The Effect of Stimulus Frequency on the Analgesic Response to Percutaneous Electrical Nerve Stimulation in Patients with Chronic Low Back Pain

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Low back pain (LBP) is one of the most common medical problems in our society. Increasingly, patients are turning to nonpharmacologic analgesic therapies such as percutaneous electrical nerve stimulation (PENS). We designed this sham-controlled study to compare the effect of three different frequencies of electrical stimulation on the analgesic response to PENS therapy. Sixty-eight consenting patients with LBP secondary to degenerative lumbar disc disease were treated with PENS therapy at 4 Hz, alternating 15 Hz and 30 Hz (15/30 Hz), and 100 Hz, as well as sham-PENS (0 Hz), according to a randomized, cross-over study design. Each treatment was administered for a period of 30 min three times per week for 2 wk. The pre- and posttreatment assessments included the health status survey short form and visual analog scales for pain, physical activity, and quality of sleep. After receiving all four treatments, patients completed a global assessment questionnaire. The sham-PENS treatments failed to produce changes in the degree of pain, physical activity, sleep quality, or daily intake of oral analgesic medications. In contrast, 4-Hz, 15/30-Hz, and 100-Hz stimulation all produced significant decreases in the severity of pain, increases in physical activity, improvements in the quality of sleep, and decreases in oral analgesic requirements ($P < 0.01$). Of the three frequencies, 15/30 Hz was the most effective in decreasing pain, increasing physical activity, and improving the quality of sleep ($P < 0.05$). In the global assessment, 40% of the patients reported that 15/30 Hz was the most desirable therapy, and it was also more effective in improving the patient's sense of well-being. We conclude that the frequency of electrical stimulation is an important determinant of the analgesic response to PENS therapy. Alternating stimulation at 15-Hz and 30-Hz frequencies was more effective than either 4 Hz or 100 Hz in improving outcome measures in patients with LBP. **Implications:** The frequency of electrical stimulation seems to be an important determinant of the analgesic efficacy of percutaneous electrical nerve stimulation. Mixed low- and high-frequency stimulation was more effective than either low or high frequencies alone in the treatment of patients with low back pain.

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Low back pain (LBP) is second only to the common cold as a cause for primary care clinic visits (1–4), and it is the second most common cause of absence from work in adults <55 yr of age (5). The current therapies for LBP include physical therapy, epidural steroid injections, opioid and nonopioid analgesic medications, implantable spinal cord-stimulating devices, as well as various psychological and behavioral modification programs.

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Concerns regarding the efficacy and side effects associated with these treatment modalities have increased interest in nonpharmacologic neuromodulation therapies such as transcutaneous electrical nerve stimulation (TENS) (6), acupuncture (7,8), electroacupuncture (9), and percutaneous electrical nerve stimulation (PENS) (10–12). Unfortunately, most of the published studies involving the use of electrical stimulation devices have used arbitrarily chosen treatment variables.

Therefore, we designed a randomized, sham-controlled, cross-over study to evaluate the effect of stimulation frequency on the acute analgesic response to PENS therapy. The comparative effects of three different frequencies of stimulation (4 Hz, alternating

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15 Hz and 30 Hz, and 100 Hz) on pain scores, physical activity, quality of sleep, and the patient's sense of well-being were evaluated in patients with LBP.

Methods

After obtaining institutional review board approval and written informed consent, 68 patients (30 men and 38 women) with LBP associated with radiologically confirmed degenerative lumbar disc disease were enrolled in this randomized, sham-controlled, investigator-masked, cross-over study. Each patient was treated with sham-PENS (no electrical stimulation) and PENS at 4 Hz, alternating 15 Hz and 30 Hz (15/30 Hz) (a mixed frequency using both frequencies at each cycle with the stimulation pulses switched on and off every 3 s), and 100 Hz for a period of 30 min, three times per week for 2 consecutive wk in a random sequence (with 1 wk off between each treatment modality). Inclusion criteria included a history of LBP that has remained unchanged on a stable oral nonopioid analgesic regimen for a period of at least 3 mo before enrolling in the study. Exclusion criteria included LBP with a radicular component (sciatica), a history of drug or alcohol abuse, major organ disease, a change in the character or severity of the pain within the last 3 mo, and an inability to reliably complete the health status survey short form (SF-36), the daily assessment tools, or the global assessment questionnaire.

