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Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: A meta-analysis of randomized controlled trials

Michael Johnson [a], Melissa Martinson [b,c,*]

[a] *Philosopher's River Consultancy, Willow Creek, MT 59760, USA*
[b] *Institute of Health Policy and Management, University of Minnesota, Minneapolis, MN, USA*
[c] *Princeton Reimbursement Group, 7650 Edinborough Way Suite 550 Minneapolis, MN 55435, USA*

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Abstract

Previous studies and meta-analyses of the efficacy of electrical nerve stimulation (ENS) for the treatment of chronic pain of multiple etiologies have produced mixed results. The objective of the present study was to determine whether ENS is an effective treatment for chronic musculoskeletal pain by using statistical techniques that permit accumulation of a sample size with adequate power. Randomized, controlled trials published between January 1976 and November 2006 were obtained from the National Libraries of Medicine, EMBASE, and the Cochrane Library. Prospective, placebo-controlled studies using any modality of ENS to treat chronic musculoskeletal pain in any anatomical location were included. The main outcome measure was pain at rest. The use of statistical methods to enhance data extraction and a random-effects meta-analysis to accommodate heterogeneity of ENS therapies permitted an adequate number of well designed trials of ENS to be included in the meta-analysis. A total of 38 studies in 29 papers, which included 335 placebo, 474 ENS, and 418 cross-over (both placebo and at least one ENS treatment) patients, met the selection criteria. The overall results showed a significant decrease in pain with ENS therapy using a random-effects model ($p < 0.0005$). These results indicate that ENS is an effective treatment modality for chronic musculoskeletal pain and that previous, equivocal results may have been due to underpowered studies.

Keywords: Meta-analysis; Musculoskeletal pain; Chronic pain; TENS, transcutaneous electrical nerve stimulation; PENS, percutaneous electrical nerve stimulation; ALTENS, acupuncture-like TENS; Power; Random-effects model; Multiple meta-regression

1. Introduction

Transcutaneous and percutaneous electrical nerve stimulation (TENS and PENS; collectively, ENS) are the application of electrical energy in various waveforms, amplitudes, and frequencies to peripheral nerves through electrodes. Since the 1970s, ENS has been widely used for the treatment of acute and chronic pain.

The most common stimulation modes are high-frequency (HF; $\geqslant 10$ Hz), low-frequency (LF; <10 Hz), variable-frequency (VF) and acupuncture-like (AL), which employs very low-frequency, high-amplitude stimulation. The mechanism of action of ENS for pain relief has been elucidated by two theories: the gate control theory (Melzack and Wall, 1965) and stimulation-induced release of endogenous endorphins (Sjolund and Eriksson, 1976).

In spite of, or perhaps because of the long history of the use of ENS, there have been few large, controlled clinical trials to evaluate its effectiveness in pain management. The results of existing studies, including randomized controlled trials (RCTs), have been inconclusive,

* Corresponding author. Address: Princeton Reimbursement Group, 9801 DuPont Avenue S., Suite 295, Minneapolis, MN 55431, USA. Tel.: +1 952 345 6404; fax: +1 952 345 6410.
E-mail address: mmartinson@prgweb.com (M. Martinson).

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with some showing a benefit of ENS (Abelson et al., 1983; Melzack et al., 1983; Chee and Walton, 1986; Fargas-Babjak et al., 1989; Gemignani et al., 1991; Fargas-Babjak et al., 1992; Marchand et al., 1993; Zizic et al., 1995; Cheing and Hui-Chan, 1999; Ghoname et al., 1999a; Yurtkuran and Kogacil, 1999; Cheing and Lo, 2003; Weiner et al., 2003; Defrin et al., 2005), and others showing none (Taylor et al., 1981; Langley et al., 1984; Lehmann et al., 1986; Machin et al., 1988; Deyo et al., 1990a,b; Lewis et al., 1994; Cheing et al., 2002).

