Effectiveness of Percutaneous Electrical Nerve Stimulation for Musculoskeletal Pain: A Systematic Review and Meta-analysis

Authors

Gustavo Plaza-Manzano[1,2] PT, PhD; Guido F Gómez-Chiguano[3] PT, MSc; Joshua A Cleland[4,5,6] PT, PhD; Jose L Arías-Buría[7,8] PT, PhD; César Fernández-de-las-Peñas[7,8] PT, PhD; Marcos J. Navarro-Santana[9] PT; MSc

Affiliations

1 Department of Radiology, Rehabilitation and Physiotherapy, Universidad Complutense de Madrid, Madrid, Spain

2 Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, Madrid, Spain

3 Clínica Dinamia Fisioterapia. Madrid, Spain.

4 Department of Physical Therapy, Franklin Pierce University, Manchester, NH, USA.

5 Physical Therapist, Rehabilitation Services, Concord Hospital, NH, USA.

6 Faculty, Manual Therapy Fellowship Program, Regis University, Denver, Colorado, USA.

7 Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Alcorcón, Madrid. Spain.

8 Cátedra Institucional en Docencia, Clínica e Investigación en Fisioterapia: Terapia Manual, Punción Seca y Ejercicio Terapéutico, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain.

9 Rehabilitación San Fernando, Madrid, Spain.

Corresponding / reprint requests author:

César Fernández de las Peñas Telephone number: + 34 91 488 88 84

Facultad de Ciencias de la Salud

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Universidad Rey Juan Carlos Fax number: +34 91 488 89 57
Avenida de Atenas s/n
28922 Alcorcón, Madrid, SPAIN
Email: cesarfdlp@yahoo.es / cesar.fernandez@urjc.es

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Significance

This meta-analysis investigating the effectiveness of PENS for the management of pain and related-disability in musculoskeletal pain conditions found that PENS could decrease level of pain intensity but not related-disability in musculoskeletal pain disorders.

Abstract

Background and Objective: To evaluate the effects of percutaneous electrical stimulation (PENS) alone or as an adjunct with other interventions on pain and related-disability in musculoskeletal pain conditions. **Databases and Data Treatment**: Search of MEDLINE, EMBASE, AMED, CINAHL, EBSCO, PubMed, PEDro, Cochrane Library, SCOPUS and Web of Science databases. Randomised controlled trials where at least one group received any form of PENS for musculoskeletal condition. Studies had to include humans and collect outcomes on pain and related-disability in musculoskeletal pain. Risk of bias was assessed by the Cochrane Guidelines, the quality of evidence by using the GRADE approach. Standardized mean differences (SMD) were calculated. **Results:** Sixteen studies were included and included heterogeneous musculoskeletal conditions with short or mid-term follow-ups. PENS alone had a large effect (SMD -1.22, 95%CI -1.66 to -0.79) on pain and a small effect (SMD -0.33, 95%CI -0.61 to -0.06) on related-disability at short-term as compared to sham. A moderate effect of PENS alone (SMD -0.71, 95%CI -1.23 to -0.19) on pain when compared to other interventions was observed. The inclusion of PENS with other interventions had a moderate effect for decreasing pain at short- (SMD -0.70, 95%CI -1.02 to -0.37) and mid-term (SMD -0.68, 95%CI -1.10 to -0.27). No effect at mid-term (SMD -0.21, 95%CI -0.52 to 0.10) on related-disability was seen. The risk of bias was generally low; but the heterogenicity of the results downgraded the level of evidence. **Conclusion:** There is low level of evidence suggesting the effects of PENS alone or in combination for pain, but not related-disability, in musculoskeletal pain.

Level of Evidence: Therapy, level 1a. **Registration number:** CRD42019131331

Key word: Percutaneous electrical stimulation, musculoskeletal pain, meta-analysis.

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1. Introduction

Musculoskeletal pain is a wide cause of disability and loss of quality of life that also has a large impact on health, economic, and social environments.(Bevan, 2015; Gaskin and Richard, 2012; Henschke et al., 2015) The economic expenditure associated with chronic pain in the United States of America is estimated in costs ranging from $261 to $300 billions.(Gaskin and Richard, 2012) In Europe, musculoskeletal pain disorders accounted for

53% of all work-related diseases and it is estimated it is responsible for 40-50% of the cost of all work-related health issues.(Bevan, 2015)

The application of electrical current for relieving musculoskeletal pain was first introduced to the medical community by Wall and Sweet.(Wall and Sweet, 1967) There are several forms of applying electrical current for chronic pain, being through skin the most common form, i.e., transcutaneous electrical nerve stimulation (TENS). Although the use of TENS for chronic pain is used worldwide, its effectiveness is not conclusive. (Resende et al., 2018) Another form of applying electrical current to treat musculoskeletal chronic pain is through a needle, i.e., percutaneous electrical stimulation (PENS). All forms of PENS are usually applied in a biphasic continuous waveform, at a low (2-5Hz) or high (80-100Hz) frequency with pulse duration ranging from 250 to 500 microseconds; however, several forms of application had been described depending on where the needles are inserted, e.g., dermatoma, muscle, or periosteal. We should differentiate between electrical stimulation intervention (PENS) and electroacupuncture, where the first inserts needles in different tissues following western medical clinical reasoning, the second one inserts the needles into acupoints following the Traditional Chinese Medicine reasoning. (Kawakita and Okada, 2006)

Several potential mechanisms have been associated with the application of PENS. For instance, stimulation of large-diameter myelinated afferent peripheral nerve fibers are triggered with the use of electrical current; therefore, PENS may decrease nociceptive signals to the central nervous system from small diameter pain fibers at the level of the spinal cord ("gate control theory").(Campbell and Taub, 1973) The application of electrical stimulation thougout a needle also brings potential effects on the activation of inhibition descending pathways of pain.(Botelho et al., 2018; Da Graca-Tarragó et al., 2016, 2019) These studies found that PENS produced an improvement in conditioned pain modulation, reduced motor-evoked potential, and increased intracortical inhibition, suggesting possible benefit in patients with central sensitization.(Botelho et al., 2018; Da Graca-Tarragó et al., 2016, 2019)

The use of PENS has been found to be effective at short-term in individuals with urology disorders, e.g., overactive bladder(Gaziev et al., 2013); however, its application usually consists of the implantation of the electrodes during the intervention period (days, weeks, months). A recent meta-analysis included PENS for the management of low back pain and found limited evidence for its application on this condition.(Nascimento et al., 2019) To date no meta-analysis has been conducted to determine the effects of PENS on different musculoskeletal pain conditions. Therefore, the current systematic review and meta-analysis

evaluates the effects of the application of PENS alone or as an adjunct to other intervention on pain and related-disability in individuals with musculoskeletal pain syndromes. A secondary objective of the meta-analysis was to examine the effects of PENS in a particular musculoskeletal pain condition.

2. Methods

This systematic review and metanalysis ddheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(Moher et al., 2009) The international Prospective Register of Systematic Reviews (PROSPERO) registration number is CRD42019131331.

2.1 Systematic Literature Search

Electronic literature searches were conducted on MEDLINE, EMBASE, AMED, CINAHL, PubMed, PEDro, Cochrane Library, SCOPUS and Web of Science from their inception to July 25, 2019. When searched databases allowed limits, searches were restricted to randomized clinical trials. We also screened the reference lists of the papers that were identified in the database searches. Bibliographical database search strategies were conducted with the assistance of an experienced health science librarian.

Population: Adults with musculoskeletal pain older than 18 years of age.

Intervention: Any form of percutaneous electrical stimulation (PENS). For this aim, the search strategy had to include one of these key words: *percutaneous electrical stimulation OR intramuscular electrical stimulation OR electrical dry needling OR percutaneous electrical nerve stimulation OR percutaneous TENS OR peripheral nerve stimulation*

Comparator: Acceptable comparators were any type of placebo, sham, or no intervention. For this aim, the search strategy included one of these key words: *sham OR placebo OR control OR no intervention*. In addition, we also included the comparison of PENS with another active intervention.

Outcomes: The primary outcome measure was pain OR related-disability OR function.

The search strategy for each database is available in **Appendix 1**

2.2 Selection Criteria

The systematic review included parallel or cross-over randomized clinical trials where at least one group received any form of PENS in a sample of patients with musculoskeletal pain conditions. We defined musculoskeletal pain when pain was non-specific, meaning that no medical underlying specific cause, e.g. infection, neoplasms, metastasis, osteoporosis, rheumatoid arthritis, fractures, inflammatory or neurological processes was detectable.

The specific inclusion criteria were 1, adults (>18 years old) with musculoskeletal pain; 2, one group receiving any type of PENS intervention; 3, an acceptable comparator with sham, placebo or control, or another active intervention; and 4, the primary outcome of the study should include pain intensity (e.g., as measured with a visual analogue scale or a numerical pain rate scale) or related-disability (e.g, as measured with a specific-disease questionaire). We excluded clinical trials including 1, electroacupuncture; 2, any form of PENS applied over the acupuncture points; and 3, pain related to neurological disorders (e.g., hemiplegia).

