

Summary and Critique of CES Monograph “Cranial Electrical Stimulation: Its First Fifty Years, Plus Three” by Ray B Smith, PhD

Overview

The monograph reports five meta-analyses of Cranial Electrotherapy Stimulation (CES) covering various human clinical trials that have been published in the US scientific literature. Each meta-analysis focuses on a particular treatment indication, as follows:

1. Insomnia: 18 studies, 648 subjects, mean improvement 62%
2. Depression: 18 studies, 853 subjects, mean improvement 47%
3. Anxiety: 38 studies, 1495 subjects, mean improvement 58%
4. Drug abstinence: 15 studies, 535 subjects, mean improvement 60%
5. Cognitive dysfunction: 13 studies, 648 subjects, mean improvement 44%

Most of these studies are limited by small samples, heterogeneity of symptoms, and overlap of conditions, which limits their rigorousness and generalizability to specific conditions, though these results may be more reflective of “real world” populations in which comorbidity tends to be the rule rather than the exception. CES appears to be a benign intervention with no serious adverse events.

About CES

Cranial electrotherapy stimulation (CES) provides small pulses of electric current across the head, and has been in clinical use in the US since 1963 and in Europe since 1953. It has been used for the treatment of various conditions, including depression, anxiety, substance abuse, fibromyalgia, and insomnia. The original FDA grandfathered a CES device similar to the one we propose to use, based primarily on safety considerations rather than efficacy.

The studies

In this monograph, a total of 67 studies with 2,910 patients were analyzed. The monograph examines clinical trials of different types, as detailed below.

Sleep studies: 18 studies were reviewed, with 648 patients total, and various sleep disorders. The overall effect size (defined here as overall percent improvement as a result of treatment) was 62% improvement, and when the studies were weighted towards the more rigorous ones, improvement was even stronger at 67%. Seven of these studies were double-blind, three were single blind, three were crossover, and five were open. In many of these studies insomnia was only one symptom forming a part of a larger syndrome. For example, fibromyalgia was seen in about 25% of the patients.

Depression studies: 18 studies were analyzed with 853 patients total. The overall effectiveness was about 47% improvement. Various types of depression were shown to respond to CES. Among these studies, seven were double-blind, two were single blind, two were crossover, and seven were open. In some cases, depression was often just a symptom within a larger syndrome, such as fibromyalgia or substance abuse. Relatively few of these studies examined "pure" major depression as the primary disorder.

Anxiety studies: 38 studies were analyzed, with 1,495 patients. The overall effectiveness was 58% improvement. Various types of anxiety responded to treatment. Among these studies, 21 were double-blind, one was single blind, four were crossover, and 12 were open. As in the prior studies, there was a wide range of diagnoses represented in the anxious samples as a whole, and the sample overall contained more psychiatric inpatients and outpatients than in the other meta-analysis groups.

Cognitive function studies: 13 studies were reviewed, with 648 patients, and an overall effectiveness of 44% improvement. Seven of these studies involved substance abusers and three involved fibromyalgia patients. Substance abusing patients averaged a 60% improvement, whereas fibromyalgia patients had a more modest improvement of 17%. Three of the studies were double-blind, four were single blind, and six were open. Obviously, cognitive dysfunction has several different etiologies. Therefore the range of diagnoses needs to be taken account when interpreting this analysis.

Drug abstinence syndrome studies: 15 studies were analyzed, with 530 patients. The overall effectiveness of CES was a 60% improvement. Among the studies, seven were double-blind, four were single blind, and four were open. The studies covered a wide range of drugs of abuse including alcohol, heroin, cocaine, marijuana, nicotine, and possibly others. The measures used to validate response were also very varied. The strongest responders to CES were methadone and marijuana patients. In controlled studies, it was noted that recidivism rates and discontinuation against medical advice were reduced by one half or more in the CES patients compared to sham.