The basic therapy consists of the placement of ten 32-gauge (0.2 mm) stainless steel acupuncture-like needle probes (ITO, Tokyo, Japan) into the soft tissue and/or muscle in the low back region to a depth of 2–4 cm according to the dermatomal distribution of the pain as illustrated in Figure 1. The 10 probes were connected to five bipolar leads (with each lead connected to one positive and one negative probe) from an investigational (non-Food and Drug Administration-approved), low-output electrical generator, which was calibrated before each series of treatments. The maximal amplitude of the electrical stimulation produced by the generator was 25 mA, with a unipolar square-wave pattern and a pulse width of 0.5 ms. The electrical current was DC, and the duty cycle was continuous. These probes were then stimulated at one of four different frequencies: 0 Hz (sham), 4 Hz, 15/30 Hz, or 100 Hz. The intensity of the electrical stimulation was adjusted to produce the highest tolerable electrical sensation without muscle contractions (except for the sham treatments).

Before initiating the first of the four (frequency) treatment modalities, patients were required to complete the SF-36 (13). The physical component summary (PCS) and mental component summary (MCS) scores were used to assess the patient's response to each of the therapeutic modalities (14). The baseline level of pain, physical activity, and quality of sleep was evaluated before the first treatment with each

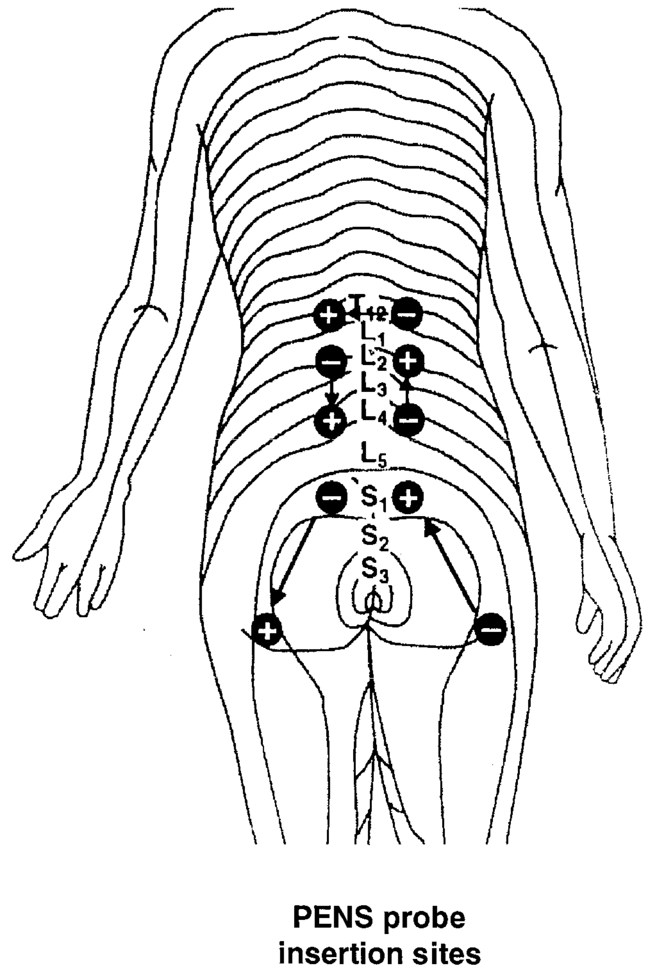

Figure 1. The location of the needle probes for the percutaneous electrical nerve stimulation (PENS) and sham-PENS treatments. With PENS therapy, each of the five bipolar leads from the low-output electrical generator was connected to a pair of needle probes, alternating the positive and negative positions as shown.

modality using standard 10-cm visual analog scales (VAS), with 0 = best to 10 = worst. Repeat VAS assessments of pain, activity, and sleep were performed three times per week before each treatment session. In addition, the pain VAS was repeated 5–10 min after each treatment session. The daily oral analgesic requirements (pills per day) were recorded in the patient's diary during each phase of the study. The SF-36 questionnaire was repeated after completing all six treatment sessions with each of the four frequency modalities. Finally, each patient completed a global assessment questionnaire comparing the relative effectiveness of the sham and the three stimulation frequencies 72 h after the final treatment session.

