short duration Recharging phase: Low voltage and long duration Frequency range: 1–1000 Hz	VAS Nerve conduction velocity (NCV) of deep peroneal, tibial and sural nerves. Sensory function: assessed via tactile, thermal and vibration sensations	FREMS induced an immediate and significant decrease in day and night pain immediately after first session. Significant improvement in the perception of cold sensation was demonstrated in the FREMS group
Conti M *et al.* [37] 2009	Electrotherapy and placebo were administered by placing four transcutaneous electrodes, applied to both lower limbs A 24-hour rest period was given between each session Placebo group: electrode placement was not accompanied with the transmission of electric current	FREMS group: 10 sessions of placebo were followed by 10 sessions of FREMS, separated by a 1-week washout. Current type: Monophase-compensated negative potential, asymmetric, sharp-spike electric pulses Peak amplitude: 0 to 255 V Pulse frequency: 1–50 Hz Pulse duration: 10–40 microseconds.	Microvascular function: Cutaneous capillary blood flow: measured by laser Doppler on 3 areas at dorsal surface of the foot Transcutaneous CO_2 tension ($TcPCO_2$) Transcutaneous O_2 tension ($TcPO_2$)	4-month follow-up presented with a 52% increase of cutaneous blood flow in resting conditions (P=.0086 *vs.* baseline) No significant changes were observed for $TcPO_2$ and $TcPCO_2$, both in resting state as well as in response to warm

Note: rTMS – Repetitive Transcranial Magnetic Stimulation; VAS – Visual analogue scale; NCS – Nerve conduction studies; tDCS – transcranial Direct Current Stimulation; TENS – Transcranial Electrical Nerve Stimulation; V – Volts; mA – milliampere; Hz – Hertz; m – milliseconds; cm – centimeter; cm^2 – centimeter square.

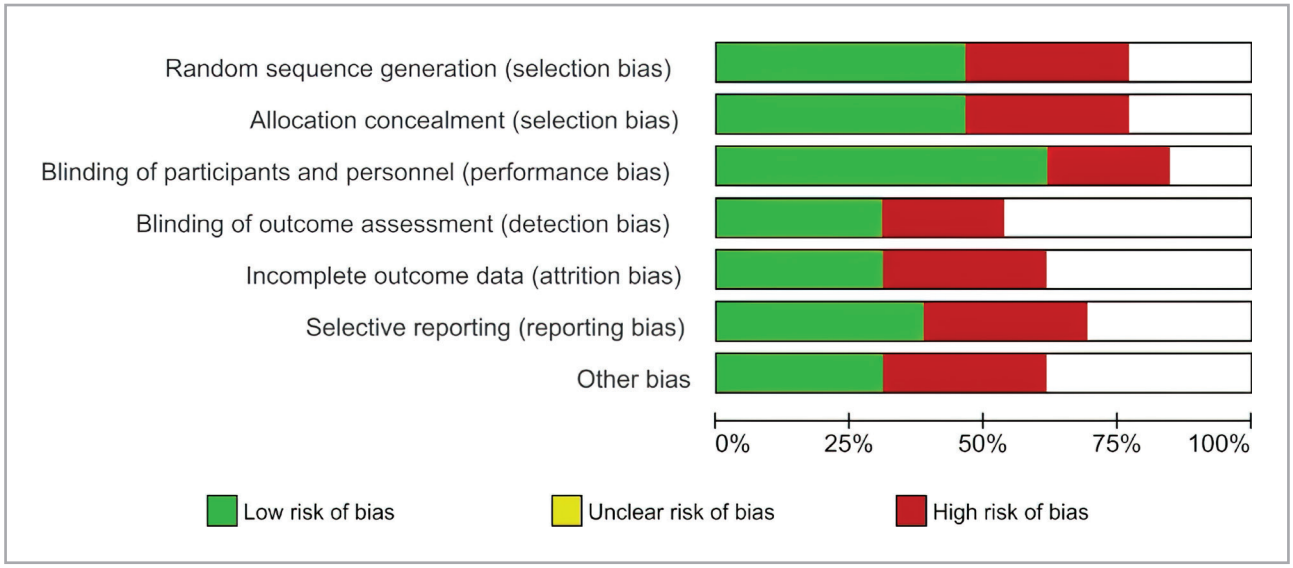

Figure 2: Risk of bias graph for included studies.

are needed to conduct a meta-analysis indicating the effectiveness of various NINM approaches among patients with DPN. Although our search was limited due to the variability of the outcome measures, the conclusion obtained from the existing evidence implies that DPN patients receiving NINM stimulation had a favorable effect on neuropathic pain, which is indicated by positive changes in pain scores and enhanced physical function, indicating an overall improvement in quality of life among patients with chronic pain associated with DPN.

