

**Scientific and Clinical
Literature Examination
for the Alpha-Stim[®] M
Microcurrent and
Cranial Electrotherapy Stimulator**

October 20, 2016

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Scientific and Clinical Literature Examination for the Alpha-Stim® M Microcurrent and Cranial Electrotherapy Stimulator

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Scientific and Clinical Literature Examination for the Alpha-Stim® M Cranial Electrotherapy Stimulator (CES)

This literature review of Alpha-Stim® technology was written by Daniel L. Kirsch, PhD, Jeffrey A. Marksberry, MD, and Larry Price, PhD. Full Curriculum Vitae's for the reviewers are located in section 10-5 of the Technical File.

Report Reviewed and Approved by:

A handwritten signature in black ink, appearing to read 'Jeff Marksberry', written in a cursive style.

Jeffrey A. Marksberry, MD
Electromedical Products International, Inc.

Date: October 20, 2016

Part I: INTRODUCTION

1. Purpose

This report presents clinical data and relevant scientific literature for the use, effectiveness and the risk/benefit of the Alpha-Stim® M cranial electrotherapy stimulation (CES) for the treatment of anxiety, insomnia, depression and microcurrent electrical therapy (MET) for pain. The purpose of the report is to summarize the scientific and clinical data on CES treatment of anxiety, insomnia, depression and pain. The strengths and limitations of the research studies included in this report will be evaluated as follows: study objectives, subjects, methods, results and quality of the research.

2. The Alpha-Stim® M

The Alpha-Stim® cranial electrotherapy stimulator is a neurological medical device that uses low level electrical signals, delivering a current of 100 to 600 microamperes (μA), at a frequency of 0.5 Hz, applied transcranially for the treatment of anxiety, insomnia, depression and pain. The device consists of an electrical pulse generator which is operated by 2 double AA batteries, patient-connect hardware which consists of ear clip electrodes, and an electroconductive solution for moistening the electrodes to assure good electrical contact through the skin. The device is accompanied by an owner's manual that provides directions for use and warnings against unsafe use. Alpha-Stim® CES treatment has been available in doctor's offices, clinics, and hospitals, and for home use upon an order from a licensed health care provider, in the United States since 1981. It is sold over the counter (without a prescription) worldwide except in the USA and Canada. When properly used in accordance with the instructions, Alpha-Stim® CES devices are safe, effective, and simple to use. A graphic representation of the parts and labels of an Alpha-Stim® M device is shown below in Figure 1. An Alpha-Stim® M Owner's Manual is attached to this submission.



Figure 1. Alpha-Stim® M

Alpha-Stim® technology uses a complex and patented bipolar asymmetric waveform consisting of multiple frequencies at a 50% duty cycle having a maximum pulse width of 0.5 Hz (2 seconds) provided over a ten second time frame with random factors to avoid habituation by the nervous system. The maximum current level is 600 microamperes. The impedance range within which the waveform parameters remain valid is from 100 Ω to 10 K Ω . It is balanced to achieve 0 net current in either direction as shown in Figure 2. The waveform is patented. (US patent No. 8612008, Europe, China, Russian and other patents pending). Used in 8 generations of Alpha-

Stim® products since 1981, the unique Alpha-Stim® technology has been proven consistently effective in many randomized double blind sham controlled studies and has been used safely by millions of people worldwide. Through the alteration of brain physics (brainwave electrical activities) and brain chemistry (neurotransmitters), research has shown that CES can significantly decrease anxiety, insomnia, depression and pain when used at a medical clinic or at home by the patient (See Part II. Review of Scientific and Clinical Literature on CES). In over 30 years of use, there have never been any significant side effects reported.

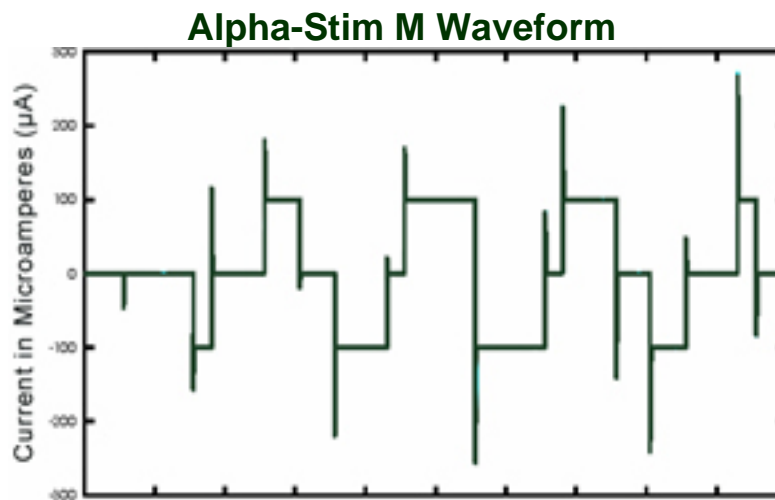


Figure 2. The Alpha-Stim® M waveform shown over a ten second time period.

Regulatory Status

The Alpha-Stim® M has US FDA 510(k) premarket clearance and has Underwriter Laboratories (UL) Safety Standards Certification in the US for the treatment of anxiety, insomnia and depression. The Alpha-Stim® M is a licensed medical device in Canada (Health Canada) The Alpha-Stim® M has been granted the CE Mark for Europe, has approval in many other countries including Japan and has International Standards Organization (ISO) certification. See Appendix A for regulatory letters of premarket clearance, European (CE Mark), Canadian, Chinese, and Japanese approvals, and safety certification.

3. Cranial Electrotherapy Stimulation

3.1. History of CES

While electricity has historically been used therapeutically on all areas of the body, cranial electrotherapy stimulation, or CES is a specific term denoting electrical stimulation to the brain. CES involves devices that deliver electrical currents transcranially through electrodes. The brain functions electrochemically and can readily be modulated by electrical intervention. Unlike peripheral electromedicine, CES has been less frequently cited in older, historic literature. Krueger is perhaps the first person to mention this use, noting in 1743 that the experimental self-application of electric current allowed him to sleep better (Kratzenstein, 1745). Aldini wrote in depth about its use in mental disease in 1802 (Aldini, 1803). Marat described the application of strong currents across the head that produced convulsions (Marat, 1784). These latter studies were a precursor to the development of electroconvulsive shock treatment (ECT) in the 1930s (Kaliwinsky, 1939).

Originally referred to as “electrosleep,” the intended purpose of early CES devices had been to induce sleep through the application of small amounts of electrical stimulation to the brain as a primary or adjunctive modality of the “sleep cure” widely employed in psychiatry throughout the early part of the 20th century.

In 1902, the French physiologist Stephen Leduc produced sleep in rabbits by the transcranial delivery of 35 volts, at 110 Hz. He attempted to extend his successes to himself with 100 Hz direct currents (DC) of 3 to 12 milliamperes (mA) of a 10% duration. While he remained conscious, he could not move or speak, and experienced blunted sensations of pain.

Using himself as a test subject, Leduc attached an electrode to his forehead and another electrode near the base of his spine. His sensations after administering a series of 50-volt pulses in the milliamperage range were similar to “... a dream but I was conscious of the absence of power to move and an inability to communicate with my colleagues; I felt the contact, the pinches, striking of pins in my forearm, but the sensations were dulled” (Leduc, 1903; Leduc et al., 1903). Despite Leduc’s reported success with electroanalgesia, these findings failed to arouse significant interest among clinical practitioners outside of the former Soviet Union and France.

In 1914 Louise Robinovitch distinguished between electrically induced sleep and analgesia, producing electric sleep in patients suffering from insomnia by applying a negative electrode to the forehead and a positive electrode to the hand. She reported that patients fell asleep within the one hour treatment period and continued to sleep after the current was discontinued (Robinovitch, 1914).

The work of Gilyarovsky and associates in the former USSR were responsible for advancing the use of electrosleep in clinical settings during the decades of the Cold War. According to declassified government documents containing English translations of the authors’ observations:

“In hospitals the procedure is performed in bed. The patient undresses and lies down as though for his night’s sleep. Usually electric sleep is administered simultaneously to a group of patients in a separate half-darkened ward. Gradually the sensation of heaviness of the lids, ideas of ‘going off’ appear, sometimes a mild dizziness occurs, and a drowsy state supervenes, which gradually deepens to the degree of physiological sleep. The patient is in a calm relaxed position, usually on his side; the respiration becomes deeper, slower and more regular; the pulse slows up by several beats a minute” (Gilyarovsky et al., 1958).

In its contemporary form, CES is a descendant of the aforementioned investigations. In the electroconvulsive shock paradigm, 120 volts at 60 Hz and 500 mA was applied in 0.2 second bursts. From this electroanesthesia was derived, which used a reduced current level of 2 volts at 700 Hz and 30 mA given for the duration of major surgery. A final derivation to electrosleep was produced by 700 Hz at 1 volt and 5 mA. Today’s CES devices typically deliver a range from 0.5 to 15,000 Hz from a 9 volt or 1.5 volt AA or AAA battery source supplying from 50 microamperes (µA) to 4 mA.

CES Comes to America

The attention of psychiatrists and experimental psychologists in the United States was heightened by clinical research conducted in Europe involving electrosleep that appeared in English language journals during the late 1960s (Kirsch, 2002; Dodge, 1967). Professional

interest coupled with popular notions of “instant sleep” achieved through techno-wizardry prompted independent consultant and businessman, Arsen Iwanovsky to market a device he named the Electrosone 50 as America’s first portable, battery-operated cranioelectrical sleep generator around 1963 (Iwanovsky et al., 1968). Prior to the device’s debut, Iwanovsky published the basic circuit schematics of the unit for the benefit of biomedical researchers and experimenters (Iwanovsky, 1971).

According to promotional materials that accompanied the device, the Electrosone 50 was used for “Assisting in the fields of relaxation and sleep... [A] very weak, pulsating electrical current produced and controlled in this instrument passes through the patient’s brain by means of four electrodes: two are placed on the closed eyelids and in the back of the neck (occipital area).” (Iwanovsky). The sleek and compact Electrosone represented a considerable improvement over the bulkiness of Gilyarovsky’s original design due to the unit’s dependence on vacuum tube technology from the 1950s (Magora et al., 1965).

When CES was first utilized in the USA, psychopharmaceutical treatments were less well known than they are today so intense interest was generated by the possibilities that this new method offered for treating difficult psychiatric cases. Studies were conducted in university laboratories to identify the mechanisms of action that putatively were responsible for the clinical responses beginning to be observed. More devices came on the market with names such as Anesthelec, Diastim, Electrodorn, Electroson, Neurometer, Neurotone, Neurotransmitter Modulator, RelaxPak and Somlec, among others (Kirsch, 2002).

The clinical intent was that electrosleep treatment should induce sleep immediately when the current was applied to the patient’s head, and that the patient should remain asleep naturally, once the sleep was induced. That did not occur, however, even though many of the earliest clinical studies in the USA focused on discovering the waveform that would successfully induce sleep (Iwanovsky, 1968). Researchers used a variety of frequencies, current levels, and waveforms as well as electrode configurations. Unfortunately, not all reports of CES use included descriptions of the waveform used, and these varied widely. Older devices utilized frequencies ranging from 100 to 4,000 hertz (Hz) and current levels up to 8 milliamperes (mA) while more recent devices utilize frequencies as low as 0.5 Hz and current intensity as low as 100 microamperes (μ A). Of course, all these variables meant that the results from different CES devices varied as well, and this remains true with the devices commercially available today (Kirsch, 2002).

The evolution of electrode placements was particularly notable. As the treatment arrived in the U.S. from Europe, devices such as the Electrosone used saline saturated gauze pads wrapped around metal plates placed over each closed eyelid connected to electrodes placed over the mastoids. At the time it was thought that the eyes were the best, if not the only place where electricity could enter the brain. Later, because of the discomfort from the pressure on the eyelids and the side effect of blurred vision lasting approximately 15 to 45 minutes immediately following treatment, researchers began to place the frontal electrodes just above each eyebrow while the rear electrodes remained over the mastoids. Subsequently the frontal electrodes were no longer used, with electrodes only placed on the mastoid processes just behind each ear, so that the current went laterally across the head instead of anterior-posteriorly. This caused vertigo so the electrodes were next moved to the temples. The typical electrode placement used today employs ear clip electrodes clipped to each ear lobe although some devices still direct the current across the temples (Kirsch, 2002).

Early Electroencephalography Research and the Subsequent Expansion Into the Treatment of Mood Disorders

When a treatment strategy that would reliably induce sleep could not be found, EEG studies were initiated to examine the possible neurophysiologic events that occurred when current was applied across the head. The first study was designed to see if there were any changes in the EEG relevant to sleep. The findings were inconclusive as some patients slept when in the treatment condition, some slept in the control condition, while others never slept during any phase of the study (Magora et al., 1965).

Another EEG study found that one 30 minute electrosleep treatment per day for five days produced slower EEG frequencies with increased amplitude in the fronto-temporal areas in all of the patients. Most patients also showed increased quality and quantity of the EEG alpha rhythm with increased amplitude in the occipital-parietal leads (Mckenzie et al., 1971).

Weiss (1973) conducted an early EEG study in a sleep laboratory, in which patients who had been diagnosed with insomnia were allowed to sleep in their usual way in the university laboratory while having their EEG monitored. Five patients were given subsensory electrosleep treatments 30 minutes daily for 10 days, and five were given sham treatments. Subsequent monitoring of their EEG sleep patterns showed that patients receiving actual treatment went to sleep faster, spent more time in stage 4 sleep during the night, had fewer nocturnal awakenings, went back to sleep sooner when they did awaken in the night, and reported significantly more restful and restorative sleep upon awakening the next morning than did the sham group. All these changes were maintained at a two year follow up (Cartwright et al., 1975).

Soon thereafter, a growing number of researchers demonstrated that CES not only ensured sound, restful sleep for patients suffering from insomnia, but was an effective treatment for stress-related symptoms as well, as determined through the use of various psychological assessment scales of anxiety and depression (e.g., Hamilton Anxiety Scale, State/Trait Anxiety Inventory, Zung Depression Scale, Profile of Mood States, etc.). More importantly, it was confirmed that numerous psychophysiologic measures, including sleep patterns, improved regardless of whether the patient slept during the treatment or not (Leduc, 1903; Magora et al., 1965).

As a result, the term “electrosleep” was dropped in the USA although it remains in use in parts of Europe. Instead, American researchers called it by several names, including “transcranial electrostimulation.” In 1978 the FDA’s Neurology Panel suggested that it be called “cranial electrotherapy.” The FDA agreed, but added the word “stimulation” to the phrase, since they were not yet convinced that it was therapeutic. The FDA also determined that CES would be only available by prescription, making the USA the only country in the world in which an order from a licensed health care practitioner must be obtained for its use, a restriction continued through today.

CES now has a foundation of more than 50 years of research and clinical use in the USA from which proof of safety and effectiveness have been well established.

Nasrallah (2009) commented on psychiatry’s future, predicting that “neurostimulation for brain repair” was one of the top six trends in clinical practice. He cited repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS); invasive and costly medical procedures. CES is also neurostimulation for brain repair and in contrast is a more cost-effective, non-invasive type of device that can be safely used by patients at home. It

can be used as an adjunct to medication or psychotherapy or as a stand-alone treatment. The only contraindications to CES are pregnancy and having a pacemaker or other implanted electrical device, and even those are doubtful.

The FDA recognizes CES devices for the treatment of anxiety, insomnia and depression (Code of Federal Regulations, 2009).

3.2. The Mechanisms of Cranial Electrotherapy Stimulation

The foundation of the CES treatment mechanism is based on the early findings by Jarzembski's research team at the University of Wisconsin. When CES was applied to the head of a primate with an implanted sensor, it was found that 42% of the externally applied electric current penetrated every sector of the brain, with the flow of current mainly canalized along the limbic system (Jarzembski et al., 1970). The limbic system is the area of the brain that regulates emotion and memory. It directly connects the lower and higher brain functions, influencing emotions, the visceral responses to those emotions, motivation, mood, and sensations of pain and pleasure. Later research conducted by Ferdjallah at the University of Texas at Austin Biomedical Engineering department, calculated from every 1 mA of current, 5 μ A/cm reaches the hypothalamus at 13.30 mm deep, and that is sufficient to affect the production and secretion of neurotransmitters (Ferdjallah et al., 1996).

In addition to the limbic system, CES may stimulate regions that regulate pain messages, neurotransmitter function, and hormone production via the hypothalamic-pituitary-adrenal axis (Kirsch, 2006). CES treatments induce changes in the EEG as seen in Figure 3, increasing alpha (8-12 Hz) relative power and decreasing relative power in the delta (0–3.5 Hz) and beta (12.5-30 Hz) frequencies (Kennerly, 2004). Increased alpha correlates with improved relaxation and increased mental alertness or clarity. Decreased delta waves indicate a reduction in fatigue. Beta wave reductions between 20-30 Hz correlate with decreases in anxiety, ruminative thoughts, and obsessive/compulsive-like behaviors.

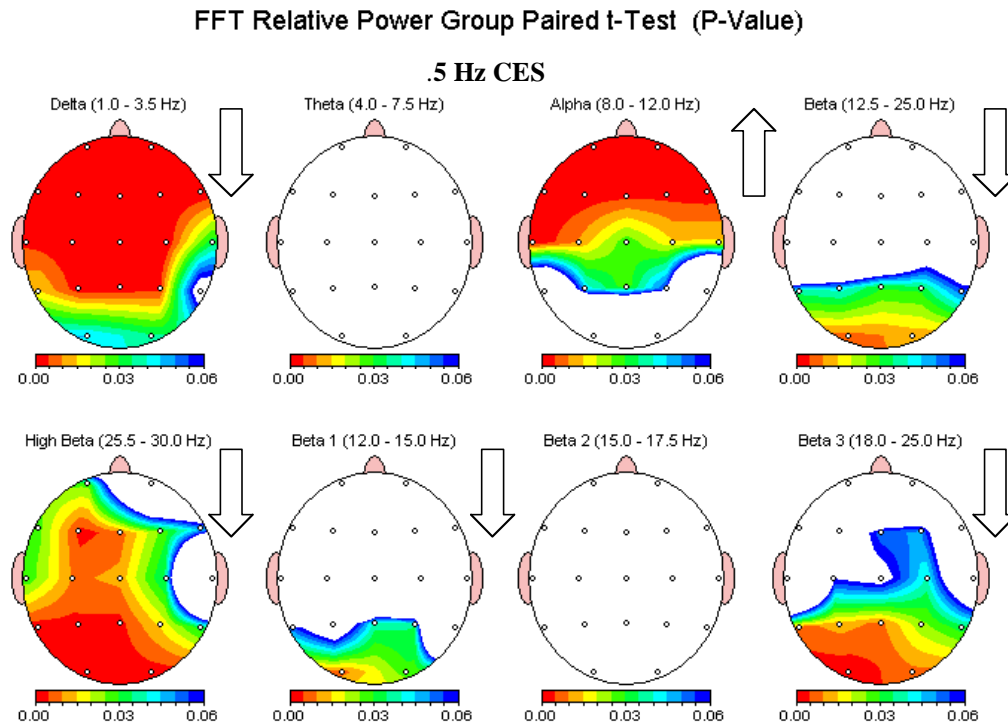


Figure 3. Significant changes in the electroencephalogram (EEG) after CES treatment organized by level of significance within frequency bands where red is the most significant ($p < .001$) and blue is the least significant ($p < .06$).

From: Kennerly, R. QEEG analysis of cranial electrotherapy: a pilot study. *Journal of Neurotherapy*. 2004; 8:112-113

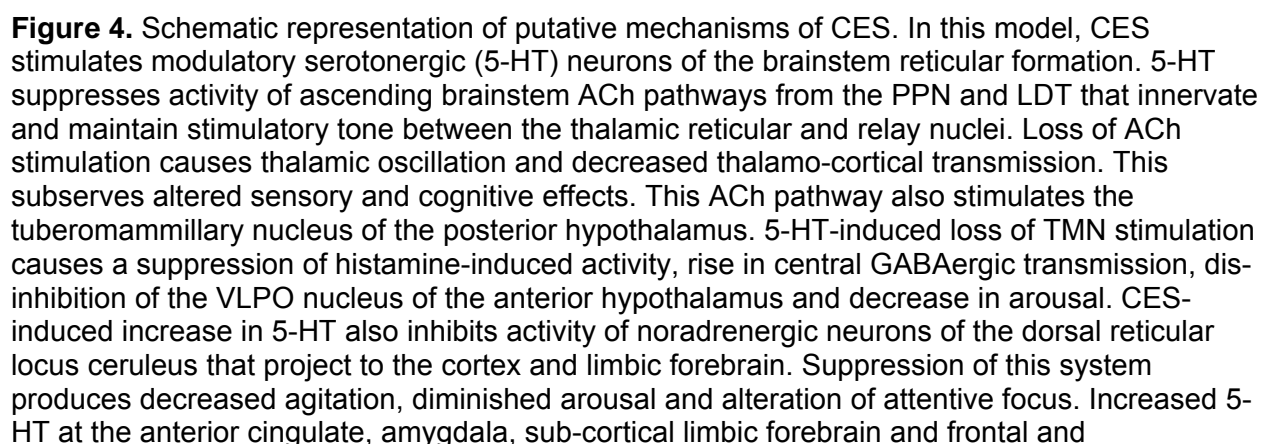
Low resolution electromagnetic tomography (LORETA) and functional magnetic resonance imaging (fMRI) studies showed that CES reached all cortical and subcortical areas of the brain, producing changes similar to those induced by anxiolytic medications (Feusner, et al., 2012; Bystritsky, et al., 2009; Kennerly, 2006). Many symptoms seen in psychiatric conditions, such as anxiety and insomnia, are thought to be exacerbated by excess cortical activation (Yassa et al., 2012; Bonnet et al., 2010). An fMRI study in an anxiety population showed that CES causes cortical brain deactivation in the midline frontal and parietal regions of the brain after one 20 minute treatment (Feusner et al., 2012). Another fMRI study was conducted as part of a randomized double blind study in a pain population revealed significantly greater decreases in average pain levels ($P = .023$) than those using a sham device or receiving usual care without CES. The active CES device was shown to significantly decrease activation of pain processing regions of the brain, such as the cingulate gyrus, insula and prefrontal cortex, compared to the sham device (Taylor et al., 2013).

CES treatments have been found to induce changes in neurohormones and neurotransmitters that have been implicated in psychiatric disorders: substantial increases in beta endorphins, adrenocorticotrophic hormone (ACTH), and serotonin; moderate increases in melatonin, norepinephrine, and cortisol, and modest increases in cholinesterase (Shealy et al., 1998; Liss et al., 1996) Table 1 shows the chemical changes in the brain identified from CES research after one 20 minute CES treatment.

Neurochemical	Change	Implications
Beta Endorphin	↑ 98%	Decreases pain
ACTH	↑ 75%	Promotes homeostasis
Serotonin (5HT)	↑ 50%	Improves mood Increases pain tolerance Decreases insomnia
Melatonin	↑ 25%	Induces sleep
Norepinephrine	↑ 24%	Increases pleasure Increases arousal
Cortisol	↓ 18%	Reduces stress response
Cholinesterase	↑ 8%	Increases relaxation

Table 1. Mean changes in neurochemicals in blood plasma after one CES session. From Kirsch, DL and Nichols, F. (2013). Information from CES research conducted by Shealy et al. (1998) and Liss and Liss (1996).

Numerous studies have demonstrated the role of the modulatory serotonergic (5-HT) neurons in cognition, emotional state, arousal, and pain modulation. Serotonergic dysfunction has been shown in mood (Mann, 1999) anxiety (Charney et al., 2002) and particular types of psychotic disorders (Lieberman et al., 1998). When applied to the ear lobes, it is likely that CES acts at modulatory serotonergic neurons within the brainstem reticular formation (see Figure 4). These serotonergic neurons ascend to innervate the rostral brainstem, as well as midbrain and forebrain structures, and descend to form polysynaptic contacts on pools of afferent neurons within the spinal dorsal horn (Dahlstrom et al., 1964). In addition, the serotonergic system regulates the release of acetylcholine (ACh) from neurons of the lateral-dorsal tegmentum (LDT) and pedunculopontine nucleus (PPN) of the brainstem. These fibers project to thalamic (inhibitory) reticular and (stimulatory) relay nuclei, and mediate thalamo-cortical de-synchrony and arousal (Steriade et al., 1988). Cholinergic projections from the LDT and PPN also project to the tuberomammillary nucleus (TMN) of the posterior hypothalamus that regulates arousal via central histaminergic stimulation of thalamic relay nuclei (Lin et al., 1988).



temporoparietal cortices regulates mood and arousal. 5-HT also acts at the cingulate and amygdala, in concert with effects at midbrain (periaqueductal gray) and via descending bulbospinal connections (within the dorsal horn) to mediate pain (refer to text for details). **(+)** = stimulatory effects; **(-)** = inhibitory effects. Abbreviations: *ACh*: acetylcholine; *5-HT*: serotonin; *CN*: central nucleus of the amygdala; *NE*: norepinephrine, *TMN*: tuberomammillary nucleus; *VLPO*: ventroposterior lateral nucleus; *PPN*: pedunculo-pontine nucleus; *LDT*: laterodorsal tegmental nucleus; *RMC*, *LC*: Reticular magnocellular nucleus/locus ceruleus

A prospective fMRI mechanistic study found Alpha-Stim cranial electrotherapy stimulation (CES) can normalize the functional connectivity in intrinsic neural circuits of adolescents with Tourette's Syndrome (TS) (Qiao, 2015). Forty-two adolescents <12 years old were given 24 weeks of daily CES treatments, 8 had fMRIs and all completed the Yale Global Tic Severity Scale (YGTSS).

Resting-state fMRI was performed on a 3T magnetic resonance unit (GE Signa Medical Systems, Twinspeed, Milwaukee). A birdcage head coil and restraining foam pads were used to minimize head motion. Functional data was acquired using a gradient-echo, T2-weighted echo-planar imaging with (BOLD) contrast pulse sequence. Thirty-two contiguous axial slices that covered the entire hemisphere and brainstem were acquired along the AC–PC plane, with a 64 × 64 matrix (repetition time = 2000 msec, echo time = 30 msec, field of view = 24cm × 24 cm, and slice thickness = 4 mm without a gap).

For fMRI analysis, Independent component analysis (ICA) with a hierarchical partner matching method was used to examine the functional connectivity between regions within the cortico-striato-thalamo-cortical (CSTC) circuit. Granger causality was used to investigate effective connectivity among these regions detected by ICA. The authors then performed pattern classification on independent components with significant group differences that served as endophenotype markers to distinguish between the adolescents initial TS markers and the normalized ones after CES.

When little is known *apriori* about the mechanistic nature of the neural system, as in this study, an attempt is made to bridge functional and effective connectivity approaches to provide a foundation for understanding the mechanisms of action that can then lead to models of effective and functional network connectivity. To this end, the authors use a state-of-the-art approach, independent components analysis (ICA) to identify regions of activation from blood oxygenation level dependent (BOLD) signal data that are involved in resting state fMRI data. This step is followed by hierarchical partner matching (HPM) to identify functional brain networks. Next, Granger Causality was used to test for significant causal relations between identified regions of interest. Granger Causality captures temporal properties of fMRI data while also controlling for the simultaneous regression of all variables in the model. These models are also known as multivariate autoregressive time series models (Price, 2012). Finally, the authors also used pattern recognition methods based on resting state fMRI data to verify the normalization in intrinsic brain functional activity and activation connectivity between TS patients before and after CES treatment.

One challenge when studying a condition such as TS is that the disease involves the motor and control systems from a biophysical and neural perspective. Importantly, the authors found that both the motor and control parts of the CTSC system lack normalization in TS patients. Specifically, they found that an increase in functional activity and connectivity in the posterior cingulate cortex (PCC) suggesting normalization (*i.e.*, return to a state similar to that of non-TS) of functional deficits associated with impaired motor inhibition.

After CES, subjects exhibited altered spontaneous functional connectivity in brain areas within the CSTC circuit involved in motor generation or control, including SMA, caudate, PFC, ACC, and default mode network (DMN), primary in the PCC. The functional activity and connectivity in motor pathways were *suppressed*, while activations in the control portions of CSTC loop were *increased* in subjects after CES compared with before CES.

Confirming the fMRI changes were decreased in YGTSS scores indicating a decrease in motor and vocal tics from baseline to the end of the 24 weeks of CES treatment was also highly significant, $p = < 0.01$. The effect size, $d = 3.913$, was ≥ 0.8 and therefore considered large (Cohen, 1988).

The Authors' concluded that the normalization of the balance between motor and control portions of the CSTC circuit may result in the recovery of TS adolescents.

Summary of Treatment Mechanisms of CES

Based on evidence available to date from fMRI, EEG and clinical neurotransmitter testing, the treatment mechanisms of CES may be summarized as:

- CES deactivates brain regions associated with overuse consistent with various disorders such as anxiety, insomnia, depression and pain (Taylor et al., 2013; Feusner et al., 2012).
- CES can normalize the balance in functional connectivity of intrinsic neural circuits in the brain (Qiao, 2015).
- CES increases alpha activity (inducing relaxation and a pleasant state of well-being), decreases delta (increasing attention and alertness) and beta activity (decreasing compulsive thoughts) (Kennerly, 2006).
- CES increases the concentration of neurochemicals such as beta endorphin and serotonin and decreases cortisol in the brain which results in improved mood, improved sleep and decreased pain (Shealy et al., 1998. Liss et al., 1996).

The above mechanisms provide evidence that CES changes brainwave electrical activities and brain chemistry. These changes are consistent with a decrease in anxiety and depression and an increase in relaxation that can help people fall asleep and decrease insomnia.