The NCSS software package (version 6.0.1; NCSS, Kaysville, UT) was used for all statistical analyses. An *a priori* power analysis with $\alpha = 0.05$, $\beta = 0.10$ (power 90%) and SD of 2.0 determined that a group size of 60 should be adequate to demonstrate a difference of 25% among the pain VAS scores for the four frequencies studied. The changes in the VAS scores were analyzed using repeated-measures analysis of variance and Student's *t*-test, with a Bonferroni correction applied for multiple comparisons. Analysis of discrete data was performed by using the χ^2 test. Changes and differences in the SF-36 scores were analyzed by using paired sample *t*-tests. Data are presented as mean values $\pm$ SD, median values, and percentages. $P < 0.05$ was considered statistically significant.

Results

The prestudy SF-36 evaluation suggested that this LBP patient population (age 46 $\pm$ 21 yr) reported significantly lower health-related quality of life scores compared with the general population. The median prestudy scores were 29.8 and 41.4 for the PCS and MCS, respectively, compared with general population norms of 50 for these two variables. The posttreatment SF-36 test results revealed that the 4-Hz, 15/30-Hz, and 100-Hz frequencies produced significant improvements over the prestudy scores for both the PCS and the MCS components ($P < 0.01$). Moreover, the absolute (mean) magnitude of the changes in PCS and MCS components at the end of each treatment period were similar with 4 Hz (7.0 and 2.8, respectively), 15/30 Hz (7.3 and 3.2, respectively), and 100 Hz (7.1 and 3.1, respectively). In contrast, the sham treatments did not show any significant improvement in posttreatment functionality.

All three frequencies of electrical stimulation produced significant decreases in the pain scores immediately after each treatment (Table 1). Compared with the sham treatments, the 4-Hz, 15/30-Hz, and 100-Hz frequencies of PENS therapy also produced statistically greater decreases in the degree of pain and improved physical activity and sleep quality at the end of the 2-wk treatment period (Fig. 2). However, the overall percent changes in pain, physical activity, and quality of sleep scores were significantly greater after electrical stimulation at 15/30 Hz compared with 4 Hz or 100 Hz.

The daily requirements for nonopioid analgesic medications are summarized in Figure 3. Compared with baseline values 24 h before starting each frequency modality, the need for oral analgesic medications was significantly decreased over the course of the 2-wk treatment period with 4 Hz, 15/30 Hz, and 100 Hz, but not with the sham treatments. Moreover, the overall percent decrease in the oral analgesic requirements was greater with 15/30 Hz (48%) than with 4 Hz (35%) or 100 Hz (33%).

Finally, the global assessment of the four modalities indicated that 15/30 Hz was the therapy preferred by 40% of the patients, whereas 28%, 30%, and 2% favored the 4 Hz, 100 Hz, and sham treatments, respectively (Table 2). In addition, the 15/30-Hz treatments were significantly more effective in improving the patient's physical activity and sense of well-being compared with the 4-Hz, 100-Hz, and sham treatments. Given a hypothetical situation, patients indicated that they would be more willing to pay out-of-pocket for the PENS treatment when it was administered at a frequency of 15/30 Hz (versus the sham treatment).

Table 1. Comparison of the Effects of the Four Frequency (F) Modalities on the VAS Pain Scores

Treatment	Sham	F 4	F 15/30	F 100
1				
Pre	5.8 ± 1.5	6.4 ± 1.6	6.0 ± 1.7	5.7 ± 1.6
Post	5.6 ± 1.8	2.3 ± 1.2*	2.5 ± 1.3*	2.7 ± 1.5*
2				
Pre	5.9 ± 1.8	6.1 ± 1.7	5.4 ± 1.7	5.4 ± 1.8
Post	5.5 ± 1.6	2.1 ± 1.4*	2.3 ± 1.3*	2.5 ± 1.3*
3				
Pre	5.8 ± 1.7	5.9 ± 1.8	5.1 ± 2.0	5.1 ± 1.9
Post	5.7 ± 1.8	2.5 ± 1.2*	2.5 ± 1.4*	2.2 ± 1.5*
4				
Pre	5.6 ± 1.6	5.1 ± 1.5	4.9 ± 1.6	5.0 ± 1.7
Post	5.5 ± 1.9	1.8 ± 1.2*	1.7 ± 1.3*	1.7 ± 1.5*
5				
Pre	5.9 ± 1.7	4.9 ± 1.8	4.5 ± 1.9	4.7 ± 1.8
Post	5.8 ± 1.9	1.4 ± 1.4*	1.3 ± 1.3*	1.6 ± 1.3*
6				
Pre	5.7 ± 1.7	4.7 ± 1.6	4.0 ± 1.4	4.5 ± 1.5
Post	5.5 ± 1.8	1.2 ± 1.2*	1.1 ± 1.4*	1.2 ± 1.5*

Values are mean ± SD.