2.3 Screening, Selection Process and Data Extraction

Articles identified from different databases were independently reviewed by two authors. First, the duplicates were removed. Second, title and abstract of the articles were screened for eligibility. Third, a full-text read of potential eligible studies was conducted. Authors were required to achieve a consensus on included trials. In case of discrepancy between both reviewers, a third author participated in the process to reach the consensus and to decide whether the study should be included or not.

Data from each trial were extracted independently by 2 authors using a standardized form including study design, sample size, population, diagnosis, interventions, outcomes and follow-up period. Both authors had to achieve a consensus on each item on the data-extraction form. In disagreements occurred, a third author made the determination..

2.4 Assessment of Methodological Quality and Risk of Bias

Risk of bias and methodological quality of the included trials were independently assessed by 2 researchers using the Cochrane Risk of Bias (RoB) assessment tool(Higgins et al., 2011) and the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003) respectively.

The RoB tool includes the following bias domains: selection bias (randomization sequence generation, allocation concealment), performance bias (blinding participants, bliding therapists), detection bias (blinding outcome assessors), attrition bias (incomplete outcome data), reporting bias (source of funding bias/selecting outcome resporting), and

other bias (sample size) (Higgins et al., 2011). Each item was classified as low risk, high risk or unclear according to the Cochrane Collaboration's tool (Higgins et al., 2011).

The PEDro score assesses the following items: random allocation; concealed allocation; beeween-groups similarity at baseline; participant blinding; therapist blinding; assessor blinding; dropout; intention-to-treat statistical analysis; between-group statistical comparison; point measures and variability data. A trial was considered of low quality when PEDro score was less than 5 points. (Maher et al., 2003).

2.5 Level of evidence

To evaluate the quality of evidence for PENS intervention, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Schünemann et al. 2008). According to GRADE, the evidence level can be classsified as high (the authors are very confideny that the intervention effect is closed to the estimated effect), moderate (the authors are some confident that the intervention effect is probably closed to the estimated effect, but there is a possibility that it is substantially different), and low (the true intervention effect can be markedly different from the estimated effect).

The quality of the evidence was calculated depending on the presence of study limitations (RoB), indirectness of evidence, unexplained heterogeneity or inconsistency of the results, imprecision of results, and high probability of publication bias (Austin et al., 2014). The evidence level was classified as high when all items were negative; moderate when one item included serious risk; low when two-three items had serious risk or one-two items showing very serious risk; or very low when all items has serious risk or more than two items showed very serious risk. This classification process of the evidence level was also independently performed by two authors, with a third one in case of controversy.

2.6 Data Synthesis and Analysis

The meta-analysis was conducted using the Review Manager statistical software (RevMan version 5.3). Data synthesis was categorized by groups according to the specific musculokeletal pain condition or body area, e.g. neck, shoulder, knee. Additionally, we also analyzed multiple comparisons between 1, PENS alone vs. sham PENS or control; or, 2, PENS plus other physical intervention vs. other physical intervention alone. The meta-analysis was performed at short and mid-term, since no long-term data were avaible.

We extracted the sample size, means and standard deviations for each variable. When the trial reported only standard errors, they were converted to standard deviations. When necessary, the mean scores and standard deviations were estimated from graphs. The between-groups mean difference (MD) of trials was converted to standardized mean

difference (SMD), with their 95% confidence interval (CI) by dividing between-groups mean differences by the pooled standard deviation. A random-effects model was used to determine the overall effect size (SMD). An effect size (SMD) of 0.8 or greater was considered large, between 0.5 to 0.8 as moderate and between 0.2 to 0.5 as small. In general, P-values < 0.05 were considered statistically significant. The overall effect sizes and the calculation of the effect size on the intensity of pain and related-disability was obtained at short (<10 weeks) and mid (>10 weeks) follow-ups from baseline.

The heterogeneity of the studies was assessed using the I^2 statistic. The Cochrane group has established the following interpretation of the I^2 statistic: 0%-40% may not be relevant/important heterogeneity; 30%-60% suggests moderate heterogeneity, 50%-90% represents substantial heterogeneity, and 75-100% represents considerable heterogeneity. (Deeks and Higgins, 2017) Data were analyzed using the Review Manager 5.3 statistical software

3. Results

3.1 Study selection

The electronic searches identified 4,159 potential studies for review. After eliminating duplicates, a total of 1,699 studies remained. One thousand, six hundred and sixty-five (n=1,665) studies were excluded, based on examination of their titles/abstracts, leaving 34 articles for full-text analysis. Another 16 were excluded for the following reasons: no control group (Belderraín et al., 2009; White et al., 2000, 2001), Korean language (Byeon et al., 2003), not including individuals with musculoskeletal pain (Ahmed et al., 1998, 2000; Ghoname et al., 1999b; Hamza et al., 2000; Ilfeld and Grant, 2016; Kinfe et al., 2016; Li and Xu, 2017; Xiao-Hong Chen and Ji-Sheng Han, 1992), use of electro-acupuncture (He and Zhang, 2017; Hsieh and Lee, 2016), use of intramuscular needling interventions (Ga et al 2007), and use of a specific percutaneous neuromodulation therapy device (Kang et al 2007). Finally, a total of 19 studies (Botelho et al., 2018; Dunning et al., 2018b, 2018a; Elbadawy, 2017; Ghoname et al., 1999a, 1999c; Da Graca-Tarragó et al., 2016, 2019; Hamza et al., 1999; Leon-Hernandez et al., 2016; Medeiros et al., 2016; Pérez-Palomares et al., 2010; Sumen et al., 2015; Topuz et al., 2004; Weiner et al., 2003, 2007, 2008, 2013; Yokoyama et al., 2004) were included (**Figure 1).**

3.2 Study characteristics

The characteristics of the participants of the included studies are shown in **Table 1. Appendix 2** sumarizes the PENS parameters applied on each of the included trials.

3.3 Methodological Quality

The methodological quality score ranged from 3 to 9 (mean: 6.3, SD: 1.8) out of a maximum of 10 points, most studies were considered of high methodological quality (PEDro score ≥ 5 points), with the exception of three studies that were considered of poor quality. The most frequent biases were blinding of the therapists and patients. **Table 2** represents the details of the PEDro scale and the total score of each of the studies included.

3.4 Risk of Bias

The details of the risk of bias assessment of the included trials are displayed in **Table 3.** No included trial was able to blind therapists, 10 trials rated high risk of bias in the item of allocation concealment, and 17 in the item of blinding of participants. In general, the risk of bias of the trials included in the current meta-analysis was low, with the exception of allocation concealment and blinding of participants.

3.5 Effects of PENS alone vs. sham PENS on pain intensity at short-term

Table 4 summarizes principal findings of the included studies. The meta-analysis found that PENS alone exhibited a large effect (SMD -1.22, 95%CI -1.66 to -0.79, n=616, Z=5.51, P<0.001) on pain intensity at short-term with high heterogeneity (I^2=82%) when compare with sham. The subgroups (conditions) analysis showed high heterogeneity (I^2=84.4%) and significant differences (P=0.002). The low back pain subgroup showed significant differences (P<0.001) but high heterogeneity (I^2=84%), and knee osteoarthritis (P=0.001) and neck pain (P=0.002) also showed differences with no heterogeneity. The comparison between PENS with sham for changes in pain intensity at short-term is shown in **Figure 2.**

3.6 Effects of PENS alone vs. other interventions in the short-term

The results revealed that application of PENS alone has a significant effect (SMD -0.71, 95%CI -1.23 to -0.19, n=371, Z=2.66, P=0.008) on pain intensity and with high heterogeneity (I^2=80%) when compared to other interventions (**Figure 3**). The subgroups analysis according to the comparison intervention showed high heterogeneity (I^2=79.1%) and significant differences (P=0.008). Only PENS vs. TENS subgroup showed significant differences (P=0.003).

3.7 Effect of PENS plus other intervention on pain intensity at short-term

When comparing PENS plus other intervention to the same intervention alone, there was a moderate effect (SMD -0.70, 95% CI -1.02 to -0.37, n=730, Z=4.16, P<0.001, **Figure 4**) for decressing pain intensity at short-term but with high heterogeneity (I^2=75%). The subgroups (pain condition) analysis revealed moderate heterogeneity (I^2=30.2%) and non-

significant differences (P=0.23). Only heel pain and knee osteoarthritis subgroups exhibited significant differences (both, P<0.01).

3.8 Effect of PENS alone or in combination on pain intensity at mid-term

The meta-analysis showed that the inclusion of PENS has a moderate effect (SMD -0.68, 95% CI -1.10 to -0.27, n=988, Z=3.21, P=0.001) for decreasing pain intensity at mid-term with high heterogeneity (I^2=89%) when compared with the comparative group (**Figure 5**). The subgroups analysis according to the comparison intervention revealed high heterogeneity (I^2=56.1%) and significant difference (P=0.03). Only PENS plus other intervention subgroup showed significant differences (P=0.007) and large effect size (SMD -1.19, 95% CI -1.87 to -0.50), but with high heterogeneity (I^2=91%).