3.3. CES Treatment Process

Instructions on how to use the Alpha-Stim® M for a CES treatment are described below:

- 4-Step Procedure:**
1. Wet Electrodes
 2. Place on Ear Lobes
 3. Turn on CES Device
 4. Set to Comfortable Current for 20 Minutes to One Hour



Figure 5. Using Alpha-Stim® CES

1. Wet the ear clips electrodes with the conductive solution and attach them to both of your earlobes.
2. Press the button to select 20 minutes.
3. Adjust the current until you barely feel it, usually described as a mild tingling sensation. Reduce current slightly if there is any discomfort. If you feel comfortable at 2 or more on the dial you can probably complete a treatment in 20 minutes. 1-2 on the dial may require 30-60 minutes. Change the timer to 60 minutes and turn off when you feel “light.”
4. At the end of treatment period, you should be “light,” with no drowsy or heavy feeling. If you feel drowsy or heavy, continue treatment until you feel “light.” This usually only takes a few more minutes.

Feelings Experienced During CES treatment

Feelings experienced during a CES treatment are shown in Figure 6. If the patient feels heavy, groggy or euphoric at the end of the allotted time, it is important to continue treatment for at least two minutes or until the patient feels “light” and the heavy feeling is gone. At the end of a CES session, the majority of patients will feel more relaxed, yet alert.

Feelings Experienced During CES Treatment Stages

Dosage equals time inversely proportional to current level
(i.e., less current requires longer treatment time per session)

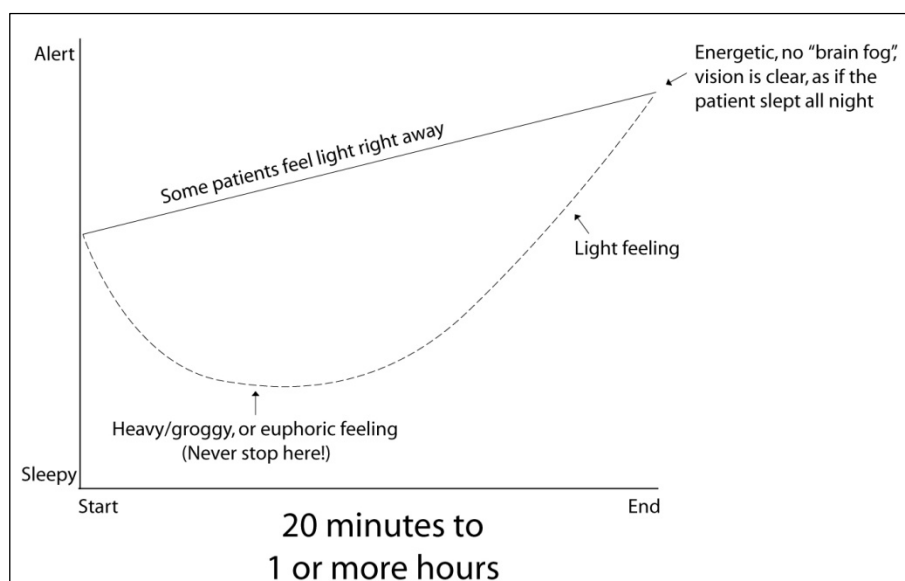


Figure 6. Feelings experienced during CES treatment stages. Source: Kirsch, DL and Nichols, F. Cranial electrotherapy stimulation for treatment of anxiety, depression and insomnia. *Psychiatric Clinics of North America*. 2013; 36(1): 169-76.

4. Microcurrent Electrical Therapy / Transcutaneous Electrical Nerve Stimulation

Microcurrent electrical therapy or MET, is a generic term used to describe a low level current form of transcutaneous electrical nerve stimulation (TENS) used for pain control typically applied for 2 to 5 minutes through probes, or self-adhesive electrodes for longer applications. MET differs slightly from traditional TENS in that MET uses lower current levels and longer pulse widths. The Alpha-Stim® MET/TENS technology produces residual and cumulative results not generally seen with higher current TENS devices. In a traditional TENS device the current is often several hundreds of times stronger than with Alpha-Stim® MET/TENS. MET is used for acute, chronic and post-traumatic pain and is a subsensory, noninvasive experience for the patient.

MET/TENS is a proven and established technology that has been used as a pain management tool or a muscle relaxant since the 1960's. MET/TENS uses mild electrical impulses as an alternative to drugs. TENS devices have been in use for many years and as an example have been used to treat pelvic pain, back pain, shoulder pain, post-surgical pain, tendinitis and bursitis, arthritis, head & neck pain, dental pain, cancer pain and many other pain related conditions.

MET/TENS therapy is approved by the FDA, is covered by many insurance carriers, has been prescribed by doctors as a safe, reliable pain management system for decades. MET/TENS devices can be purchased by the user over the counter or direct on-line from a retailer.

PART II: REVIEW OF SCIENTIFIC AND CLINICAL LITERATURE ON CRANIAL ELECTROTHERAPY STIMULATION

1. Research Overview

1.1 Research Equivalence

Electromedical Products employs 3 methods of obtaining relevant clinical information. These methods include literature search, clinical investigation and clinical experience. The Alpha-Stim® 2000 was first introduced in 1981 while the newest Alpha-Stim® models AID and M were introduced in 2012. While the device design has changed incrementally over the years, the waveform and output parameters have remained the same. The output characteristics remaining constant means research subjects received the same Alpha-Stim® treatment in 1981 as they do today. Research done using previous models of Alpha-Stim® during the 1980's and 1990's would still be replicable today using the new models.

1.2 Data generated through literature search

The objective of the literature search is to ensure any relevant data related to Alpha-Stim® safety and efficacy would be included in the Clinical Examination. The studies used for the Clinical Examination were chosen using PubMed, PubMed Central, Google Scholar and clinicaltrials.gov which are considered the industry standard. Keywords used when searching included cranial electrotherapy stimulation, cranial stimulation, Alpha-Stim®, microcurrent electrical therapy, microcurrent therapy, neuromodulation and noninvasive cranial stimulation. Google alerts are also monitored for any information pertaining to cranial electrotherapy stimulation, cranial stimulation, Alpha-Stim®, microcurrent electrical therapy, microcurrent therapy, neuromodulation and noninvasive cranial stimulation. Study types searched for included randomized controlled trials, open label studies, case studies and case series, meta-analysis and review articles. Studies were excluded if they used a different device or if the primary and secondary measures were not indicated uses.

EPI searches for new studies every 6 months and will exclude any previously discovered Alpha-Stim® studies. EPI also continually monitors Google alerts for new relevant research. There have been no serious adverse events reported in any of the reviewed literature.

Example of EPI Literature Search:

Searches of the following databases PubMed, PubMed Central, clinicaltrials.gov and GOOGLE SCHOLAR and also conducted a GOOGLE search of web pages using the following terms:

- “cranial electrotherapy stimulation” AND
- “Alpha-Stim” OR
- “Anxiety” OR
- “Depression” OR
- “Insomnia” OR
- “Pain”
- “Microcurrent Electrical Therapy” AND
- “Alpha-Stim” OR
- “Pain”

Limits Activated:

- All studies published in English from October 1, 1981 – December 31, 2015.
- Only studies that used Alpha-Stim® cranial electrotherapy stimulation (CES) or transcutaneous electrical nerve stimulation (TENS) devices were included.
- Only studies that included the approved indications of anxiety, depression, insomnia and pain were included.

1.3 Clinical Investigation

EPI is often contacted by potential researchers who wish to carry out studies using the Alpha-Stim®. EPI works to build a relationship with these individuals who are using its device for medical research and they are contacted quarterly for research updates. Once the study is complete, researchers are eager to share results with EPI. This gives us direct access to the research without having to carry out a literature search. EPI often receives studies that are never listed on PubMed making them more difficult to search. EPI has archived research since the launch of the Alpha-Stim® 2000 in 1981. All of the research on the indicated uses of anxiety, insomnia, depression and pain can be found at www.alpha-stim.com/researchandreviews. The studies used in this CER are located in section 10-3 of the Technical File.

1.4 Clinical Experience

One source of clinical experience comes from post marketing data. User surveys are attached to warranty cards included with each Alpha-Stim® device sold. Once the warranty card is sent in, the information is entered into a database. EPI exports this information every 2 years and sends it to a statistician who provides analysis of the data. The information is also part of EPI's post-marketing surveillance program requirements and is often published. The survey is a living document and is added to continually as new warranty cards are uploaded. This data is also monitored for adverse event and side effects. Any issues are immediately brought to management and the appropriate QMS is activated. In 35 years of marketing Alpha-Stim® devices there have been no serious adverse events reported nor have there been any clinically relevant field corrective actions such as recalls, notifications or hazard alerts.

2. Table of Alpha-Stim® Studies by Variable Studied

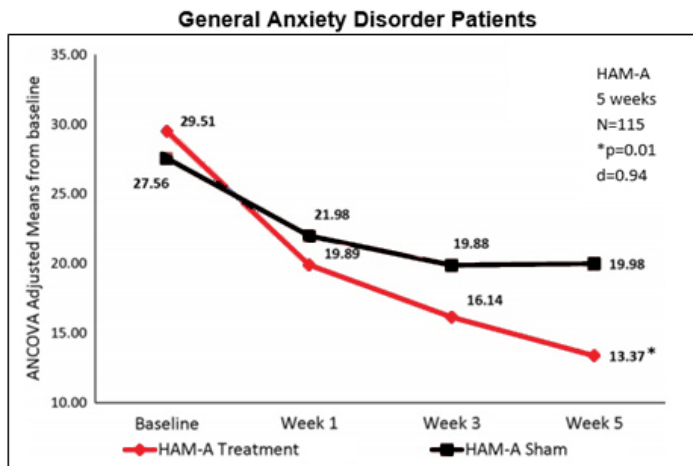
Tables of CES studies by condition and type of study are included in Appendix B. Abstracts are organized by the type of study. Studies listed under the key variables of anxiety, insomnia, depression and pain for this review are shown in Table 2.

Alpha-Stim randomized, double-blind, sham controlled clinical trials	Other Alpha-Stim randomized clinical trials	Alpha-Stim open label, case series studies
ANXIETY		
Barclay (2014) Kolesos (2013) Mellen (2008) Strentzsch (2008) Cork (2001) Lichtbroun (2001) Winick (1999) Voris (1995) Gibson (1987)	Hill (2015) Lu (2014) Lee (2013) Kim (2008) Chen (2007)	Mellen (2016) Gong (2016) Libretto (2015) Bystritsky (2008) Lu (2005) Overcash (1999)
INSOMNIA		
Taylor (2013) Lande (2013) Lichtbroun (2001)		
DEPRESSION		
Barclay (2014) Mellen (2009)	Chen (2007)	Gong (2016) Libretto (2015) Amr (2013) Bystritsky (2008) Lu (2005)
PAIN		
Lee (2013) Taylor (2013) Taylor (2013) Tan (2011) Rintala (2010) Tan (2006) Cork (2004) Lichtbroun (2001) Sizer (2000) Heffernan (1997) Roth (1986)		Keizer (2016) Libretto (2015) Kirsch (2011) Holubec (2009) Lee (2004) Kulkarni (2001) Alpher (1998) Zimmerman (1987) Bauer (1983)
Post-marketing Surveys: 2011, 2007-2013. All surveys include anxiety, insomnia, depression and pain (US FDA approved indications)		

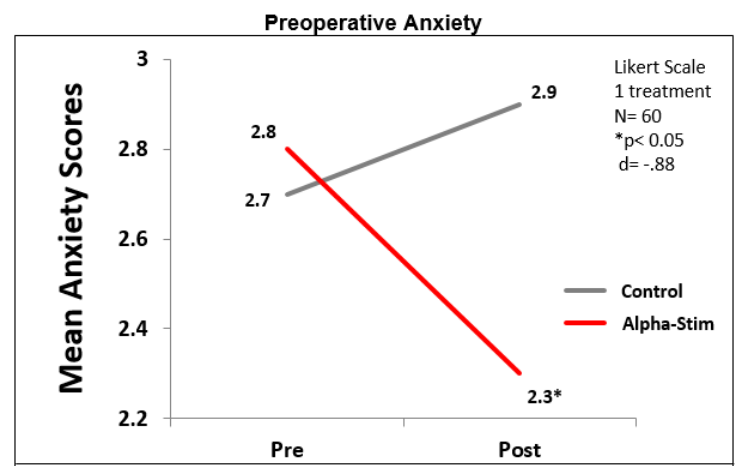
Table 2. Table of Alpha-Stim® studies by variable studied.

3. Graphic Summary of Studies

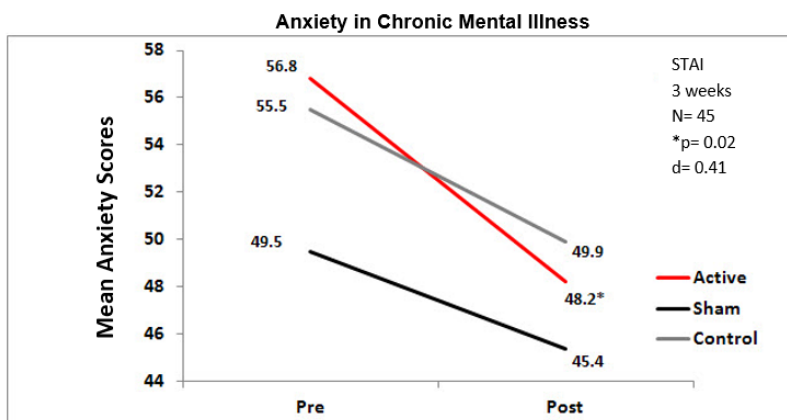
3.1. Anxiety



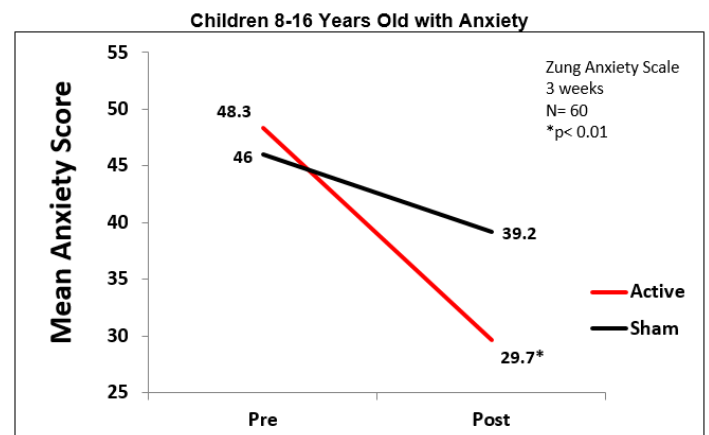
Barclay (2014)



Kim (2008)

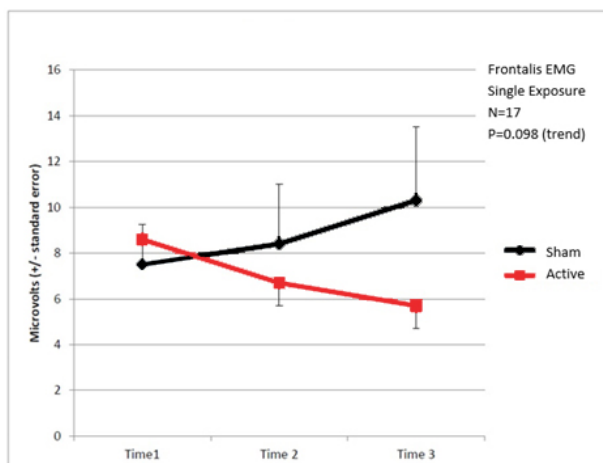


Strentzsch (2008)



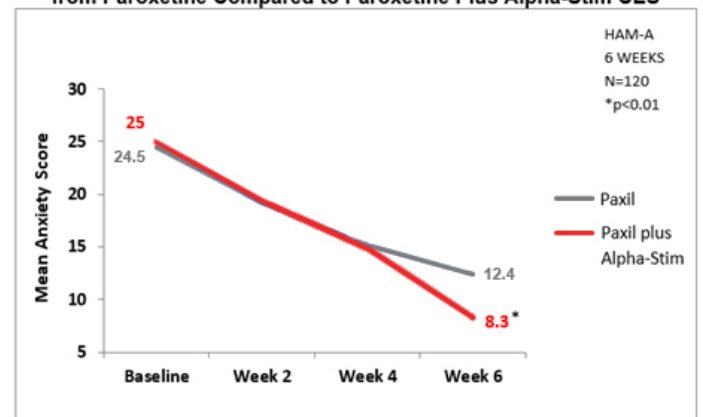
Chen (2007)

Reduction in Induced Anxiety from the Affective Picture System



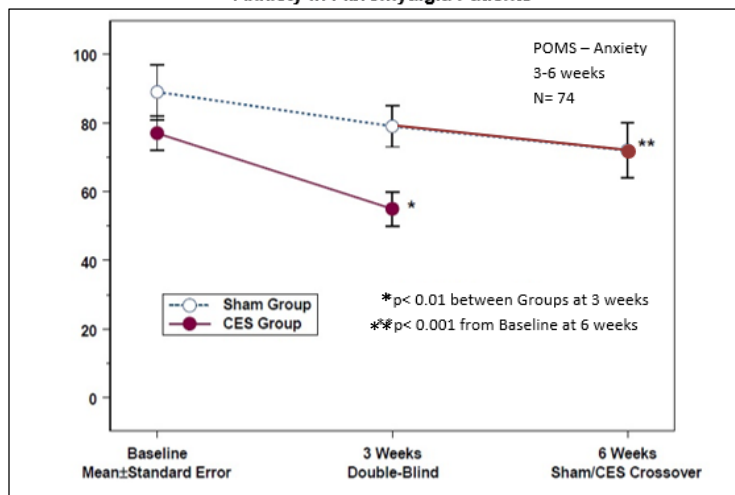
Hill (2015)

Reduction in Anxiety from Paroxetine Compared to Paroxetine Plus Alpha-Stim CES



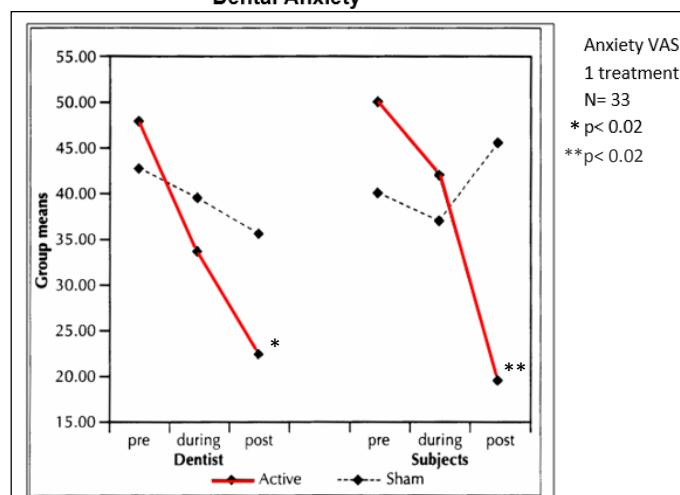
Lu (2014)

Anxiety in Fibromyalgia Patients



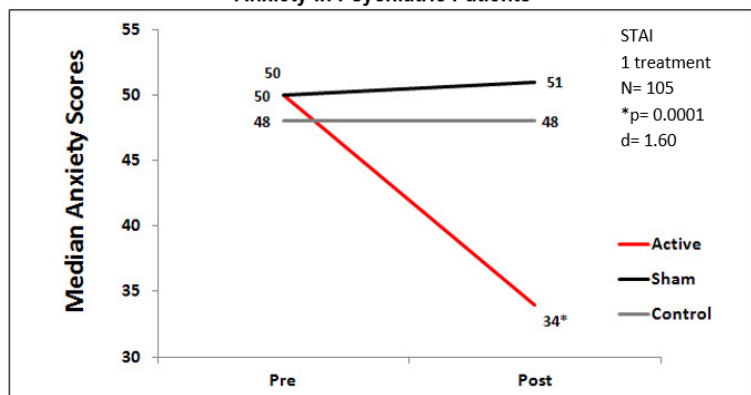
Cork (2004)

Dental Anxiety



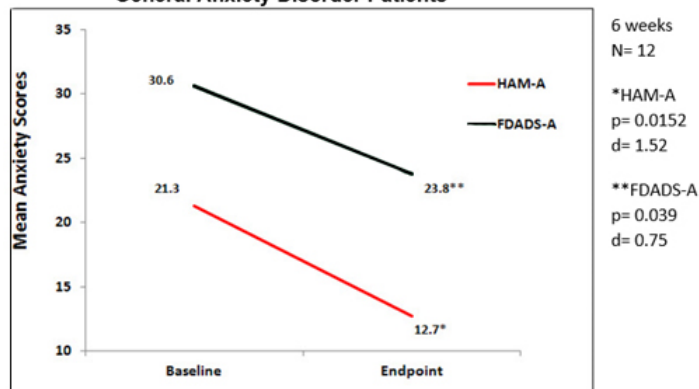
Winick (1999)

Anxiety in Psychiatric Patients



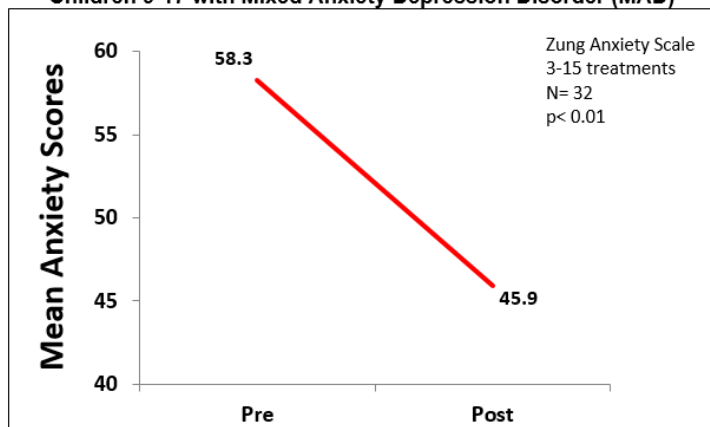
Voris (1995)

General Anxiety Disorder Patients



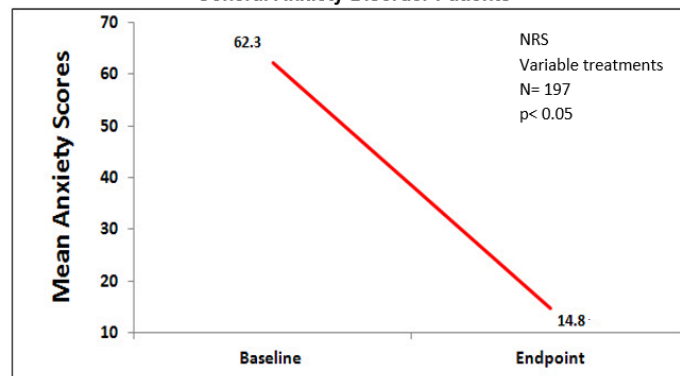
Bytitsky (2008)

Children 9-17 with Mixed Anxiety Depression Disorder (MAD)

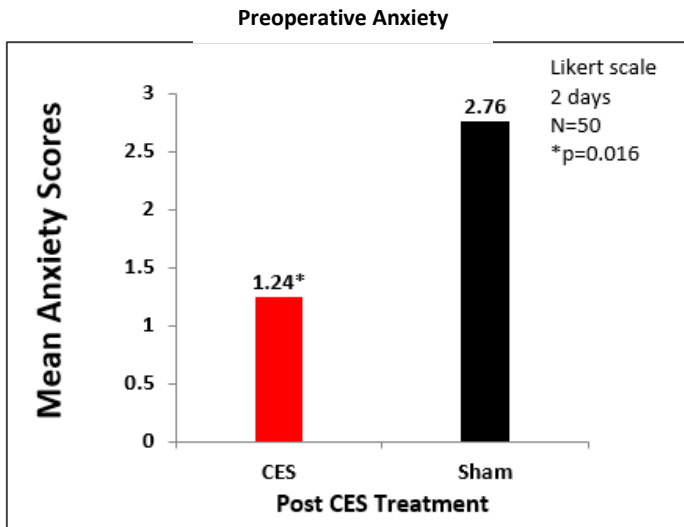


Lu (2005)

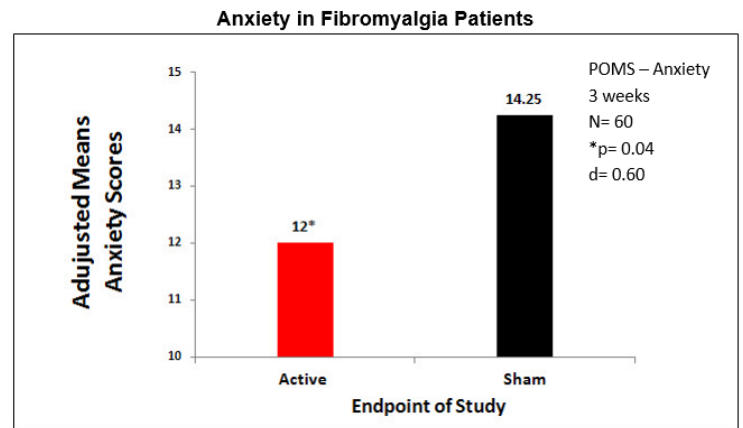
General Anxiety Disorder Patients



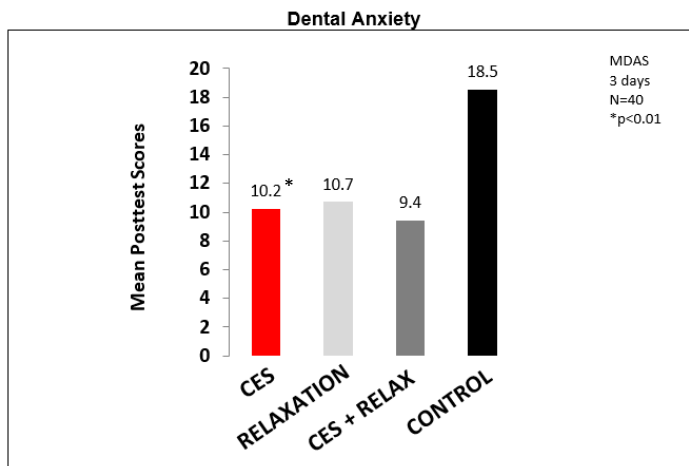
Overcash (1999)



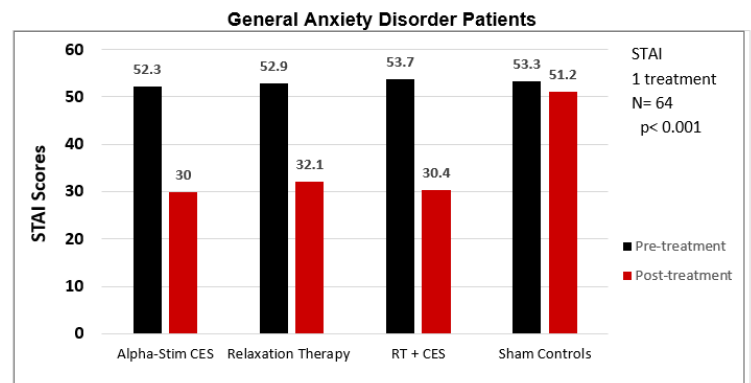
Lee (2013)



Lichtbroun (2001)



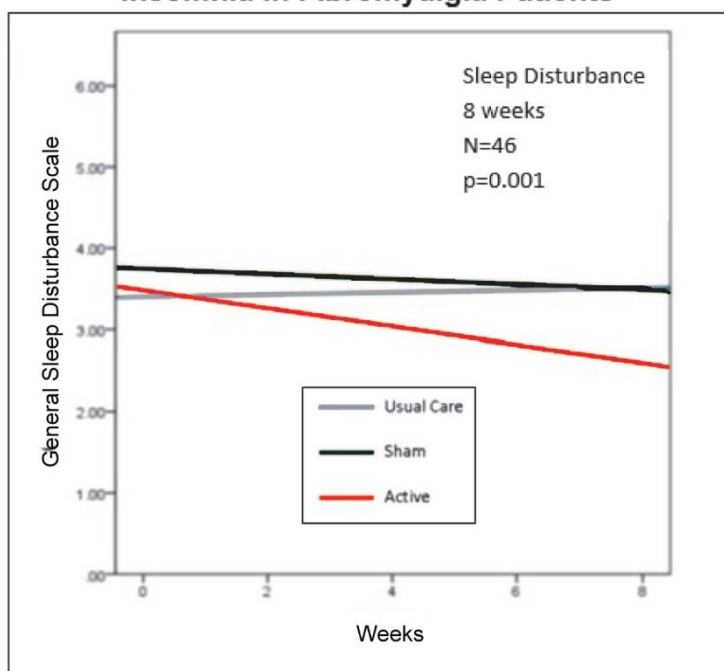
Kolescos (2013)



Gibson (1987)

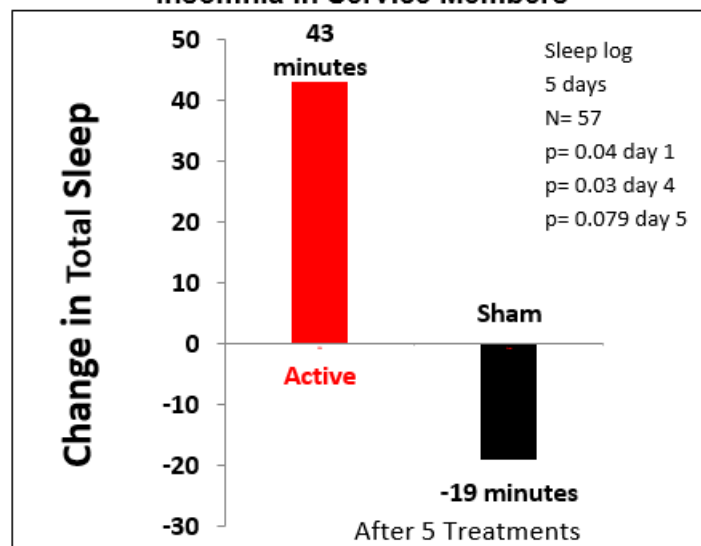
3.2. Insomnia

Insomnia in Fibromyalgia Patients



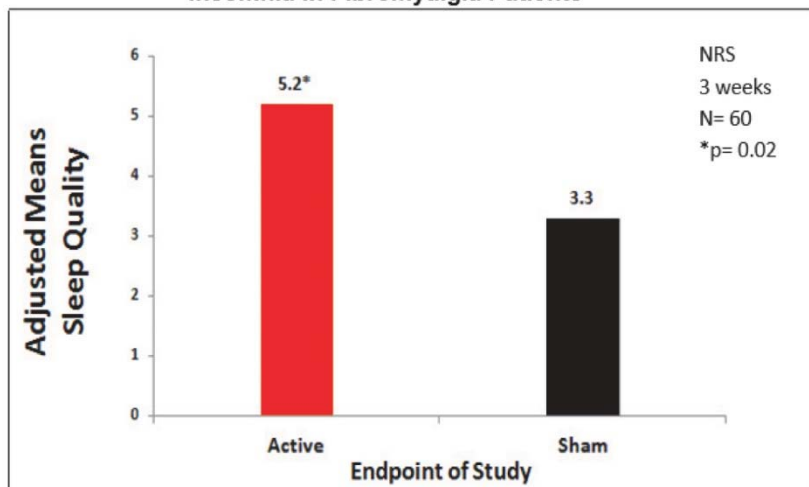
Taylor (2013)

