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# Electrical stimulation and electromagnetic field use in patients with diabetic neuropathy: systematic review and meta-analysis

Cinara Stein<sup>1</sup>, Bruna Eibel<sup>2</sup>, Graciele Sbruzzi<sup>2,3</sup>, Pedro D. Lago<sup>1</sup>, Rodrigo D. M. Plentz<sup>1,2</sup>

**ABSTRACT | Background:** Painful diabetic neuropathy (PDN) is a common complication of diabetes mellitus, and pharmacological therapies are ineffective in many patients. Therefore, other treatment modalities should be considered, including electrical stimulation and electromagnetic fields. **Objectives:** The research objective was to evaluate the effect of treatment with electrical stimulation and electromagnetic fields on pain and sensitivity in patients with painful diabetic neuropathy compared with placebo or another intervention. **Method:** We searched the following electronic databases (from inception to April 2012): MEDLINE (accessed by PubMed), LILACS, Physiotherapy Evidence Database (PEDro), EMBASE and Cochrane CENTRAL. We included randomized trials that compared electrical stimulation or electromagnetic fields with control groups in which the objective was to assess pain and sensitivity in patients with PDN. Two reviewers independently extracted the data. A random-effects model was used for the main analysis. **Results:** The search retrieved 1336 articles, of which 12 studies were included. Reductions in the mean pain score were significantly greater in the TENS (transcutaneous electrical nerve stimulation) group than in the placebo group [ $-0.44$  (95% CI:  $-0.79$  to  $-0.09$ ; I<sup>2</sup>: 0%)]. There was no improvement in pain relief when electromagnetic fields were compared with the control group [ $-0.69$  (95% CI:  $-1.86$  to  $0.48$ ; I<sup>2</sup>: 63%)]. **Conclusions:** We found that TENS improved pain relief in patients with diabetic neuropathy, while no such improvement was observed with the use of electromagnetic field treatment. Due to the methodological differences between the studies, a meta-analysis for the outcome of sensitivity could not be performed.

**Keywords:** physical therapy; diabetic neuropathies; electrical stimulation; electromagnetic fields; pain; review.

## HOW TO CITE THIS ARTICLE

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## ● Introduction

Diabetes mellitus (DM) is a common chronic disease with a predicted prevalence of 366 million patients by 2030<sup>1</sup>. Peripheral neuropathy is one of the most serious complications of both type 1 and type 2 DM<sup>2</sup>, with a prevalence to up 50% of DM cases<sup>3</sup>. One of the most distressing symptoms that people can suffer from is neuropathic pain and paresthesia<sup>4</sup>. Painful diabetic neuropathy (PDN) can cause symptoms that last for years and severely impair quality of life<sup>5</sup>, and the PDN prevalence is 26.4% in DM<sup>6</sup>.

The etiology of diabetic neuropathy is not well understood because it is based on the clinical symptoms of individuals. The treatment options are limited, which may explain why up to 50% of patients have not requested or received treatment for the condition<sup>7</sup>. Analgesics, antidepressants and

anticonvulsants are often prescribed, with varied responses<sup>8</sup>. As several studies have suggested, nonpharmacological options, such as electrical stimulation, which represents one of the more benign therapies for this condition<sup>9</sup>, may contribute to a better quality of life and fewer complaints of pain<sup>10</sup>.

In randomized trials, various types of electrotherapy, such as transcutaneous electric nerve stimulation (TENS)<sup>11-15</sup>, pulsed electromagnetic fields<sup>16-19</sup>, static magnetic field therapy<sup>20</sup>, low-frequency pulsed magnetic field<sup>21</sup>, high-frequency external muscle stimulation (HF)<sup>22</sup>, frequency-modulated electromagnetic neural stimulation (FREMS)<sup>23</sup> and percutaneous electrical nerve stimulation (PENS)<sup>24</sup>, have been reported to show beneficial effects, such as decreased pain and improved sensitivity, due to

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electric stimulation in the treatment of patients with PDN.

Previous randomized trials showed the beneficial effects of electrical stimulation in the treatment of patients with PDN compared with placebo. However, studies comparing these benefits with those obtained from placebo had small sample sizes and showed conflicting results<sup>11-15,18-24</sup>. A systematic review of the evidence would allow for a more precise evaluation of its effectiveness and, if the benefits are proven, aid in disseminating the use of electrical stimulation. Therefore, the aim of our study was to systematically review the effect of treatment with electrical stimulation and electromagnetic field use on pain and sensitivity in patients with PDN compared with placebo or another intervention.

## ● Method

This systematic review was performed in accordance with the Cochrane Collaboration and statements for systematic review<sup>25</sup> and Preferred Reporting Items for Systematic Review and Meta-analyses: The PRISMA Statement<sup>26</sup>.