Pharmacological treatment, as a management strategy for DM-related neuropathic pain, generally becomes refractory over time [33]. Since chronic pain is an adaptive condition, it should be treated by regulating brain plasticity, which is regarded as the origin of all structural and functional variations and learning and coping mechanisms [36]. These mechanisms act by altering the primary motor cortex (M1) to enhance its potential for adaptation, while pain control mechanisms were activated to suppress pain signals. The analgesic effects are caused by endogenous opioids modulating cortical circuits that activate descending inhibitory pain control systems through the periaqueductal grey matter. Motor cortex stimulation acts by increasing local excitability at M1 and has been known to show effectiveness in managing symptoms arising due to persistent neuropathic pain [40–42]. M1 stimulation influences pain's sensory components, leading to an analgesic effect. Functional magnetic resonance imaging studies among healthy individuals to determine the impact of high-frequency rTMS over M1 have shown to cause considerable deactivation in distant nociceptive brain areas and the sensory perception threshold. Pain in the distal lower limbs, which has previously been challenging to target, is effectively reduced by stimulating deeper cortical regions without causing deleterious effects [43, 44].

It has been suggested that altering M1 using high-frequency rTMS or anodal tDCS reduces hyperactivity in regions that are responsible for chronic pain, such as the medial thalamus, anterior cingulate cortex and upper brain stem [44, 45]. Compared to DLPFC and sham stimulation, anodal tDCS at the M1 dramatically reduced pain and PT to pressure. Also, patients with PDPN presented with analgesic benefits of tDCS at M1 [25]. The results are in line with other research that emphasized the role of anodal tDCS in significantly reducing pain in individuals with different kinds of chronic pain syndrome [45–47].

The findings may shed some light on the processes behind rTMS-induced analgesia. A complex spinal interneuronal network under the control of descending pain pathways diffuses noxious inhibitory control systems or other descending serotoninergic systems from the nucleus raphe magnus that modulates the RI, which is regarded as a quantitative index of spinal transmission of nociceptive. Findings are suggestive of spinal nociceptive neuron hyperexcitability, seen in VAS ratings, are supported by a reduction in the RIII area and may be conclusive of rTMS-induced activation of descending inhibitory control pathways [28].

Potential benefits of electrotherapy and electromagnetic stimulation in augmenting angiogenesis were indicated by an improvement of microvascular circulation at 4 months of follow-up [36]. Also, enhancement