3.9 Effect of PENS alone or in combination on related-disability at short-term

We found that PENS had a significant small effect (SMD -0.33, 95%CI -0.61 to -0.06, n=738, Z=2.36, P=0.02) on related-disability at short-term with high heterogeneity (I^2=69%) when compared with the comparative group (**Figure 6**). The subgroup analysis according to the comparison intervention found low heterogeneity (I^2=31.4%) and non-significant differences (P=0.22): neither PENS group showed significant differences.

3.10 Effect of PENS alone or in combination on related-disability at mid-term

When comparing the use of PENS alone or its use with other intervention to a comparative group, there was no significant effect (SMD -0.21, 95%CI -0.52 to 0.10, n=568, Z=1.31, P=0.19) on related-disability at mid-term and with high heterogeneity (I^2=71%). The subgroup analysis according to the comparison intervention revealed a moderate heterogeneity (I^2=53.4%) and non-significant difference (P=0.12). Neither of the PENS subgroups shows significant differences (**Figure 7**).

3.11 Quality of evidence (GRADE)

Table 5 displayed the details of GRADE assessment showing RoB, inconsistency of the results, indirectness of evidence, imprecision of results, and high probability of publication bias. The evidence was downgraded mostly for the presence of risk at the level of heterogeneity (inconsistency) and the insufficient number of participants to meet the desired significance and power (imprecision). In fact, all significant comparisons (n= 12) showed low-quality level of evidence, whereas three non-significant comparisons presented moderate-quality level of evidence (**Table 5**).

4. Discussion

4.1 Effectiveness of PENS alone for musculoskeletal pain

The main objective of this systematic review and meta-analysis was to determine the effects of PENS therapy for the management of musculoskeletal pain conditions. The results show low evidence suggesting that PENS alone get a large effect compared to sham and a moderate effect when compared to other interventions for decreasing pain intensity at short-term. The combination of PENS with other interventions also had low evidence for a moderate effect for decreasing pain intensity than comparative intervention alone. No clear effects of PENS, either alone or in combination, on related-disability were observed.

This is the first systematic review and meta-analysis analyzing the impact of PENS, excluding electroacupuncture, on pain intensity and related-disability in musculoskeletal pain conditions. We found that PENS was more effective than sham-PENS on pain relief at short-term, but not mid-term. Most trials (77%) comparing the effects of PENS alone against sham intervention (Botelho et al., 2018; Ghoname et al., 1999a, 1999c; Da Graca-Tarragó et al., 2016; Hamza et al., 1999; Topuz et al., 2004; Weiner et al., 2007) reported statistically significant differences on pain. The most frequent comparators included sham interventions using needle placement in the same place as the real-PENS intervention but without the application of electrical current (Ghoname et al., 1999a, 1999c; Hamza et al., 1999; Weiner et al., 2007, 2008, 2013), one study used placebo-TENS as sham (Topuz et al., 2004) and the other two trials used electrodes in the same placement than the needle but without electrical current (Botelho et al., 2018; Da Graca-Tarragó et al., 2016). When analyzing the effects of PENS by musculoskeletal pain conditions, all were significant although low back pain was associated with heterogeneous results. Our positive findings related to knee osteoarthritis are in line with those reported by Chen et al. (2017a) who reported that electroacupuncture was effective for reducing pain intensity and improving function in this population. Current and previous results would provide evidence that the application of electrical current with needles, independently of the underlying model, can be effective for the management of musculoskeletal pain conditions. Nevertheless, it is relevant to consider that this positive effect was not seen at mid-term follow-up, probably because the potential clinical effect of the sham approach (i.e., dry needling, acupuncture) application without electrical current stimulation (Chen et al., 2017b). In fact, sham-interventions avoiding the potential effect of

the needle without electrical current (i.e., dry needling), for example, using sham-needles, are clearly needed.

In our metanalysis, we also find significant difference between PENS and other therapies; however, it is difficult to generalize this analysis, because the multiple and the different comparative interventions (i.e., exercise, TENS, manual therapy) used in a small number of studies. For instance, the comparison between the application of TENS and PENS was performed in only two studies (Topuz et al., 2004; Yokoyama et al., 2004) and there was a significant difference in favour of PENS. Our findings are similar to those by Wu et al (2018) who reported significant differences at short-term between the different modalities of percutaneous electrical stimulation (e.g., electroacupuncture or PENS) on pain relief but no differences at longer follow-ups or no effects in related-disability. Nevertheless, these authors only included two studies in the quantitative analysis; hence, their results should be considered with caution. Based on the current results, PENS may represent a potential therapeutic intervention for the treatment of musculoskeletal pain, but further studies are now required.

4.2 Combination of PENS with other interventions for musculoskeletal pain

This meta-analysis reported that combination of PENS with other interventions was more effective than the application of the comparative intervention alone; however, this assumption seems to be pain population dependent. For instance, adding PENS to other interventions for knee osteoarthritis (Dunning et al., 2018a; Elbadawy, 2017) or plantar heel pain (Dunning et al., 2018b) exhibited moderate effects for reducing pain and related-disability at short- and mid- follow-ups. This seems expected since a multimodal approach usually provide better outcomes in musculoskeletal pain conditions. On the other hand, adding PENS to other interventions for low back pain was not more effective than sham-PENS and the same intervention or the intervention alone (Weiner et al., 2008). It is important to consider the sham-PENS used in this study consisted of a dry needling intervention, an intervention that has also a potential clinical effect in pain and related-disability in individuals with low back pain. In fact, Weiner et al. (2008) did not find significant differences between sham-PENS, PENS, PENS plus exercise or sham-PENS plus exercise therapy, probably because exercise has strong clinical recommendation for the management of low back pain.(Foster et al., 2018) Nevertheless, according to the results of this study, if PENS produced a similar effect to exercise in this population, this intervention would represent a promising approach for low back pain. More studies are necessary to further determine this hypothesis.

4.3 Parameters of PENS for musculoskeletal pain

An important topic for discussion is the electrical parameters (frequency, duration, intensity, pulse width) and the needle placement of PENS, since they could influence the outcomes. Ghoname et al (1999c) found that a frequency of 15/30 Hz was more effective than low (4Hz) or high (100Hz) frequencies. Low frequency electric stimulation produces an activation of μ and δ opioid receptors, high frequency stimulates δ and k opioid receptors, whereas 2-15Hz seems to activate all type of receptors (μ, δ, and k). The activation of μ agonist are related with peripheral antinociceptive effect than δ and k agonists, explaining the effects of PENS.(Chen and Han, 1992; Santos et al., 2013; Sluka et al., 1999; Xiao-Hong Chen and Ji-Sheng Han, 1992). Santos et al. (2013) found a decrease of the hyperalgesia induced by peripheral injection of serotonin after application of low-frequency current, but not after high-frequency, supporting different underlying mechanisms depending on frequency of the electrical current. Similarly, Vance et al (2012) observed changes in the pressure sensitivity at the site of the injury with both low-frequency and high-frequency stimulation, but only high-frequency induced changes in pressure pain sensitivity in an area outside of the injury, suggesting that both frequencies produced changes in primary hyperalgesic areas, but high-frequency caused a reduction in secondary hyperalgesia. Different underlying mechanisms for analgesia depending on the frequency of the PENS could produce different clinical manifestations; therefore, personalized application of frequency of the electrical current should be adapted for specific pain populations.

Hamza et al (1999) found that longer applications (>15min) provided better clinical results than shorter applications (<15min), being 30min was the most appropriate duration for obtaining clinical benefits. The intensity of the electrical current is another critical parameter related to effectiveness (Sluka et al., 2013). The intensity of stimulation is associated to changes in pain sensitivity, since intensity should be increased during the treatment for improving the hypoalgesic effect and for preventing the analgesic tolerance (Sato et al., 2012). Similarly, increasing pulse amplitude improved hypoalgesic effects of TENS in healthy subjects,(Pantaleão et al., 2011) which could also be considerated during the PENS application to enhance clinical effects. A recent systematic review about PENS for myofascial pain concluded that the number and the frequency of treatments did not influence clinical oucomes; however, treatment duration could be a relevant factor for providing significant effects.(Ahmed et al., 2018)

Another important parameter is the needle placement. White et al (2000, 2001) compared local or remote needle insertion and electrode pairing patterns, observing that

needle placement alters the efficacy of PENS. In fact, needles can be placed in different tissues, e.g., nerve, muscles, bone, joint, during the application of PENS. For instance, Arias-Buría et al (2019) applied PENS targeting the radial nerve for a patient with refractory lateral elbow pain and obtained a quick resolution of the symptoms for a follow-up of 2 years. Most studies included in this review placed the needles over dermatomes, muscles or joint tissues, but not over neural tissues. Therefore, needle placement could be a relevant factor for effects of PENS depending on the underlying mechanisms in a particular pain condition.