## Search strategy

We searched the following electronic databases (from inception to April 2012): MEDLINE (accessed by PubMed), LILACS, Physiotherapy Evidence Database (PEDro), EMBASE and Cochrane Central Register of Controlled Trials (Cochrane CENTRAL). The search terms used included 'diabetic neuropathies', 'diabetic polyneuropathy', 'diabetic asymmetric polyneuropathy', 'TENS', 'transcutaneous electrical nerve stimulation', 'transcutaneous electrical stimulation', 'electric stimulation', 'electrical stimulation', 'electromagnetic fields', 'electromagnetic field', 'field,electromagnetic' and a string of words previously proposed<sup>27</sup>, which yielded a high sensitivity in the search for randomized controlled trials (RCTs). To enhance the sensitivity of our search, we did not include words related to the outcomes of interest. There were no language restrictions.

The references included in the published articles identified in these searches were used as an additional source to identify other clinical trials. The complete search strategy used for the PubMed database is shown in Table 1.

**Table 1.** Literature search strategy used for the PubMed database.

#1	Diabetic Neuropathies OR Diabetic Neuropathy OR Neuropath\$, Diabetic OR Diabetic Polyneuropath\$ OR Polyneuropath\$, Diabetic OR Asymmetric Diabetic Proximal Motor Neuropathy OR Diabetic Asymmetric Polyneuropathy OR Asymmetric Polyneuropath\$, Diabetic OR Diabetic Asymmetric Polyneuropathies OR Polyneuropath\$, Diabetic Asymmetric OR Diabetic Autonomic Neuropathy OR Autonomic Neuropath\$, Diabetic OR Diabetic Autonomic Neuropathies OR Neuropath\$, Diabetic Autonomic OR Symmetric Diabetic Proximal Motor Neuropathy OR Diabetic Amyotrophy OR Amyotroph\$, Diabetic OR Diabetic Amyotrophies OR Diabetic Neuralgia OR Diabetic Neuralgias OR Neuralgias, Diabetic OR Diabetic Neuropath\$, Painful OR Neuropath\$, Painful Diabetic OR Painful Diabetic Neuropath\$ OR Neuralgia, Diabetic OR Diabetic Mononeuropath\$ OR Mononeuropath\$, Diabetic OR Diabetic Mononeuropathy Simpl\$ OR Mononeuropathy Simpl\$, Diabetic OR Simpl\$, Diabetic Mononeuropathy OR Diabetes Complication\$ OR Diabetes Complication OR Diabetes-Related Complication\$ OR Diabetes Related Complications OR Diabetic Complication\$ OR Complications of Diabetes Mellitus OR Diabetes Mellitus Complication\$
#2	Electric\$ Stimulation OR Electrical Stimulation\$ OR Stimulation\$, Electrical OR Stimulation\$, Electric OR Electric Stimulation\$ OR Electric Stimulation Therapy OR Therapeutic Electric Stimulation OR Electric Stimulation, Therapeutic OR Stimulation, Therapeutic Electric OR Therapy, Electric Stimulation OR Stimulation Therapy, Electric OR Electrotherapy OR Transcutaneous Electric\$ Nerve Stimulation OR Electrical Stimulation, Transcutaneous OR Stimulation, Transcutaneous Electrical OR Transcutaneous Electrical Stimulation OR Percutaneous Electric\$ Nerve Stimulation OR Transdermal Electrostimulation OR Electrostimulation, Transdermal OR Transcutaneous Nerve Stimulation OR Nerve Stimulation, Transcutaneous OR Stimulation, Transcutaneous Nerve OR Electric Stimulation, Transcutaneous OR Stimulation, Transcutaneous Electric OR Transcutaneous Electric Stimulation OR TENS OR Electroanalgesia OR Analgesic Cutaneous Electrostimulation OR Cutaneous Electrostimulation, Analgesic OR Electrostimulation, Analgesic Cutaneous OR Electromagnetic Fields OR Electromagnetic Field OR Field, Electromagnetic OR Fields, Electromagnetic
#3	Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]
#4	#1 AND #2 AND #3

## Eligibility criteria

We included RCTs that evaluated electrical stimulation (TENS, HF, FREMS, or PENS) or electromagnetic fields in the treatment of PDN. We included studies that compared electrical stimulation or electromagnetic fields with placebo in which the objective was to assess pain and sensitivity. In all studies, the placebo consisted of no electric current transmission or no exposure to magnetic fields. We only included studies that applied electrical stimulation to the lower and upper extremities. The exclusion criteria were the following: (1) the inclusion of subjects other than PDN patients; (2) an unreliable description of what was considered PDN; and (3) lack of control group data description.

