Original Article

Cranial Electrical Stimulation Improves Symptoms and Functional Status in Individuals with Fibromyalgia

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■ Abstract:

**To investigate the effects of microcurrent cranial electrical stimulation (CES) therapy on reducing pain and its associated symptoms in fibromyalgia (FM), we conducted a randomized, controlled, three-group (active CES device, sham device, and usual care alone [UC]), double-blind study to determine the potential benefit of CES therapy for symptom management in FM. Those individuals using the active CES device had a greater decrease in average pain ($p = .023$), fatigue ($p = .071$), and sleep disturbance ($p = .001$) than individuals using the sham device or those receiving usual care alone over time. Additionally, individuals using the active CES device had improved functional status versus the sham device and UC groups over time ($p = .028$).
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Fibromyalgia (FM) is a chronic syndrome characterized by widespread pain, tenderness, and hypersensitivity to pain. FM is often categorized with other pain syndromes, including irritable bowel syndrome, temporomandibular disorder, and headache (Aaron, Burke, & Buchwald, 2000). FM affects between 2% and 4% of the U.S. population (Clauw & Crofford, 2003; Mease, 2005). Women are almost ten times more likely to have FM than men, with the prevalence of FM increasing with age, from <1% in women aged 18-30 years to almost 8% in women aged 55-64 years (Wolfe et al., 2010).

In addition to localized pain, FM is associated with "systemic" responses, including sleep disturbances, fatigue, and enhanced perceived stress, which lead to impaired functional status. Most persons with FM report sleep disturbances that include longer sleep latencies, sleep fragmentation with frequent awakenings, and feelings of not being rested after sleep (Osorio, Gallinaro, Lorenzi-Filho, & Lage, 2006; Theadom & Cropley, 2008; Theadom, Cropley, & Humphrey, 2007), which often contribute to other symptoms in FM, including

fatigue and impaired daytime functioning. In addition, poor sleep quality, which is reported by 88%-98% of persons with FM, contributes to impaired daytime functioning (Cote & Moldofsky, 1997) and fatigue (Wolfe, Hawley, & Wilson, 1996). Pain can disrupt sleep (Affleck, Urrows, Tennen, Higgins, & Abeles, 1996; Nicassio, Moxham, Schuman, & Gevirtz, 2002), and sleep deprivation can produce hyperalgesic changes (Affleck et al., 1996; Lautenbacher, Kundermann, & Krieg, 2006) or make a person more reactive to pain and stress (Hamilton, Catley, & Karlson, 2007). Evidence suggests that fatigue in persons with FM is directly related to sleep disturbances even after controlling for demographic variables and negative affect (Landis et al., 2003; Nicassio et al., 2002; Theadom & Cropley, 2008). Day-to-day increases in fatigue are associated with increased negative affect in those with FM (Zautra, Fasman, Parish, & Davis, 2007). Perceived stress has been reported to be higher in persons with FM compared with healthy control subjects (Theadom & Cropley, 2008; Thieme et al., 2006). High levels of perceived stress are associated with increased pain, more frequent sleep disturbances, and fatigue (Healey et al., 1981; Theadom & Cropley, 2008; Uveges et al., 1990). It has been suggested that FM may be related to hypofunctional stress systems, particularly in the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (Okifuji & Turk, 2006; van Houdenhove, 2003).