VAS = visual analog scale, with 0 = no pain to 10 = worst pain imaginable.

* Significantly different from values before (pre) each treatment session ($P < 0.01$).

Discussion

Analogous to previously reported findings in animals with electroacupuncture (15), these data suggest that the frequency of electrical stimulation influences the analgesic response to PENS therapy in patients with chronic LBP. Compared with low- (4 Hz) and high- (100 Hz) frequency stimulation, a mixed pattern (15/30 Hz) of electrical stimulation produced the greatest decrease in pain and improvement in physical activity and quality of sleep at the end of a 2-wk treatment period.

Using a rat model for studying electroacupuncture, Chen et al. (15) reported that the dense-disperse mode of electrical stimulation (alternating 2 Hz and 15 Hz) was more effective than a fixed frequency of stimulation at either 2 Hz or 100 Hz in producing experimental analgesia. According to Sun and Han (16), the enhanced analgesia produced by alternating frequencies results from the differing effects of the frequency of stimulation on the pattern of neurotransmitter release within the central nervous system (CNS). At

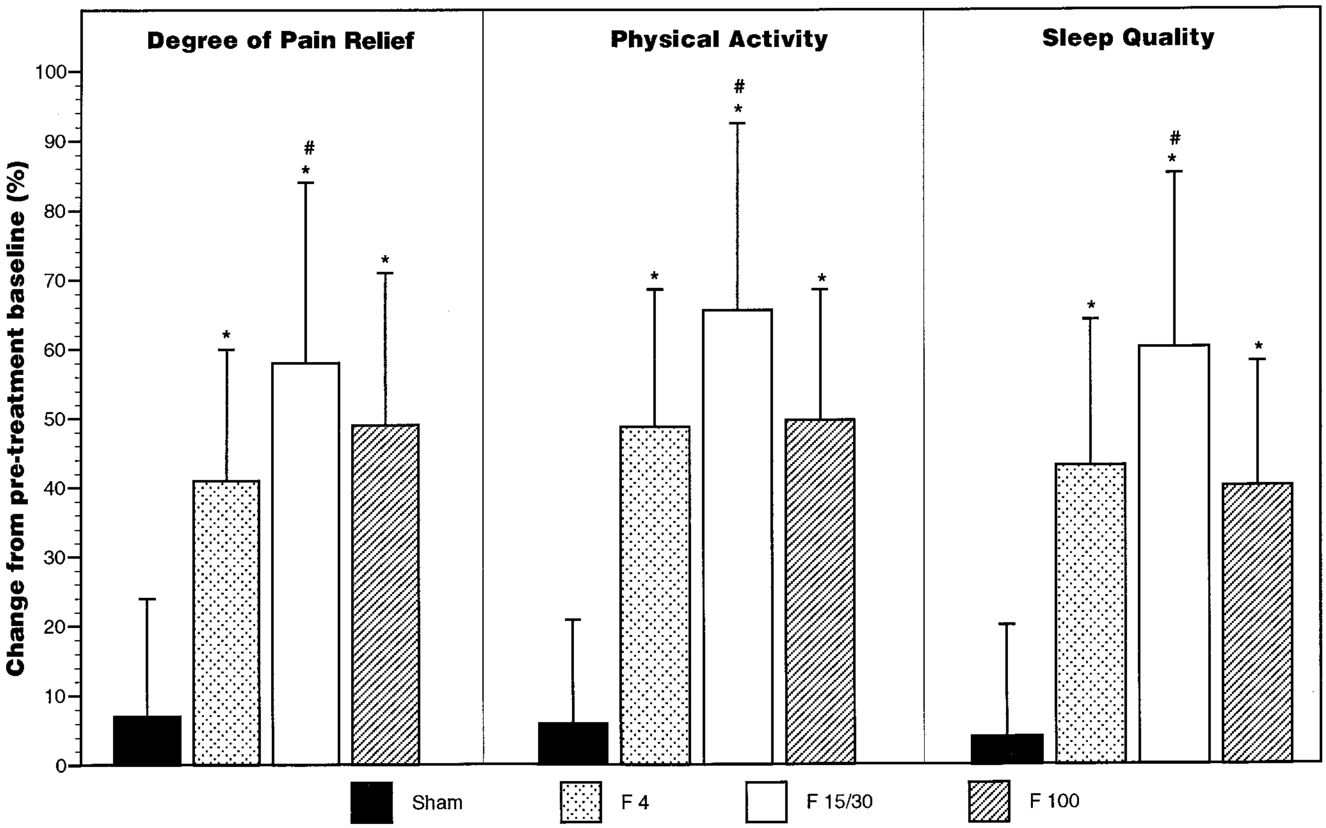

Figure 2. Comparison of the percent changes from baseline value (24 h before the first treatment session with each modality) in the degree of pain relief, physical activity, and sleep quality at the end of each 2-wk treatment period. Data are mean values ± SD. * $P < 0.05$ compared with the sham-percutaneous electrical nerve stimulation values. # $P < 0.05$ compared with F4 and F100 values.