## Study selection and data extraction

The titles and abstracts of all articles identified using the search strategy were evaluated by two investigators (C.S. and B.E.) in duplicate. All abstracts that did not provide enough information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full-text articles and made their selection in accordance with the eligibility criteria. Disagreements between the reviewers were solved by consensus. The main outcome extracted was pain relief. Other outcomes of interest were sensitivity and the length of treatment.

## Assessment of risk of bias

The major quality issues assessed were the following: adequate sequence generation, allocation concealment, blinding, blinding assessors, description of losses and exclusions and intention-to-treat analysis. Studies without a clear description of the use of intention-to-treat analysis were considered not to have fulfilled this criterion.

The lack of a description of how the allocation list was concealed was judged as an absence of allocation concealment. The only possible blinding in this type of study was outcomes assessment. Studies in which there was no description of this type of blinding were judged to be open. This appraisal was independently performed by two reviewers.

## Data analysis

Pooled-effect estimates were obtained by comparing the least square mean percentage change from baseline to study end for each group. Regarding continuous outcomes, if the unit of measurement was consistent across trials, the results were presented as

the weighted mean difference with 95% confidence intervals (CIs), and if the unit of measurement was inconsistent, the results were expressed as the standard mean difference with 95% CIs<sup>25</sup>. Calculations were performed using a random-effects method. An  $\alpha$  value  $\leq 0.05$  was considered statistically significant. The statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the inconsistency  $I^2$  test, in which values above 25% and 50% were considered indicative of moderate and high heterogeneity, respectively<sup>28</sup>. All analyses were conducted using Review Manager, version 5.0. A sensitivity analysis was carried out considering the statistical heterogeneity and the duration of the intervention studies.

## Results

### Description of studies

The search strategy yielded 1336 abstracts, of which 14 studies were considered as potentially relevant and retrieved for detailed analysis. However, only 12 studies with a total of 817 patients with PDN met the eligibility criteria for the systematic review. Figure 1 shows the flow diagram of the studies included in this review, and Table 2 summarizes the characteristics of these studies.

Five trials<sup>11-15</sup> compared TENS to placebo (total  $n=132$ , of which 75 were on TENS), one trial<sup>22</sup> compared TENS to HF (total  $n=41$ , of which 21 were on TENS), one trial<sup>23</sup> compared FREMS to placebo (total  $n=62$ , of which 31 were on FREMS), one trial<sup>24</sup> compared PENS to placebo (total  $n=50$ , of which 25 were on PENS), and four trials<sup>18-21</sup> compared electromagnetic field to placebo (total  $n=532$ , of which 268 were on electromagnetic field).

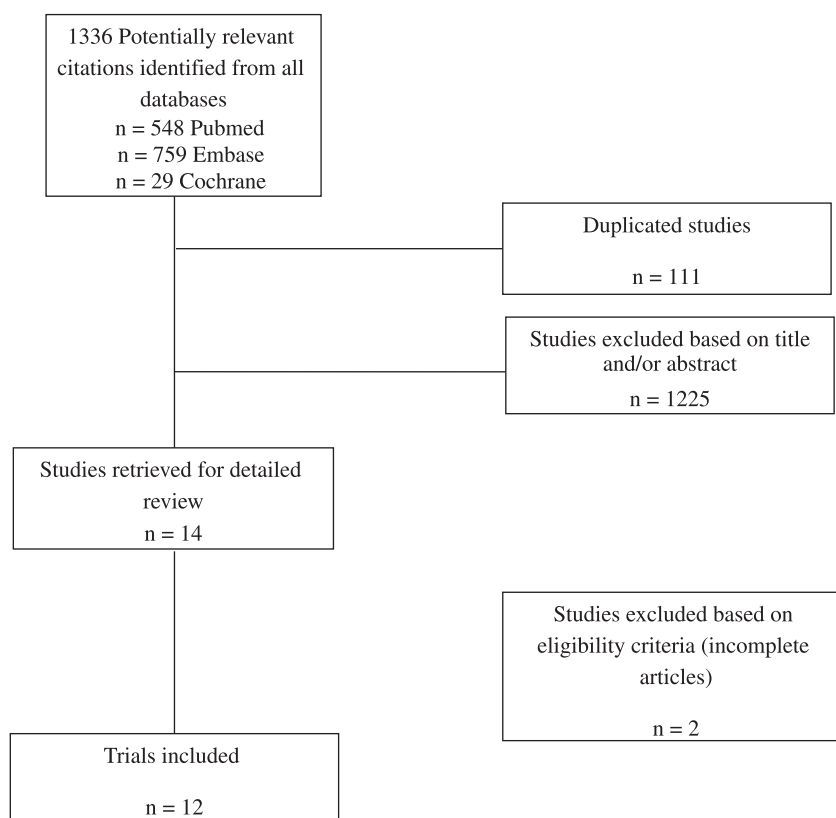
### Risk of bias

The included studies showed 58% adequate sequence generation and 0% allocation concealment, and 50% were blinded, 33% had blinded assessors, 50% presented a description of loss and exclusions, 17% had an intention-to-treat analysis, and 83% had no intention-to-treat analysis.