The first-line management of FM typically involves pharmacotherapy, with several classes of drugs having been evaluated for efficacy of symptom management, including antidepressants (e.g., amytriptiline, fluoxetine, duloxetine), opiate analgesics (e.g., tramadol), and calcium channel blockers (e.g., pregabalin) (Arnold et al., 2002; Crofford et al., 2005). Although most of these agents have shown some efficacy (in up to 50% of patients), the effects on pain are modest (Arnold, Keck, & Welge, 2000; Arnold et al., 2004). Therefore, there is a need for additional treatment approaches. Based on the evidence that brain processing of pain is disturbed in FM, treatment with actions targeted toward the brain should be particularly promising. Over the years, several types of electrical stimulation of the brain have been used to reduce pain or depression (Rasmussen, 2011; Sampson, Kung, McAlpine, & Sandroni, 2011). However, most electrical stimulation procedures use high-strength current (electroconvulsive therapy) or electrical field (repetitive transcranial electromagnetic stimulation), and therefore the use of these modalities is limited to specialized facilities with trained health care professionals. In contrast, microcurrent cranial electrical stimulation (CES) devices (such as Alpha-Stim; Electromedical Products International, Mineral Wells, TX) deliver modified square-wave biphasic stimulation at 0.5 Hz and 100 μA. Alpha-Stim is FDA approved (FDA K903014) and is suitable for at-home use, expanding the potential range of therapeutic applications.

Whereas the mechanisms of CES are still speculative, it is generally believed that the effects are primarily mediated through a direct action on the brain, likely at the limbic system, hypothalamus, thalamus, and/or the reticular activating system (Ferdjallah, Bostick, & Barr, 1996). Rat studies have shown as much as a three-fold increase in endorphin concentration after only one CES treatment (Krupitsky et al., 1991). In humans, electroencephalographic (EEG) studies have shown that CES can influence alpha activity (increase or decrease) and decrease delta and theta activity. In human participants with pain, CES treatment reportedly changed EEG patterns to more closely resemble pain-free participants. In preliminary clinical studies using the LISS Cranial Stimulator, participants had increases in plasma serotonin and β-endorphin (Liss & Liss, 1996).

Although CES is not a new technique, it is not in common use by rheumatologists practicing conventional medicine with patients who have FM. In response to one study (Lichtbroun, Raice, & Smith, 2001) that lasted 3 weeks and reported significant improvements in FM pain and quality of life in those with active CES compared with those with the sham device, a rheumatologist stated that longer follow-up of these participants, especially in a controlled, double-blind setting, would be useful. Therefore, the goal of the present study was to examine the effects of CES therapy, using a double-blind, randomized, controlled design, on reducing pain and its associated symptoms in FM.

METHODS

Subjects

Potential participants were recruited from rheumatology practices in Central Virginia communities. After persons expressed interest in the study, the study coordinator thoroughly described the study and reviewed the University of Virginia Institutional Review Board–Health Sciences Research–approved consent form with them. Those who agreed to participate signed the consent form, a copy of which was given to the study participant.

Inclusion and Exclusion Criteria

The criteria for inclusion in the study were: 1) meeting the diagnostic criteria for FM as established by the

American College of Rheumatology (Wolfe et al., 1990); 2) reporting an initial pain level ≥3 on a numeric rating scale (NRS) of 0-10; 3) having stable medication use related to FM for ≥4 weeks; and 4) able to read, write, and understand the English language. Potential participants were excluded if they were pregnant or breastfeeding, had epilepsy or a history of seizures, or had a pacemaker and/or other implanted device (e.g., insulin pump, opioid pump, or defibrillator). Forty-six persons with a confirmed diagnosis of FM (3 men and 43 women) were enrolled and assigned to one of the three study groups: usual care alone (UC; n = 15); active CES device (n = 17), and sham device (n = 14). All participants remained on their usual care regimen during the study, including medications.

CES Intervention

Participants in the two device groups were given a brief educational session during the first study visit on using the Alpha-Stim CES device and were instructed to use the device for 60 continuous minutes each day for 8 weeks. Participants in the CES device group received devices that were active and preset at the factory to provide a maximum of 60 minutes of modified square-wave biphasic stimulation at 0.5 Hz and 100 μA, the lowest setting that has been used in earlier studies with patients with FM and below the level of perception. Participants in the sham device group received sham devices that appeared to be activated but did not deliver any stimulation. Because the factory set up the devices, participants were unable to change the settings. To monitor device usage, participants documented at what time and for how long the device was used each day.