2 Hz, analgesia was alleged to be mediated by stimulation of μ and δ opioid receptors, whereas, at 100 Hz, analgesia was reportedly mediated by activation of κ opioid receptors in the CNS (16).

In studying the effect of the frequency of electroacupuncture stimulation on the release of substance P in the spinal cord, Chen et al. (17) also found that 15 Hz was more effective than either lower (2, 4, or 8 Hz) or higher (30 or 100 Hz) frequencies of electrical stimulation. Analogous to the findings of Sun and Han (16), Goldstein and Naidu (18) also reported that high-frequency (100 Hz) electroacupuncture-induced analgesia was mediated by the activation of κ opioid receptors, whereas low-frequency stimulation (2 Hz) activated μ and δ opioid receptors. One might speculate that using a combination of intermediate frequencies (e.g., alternating 15 Hz and 30 Hz) would activate both subtypes of opioid receptors. However, opioid receptor binding studies would have to be performed to determine the pattern of opioid receptor activation that occur when mixed frequencies of electrical stimulation are used to produce electroanalgesia in humans.

Controversy still surrounds the optimal frequency of electrical stimulation for TENS therapy (19). For example, Walsh et al. (20) reported that a low frequency (4 Hz) of stimulation had a greater hypoalgesic effect than high-frequency (100 Hz) stimulation using an experimental pain model. However, Johnson et al. (21) reported that using high-frequency stimulation (20–80 Hz) produced greater analgesic effects than low-frequency stimulation (10 Hz). Consistent with our findings using PENS therapy, Hansson and Ekblom (22) reported significant pain relief at both high and low frequencies of electrical stimulation. In a recent TENS study, Hamza et al. (23) found that mixed-frequency electrical stimulation at 2 and 100 Hz produced greater postoperative analgesic-sparing effects than either 2 Hz or 100 Hz alone. Thus, it seems that both PENS and TENS therapies are most effective when administered using mixed frequencies of electrical stimulation.

The deficiencies in the current study design relate to an inability to effectively blind the patients, although a sham treatment was included because of the unique nature of the electrical sensation produced by the active PENS treatments. In an attempt to minimize investigator bias, all patient assessments were performed by one of the investigators not involved in actually administrating the PENS therapy. To avoid

