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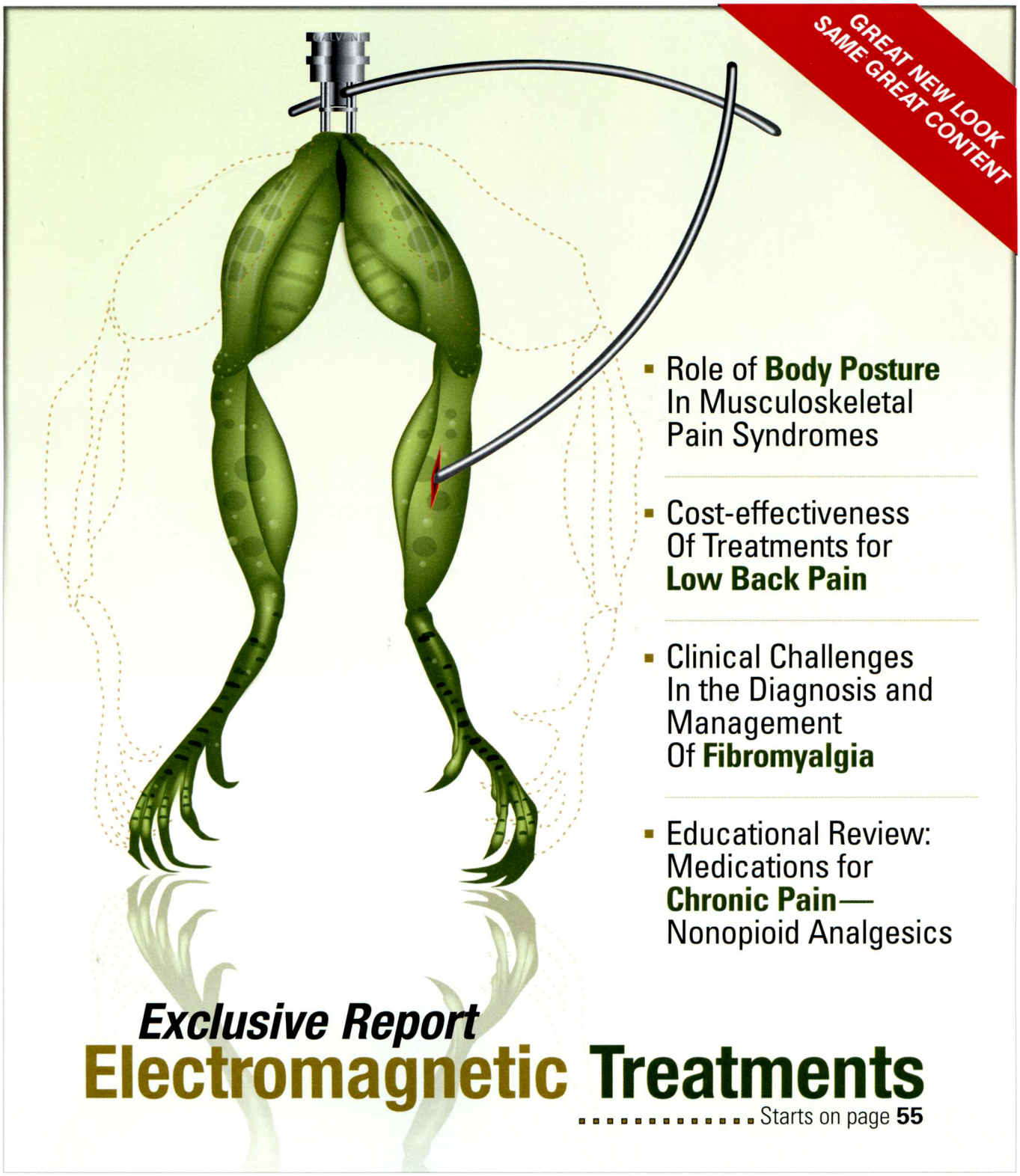
GREAT NEW LOOK
SAME GREAT CONTENT



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Exclusive Report

Electromagnetic Treatments

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Advances in Cranial Electrotherapy Stimulation

Low-level microcurrents applied through the head show promise in the management of a number of pain-related conditions.