It is likely that the majority of these studies were underpowered. The standard deviations reported were typically large relative to the scale on which pain was measured, which necessitates large sample sizes. The largest RCTs in this review included 60–75 patients per group (Deyo et al., 1990a,b; Ghoname et al., 1999a,b; Hamza et al., 1999). Several authors have used literature reviews and meta-analyses to attempt to rectify this lack of statistical power, but have drawn mixed conclusions. Some have found ENS effective in relieving pain (Long, 1991; Albright et al., 2001c; Osiri et al., 2002; Brosseau et al., 2004), others have not (Albright et al., 2001a,b,d; Price, 2001; Brosseau et al., 2002; Milne et al., 2002; Carroll et al., 2004; Khadikar et al., 2005). Despite the intention to increase statistical power, these meta-analyses typically included a small number of studies and patients, making them underpowered to reliably detect a treatment effect. One study, however, successfully compiled a sample size (1350 total patients) large enough to conduct an adequately-powered meta-analysis (Bjordal et al., 2003). In that study, the authors found that TENS significantly reduces analgesic consumption post-operatively. However, that study did not address whether TENS alone was effective at reducing pain.

The primary objective of this meta-analysis was to determine whether ENS reduces chronic musculoskeletal pain more effectively than placebo. The secondary objectives were to determine whether therapy parameters including ENS frequency, duration of therapy, type of ENS electrode, improvements in design, and scientific rigor of the study affected the degree of pain relief.

2. Methods

Where appropriate, guidelines for quality of reporting of meta-analyses were followed (Moher et al., 1999).

2.1. Search strategy

Journal articles published between January 1976 and November 2006 from the Cochrane Library, EMBASE, and the National Library of Medicine database were searched using the keywords listed in Table 1. The search was constrained to published articles written in English. Two reviewers independently reviewed each retrieved title for a controlled study of ENS; papers that passed this screening were reviewed against the inclusion/exclusion criteria (below).

Table 1
Keywords in the literature search

ENS	Electrical nerve stimulation
PENS	Percutaneous electrical nerve stimulation
TENS	Transcutaneous nerve stimulation
TNS	Nerve stimulation
ALTENS	NeuromuscS electricS
AL-TENS	Electrical stimulation
Transcutaneous electrical nerve stimulation	Exp. electric stimulation therapy
Transcutaneous electric nerve stimulation	Electrostimulation
Transcutaneous electrical nerve stimulator	Electroanalgesia
(ElectricS adj nerve) or therapy	Electroacupuncture
ElectricS adj (stimulation or muscle)	Acupuncture-like TENS
Electromagnetic or electrotherap$	High volt or pulsed or current

2.2. Study identification

Only primary research studies were included in the analysis. Meta-analyses, literature reviews, and other articles summarizing primary research were reviewed but not considered for inclusion in this analysis.

2.3. Inclusion/exclusion criteria

In order to increase the number of studies in this meta-analysis, and thus the sample sizes of the ENS group and placebo control group, we used scientifically justifiably broad inclusion criteria. Inclusion criteria were chosen to be neutral or to bias the results against the effectiveness of ENS.

The analysis was limited to studies of pain of musculoskeletal origin. We excluded studies of pain other than musculoskeletal origin, and of mixed pain types. The analysis was generally limited to studies involving chronic pain ($\geqslant$3 months duration). However, if the study included a mix of pain durations but appeared from description or context to include mostly chronic pain, it was included as long as it met the other inclusion/exclusion criteria.

Studies of any anatomic locations of chronic musculoskeletal pain (e.g., back, neck, hip, knee) were included as mechanism, rather than anatomical location of pain, is likely to be a critical factor for therapy (Woolf et al., 1998). The mechanism of action of ENS is known to generalize over diverse anatomic regions. Heterogeneity may be increased by such pooling, however, making a random-effects meta-analysis preferable to a fixed-effects analysis.