Insomnia in Service Members



Lande (2013)

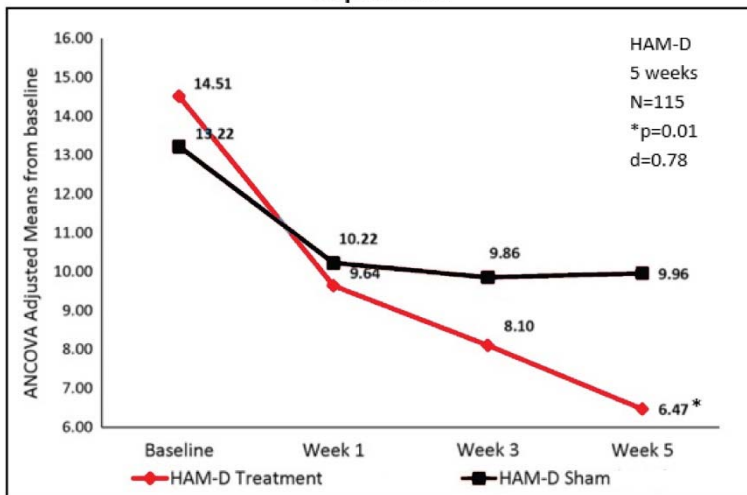
Insomnia in Fibromyalgia Patients



Lichtbroun (2001)

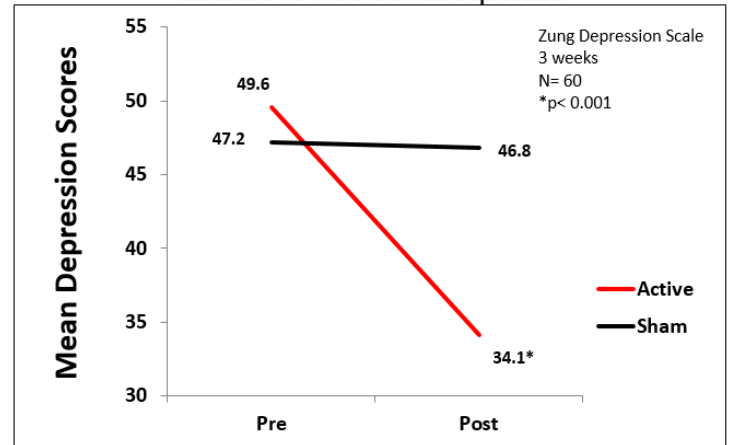
3.3. Depression

Depression



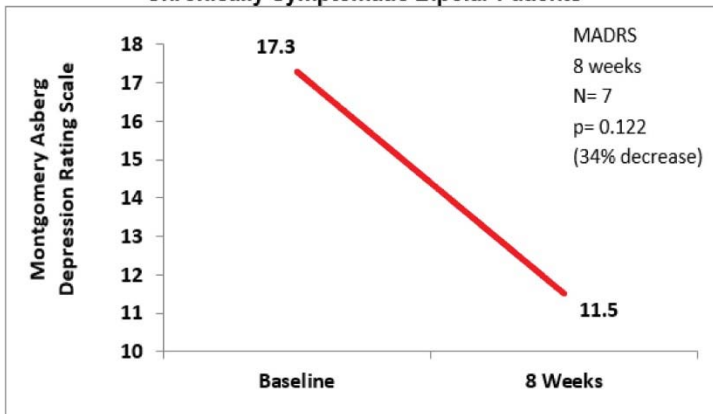
Barclay (2014)

Children 8-16 Years Old with Depression



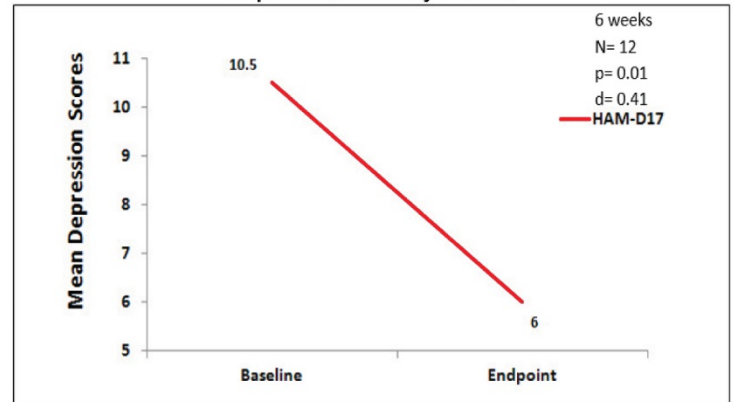
Chen (2007)

Chronically Symptomatic Bipolar Patients



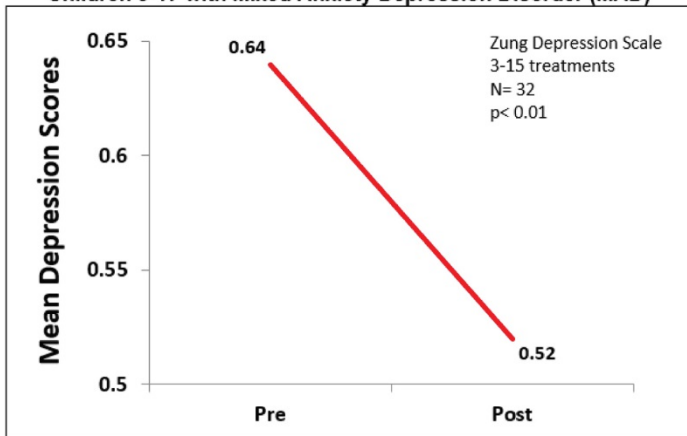
Amr (2013)

Depression in Anxiety Patients



Bysritsky (2008)

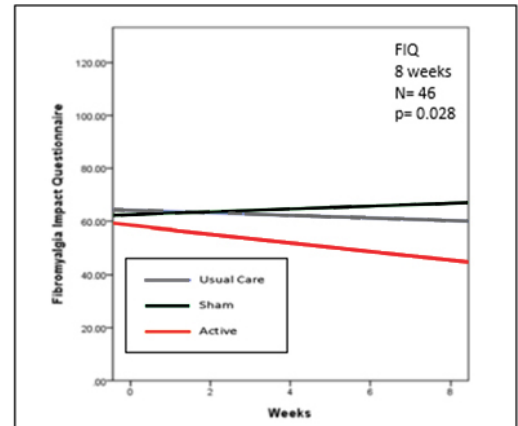
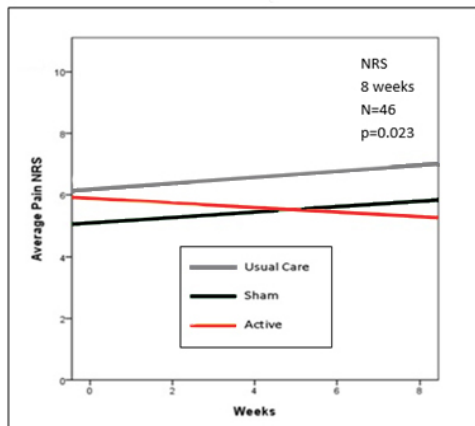
Children 9-17 with Mixed Anxiety Depression Disorder (MAD)



Lu (2005)

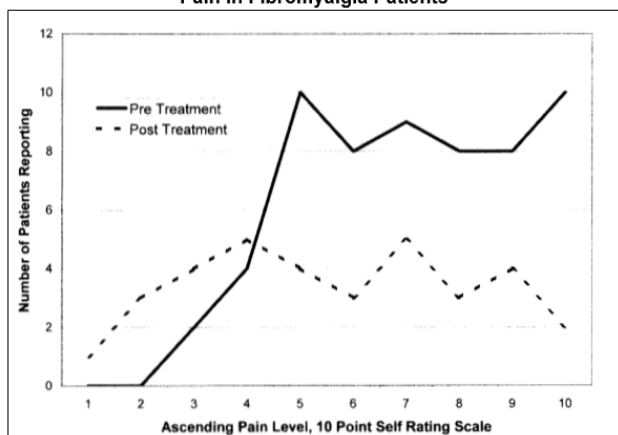
3.4 Pain

Pain in Fibromyalgia Patients



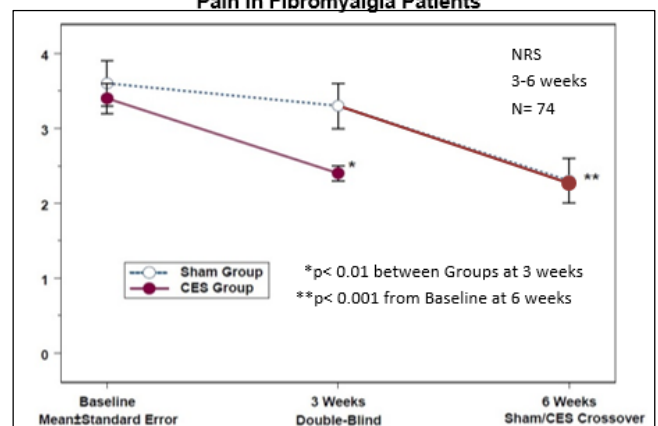
Taylor (2013)

Pain in Fibromyalgia Patients



Lichtbroun (2001)

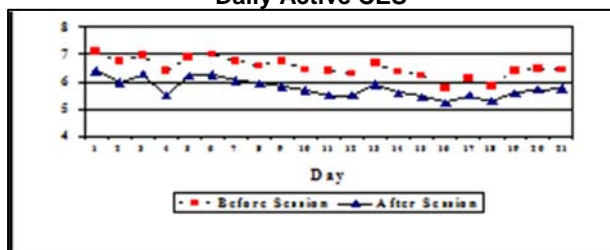
Pain in Fibromyalgia Patients



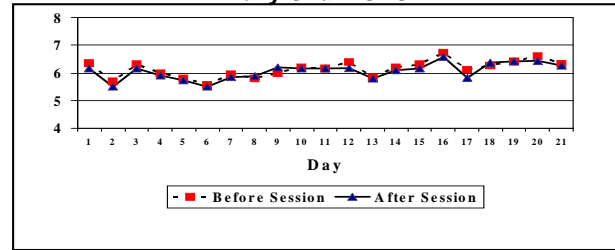
Cork (2004)

Pain in Veterans from Spinal Cord Injury

Daily Active CES

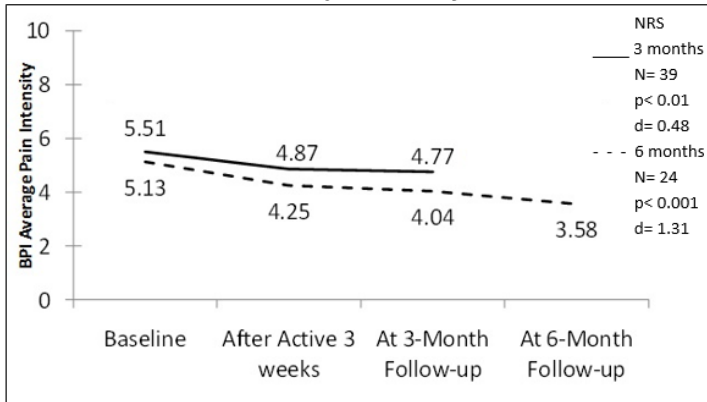


Daily Sham CES



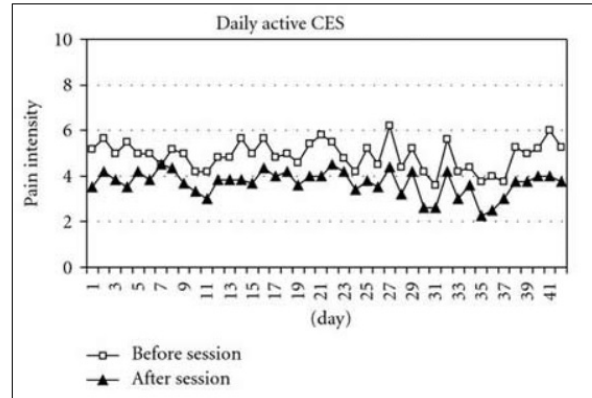
Tan (2006)

Pain from Spinal Cord Injuries



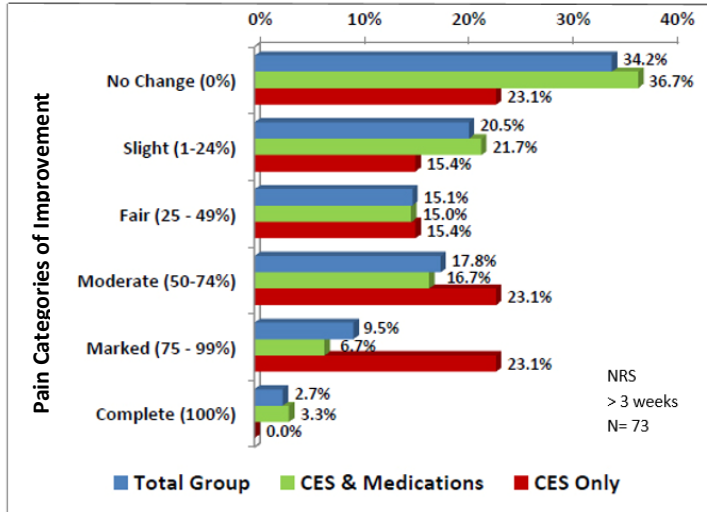
Tan (2011)

Pain in Parkinson's Patients

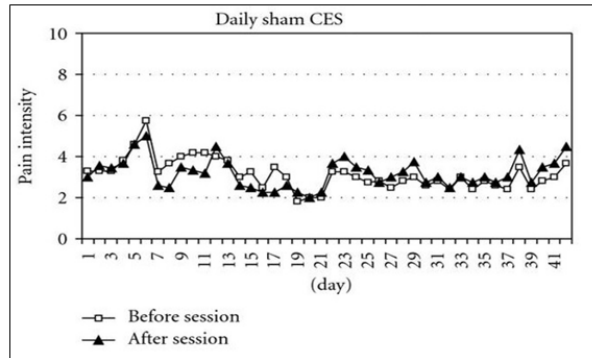


NRS
41 treatments
 $N = 4-6$
 $p = 0.045$

Pain in Service Members



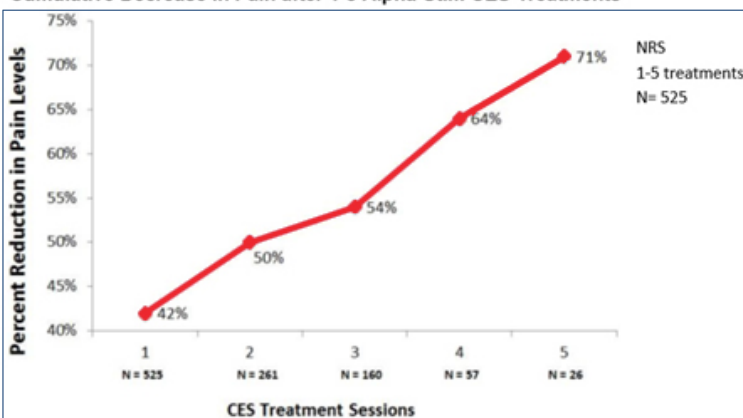
Kirsch (2015)



NRS
41 treatments
 $N = 4-6$

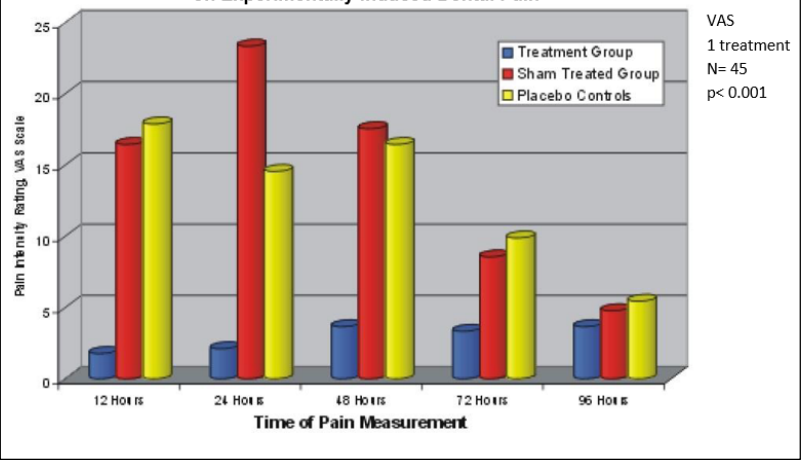
Rintala (2010)

Cumulative Decrease in Pain after 1-5 Alpha-Stim CES Treatments



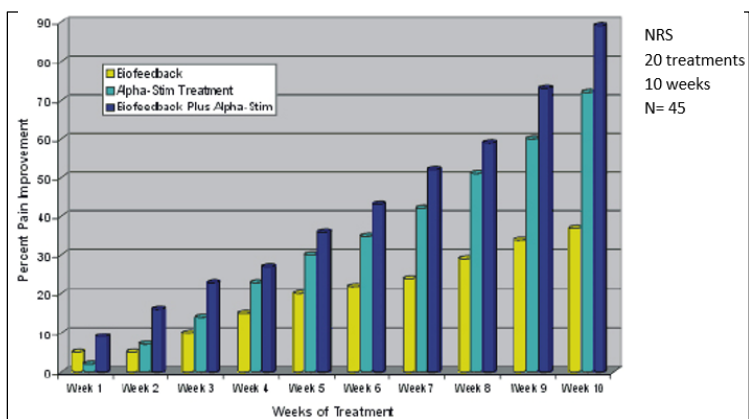
Holubec (2009)

The Effect of One, 20 Minute Alpha-Stim MET Treatment on Experimentally Induced Dental Pain



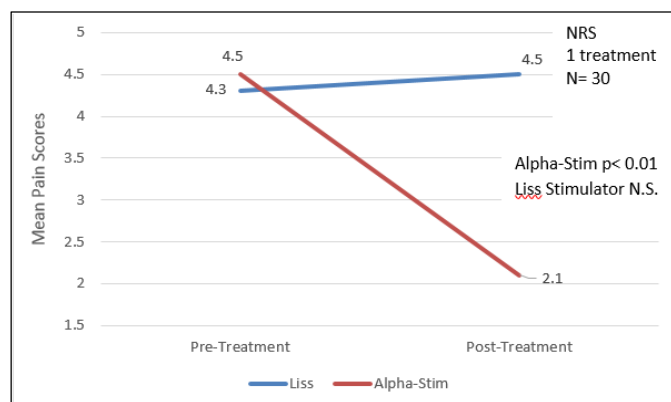
Roth (1986)

Comparison of Biofeedback, Alpha-Stim Microcurrent Stimulation, and Both Together in Reducing Pain in Chronic Back Pain Patients



Zimmerman (1987)

**Pain in Degenerative Joint Disease
Alpha-Stim vs. Liss Stimulator**



Heffernan (1997)

4. Abstracts of Randomized Controlled Trials CES Studies

4.1. Hill (2015)

Hill, Nolan. The effects of alpha stimulation on induced anxiety. Digital Commons @ ACU, *Electronic Theses and Dissertations*. Paper 6, 2015; <http://digitalcommons.acu.edu/etd/6>

Device

Alpha-Stim®

Key Variable

Reduction of induced anxiety using Alpha-Stim CES

Objective

The objective of the study was to use Alpha-Stim CES to reduce stress levels as measured by physiological markers

Design

This was a double-blind placebo controlled study (n=17)

Primary Effectiveness Endpoint

EMG (facial electromyography)

Secondary Outcome Measures

EDG (sweat gland activity) and heart rate

Key Inclusion Criteria

The participants were volunteers recruited from a college campus. The procedures were explained as well as risks and benefits prior to obtaining consent.

Protocol Summary

Participants were exposed to stimuli derived from the International Affective Picture System (IAPS) database that were chosen for their ability to elicit anxiety. A repeated measures analysis of variance was performed on recorded physiological data (EDG, HR, EMG) and subjective experience of anxiety as measured with Subjective Units of Distress Scale.

Device Application Protocol

Subjects were assigned a coded number which matched up with an active or a sham Alpha-Stim device. Subjects were treated while they were exposed to anxiety eliciting stimuli at the rate of 1 picture every 60 seconds for a total of 60 minutes.

Study Blinding

The Alpha-Stim was set to 100 microamps which is sub sensory for patients. Subjects were randomized as to which device they received. Half of the devices were active while the rest were nonconductive.

Results

Data Analysis

Analysis of subjective units of distress scores showed that repeated exposure to anxiety eliciting pictures produced decreasing levels of distress over time ($F(1,13) = 5.831, p = .031$). EDG

analysis revealed no statistically significant results. HR analysis revealed that CES produced lower heart rates throughout the exposure (main effect of treatment; $F(1,12) = 120.907$ $p < .001$), and a trend toward increased heart rate during the exposure (treatment by time interaction; $F(1,12) = 3.514$, $p = .085$). Frontalis EMG analysis revealed a trend for the treatment groups to differ in their experience of negative emotional valence over the course of the exposure ($F(1,12) = 3.209$, $p = .098$).

Reduction in Induced Anxiety from the Affective Picture System

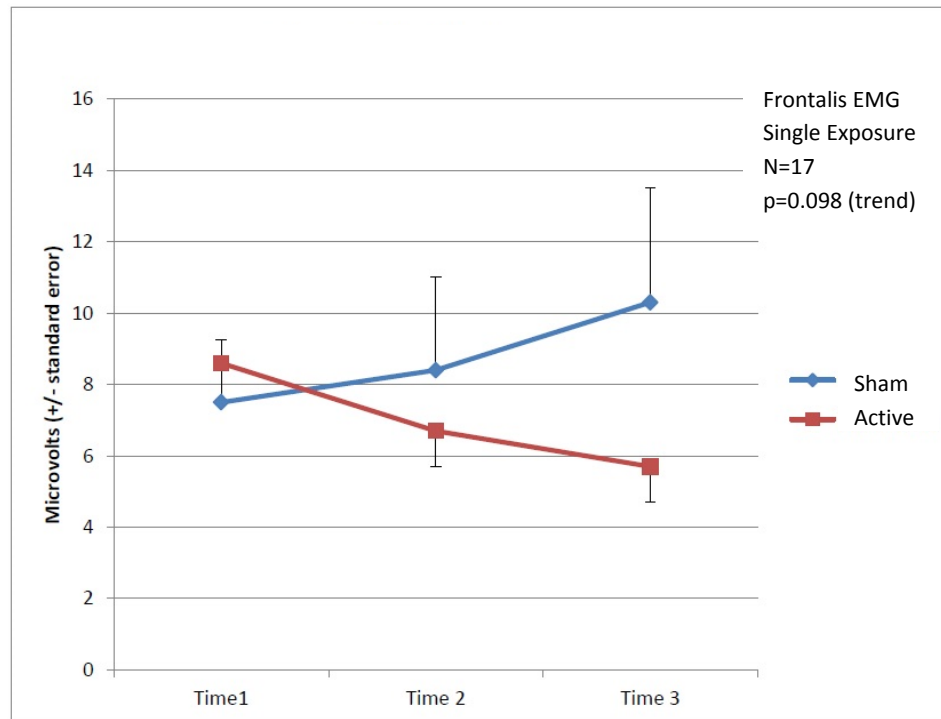


Figure 7. Mean EDG activity (in microVolts), captured after each exposure. Bars indicate standard error.

Conclusion

This research shows that CES can decrease levels of arousal and negative valence induced by exposure to anxiety provoking stimuli without affecting the course of exposure as measured by SUDS.

4.2. Barclay (2014)

Barclay TH and Barclay RD. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. *Journal of Affective Disorders*. 2014; 164: 171-177. Presented at the American Psychological Association National Conference, Honolulu, HI, July 2013.

Device

Alpha-Stim®

Key Variables

Anxiety, Depression

Objective

The purpose of this study was to examine the efficacy of CES for the treatment of anxiety and depression.

Design

This was an IRB approved 5 week study that used a randomized, sham controlled, double-blind design in which subjects in the treatment and sham groups participated in a daily one hour treatment of CES using active or sham Alpha-Stim® CES devices. The sham device was identical to the active CES device, except it did not conduct an electrical current. The active CES device was set to 100 μ A, a subsensory level. The subjects, investigators, physicians and staff were all masked as to the identity of the device.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the last post-treatment scores on the Hamilton Anxiety Rating Scale (HAM-A) compared to the sham treatment at the endpoint of the 5 week study.

Secondary Outcome Measures

The secondary outcome measure was the change from baseline in the last post-treatment scores on the Hamilton Depression Rating Scale (HAM-D₁₇) compared to the sham treatment at the endpoint of the 5 week study.

Key Inclusion Criteria

1. Male and female participants between 18-65 years of age.
2. Diagnosis of an anxiety disorder was verified by a licensed clinical psychologist in an interview using the DSM-IV criteria.
3. Must score > 15 on the HAM-A.
4. Score on HAM-A must be higher than score on the HAM-D₁₇.
5. If on antidepressant medication, the medication and dose must be stable for at least 3 months before entering study.
6. Must be in good health; chronic medical conditions must be stable.

Key Exclusion Criteria

1. Pregnancy, planning to become pregnant or nursing.
2. Presence of implanted pacemakers, pumps or electrical stimulators.
3. Use of Benzodiazepines more than twice per week.
4. Met DSM-IV criteria for an Axis I diagnosis, other than an anxiety disorder.
5. Participant judged by investigator to be a risk for suicide or has attempted suicide one or more times within the past 12 months.

6. Current alcohol or substance abuse.
7. Participants exhibiting a psychiatric condition that would require inpatient or partial psychiatric hospitalization.

Protocol Summary

The Alpha-Stim® CES active and sham devices were randomized by the manufacturer and the devices were packed in the device box in the order which they were to be assigned. Subjects were assigned a device based on the order the devices came out of the box. Baseline measures were done prior to the first CES treatment. Subjects had 5 weeks of daily CES treatment for 60 minutes with either an active or sham device. Mid-point measures were done at the end of 3 weeks and endpoint measures were done at the end of 5 weeks.

Device Application Protocol

The active CES device was pre-set and locked by the manufacturer at 100 μ A which is a subsensory level. The sham CES device was pre-set and locked by the manufacturer so that it did not emit electricity. The length of treatment, 60 minutes, was also pre-set and locked by the manufacturer for both active and sham devices.

Study Blinding

The subjects, investigators, physicians and staff were masked as to the identity of the device, active or sham.

Pre-Specified Criteria for Success

Pre-specified criteria for success was set at $\geq 50\%$ improvement in anxiety and separately, $\geq 50\%$ improvement in depression.

Power Analysis and Sample Size

A power analysis was done and indicated that for two groups and at least one covariate that 107 subjects were needed for an ANCOVA analysis, an effect size of $d=0.50$ and $p=0.05$.

Results

Subjects

Of the 115 subjects who enrolled in the study, 108 subjects completed the study. There were 57 subjects in the active CES group and 51 subjects in the sham CES group.

Baseline Measurements: Group Equivalence

There was no statistically significant difference at baseline between active CES and sham treatment groups on anxiety, depression and subject characteristics of age, gender, use of prescribed medication and type of anxiety or depression disorder.

Data Analysis

Subjects completed mid-point testing at the end of 3 weeks and endpoint testing at the completion of the last treatment at the end of their week 5 visit. Data were analyzed using ANCOVA and descriptive statistics. Cohen's d was used to determine effect sizes (Cohen, 1998)

Anxiety

There was a significant difference between the active and sham groups for anxiety from baseline to endpoint of study ($p < 0.001$, $d = 0.94$). The HAM-A scores decrease in the active group of 32.8% (19.89 to 13.37) was more than 3 times the mean decrease of 9.1% (21.98 to 19.98) on the HAM-A for the sham group (See Figure 8). Eighty-three percent (83%) of the active CES group had a decrease of $\geq 50\%$ decrease in anxiety scores on the HAM-A from baseline to endpoint of study. Note: All subjects must have met DSM-IV criteria for anxiety and scored > 15 on the HAM-A to be included in the study.

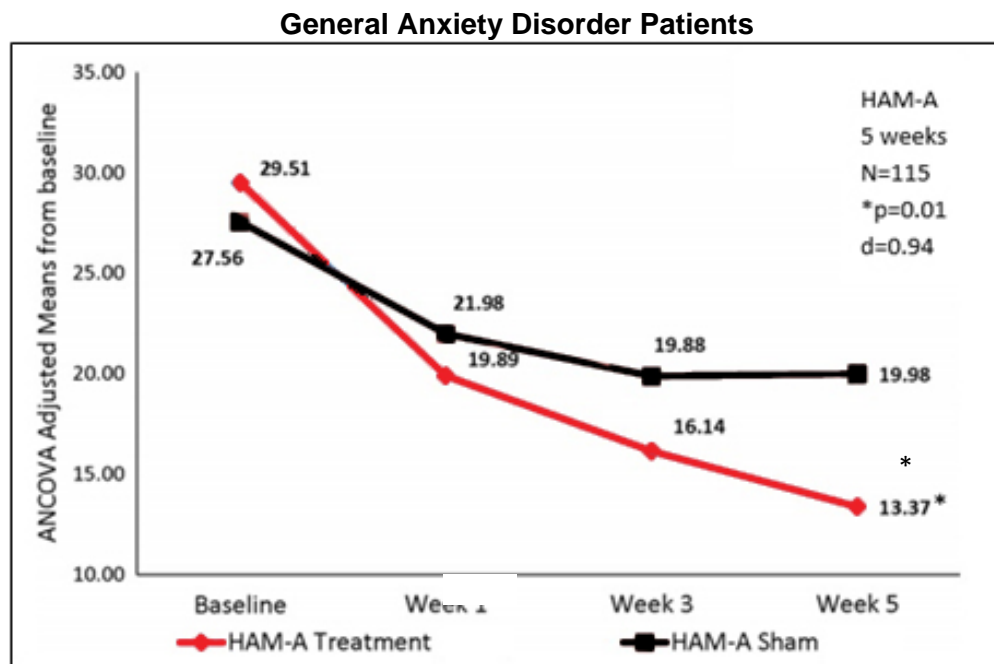


Figure 8. Mean Anxiety Scores by Group.