Proposed mechanisms of action of CES

The mechanism of CES remains largely a mystery. Various models have been proposed: 1) CES may rebalance neurotransmitters in the brain that are out of balance. Animal studies appear to substantiate this particular model. 2) Acupuncture-related theories involving the balance of energy flow throughout the body have also been used to explain the efficacy of CES. CES may interact with the limbic system; the electrodes are placed at various locations on the head and the stimulating current that passes through the head has been shown to travel through the entire brain including the limbic system. Other investigations have suggested that the vascular system is involved in the response to CES as an energy flow system, though this is not well studied. 3) In EEG and MRI studies, CES has been shown to effect changes in the brain's neural firing patterns. No seizures have ever been reported, however. 4) Neurohormonal studies have been completed showing that CES can return the organism to more normal conditions that may be out of balance in depression. Hormones of interest may include DHEA, testosterone, estrogen, and IGF-1. 5) There is a synchronicity theory that suggests that individuals have a "master clock", perhaps representing another view of the circadian system, and that CES may reset this body clock when it has fallen out of synchrony. 6) Finally, CES has been proposed to function as an adaptogen. This term refers to a compound that assists the body in battling the effects of chronic stress. CES may increase the body's resistance to adverse influences by a wide range of physical, chemical, and biochemical factors that have a normalizing effect on the body. This may occur through the cytokine system,

though there are as of yet no published studies examining the relationship between CES and cytokines. The author seems to favor the adaptogen model as the best explanation for the observed benefit of CES.

Recommended approach to treatment

Typical protocols for testing CES involve treating patients from about 45-60 minutes daily for three weeks. The unit is usually set to pulse 100 pulses per second (pps). An unpublished "dose-finding study" carried out by the author appears to suggest an optimal stimulation level, to be set just below the patient's sensation thresholds or "comfort level," which may vary with each patient. This is similar to the approach taken with electroacupuncture, in which currents are set to the maximum that is tolerated comfortable by the patient. It has been observed that once a patient's condition has remitted, CES appears to have no further effect. This seems to prevent any addiction or habit formation to CES. Treatment is often stopped if the patients feel they have reached their maximum level of improvement before the end of the three weeks. In addition, some studies have shown that CES response may occur after as little as 20 minutes of treatment. However it is still recommended that clinicians treat for at least 45 minutes a day and pursue the treatment for about three weeks.

Safety considerations

Among the 2,910 patients examined in the above meta-analyses, none have had significant side effects. No evidence of seizures or migraines has ever been documented in patients receiving CES. CES appears to be safe and effective in children as well as adults, including the elderly. In a 1974 examination sponsored by the FDA, they found no evidence of human harm from this device. From then on, the FDA's position has been that CES is not a significant risk device.

Conclusions and research considerations

The monograph presents a broad overview of the available body of research on CES. The monograph, while exhaustive in its breadth, is somewhat lacking in details about the specific studies, but does include a detailed reference list of 80 articles that have been cited. We have included this list for your reference. As a whole, the reviewed studies are limited by a number of factors, such as generally small samples and heterogenous populations of patients and diagnoses. Other limitations include a variety of different assessment instruments. With regard to depression, the focus of our proposed study, results appear to be promising, with an overall improvement of about 47%, which appears close to what we expect to see with standard antidepressants. However, it should be noted that most of the above studies included patients with conditions other than major depressive disorder, and so the diversity of diagnoses, including substance-abuse, head injuries, fibromyalgia, and others limits the generalizability of these findings to populations with MDD per se, though as mentioned earlier, these samples may be more reflective of those seen in "real world" settings. While the preliminary results are encouraging, clearly we need more rigorous investigations on this treatment modality.

The author of the monograph notes that the crossover design is not optimal for testing CES. Improvement that begins by about a week of treatment tends to continue, even after

treatment is stopped. Therefore there is a notable carryover effect that can confound findings when patients are crossed over from active treatment to sham. For this reason, cross-over designs are not encouraged for testing CES. Also of interest, no placebo effect from CES has been shown when the effect was specifically controlled for.

Regarding safety concerns, CES has been shown to be very benign, with no reports of serious adverse effects. Many patients who use of CES will experience vivid and colorful dreams. This is not harmful or disturbing; in fact, patients tend to look forward to it.

The pilot study that we are proposing will be rigorous, and will recruit patients specifically with the DSM-IV diagnosis of major depressive disorder; we will likewise exclude patients with certain comorbidities as outlined in our protocol. If our pilot study suggests a beneficial effect from CES, it will set the stage for more rigorous studies with larger samples that we hope will provide a more definitive statement as to the efficacy and safety of CES as a treatment for major depressive disorder.