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Editor's Note

One of pain research's great revelations in the past decade is that severe pain may cause abnormal neuroplasticity of neurons and/or glial cells in the central nervous system. Unfortunately, central abnormal neuroplasticity may be accompanied by loss of tissue and embedding of the memory of pain. Consequently, there is great interest in whether electromagnetic measures may reverse or palliate this development. *Practical Pain Management* therefore asked Drs. Kirsch and Marksberry to give us an up-to-date status report on cranial electrotherapy stimulation.

Photo courtesy of Daniel L. Kirsch, PhD

Cranial electrotherapy stimulation (CES) is the use of low-level microcurrent applied through the head to the brain for medical and psychiatric/psychological purposes. Although CES is primarily used for the management of anxiety, insomnia, and depression, there is a growing body of evidence that suggests that it will play a role in pain management over the coming decades.[1]

Indeed, in a recent report from the office of the army surgeon general, CES was included as a complementary and alternative (CAM) tier II modality.[1] In one Veteran's Administration study of patients with severe head and neck cancer pain, CES was effective even in patients in whom morphine failed to provide adequate control of their pain.[2] More recently, VA studies have shown CES to be highly effective in the management of patients with chronic pain with such refractory conditions as spinal cord injuries and in refractory populations such as patients with Parkinson's disease (PD).

Modern pain theorists are looking more toward the cerebral cortex to provide an additional basis for understanding pain-related disorders. The successes of CES for pain management may contribute to our understanding of the centrally mediated mechanisms of pain. At the very least, it is rapidly becoming an evidence-based intervention for pain management.

Refractory Pain

An open, clinical trial in pain management was undertaken to assess the effectiveness of CES and microcurrent electrical therapy (MET) using the same device on the body.[3] Twenty patients with refractive chronic pain in a Korean hospital were studied. Patients ranged in age from 18 to 75 years (mean age, 44 years) and included 15 women. Treatments were scheduled for 1 hour per day, 5 days a week, for 3 weeks. The current used ranged from 100 to 300 microamperes and often varied from day to day. Although of those completing the study, 3 of 20 patients obtained no relief from this treatment, 6 obtained complete relief, and an additional 8 patients received significant relief of 33% to 94%.

When length of time they had the pain was evaluated, it was found that patients who had been in pain for 2 and 4 months improved by

94% and 100%, respectively. The researchers concluded that the combination of CES and MET is an effective treatment for patients with chronic pain as well as for pain of shorter duration.

A recent double-blind crossover study of CES for chronic pain in patients with spinal cord injury (SCI) was conducted in the United Kingdom.[4] Treatments were applied twice daily for 53 minutes on 4 consecutive days. After a washout period of 8 weeks, all subjects returned to treatment and were crossed over to the opposite condition (active to sham and sham to active).

Pain levels were significantly lower (P=.0016) in CES-treated subjects than in sham-treated subjects (P=.50). After crossover, sham subjects also showed significant improvement (P<.005). Subjects receiving CES reported using significantly less analgesic medication (46% of the average pre-treatment level; P<.05) and significantly less (53% of the average pre-treatment level; P<.05) combined antidepressant and anxiolytic medications. No significant differences were found between groups in plasma assays. However, there were marked differences (P<.05) between groups in salivary cortisol concentrations in the first arm, and salivary cortisol was also lowered significantly (P<.05) in the sham group from active CES after crossover to active treatment. The authors added that no adverse reactions were reported and that subjects reported a feeling of relaxation that coincided with lower blood pressure.

Another randomly controlled study examined the effects of daily, 1-hour active (N=18) or sham (N=20) CES treatments for 21 consecutive days on pain intensity and interference activities.[5] Subjects consisted of 38 veterans (6 months to 60 years after their SCI) who were receiving care at a Department of Veterans Affairs SCI Center. Treatments were self-administered at home. The active CES group reported significantly decreased daily pain intensity (P=.03) compared with the sham group. The active CES group also showed significantly decreased pain interference (P=.004). The average change in daily pain intensity from pre- to post-session was significantly larger (P=.03) for the active CES group (mean = −0.73) than the sham CES group (mean = −0.08).