Study Questionnaires

Participants completed questionnaires on demographics and general information related to FM, pain, fatigue, sleep disturbances, perceived stress, functional status, and psychologic factors at baseline. All participants recorded their pain ratings each night in the diary using a 0-10 NRS and recorded any unusual symptoms or feelings they experienced that day. The NRS is a simple yet sensitive measure of pain intensity that has yielded reproducible results in many different patients with various diagnoses, including FM (Harris & Clauw, 2008). All participants were instructed to call the study coordinator if they experienced any unusual feelings. One day each week, all participants completed questionnaires on pain (Short-Form McGill Pain Questionnaire [SF-MPQ]), fatigue (Lee's Fatigue Inventory), sleep disturbances (General Sleep Disturbance Scale [GSDS]), perceived stress (Daily Stress Inventory [DSI]), and

functional status (Fibromyalgia Impact Questionnaire [FIQ]).

The SF-MPQ consists of 15 items rated on a 0-4 scale (none, mild, moderate, severe). Researchers have found the SF-MPQ to be reliable and valid (Melzack, 1987). Lee's Fatigue Inventory (Lee, Hicks, & Nino-Murcia, 1991) consists of 18 items that assess fatigue and energy using a 0-10 NRS. Only the fatigue subscale was used for this study. The scale has internal consistency and established validity (Lee et al., 1991). The 21-item GSDS rates the frequency of sleep problems over the past week on a 0-7 scale (0 = never; 7 = every day) and has established reliability and validity (Achterberg, McGraw, & Lawlis, 1981). The DSI measures minor stress and has established reliability and validity (Brantley, Dietz, McKnight, Jones, & Tulley, 1988). Reliability and validity have been documented in persons with FM (Burckhardt, Clark, & Bennett, 1991). Once a week, the study coordinator called all participants to monitor adverse effects and the use of devices.

Blood Pressure Monitoring

Given the potential effects of CES on serotonin biology and the role that serotonin plays in regulating blood pressure, study participants monitored their blood pressure daily over the course of the study with the use of a blood pressure monitor (Model HEM-711DLX; Omron Healthcare, Bannockburn, IL) provided by the study. Participants were instructed to take their blood pressure every evening before going to bed, recording the blood pressure reading in a daily diary. Participants were instructed to call the study coordinator if their blood pressure was reduced by 10% and the reduction was sustained for 1 week; in the event that participants on antihypertensive medications experienced a sustained reduction in blood pressure, they would be instructed to notify their primary care physicians to determine if their medications needed to be reduced.

Statistical Analyses

Separate multilevel models (Littell, Milliken, Stroup, Wolfinger, & Schabenberger, 2006) were used to estimate mean differences among the three groups for each of the pain measures (NRS and SF-MPQ). Model parameters were estimated by restricted maximum likelihood, and the within-subject variance-covariance matrix modeled in the form determined by the Akaike Information Criterion (Littell et al., 2006). To identify possible confounding of medication adjustments, individual slopes were graphically plotted for the outcome measures, drawing reference lines for any changes in medications. These graphs allowed visualization of whether an individual's slope changed at or after the medication adjustment. Random coefficient regression

models (for each outcome) were used to fit the data collected each week with the use of weekly data points to estimate intercepts and slopes for each group. At level 1 (within-subject analysis), the models essentially averaged each participant's intercept and slope while accounting for serial correlation among measurements taken on the same participant. Daily blood pressure data were averaged over every 7 days to create a mean blood pressure for each week of the study. To determine if blood pressure differed over time, a multi-level model analysis was used.

RESULTS

Sample Characteristics
The sample consisted primarily of White women who on average had a high school education or slightly above (Table 1). At baseline, 20%-50% were experiencing an FM flare. Differences in demographic (Table 1) and baseline study variables (Table 2) among the three study groups were tested. There were no significant differences in either demographic (Table 1) or study variables (Table 2) at baseline among the groups.