Depression

There was a significant difference between the active and sham groups for depression from baseline to endpoint of study ($p < 0.001$, $d = 0.78$). The HAM-D₁₇ scores decrease in the active group of 32.9% (9.64 to 6.47) was more than 12 times the mean decrease of 2.6% (10.22 to 9.96) on the HAM-D₁₇ for the sham group (See Figure 9). Eighty-two percent (82%) of the active CES group had a decrease of $\geq 50\%$ decrease in depression scores on the HAM-D₁₇ from the baseline to the endpoint of study.

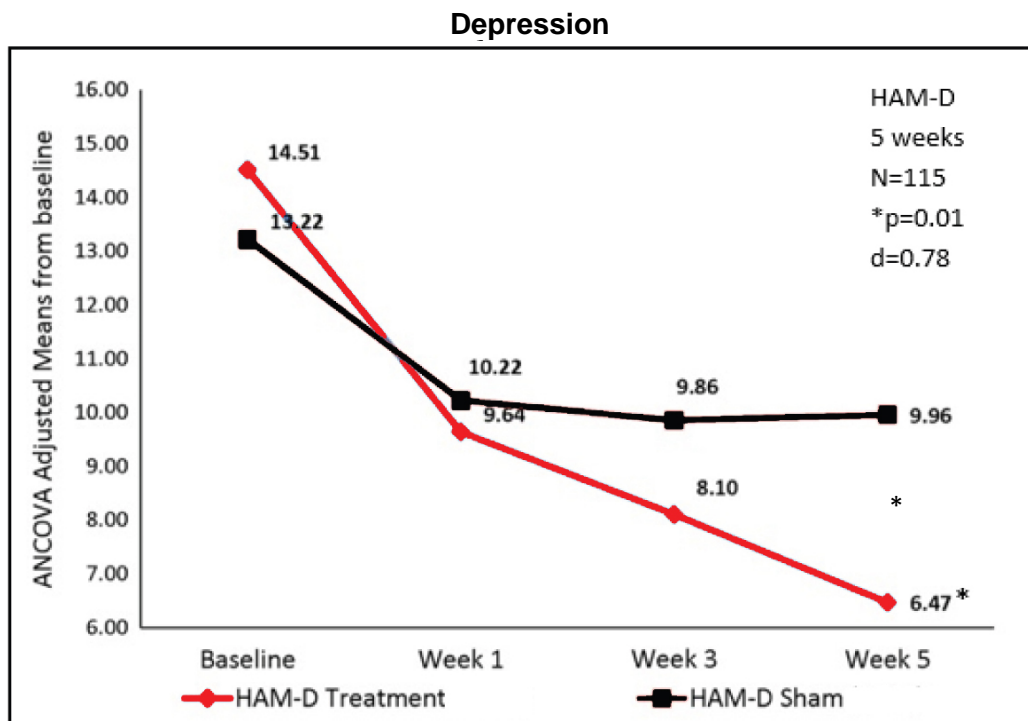


Figure 9. Mean depression scores by group.

Quality of the Research

This is a strong study that used a randomized, sham controlled, double-blind design. Active and sham Alpha-Stim® devices were pre-set and locked at the designated levels for each specific group to maintain current level and treatment time by the manufacturer. Sham devices were the same as active, except they did not emit electricity. Randomization of devices was done by the manufacturer and followed according to the protocol by the investigators. Individuals had to meet the DSM-IV criteria for anxiety disorder to be in the study. Pre-specified criteria for success were established for the study. CES treatments were done daily for 60 minutes for both active and sham groups. ANCOVA was the appropriate analysis for the data on anxiety and depression. All subjects (N=108 at end of study) completed the HAM-D at baseline and endpoint of study. A limitation of the study is that the number of individuals within the total groups who met the DSM-IV criteria for depression was small (12 in the active CES group and 11 in the sham group), however the total active CES group had significantly lower scores on the HAM-D₁₇ from baseline to endpoint of study than the total sham CES group ($p < 0.001$, $d = 0.78$). The range for no depression is 0 to 7 on the HAM-D₁₇, so there was ample room for subjects in the active CES group to have lower scores on the HAM-D₁₇ at endpoint of study from CES treatments. This is most likely what happened, in addition to subjects who had depression, subjects within the “normal” range on the HAM-D₁₇ had lower scores at endpoint representing an improved mood status.

4.3. Lu (2014)

Lu Ling and Hu Jun. A Comparative study of anxiety disorders treatment with Paroxetine in combination with cranial electrotherapy stimulation therapy. *Medical Innovation of China*. 2014; 11(08): 080-082.

Device

Alpha-Stim®

Key Variable

Anxiety

Objective

The objective was to explore the add-on effect of cranial electrotherapy stimulation therapy in the treatment of anxiety disorders.

Design

Randomized controlled trial, (N=120)

Primary Effectiveness Endpoint

Hamilton Anxiety Scale (HAM-A)

Secondary Outcome Measures

Clinical Global Impression Scale (CGI-SI)

Protocol Summary

Patients enrolled in the study (N=120) entered the 6-week treatment period after a one week washout. The control group was given daily paroxetine (10 – 20 mg) while the treatment group received daily paroxetine (10 – 20 mg) and daily cranial electrotherapy stimulation (CES) treatments. The treatment course was 6 weeks in duration. The primary measurement of efficacy was reductive ratio in the HAM-A and CGI-SI with ≥75% being clinically cured, 50 – 74% obviously improved, 25 – 49% improved and <25% as ineffective. The WHO quality of life measurement was used to measure quality of life factors at baseline and week 6.

Device Application Protocol

Patients treated with Alpha-Stim CES at 0.5 Hz, between 50 – 500 µA for 60 minutes a day for a total of 42 days. In the first treatment investigators increased the current until the subjects reported a tingling or dizziness. At that point the current was reduced to a subsensory level. The patients treated at this level for the duration of the study.

Data Analysis

A database was created with double entry of data, and SPSS 15.0 software was used for statistical analysis of the data obtained. The measurement data was expressed as ($\bar{x} \pm s$), t-test was used for comparison. The enumeration data was tested with χ^2 , where $P < 0.05$ signifies a statistically significant difference.

Baseline Measurements: Group Equivalence

There was no statistical difference between the control and treatment group at baseline.

Results

HAM-A

Both the control and the treatment group showed improvement in HAM-A scores with each consecutive measurement. The comparison of HAM-A scores showed no significant changes between control and treatment groups at baseline, week 2 or week 4 but there was a significant difference in the two groups at week six ($p<0.01$). The treatment group which consisted of daily Paxil and CES improved significantly more than the control group which received Paxil alone.

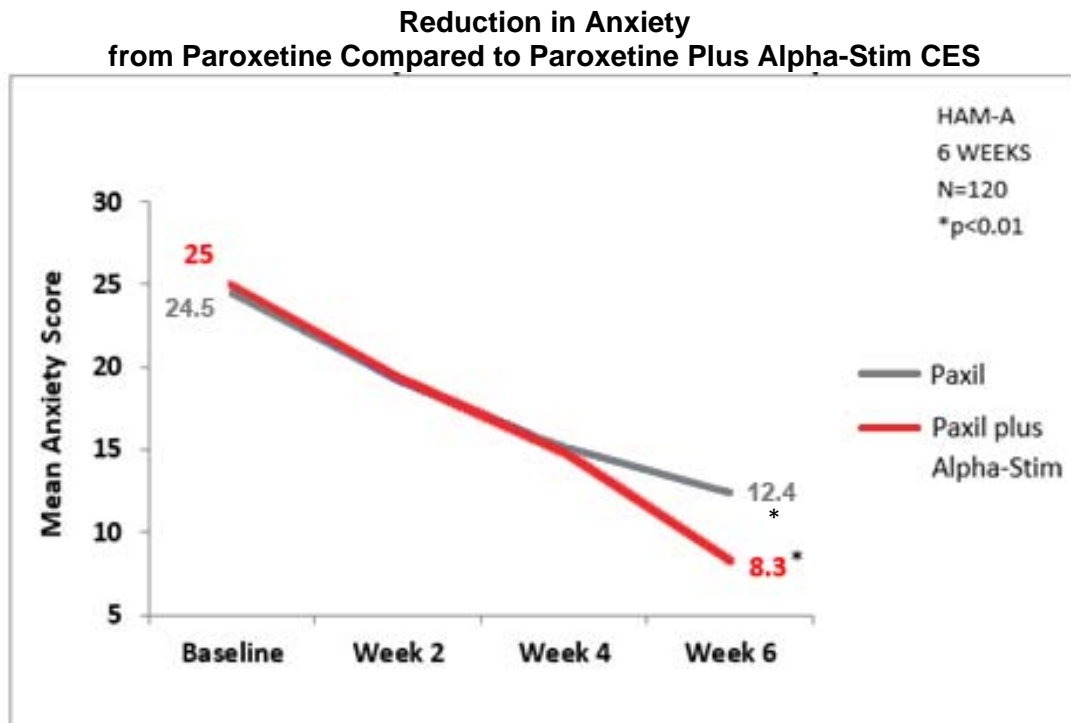


Figure 10. This graph shows compares the improvement in anxiety scores between the treatment and control groups.

CGI-S/

The control group and the treatment group yielded significant improvement from baseline to the six week endpoint. While both groups reported significant improvement, there was more improvement in the treatment group and the difference between the control and treatment groups was also statistically significant ($P<0.05$).

Quality of Life

The quality of life scores reduced significantly ($p<0.05$) over the six week treatment course but there was no significant difference between the control and treatment groups.

Subjects

The control group (N=60) received 10 – 20 mg of paroxetine while the treatment group (N=60) received 10 – 20 mg of paroxetine combined with daily CES treatments.

Conclusion

The results of this study showed that six weeks of combining Paxil with daily CES treatments, yielded significant improvement over Paxil alone on the HAM-A scale from baseline to 6 weeks out. This was confirmed with the HAM-A ($p < 0.01$) and the CGI-SI ($p < 0.05$). There was also a significant reduction in quality of life however there was no significant difference between the control and treatment groups.

4.4. Kolescos (2013)

Kolesos ON, Osionwo HO, Akkhigbe. The role of relaxation therapy and cranial electrotherapy stimulation in the management of dental anxiety in Nigeria. *ISOR Journal of Dental and Medical Sciences*, 2013; 10(4): 51-57.

Device

Alpha-Stim®

Key Variable

Dental Anxiety

Objective

The purpose of this study was to assess the therapeutic efficacy of 3 treatment modalities: relaxation therapy (REL), cranial electrotherapy stimulation (CES), and a combination treatment of relaxation therapy and CES for the treatment of dental anxiety.

Design

This was an IRB approved study that used a quasi-experimental research design that was randomized and had pre-post measures.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the post-treatment scores on the Modified Dental Anxiety Scale (MDAS) among the 4 groups (the 3 treatment groups and the control group) at the endpoint of the study.

Key Inclusion Criteria

1. Male or female subjects ≥ 18 years old.
2. Subjects who were experiencing oral pain conditions for at least 3 months.
3. Pain was due to identifiable physical oral pathology and verified by a dentist.
4. Subjects had high anxiety scores of ≥ 14.25 on MDAS.

Key Exclusion Criteria

1. Pregnancy, planning to become pregnant or nursing.
2. Presence of implanted pacemakers, pumps or electrical stimulators.
3. Facial pain.
4. Acute oral pain less than three months.
5. Psychogenic oral pain.
6. Pain due to oral cancer.
7. Traumatic injuries associated with oral pain.
8. Individuals with gross mental abnormality or other diagnosable neurological disorders.

Protocol Summary

Respondents who reported high dental anxiety (≥ 14.25) and who agreed to come for the therapeutic interventions for the next 3 days were randomly assigned to 1 of 4 groups; relaxation therapy group, CES treatment group, both treatments simultaneously group and the no treatment control group based on the order in which they arrived back at the psychological assessment room after they had been treated by the dentist. During the relaxation therapy session, subjects listened to 30 minutes of relaxation training that was played on an MP-3 audio recorder via head phones. Subjects in the combined relaxation and CES treatment group did a 45 minute CES treatment while listening to the relaxation instructions. Subjects in the CES

treatment group completed a 45 minute CES treatment. Treatment sessions for all subjects took place in the same room between 9 AM to 12 noon each day. After the three days of treatment, subjects returned to the Dental Centre the following Monday to complete the MDAS.

Device Application Protocol

The CES treatment was given with the Alpha-Stim®. The device was set at 0.5 Hz and the current was increased until the subject felt “light-headed” and then decreased “to their comfort level.” The length of treatment was 45 minutes. Each subject had one individual meeting with the lead investigator during the 3 days.

Results

Subjects

One hundred thirty-eight (138) potential subjects reported high anxiety on the MDAS. Of these 40 respondents agreed to participate and completed the study. The primary reasons given for not participating in the study was inadequate time, cancelled appointments or did not live in the city where the study was conducted.

Baseline Measurements

Baseline measures for dental anxiety for subjects in the 3 treatment groups and the control group were taken on acceptance into the study.

Data Analysis

One-way ANOVA was used to compare mean dental anxiety scores across the 4 groups. The t-test for independent samples was used to compare the mean scores of dental anxiety at pre-test and post-test. Descriptive statistics and reliability assessment (Cronbach alpha and split-half method), and post hoc Scheffe’s test were also used.

Dental Anxiety

The CES group means ($M=10.20$), the relaxation group ($M=10.70$) and the combined treatment group ($M=9.40$) had significantly lower dental anxiety ($p<0.01$) than the control group ($M=18.30$) at the endpoint of the study as seen in Figure 11. Each of the 3 treatments significantly decreased dental anxiety ($p < 0.05$) from pre-test to post-test. There was no statistically significant difference among the treatment groups on dental anxiety. Based on the findings of this study, CES was as effective at decreasing dental anxiety as relaxation therapy and the combined treatment group. However, CES is easier to use compared to learning relaxation techniques.

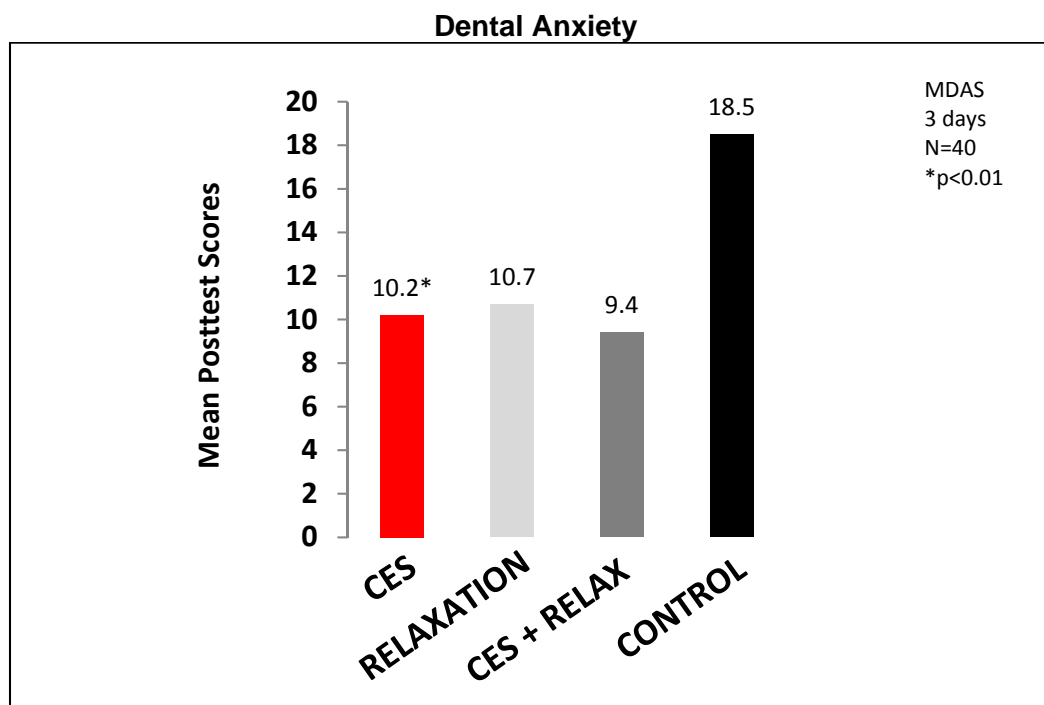


Figure 11. Mean dental anxiety scores by group at the end of the study.
CES=active group, RELAXATION=relaxation instruction group, CES+REL=combined group.

Quality of the Research

Strength of this clinical study include: (1) The use of a randomized quasi-experimental research design that had pre-post measures; (2) use of valid and reliable MDAS scale; and (3) The cut-off score for dental anxiety on the MDAS in this study was established in a previous pilot study. Limitations include: (1) The small N, there were 10 subjects in each of the 4 groups; and (2) CES treatments were individualized for each subject, thus there was a lack of standardization of CES current. The finding of this study is that CES significantly decreases dental anxiety, is as effective in decreasing anxiety as relaxation, and is easier to use than learning relaxation techniques is consistent with previous findings by Gibson et al, in 1987. The finding that CES significantly decreases anxiety is also consistent with other Alpha-Stim® CES studies that found CES significantly decreases anxiety.

Reference

Gibson, Thomas H. and O'Hair, Donald E. Cranial application of low level transcranial electrotherapy vs. relaxation instruction in anxious patients. *American Journal of Electromedicine*. 1987; 4(1): 18-21.

4.5. Lee (2013)

Lee SH, Kim WY, Lee CH, Min, TJ, Lee YS and Kim JH. Effects of cranial electrotherapy stimulation on preoperative anxiety, pain and endocrine response. *Journal of International Medical Research*. 2013; November 21.

Device

Alpha-Stim®

Key Variables

Preoperative anxiety and pain

Objective

The purpose of this study was to investigate the efficacy of CES for the treatment of preoperative anxiety, withdrawal response during injection of rocuronium, postoperative pain, and stress hormone levels.

Design

This was an IRB approved study that used a randomized, sham controlled, double-blind design in which subjects in the treatment group received one 20 minute CES treatment the day before surgery and one 20 minute treatment just prior to surgery. The sham group received the same number and length of CES treatments with a sham CES device.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the last post-treatment scores on a 5 point Likert scale, where “1” indicated no anxiety to “5” indicated extremely anxious as compared to the sham treatment group at the endpoint of the study. The VAS was used to measure changes in pain levels.

Key Inclusion Criteria

1. Female participants between 20-65 years of age.
2. Diagnosis of suspected thyroid cancer and scheduled for surgery.
3. American Society of Anesthesiologists (ASA) physical status classification I or II.

Key Exclusion Criteria

1. Pregnancy, planning to become pregnant or nursing.
2. Presence of implanted pacemakers, pumps or electrical stimulators.
3. Age > 65 years.
4. Body mass index ≥ 25 .
5. Diagnosed with renal disease, endocrine or neuromuscular disease.
6. Current use of psychiatric drugs.

Protocol Summary

Subjects were randomized to either an active CES or control group using computer generated random numbers. All subjects in the active and sham groups had a CES treatment between 8:00 - 10:00 PM on the day before surgery and between 7:00 - 9:00 AM on the day of surgery.

Device Application Protocol

The active CES device was pre-set at 100 μ A which is a subsensory level. The sham device was identical to the active CES device, but did not emit electricity. The length of treatment, 20

minutes, was also pre-set for both active and sham devices. Anxiety was assessed in the pre-operative holding area after the CES treatment.

Study Blinding

The subjects, investigators, physicians and staff were masked as to the identity of the device, active or sham.

Pre-Specified Criteria for Success

Pre-specified criteria for success was $p=0.05$.

Results

Subjects

There were 50 subjects in this study, 25 in the active CES group and 25 in the sham CES group. All 50 subjects completed the study.

Baseline Measurements: Group Equivalence

There was no statistically significant difference at baseline between active CES and sham treatment groups on age, height or body weight.

Data Analysis

Data were analyzed using the exact V^2 test, the Mann Whitney U-test and descriptive statistics.

Anxiety

There was a significant difference between the active and sham groups for anxiety in favor of the active CES group at endpoint of study ($p<0.016$). The active CES group had significantly lower anxiety scores at the endpoint of the study on the Likert anxiety scale (Figure 12).

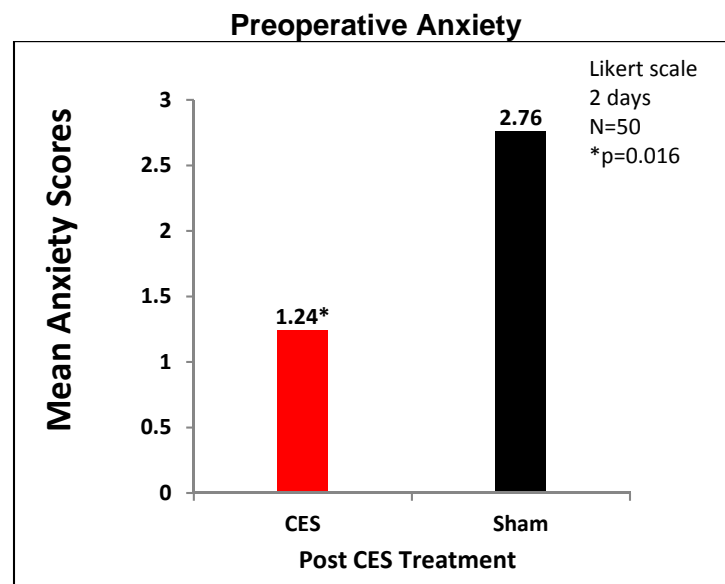


Figure 12. The CES group had significant lower anxiety scores than the sham group after CES treatment (active or sham) in the preoperative holding area ($p=0.016$).

Pain

Although 3 patients out of 20 obtained no relief from this treatment, 6 obtained complete relief, and an additional 8 patients received significant relief of 33% – 94%. When treatment response by the length of time they had the pain was evaluated it was found that patients who had been in pain for 2 months and 4 months improved 94% and 100%.

Quality of the Research

Strengths of the study include: (1) A randomized, sham controlled, double-blind design was used; (2) Active and sham devices were pre-set for each group for current level and time. (2) Sham devices were the same as active devices, except they did not emit electricity. Limitations include: baseline measures were not taken for anxiety prior to study. Including a baseline measure of anxiety would strengthen this study. A limitation cited by the investigators was the inability to control for any possible placebo effect experienced by the control group due to sham treatment. They recommended that in future research, 3 groups be included; active, sham and a placebo control group. The findings of this study are consistent with the findings of other CES studies on anxiety; CES decreases anxiety.

4.6. Taylor (2013)

Taylor AG, Anderson JG, Riedel SL, Lewis JE, Kinser PA and Bourguignon C. Cranial electrical stimulation improves symptoms and functional status in individuals with fibromyalgia. *Pain Management Nursing*. 2013; 14(4): 327-335.

Device

Alpha-Stim®

Objective

To investigate the effect of a specified treatment course with CES on fibromyalgia (FM) patients' sleep disturbance, pain, fatigue, and the impact of fibromyalgia on functional status when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.

Key Variable

Insomnia (Sleep Disturbance), Pain

Design

This was an IRB approved 8 week, randomized, sham controlled, double blind clinical trial. Subjects in the active CES and sham groups did a 60 minute treatment every day for 8 weeks. A third control group received usual care. Sleep disturbance is the variable of interest for this report.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the last post-treatment scores on the outcomes measures for sleep disturbance, pain, fatigue and functional status compared to the sham treatment group at the endpoint of the 8 week study.

Key Inclusion Criteria

1. Male and female subjects with fibromyalgia ranging ≥ 21 years of age.
2. Diagnosis of fibromyalgia was verified using the criteria established by the American College of Rheumatology.
3. Reported an initial pain level equal to or greater than 3 on a 0 - 10 numeric rating scale (NRS).
4. Had stable medication use related to FM for at least 4 weeks.
5. Ability to read, write, and understand the English language.

Key Exclusion Criteria

1. Pregnant or breast-feeding.
2. Presence of implanted pacemaker, pump or stimulator device.
3. History of seizures.

Protocol Summary

Randomization assignment was established prior to the start of the study by the manufacturer of the Alpha-Stim device. Baseline measures were taken prior to start of treatment period and again at the endpoint of the study. No change was made in the medical management of the patient during the study. Participants in the active CES and sham groups were instructed to use the Alpha-Stim CES 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 maximum of 60 minutes of modified square-wave biphasic stimulation at 0.5 Hz and 100 μ A, the

lowest setting that has been used in previous studies with patients with FM and below the level of perception. Participants in the sham device group received sham devices that were identical to the active device, but did not deliver any electrical stimulation. Device use was monitored by asking participants to document at what time and for how long the device was used each day.

Device Application Protocol

The active CES device was pre-set and locked by the manufacturer at 100 μ A which is a subsensory level. The sham CES device was pre-set and locked by the manufacturer so that it did not emit electricity. The length of treatment, 60 minutes, was also pre-set and locked by the manufacturer for both active and sham devices.

Study Blinding

The subjects, investigators, physicians and staff were all masked as to the identity of the device.

Results

Subjects

The sample consisted “primarily of Caucasian females” who on average had a high school education or slightly above. Forty-six (46) subjects, 17 active CES, 14 Sham and 15 controls, completed the testing after the last treatment at the week 8 visit.

Baseline Measurements

There were no statistically significant differences at baseline between active, sham and control groups for any of the demographic or outcome variables.

Data Analysis

Data were analyzed using separate multilevel models to estimate mean differences among the 3 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 Akaike’s AIC criterion. Random coefficients regression models (for each outcome) were used to fit the data collected each week using 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.

Sleep Disturbance (Insomnia)

While all 3 groups reported scores that were in 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 ($p=0.001$). Figures 13, 14 and 15 show the mean change over time in symptoms, and functional status over time among the active group, sham group and control group for all variables in the study.

Insomnia in Fibromyalgia Patients

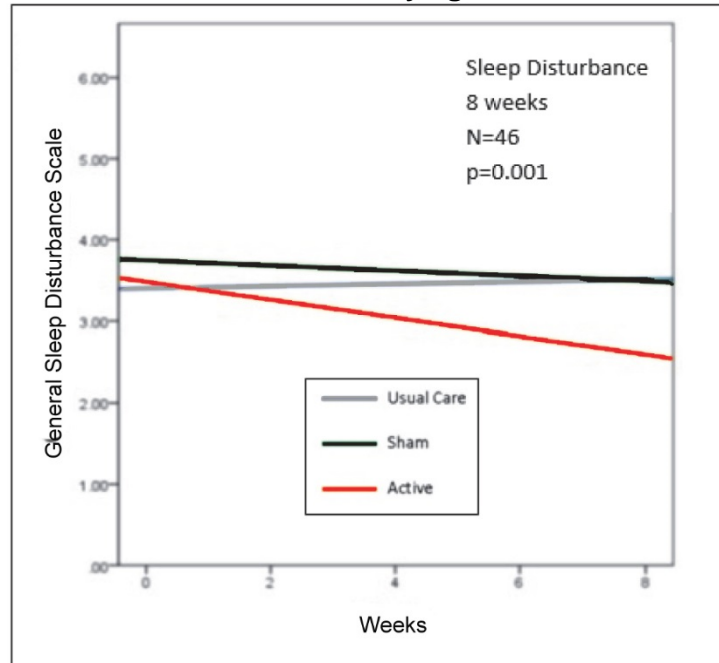


Figure 13. Mean changes in sleep disturbance over time among the active group, sham group and control group ($p=0.001$).

Pain in Fibromyalgia Patients

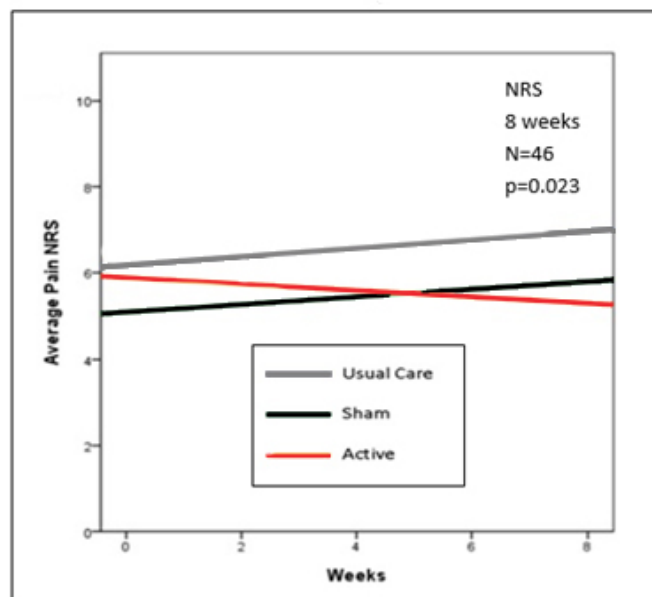


Figure 14. Mean changes in pain over time among the active group, sham group and control group ($p=0.023$).