After the double-blind phase, the sham group was offered the opportunity to cross over to an open-label phase with an active CES device for another 21 consecutive days. The 17 sham CES participants who subsequently participated in the open-label phase reported significant post-session pain reduction (P=.003). None of the changes in the pain intensity subscale items was statistically significant for any of the 3 groups. However, in paired t-tests for the active CES group, 7 of the 10 individual pain interference subscale items significantly changed and reflected small to moderate effect sizes. This included general activity (Cohen's d = 0.67), self-care (Cohen's d = 0.58), sleep (Cohen's d = 0.53), social activities (Cohen's d = 0.51), normal work (Cohen's d = 0.45), enjoyment of life (Cohen's d = 0.42), and recreational activities (Cohen's d = 0.38). A paired t-test within the active CES group showed that the composite pain interference score for both groups decreased significantly (mean change = 14.6, P=.004, Cohen's d = 0 .50). Neither the individual BPI pain interference subscale items nor the composite pain interference score changed significantly in the sham group (mean change = −4.7, P=.24). After crossover into the open-label phase, pain interference with sleep decreased significantly (Cohen's d = 0.40). Changes were greater in the 3 participants in the active group who had nontraumatic SCI.

The researchers concluded that CES can effectively treat chronic pain in people with SCI and may lower the burden of long-term pharmacologic management.

To further test that conclusion, the VA researchers conducted a comprehensive, 3-year, multi-site study following a similar protocol with the addition of a 6-month arm to determine if the longer treatment period increased the results in pain reduction.[6] The number of days during the follow-up in which the device was used ranged from 5 to 186 (mean = 88.6, standard deviation [SD] = 58.5). For participants who used the device at least once during the 6-month follow-up period, the total number of days the device was used was significantly inversely correlated to depressive symptomatology (10-Item Center for Epidemiologic Studies Depression Scale [CES-D-10], N = 38, r = 0.41, P=.011) and perceived stress (10-Item Perceived Stress Scale [PSS-10], n = 38, r = 0.41, P=.011). People with less depressive symptomatology and less perceived stress were likely to use the device more often than those with more depressive symptomatology and stress. Frequency of use was not significantly related to demographic characteristics or measures of pain, changes in pain, or health obtained either at study entry or at the beginning of follow-up.

At 3 months, 56% of the 41 patients were somewhat or very satisfied with the device. At 6 months' follow-up, 85% of the 26 respondents were somewhat or very satisfied with the device. At both times, more than 50% reported that the device relieved pain at least a moderate amount, and more than 40% reported that it improved their mental health. More than two thirds said they would continue to use the device if they could keep it.

Although CES is primarily used for the management of anxiety, insomnia, and depression, there is a growing body of evidence that suggests that it will play a role in pain management over the coming decades.

Traumatic Brain Injuries

Functional magnetic resonance (fMRI) imaging and low-resolution tomography (LORETA) studies reveal that CES penetrates the cranium and affects the brain consistent with anxiolytic changes (Figure 1).[7,8] Accordingly, it is a small conceptual step to move up the

central nervous system from the spine to the cortex. One of the first reports of the use of CES in mild traumatic brain injuries (mTBI) patients was published in 1988. It was clinical case presentations of two patients undergoing 40 minutes of CES treatment daily for three weeks. The major focus was on their post-traumatic amnesia and subsequent cognitive deficits. The first patient had a 55% improvement in immediate recall and a 56% increase in delayed recall. The second patient had improved 28% on immediate recall and 39% on delayed recall.[9]

A subsequent double-blind, randomly controlled trial of mTBI patients was then published in 1994 on 21 TBI patients who were living in a supervised care home.[10] Their time since injury ranged from 6 months to 32 years and their ages ranged from teenagers to those in their 40s and 50s (the average age was 30 years old). The subjects were randomly assigned to CES treatment (N=10), sham CES treatment (N=5), or "wait in line" controls (N=6). The therapists, patients, and the statistician all remained blind to treatment conditions.

CES or sham CES was administered below sensation threshold Monday through Thursday for 3 weeks for a total of 12 one-hour sessions. It was found that anxiety and depression scores improved significantly in the treatment group, but not in the placebo (sham treated) group or the wait in line control group. Their fatigue scores also improved significantly, as did their cognitive function scores and their Total Mood Disturbance score on the Profile of Mood States psychometric test.

CES is currently being studied for mTBI at Baylor University and a Veterans Affairs Medical Center hospital. The Army is looking into the possibility of studying this as well, with a focus on the possible mechanisms.