### Effects of interventions

#### Pain

Of the included articles, five studies used TENS versus placebo, four used electromagnetic field versus placebo, one study compared TENS versus HF, one



**Figure 1.** The flow diagram of studies included in the review.

study compared FREMS versus placebo, and two studies compared PENS versus placebo.

### ***Transcutaneous electric nerve stimulation versus placebo***

There was pain improvement in the articles that compared TENS versus placebo<sup>11-15</sup> [ $-0.44$  (95% CI:  $-0.79$  to  $-0.09$ ; I<sup>2</sup>: 0%,  $p=0.01$ )] (Figure 2A).

#### **Treatment duration**

In a sub-analysis of studies on TENS in patients with PND at different treatment durations, four studies<sup>11,13-15</sup> involved treatment for two, four and six weeks, which resulted in improvement in pain relief compared to placebo [ $-0.54$  (95% CI:  $-1.02$  to  $-0.06$ ; I<sup>2</sup>: 26%,  $p = 0.03$ )] (Figure 2A).

Two other studies<sup>12,13</sup> involved 12 weeks of treatment with TENS compared to placebo and showed no significant reduction in pain [ $-0.47$  (95% CI:  $-1.10$  to  $0.16$ ; I<sup>2</sup>: 0%,  $p=0.14$ )] (Figure 2A).

### ***Electromagnetic field versus placebo***

Of the articles comparing electromagnetic field use versus placebo group, one showed no significant

improvement in pain relief [ $-0.69$  (95% CI:  $-1.86$  to  $0.48$ ; I<sup>2</sup>: 63%,  $p=0.25$ )] (Figure 2B)<sup>18-21</sup>.

### ***Transcutaneous electric nerve stimulation versus HF***

A meta-analysis could not be performed, as there was only one included study that compared TENS versus HF. This study<sup>22</sup> showed that HF was more effective than TENS in relieving pain in patients with PDN (80% versus 33%,  $p<0.05$ ).

### ***Frequency-modulated electromagnetic neural stimulation versus placebo***

The study<sup>23</sup> demonstrated a decrease in pain before and after treatment with FREMS in the day-time pain score ( $37.1\pm5.3$  to  $26.2\pm3.9$ ,  $p=0.0025$ ) and night-time pain score ( $38.1\pm5.5$  to  $28.5\pm3.8$ ,  $p=0.0107$ ) compared with placebo [ $(31.2\pm3.9$  to  $31.9\pm4.2$ , NS) and  $(33.3\pm3.8$  to  $30.4\pm4.2$ , NS), respectively].

### ***Percutaneous electrical nerve stimulation versus placebo***

The study<sup>24</sup> showed a reduction in pain when the periods before and after treatment with PENS

**Table 2.** Characteristics of the included studies.

Study, year	Methods	Patients (n)	Age, years [(mean ± SD) or mean (range)]	Male gender (n)	Features
<b>TENS versus placebo</b>					
Cheing and Luk <sup>14</sup>	TENS group vs Placebo group	10 / 9	32±11 / 38±13	8 / 8	<b>TENS group:</b> Pulse= 200 µs; frequency= 100 Hz; the intensity was adjusted to produce a tingling sensation that was strong but tolerable. <b>Placebo group:</b> No active treatment. - Both groups received 10 20 min sessions for two consecutive weeks in the hands.
Forst et al. <sup>13</sup>	TENS group vs Placebo group	12 / 7	57.6±11.5 / 59.4±8.6	6 / 4	<b>TENS group:</b> Pulse= 280 µs; frequency= 4 Hz; individual intensity between 5-70 mA. <b>Placebo group:</b> No active treatment. - Both groups received 60 min sessions daily for 12 weeks in the peroneal nerve.
Gossrau et al. <sup>15</sup>	TENS group vs Placebo group	21/19	67.91±12.13/ 65.95±7.05	*	<b>TENS group:</b> Pulse= 30 - 40 µs; frequency= 2 Hz. <b>Placebo group:</b> No active treatment. - Both groups received 30 min sessions for 4 weeks with three visits each week in the proximal dorsum pedis and on top of the caput fibulae on both legs.
Kumar et al. <sup>12</sup>	TENS group vs Placebo group	14 / 9	59±7.5 / 58±12	4 / 6	<b>TENS group:</b> Pulse= 400 µs, intensity= ≤ 35 mA; frequency= 2-70 Hz. <b>Placebo group:</b> No active treatment. - Both groups received 30 min sessions daily for 12 weeks at home in both lower extremities. * All patients were treated with amitriptyline for 20 weeks before electrotherapy.
Kumar and Marshall <sup>11</sup>	TENS group vs Placebo group	18 / 13	53±17 / 59±11	7 / 5	<b>TENS group:</b> Pulse= 400 µs, intensity= ≤ 35 mA; frequency= 2-70 Hz; <b>Placebo group:</b> No active treatment. - Both groups received 30 min sessions daily for 4 weeks at home in both lower extremities.