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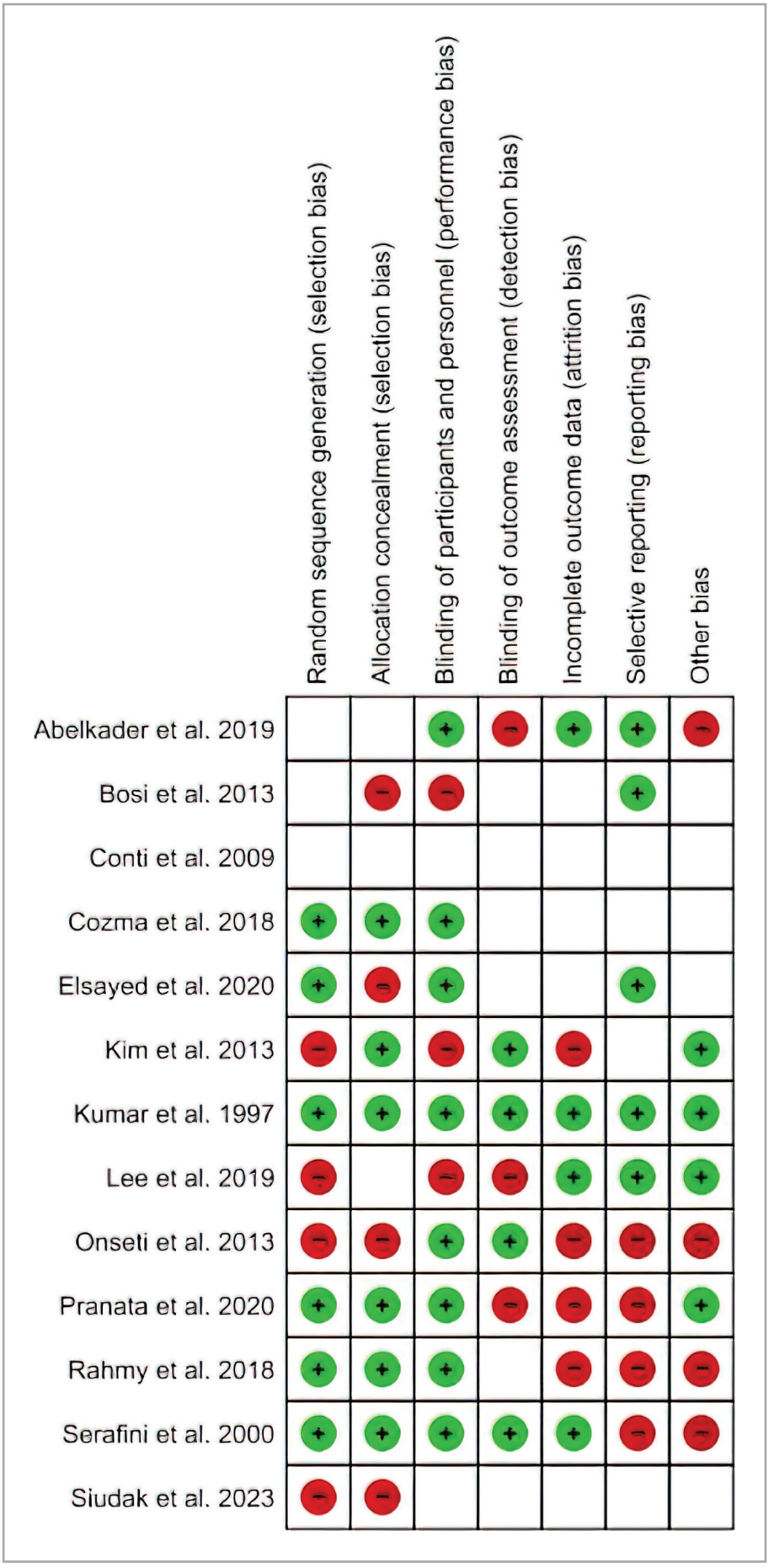

Figure 3: Risk of bias summary for included.

in micro-vascular function parallels that of peripheral nerve function. FREMS as a treatment strategy led to the potential enhancement of endoneurial blood flow, indicating its effects on managing neuropathy. It is known to act by mechanisms causing an increase in microvascular blood flow, a rise in smooth cell-mediated vasomotor activity6 and release of vascular endothelial growth factors [48, 49]. 50% of responders in a study subjected to intermittent treatment sessions with FREMS responded positively, and the results obtained were as effective as the first-line drugs duloxetine and pregabalin, with the advantage of having no pertinent side effects [50].

Apart from a considerable improvement in cold sensation thresholds, the effects of FREMS on thermal, vibrational and tactile perceptions were equally ambiguous. Even though the exact mechanism underlying its role is yet to be confirmed, treatment using FREMS is risk-free and leads to a substantial decrease in daytime and nighttime pain among individuals with symptomatic diabetic polyneuropathy. ST has a role like therapeutic TENS [36]. Although varied interpretations have been made on the exact mechanisms of stimulation, significant improvement in pain scores was observed post-treatment [33]. Marineo *et al*. proposed that electrodes emit "non-pain" impulses that are relayed to peripheral receptors through C-fibers and A-delta fibers, which subsequently modify and lessen the perception of pain [51]. Although there is no documented advice regarding the placement of the electrodes, positioning electrodes at points proximal and distal to painful locations, corresponding to dermatomes connected to painful areas as a preferred site, served as potentially beneficial in decreasing pain [52, 53]. However, some patients reported pressure and itching sensations in the location that was previously uncomfortable during ST.