4.4 Strengths and limitations of the current review

Although this is the first meta-analysis analyzing the effects of PENS, excluding electro-acupuncture, on pain and related-disability in musculoskeletal pain, the results should be analyzed according to the potential strengths and limitations. Strengths of the current meta-analysis include comprehensive literature search, methodological rigor, data extraction, rigorous statistical analysis, and the inclusion of randomized controlled trials of high quality in the quantitative analysis. Among the limitations, we recognized that the number of randomized controlled trials looking the effects of PENS on some particular musculoskeletal pain conditions was small, e.g., just only one trial for plantar heel pain. Additionally, not only the number of trials was small, they also evaluated the application of PENS in different ways, e.g., alone or combined with other interventions, or compared PENS vs. sham-PENS or PENS vs. other intervention. Another potential limitation is the inconsistency and imprecision of the results of some of the included trials; therefore, the results should be taken with caution at this stage. These limitations were considered when the GRADE analysis was performed, and thus, the evidence was clearly downgraded by heterogeneity and RoB. Third, no study reported long-term follow-up period, so it is not know the effects of PENS over 3-6 months. Finally, some statistical analyses were based on conversion for MD to SMD, which could should be considered with caution.

4.5 Clinical and research implications

Although the overall level of evidence was low, the application of PENS could potentially be beneficial in subgroups of patients with musculoskeletal pain conditions. Due to the low level of evidence and the heterogenicity on the application methods, there is a great uncertainty regarding the effectiveness of PENS for musculoskeletal pain. There is clear needed for well-designed randomized clinical trials examining the effects of PENS alone or in combination with other therapy interventions, particularly at long-term follow-up periods. Trials should be designed to compare the effects of real vs. sham-PENS to allow understanding of this type of treatment. In addition, trials examining the most appropriate

parameters (i.e., frequency, duration, intensity of the electrical current) and the anatomical locations should be now conducted to create reproducible results.

5. Conclusions

This meta-analysis found low-evidence supporting that application of PENS alone was effective to reduce pain intensity at short-, but not mid-, term when compared to sham-PENS and to other therapies in some pain conditions. The combination of PENS plus other intervention also showed low evidence level of more effectiveness than other interventions alone on pain at short and mid-terms. The effects of PENS, either alone or combined with other intervention, for related-disability was unclear. More high-quality trials are needed for further determine the clinical effects of PENS for musculoskeletal pain.

Conflict of Interest

There are no conflicts of interests declared by the authors. No funds were received.

Author contributions

All authors contributed to the study concept and design. GPM GGC and MNS conducted literature review and did main statistical analysis. All authors contributed to interpretation of data. CFdlP and JC contributed to drafting the paper. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

Legend of Figures

Figure 1: PRISMA Flow diagram

Figure 2: Comparison between the effects of PENS alone versus sham-intervention on pain intensity at short-term

Figure 3: Comparison between the effects of PENS alone versus other interventions on pain intensity at short-term

Figure 4: Comparison between the effects of PENS plus intervention versus intervention alone on pain intensity at short-term

Figure 5: Comparison between the effects of PENS alone versus comparable intervention on pain intensity at mid-term

Figure 6: Comparison between the effects of PENS alone versus comparable intervention on related-disability at short-term

Figure 7: Comparison between the effects of PENS alone versus comparable intervention on related-disability at mid-term

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Table 1. Participant characteristics of included studies

	Design	Group	Sample Size	Female (%)	Age (years)	Pain duration
Low Back Pain						
Ghoname et al. 1999	Crossover-RCT	G1,G2,G3,G4	60	31 (51.66%)	43 ± 1.9	>3 months
Ghoname et al. 1999	Crossover-RCT	G1,G2,G3,G4	68	38 (55.88%)	46 ± 21	>3 months
Hamza et al. 1999	Crossover-RCT	G1,G2,G3,G4	75	NR	47 ± 18	38 ± 13 months
Weiner et al. 2003	RCT	G1	17	11 (64.70%)	74.1 ± 4.6	10.6 ± 11.1 years
		G2	17	7 (41.17%)	73.5 ± 5.7	16.6 ± 16.4 years
Topuz et al. 2004	RCT	G1	12	11 (91.70%)	41.92 ± 7.7	16.81 ± 8.75 months
		G2	15	9 (60%)	45.2 ± 11.19	16.46 ± 9.78 months
		G3	15	11 (73.3%)	50.13 ± 11.97	20.53 ± 14.42 months
		G4	13	10 (76.90%)	37.92 ± 14.49	15.30 ± 13.28 months
Yokoyama et al. 2004	RCT	G1	18	11 (61.11%)	60 ± 12	15 ± 7months
		G2	17	9 (52.94%)	58 ± 14	15 ± 8 months
		G3	18	10 (55.55%)	59 ± 13	13 ± 6 months
Weiner et al. 2008	RCT	G1	47	26 (55.31%)	74 ± 5.6	10 years
		G2	45	23 (51.11%)	73.9 ± 5.2	9 years
		G3	48	25 (52.08%)	74.3 ± 6.4	7 years
		G4	44	24 (54.54%)	73.3 ± 6	5 years
Pérez-Palomares et al. 2010	RCT	G1	67	54(81.3%)	<40: 34,4%, 40-60: 45,3%	0-3 months: 15,6% 3-6 months: 25%

					<60: 20,3%	6-12 months: 15.6% >12months: 43.7%
		G2	68	44(67.20%)	<40: 50%, 40-60: 31% <60: 19%	0-3 months: 25,8% 3-6 months: 25.8% 6-12 months:10,3% >12months: 36.2%
Knee Osteoarthritis						
Weiner et al. 2007	RCT	G1	44	26	71.5 ± 5.6	7.6 ± 7.4 years
		G2	44	22 (50%)	71.4 ± 5.2	8.4 ± 7.4 years
Weiner et al. 2013	RCT	G1	63	8 (12.7%)	67.1 ± 8.9	5.7 ± 6.4 years
		G2	64	10 (15.6%)	65.8 ± 8.7	6.2 ± 6.8 years
		G3	63	9 (17.5%)	66.8 ± 10.4	7.2 ± 8.3 years
Da Graça Tarragó et al. 2016	RCT	G1	13	13 (100%)	62.15 ± 7.44	6.67 ± 1.59 years
		G2	13	13 (100%)	66.85 ± 7.53	6.49 ± 1.48 years
Elbadawy 2017	RCT	G1	30	20 (66.66%)	59.43 ± 4.17	11.08 ± 1.88
		G2	30	20 (66.66%)	59.93 ± 4.35	10.25 ± 2.16
Dunning et al. 2018	RCT	G1	121	56 (46.28%)	58.1 ± 13.1	4.6 ± 5.1 years
		G2	121	55 (45.45%)	57.1 ± 13.2	4.5 ± 4.7 years
Da Graça Tarragó et al. 2019	RCT	G1	15	15 (100%)	66 ± 9,08	NR
		G2	15	15 (100%)	64.14 ± 9.82	NR
		G3	15	15 (100%)	64.40 ± 6.02	NR
		G4	15	15 (100%)	63.87 ± 7.07	NR

Mechanical Neck Pain						
León-Hernández et al. 2016	RCT	G1	30	24 (77,4%)	23.32 ± 4.77	16.03 ± 17.23 months
		G2	29	22 (71%)	26.81 ± 9.63	19.36 ± 19.23 months
Sumen et al. 2015	RCT	G1	16	10 (62.5%)	41.6 ± 9.26	12.76 ± 9.9 months
		G2	15	11 (73.33%)	39 ± 11.65	14.13 ± 6.02 months
		G3	16	11 (68.75%)	35.26 ± 11.70	11.86 ± 12.20 months
Medeiros et al. 2016	RCT	G1	11	11 (100%)	49.18 ± 11.63	NR
		G2	12	12 (100%)	45.83 ± 9.63	NR
		G3	12	12 (100%)	47.25 ± 11.00	NR
		G4	11	11 (100%)	46.73 ± 13.09	NR
Botelho et al. 2018	RCT	G1	12	12 (100%)	46 ± 13.55	NR
		G2	12	12 (100%)	48.36 ± 10.97	NR
Plantar Heel Pain						
Dunning et al. 2018	RCT	G1	53	26 (49.05%)	42.6 ± 11.6	336.4 ± 288.8 days
		G2	58	21 (36.20%)	39.1 ± 10.4	386.1 ± 451.1 days

NR: Not reported; NA: Not applicable; RCT: Randomized clinical trial

Table 2. Score of randomized clinical trials with PEDro scale

	1	2	3	4	5	6	7	8	9	10	TOTAL
Low Back Pain											
Ghoname et al. 1999	Y	N	N	N	N	N	N	N	Y	Y	3
Ghoname et al. 1999	Y	N	N	N	Y	N	N	N	Y	Y	4
Hamza et al. 1999	Y	N	N	N	N	N	N	N	Y	Y	3
Weiner et al. 2003	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Topuz et al. 2004	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Yokoyama et al. 2004	Y	N	Y	N	N	N	Y	N	Y	Y	5
Weiner et al. 2008	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Pérez-Palomares et al. 2010	Y	N	Y	N	N	N	Y	N	Y	Y	5
Knee Osteoarthritis											
Weiner et al. 2007	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Weiner et al. 2013	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Da Graça Tarragó et al. 2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Elbadawy 2017	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Dunning et al. 2018	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Tarragó et al. 2019	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Mechanical Neck Pain											
León-Hernández et al. 2016	Y	N	Y	N	N	Y	N	N	Y	Y	5
Sumen et al. 2015	Y	N	Y	N	N	Y	N	N	Y	Y	5
Medeiros et al. 2016	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8

Botelho et al. 2018	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Plantar Heel Pain											
Dunning et al. 2018 [16]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7

1: Random Allocation of Participants; 2: Concealed Allocation; 3: Similarity Between Groups at Baseline; 4: Participant Blinding; 5: Therapist Blinding; 6: Assessor Blinding; 7: Fewer than 15% Dropouts; 8: Intention- to-Treat Analysis; 9: Between- Group Statistical Comparisons; 10: Point Measures and Variability Data.