\*Trial did not report the number of males; \*\* Trials did not report a separate number of male subjects for EE versus placebo; \*\*\* These values refer to the initial number of subjects (treatment group=141 and sham group=118); TENS: transcutaneous electrical nerve stimulation; HF: high-frequency external muscle stimulation; FREMS: frequency-modulated electromagnetic neural stimulation; PENS: percutaneous electrical nerve stimulation; PEMF: pulsed electromagnetic fields; / EE vs control group.



Table 2. Continued...

Study, year	Methods	Patients (n)	Age, years [(mean ± SD) or mean (range)]	Male gender (n)	Features
<b>TENS versus HF</b>					
Reichstein et al. <sup>22</sup>	TENS group vs HF group	21 / 20	57.8±12.5 / 64.2±12.7	10 / 12	<b>TENS group:</b> Pulse= 400 µs; frequency= 180 Hz; voltage= ≤35 V; Intensity was adjusted according to the patient and ranged from 20 to 30 mA. <b>HF group:</b> Pulse= ≤ 350 mA, voltage= ≤ 70 V, frequency= 4096 Hz, which was increased to 32768 Hz within 3 s; the maximum frequency was used for 3 s and then down-modulated from 32768 to 4096 Hz. Intensity was adjusted to a pleasant level that did not produce any pain or uncomfortable paresthesia. - Both groups received 30 min sessions daily for three consecutive days in both lower extremities.
<b>FREMS versus placebo</b>					
Bosi et al. <sup>23</sup>	FREMS group vs Placebo group	31/31	63.1±3.1 / 59.2±3.1	*	<b>FREMS group:</b> Pulse= 10 – 40 µs; frequency= 1 - 50 Hz, peak amplitude variable from 0 – 255 V. <b>Placebo group:</b> No active treatment. - Both groups received 10/30 min sessions for three consecutive weeks in the lower extremities.
<b>PENS versus placebo</b>					
Hamza et al. <sup>24</sup>	PENS group vs Placebo group	25 / 25	56±8 / 54±9	22**	<b>PENS group:</b> Pulse= 500 µs; voltage= 25 mA; frequency= 15 and 30 Hz. Intensity was adjusted to the highest tolerable level without producing muscle contractions. <b>Placebo group:</b> needles only. - Both groups received 30 min sessions 3 times per week for 3 consecutive weeks in the leg and foot bilaterally.