Pain in Fibromyalgia Patients

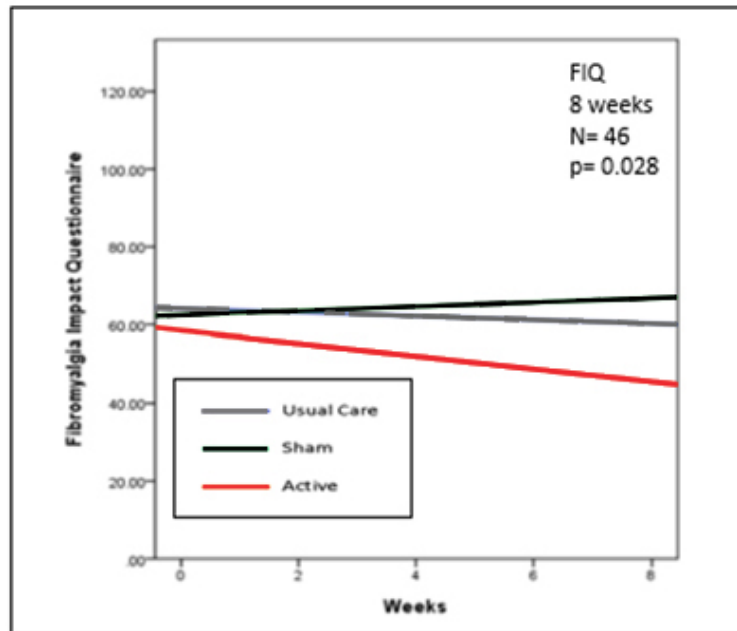


Figure 15. Mean change in symptoms and functional status over time among the active group, sham group and control group ($p=0.028$).

Quality of the Research

Strengths of this study include: (1) use of a randomized, sham controlled, double-blind design (The investigators chose to use the Alpha-Stim RCT research protocol for the study); (2) active and sham Alpha-Stim devices were pre-set and locked at the designated levels for each specific group for current level and time by the manufacturer at the factory and sham devices were the same as active, except they did not emit electricity; (3) randomization of devices was done by the manufacturer according to the protocol by the investigators; (4) diagnosis of fibromyalgia was verified using the criteria established by the American College of Rheumatology before subjects could be in the study; and (5) the structured and detailed protocol for the CES treatments for both active and sham groups.

4.7. Lande (2013)

Lande RG and Gragnani C. Efficacy of cranial electric stimulation for the treatment of insomnia: A randomized pilot study. *Complementary Therapies in Medicine*. 2013; 21: 8-13.

Device

Alpha-Stim®

Key Variable

Insomnia

Objective

The purpose of this pilot study was to examine the potential efficacy of CES for the treatment of insomnia.

Design

This was an IRB approved 5 day pilot study that used a randomized, sham controlled, double-blind design.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the total sleep time (from sleep log) for the active group compared to the sham treatment group at the endpoint of study.

Secondary Outcome Measures

The secondary outcome measure was the change from baseline in the last post-treatment scores on the time to sleep onset and number of awakenings from sleep logs for active CES subjects compared to the sham treatment at the endpoint of study.

Key Inclusion Criteria

1. Male and female active duty Service Members receiving mental health care at the Psychiatry Continuity Service at Walter Reed National Military Medical Center, Bethesda, Maryland.
2. Must have score ≥ 21 on the psychiatric impairment rating scale (PIRS).

Key Exclusion Criteria

1. Pregnancy, planning to become pregnant or nursing.
2. Presence of implanted cardiac pacemakers, pumps or electrical stimulators.
3. Subjects determined by clinical evaluation and self-administered psychometric tests as actively suicidal, having a seizure disorder history or active vertigo.

Protocol Summary

The device manufacturer pre-set the active and sham devices. The active CES device was set and locked at 100 μ A. The sham CES device was set and locked at "0" so that it did not emit electricity. Subjects were randomly assigned to a sham or active CES group by the investigator who randomly selected a device from the box containing 10 active CES devices and 10 sham CES devices. Each subject received a 60 minute active or sham CES treatment daily for 5 days. Subjects completed a sleep log daily for the 5 days. After the 5 days, subjects completed a sleep log at 2 follow-up points, 3 days and 10 days.

Device Application Protocol

The active CES device was pre-set and locked by the manufacturer at 100 μ A which is a

subsensory level. The sham CES device was pre-set and locked by the manufacturer so that it did not emit electricity. The sham device was identical to the active CES device, except it did not emit electricity. The 60 minutes length of treatment was also pre-set and locked by the manufacturer for both active and sham devices.

Study Blinding

The subjects, investigators and staff were all masked as to the identity of the device, active or sham.

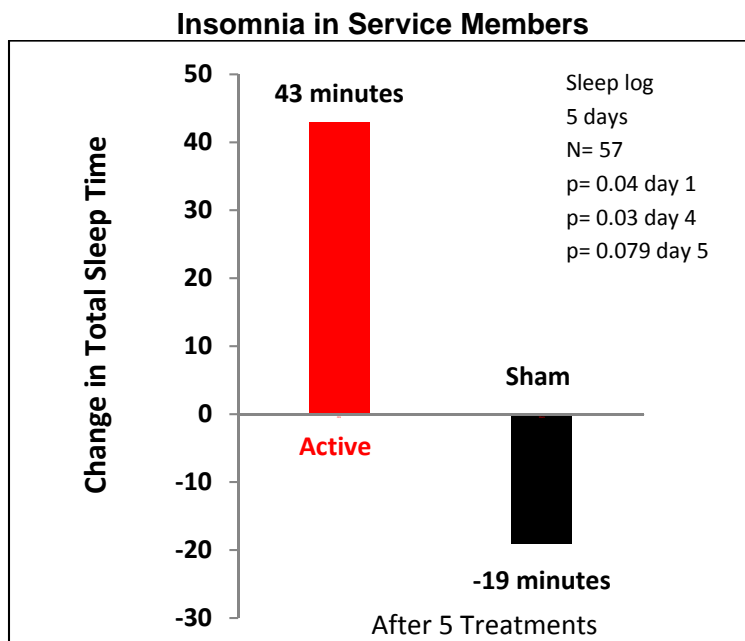


Figure 16. This figure shows the change in total sleep time in minutes between the active group, which had plus 43 more minutes of sleep and the sham group which had 19 fewer minutes of sleep a night after only 5 treatment sessions (p=0.079).

Subjects

Fifty-seven (57) subjects enrolled and completed the study; 46 males and 11 females. There were 28 in the active CES group and 29 in the sham CES group. Over three-quarters of the subjects completed the full 5 CES treatments (N=44. 77%).

Data Analysis

Data were analyzed using descriptive statistics, chi-square, 2 way analysis of variance and independent sample t-tests.

Total Sleep Time

The total time slept approached significance (p=0.079) on day 5 in favor of the active CES group. The active CES group average about 43 extra minutes' total sleep time while the sham CES group subjects reported an average of 19 minutes less sleep time. A gender difference also emerged. Men in the active CES group who completed 5 sessions of CES reported a significant improvement in total time slept at 2 points in the study, after the initial (p=0.04, d=0.41) and after the fourth (p=0.03, d=0.49) treatments as compared to men in the sham group. There were no significant changes among the females.

Quality of the Research

This pilot study was done in preparation for a grant proposal submission. Strengths of the study include: (1) the use of a randomized, double-blind, sham controlled design; and (2) the detailed CES device protocol and the structured protocol for the CES treatments. The major limitation of this study is the number of CES treatments. For the treatment of insomnia the recommended protocol is a minimum of daily CES treatments for at least 4 weeks and 6 to 8 weeks is sometimes required. The investigators state that the small N of the study was a limitation of the study. However, based on the effect size for insomnia, the N of 57 is adequate to detect the effect of CES if subjects in the active CES group have the recommended amount of daily treatments, 4 to 8 weeks.

4.8. Taylor (2013)

Taylor AG, Anderson JG, Riedel SL, Lewis JE and Bourguignon C. A randomized, controlled, double-blind pilot study of the effects of cranial electrical stimulation on activity in brain pain processing regions in individuals with fibromyalgia. *Explore*. 2013; 9(1): 32-40.

Device

Alpha-Stim®

Key Variables

Pain Processing on fMRI

Objective

To investigate the effects of microcurrent cranial electrical stimulation (CES) therapy on activity in pain processing brain regions.

Design

A randomized, controlled, three-group, double-blind pilot study.

Participants

Persons with physician-diagnosed fibromyalgia.

Intervention

Active CES device, sham device, and usual care alone.

Results

Those individuals using the active device had a greater decrease in average pain ($P = .023$) than individuals using the sham device or receiving usual care alone over time. Analyses of the functional magnetic resonance imaging data on a subset of six participants from each of the two device groups show that individuals using an active CES device had a decrease in activation in the pain processing regions of the brain, such as the cingulate gyrus, insula, and prefrontal cortex, compared to those using a sham device.

Conclusions

The observed decrease in activation in the pain processing regions may indicate a decrease in neural activity in these regions that may be related to decreased pain. This is the first randomized, controlled trial of CES in patients diagnosed with fibromyalgia to report functional magnetic resonance imaging data.

4.9. Tan (2011)

Tan G, Rintala D, Jensen MP, Richards JS, Holmes SA, Parachuri R, Lashgari-Saegh S and Price LR. Efficacy of cranial electrotherapy stimulation for neuropathic pain following spinal cord injury: a multi-site randomized controlled trial with a secondary 6-month open-label phase. *The Journal of Spinal Cord Medicine*. 2011; 34(3): 285-296.

Device

Alpha-Stim®

Key Variables

Pain

Objective

To evaluate the effectiveness of cranial electrotherapy stimulation (CES) on pain with spinal cord injury.

Design

This IRB approved study used a randomized, sham controlled clinical trial design in which the subjects in the active CES and sham groups had CES treatments for 21 days. This was followed by a 6 month open label phase.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change in baseline pain compared to post-treatment in both the active and sham groups. Pain reduction was also analyzed at 3 months and 6 months.

Key Inclusion Criteria

1. Adults with SCI and chronic neuropathic pain at or below the level of injury.
2. At least 18 years old
3. Pain was rated at 5 or more on a 10 point scale
4. Pain had to be of at least 6 months duration

Key Exclusion Criteria

1. Active substance abuse problem
2. Serious psychological or psychiatric disorder
3. Implanted electrical device

Protocol summary

Subjects were randomized into active or sham groups and treated daily with cranial electrotherapy stimulation (CES) for 21 consecutive days. Pain was measured pre and post treatment. The treatment was done at 100 microamp for 60 minutes in order to remain subsensory for blinding purposes. There was also an open label follow up phase for 3 and 6 months.

Results

The active treatment group had a significantly greater average decrease in pain from before to after the daily treatments compared to the sham group ($p<0.05$). There was also significant changes on BPI intensity ($p<0.001$), BPI interference ($p<0.001$), SF-36 pain ($p<0.001$), PQAS paroxysmal pain ($p<0.001$), PQAS deep pain ($p<0.01$), and maladaptive coping ($p<0.001$).

In the long term open label phase subjects reported significant linear decrease in pain at 3 months ($p < 0.01$, $d = 0.48$) and 6 months ($p < 0.001$, $d = 1.31$).

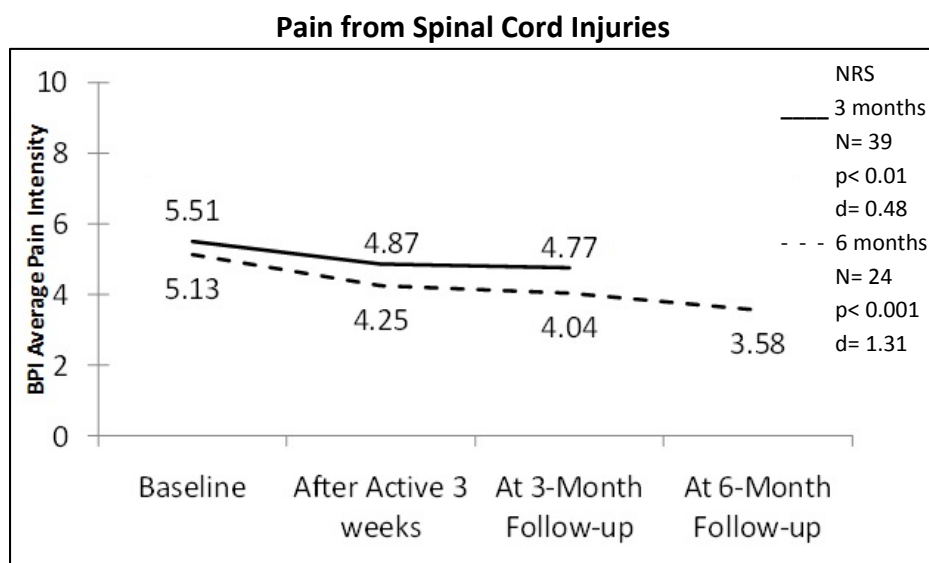


Figure 17. Change in pain ratings in SCI patients over 6 months.

4.10. Rintala (2010)

Rintala DH, Tan G, Willson P, Bryant MS and Lai ECH. Feasibility of using cranial electrotherapy stimulation for pain in persons with Parkinson's disease. *Parkinson's Disease*. 2010. 8 pages.

Device

Alpha-Stim®

Key Variables

Pain

Objective

To evaluate the effectiveness of cranial electrotherapy stimulation (CES) on musculoskeletal pain in persons with Parkinson's Disease.

Design

This IRB approved study used a randomized, sham controlled clinical trial design in which the subjects in the active CES and sham groups had CES treatments for 6 weeks. Treatments were done at 100 microamps for 40 minutes.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was pain measured on a 0 – 10 scale both pre and post CES treatment.

Key Inclusion Criteria

1. Diagnosis of Parkinson's
2. Chronic musculoskeletal pain of at least 6 months
3. Average pain of at least 5 on a 0 – 10 scale
4. Speak and understand English

Key Exclusion Criteria

1. Current substance abuse problem
2. Currently being treated for psychological or psychiatric condition
3. Moderate to severe cognitive impairment
4. Implanted electrical device

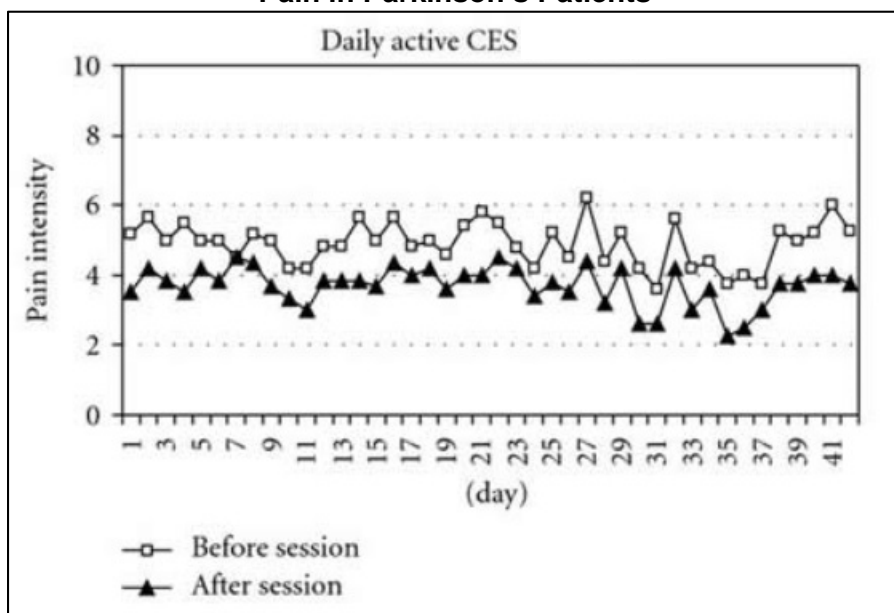
Protocol summary

Subjects were randomized into active or sham groups and treated daily with cranial electrotherapy stimulation (CES) for 6 weeks. Pain was measured pre and post treatment. The treatment was done at 100 microamp for 40 minutes in order to remain subsensory for blinding purposes.

Results

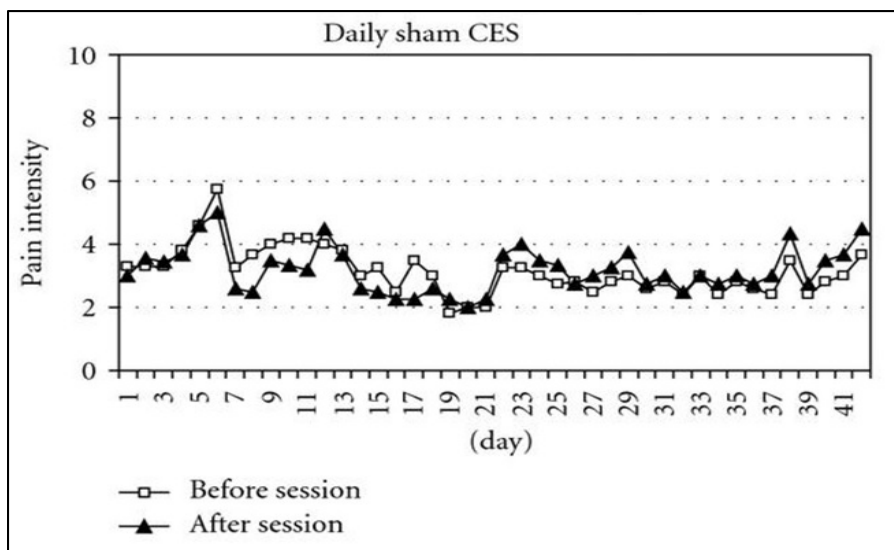
The active group's average daily pain rating was 4.89 ± 1.22 before and 3.75 ± 2.04 after the treatment yielding an average decrease of 1.14 ± 1.21 points. The sham group's average daily pain rating was 3.82 ± 1.76 before and 3.59 ± 1.75 after treatment yielding an average decrease of 0.23 ± 0.33 . The average difference between the groups in change scores (1.14 versus 0.23) was significant ($p=.045$), indicating that pain reduction in the active group was greater than that in the sham group.

Pain in Parkinson's Patients



NRS
41 treatments
N= 4-6
p= 0.045

Figure 18. Change in daily pain ratings for active CES group.



NRS
41 treatments
N= 4-6

Figure 19. Change in daily pain ratings for sham CES group.

4.11. Mellen (2009)

Mellen RR and Mackey W. Reducing sheriff's officers' symptoms of depression using cranial electrotherapy stimulation (CES): A controlled experimental study. *The Correctional Psychologist*. 2009; 41(1): 9-15.

Device

Alpha-Stim®

Key Variables

Depression, Anxiety

Objective

To evaluate the effect of a specified treatment course with CES on sheriff officers' depression and anxiety when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.

Design

An IRB approved 3 week randomized, sham treatment controlled, double-blind clinical trial. The sham device was identical in appearance to the active CES device, but did not conduct an electrical current. The active CES device was set to 100 µA, a subsensory level. The subjects and investigators were masked to the identity of the device.

Primary Effectiveness Endpoints

The primary effectiveness endpoint was the change from baseline in the last post-treatment scores on the outcome depression measures (BDI and BSI-D) and anxiety measures (BAI and BSI-A) compared to the sham treatment group at the endpoint of the study.

Key Inclusion Criteria

- Officers from the Sheriff's staff ≥ 21 years of age.

Key Exclusion Criteria

- Pregnancy
- Presence of implanted pacemakers, pumps or stimulators

Protocol Summary

Randomization assignment was established prior to the start of the study. Evaluations of primary effectiveness endpoint measures were taken at baseline 2 days before treatment began. Post-assessments were taken the week following each subject's final treatment. Following the baseline tests, subjects were taught to use the CES devices and were instructed to do a CES treatment for 20 minutes daily for 20 days. While doing a CES treatment, subjects went about their daily tasks.

Device Application Protocol

The active CES device was pre-set and locked by the manufacturer at 100 µA which is a subsensory level. The sham CES device was pre-set and locked by the manufacturer so that it did not emit electricity. The length of CES treatments was also pre-set and locked by the manufacturer for both the active and sham devices.

Study Blinding

The subjects, investigators and staff were masked to the identity of the devices.

Outcome Measures

The Beck Anxiety Inventory was used to measure anxiety (Beck et al, 1988a) and the Beck Depression Inventory was used to measure depression (Beck et al., 1988b). Both scales have established reliability and validity. The Brief Symptom Inventory Anxiety Subscale and the Brief Symptom Inventory Depression Subscale were also used to measure anxiety and depression. The Brief Symptom Inventory has established reliability and validity (Meachen et al., 2008).

Results

Subjects

A total of 21 subjects completed the study, 10 females and 11 males.

Data Analysis

Data were analyzed using the independent-samples t-test to compare the difference between the active CES and sham groups on depression and anxiety scores.

Depression

The active CES group had significantly lower depression scores on the BDI ($p < 0.05$) and the BSI-D ($p < 0.01$) than the sham group.

Anxiety

There was no significant difference on anxiety scores between the active CES and sham group. The unexpected non-significant result for anxiety is most likely due to a protocol deviation. Because of a heavy workload for subjects who were parole officers, outcome measurement of state (situational) anxiety and depression were rescheduled and done one week after the final CES treatment. While the findings for depression were stable and remained significant, post-test evaluations for state anxiety should have been done immediately after the completion of the last CES treatment as state anxiety varies depending on the immediate situation. This is the most likely reason for the non-significant anxiety findings taken one week after the final CES treatment. Table 3 shows the results of statistical analyses of the outcome measures.

Outcome Variables	Scale	P Values
Depression	Beck Depression Inventory	$P < 0.01$
Depression	Brief Symptom Inventory- Depression Subscale	$P < 0.05$
Anxiety	Beck Anxiety Inventory	n.s.
Anxiety	Brief Symptom Inventory- Anxiety Subscale	n.s.

Table 3. P-Values for Comparison of Active CES and Sham groups on depression and anxiety outcome measures.

Quality of the Research

Strength of this study are: the Alpha-Stim double-blind, sham controlled RCT protocol was used; and active CES devices were set at the subsensory level of 100 μ A and sham CES devices set so they did not emit electricity. The CES devices were pre-set to these specifications by the manufacturer. Limitations of the study are: the small N; and endpoint measures were not taken as scheduled in the protocol but rather one week after the final CES treatment because of an unexpected heavy workload that interfered with the clinical trial. Change in depression was stable and significant, but change in state anxiety was non-significant. Since state anxiety changes from moment to moment with the situation, the deviation from the Alpha-Stim CES protocol in the measurement of anxiety one week later as opposed to right after the last CES treatment most likely accounts for the non-significant findings for anxiety.

4.12. Strentzsch (2008)

Strentzsch, Julie A. An examination of cranial electrotherapy stimulation (CES) on alpha-amylase levels, cortisol levels and state-trait anxiety scores in the chronically mentally ill. *Doctoral Dissertation, Saint Mary's University, San Antonio, Texas, 2008.*

Device

Alpha-Stim®

Key Variable

State Anxiety

Objective

To evaluate the effect of a specified treatment course with CES on chronically mentally ill patients' anxiety when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.

Design

This was an IRB approved 3 week randomized, sham controlled, double-blind, clinical trial.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the last post-treatment scores on the State Anxiety Inventory (SAI) compared to the sham group at the end point of the study.

Secondary Outcome Measures

Secondary outcome measures of trait anxiety; cortisol and alpha-amylase levels were measured at the end of the 3 week study.

Key Inclusion Criteria

- Chronically mentally ill outpatients attending a partial hospitalization program.
- Diagnosis of anxiety by subject's physician.

Key Exclusion Criteria

- Pregnancy
- Presence of implanted pacemakers, pumps or stimulators

Protocol Summary

Baseline measures were taken on the day the subjects were accepted into the study. The active and sham groups had CES treatments every day at 11 am during a therapy session. The control group attended the therapy session but was not connected to a CES device. At the end of 3 weeks, primary and secondary outcome measures were repeated.

Device Application Protocol

The active CES device was pre-set and locked by the manufacturer at 100 µA which is a subsensory level. The sham CES device was pre-set and locked by the manufacturer so that it did not emit electricity. The length of treatment, 60 minutes, was also pre-set and locked by the manufacturer for both active and sham devices. There were an equal number of active and sham devices. Randomization of the devices was done at the factory and the devices were packed in the order that they would be assigned to subjects.

Study Blinding

The subjects, investigators and staff were all masked as to the identity of the device.

Outcome Measures

The Spielberger State/Trait Anxiety Inventory was used to measure anxiety. It has established reliability and validity (American Psychological Association, 2014; Spielberger 2010).

Results

Subjects

A total of 45 subjects were enrolled and 38 subjects completed all post-test requirements; active CES group (N=15), sham group (N=15), and usual care control group (N=8). Diagnoses included bipolar disorder (N=13, 31%), generalized anxiety disorder (N=5, 12%), major depressive disorder (N=4, 10%), schizoaffective disorder (N=9, 21%) and schizophrenia (N=11, 26%).

Baseline Measurements: Group Equivalence

There were no statistically significant differences at baseline among the groups for any of the outcome measures.

Data Analysis

Data were analyzed using paired samples t-tests.

Anxiety

The active CES group had significantly lower scores on the State Anxiety Index (SAI), indicating less state anxiety, than the sham group ($P=.02$, $d = -.41$) or control group. As expected, since trait (chronic) anxiety is usually a stable personality trait it is less responsive to change than state anxiety (Spielberger, 2010) there was no significant difference between the active and sham groups on trait anxiety. There was no significant difference among groups on the variables of cortisol and alpha-amylase levels. Figure 20 shows results of statistical analyses of outcome measures for state anxiety for the 3 groups.

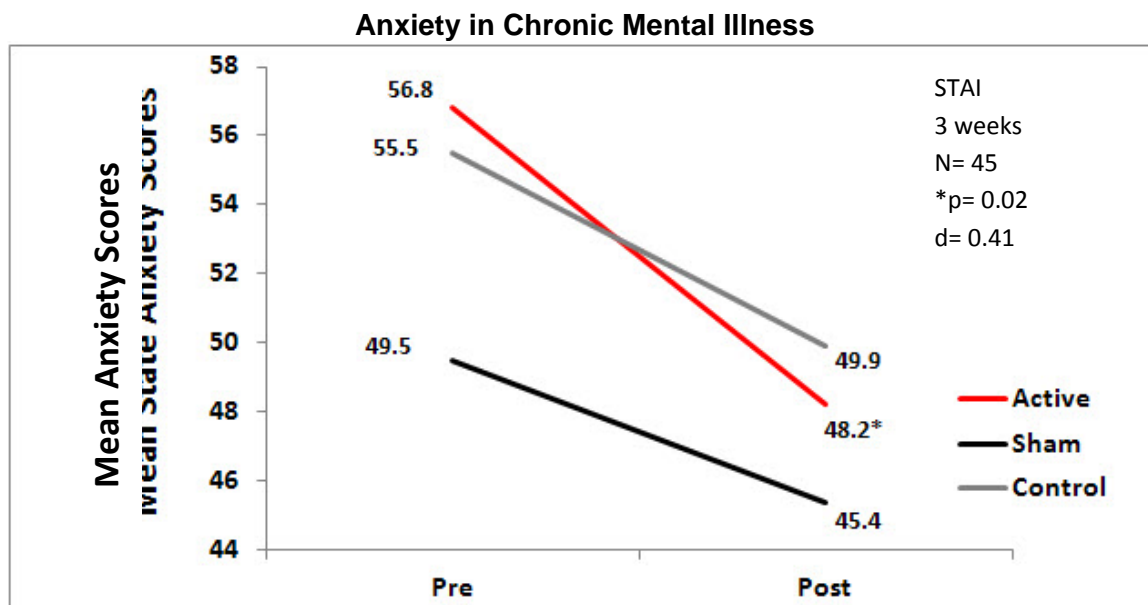


Figure 20. Mean state anxiety scores by group.

Quality of the Research

Strengths of this study are: use of a randomized, sham controlled, double-blind design (The investigator chose to use the Alpha-Stim RCT research protocol for the study); active and sham Alpha-Stim devices were pre-set and locked at the designated levels for each specific group for current level and time of treatment by the manufacturer at the factory; sham units were the same as active units, except they did not emit electricity; randomization of devices was done by the manufacturer and followed according to the protocol by the investigator; diagnosis of anxiety was verified using the criteria from the DSM-IV before subjects could be in the study; and the use of a structured and detailed protocol for the CES treatments for both active and sham groups. Previous effect sizes from other CES studies for anxiety indicate the N of the study had sufficient power to detect differences. A limitation of this 2008 study is the use of paired samples t-tests which was a common practice at that time. Today, an analysis of covariance would most likely be used and it would provide a more comprehensive description of the data. The effect size in this study for anxiety approached moderate ($d=0.41$) in contrast to the moderate to very large effect sizes for anxiety in other Alpha-Stim CES RCT studies. This is probably due to the limited treatment time of 3 weeks in this chronically mentally ill patient population. The significant finding of this study that CES decreases anxiety is consistent with other Alpha-Stim studies that had similar findings.

4.13. Mellen (2008)

Mellen RR and Mackey W. Cranial electrotherapy stimulation (CES) and the reduction of stress symptoms in a sheriff's jail security and patrol officer population: a pilot study. *American Jails*. 2008; 22(5): 32-38.

Device

Alpha-Stim®

Key Variable

Stress related symptoms

Objective

This double blind study examined the ability of CES to reduce stress related symptoms in the security and patrol officer's staff of a rural sheriff's jail.

Design

All 22 subjects completed 20, 20 minute sessions of the Treatment Group (N=11) and Control Group (N=11) on the pre-treatment Brief Symptom Inventory (BSI) or sub-scales. This was true for the clinical scales and the global scales suggesting both groups were similar, as measured by the BSI.

Primary Effectiveness Endpoint

Brief Symptom Inventory (BSI)

Secondary Outcome Measures

Global Index, Positive Symptom Distress, Positive Symptom Total

Key Inclusion Criteria

Security and patrol officer's staff of a rural sheriff's jail

Key Exclusion Criteria

Pregnancy or implanted medical device

Protocol Summary

All 22 subjects completed 20, 20 minute sessions of the Treatment Group (N=11) and Control Group (N=11) on the pre-treatment Brief Symptom Inventory (BSI) or sub-scales.