Most variations of ENS therapy were included in the analysis. All frequency types of ENS were included: LF, HF, and AL. Two studies (Weiner et al., 2003; Law and Cheing, 2004) used stimulation frequencies in the low and high ranges; these are called variable-frequency (VF) TENS therapies. Each frequency type was analyzed separately and combined in a meta-regression. Any number and placement of electrodes was considered acceptable for study inclusion. Thus, both TENS and PENS were included in the study because they differ primarily in the structure of the electrodes.

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All lengths of therapy were included. To determine whether the effect of ENS changes over time, a meta-regression of treatment effect on duration was performed.

Combination therapies of ENS with analgesics or exercise or other concomitant therapy were included under the following conditions: (1) that the same amount of concomitant therapy was given to the ENS and control groups or (2) that the patient controlled the amount of concomitant therapy used. These ancillary measures, if successful, should reduce pain, and potentially decrease the size of the ENS treatment effect.

Only randomized, placebo-controlled trials were included in order to estimate the amount of the improvement that is attributable to ENS over the placebo effect (Marchand et al., 1993). Studies with controls in which the patient received no treatment were excluded; studies with potentially active (effective) controls such as acupuncture were excluded; and studies with controls of unknown effectiveness such as massage or behavior modification were excluded. Well done blinding has been shown to be moderately effective with both patients and evaluators if patients had not experienced ENS treatments previously, since low-frequency ENS causes muscle contractions and high-frequency causes paresthesia (Deyo et al., 1990a,b).

2.4. Outcome measures

Studies were required to measure pain at rest to be included in the analysis. Studies that measured load bearing, joint mobility, or other indirect aspects of pain relief were not included. Pain had to be measured either: (1) at baseline and again after treatment, or (2) as a single measure of degree of pain relief after treatment. Any scale for assessing pain was considered acceptable, as the transformation to the standardized mean difference for the meta-analysis would standardize the results from different scales (Lipsey and Wilson, 2001).

2.5. Trial quality assessment

Two independent reviewers, one neurologist (MJ) and one statistician (MM), graded the papers using the method of Jadad (Jadad, 1996) and then extracted the data using standardized forms. This method yields a Jadad score ranging from 0 to 5. To this the reviewers added one modification: 1/2 point was assigned for single blinding and 1 point for double blinding. All discrepancies were resolved by discussion and re-examination of the papers.

2.6. Data extraction

The goal of data extraction was to obtain the difference between treatment groups of mean pain differences before and after treatment, and the standard error of this difference.

In studies with treatments repeated over time, the baseline pain measurement and the final post-treatment measurement were used, ignoring measurements taken after therapy had been discontinued. Some studies provided the mean pre–post-treatment difference for each group (2 means), and others provided the mean pain scores before and after treatment for each treatment group (4 means). In some studies, necessary data were extracted from graphs and alternative statistics. In one study (Lundeberg, 1984), pain relief was measured as a categorical variable; these data were converted to means and standard deviations. In all cases, a mean pre–post difference and within-group standard deviation were calculated. The list of studies used in the analysis and the specific methods used to extract data from each are provided in supplementary Table 2.

2.7. Analytic methods

The combined results were assessed using Comprehensive Meta-Analysis 2.2.027 (Biostat, Inc., Englewood, NJ). Because of the different pain scales used in the studies, the standardized mean difference was used as the effect size (Lipsey and Wilson, 2001). The multiple meta-regression was performed using STATA 9.2 (StataCorp LP, College Station, TX) using the modification to the standard error (SE) of coefficients detailed in Lipsey and Wilson (2001).

The methods used for analysis followed the Cochrane Guidelines (Deeks et al., 2003). A random-effects meta-analysis model was used to deal with the clinical reality of heterogeneity in the ENS therapies and heterogeneity of musculoskeletal treatment sites. A sensitivity analysis was performed by limiting the analysis to those studies with a Jadad score of at least 4. Meta-regression was used to explain some of the variation in effect sizes by analyzing the relationships between effect size and Jadad score, time of final therapy session, design improvements, electrode type, and stimulation frequency.