Table 3: Assessment of risk of bias of the included studies

Study	Randomization Sequence Generation	Allocation concealment	Blinding of participants	Blinding of therapist	Blinding of assessor	Incomplete outcome data	Selective outcome reporting	Others
Low Back Pain								
Ghoname et al. 1999	Low	High	High	NA	Unclear	Low	Low	High
Ghoname et al. 1999	Low	High	High	NA	Low	Low	Low	High
Hamza et al. 1999	Low	High	High	NA	Unclear	Low	Low	High
Weiner et al. 2003	Low	High	High	NA	Low	Low	Low	Low
Topuz et al. 2004	Low	Low	High	NA	Unclear	Low	Low	Low
Yokoyama et al. 2004	Low	High	High	NA	Unclear	Low	Low	Low
Weiner et al. 2008	Low	High	High	NA	Low	Low	Low	Low
Pérez-Palomares et al. 2010	Low	High	High	NA	Unclear	Low	Low	Low
Knee Osteoarthritis								
Weiner et al. 2007	Low	High	High	NA	Low	Low	Low	Low
Weiner et al. 2013	Low	Low	High	NA	Low	Low	Low	Low
Da Graça Tarragó et al. 2016	Low	Low	Low	NA	Low	Low	Low	Low
Elbadawy 2017	Low	Low	High	NA	Low	Low	Low	Low
Dunning et al. 2018	Low	Low	High	NA	Low	Low	Low	Low
Tarragó et al. 2019	Low	Low	Low	NA	Low	Low	Low	Low
Mechanical Neck Pain								
León-Hernández et al. 2016	Low	High	High	NA	Low	Low	Low	Low

Sumen et al. 2015	Low	High	High	NA	Low	Low	Low	Low
Medeiros et al. 2016	Low	Low	High	NA	Low	Low	Low	Low
Botelho et al. 2018	Low	Low	High	NA	Low	Low	Low	Low
Plantar Heel Pain								
Dunning et al. 2018	Low	Low	High	NA	Unclear	Low	Low	Low

NA= Not Applicable

Table 4: Effects of PENS on pain and related-disability for musculoskeletal pain conditions

Study	Intervention(s)	Sample size	Intervention duration (sessions/weeks)	Comparison and outcome measure	Between-groups differences (95%CI) [SMD (95%CI)]
Low Back Pain					
Ghoname et al. 1999	G1: PENS	60		Pain intensity (VAS)	
(cross-over RCT)	G2: Sham-PENS	60	3 x 3 weeks	G1 vs G2	3wk: -2.10 (-2.70, -1.50) [-1.25]
	G3: TENS	60		G1 vs G3	3wk: -2.20 (-2.80, -1.60) [-1.31]
	G4: Exercise	60		G1 vs G4	3wk: -3.00 (-3.60, -2.40) [-1.79]
Ghoname et al. 1999	G1: Sham PENS	68		% of change in pain (VAS)	
(cross-over RCT)			3 x 2 weeks	G2 vs G1	2wk: -33.90 (-39.95, -27.85) [-1.87]
	G2: PENS 4Hz	68		G3 vs G1	2wk: -50.84 (-58.24, -43.44) [-2.29]
	G3: PENS 15/30Hz	68		G4 vs G1	2wk: -42.13 (-48.69, -35.57) [-2.15]
	G4: PENS 100Hz	68			
Hamza et al. 1999	G1: Sham PENS	75		% of change in pain (VAS)	
	G2: PENS 15min	75	3 x 3 weeks	G2 vs G1	3wk: -12.00 (-18.08, -5.92) [-0.63]
	G3: PENS 30 min	75		G3 vs G1	3wk: -35.00 (-41.08, -28.92) [-1.83]
	G4: PENS 45min	75		G4 vs G1	3wk. -31.00 (-37.08, -24.92) [-1.62]
Weiner et al. 2003	G1: PENS +	17		Pain intensity (McGill Pain Q)	
	physical therapy	17	2 x 6 weeks	G1 vs G2	6wk: -5.81 (-10.16, -1.46) [-0.88]
	G2: Sham PENS +				18wk: -5.63 (-9.73, -1.53) [-0.90]
	physical therapy			Disability (Roland-Morris)	
				G1 vs G2	6wk: -3.25 (-6.29, -0.21) [-0.70]

					18wk: -2.93 (-6.11, 0.25) [-0.60]
Topuz et al. 2004	G1: Placebo TENS	12		Current pain intensity (VAS)	
	G2: High Fr. TENS	15	5 x 2 weeks	G1 vs G4	2wk: -3.77 (-5.02, -2.52) [-2.25]
	G3: Low Fr. TENS	15		G2 vs G4	2wk: -0.81 (-2.37, 0.75) [-0.39]
	G4: PENS	13		G3 vs G4	2wk: -1.01 (-2.35, 0.33) [-0.57]
				Disability (Oswestry)	
				G1 vs G4	2wk: -11.69 (-14.92, -8.46) [-2.71]
				G2 vs G4	2wk: -2.93 (-6.84, 0.98) [-0.53]
				G3 vs G4	2wk: -1.80 (-5.21, 1.61) [-0.38]
Yokoyama et al. 2004	G1: PENS	18		Pain intensity (VAS)	
	G2: TENS	17	2 x 8 weeks	G1 vs G2	8wk: -1.60 (-2.33, -0.87) [-1.42]
	~~G3: PENS + TENS~~	18			12wk: -1.20 (-2.03, -0.37) [-0.94]
Weiner et al. 2008	G1: PENS	47		Intensity of pain, average pain	
	~~G2: PENS + Exercise~~	45		past week (pain thermometer)	
			2 x 6 weeks	G1 vs G4	6wk: -0.10 (-0.48, 0.2847) [-0.11]
	G3: Sham PENS	48			24wk: 0.00 (-0.45, 0.45) [0.00]
	G4: Sham PENS + Exercise	44		G1 vs G3	6wk: -0.10 (-0.47, 0.27) [-0.11]
					24wk: 0.10 (-0.34, 0.54) [0.09]
				G1 vs G2	6wk: 0.00 (-0.41, 0.41) [0.00]
					24wk: 0.10 (-0.35, 0.55) [0.09]
				G2 vs G4	6wk: -0.10 (-0.43, 0.23) [-0.12]

					24wk: -0.10 (-0.56, 0.36) [-0.09]
				Disability (Roland Morris)	
				G1 vs G4	6wk: 0.40 (-1.49, 2.29) [0.09]
					24wk: 0.70 (-1.27, 2.67) [0.15]
				G1 vs G3	6wk: 0.10 (-1.58, 1.78) [0.02]
					24wk:0.90 (-0.89, 2.69) [0.20]
				G1 vs G2	6wk: 0.00 (-1.86, 1.86) [0.00]
					24wk: 0.00 (-1.74, 1.74) [0.00]
				G2 vs G4	6wk: 0.40 (-1.53, 2.33) [0.09]
					24wk: 0.70 (-1.31, 2.71) [0.14]
Pérez-Palomares et al. 2010	G1: PENS	67		Pain intensity (VAS)	
	G2: Dry needling	68	3 x 3 weeks	G1 vs G2	3wk: 0.03 (-0.79, 0.85) [0.01]
				Disability (Oswestry)	Not data available to calculate the effect of size. Not significant between-groups differences were found.
				G1 vs G2	
Knee Osteoarthritis					
Weiner et al. 2007	G1: PENS	44		Pain (WOMAC Pain)	
				G1 vs G2	6wk: -1.87 (-3.33, -0.41) [-0.53]
			1 x 6 weeks		12wk: 0.35 (-1.29, 1.99) [0.09]
	G2: Sham PENS	44		Disability (Total WOMAC)	
				G1 vs G2	6wk: -3.91 (-8.50, 0.68) [-0.35]
					12wk: -1.25 (-6.15, 3.65) [0.11]