Study Blinding

This was a double blind RCT

Results

No changes were found between pre- and post-assessment means for the control group. However significant changes were found in the treatment group's BSI results, suggesting a positive influence from using CES. In addition, the treatment group findings support the argument that Alpha-Stim CES provides a global brain modulation. Differences in pre/post-treatment means for the treatment group were: 1. Somatization: measures bodily complaints ($P<.008$), 2. Obsessive/Compulsive: repetitive thoughts and actions ($P<.020$), 3. Interpersonal Sensitivity: difficulties with interpersonal relationships ($P<.077$), 4. Depression: sad mood, loss of energy, difficulty sleeping or sleeping too much ($P<.015$), 5. Anxiety: excessive worry,

($P < .015$). Hostility: feelings of anger toward others and the world ($P < .077$), 7. Phobia: excessive fearful reactions toward objects, insects and such ($P < .177$), 8. Paranoia: excessive fears that are not supported by evidence ($P < .066$), 9. Psychoticism: these individuals can appear unusual and emotionally distant ($P < .050$). The BPI also has 3 global scales for measuring stress: 1. Global Index: the most sensitive measure of stress ($P < .007$), 2. Positive Symptom Distress: degree of stress being reported ($P < .042$), and 3. Positive Symptom Total: total number of symptoms endorsed by a subject ($P < .004$).

Subjects

Attendance by the treatment group was higher than the control group: 71% for the treatment group compared to 41% for the control group. The attrition rate for the experimental group was 29% and for the control group 59%. The most common reason for not completing the program was non-compliance, e.g., failure to attend, a failed drug test or other program rule violations. One of the 4 experimental group dropouts was due to injuries related to a car accident.

Conclusion

The authors concluded that Alpha-Stim seems to provide a global modulation effect in substance abusers. The effect could be calming the subjects and allowing them to access the cortical and sub-cortical areas of the brain that they need for making better decisions. Results supported the use of CES for reducing clinical and stress symptoms in the treatment group and maintaining attendance in treatment.

4.14. Kim (2008)

Kim HJ, Kim WY, Lee YS, Chang MS, Kim JH and Park YC. The effect of cranial electrotherapy stimulation on preoperative anxiety and hemodynamic responses. *Korean Journal of Anesthesiology*. 2008; 55(6): 657-661.

Device

Alpha-Stim®

Key Variable

Preoperative Anxiety

Objective

To evaluate the effect of a specified treatment course with CES on patients' preoperative anxiety levels when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.

Design

This was an IRB approved randomized, investigator-blinded, clinical trial. The active CES device was set to "just below" 200 μ A, where subjects did not feel a tingling sensation.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the post-treatment scores on the Likert anxiety scale compared to the sham group at the end point of the study.

Key Inclusion Criteria

1. Preoperative patients between the ages of 18-65 awaiting surgery under general anesthesia.
2. Must meet the American Association of Anesthesiology Physical Classification Criteria 1 and 2.

Key Exclusion Criteria

1. Pregnancy.
2. Presence of implanted pacemakers, pumps or stimulators.
3. BMI over 25, and having endocrinological, musculoskeletal, liver and kidney or vascular disorders.
4. Individuals awaiting high anxiety procedures such as tumor removal or amputation.
5. Individuals who were taking antidepressant and other psychotropic medications.

Protocol Summary

Detailed explanations for study purpose and procedures were provided to the patient and their families and consents were obtained the night before the surgery. They were told that they will be held for 20-30 minutes in the pre-surgical waiting area and they will either receive or not receive CES and what sensation to expect from CES pretreatment in order to reduce anxiety. All subjects were given glycopyrrolate 0.2 mg IM as a premedication about one hour before induction of anesthesia. They were brought to the waiting area to be evaluated by the same anesthesiologist who visited them the night before. They were asked about their level of anxiety and blood pressure and pulse rate was measured as a physiological index of anxiety. Anxiety was rated using a Likert Scale measuring the subjective experience of anxiety on a scale of 1 (low) to 5 (high). Subjects were randomly assigned to either a control group (n=30) who received supportive nursing care or a CES group (n=30) who received a 20 minute CES pretreatment in the operating room waiting area by Alpha-Stim fixed at below 200 μ A, 0.5 Hz.

Ear clips were attached to the ear lobes and the current level was adjusted to below the feeling of a tingling sensation in the ear lobes or feeling dizzy.

Study Blinding

The investigators were masked to which subjects reviewed CES or were controls.

Results

Subjects

Sixty (60) adults between the ages of 18-65 were subjects in this study. Subjects were waiting for surgery under general anesthesia and met the American Association of Anesthesiology Physical Classification Criteria 1 and 2. Subjects were having orthopedic, gynecological and ear, nose and throat procedures requiring about 2 hours and the surgical procedures had similar risk factors.

Baseline Measurements: Group Equivalence

There were no statistically significant differences at baseline between active CES and sham treatment groups on the outcome anxiety measure. There were no differences in age, gender, height and weight distribution between the 2 groups. There was no difference in anxiety scores of surgical pre-operative room measurements between the CES and control groups.

Data Analysis

Data were analyzed using t-test to compare the CES and control groups on anxiety scores.

Anxiety

As seen in Figure 21 the CES group had lower anxiety scores on the Likert scale compared to the control group at the endpoint of the study ($p < 0.01$, $d = -.88$).

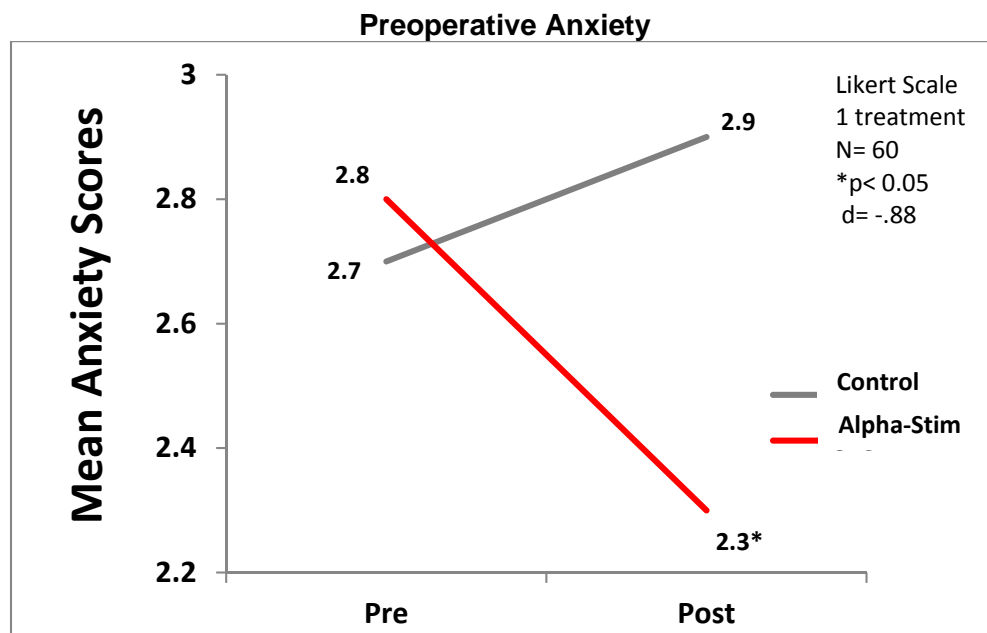


Figure 21. Mean Anxiety Score by Group.

Quality of the Research

Strengths of this study include: (1) The randomized controlled clinical trial design (2) An adequate N of 60 to detect differences between the active and sham groups and (3) The blinding of the investigators to which subjects received CES treatments. The use of a sham CES device would have increased the strength this study. The findings of this study that CES decreases anxiety are consistent with other RCTs using Alpha-Stim® CES technology.

4.15. Chen (2007)

Chen Y, Yu L, Zhang J, Li L, Chen T and Chen Yi. Results of cranial electrotherapy stimulation to children with mixed anxiety and depressive disorder. *Shanghai Archives of Psychiatry*, 2007; 19(4): 203-205.

Device

Alpha-Stim®

Key Variables

Anxiety, Depression

Objective

The purpose of this study was to examine the efficacy of CES for the treatment of mixed anxiety and depressive disorder (MAD) in children.

Design

This study used a randomized, sham controlled clinical trial design in which subjects in the active CES and sham groups had CES treatments for 15 days.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the last post-treatment scores on the Zung Self-Rating Depression Scale (SDS) and the Zung Self-Rating Anxiety Scale (SAS) compared to the sham CES group at the endpoint of study.

Key Inclusion Criteria

1. Male or female children between 8 to 16 years of age.
2. Diagnosis of mixed anxiety and depression disorder (MAD) by a “specialist physician” prior to acceptance into the study (Experimental group only).
3. Must score > 40 on the combined scores of the SAS and SDS.

Key Exclusion Criteria

1. Pregnancy, planning to become pregnant or nursing.
2. Presence of implanted pacemakers, pumps or electrical stimulators.
3. Subjects have taken drug therapy for MAD or emotional disorders.

Protocol Summary

Subjects for the experimental group were randomly selected from children with MAD who met the criteria for entry into the study and who were patients at the Children’s Psychological Health Clinic at Nanjing Brain Hospital. Subjects for the control group were randomly selected from a group of children with emotional problems who were recommended by their teacher at elementary or middle schools in the city and met the > 40 score criteria on combined SAS and SDS scores but did not meet the diagnostic criteria for anxiety disorder or depressive disorder. Baselines measures were done prior to the first active or sham CES treatment and endpoint measures were done after the completion of the final CES treatment.

Device Application Protocol

The current of the active CES device was set at a comfortable level for the active group subjects, between 100 – 500 μ A. The current of the sham CES device was increased until the sham subject felt a “skin sensation,” then decreased and shut off, so that the device did not emit electricity. Neither group felt any sensation from the device for the remainder of the treatment.

The length of each treatment was 10-15 minutes. The treatment schedule was 5 daily CES treatments followed by 2 days off and then this schedule was repeated 2 more times.

Results

Subjects

There were 60 subjects in the study, 30 in each group. In the active CES group there were 25 males and 5 females. In the sham group there were 19 males and 11 females. All subjects were between 8 to 16 years of age. There were no significant differences in gender and age between the two groups.

Data Analysis

Chi-Square and ANOVA were used to analyze the data.

Anxiety

There was a significant difference between the active and sham groups for anxiety at endpoint of study ($p < 0.01$), Figure 22.

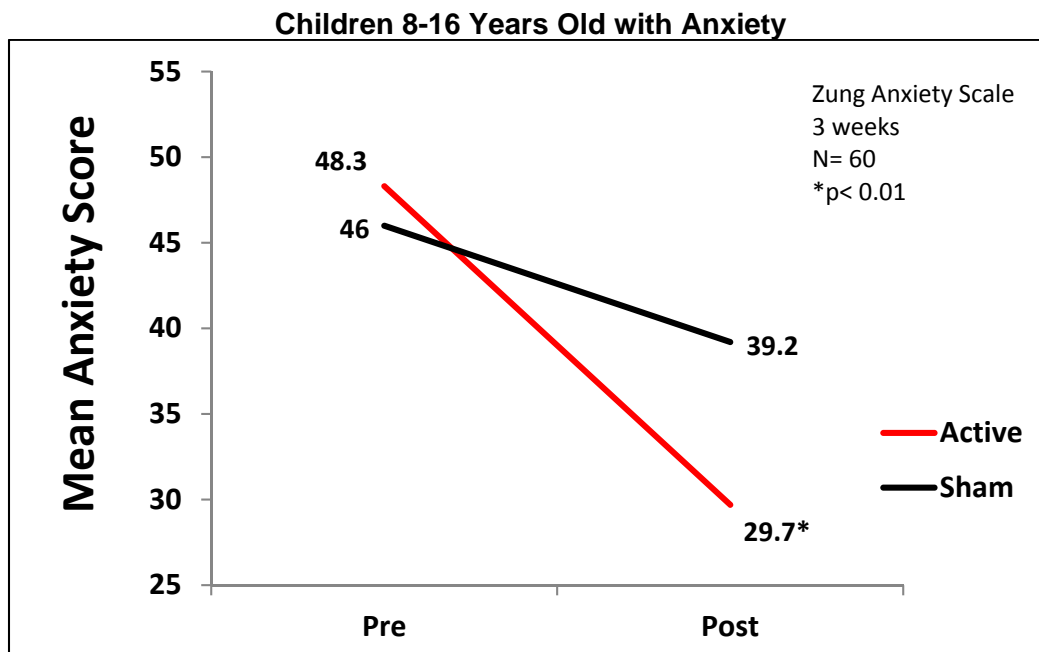


Figure 22. Mean Anxiety Scores by Group.

Depression

There was a significant difference between the active and sham groups for depression at endpoint of study ($p < 0.01$), Figure 23.

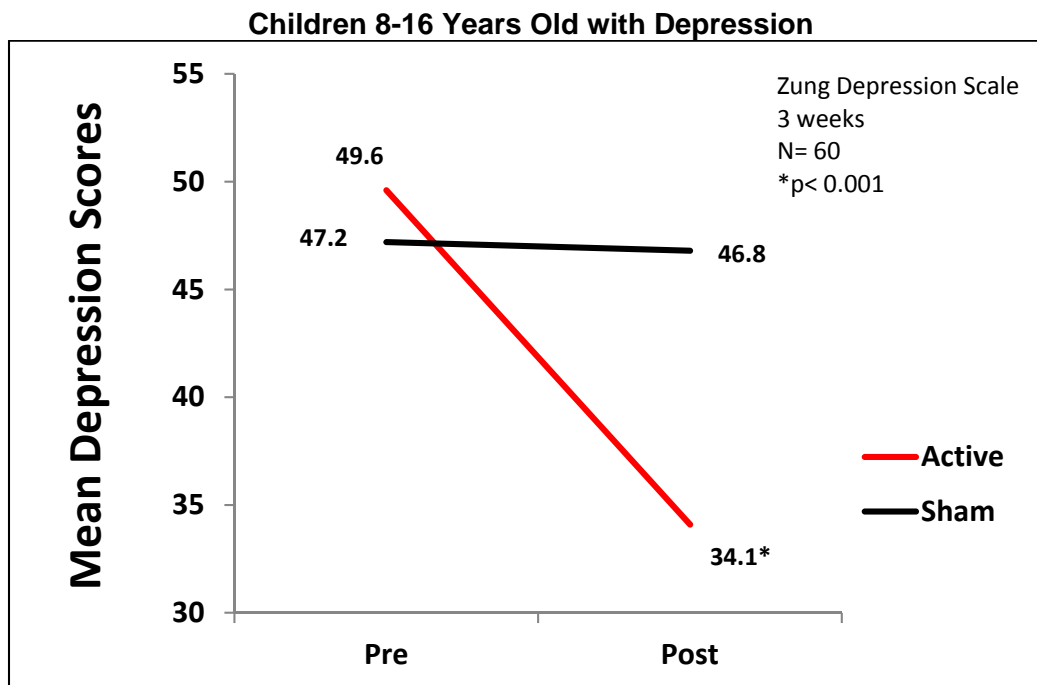


Figure 23. Mean depression scores by group.

Quality of the Research

Strengths of this clinical study include: (1) The investigators used a randomized, sham controlled design; (2) The diagnosis of MAD was verified by a physician prior to acceptance into the study for the experimental group; (3) Sham CES devices were the same as active CES devices except they did not emit electricity; and (4) Based on the effect sizes for anxiety and depression in other Alpha-Stim® CES studies, this was an adequately powered study with an N of 60. A limitation of this study is that the sham group did not meet the criteria for MAD. One possible explanation for this is that recruitment of enough children with MAD was a problem. Another limitation is that the current for the active group (100 - 500 μA) and length of CES treatment (10 - 15 minutes) for all subjects were not the same. The findings from this study on the significant effect of CES on anxiety and depression are similar to those found by Lu in children (Lu et al., 2005) and in other Alpha-Stim CES studies with adult subjects.

4.16. Tan (2006)

Tan GR, Diana H, Thornby J, Yang J, Wade W and Vasilev C. Using cranial electrotherapy stimulation to treat pain associated with spinal cord injury. *Journal of Rehabilitation Research and Development*. 2006; 43(4): 461-474.

Device

Alpha-Stim®

Key Variables

Pain

Objective

The purpose of this study was to investigate the efficacy of CES for the treatment of pain associated with spinal cord injury.

Design

This is an IRB approved double-blind, sham controlled design with random assignment examining the effects of daily one hour active (N = 18) or sham (N = 20) CES treatments for 21 consecutive days on pain intensity and interference activities in 38 male veterans who had received care at a Department of Veterans Affairs spinal cord injury (SCI) Center. Treatments were self-administered at home.

Primary Effectiveness Endpoint

Daily pain intensity scale from 1 - 10

Key Inclusion Criteria

Veterans who were 6 months to 60 years post SCI with chronic musculoskeletal or neuropathic pain were recruited in from the Michael E. DeBakey VA Medical Center in Houston, Texas.

Key Exclusion Criteria

Exclusion criteria were documented history of noncompliance, evidence of substance abuse, and history of severe cognitive and or mental disorder that might interfere with the treatment regimen.

Protocol Summary

Subjects received 60 minutes of CES each day for a total of 21 days. Pain intensity and pain interference was measure pre and post treatment each day. These treatments were self-administered at home. After the double blind phase, the sham group was offered the opportunity to participate in an open label phase with active CES for another 21 days.

Device Application Protocol

Daily 60 minute treatments of CES to be administered at home

Results

Subjects

There were 40 veterans who were 6 months to 60 years post SCI with chronic musculoskeletal or neuropathic pain were recruited in from the Michael E. DeBakey VA Medical Center in Houston, Texas.

Pain in Veterans from Spinal Cord Injury

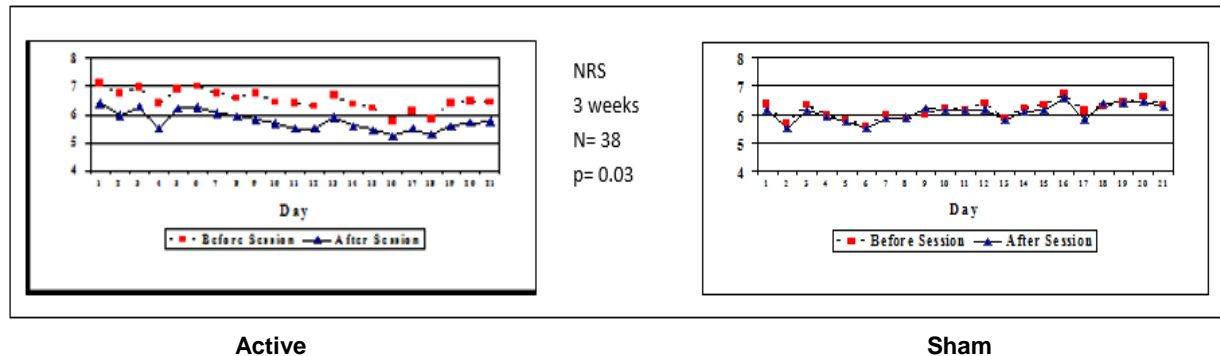


Figure 24. The active CES group reported significantly decreased daily pain intensity ($p = 0.03$) compared with the sham CES group. The active CES group also showed significantly decreased pain interference ($p = 0.004$).

Conclusion

After the double-blind phase, the sham group were offered the opportunity to participate in an open label phase with an active CES device for another 21 consecutive days. 17 of the sham CES treated subjects (85%) agreed to the open label phase. The active and sham CES groups did not differ significantly with regard to their average precession pain ratings (mean equals 6.46 active CES versus 6.08 sham CES). The average change in daily pain intensity from pre- to post session was significantly larger for the active CES group (mean = -0.73) than the sham CES group (mean = -0.08, $P = 0.03$). The treatment effect size was medium to large (Cohen $d = 0.76$). Participants who received sham CES did not show significantly reduced pain ($P = 0.34$), whereas participants who received active CES did show significantly reduced pain ($P = 0.02$). The 17 sham CES participants who subsequently participated in the open label phase reported significant post session pain reduction ($P = 0.003$).

4.17. Cork (2004)

Cork RC, Wood P, Ming N, Shepherd C, Eddy J and Price L. The effect of cranial electrotherapy stimulation (CES) on pain associated with fibromyalgia. *The Internet Journal of Anesthesiology*. 2004; 8(2).

Device

Alpha-Stim®

Key Variable

Anxiety

Objective

To evaluate the effect of a specified treatment course with CES on fibromyalgia patients' anxiety, pain, tender point scores, and functional impairment when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria. The findings for the variable of anxiety are discussed in this abstract.

Design

An IRB approved 6 week study that included a 3 week randomized, sham treatment controlled clinical trial arm followed by a 3-week open label arm in which subjects in the sham group participated in a treatment course of CES. The investigators used the Alpha-Stim® double-blind, sham-controlled RCT protocol for this study.

Primary Effectiveness Endpoint: Anxiety

The primary effectiveness endpoint for anxiety in the Phase I RCT was the change from baseline in the last post-treatment scores on the Profile of Mood States (POMS) compared to the sham treatment group at the end of week 3 of the study. The primary effectiveness endpoint for anxiety in the Phase II open label arm was the change from baseline in the last post-treatment scores on the POMS to post-test at the end of week 6 of the study.

Other effectiveness outcome measures were measured at the end of week 3 of the study and included both clinician rated and patient rated outcome measures. The following clinician rated measures was included: Tender point score evaluation. The following patient rated measures were included: McGill Pain Questionnaire (SF-MPQ), and Oswestry Score for functional impairment from pain.

Key Inclusion Criteria

- Male and female subjects with fibromyalgia ranging from 22 – 75 years of age.
- Diagnosis of fibromyalgia was verified by a physician pain specialist using the criteria of the American College of Rheumatology Criteria for the Classification of Fibromyalgia (Wolfe et al., 1990).

Key Exclusion Criteria

- Pregnancy.
- Presence of implanted pacemakers, pumps or stimulators.
- Superficial or internal ear infections.

Protocol Summary

Randomization assignment was established prior to the start of the study by the manufacturer of Alpha-Stim CES devices. Evaluations of primary effectiveness endpoint and secondary outcome

measures were taken at baseline prior to the start of the treatment period. No change was made in the medical management of the patients during the study.

The protocol consisted of 2 phases:

Phase I: 3 weeks of treatment with either the active CES device or the sham device. Following the baseline tests, subjects were taught to use the CES device, and were instructed to use it every day for 1 hour over the 3 week period. At the end of 3 weeks, the subjects returned to the clinic, and primary and secondary outcome measures were repeated.

Phase II: After the blinding was broken subjects in the sham group were given the option to receive active CES for 3 weeks. Those that elected to do so returned to the clinic after the 3 week period and were retested.

Device Application Summary

The active CES device was pre-set and locked by the manufacturer at 100 μ A which is a subsensory level. The sham CES device was pre-set and locked by the manufacturer so that it did not emit electricity. The length of treatment, 60 minutes, was also pre-set and locked by the manufacturer for both active and sham devices. The sham device was identical in appearance to the active CES unit, but did not conduct an electrical current. The devices were randomized by the manufacturer and then packed in a device box in the order they should be given to subjects.

Study Blinding

The subjects, investigators, physicians and staff were all masked to the identity of the devices

Outcome Measures

The Profile of Mood States (POMS) was used to measure anxiety. The POMS has established reliability and validity (McNair et al., 2014).

Results

Subjects

A total of 74 subjects were enrolled, 70 females and 4 men ranging in age from 22 – 75 (M = 53) years of age. The average duration of symptoms was 7.3 years (range 1 -21 years). Subjects were randomized to the active CES group (N=39) or sham group (N=35).

Baseline Measurements

There were no statistically significant differences at baseline between active CES and sham treatment groups for any of the outcome measures.

Data Analysis

Data were analyzed with repeated measures analysis of variance, with least significant difference a posteriori testing in both Phase I and Phase II of the study.

Phase I RCT Effectiveness Results: Week 3

Seventy-four (74) subjects, 39 active CES and 35 Sham, completed the testing at the completion of week 3 visit. The active CES group had significantly decreased anxiety scores, tender points and pain compared to sham group. There was no significant difference between groups on pain as measured by the McGill Pain Questionnaire, or functional impairment. Table 4 shows results of statistical analyses of all outcome measures.

Outcome Variable	Scale	P Values
Anxiety	POMS	P < 0.01
Pain Intensity	NRS	P < 0.01
Tender Point Score	Tender Point Score	P < 0.01
Pain	SF-MPQ	n.s.
Functional Impairment	Oswestry Score	n.s.

Table 4. P-Values for Comparison Between Active and Sham Treatment Means Changes from Baseline to Week 3

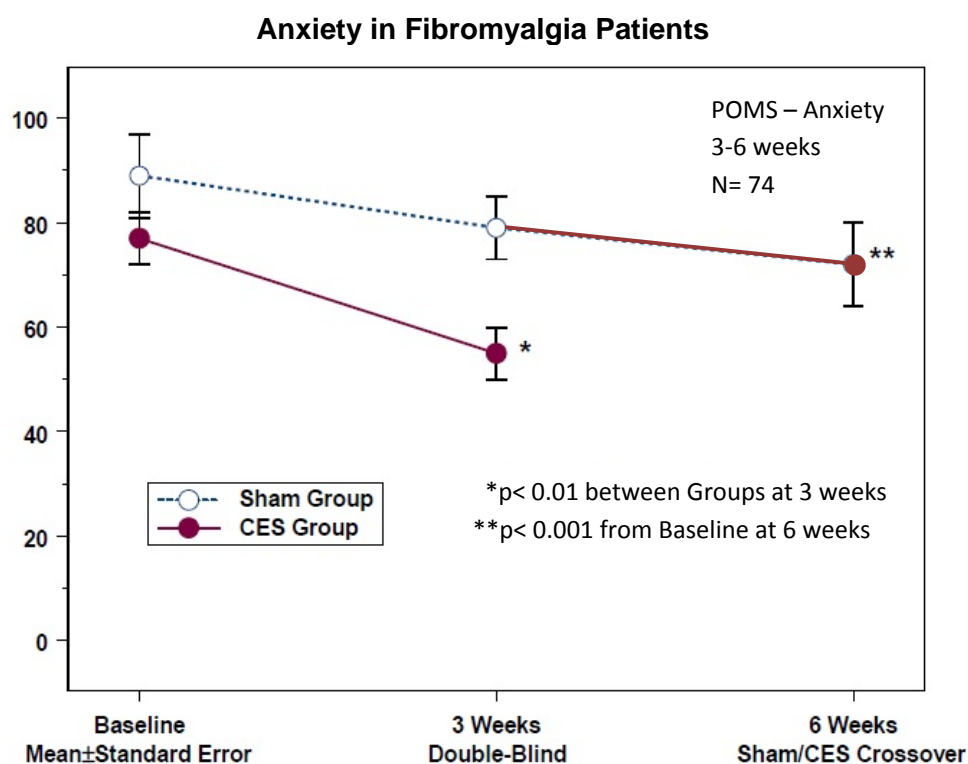


Figure 25. Patient mood as measured by the Profile of Mood States (POMS). A higher score represents more anxiety. The anxiety reported by the CES group after 3 weeks of CES was significantly less than the anxiety reported by the sham group after 3 weeks of sham treatment ($p<0.01$). After crossover and 3 weeks of subsequent CES treatment, the sham group reported a significant decrease in anxiety levels from their baseline scores ($p<0.001$).

Phase II Open Label Effectiveness Results: 6 Weeks

Data were analyzed with repeated measures analysis of variance, with least significant difference a posteriori testing. Table 5 shows results of statistical analyses of outcome measures at week 6. Figure 26 shows patient mood as measured by the POMS where higher scores represent more anxiety.

Outcome Variables	Scale	P Values
Anxiety	POMS	$P < 0.001$
Pain Intensity	NRS	$P < 0.001$
Pain	SF-MPQ	$P < 0.001$
Tender Point Scale	Tender Point Scale	$P < 0.001$
Functional Impairment	Oswestry Score	n.s.

Table 5. P-Values for Changes from Baseline within CES Open Label Group at week 6

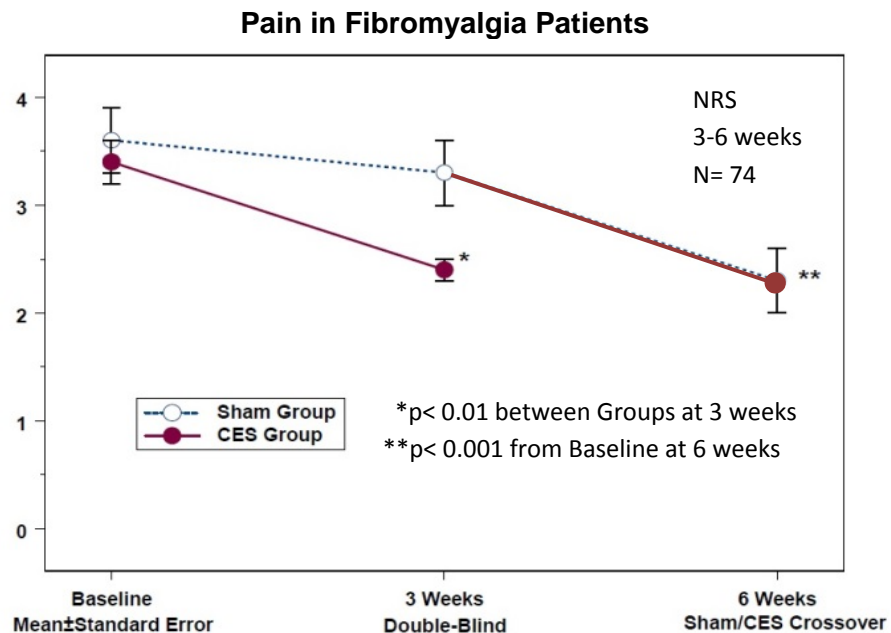


Figure 26. Patient pain as measured by a Numerical Rating Scale (NRS). A higher score represents more pain. The pain reported by the CES group after 3 weeks of CES was significantly less than the pain reported by the sham group after 3 weeks of sham treatment ($p < 0.01$). After crossover and 3 weeks of subsequent CES treatment, the sham group reported a significant decrease in pain levels from their baseline scores ($p < 0.001$).