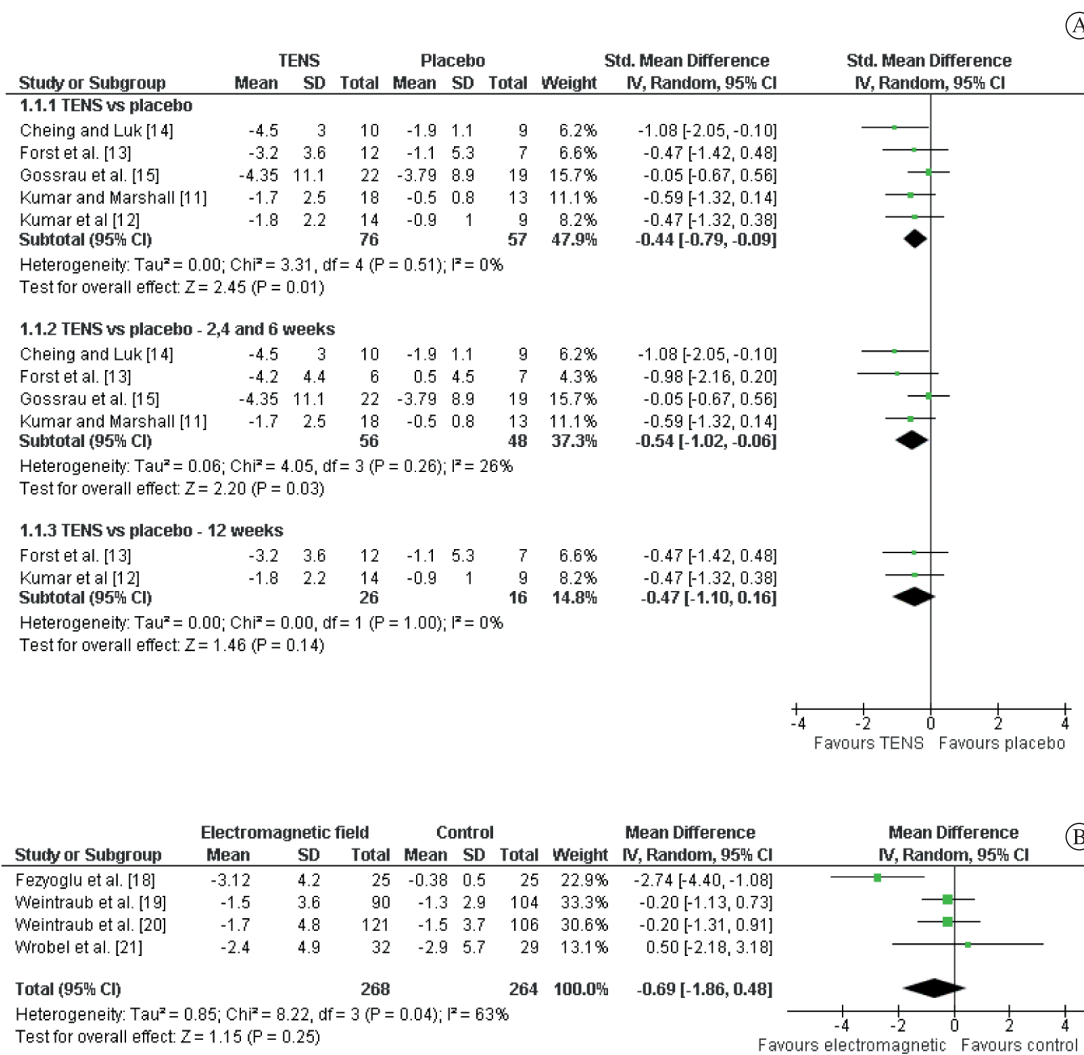
\*Trial did not report the number of males; \*\* Trials did not report a separate number of male subjects for EE versus placebo; \*\*\* These values refer to the initial number of subjects (treatment group=141 and sham group=118); TENS: transcutaneous electrical nerve stimulation; HF: high-frequency external muscle stimulation; FREMS: frequency-modulated electromagnetic neural stimulation; PENS: percutaneous electrical nerve stimulation; PEMF: pulsed electromagnetic fields; / EE vs control group.

Table 2. Continued...

Study, year	Methods	Patients (n)	Age, years [(mean $\pm$ SD) or mean (range)]	Male gender (n)	Features
<b>Electromagnetic fields versus placebo</b>					
Fezyoglu et al. <sup>18</sup>	Pulsed electromagnetic field group vs Placebo group	25/25	59.08 $\pm$ 8.81/ 62.08 $\pm$ 9.04	15/13	<p><b>Pulsed electromagnetic field group:</b> PEMF (BTL Benesov, Czech Republic, the AC input 230 V/50-60 Hz, 2x Fuse T6.3A, input power: 600 VA) Magnet Therapy device was used.</p> <p><b>Placebo group:</b> identical in all characteristics except for the demagnetization procedure.</p> <p>-Both groups used the device for one hour per day for 10 days in the foot bilaterally.</p>
Weintraub et al. <sup>20</sup>	Static magnetic field group vs Placebo group	121/106	62.6 $\pm$ 11.3*** / 63.2 $\pm$ 11.2***	75/60***	<p><b>Static magnetic field group:</b> The strength of the magnetic field was 450 G, as measured with a conventional gauss meter on the surface of the insoles at the center of the triangle (10000 G=1T).</p> <p><b>Placebo group:</b> unmagnetized device.</p> <p>-Both groups used the device for 24 hours per day for 16 weeks in the foot bilaterally.</p>
Weintraub et al. <sup>19</sup>	Low-frequency pulsed magnetic field group vs Placebo group	90 / 104	61.1 $\pm$ 10.4 / 60.6 $\pm$ 12.4	43.3% / 44.2%	<p><b>Low-frequency pulsed magnetic field group:</b> 6 individual (1800 G) magnetic sphere units, 3 under each foot, that were driven individually by a 6 V DC motor. A speed control circuit allowed a range of 500 to 1500 revolutions per minute. Supersaturation of the target area from every angle at 25 times per second at maximum 1500 revolutions per minute was achieved.</p> <p><b>Placebo group:</b> identical in all characteristics except for the demagnetization procedure</p> <p>-Both groups received 2 hours per day in divided sessions of 10 to 30 min for 12 weeks in the foot bilaterally.</p>
Wróbel et al. <sup>21</sup>	Low-frequency pulsed magnetic field group vs Placebo group	32 / 29	53.6 $\pm$ 13.6 / 55.5 $\pm$ 10.4	12 / 13	<p><b>Low-frequency pulsed magnetic field group:</b> The electromagnetic waves generated by the Viofor JPS were a complex sequence of pulses at a frequency of approximately 180-195 Hz, with a low-frequency pulsed magnetic field of up to 100 <math>\mu</math>T. The electrical field intensity was approximately 130 V/m.</p> <p><b>Placebo Group:</b> No active treatment</p> <p>-Both groups received 20 min sessions five times per week for 3 consecutive weeks in the trunk and lower limbs.</p>