Weiner et al. 2013	G1: PENS and PENS boosters	57	1 x 10 weeks	Pain (WOMAC Pain)	
				G1 VS G2	10wk: 0.10 (-1.42, 1.62) [0.02]
	G2: PENS and Sham PENS boosters	58			36wk:-0.50 [-1.80, 0.80] [-0.14]
	G3: Sham PENS	61		G1 vs G3	10wk: -1.10 (-2.54, 0.34) [-0.27]
					36wk: -1.50 (-2.66, -0.34) [-0.47]
				G2 VS G3	10wk: -1.30 (-2.8, 0.1) [-0.32]
					36wk: -1.10 (-2.6, 0.32) [-0.27]
Da Graça Tarragó et al. 2016	G1: PENS	13	1 session	Pain intensity (VAS)	
	G2: Sham PENS	13		G1 vs G2	Immediate: -1.21 (-2.28, -0.14) [-0.84]
Elbadawy 2017	G1: PENS + home exercises	30	1 x 10 weeks	Pain intensity (VAS)	
				G1 vs G2	10wk: -1.48 (-1.94, -1.02) [-1.61]
	G2: TENS + Home exercises	30			34wk -2.26 (-2.66, -1.86) [-2.84]
				Disability (KOOS	
				G1 vs G2	10wk: -4.36 (-7.32, -1.40) [-0.74]
					34wk -5.14 (-8.17, -2.11) [-0.85]
Dunning et al. 2018	G1: Manual therapy + exercise	118	1-2 x 6 weeks	Pain (WOMAC Pain)	
				G2 vs G1	6wk: -2.10 [-2.88, -1.32] [-0.69]
					12wk: -3.1 (-3.9, -2.3) [-0.90]
	G2: PENS + Manual therapy + Exercise	117		Disability (WOMAC Total)	
				G2 vs G1	6wk: -10.4(-13.7, -7.1) [-0.76]
					12wk −13.9 (−17.4, −10.4) [-0.94]

Da Graça Tarragó et al. 2019	G1: PENS + Transcranial direct current	15	5 x 5 days	Pain intensity (VAS)	
				G1 vs G2	5days: -1.46 (-2.03, -0.89) [-1.80]
				G1 vs G3	5days: -1.30 (-2.72, 0.12) [-1.83]
	G2: Sham PENS + transcranial direct current	15		G1 vs G4	5days: -1.82 (-2.37, -1.27) [-2.32]
	G3: PENS + Sham Transcranial direct current	15			
	G4: Sham PENS + Sham transcranial direct current	15			

Mechanical Neck Pain					
León-Hernández et al. 2016	G1: Dry needling	30	1 session	Pain intensity (VAS)	
	G2: Dry needling plus PENS	29		G2 vs G1	Immediate: -1.82 (-3.11, -0.53) [-0.71]
					3days: 0.21 (-1.20, 1.62) [0.08]
				Disability (NDI)	
				G2 vs G1	3days: 1.70 (-1.70, 5.10) [0.25]
Sumen et al. 2015	G1: Low Laser Therapy + Stretching	16	5 x 2 weeks	Pain intensity (VAS)	
	G2: PENS + Stretching	15		G2 vs G1	2wk: -0.40 (-1.56, 0.76) [-0.24]
					6wk: -1.20 (-2.46, 0.06) [-0.66]
				G2 vs G3	2wk: -1.60 (-2.77, -0.43) [-0.95]

	G3Stretching	16			6wk: -2.87 (-3.88, -1.86) [-1.99]
				Disability (NDI)	
				G2 vs G1	2wk: 3.20 (-5.03, 11.43) [0.27]
					6wk: -2.20 (-11.97, 7.57) [-0.16]
				G2 vs G3	2wk: -1.54 (-10.29, 7.21) [-0.12]
					6wk: -6.40 (-15.14, 2.34) [-0.51]
Medeiros et al. 2016	G1: PENS + TMS	11		Pain intensity (VAS)	
	G2: Sham PENS + TMS	12	1 x 10 days	G1 vs G2	10days: 0.29 (-1.51, 2.09) [0.13]
	G3: PENS + Sham TMS	12		G1 vs G3	10days: -0.85 (-2.68, 0.98) [-0.36]
	G4: Sham PENS + Sham TMS	11		G1 vs G4	10days: -1.46 (-2.03, -0.89) [-1.80]
Botelho et al. 2018	G1: Sham PENS	12	10 sessions	Pain intensity (VAS)	
	G2: PENS	12		G1 vs G2	2wk: -1.20 (-1.84, -0.56) [-1.44]
					12wk: -1.41 (-3.40, 0.58) [-0.55]
Plantar Heel Pain					
Dunning et al. 2018	G1: Manual therapy + US + Exercise	53	1-2 x 4 weeks	Pain (first step morning)	
				G2 vs G1	4wk: -1.6 (-2.4, -0.8) [-0.74]
					12wk: -2.2 (-2.8, -1.6) [-1.36]
	G2: PENS + Manual therapy + US + Exercise	58		Disability (Foot Functional Index)	
				G2 vs G1	4wk: -6.5 (-12.1, -0.9) [0.43]
					12wk: -9.9 (-16.0, -3.8) [0.58]

G: Group included in the study; wk: weeks; PENS: Percutaneous electrical stimulation; TMS: Transcranial magnetic stimulation; WOMAC: Western Ontario and McMaster Universities Questionnaire; KOOS: Knee Injury and Osteoarthritis Outcome Score; VAS: Visual analogue scale; NDI: Neck Disability Index.

Table 5. GRADE Evidence profile for the effects of PENS on pain and related-disability for musculoskeletal pain

Number of studies	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Publication bias	Quality evidence	SMD [95%CI]
PENS Alone VS Sham PENS or Placebo on Pain Intensity (short-term: 0 -10 weeks)							
PENS alone VS Sham PENS* 9 trials (n=616)	No	Serious (I^2 82%)	No	No	Serious	Low	-1.22 [-1.66, -0.79]*
PENS alone VS Sham PENS Low Back Pain - 5 trials (n=360)	No	Serious (I^2 84%)	No	No	No	Low	-1.49 [-2.10, -0.88]*
PENS alone VS Sham PENS Knee Osteoarthritis* 3 trials (n=232)	No	No (I^2 0%)	No	Very serious	No	Low	-0.43 [-0.69, -0.17]*
PENS alone VS Sham PENS Mechanical Neck Pain* 1 trial (n=24)	No	No	No	Very serious	No	Low	-1.44 [-2.36, -0.53]*
PENS Alone VS Other Interventions on Pain Intensity (short-term: 0 -10 weeks)							
PENS alone VS other interventions 5 (N=371)*	No	Serious (I^2 80%)	Serious	No	No	Low	-0.71 [-1.23, -0.19]*
PENS alone VS TENS* 3 trials (n=115)	No	No (I^2 39%)	No	Very serious	No	Low	-0.93 [-1.44, -0.42]*
PENS alone VS Exercise 1 trial (n=91)	No	Very serious (I^2 92%)	No	Very serious	No	Low	-0.84 [-2.54, 0.85]
PENS alone VS Dry needling	No	No	No	Very serious	No	Low	0.01 [-0.33, 0.35]