Of the 116 individuals eligible for the study, 57 (49.1%) enrolled. Reasons for declining to be in the study included a reluctance to commit to filling out the study questionnaires and living too far from the study site. Eighteen individuals expressing interest in the study were excluded because they lived outside the state. Attrition is shown in Figure 1, which reveals that seven individuals did not complete the study (two in the active CES device group, four in the sham device group, and one in the UC group). The major reason given for not completing the study was the amount of questionnaires to be completed weekly.

Symptom Data Analysis
The change in the slope for average pain in the UC and sham device groups both significantly increased over time compared with the active CES group, indicating more pain over the course of the study, whereas the active CES group had a decreasing slope, indicating that the report of pain was decreasing over the course of the study ($p = .023$; Fig. 2A). Slopes for fatigue in the UC and sham device groups remained almost the same, whereas the active CES group had a decreasing slope from baseline to the end of the study, indicating that the report of fatigue was decreasing over the course of the study, although this change was not statistically significant ($p = .071$; Fig. 2B). On the GSDS, any score >3 indicates insomnia, with a lower score on the GSDS indicative of a better outcome. Although all three groups reported scores that were within the insomnia range at baseline, the active CES group was the only group that reported decreased scores over the course of the study and completed the study with scores below the range of insomnia ($p = .001$; Fig. 2C). On the FIQ, scores can range from 0 to 100, with higher scores translating to decreased functional status. Although all three groups reported baseline FIQ scores at ~60, the active CES group was the only group that reported decreased scores over the course of the study and ended the study with statistically lower scores on the FIQ than the UC and sham device groups ($p = .028$; Fig. 2D).

Blood Pressure Data Analysis
Mean weekly systolic blood pressure (SBP) and diastolic blood pressure (DBP) data for the sham device and active CES groups are presented in Figure 3. No significant difference in blood pressure (BP) was observed in the

TABLE 1.
Demographic Data of the Sample

	Total Sample (N = 46)	Active CES Group (N = 17)	Sham Device Group (N = 14)	Usual Care Alone Group (N = 15)	p Value
Age, y (mean ± SD)	50.8 ± 10.4	51.9 ± 10.6	51.5 ± 10.9	48.6 ± 9.8	.61
Gender					.99
Male	3 (6.5%)	1 (5.9%)	1 (7.7%)	1 (6.7%)	
Female	43 (93.5%)	16 (94.1%)	13 (92.3%)	14 (93.3%)	
Race					.97
White	41 (88.9%)	15 (88.9%)	13 (90%)	13 (87.5%)	
Nonwhite	5 (11.1%)	2 (11.1%)	1 (10%)	2 (12.5%)	
Years of education	13.7 ± 2.1	13 ± 1.7	14.1 ± 1.7	14.1 ± 2.7	.18
Experiencing FM flare at baseline					.79
No	21 (45.7%)	14 (80%)	7 (53%)	6 (43.3%)	
Yes	23 (50%)	3 (20%)	6 (40%)	8 (50%)	
Unanswered	2 (4.3%)		1 (7%)	1 (6.7%)	

TABLE 2.
Symptoms at Baseline (Mean ± SD)

	Total Sample (N = 46)	Active CES Group (N = 17)	Sham Device Group (N = 14)	Usual Care Alone Group (N = 15)	p Value
Average pain (0-10 NRS)	5.8 ± 1.8	5.8 ± 1.9	5.7 ± 1.6	6.0 ± 2.1	.88
Fatigue	6.53 ± 1.89	6.12 ± 1.89	6.66 ± 2.0	6.85 ± 1.74	.50
Fibromyalgia impact	64.51 ± 17.5	61.36 ± 18.2	65.98 ± 17.9	66.31 ± 16.9	.65
Depression	26.0 ± 13.3	23.9 ± 11.8	29.5 ± 13.7	24.1 ± 14.2	.36
General sleep disturbance	3.8 ± 0.87	3.75 ± 0.94	4.01 ± 0.80	3.6 ± 0.86	.37
Daily stress impact	3.44 ± 1.3	3.86 ± 1.2	3.05 ± 1.1	3.39 ± 1.3	.65

active CES group versus the sham device group, indicating that the CES had no effect on lowering BP.