Seven of the 29 papers used in the analysis included more than one ENS modality (Langley et al., 1984; Lehmann et al., 1986; Graff-Radford et al., 1989; Ghoname et al., 1999a; Ghoname et al., 1999b; Law and Cheing, 2004; Topuz et al., 2004). Although in these studies both ENS modalities were compared to the same sham-ENS control group, they were treated in the primary meta-analysis as two separate studies. This violates the assumption of independence, but was unlikely to substantially affect the results because the non-independent studies represented a small fraction of the total (9 out of 38 studies or 24%). The number of placebo patients that were "double counted" by being used in two or three comparisons was 63 out of 753 (8.4%).

3. Results

3.1. Study characteristics

A total of 134 original-research papers were reviewed; 29 papers with 38 studies met the inclusion criteria (see Fig. 1 for flow diagram). There were 32 TENS studies (19 HF-TENS, 6 LF-TENS, 1 VF-TENS, 4 AL-TENS, and 2 TENS of unspecified stimulation frequency) and 6 PENS studies (2 HF-PENS, 3 LF-PENS and 1 VF-PENS). Nine studies received a Jadad score below 3. There were a total of 1227 patients: 892 ENS patients and 753 placebo patients (418 of the patients participated in cross-over trials and are included in both the placebo and ENS counts). Of the 753 placebo patients, 63 (8.4%) served as controls in more than one comparison.

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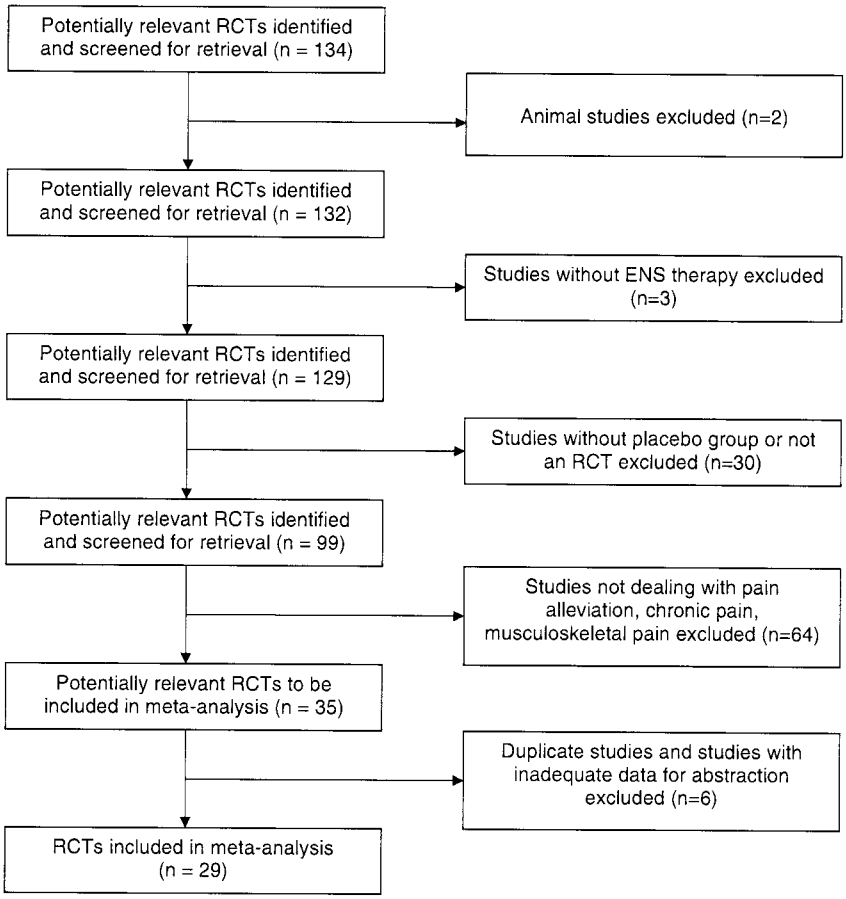

Fig. 1. Flow diagram for inclusion and exclusion of selected studies. Potentially relevant articles were retrieved by searching the national libraries of medicine databases, EMBASE, and the Cochrane Libraries, and were screened for inclusion based on the inclusion/exclusion criteria outlined in the Section 2.