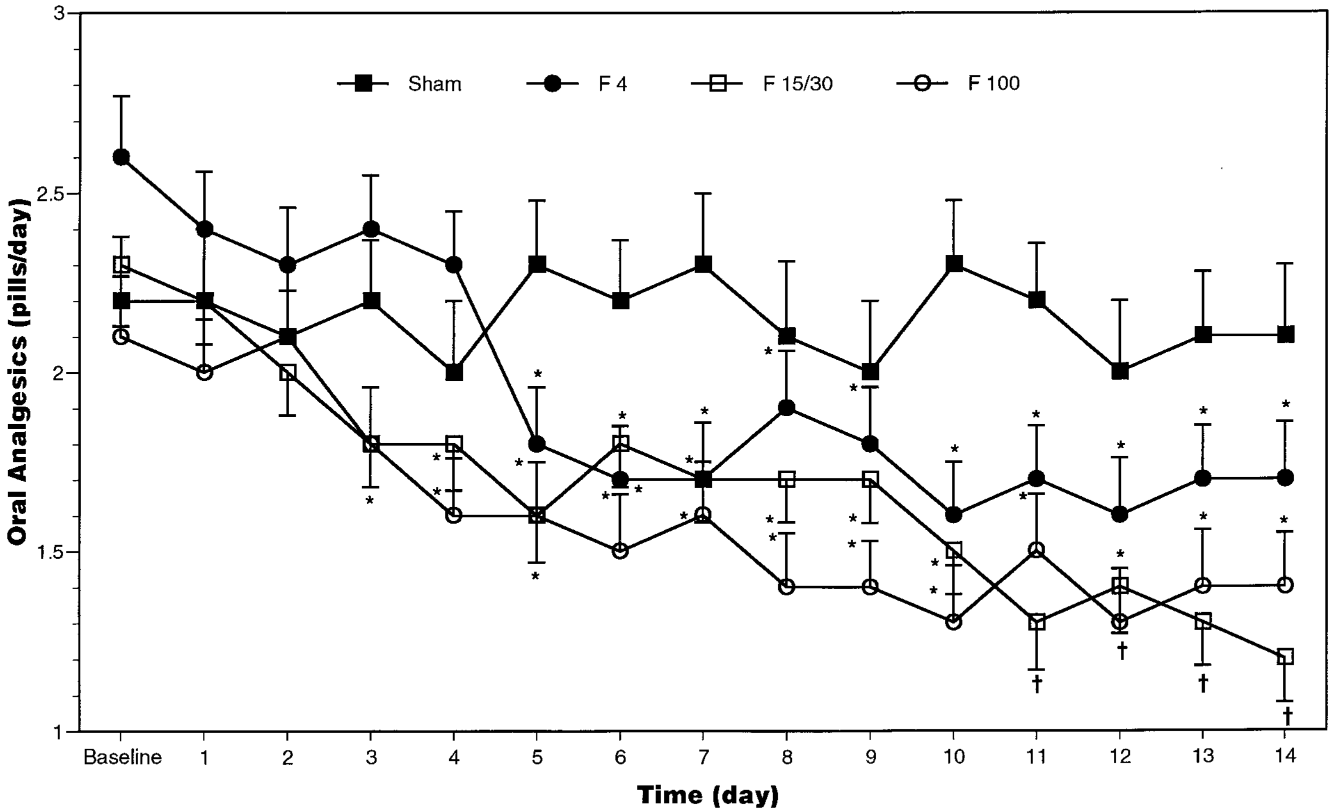

Figure 3. Changes in the daily oral intake of nonopioid analgesic medications (pills per day) during the 2-wk treatment period with each of the four frequency modalities. Data are mean values ± SEM. * $P < 0.05$ and † $P < 0.01$ compared with values 24 h before the first treatment (baseline).

Table 2. Overall Patient Evaluation of the Relative Effectiveness of the Three Different Frequencies (F) and Sham Therapies After All Six Treatment Sessions with Each Modality

	Sham	F 4	F 15/30	F 100
Most desirable modality	2	28*	40*†‡	30*
Improved physical activity	3	30*	38*†‡	29*
Improved sense of well-being	5	23*	44*†‡	28*
Preferred pain therapy	2	28*	40*†‡	30*
Willing to pay extra for therapy	3	25*	45*†‡	27*

Values are expressed as percentages.
* Significantly different from the sham treatments ($P < 0.05$).
† Significantly different from the F4 treatments ($P < 0.05$).
‡ Significantly different from the F100 treatments ($P < 0.05$).

prejudicing patients in favor of the active PENS treatments, the sham treatment was described to the patients as "acupuncture-like" therapy. Because the needles for the sham-PENS treatments were placed in the same dermatomal montage used for the PENS therapy, rather than at specific acupoints, it would be inappropriate to conclude that classic Chinese acupuncture is of no benefit based on these findings. In addition, the use of alternating 15-Hz and 30-Hz frequencies (rather than alternating 4 Hz and 100 Hz) may be a limitation because of the limitations of the electrical generator used in this study. The study was designed to cover the widest possible frequency range (4–100 Hz), but the stimulating device was not able to combine these frequencies when used in the alternating stimulation mode. In a future study, it would be of interest to compare 15-Hz and 30-Hz frequencies of electrical stimulation alone with an alternating 15/30-Hz pattern.

Given the interest of both patients and healthcare providers in unconventional (or so-called complementary) medical therapies (24,25), it is not surprising that nonpharmacologic electroanalgesic therapies (e.g., PENS, electroacupuncture) are increasing in popularity. Future studies in patients with LBP should focus on the effects of these nontraditional modalities on long-term outcome measures (e.g., chronic analgesic use, return to work) when used to supplement conventional analgesic medications and physical therapy as part of a multimodal treatment program (26).

In conclusion, using a mixed frequency (alternating 15 Hz and 30 Hz) of PENS was more effective than either low (4 Hz) or high (100 Hz) frequencies alone in improving short-term outcome measures in patients with LBP.

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