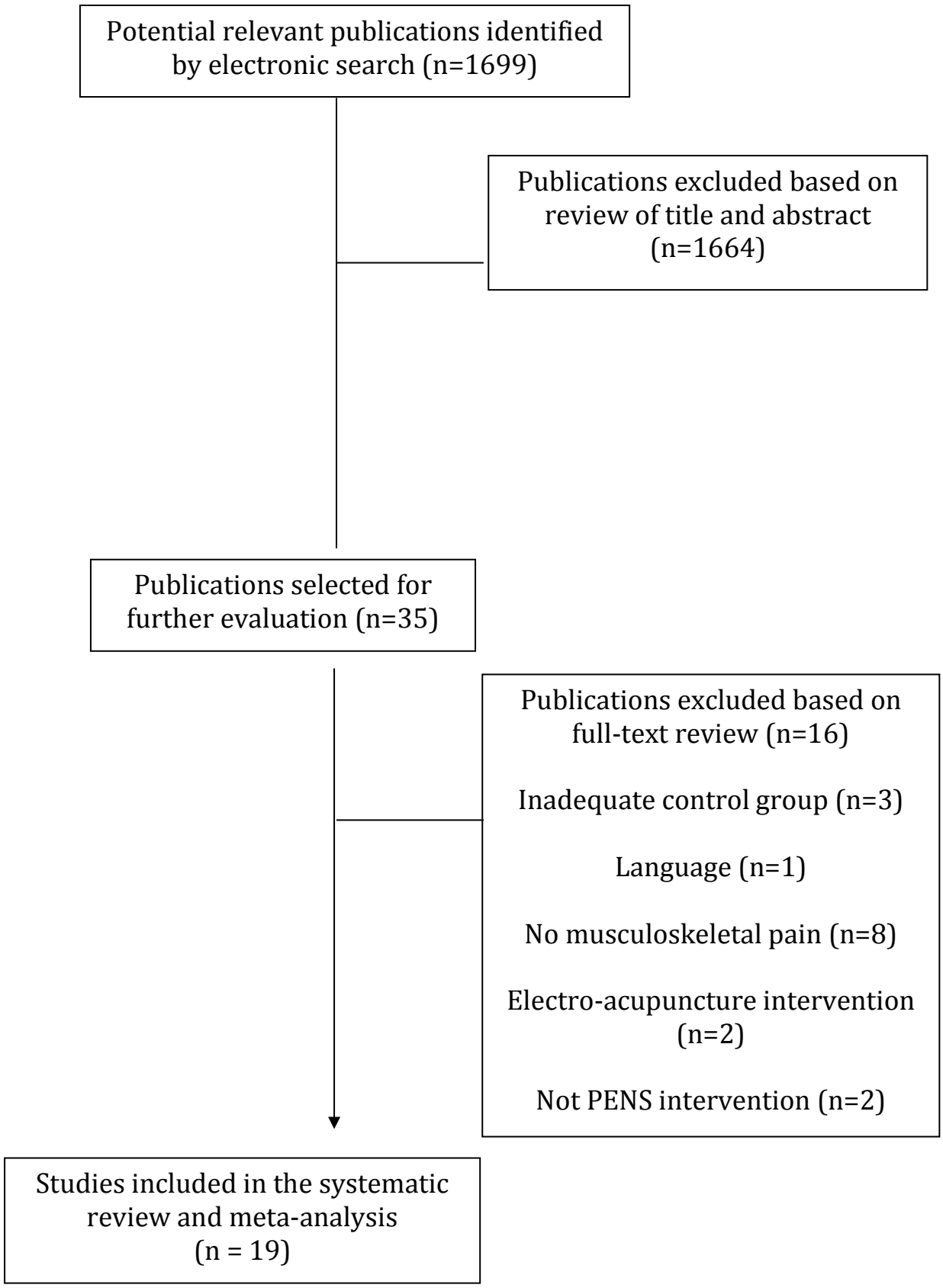
1 trial (n=135)							
PENS plus Other Intervention VS Other Intervention Alone on Pain Intensity (short-term: 0 -10 weeks)							
PENS plus other interventions VS other interventions* - 10 trials (n=730)	No	Serious (I^2 75%)	No	No	Serious	Low	-0.74 [-1.21, -0.27]*
PENS plus other interventions VS other interventions Low Back Pain - 2 trials (n=123)	No	Serious (I^2 69%)	No	Serious	No	Low	-0.44 [-1.17, 0.29]
PENS plus other interventions VS other interventions Knee Osteoarthritis* - 3 trials (n=325)	No	Very serious (I^2 84%)	No	Serious	No	Low	-1.30 [-2.08, -0.52]*
PENS plus other interventions VS other interventions Mechanical Neck Pain - 4 trials (n=171)	No	Serious (I^2 63%)	No	Serious	No	Low	-0.36 [-0.89, 0.16]
PENS plus other interventions VS other interventions Plantar Heel Pain* 1 trial (n=111)	No	No	No	Serious	No	Low	-1.44 [-2.36, -0.53]*
PENS alone or in Combination on Pain Intensity (mid-term: > 10 weeks)							
PENS VS Comparative Group* 9 trials (n=988)	No	Very Serious (I^2 89%)	Serious	No	Serious	Low	-0.68 [-1.10, -0.27]*
PENS plus other interventions VS other interventions* 5 trials (n=536)	No	Very serious (I^2 91%)	No	No	No	Low	-1.19 [-1.87, -0.50]*

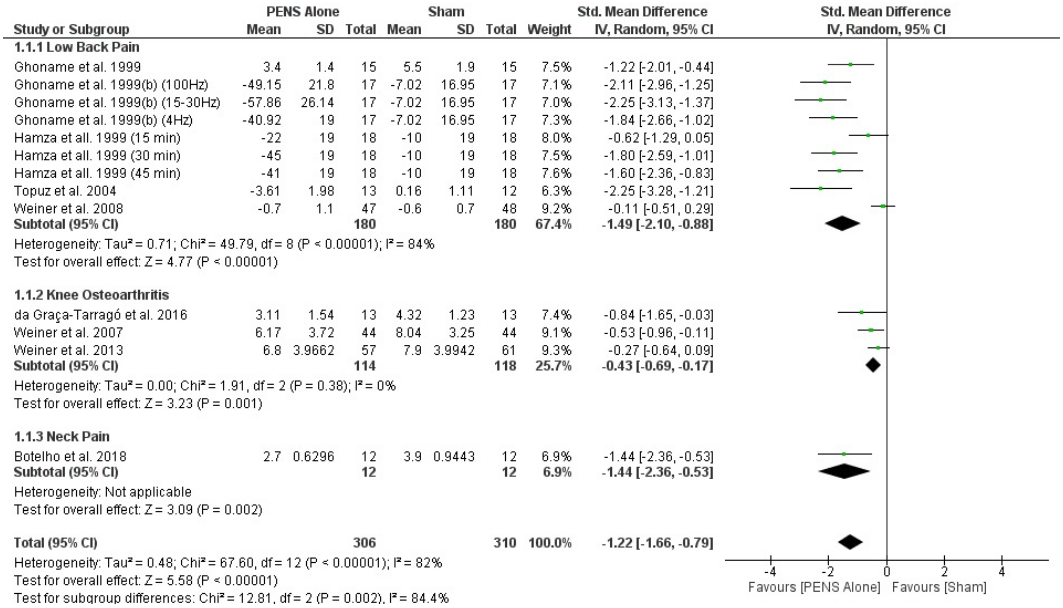
PENS alone VS other intervention 2 trials (n=126)	No	Very serious (I^2 80%)	No	Serious	No	Low	-0.42 [-1.34, 0.49]
PENS alone VS Sham PENS 4 trials (n=326)	No	Serious (I^2 54%)	No	Serious	No	Low	-0.16 [-0.50, 0.17]
PENS alone or in Combination on Related-Disability (short-term: 0 -10 weeks)							
PENS VS Comparative Group* 8 trials (n=738)	No	Serious (I^2 69%)	Serious	No	Serious	Low	-0.33 [-0.61, -0.06]*
PENS plus other intervention VS other intervention - 6 trials (n=383)	No	Serious (I^2 59%)	No	No	No	Moderate	-0.26 [-0.59, 0.07]
PENS alone VS Sham PENS 3 trials (n=208)	No	Very serious (I^2 90%)	No	Serious	No	Low	-0.83 [-1.83, 0.17]
PENS alone VS TENS 1 trial (n=56)	No	No	No	Very Serious	No	Low	-0.46 [-0.99, 0.07]
PENS alone VS other interventions 1 trial (n=91)	No	No	No	Very serious	No	Low	0.09 [-0.33, 0.50]

PENS alone or in Combination on Related-Disability (mid-term: > 10 weeks)							
PENS VS Control group 5 trials (n=568)	No	Serious (I^2 71%)	Serious	No	Serious	Low	-0.21 [-0.52, 0.10]
PENS plus other intervention VS other intervention - 4 trials (n=294)	No	Serious	No	No	No	Moderate	-0.46 [-0.91, 0.00]

		(I^2 72%)					
PENS alone VS Sham PENS 2 trials (n=183)	No	No (I^2 6%)	No	Serious	No	Moderate	0.05 [-0.25, 0.35]
PENS alone VS other interventions 1 trial (n=91)	No	No	No	Very serious	No	Low	0.15 [-0.27, 0.56]

Figure 1: PRISMA Flow diagram





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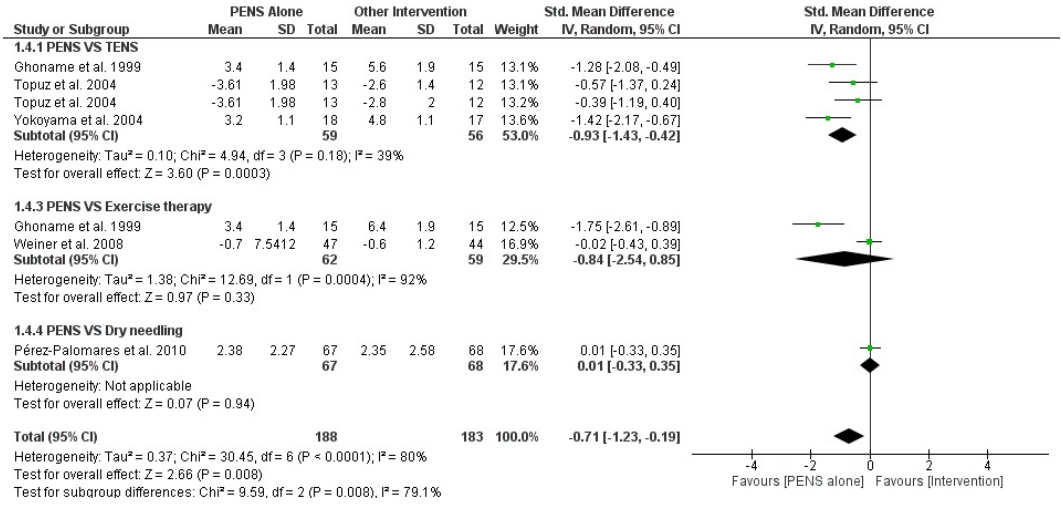