DISCUSSION

Analyses of the study data indicate the potential benefit of CES therapy for symptom management in FM. Those individuals using the active device had a greater decrease in average pain, fatigue, and sleep disturbance than individuals using the sham device or those in the UC group over time (Fig. 2). Additionally, individuals using the active CES device had improved functional status versus the sham device and UC groups over time (Fig. 2).

Three pilot studies using the Alpha-Stim CES device have explored the effects of this therapy on pain, sleep, fatigue, depression, and mood, specifically in persons with FM over a 3-week intervention period, and found that participants reported decreased pain and tenderness after using the Alpha-Stim device (Cork et al., 2004; Lichtbroun et al., 2001; Tyers & Smith, 2001). Two of the studies reported improvements in subjective sleep quality (Lichtbroun et al., 2001; Tyers & Smith, 2001), but only one study found a significant reduction in fatigue (Tyers & Smith, 2001). All three studies reported improvements in depression or mood. None of these studies specifically measured stress in persons diagnosed with FM.

The safety of low-strength CES devices has been demonstrated with very few adverse effects (Rose, Taylor, Bourguignon, Utz, & Goehler, 2008; Rose, Taylor, & Bourguignon, 2009). Although the Alpha-Stim Web site suggests that caution should be exercised when using CES with patients being treated with antihypertensive drugs given that the combined use of CES with these drugs could potentially lower the patient's BP, very few studies have measured CES effects on BP. Flemenbaum (1974) conducted an open trial of CES in patients with symptoms of anxiety, depression, and insomnia that were refractory to

treatment. Although BP was not a documented measure, the author stated that "other psychophysiological symptoms like asthma and blood pressure had become controllable by regular medical treatment" by the 6-month follow-up. Taylor, Lee, and Katims (1991) reported on three studies evaluating BP after using transcutaneous CES (TCES), which has the same Hz as the Alpha-Stim device but stimulation is delivered at a higher strength. In the first of those three studies, those receiving one 30-minute 100 Hz TCES session had reductions of SBP and DBP compared with those in the sham device and control groups. A second study
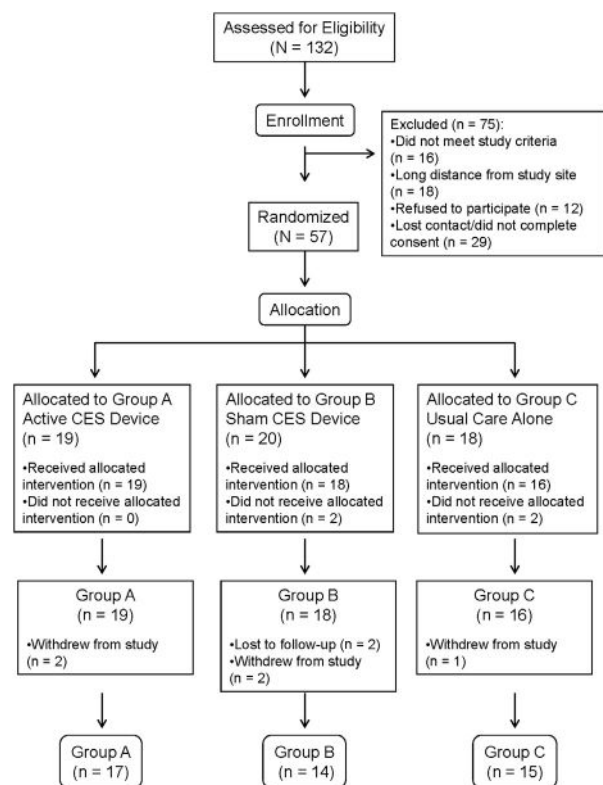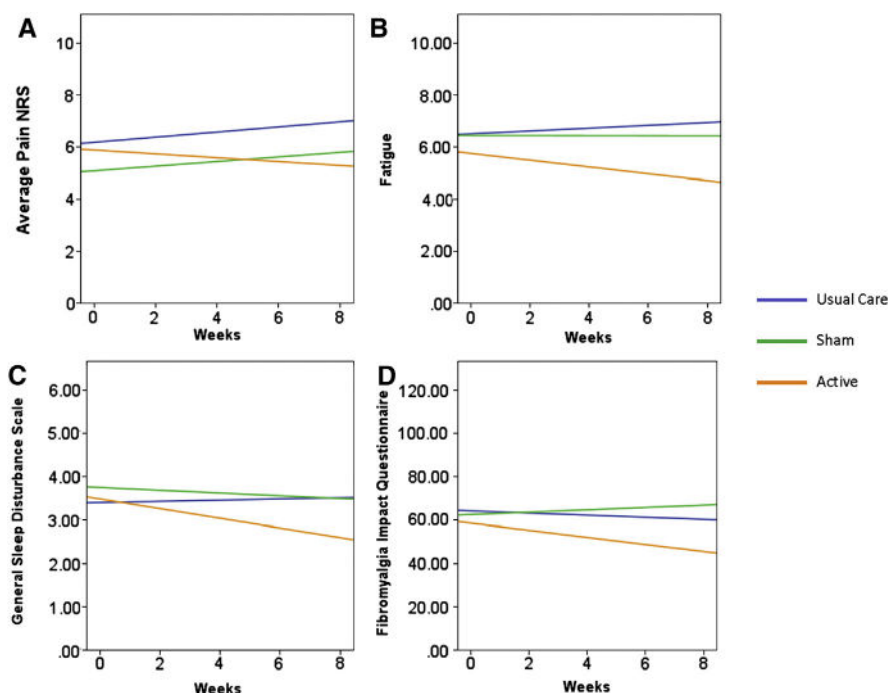