Parkinson's Disease

A double-blind, randomized controlled trial by the VA was undertaken to assess the feasibility of treating musculoskeletal pain in the lower back and/or lower extremities in people with PD.[11] Nineteen subjects with PD and pain in the lower back and/or lower extremities were selected. Of the 13 who provided daily pain rating data, 6 were randomly provided with active CES devices and 7 with sham devices to use at home for 40 minutes per day for 6 weeks. They recorded their pain ratings on a 0 to 10 scale immediately before and after each session. Those receiving active CES had, on average, a 1.14-point decrease in pain compared with a 0.23-point decrease for those receiving sham CES (Wilcoxon $Z = -2.20$, $P=.028$). The researchers concluded that use of CES at home by people with PD is feasible and may be somewhat helpful in decreasing pain.

Headaches

A number of studies have reported the benefit of CES in the treatment of headaches—both tension-type and migraine.[12-14] More recently, the effects of CES on intractable headaches in 75 patients with fibromyalgia were studied in a rheumatology practice.[15] This group was given CES treatments for 20 minutes, 4 times a day for 1 month, with a 2-month follow-up. Pain frequency and intensity were rated on a 10-point scale. The patients rated their improvement at 70% or more both immediately following the treatment and at 2-month follow-up.

There are currently 2 migraine headache studies under way. The first study is looking at the reduction in pain by CES during active headaches. The researchers are treating the subjects with CES while measuring pain levels at regular intervals to determine the significance in pain reduction. The other study is looking at the use of CES prophylactically for 20 minutes per day in an effort to prevent migraines. A headache journal will be kept to measure the frequency and duration of headaches, and the outcomes will then be compared with pre-treatment data.

Fibromyalgia

Two studies of CES for fibromyalgia have been published, and 2 more are under way. The forthcoming American study has included functional magnetic resonance imaging (fMRI) imaging. Both of the completed protocols provided for double-blind, placebo-controlled studies. The patients were randomly assigned to receive either CES treatment below sensation threshold at 100 microamperes of current, at 0.5 Hz, on a 50% duty cycle or sham treatment via devices set exactly like the active ones but using electrodes that would not transmit any current. A third group of placebo-controlled subjects sat out the 3 weeks without access to the CES device to serve as controls for any placebo effect in the sham-treated patients.

In the first arm of the studies, only one third of the subjects in each group received actual CES treatment for their fibromyalgia. Following the 3-week trial, the untreated subjects who served as controls were offered 3 weeks of CES treatment for 1 hour per day in an open clinical format. They would often receive treatment at higher current intensity because there would be no need to treat them below sensation level and they could set the current to any level they chose.

The first double-blind study, approved by the Investigational Review Board of the Robert

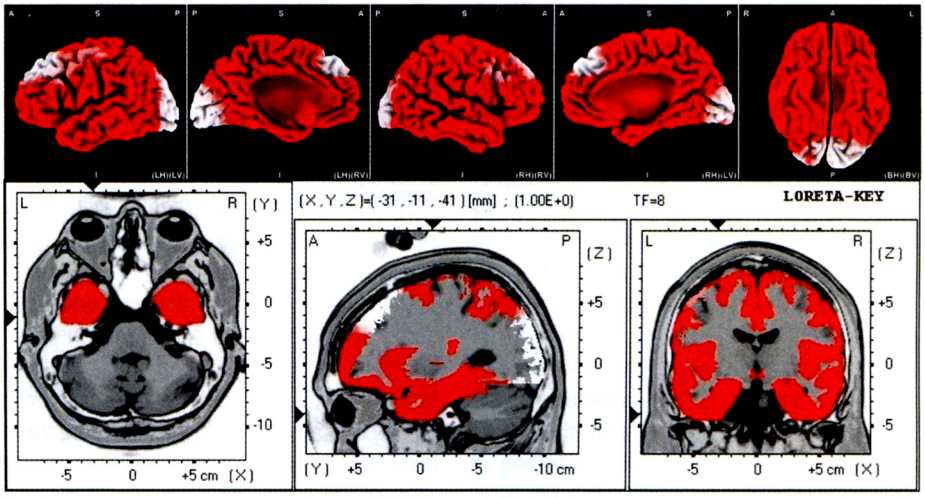


Figure 1. Paired *t*-test for 8-Hz low-resolution tomography (LORETA) showing significant changes in affected areas of the brain after a single 20-minute session of CES at 0.5 Hz. Courtesy of Dr. Richard Kennerly.