\*Trial did not report the number of males; \*\* Trials did not report a separate number of male subjects for EE versus placebo; \*\*\* These values refer to the initial number of subjects (treatment group=141 and sham group=118); TENS: transcutaneous electrical nerve stimulation; HF: high-frequency external muscle stimulation; FREMS: frequency-modulated electromagnetic neural stimulation; PENS: percutaneous electrical nerve stimulation; PEMF: pulsed electromagnetic fields; / EE vs control group.





**Figure 2.** A) The mean weighted difference and 95% confidence interval (CI) in pain for treatment with transcutaneous electrical nerve stimulation (TENS) versus placebo. B) The mean weighted difference and 95% CI in pain for treatment with the electromagnetic field versus control.

were compared ( $6.2\pm1.0$  to  $2.5\pm0.8$ ,  $p<0.05$ ). This reduction did not occur in the placebo group ( $6.4\pm0.9$  to  $6.3\pm1.1$ , NS).

**Sensitivity**

Of the included articles, two studies used TENS versus placebo, and another study compared FREMS versus placebo.

**Transcutaneous electric nerve stimulation versus placebo**

Two studies assessed sensitivity in patients with diabetic neuropathy. One study<sup>14</sup> evaluated sensitivity using 10 different textures and showed an improvement in sensitivity compared with the

placebo group on the 7th day ( $8.0\pm2.6$  versus  $5.5\pm1.8$ ,  $p=0.005$ ) and 11th day ( $9.3\pm3.0$  versus  $6.6\pm1.9$ ,  $p=0.006$ ) of treatment with TENS.

The other study<sup>13</sup> evaluated the effectiveness of TENS at the threshold of sensory nerves in the lower limb compared to the control group. Although there were no significant changes in either group, there was a tendency toward an improvement in the sensitivity to heat and cold and the heat pain perception threshold in the TENS group.

**Frequency-modulated electromagnetic neural stimulation versus placebo**

The study<sup>23</sup> evaluated changes in sensitivity to monofilament and vibration perception thresholds

before and after FREMS. The authors observed a decrease in the number of points that were insensitive to the Semmes-Weinstein monofilament ( $5.8 \pm 0.8$  to  $4.6 \pm 0.9$ ,  $p < 0.0077$ ) and a decrease in the vibration perception threshold ( $35.5 \pm 1.6$  to  $33.4 \pm 1.6$ ,  $p < 0.0001$ ). None of the outcome measures changed significantly during treatment with placebo.

## • Discussion

### Summary of evidence

We conducted this study to evaluate the evidence available on the effectiveness of electrical stimulation and electromagnetic stimulation in patients with diabetic neuropathy. The results show that electrical stimulation applied using TENS was an adjunct treatment option that provides an improvement in pain relief in patients with PND. However, electromagnetic stimulation showed no effect on pain relief.

The use of electrical stimulation in patients with diabetic neuropathy has been proposed as an alternative non-pharmacological treatment<sup>9</sup>. The effects of TENS may be explained by the production of endogenous opioids and gate control mechanisms. Several studies have demonstrated that low-frequency TENS increases the release of endogenous opioids, which have modulatory effects on the nucleus of the solitary tract (NTS) and, consequently, on the central nervous pathway of cardiovascular control<sup>29,30</sup>.

In contrast, some authors report that high-frequency TENS acts by stimulating large-diameter afferent fibers, inhibiting second-order neurons in the dorsal horn and preventing impulses carried by small-diameter fibers from being transmitted<sup>31</sup>. This theory proposes that unmyelinated C fibers and thinly myelinated A- $\delta$  fibers transmit information to the spinal cord, resulting in reflex sympathetic vasoconstrictor stimulation. Its effects are associated with one primary mechanism in which this electrical current produces pain relief, the “gate control theory”<sup>32</sup>. More recent literature has shown that both low- and high-frequency TENS reduces pain through the activation of opioids receptors. Low-frequency TENS activates mu opioid receptors, and high-frequency TENS activates delta opioid receptors<sup>33</sup>.

However, the effects of electromagnetic stimulation result from interruptions in the direct or indirect activation of afferent signals from fiber type C to the distal part of the axon, which produces an antinociceptive effect<sup>20</sup>.