FIGURE 1. ■ CONSORT flow diagram.

FIGURE 2. ■ Change in symptoms and functional status over the course of the study. Separate multilevel models were used to estimate mean differences among the three groups for (**A**) pain ($p = .023$), (**B**) fatigue ($p = .071$), (**C**) sleep disturbance ($p = .001$), and (**D**) functional status over time ($p = .028$). Data presented are mean change over time.

examining the effects of one 30-minute session of 100 Hz TCES reported reductions in SBP but not in DBP or in peripheral vascular tension in the active TCES group compared with the control group. The third study also reported reductions in SBP but not in DBP after one session in the active TCES group compared with the control subjects. Although the overall conclusion of the three studies was that TCES can bring about reductions in BP compared with control subjects, the studies had methodologic limitations, including that TCES was used at only one session. Therefore, it was unclear whether or not the reduction in BP would be sustained over time. Although there have been a few studies on CES effects on BP in other populations, no studies were located that investigated the effects of CES on BP in persons with FM. One study in persons with FM that did not use CES reported that those with FM had higher overall BP levels and greater BP increases in response to stressor tasks compared with healthy control subjects (Light et al., 2009). The present study is the first RCT to demonstrate no effect of CES on either SBP or DBP, illustrating the safety of this device.

Although medication use was not controlled for in the present findings regarding symptoms, those data were collected and will be included in future analyses. No follow-up period was conducted after the end of treatment; however, the influence of participant

expectation was examined. Despite these several weaknesses, the robust design of the present study was developed to address the methodologic issues from previous studies of the Alpha-Stim CES device.
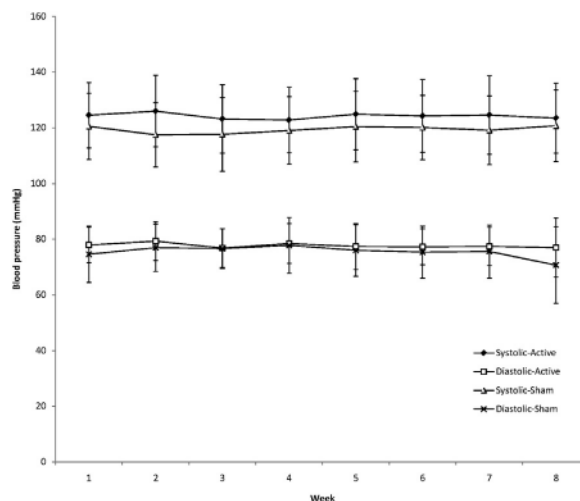

FIGURE 3. ■ Blood pressure measures over the course of the study. Systolic and diastolic blood pressure was recorded daily in the two CES device groups (active and sham) to determine any potential effects on blood pressure. Data presented represent weekly sample mean ± SD for systolic and diastolic blood pressure.

The first methodologic issue of the earlier studies relates to overall study design. Cork et al. (2004) labeled their study as a crossover design; however, a true crossover design was not used, because at the completion of 3 weeks of double-blinded device use (either active or sham), the groups were unblinded and the sham device group was given the opportunity to receive the active CES device for 3 weeks, if desired, similar to a modified wait-list control group rather than a crossover. Consequently, those in the sham device group who elected to continue the study for another 3 weeks knew that they were now using an active device. The study by Tyers and Smith (2001) did not use a sham device group, but rather compared active CES device alone to an active device plus chiropractic therapy. Furthermore, participants in the study were not truly randomized (Tyers & Smith, 2001). Every third person received the active CES device alone, a sampling method that could be biased. Moreover, all participants knew they had an active device.