Numerous theories have been proposed to explain the mechanism of action of TENS, including modulation of descending inhibitory pathways, peripheral calcitonin release, increased gate control for pain threshold, elimination of the windup phenomenon and reduction of impulses from damaged nerves. Similar to scrambler therapy, a specific mechanism of treatment has not yet been identified.53 Electrical stimulation can assist the body in releasing endorphins, which are natural analgesics that help patients relax, in addition to inhibiting nerves that innervate the painful location [54]. Stimulating A-beta peripherals in the dorsal horn region modifies A-delta and C fibers responsible for pain transmission. Mechanisms involving the signal termination process are supported by the notion of pain gates. TENS works by stimulating big nerve fibers, which suppress second-order neurons' activity in the spinal cord and obstruct the transmission of pain signals carried by tiny nerve fibers. The "gate control theory" is the accepted justification through which electrical currents relieve pain. Findings obtained from previous research back up the conclusions of the studies included in the present review. The impact of TENS on neuropathic pain claims that patients in the intervention group presented with lower pain levels (different) than the control group post-treatment [29, 31].

Our findings are conclusive of the potential benefits of various NINM approaches in decreasing pain severity among patients with DPN. However, natural history studies have added to evidence stating that modifications in diet and exercise slow the course of neuropathy or even cause epidermal nerve fibers to regenerate. Therefore, glycemic control in the patient and management of lifestyle changes like aerobic exercise are crucial to maximize the therapeutic benefit of NMIM in patients with diabetic peripheral neuropathy [33].

A few limitations in the literature included in this current review on the various NINM approaches in managing DPN are addressed hereafter. Patients using analgesics were not excluded from the review, and the participants weren't chosen based on the extent to which the neuropathic symptoms appeared. As a result, people with more severe diabetic neuropathy may not benefit from the findings. Trials included in the review have a small number of participants, which may have limited the ability to conduct a comprehensive analysis. Additionally, no neurological evaluation was performed after the follow-up. Also, the majority of research focused on somatosensory PT and did not evaluate other forms of PT. Gender differential that may be significant given that DSPN differs across genders was not highlighted in the study's findings. Most of the studies did not measure blood sugar or HbA1c levels during the course of the trial, despite the fact that DSPN is highly related to glycemic management. Additionally, studies took into account no other clinical information, such as nutritional data.

Future research, including randomized controlled trials, is required to acquire an expensive understanding by examining therapeutic benefits extending over a long period of time and concentrating on nociceptive processes underpinning NINM approaches to treat chronic pain. In addition, further research is required to determine if focused and somatotopically directed stimulation could improve the analgesic efficacy. Additionally, carryover and crossover effects could be examined through trials. Studies that target adopting

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specific and optimized aspects such as equipment type, intensity and polarity of stimulation are needed to maximize and give persistent analgesic benefits. To further support these findings, clinical, biochemical and instrumental tests are required. Future research will fill in these gaps, evaluate whether longer, more powerful stimulation periods will result in longlasting positive benefits and determine whether chronic maintenance sessions are feasible. Evidence regarding the cost-effectiveness of different treatment approaches in managing DPN is still lacking and, thus, should be conducted in the near future.

Conclusion

DPN management remains challenging, particularly for a significant portion of diabetic patients who either suffer from pain caused by neuropathic drugs or experience side effects that restrict their dosage. In such cases where treatment options are limited, neuromodulation devices provide a glimmer of hope. Preliminary data from research investigations included in this review confirms the favorable effect of several NINM approaches in treating pain and enhancing physical function in DPN patients. All of these methods made it feasible to securely access deeper cortical regions that are otherwise impossible to reach. Although participants' use of painkillers has decreased substantially, there is still a lack of high-quality, side-by-side clinical trials comparing these therapeutic approaches, and since the published studies employed different methodologies, it's challenging to determine which treatment approach is the most successful.

Conflict of interest

The authors declare no conflict of interest.

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