One hundred and five papers were excluded from the analysis (Fig. 1). The reasons for exclusion were: no human subjects (animal study; $n = 2$), no ENS therapy ($n = 3$), no placebo group or not an RCT ($n = 30$), studies not dealing with chronic, musculoskeletal pain alleviation ($n = 64$), duplicate studies or inadequate data for abstraction ($n = 6$).

The included studies are listed in supplementary Table 3. One study (Lundeberg, 1984) had a score of 2 by the usual definition of "blinding" or "masking" in clinical trials. The patients in the control group received a placebo drug that they were told was a powerful new analgesic. Although we did not upgrade the score to include a point for blinding, this study met our requirement of having adequate control of the placebo effect.

Supplementary Table 4 provides additional information about the included studies, especially the efficacy of the ENS and placebo therapies. Efficacy is measured in percent reduction in pain (a negative value).

3.2. Analysis of the primary objective

Supplementary Table 5 shows the statistical analysis by article and overall. It gives a description of the control and ENS samples as a function of ENS subgroup, control type, and treatment duration. The pain differences between ENS and control groups are converted to the standardized mean difference.

For all studies combined, ENS reduced pain significantly more than placebo using a random-effects model ($p < 0.0005$). (The fixed-effects model was also highly significant at $p < 0.0005$, but the Q-test for homogeneity of the effect sizes was significant at $p < 0.0005$, indicating that this model is not appropriate). Fig. 2 shows the corresponding graphical analysis. Of the 38 studies included in the analysis, 35 favored ENS therapy relative to placebo, with 24 studies showing a significant benefit of ENS therapy compared to placebo. On average, the pain relief provided by ENS was nearly three times the pain relief provided by placebo.