The second methodologic issue of the earlier studies is that none of those trials collected any data using objective measures. A major roadblock for acceptance of nonpharmacologic complementary therapies is the perception that these therapies do not provide real biologically based effects, but rather that any perceived benefits derive from placebo effects and expectation. Therefore, treatment outcome studies that rely entirely on subjective measures cannot speak to the potential biologic substrates or benefits or address concerns that these modalities are not "real" therapies.

The third methodologic issue of the previous trials relates to statistical analysis. Tyers and Smith (2001) did no statistical analysis and only presented percent improvement. Lichtbroun et al. (2001) had three groups with data at baseline and after intervention but appeared to use multiple *t* tests comparing the baseline and postintervention outcomes for each group separately rather than using an analysis that simultaneously tested all groups against each other (i.e., analysis of covariance). Cork et al. (2004) used an appropriate repeated-measures analysis for comparing baseline to 3-week differences between groups (active and sham devices); however, for the sham device group participants who at the end of the first 3 weeks elected to use the active CES device, only baseline to post–active device use was compared, and no comparison across the three time points or of group differences was conducted.

The last methodologic issue of the earlier studies is the length of the intervention period of only 3 weeks, which was used in all three studies. However, this may be too short a term to determine if improvements will continue, be maintained, or drop off over a longer period.

The present study sought to address the methodologic issues of the earlier trials. Strengths of this study include: the use of a randomized, double-blind, placebo-controlled experimental design; numerous subjective and objective measures of symptoms associated with FM; appropriate statistical analyses; and an 8-week study period. Based on the findings of this study, the use of CES shows promise in the management of FM symptoms, given the decreased pain and significant improvements in other symptoms and functional status. Ideally, patients with FM would be able to obtain a prescription for the device from their health care provider, potentially allowing for coverage of the cost of the device by health insurance. CES devices could be obtained from the company, pharmacy, or the health care provider, as with other medical devices. It is envisioned that the device would be used for symptom management in the home setting by patients with FM based on evidence-based recommendations from their health care providers. Additional analyses of the data from the current study will be conducted to correlate symptom assessments with psychological factors. Sleep actigraphy data also will be analyzed for effects on objective measures of sleep.

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