Quality of the Research

Strength of this study are; use of a double-blind, sham controlled RCT design; the active and sham devices were preset for time and current level, and the sham CES device was identical to the active CES device except they did not emit electricity; the study was adequately powered with an N of 74, based on the research on the effect sizes for CES for treatment of anxiety. This 2004 study measured general anxiety using the POMS scale which was commonly used at that time and has established clinical and research utility in the literature. Today, a more likely choice by investigators would be the Hamilton Anxiety Rating Scale or other similar anxiety scale. The significant finding for anxiety in this study is consistent with findings from other CES RCTs that showed CES significantly decreases anxiety.

Author Affiliation

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4.18. Lichtbroun (2001)

Lichtbroun AS, Raicer MMC and Smith R. The treatment of fibromyalgia with cranial electrotherapy stimulation. *Journal of Clinical Rheumatology*. 2001; 7(2): 72-78.

Device

Alpha-Stim®

Key Variables

Anxiety, Sleep Quality (Insomnia) and Pain

Objective

To evaluate the effect of a specified treatment course with CES on fibromyalgia patients' sleep quality, anxiety, depression, anger, tender point scores, self-rated pain, vigor, fatigue, confusion, feelings of well-being, and quality of life when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.

Design

An IRB approved 6 week study that included a 3 week randomized, sham treatment controlled, double-blind clinical trial arm followed by a 3 week open label crossover arm in which subjects in the sham and control groups could elect to participate in a treatment course of CES.

Primary Effectiveness Endpoint

The primary effectiveness endpoint in the RCT was the change from baseline in the last post-treatment self-rated scores on the 10 point Numerical Rating Scale (NRS) for overall pain, quality of sleep, feelings of well-being and quality of life, and Profile of Mood States (POMS) subscales compared to the sham treatment group at the end of week 3 of the study.

The primary effectiveness endpoint in the open label crossover arm was the change from baseline in the last post-treatment scores on the 10 point Numerical Rating Scale (NRS) to post-test for overall pain, quality of sleep feelings of well-being and quality of life, and POMS subscales at the end of week 6 of the study. Effectiveness outcome measures were completed at the end of week 3 of the RCT study and at the end of the open label crossover arm 3 weeks later.

Key Inclusion Criteria

- Male and female subjects with fibromyalgia ≥ 21 years of age.
- Diagnosis of fibromyalgia was verified by a board certified rheumatologist using the criteria established by the American College of Rheumatology.

Key Exclusion Criteria

- Pregnancy
- Presence of implanted pacemakers, pumps or stimulators.

Protocol Summary Randomization assignment was established prior to the start of the study. The measurements of primary effectiveness endpoint were taken at baseline, prior to start of treatment period. No change was made in the medical management of the patient during the study. The protocol consisted of two arms:

- RCT arm: 3 weeks of treatment with either the active CES device or the sham device.
- Following the baseline tests, subjects were taught to use the CES device, and were instructed to use it every day for one hour over the 3 week period. At the end of 3 weeks, the subjects returned to the clinic, and outcome measures were repeated.

- Open label crossover arm: At this time blinding was broken and subjects in the sham and control groups were given the option to receive active CES for 3 weeks. 23 of the 40 subjects in the sham group elected to participate in the open label crossover arm. Subjects used the CES device daily for 1 hour for 3 weeks. At the completion of the 3 week open label crossover arm, subjects were retested on study outcome measures.

Device Application Protocol

Subjects were randomly assigned into 3 separate groups, either active CES at a subthreshold level, sham group or control by drawing subjects names out of a container. The active CES device was set to 100 μ A, a subthreshold level. The sham device was identical in appearance to the active CES unit, but used ear clips made for this study that did not conduct an electrical current.

Study Blinding

The subjects, investigators, physicians and staff were all masked as to the identity of the device.

Outcome Measures

The Profile of Moods (POMS) subscale A was used to measure. Sleep quality was measured by a 10 point numerical rating scale. All scales used have established reliability and validity (McNair et al., 2014, 1971; Farrar et al., 2008).

Results

Subjects

A total of 60 subjects were enrolled, 58 females and 2 men ranging in age from 23 – 82 (M = 50) years of age. All 60 subjects completed the post-testing at the completion of the last treatment at the end of their week 3 visit. The average duration of symptoms was 11 years (range 1 – 40 years). Subjects were randomized to the active CES group (N=20), sham group (N=20) or a wait-in-line placebo control group (N=20).

Baseline Measurements: Group Equivalence

There was no statistically significant difference at baseline between active CES and sham treatment groups on any of the 12 outcome measures.

Data Analysis

In December 2011, the data from this 2001 Lichtbroun study were reanalyzed to by Dr. Larry Price, statistical consultant to Electromedical Products International, Inc. to verify the findings previously reported and to conduct additional more powerful analyses that could provide a more comprehensive description of the findings. The raw data was analyzed using analysis of covariance (ANCOVA) and Mann-Whitney U. The investigators originally used a one-way analysis of variance (ANOVA) to comparing baseline and endpoint study outcomes.

Primary Effectiveness Results: Week 3

The active CES group had significant findings on 8 of the 11 variables compared to the sham group: significantly lower anxiety scores ($p=0.04$, $d = -.60$), higher quality of sleep scores ($p = 0.02$, $d = .45$), lower pain scores ($p = .004$, $d = .65$), higher feelings of well-being scores ($p = .007$, $d = .73$), higher quality of life scores ($p = .000$, $d = .97$), lower fatigue scores ($p = 0.03$, $d = -.72$) and lower anger scores ($p = 0.04$, $d = .60$) compared to sham group (See Table 6). The treatment effect sizes between active CES and sham group ranged from $-.36$ to $.97$ on 8 significant variables, with a pooled effect size of $.64$. Table 6 shows results of statistical

analyses of outcome measures and Figures 27, 28 and 29 show the results between groups in anxiety scores, sleep quality, and pain.

Outcome Variables	Scale	Analysis	P Values, Cohen's <i>d</i>
Tender point Score	Tender point scale	ANCOVA	$p = .02, d = -.36$
Pain	Self-report NRS	ANCOVA	$p = .004, d = .65$
Quality of Sleep	Self-report NRS	ANCOVA	$p = 0.02, d = .45$
Well-being	Self-report NRS	ANCOVA	$p = .007, d = .73$
Quality of Life	Self-report NRS	ANCOVA	$p = .000, d = .97$
Fatigue	POMS-F Subscale	ANCOVA	$p = 0.03, d = .72$
Anxiety	POMS-Anxiety Subscale	Mann-Whitney U	$p = 0.04, d = .60$
Anger	POMS-Anger Subscale	Mann-Whitney U	$p = 0.04, d = .60$
Vigor	POMS-V Subscale	ANCOVA	n.s.
Confusion	POMS-C Subscale	ANCOVA	n.s.

Table 6. P-values for comparison between active CES and sham groups at week 3.

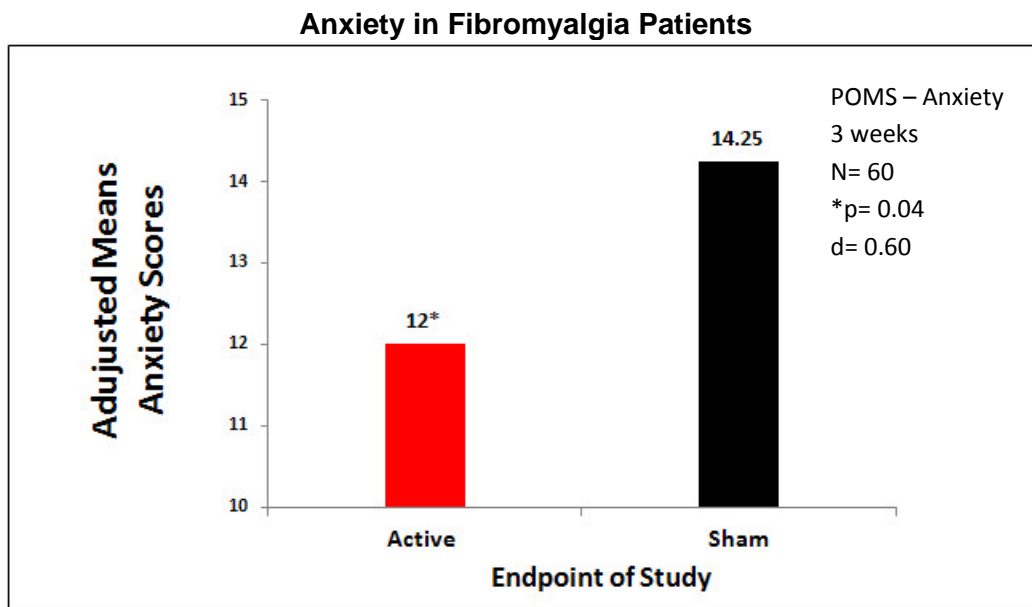


Figure 27. Mean anxiety scores by group.

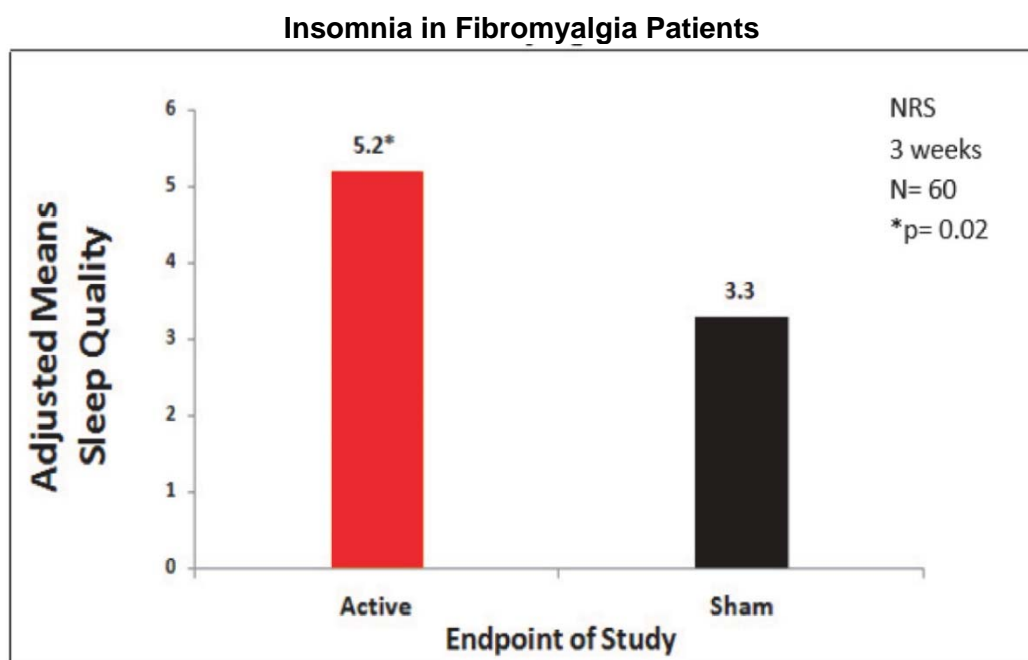


Figure 28. Sleep quality results by group.

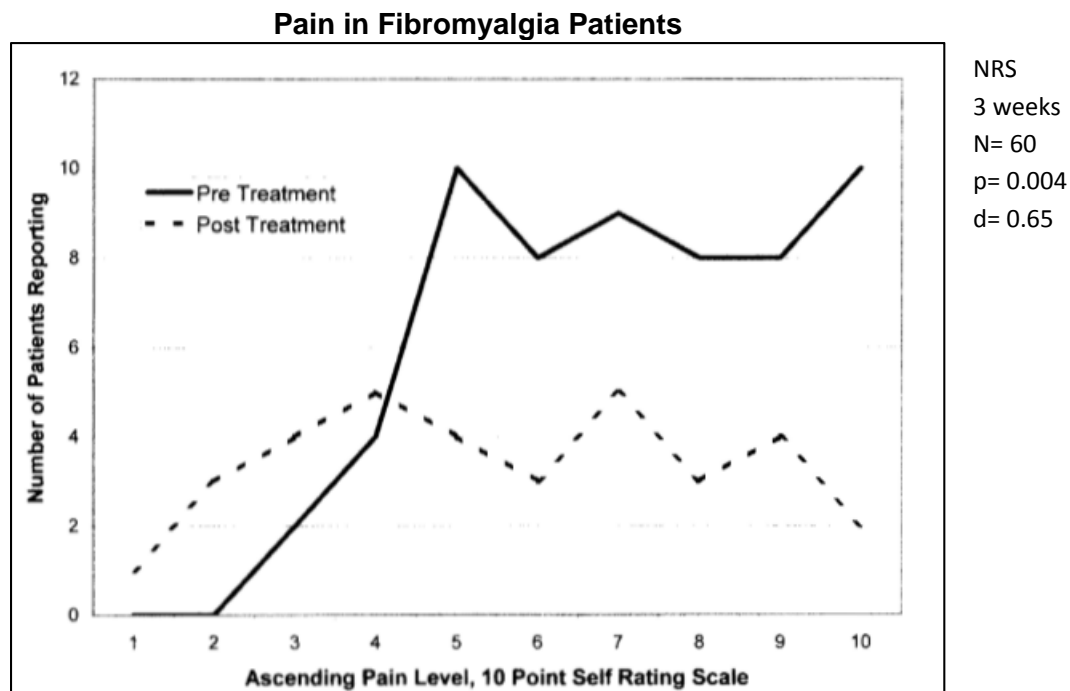


Figure 29. Pain results by group.

Open Label Crossover Results: Week 6

After completion of the RCT arm, 23 of the 40 sham or control patients opted for actual CES in an open label crossover arm where they could increase the current in accordance with the standard clinical protocols for Alpha-Stim CES. Data were analyzed with repeated measures analysis of covariance variance, with least significant difference a posteriori testing. Table 7 shows results of statistical analyses of outcome measures at week 6.

Outcome Variables	Scale	P Values
Tender Point Scale	Tender Point Scale	p <0.001
Self-Rated Pain	NRS	p <0.05
Quality of Sleep	NRS	p <0.001
Well-Being	NRS	p <0.001
Vigor	POMS-V	p <0.01
Fatigue	POMS-F	p <0.03

Table 7. P-Values for changes from baseline to post-test within open label crossover group at week 6.

Quality of the Research

Strengths of this study are: use of a randomized, sham controlled, double-blind design (the investigators chose to use the Alpha-Stim RCT research protocol for the study); active and sham Alpha-Stim devices were pre-set and locked at the designated levels for each specific group for current level and time by the manufacturer at the factory and sham units were the same as active units, except they did not emit electricity; randomization of devices was done by the manufacturer and followed according to the protocol by the investigators; use of 3 groups, active, sham and the control group; and the structured and detailed protocol for the CES treatments for both active and sham groups. A limitation of the original data analysis is that it used analysis of variance (ANOVA) and no within or between group effect sizes were included. In the 2011 reanalysis of the data, analysis of covariance (ANCOVA) was used to provide a more comprehensive description of the findings. The Profile of Mood States (POMS) subscales were used to measure anxiety. This was a common approach in the late 1990s and early 2000s. Today, the Hamilton Anxiety Rating Scale or similar rating scale that focuses entirely on the anxiety would most likely be used. The findings for anxiety and sleep quality in this study are consistent with the findings of other Alpha-Stim studies that found CES significantly decreases anxiety and improves sleep quality.

4.19. Sizer (2000)

Sizer P, Sawyer S, Brismee J, Jones K*, Bruce J*, Slauterbeck J. Texas Tech University Health Sciences Center and *University Medical Center, Lubbock, Texas, USA. The effect of microcurrent stimulation on postoperative pain after patellar tendon-bone anterior cruciate ligament reconstruction. Presented at the American Physical Therapy Association Annual Conference and Exposition, Indianapolis, Indiana; June, 2000.

Device

Alpha-Stim®

Key Variable

Pain

Purpose

The purpose of this study was to determine the effectiveness of microcurrent electrical therapy in providing pain relief to a selected post-operative patient population.

Subjects

Subjects were 19 females and 22 males (mean age of 21.1) who received arthroscopic bone-patellar tendon-bone anterior cruciate ligament (ACL) reconstruction.

Methods and Materials

Subjects were randomly assigned to one of two treatment groups ("Microcurrent" or "Placebo" Groups) in a double blind experimental design. Using a portable microcurrent device (Alpha-Stim® 100 by Electromedical Products International, Inc, Mineral Wells, Texas), the Microcurrent Group received 100 microamperes of microcurrent at 0.5 Hz with a 50% duty cycle, which was below the subject's perception threshold. The Placebo Group followed the same protocol with a placebo stimulator. All subjects were instructed to use the microcurrent unit as needed for pain relief in one-hour sessions, with at least 30 minutes between sessions. The 10 days postoperative microcurrent protocol accompanied a standardized physical therapy rehabilitation program. The subjects made daily entries into a logbook, recording frequency of microcurrent use, pain medication intake, and constant pain levels on a visual analog scale (0 to 10).

Analysis and Results

The subjects' pain levels (dependent variable), which decreased over time, were lower for all 10 post-operative days in the Microcurrent Group (n=25) compared to the Placebo Group (n=16). A 2 ("Treatment Group") x 10 ("Post-Operative Time") ANOVA (with repeated measures on "Post-Operative Time") demonstrated a significant between-subjects main effect for the "Treatment Group" factor [$F(1,39)=9.29$, $p=0.004$], indicating that a statistically lower degree of post-operative pain was experienced by the subjects receiving microcurrent. In addition, a significant within-subjects main effect for the "Post-Operative Time" factor ($[F(9,9)=18.672$, $p<0.0001]$) was obtained.

Conclusion

These results indicate that Alpha-Stim microcurrent electrical therapy is beneficial for post-operative pain control after ACL reconstruction.

4.20. Winick (1999)

Winick RL. Cranial electrotherapy stimulation (CES): A safe and effective low cost means of anxiety control in a dental practice. *General Dentistry*. 1999; 47(1): 50-55.

Device

Alpha-Stim®

Key Variable

Anxiety

Objective

To evaluate the effect of CES on dental patients' anxiety when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.

Design

This was an IRB approved, randomized, sham controlled, double-blind, clinical trial. The subjects, investigator and staff were all masked as to the identity of the device.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline measures of anxiety scores compared to the sham group at the completion of the dental procedures.

Key Inclusion Criteria

1. Dental patients having common dental surgical procedures.
2. Male and female subjects ≥ 20 years of age.
3. Must report having anxiety about the dental procedure.

Key Exclusion Criteria

- Pregnancy
- Presence of implanted pacemakers, pumps or stimulators
- Persons who reported no anxiety about the dental procedure were excluded from this study.

Protocol Summary

Patients were randomly assigned to the active CES group (N = 16), or sham CES (N = 17) group in the order they arrived for various dental procedures. A "double-blinding box" provided by the manufacturer of the Alpha-Stim CES device was used so neither the patient nor the dentist was aware of who was receiving actual stimulation. The 100 mm Visual Analogue Scale (VAS) of "not anxious" on the left to "very anxious" on the right was used at baseline, midpoint of the procedure and at the endpoint of the dental procedures by both the patient and dentist, and an inverse 7 point Likert scale with 1 "more anxious" to 7 "less anxious" was used at the conclusion of each treatment as a method to corroborate the findings from the VAS scale. On the VAS a higher score indicated more anxiety while on the inverse Likert scale a lower scale indicated more anxiety.

Device Application Protocol

Subjects were randomized to either the active or sham groups in the order that they arrived at the dental office. Baselines measures were done just prior to the active or sham CES treatment. Outcome measures were done at mid-point in the procedure and endpoint measures were done right after the completion of the procedure. The active CES device was pre-set at 200 μ A and the sham CES device was set to "0" so the ear-clip electrodes did not emit electricity. The time

on both the active and sham devices was set to “continuous,” so the CES treatment continued until the procedure was done.

Study Blinding

The subjects, investigator and staff were all masked as to the identity of the device.

Results

Subjects

A total of 33 subjects, 9 males and 24 females, 20 to 59 years old, completed the study.

Baseline Measurements

Baseline measurements were taken prior to the start of the procedure and before the active CES or sham treatment. There was no significant difference in anxiety levels at baseline between the active and sham groups.

Data Analysis

Data were analyzed using the student t-test (unpaired) comparing the active and sham groups at baseline, mid-point and endpoint of study.

Anxiety

The mean value for the dentist's and patient's baseline evaluations tended to be higher in the treatment group at the start probably due to the more severe procedures in that group compared to the sham group, but was not significant. The active CES group had lower anxiety scores (VAS) from baseline to endpoint of the study than the sham group as measured by the investigator ($p < .02$) and subjects ($p < .02$), see Figure 30. Findings using an inverse Likert scale corroborated these findings for both the investigator evaluation ($p < .01$) and subjects' evaluation ($p < .01$).

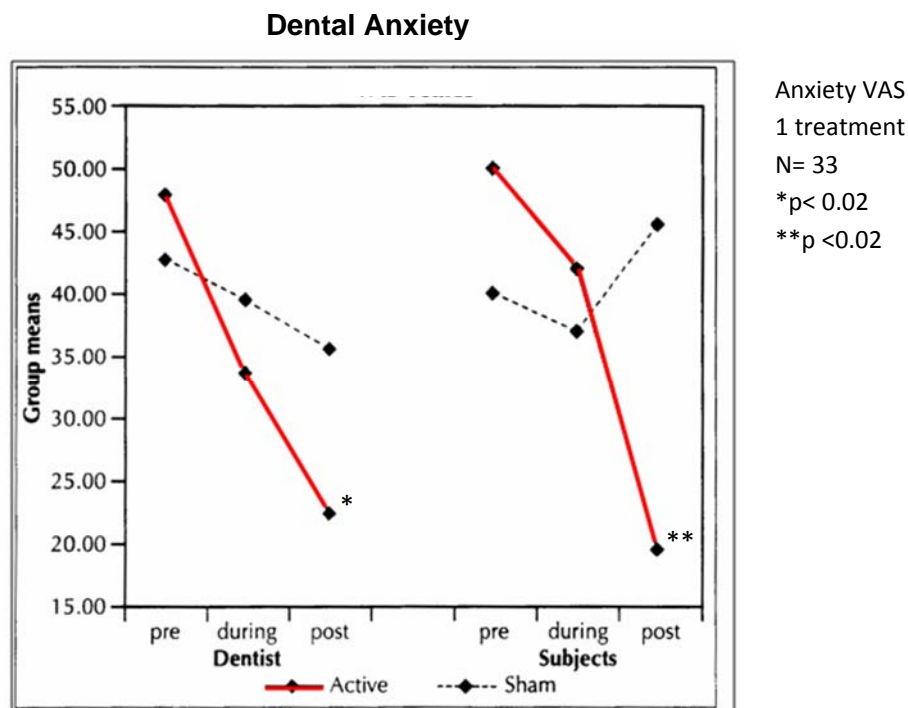


Figure 30. Comparison of group means on VAS anxiety scale by group over time.

Quality of the Research

Strengths of this study include: (1) use of a randomized, sham controlled, double-blind design; (2) active and sham Alpha-Stim devices were pre-set at the designated levels for each specific group for current and time; (3) sham devices were the same as active devices except they did not emit electricity; (4) all subjects had common dental procedures such as fillings, crowns or bridge, or dental exams and cleaning; (5) all subjects reported dental anxiety at baseline in order to be in the study; (6) an inverse Likert scale was used post-test as a method to corroborate the findings from the VAS scale; and (7) the subjects, investigator and staff were all masked as to the condition of the device. The small N (33) in this study could be considered a limitation of the study. However, based on the moderate to large effects sizes for anxiety in the literature, the N of 33 for this study was large enough to detect a significant difference between the active CES and sham CES groups in favor of the active CES group. This study was done in 1999 and the investigator used student t-tests to analysis the data which was common in that time period. Today, an investigator would most likely use repeated measures ANCOVA for data analysis. However, this study showed that CES decreases anxiety and this is consistent with the findings of other Alpha-Stim research that found CES decreases anxiety.

4.21. Heffernan (1997)

Heffernan M. The effect of variable microcurrents on EEG spectrum and pain control. *Canadian Journal of Clinical Medicine*. 1997; 4(10): 4-11.

Device

Alpha-Stim®, Liss Stimulator, BK Instruments

Key Variables

Pain and EEG changes

Objective

The purpose of this study was to determine the change on EEG spectrum and pain levels with different microcurrents

Design

This was a double blind study which used different microcurrents to treat pain while looking at EEG changes

Primary Effectiveness Endpoint

Pain and EEG changes

Key Inclusion Criteria

Chronic pain patients

Protocol Summary

In phase 1 of this double blind study, researchers proposed a model of spectral smoothing using EEG as a measure of regeneration and pain reduction. Two minute averages of root mean square EEG amplitude versus frequency were compared between pain free subjects and subjects with degenerative joint disease. The differences in EEG's allowed researchers to determine pain levels based on EEG results.

In phase 2, 30 patients with DJD were assigned to 1 of 3 groups. Patients were treated with either Alpha-Stim®, Liss Device or BK instruments medical device. The EEG results were analyzed once treatment was applied.

Results

Post stimulation spectral smoothing and pain control was found to be superior with the Alpha-Stim® ($P<.01$). Alpha-Stim also produced significant pain control with a five minute test dose 4.5 to 2.1, ($P<.01$) versus 4.3 to 4.5 ($P>.01$) with the Liss Stimulator and 4.6 to 4.8 ($P>.01$) with the control device.

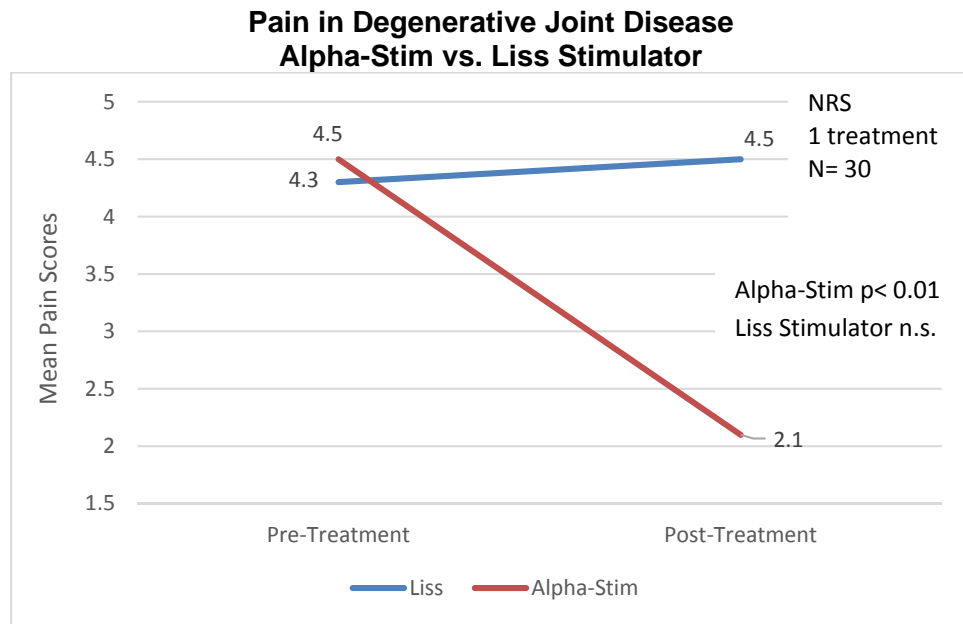


Figure 31. Mean pain scores by group.

Conclusion

The researcher discusses these findings by proposing a theory of rapid pain control from regenerative restoration of normal cellular electrical fields. This theory of rapid pain reduction by electric field restoration is then contrasted with pain control by stress induction and increased production of endorphins. Finally, the researcher discusses implications of using the spectral smoothing of both EEG and body fields as a model of reversing the negative, carcinogenic effects of externally applied extremely low frequency (ELF) when used therapeutically or delivered inadvertently from human electrical power usage. No side effects were reported.

4.22. Voris (1995)

Voris MD. An investigation of the effectiveness of cranial electrotherapy stimulation in the treatment of anxiety disorders among outpatient psychiatric patients, impulse control parolees and pedophiles. *Delos Mind/Body Institute Newsletter*. 1995. Dallas and Corpus Cristi, Texas.

Device

Alpha-Stim®

Key Variable

Anxiety

Objective

To evaluate the effect of a specified treatment course with CES on anxiety in outpatient psychiatric patients when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.

Design

This was an IRB approved randomized, sham controlled, double-blind study in which subjects received either active CES or sham cranial electrotherapy stimulation for one 20 minute treatment during their regular group therapy session. There was also a usual care control group. The subjects, investigators, statistician and staff were all masked as to the identity of the device.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline to the post-treatment measurement scores for anxiety of the active group compared to the sham treatment group and control group at the completion of the treatment period.

Secondary Outcome Measures

The secondary effectiveness endpoints were the change from baseline in the post-treatment scores for the physiological parameters of muscle tension and vasodilation as measured by electromyogram (EMG) and finger temperature (FT) for all 3 groups.

Key Inclusion Criteria

- Male and female subjects with anxiety attending group therapy session dealing with anxiety issues.
- Diagnosis of anxiety was verified by a psychiatrist and confirmed using the State Anxiety Inventory (SAI).

Key Exclusion Criteria

- Pregnancy.
- Presence of implanted pacemakers, pumps or stimulators.

Protocol Summary

The subjects were randomized based on which seats they took in the group therapy room. Prior to the individuals entering the room each seat had been assigned a treatment. This method of randomization was selected so subjects had the freedom to choose where they sat for group therapy, as usual. Using a "blinding box" the investigators and subjects were unaware as to which subject was receiving active or sham treatment. There were 3 experimental populations: 1) group A: individuals receiving active CES treatment; 2) group B: individuals receiving sham CES; and 3) group C: individuals receiving usual care only (control). The control subjects were

known because they were not wearing ear clip electrodes hooked up to a device. Over a period of 10 days, all the clinic therapy groups that worked with anxiety were tested. All subjects were tested using the dependent variables of the State Trait Anxiety Inventory (STAI), EMG, and FT, before and again immediately following the treatment condition. The STAI was done first, followed by EMG on the frontalis muscle and then skin temperature measured by a hand held temperature probe. All 3 dependent variables were administered again immediately post treatment. Baseline measures were taken prior to the one 20 minute CES treatment and at the completion of group therapy for both the active and sham groups. No change was made in the medical management of the patients during the single session study.