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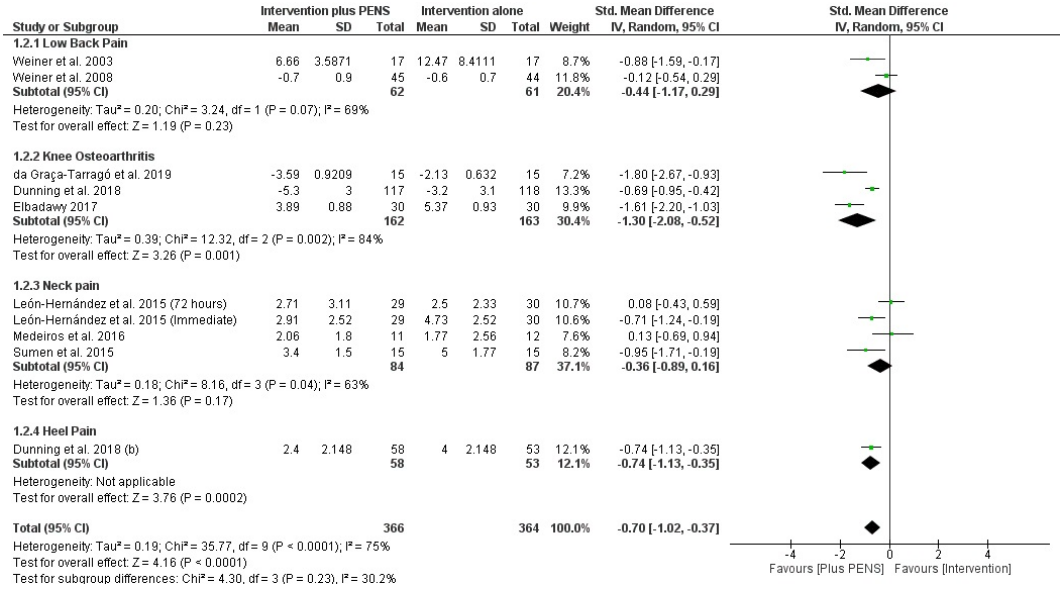

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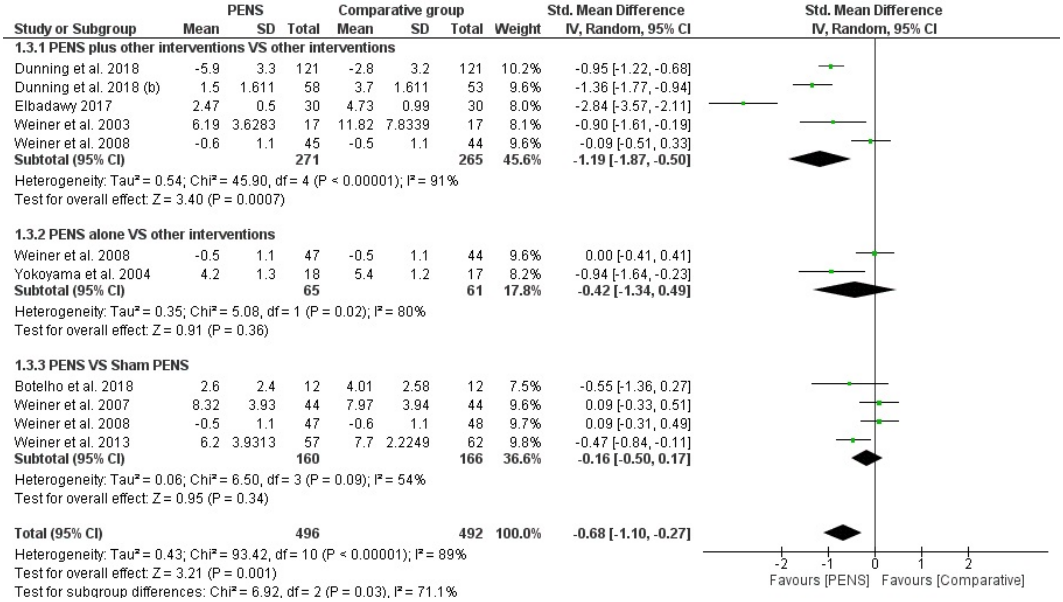

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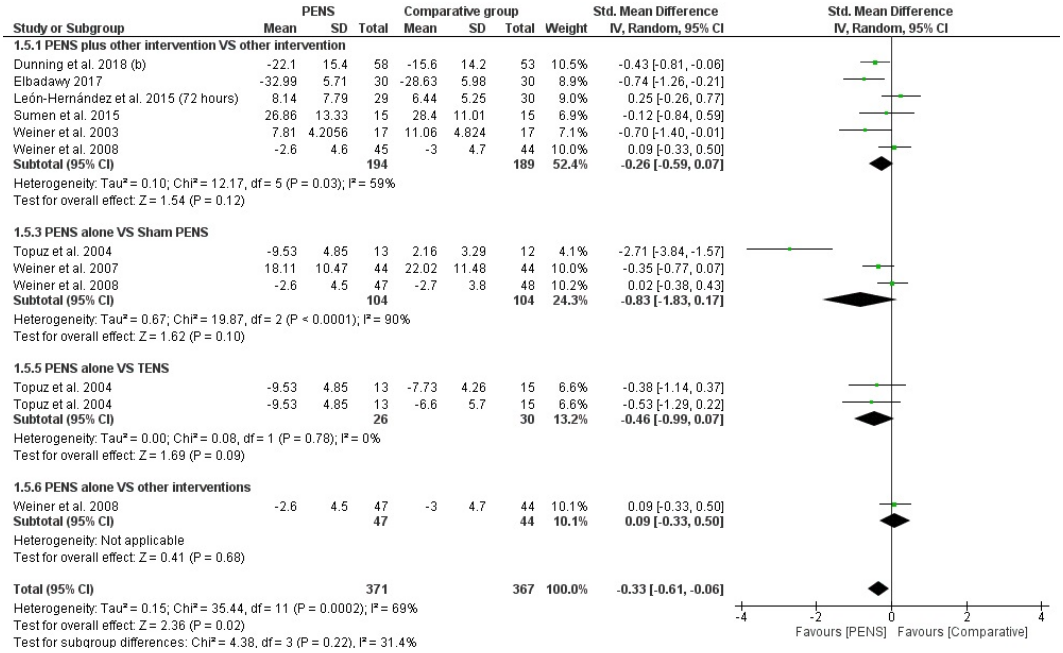

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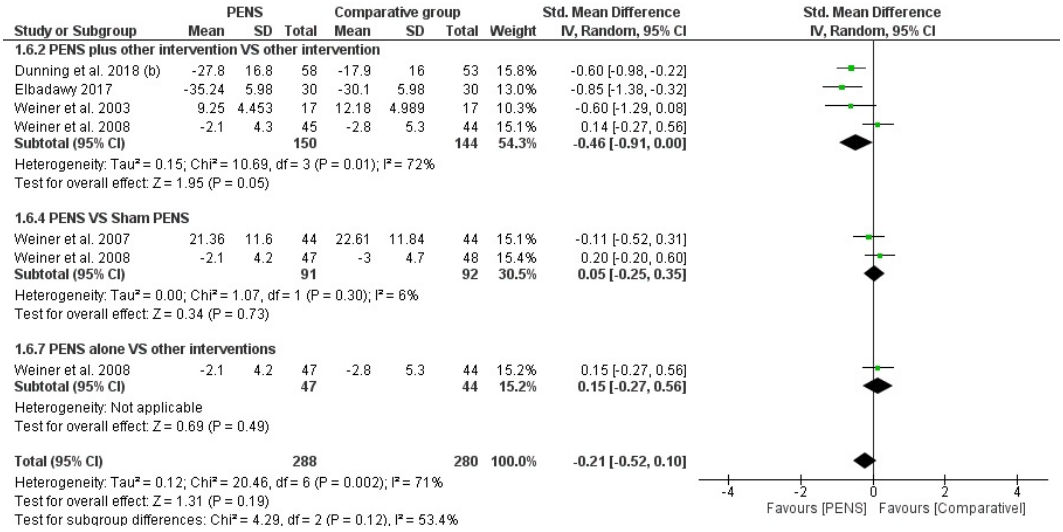

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