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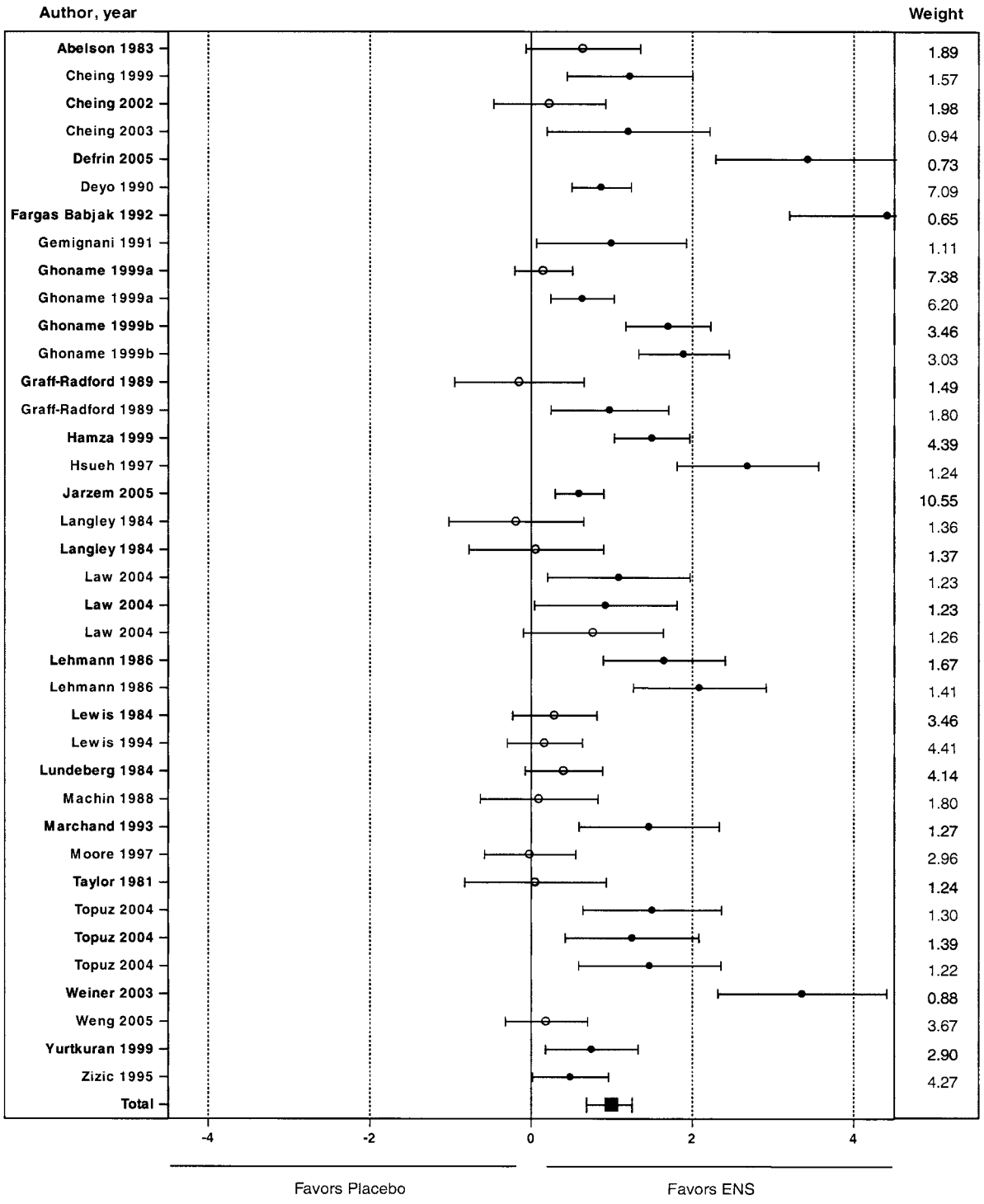

Fig. 2. **Results of the analysis of primary objective.** Each study included in the analysis is represented by the confidence interval of its standardized mean difference with the point estimate represented by a circle in the interval. Points that fall to the right of the solid, vertical line favor ENS therapy over placebo. Filled circles represent studies that show significant differences in the standardized mean difference between ENS and placebo. The cumulative result of all studies included is represented by the filled square at the bottom of the figure.

Seven of the papers included more than one ENS treatment group, and thus permitted more than one comparison (sub-study) of placebo to ENS to be made (Langley et al., 1984; Lehmann et al., 1986; Graff-Rad-

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ford et al., 1989; Ghoname et al., 1999a,b; Law and Cheing, 2004; Topuz et al., 2004). Including both sub-studies in the analysis violated the assumption of independence. However, this did not have a material effect on the study results. When only one sub-study from each paper was included in the analysis, the p-value of the comparison was still $p < 0.0005$. (To maintain the maximum amount of diversity among the included studies, we dropped comparisons in descending order of the number included: HF-TENS comparisons first, then LF-TENS, then LF-PENS.)

3.3. Analysis of the secondary objectives

In order to explain some of the variation in effect sizes, the relationships between treatment effect size and Jadad score, improvements to the technology, duration of therapy, electrode type, and stimulation frequency, a multiple meta-regression was performed. (The 'year of publication' was used as a surrogate for improvements to the technology.) We removed regressors until all of those remaining were significant at $\alpha = 0.05$; only electrode type (TENS vs. PENS) was significant ($p = 0.014$), with PENS being more effective than TENS.

A sensitivity analysis was done with respect to study quality and effect size. For example, one concern is that less rigorous studies, i.e., those with lower Jadad scores, have a larger effect size than do more rigorous studies. To address this concern, we limited the analysis to those studies with a Jadad score of 4 or better. There were 15 comparisons that met this criterion with $p < 0.0005$ (random effects).