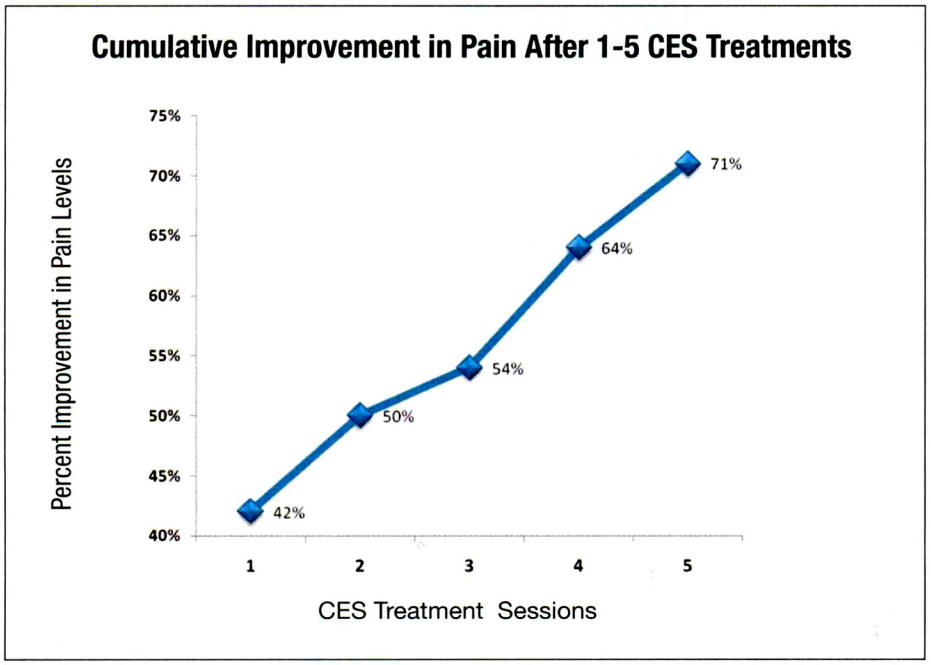


Figure 2. Graph shows cumulative effects across 5 CES treatments in a pain population.
CES, cranial electrotherapy stimulation

Wood Johnson Medical School, involved 60 patients at a rheumatology clinic.[16] There were 20 subjects in each of the 3 groups. The age range was from 23 to 82 years (mean, 50). There were 2 men and 58 women suffering from fibromyalgia from 1 to 40 years (mean, 11 years). Measures included the rheumatologist's evaluation of each patient's tender points pre- and post-study and the patient-completed 10-point self-rating of overall level of pain, quality of sleep, feeling of well-being, and quality of life. Patients also completed the Profile of Mood States, a standardized psychological test of depression, anxiety, fatigue, and cognitive function, among other factors.

It was found that the CES-treated fibromyalgia patients improved significantly on every measure following 3 weeks of CES treatment. Neither the sham-treated nor the placebo-control patients showed improvement in any area measured. Treated patients showed a significant improvement in both tender point scores ($P<.01$) and self-rated scores of general pain level ($P<.002$). The number of subjects rating their quality of sleep as poor dropped from 60% at the beginning of the study to 5% ($P<.02$). In addition, there were significant gains in the self-rated feeling of well-being ($P<.05$) and quality of life ($P<.03$), plus fairly dramatic gains in 6 stress-related psychological test measures of the Profile of Mood States. No placebo effect was found among the sham-treated patients.

After the double-blind study, 23 of the 40 control patients opted for actual CES in an open clinical trial in which they could increase the current in accordance with the standard clinical protocols for CES. They also showed a significant improvement in tender point scores ($P<.001$), self-rated pain ($P<.005$), quality of sleep ($P<.001$), feeling of well-being ($P<.001$), and quality of life ($P<.001$). Overall, there was a 27% reduction in self-rated pain and a 28% decrease in the tender point scores in the treated group.

The authors concluded that CES is as effective as the drug therapies, with no negative side effects, and deserves further consideration as an additional agent for the treatment of fibromyalgia.