Our study also showed that TENS treatment provided an improvement in pain relief at different times of treatment and a decrease in the hypersensitivity of the hands of patients compared to placebo<sup>14</sup> and improvement in the threshold of sensory nerves of the lower limbs compared to placebo<sup>13</sup>. Additionally, we observed that FREMS induced an increase in sensory tactile perception, as assessed with a monofilament, and a decrease in the foot vibration perception threshold. The pain in these patients most likely occurs due to central sensitization of spinal nociceptive neurons induced by ectopic activity in injured fibers<sup>34</sup>. The ongoing peripheral neural activities may enhance the release of neurotransmitters in the spinal cord, which may cause hyperexcitable responses to subsequently evoked stimuli<sup>34</sup>. Most likely due to the above-mentioned action mechanisms, chronically applied TENS acts throughout this process by reducing the symptoms related to pain.

### Strengths and limitations of the review

The studies included in this review are of limited methodological quality and show some biases that weaken the power of the information. Eight studies properly described the generation of a random sequence<sup>13,14,18,19,20,22,23</sup>.

No study clearly described allocation concealment. Only six studies were blinded<sup>12,13,19,20,21,23</sup>, and only four studies described the blinding of the assessors<sup>19,20,21,23</sup>. In addition, six studies reported losses and exclusions that occurred during the treatment period<sup>11,12,14,21,23,24</sup>. Two studies<sup>13,20</sup> reported the analysis by intention to treat.

Therefore, the sensitivity analyses were hampered by a lack of methodological quality of the included studies and the small number of studies and participants.

A meta-analysis of all the articles included in this systematic review could not be performed due to the different types of electrical stimulation applied and the different methods used to assess pain and evaluate sensitivity. Moreover, three studies<sup>13,14,23</sup> assessed the sensitivity of different techniques.

In the meta-analysis of TENS versus placebo, four studies<sup>11-13,15</sup> applied TENS to the lower limbs, and only one study applied it to the upper limbs 14 and demonstrated improvement in pain sensation. Despite the structural and functional differences of the upper and lower limbs, diabetic neuropathy manifests in the extremities (“boot” and “glove”) due to the involvement of peripheral nerves, which explains the application of TENS in these regions. In one study<sup>12</sup>,

it was found that treatment with amitriptyline for 20 weeks before the electrical stimulation may also affect the outcome.

However, in the meta-analysis of studies involving TENS versus placebo, the criteria for pain assessment were different. Two studies<sup>11,12</sup> rated the level of pain and discomfort on a scale of 0 to 5 and included questions intended to provide a description of the symptoms, paresthesias, intensity and frequency of pain, sleep disturbance in relation to neuropathic pain and functional impairment, while three other studies<sup>13-15</sup> assessed pain using a visual analog scale from 0 (no pain) to 10 (unbearable pain). For the analysis of data, information relating to the scales of pain was normalized, and despite the different instruments used for the purpose of evaluation in the studies, there was no heterogeneity.

In the meta-analysis of electromagnetic stimulation versus placebo, there was no significant improvement in pain relief for patients who received electromagnetic stimulation. This can be explained by the methodological differences between the included studies in terms of the parameters of magnetic fields used (exposure profile). The devices used to generate the magnetic fields were different between studies, as one study assessed the exposure to a pulsed electromagnetic field<sup>18</sup>, another study assessed exposure to a static magnetic field<sup>20</sup>, and two studies assessed low-frequency pulsed magnetic exposure<sup>19,21</sup>. Regarding exposure duration, one study performed less exposure<sup>21</sup>, and two studies had shorter total exposure times<sup>18,21</sup>. In addition, two studies had a small number of patients<sup>18,21</sup>.

In the sub-analysis of treatment duration, two articles<sup>12,13</sup> evaluated pain after 12 weeks of treatment and found no significant improvement. This can be explained by the small number of studies included in the sub-analysis and the insufficiency of the sample size to demonstrate efficacy.

### Comparison with other studies

Recently, Jin et al.<sup>35</sup> published a meta-analysis of randomized controlled studies with the objective of evaluating the effectiveness of TENS in peripheral diabetic neuropathy. This article included only three studies involving a total of 78 patients, and the authors concluded that TENS may be safe and effective in treating the symptoms of diabetic neuropathy. Although the above study answers one of our research questions, it differs from ours in that it does not include other types of electrical stimulation or electromagnetic stimulation and in the small number of studies included.

## ● Conclusions

In conclusion, transcutaneous electric nerve stimulation therapy may be an effective and safe strategy for the treatment of symptomatic diabetic neuropathy. By contrast, there was no improvement with the use of electromagnetic fields. Due to the methodological differences between the included studies, it was not possible to perform a meta-analysis of the outcome of sensitivity. The limited number of studies involving electrical stimulation and electromagnetic stimulation, the different treatments studied, the different parameters used and the low quality of included studies demonstrate the need for further randomized clinical trials designed with greater methodological rigor to establish the true efficacy of these therapies in diabetic neuropathy.

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