Similarly, we analyzed sensitivity of ENS frequency type on effect size. HF-ENS alone produced a significant treatment effect ($p < 0.0005$). LF-ENS also produced a significant effect ($p < 0.0005$) and AL-ENS ($p = 0.053$) fell just short of significance; VF-ENS was not significant. We also analyzed electrode type: both TENS $p < 0.0005$ and PENS ($p < 0.0005$) produced significant treatment effects.

4. Discussion

This meta-analysis showed a highly significant reduction in pain with the use of ENS compared to placebo controls. While this has not been the first analysis to draw such a conclusion, prior studies with positive results have done little to quell the controversy over the effectiveness of ENS. The clear results of this study establish the efficacy of ENS on chronic musculoskeletal pain.

The disparity in the results of previous studies and meta-analyses is most easily explained by a lack of statistical power in many of those studies. A difference between the current and previous meta-analyses was the inclusion of data from many studies to achieve sufficient power. Importantly, both the present analysis and the analysis by Bjordal et al. (2003) had total sample sizes of over 1000 patients, providing sufficient statistical power. This is still a relatively small number of patients as evidenced by other meta-analyses on the efficacies of chronic pain therapies that have sample sizes of 2839 (Elia and Tramer, 2005) and 5726 patients (Edwards et al., 2004). Sample size, and hence power, is especially important in studies involving pain management due to the inherent variability in reporting of pain measures. While several authors have contended that the use of broad inclusion criteria is inappropriate and can lead to misleading conclusions (Carroll et al., 2004) we feel that the benefits of such criteria (increased power) outweigh the drawbacks (increased heterogeneity).

This analysis used many of the statistical tools available for data extraction and analysis, some of which may have introduced inaccuracies into the statistical estimates. For example, the use of an approximation to the standard deviation based on the range and sample size is not as precise an estimate of the standard deviation as the sample standard deviation is. We used these estimates with the assumption that the errors they introduced were random – sometimes overestimating the statistic, other times underestimating it. The result would be to decrease the precision of each study, making it less likely that we would be able to detect a significant benefit of ENS in the meta-analysis. However, we believed that the benefit of estimating these statistics – that an adequate number of papers (and thus study subjects) would be usable in the meta-analysis – would outweigh the drawbacks.

The studies included a variety of anatomical locations, ENS modalities, therapy durations, etc. This heterogeneity was likely to have caused the effect sizes to vary among studies. A fixed-effects model assumes that the effect sizes are estimates of the same (fixed) effect size and all of the variation is due to sampling error. Conversely, a random-effects model assumes that the effect sizes are a random sample drawn from a population of effect sizes, and the variation is due to the population variance plus sampling error. This heterogeneity was accommodated by a random-effects meta-analysis (Lipsey and Wilson, 2001).

A distinguishing factor in this meta-analysis was the inclusion of all locations of chronic musculoskeletal pain. We chose not to limit the studies to those involving pain of a specific anatomical region to increase the papers and subjects in the analysis. This decision was mechanistically sound, as both proposed modes of action for ENS (the gate control theory or the release of endogenous endorphins) are not dependent upon anatomical locus. Clinically, this heterogeneity is justified as the ENS practitioner treats a diagnosis of musculoskeletal pain using a general multimodal approach that is not joint or location specific.

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The use of broad inclusion criteria allowed for a significantly larger patient population to be studied relative to other meta-analyses. It is likely that the increased statistical power in the current analysis accounts for the differences in conclusions that have been reached by various authors. For instance, the Ottawa Panel (Brosseau et al., 2004), found that TENS provided significant improvements in joint pain caused by rheumatoid arthritis, and thereby included the use of TENS in their evidence-based clinical practice guidelines. This conclusion was based on 2 studies of HF-TENS with a total of 29 TENS and 27 control patients. However, Brosseau et al. (2002) found, "no evidence to support the use or nonuse of TENS alone in the treatment of chronic low back pain", which they attributed to, "the small number of studies responding to the criteria to be included in this meta-analysis".