A similar protocol was completed by researchers at the pain clinic in Shreveport at Louisiana State University Medical School.[17] Thirty-nine fibromyalgia patients were randomly allocated to CES and 35 patients were allocated to a sham group. Pain intensity, McGill Pain Score, tender point score, profile of mood states, and Oswestry score measurements were taken at baseline and after 3 weeks. Three weeks after crossover of the sham group, all measurements were repeated. Significant CES effects were identified, revealing an improvement in pain intensity ($P<.01$ compared with sham; $P<.001$ in sham group after crossover), McGill score (not significant in initial 3-week trial; $P<0.001$ in sham group after crossover), tender point score ($P<.01$ compared with sham; $P<.001$ in sham group after crossover), and Profile of Mood States ($P<.01$ compared with sham; $P<0.001$ in sham group after crossover). No significant effect was observed on the Oswestry score, which is used as a quantitative measure of disability rather than as a functional assessment of pain, so one might reasonably conclude that longer follow-up would be necessary to see changes in this.

The authors concluded that CES appears to be an effective, well-tolerated treatment for fibromyalgia. Given the demonstrated safety of this noninvasive modality, those involved in the treatment of fibromyalgia should include it in their clinical armamentarium.

Cumulative Effects

In a study of the cumulative effects of CES for chronic pain, 525 consecutive patients with pain in a pain management clinic were administered up to five 20-minute CES treatments.[18] They fell out of the study as the need for additional intervention, usually by injection, became apparent. A total of 343 (65.33%) were female; ages ranged from 9 to 91 years with a mean of 44.49 ± 12.25. After the first treatment, 261 were given a second treatment at their next visit, 160 were given 3 treatments, 57 were given 4 treatments, and 26 were given 5 treatments (see Figure 2). The 79.81% who responded to the first treatment experienced a 42.40% reduction in self-rated pain, with 5.14% declaring themselves pain-free. Cumulative results were seen among those subsequently treated.

In subsequent visits, the number of patients grew smaller. However, the improvement was greater, even though there was a higher initial pain level in these groups. There was an overall 70.64% reduction in pain after 5 treatments, including 15.38% of the remaining patients reporting no pain. Accordingly, this study gives credence to the claim that CES has a positive cumulative effect in refractory patients with a wide range of pain-related disorders.

Discussion

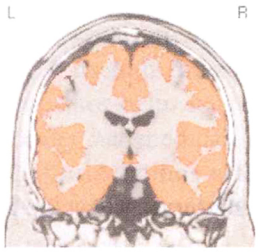
There are more than 150 CES studies representing a wide range of study designs, from mechanistic imaging studies to double-blind, randomized placebo-controlled trials.[19] More needs to be done to elicit the mechanisms for CES in the treatment of pain. Two studies that looked for a possible increase in endorphins did not find it, although one did find an increase in serotonin and a decrease in cholinesterase.[20]The other study found an increase of monoamine oxidase (MAO)-B in blood platelets and an increased concentration of gamma-aminobutyric acid (GABA) in the blood following CES treatments but did not find an increase in serotonin, dopamine, or beta-endorphins in the blood.[21]

Heffernan found that certain types of CES stimulation, applied to the body, reduced the fast Fourier transform root mean square of the electroencephalography (EEG) significantly, leveling out the peaks normally found in patients without pain and changing the EEG into the smooth pattern normally found in pain-free patients. The patients with degenerative joint disease rated their pain as significantly reduced concurrent to the spectral smoothing of the EEG.[22] He also found a significantly concentrated chaos correlation dimension in the EEG following CES, suggesting a heightened organization of a formerly less organized EEG in patients with pain.[23] This also was accompanied by a reduction in pain and stress symptoms.

A growing number of civilian and military pain clinics around the world are now using CES. Most use it as an add-on therapy to other interventions for which results are often augmented by CES. The use of CES in patients with pain is increasingly being supported by research outcomes. Its proven efficacy in controlling the anxiety, insomnia, and depression in pain populations is a significant added benefit. Side effects are rare, minor, and self-limiting, consisting primarily of headaches and skin irritation at the electrode sites in light-skinned people. Once the device is purchased, it costs very little to use and lasts for years. As a cost-effective, non-medication treatment for the management of pain, especially in patients with chronic pain, CES usage can only increase as practitioners become more aware of its existence, efficacy, safety, and ease of use. ■

Author's Bio: *Daniel L. Kirsch, PhD has disclosed that he is the chairman of Electromedical Products International, Inc., and the inventor of the Alpha-Stim technology.*

Dr. Jeffrey A. Marksberry, MD, has disclosed that he is an employee of Electromedical Products International, Inc.



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