The use of broad inclusion criteria could bias a meta-analysis in favor of showing an effect. The inclusion requirements were constructed so that if there were bias, it would be against the effectiveness of ENS. For example, the inclusion of several modalities of ENS: LF, HF, VF, and AL would weaken the observed treatment effect if one were not effective, or if all were effective in varying degrees. The analysis would conclude that ENS is effective if the average effectiveness were better than placebo.

Both heterogeneity and statistical power increase as studies and subjects are added to the meta-analysis. The effect of cumulative heterogeneity is to decrease the statistical significance and therefore the power of the test by increasing the variance. The effect of increasing the sample size is to increase the power – and thus increase the chance of finding a treatment effect. The only advantage of broad inclusion criteria is if the sample size increases the power more than the heterogeneity increases the variance – in effect, there is a race between the two. The significant positive treatment effect of ENS on chronic musculoskeletal pain in this study argues that in this case, sample size won.

In the meta-regression, PENS was significantly more effective at relieving pain than was TENS. This result supports our conclusion that the effect of ENS is more than a placebo effect, as PENS provides direct stimulation to the nerves. Its energy is less dissipated by skin, fat and muscle tissue than is the energy used in TENS.

As with any meta-analysis, publication bias was a concern, as published studies tend to be weighted in favor of those showing significant treatment effect. For instance, approximately 70% of a sample of urological papers demonstrated a significant treatment effect (Breau et al., 2006). However, it appeared to be less of an issue in the current analysis. The classic test for publication bias, the fail-safe N, estimated that 2927 unpublished studies with negative results would have to exist to increase the p-value of the meta-analysis to 0.05 or greater. In addition, of the 38 studies included, 14 showed no significant effect of ENS therapy based on our analytic techniques. The hypothesis of publication bias is testable in another way if we assume that journal editors are indiscriminate in rejecting negative results caused by low power and those caused by valid negative results. When the analysis was restricted to the 14 articles that did not show a significant effect of ENS, the p-value was still significant in favor of ENS ($p = 0.016$ both models). We conclude that if publication bias was operating on ENS studies, it did not affect the results of this meta-analysis.

The debate over the efficacy of ENS therapy for the treatment of chronic pain has been a long-standing one. The conclusions from this meta-analysis demonstrate that definitive answers regarding the efficacy of the various frequencies, modalities and durations of ENS therapy can only be obtained by studies that are sufficiently powered. Further, subsequent studies should also carefully consider the analytic techniques to be employed. Given that many of the stimulation parameters are set by the patient (e.g. intensity), the use of a random-effects model in subsequent analyses is justified.

Along with the efficacy of ENS demonstrated here, other benefits of ENS therapy have also been identified. A survey of 376 chronic pain patients who had been using TENS therapy for at least six months revealed that TENS use was associated with less pain interference at home and work, decreased use of other therapies, and decreased consumption of additional pain medications. Further, these patients also reported average satisfaction and comfort ratings of 8.19 and 8.35 on a scale of 1–10, respectively (Fishbain et al., 1996).

As the number of available pharmacological options for the management of chronic pain has decreased due to recently appreciated side effects, the need to provide scientifically sound evidence regarding the efficacy of ENS therapy is as pressing as ever. TENS therapy has been shown to significantly reduce analgesic consumption, and to potentially reduce the incidence of opiate-induced side effects following surgery (Bjordal et al., 2003), showing its value as an adjunctive therapy. Further, given that most modalities of ENS therapy are covered by major insurers, including Medicare, and that the number of contraindications is low (demand-type pacemaker or cardiac defibrillator, undiagnosed pain, and application of electrodes transcerebrally or over the carotid sinus), the therapy is available to most patients. Those conclusions, combined with the fact that the present analysis shows that ENS therapy provides significant pain relief on its own, indicate that ENS is a viable treatment of chronic pain.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2007.02.007.

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