Device Application Summary

The sham device was identical in appearance to the active CES unit, but did not conduct an electrical current. The active CES device was set to 300 μ A. A “double-blinding” box was used to conceal the CES device from view of the subjects and research team.

Study Blinding

Investigators, subjects, research staff and statistician were all masked to the identity of the devices.

Outcome Measures

Spielberger's State Anxiety Inventory was used to measure anxiety. The scale has established reliability and validity (American Psychological Association, 2014; Spielberger 2010).

Physiological measures, EMG, EDR and finger temperature, which are indications of decreased anxiety were also measured to validate level of anxiety (Bond et al., 1971).

Results

Subjects

A total of 105 subjects completed the study consisting of an active CES group (N= 38), sham group (N=35) and control group (N=32).

Baseline Measurements: Group Equivalence

There were no statistically significant differences at baseline between the active CES and sham treatment groups for any of the outcome measures.

Data Analysis

Data were analyzed using the independent-samples t-test to compare the difference between the active CES and sham groups on depression and anxiety outcome scores. The median was used rather than the mean to eliminate scores that fell widely out of range and would have skewed the data interpretation. Scores on the STAI between 40 and 70 were accepted at pre-test. Scores between 75 and 95 were accepted on skin temperature and scores higher than 4.0 was accepted for EMG at pretest. No restrictions were placed on posttest scores.

Anxiety

The active CES group had significantly lower anxiety scores on the State Anxiety Inventory (SAI) compared to sham group ($p=.0001$, $d = -1.60$) and control groups. The active CES group had significantly lower scores on EMG ($p=.0001$, $d = -1.08$) and increased scores on finger temperature ($p=.0141$, $d = .50$) than sham and control groups, indicating less anxiety. Figures 32, 33 and 34 show results of statistical analyses of outcome measures for the active group compared to the sham and control groups.

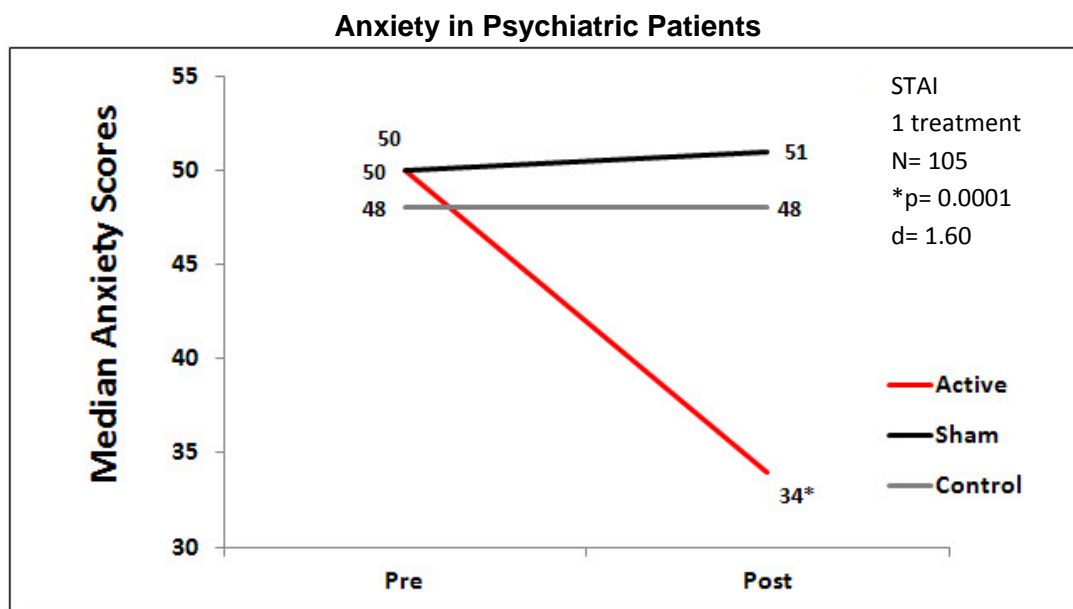


Figure 32. Median state anxiety scores by group.

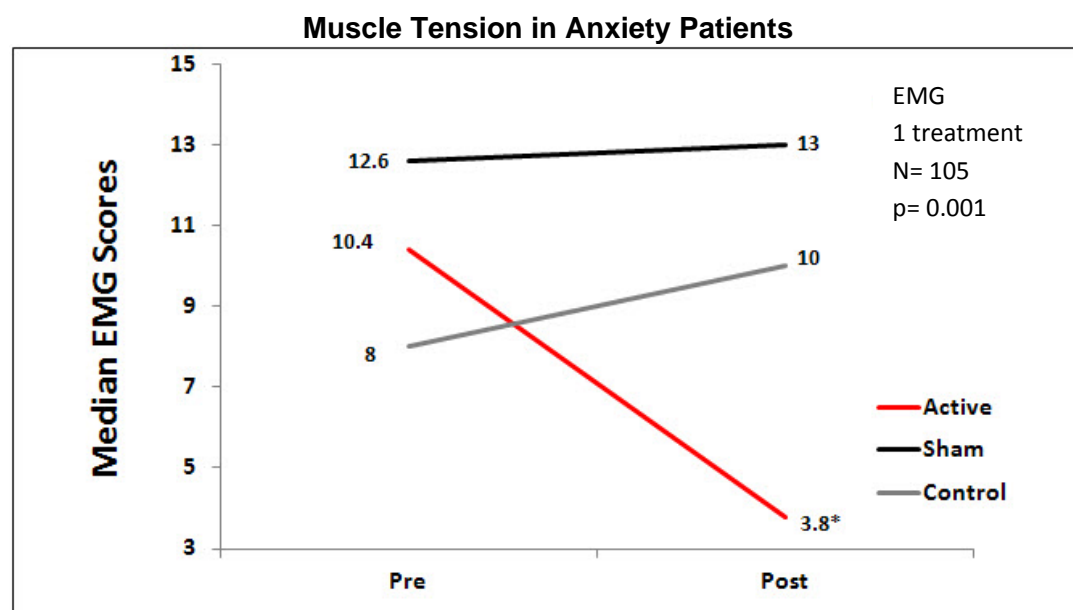


Figure 33. Median EMG scores by group.

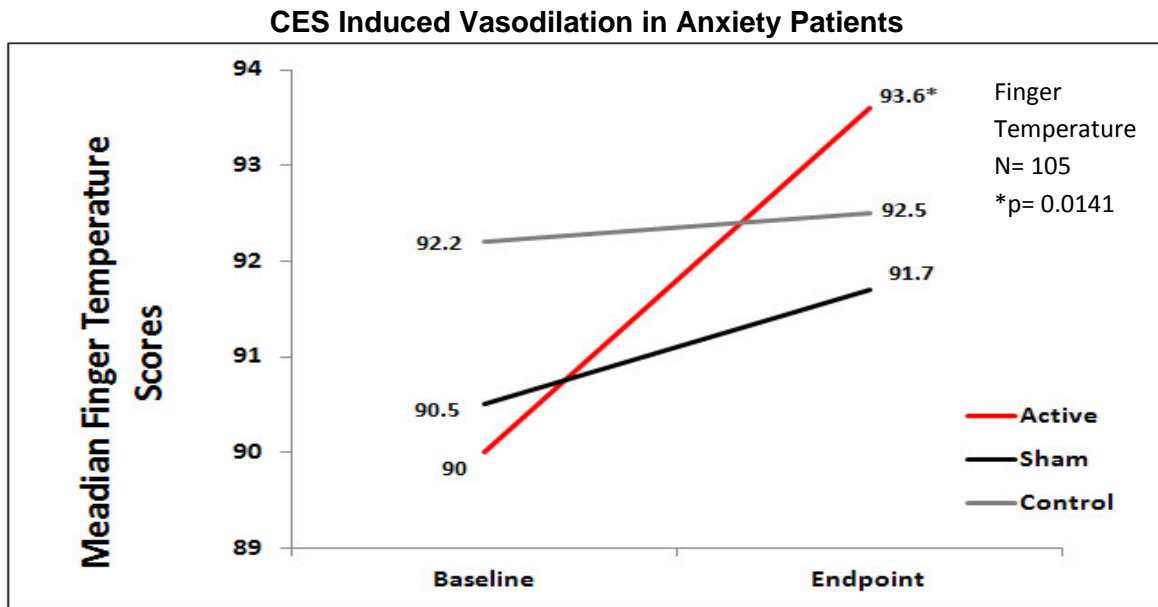


Figure 34. Median Finger Temperature Scores by group.

Quality of the Research

This was the first Alpha-Stim CES study that used the Alpha-Stim masked, sham controlled, randomized clinical trial research protocol. The study has served as a foundation for the development of RCTs on the effectiveness of CES for the treatment of anxiety. Strengths of the study are (1) the rigor of the research design and the use of 3 groups- active, sham and control, (2) the study was adequately powered with an N of 105, (3) diagnosis of an anxiety disorder was confirmed by a psychiatrist, (4) the research team, subjects and statistician were masked to the identity of the devices, and (5) the use of a valid subjective state anxiety scale (SAI) confirmed by objective physiological measures of anxiety. The investigator noted a limitation of the study was the method of randomization based on seating. The general outpatient psychiatric subjects tended to arrive early and select a chair resulting in more of these subjects in the active CES group than in the sham and control groups. There were fewer parolees, who usually arrived later, in the active group and more in the sham and control groups. While the chair method was used to be consistent with the usual routine in group therapy, for future studies the investigator recommended that subjects be randomly assigned by group.

4.23. Gibson (1987)

Gibson TH and O'Hair DE. Cranial application of low level transcranial electrotherapy vs. relaxation instruction in anxious patients. *American Journal of Electromedicine*, 1987; 4(1): 18-21.

Device

Alpha-Stim®

Key Variable

Anxiety

Objective

To measure the effectiveness of Alpha-Stim CES alone, relaxation therapy alone and Alpha-Stim CES plus relaxation therapy for the treatment of anxiety.

Design

Single blind randomized controlled trial

Primary Effectiveness Endpoint

State Trait Anxiety Inventory

Secondary Outcome Measures

Frontalis muscle electromyogram

Key Inclusion Criteria

Scored 50 or above on the State Trait Anxiety Inventory (STAI)

Protocol Summary

Subjects were randomly assigned to 20 minutes relaxation training (RT) on audio tape only, Alpha-Stim CES only, RT plus CES, or to a control group which listened to a neutral audio tape and received sham CES. Treatment time was 1, 20 minute session, and relaxation was measured by frontalis muscle electromyogram (EMG) and a post treatment STAI.

Study Blinding

Single blind

Outcome Measures

State Trait Anxiety Inventory and frontalis muscle electromyogram

Results

Subjects

64 volunteer subjects responded to newspaper advertisements, 32 males and 32 females, ranging in age from 22 to 55 years old (mean = 36.64), who scored 50 or above on the State Trait Anxiety Inventory (STAI).

Data Analysis

Subjects responded on the STAI significantly ($P < .001$) better than controls and equally to either RT alone with a means of 52.88 pretest to 32.19 post, CES alone: 52.31 pre to 30.06 post, or

both RT and CES together: 53.69 pre to 30.44 post. The control group only dropped from 53.25 to 51.94. The EMG trend paralleled the STAI with means of 15.64 μ V to 11.10 post test in the RT alone, 17.12 to 11.17 μ V in the CES alone, 17.41 to 9.77 μ V in the combined group, and 14.14 to 14.47 μ V in the control group. Analysis of variance for EMG scores showed highly significant F-ratios for the time variance term and the group X time interaction term. Results were further verified by Tuckey's tests for pair-wise comparisons.

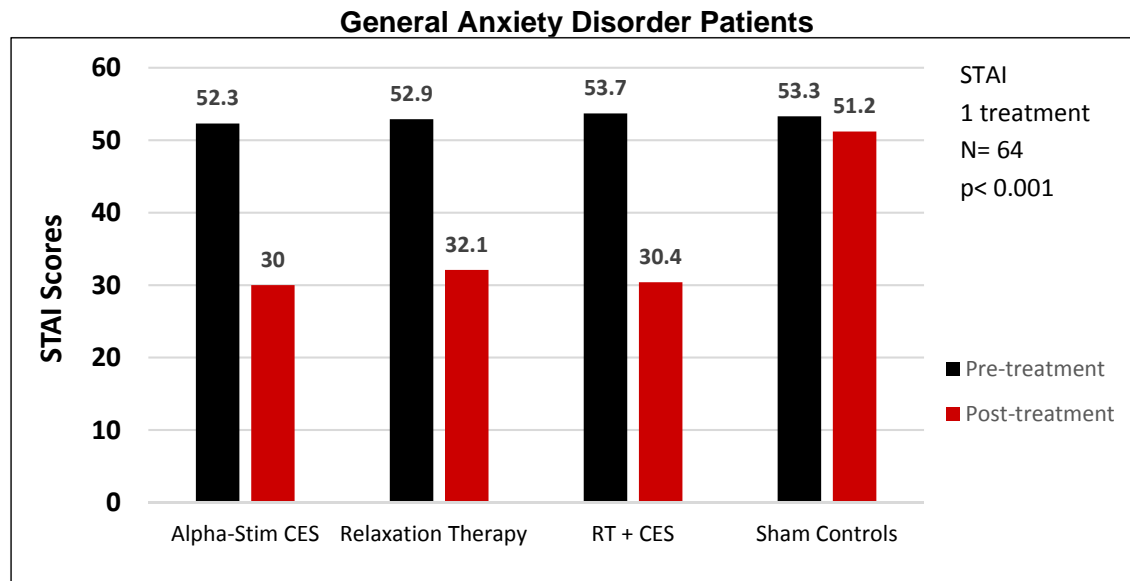


Figure 35. The effects of relaxation therapy alone, Alpha-Stim CES alone or both in the treatment of anxiety.

Conclusion

The authors concluded that the results of this study indicate that the Alpha-Stim may be a useful adjunctive therapy for short term treatment of symptoms of anxiety. The treatment appears to have about the same efficacy as the same amount of time of relaxation instructions, but is easier to administer. No side effects were reported.

4.24. Roth (1986)

Roth PM and Thrash WJ. Effect of transcutaneous electrical nerve stimulation for controlling pain associated with orthodontic tooth movement. *American Journal of Orthodontics*. 1986; 90(2): 132-138.

Device

Alpha-Stim®

Key Variables

Pain

Objective

This study was designed to test the efficacy of using Alpha-Stim® MET to treat pain associated with orthodontic tooth movement.

Design

This study was an IRB approved randomized controlled trial with a placebo and control group.

Primary Effectiveness Endpoint

Pain ratings using VAS

Protocol Summary

Patients were randomly assigned to an Alpha-Stim® (TENS) group, a placebo group, and a control group following the signing of an institutionally approved consent form at Baylor College of Dentistry in Dallas, Texas. They were further subdivided into 18 seconds intraoral stimulation of 50 µA at 0.5 Hz, and 20 minutes of extraoral stimulation of 500 µA at 0.5 Hz, and 1, 2, and 3 day treatment duration groups. In each subject Unitek S-1 elastic orthodontic separators were placed mesial and distal to the upper first molars, bilaterally. Subjects were asked to rate their discomfort every 12 hours for 4 days with a 10 cm visual analogue scale (VAS) ranging from no pain to severe pain.

Results

The graph shows that the one, 20 minute Alpha-Stim® treatment reduced pain to the level that would be achieved in all three groups at the end of the four day rating period when all mouths were essentially healed. Though the 24 hour period ratings seemed to indicate a placebo effect from the sham treated patients when compared with the placebo controls, there was no significant difference found on testing of the means. In fact, there were no statistically significant differences in the sham treated and placebo control patients at any rating period, showing that while the actual treatment was significantly effective in eliminating peridontal pain in these patients, there was no placebo effect from the treatment condition.

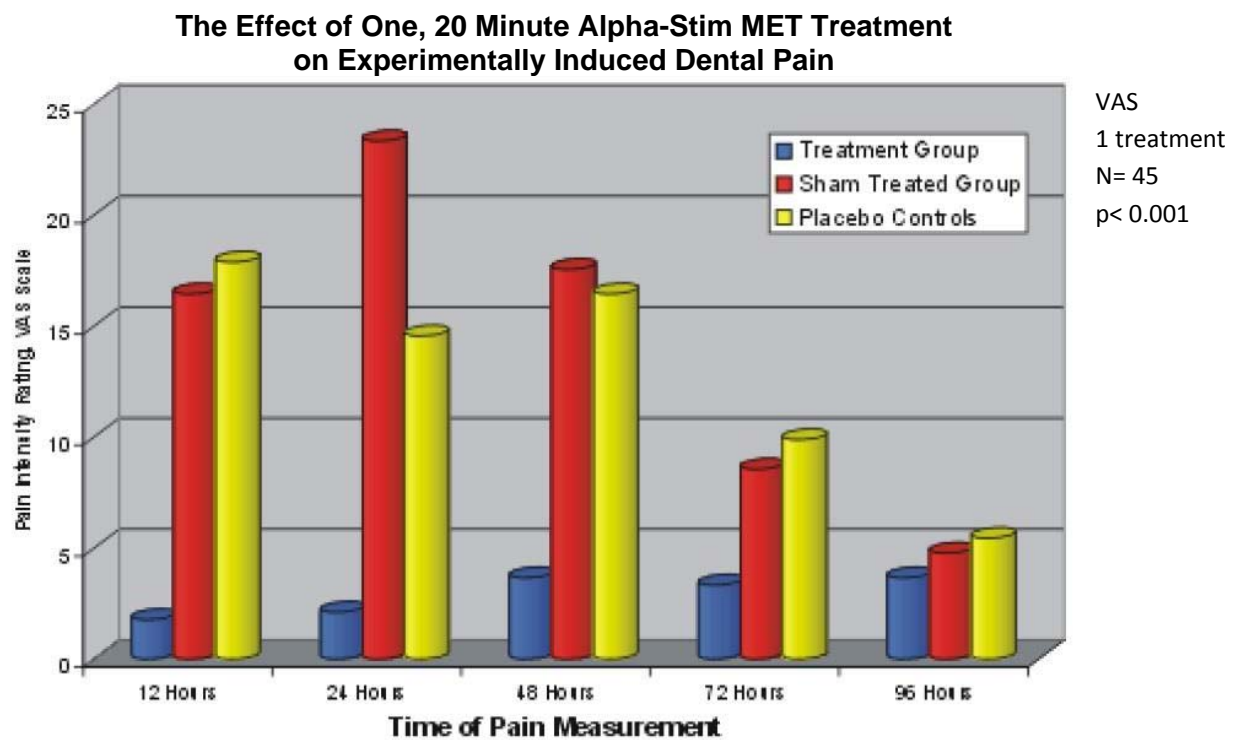


Figure 36. The effect of one, 20 minute treatment on periodontal pain due to orthodontic procedures.

Subjects

45 adult subjects, 27 men and 18 women, between 22 and 41 years old (mean of 28 years) were randomly assigned to an Alpha-Stim® group, a placebo group, and a control group following the signing of an institutionally approved consent form at Baylor College of Dentistry in Dallas, Texas.

Conclusion

The authors noted that the clinical application of their findings is significant. They describe possible mechanisms of action, many potential benefits to dental patients, and suggest that perhaps a reduction in the pain experienced during orthodontics would lead to better patient compliance.

5. Abstracts of CES Open Label and Case Series Studies

5.1. Mellen (2016)

Mellen RR, Case J and Ruiz DJ. Cranial electrotherapy stimulation (CES) as a treatment for reducing stress and improving prefrontal cortex functioning in victims of domestic violence. *International Association for Correctional and Forensic Psychology Newsletter*. 2016; 48(3): 12-15.

Device

Alpha-Stim®

Key Variable

Anxiety

Objective

The objective of this study was to determine if Cranial Electrotherapy Stimulation (CES) was effective for reducing post traumatic stress and improving prefrontal cortex functioning in victims of domestic violence.

Design

This was an open label study design.

Primary Effectiveness Endpoint

Brief Symptom Inventory (BSI)

Secondary Outcome Measures

Behavioral Rating Inventory of Executive Function (BRIEF-A) including the Behavioral Regulation Index and the Metacognition Index.

Key Inclusion Criteria

The study sample included females who were victims of domestic violence and living in a shelter.

Protocol Summary

Due to the high resident turnover rate in domestic violence shelters, the protocol only required daily 20 minutes CES treatments for 5 consecutive days.

Outcome Measures

Outcome measures included the Brief Symptom Inventory (BSI), the Behavioral Rating Inventory of Executive Function (BRIEF-A) including the Behavioral Regulation Index and the Metacognition Index.

Subjects

This study included 10 females who were victims of domestic violence and living in a shelter. The average age was 45 years old and most reported either being married to or living with the abuser.

Results

Table 1 below shows the changes in the primary and secondary measurements after 5 CES treatments.

Brief Symptom Inventory (BSI)	Global Severity Index	P=0.02
	Positive Symptom Total	P=0.05
	Positive Symptom Distress	P=0.012
Behavioral Rating Inventory of Executive Function (BRIEF A)	Global Executive Composite Score	P=0.028
	Metacognition	P=0.06
	Behavior Regulation Scale	P=0.009

Table 9. This table contains results from the primary and secondary study measures.

Conclusion

All three BSI global scales and 2 of 3 scales in the BRIEF-A found significant reductions in stress levels for the 10 sheltered residents. The 9 clinical measures of the BSI did not achieve statistical significance; however, the trend lines indicated positive changes in all nine of the clinical variables suggesting movement toward more normalized functioning in each category. Specifically, there were reductions seen in somatization, obsessive-compulsive thinking, reduced levels of depression, anxiety, hostility and improved ability to relate interpersonally. There are also reductions in phobic anxiety, paranoid ideation and psychoticism.

The study shows that CES may contribute to reductions in psychological stress experienced by victims of domestic abuse. The results from the BRIEF-A suggest improvements in global functioning within the cortical and subcortical areas of the brain that may improve victims' abilities to think more clearly and make better decisions.

5.2. Keizer (2016)

Keizer B, Sposato L and Yancosek K. A progressive treatment for a chronic progressive disease: the war against complex regional pain syndrome. *The Pain Practitioner*. 2016; 6(1): 26-31.

Device

Alpha-Stim®

Key Variable

Pain

Objective

This is a case study on the use of Alpha-Stim® CES and InterX Therapy Device for the treatment of Complex Regional Pain Syndrome (CRPS).

Design

This case study followed one patient with debilitating CRPS. The study discusses his treatment course and the results he was able to achieve.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline pain levels and functionality.

Key Inclusion Criteria

This patient was seen at The Fort Sam Houston Center for the Intrepid clinic in San Antonio, Texas.

Protocol Summary

This patient was treated with Alpha-Stim® CES for 20 to 60 minutes. Afterward he was treated with InterX Therapy Device. The patient did 3 treatments in the clinic before being sent home with his own devices. He used these at home and was followed up with at 3 months.

Device Application Protocol

The patient was treated with 20 – 60 minutes of Alpha-Stim® CES and InterX Therapy for 15 – 30 minutes.

Outcome Measures

The study discussed the patients pain level as well as his functionality.

Results

At the 3 month follow up the patient reported significant pain and was able to return to work full time. He was able to avoid the ketamine infusion treatment and surgery to implant a spinal stimulator.

Subjects

This is a single case study which involved a 52 year old veteran.

Data Analysis

The data was self-reported by the patient involved.

Quality of the Research

This case study was beneficial in creating a blue print for a potentially effective means of treating CRPS. The researchers noted that CRPS ranks at the top of the McGill Pain Index and it remains one of most treatment resistant causes of pain. More research with larger patient numbers and blinding methods needs to be carried out in order to better understand the efficacy of using CES to treat CRPS.

Conclusion

The researchers concluded this to be a success story and intend on treating more CRPS patients with the same protocol. After the subject followed the protocol at home for 3 months he was no longer a candidate for ketamine infusion or surgery and had returned to work full time.

Author Affiliations

Benjamin Keizer, PhD works for the Army Medical Department as leader of the Rehabilitation and Performance Psychology group at the Center for the Intrepid, Fort Sam Houston, Texas.

5.3. Gong (2016)

Gong BY, Ma HM, Zang XY, et al. Efficacy of cranial electrotherapy stimulation combined with biofeedback therapy in patients with functional constipation. *Journal of Neurogastroenterology and Motility*. 2016; 22(3): 497-508.

Device

Alpha-Stim®

Key Variable

Wexner constipation score

Objective

The study was designed to see if Alpha-Stim CES would help to reduce functional constipation among mental and psychological disorders.

Design

Open label study in which patients either received biofeedback therapy or biofeedback combined with CES

Primary Effectiveness Endpoint

Wexner constipation scale

Secondary Outcome Measures

Self-rating anxiety scale (SAS) and self-rating depression scale (SDD)

Protocol Summary

Seventy-four patients who suffered from functional constipation secondary to mental and psychological disorders were divided into 2 separate groups. The control group received biofeedback therapy and the treatment group received biofeedback therapy and Alpha-Stim CES.

Results

After treatment, the participants in the experiment group had significantly lower scores of SAS, SDS, and Wexner constipation score than the control group (all $P < 0.05$). The number of successful expulsion in the experiment group was larger than the control group ($P = 0.016$).

Conclusion

CES combined with BFT was effective in improving psychological status of anxiety and depression, along with bowel symptom in patients with functional constipation.

5.4. Amr (2013)

Amr M, El-Wasify M, Elmaadawi A, Roberts J and El-Mallakn R. Cranial electrotherapy stimulation for the treatment of chronically symptomatic bipolar patients. *Journal of ECT*. 2013; 29(2): 31-32.

Device

Alpha-Stim®

Key Variable

Bipolar Depression

Objective

The aim of the study was to determine if CES is beneficial for chronically symptomatic bipolar subjects.

Design

This study was a retrospective chart review

Primary Effectiveness Endpoint

Clinical Global Impression

Secondary Outcome Measures

Assessment of function, Montgomery Asberg Depression Rating Scale and the Young Mania Scale.

Key Inclusion Criteria

This was a retrospective chart review which included subjects treated with Alpha-Stim CES for symptoms of chronic bipolar disorder.

Protocol Summary

Each patient was instructed to set the current between 10 and 500 microamps and a frequency of 0.5 Hz, for 1 or 2 daily sessions ranging from 20 to 60 minutes each. The electrical current was delivered by 2 wet electrodes that were clipped to both ear lobes.

Results

Five women and 2 men participated. The mean (SD) age was 42.3 (6.4) years. Four had type II illness, and 3 had type I. All patients were on anticonvulsant mood stabilizers or lithium and a second-generation antipsychotic. Most were also on other medications that addressed anxiety, sleep disturbance, or attentional problems. The patients titrated their duration and current strength to their perceived optimal level. Nearly always this corresponded to a setting of 400 microamps, for 30 minutes daily. Two patients used the maximum setting of 500 microamps, for 1 hour daily. Most patients varied the length of the sessions on a daily basis, usually in response to their level of distress on that particular day, so that an accurate duration could not be determined. Clinical Global Impression significantly decreased.

TABLE 1. Mean Scores of the Study Outcomes at the Baseline and End of Treatment

	Baseline, Mean (SD)	End of Study Week 8, Mean (SD)	Significance Test	Percent Changes
MADRS	17.3 (2.9)	11.5 (3.5)	$t = 2.6, P = 0.122$	34% decrease
YMS	4.8 (4.1)	3.8 (2.9)	$t = 0.6, P = 0.635$	21% decrease
CGI	2.7 (0.6)	2.0 (0.0)	$t = 0, P < 0.001$	24.8% decrease
GAF	68.3 (5.8)	71 (7.9)	$t = 1, P = 0.5$	3.7% increase

GAF, Global Assessment of Function; MADRS, Montgomery Asberg Depression Rating Scale; YMS, Young Mania Scale.

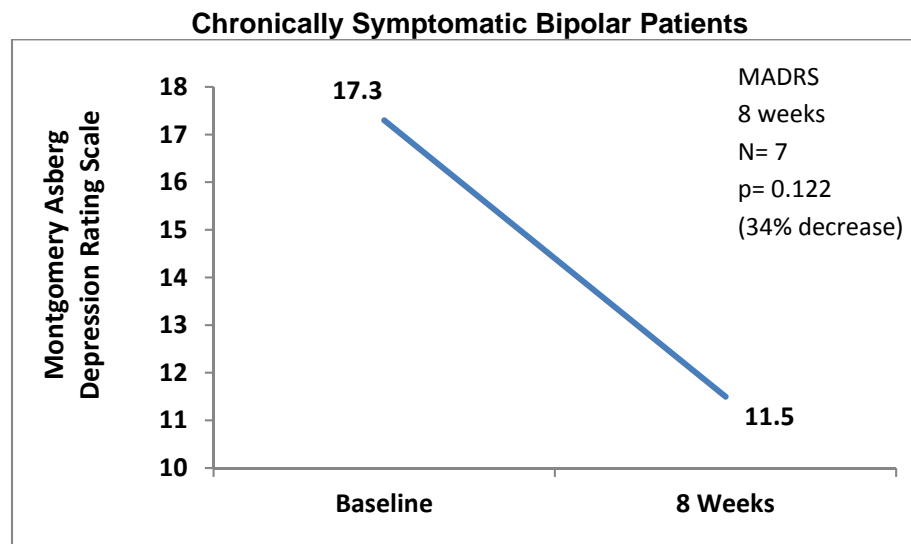


Figure 37. Change in Montgomery Asberg Depression Rating Scale over eight weeks.

Conclusion

This study has several limitations. First, this was a retrospective naturalistic study without a sham group. Second, the small study sample did not allow for adequate power for the effect size of improvement with CES. Despite these limitations, this study demonstrates that nearly half of CSBP patients feel the improvement in symptoms is worth the financial investment in the device. A larger sample size, a longer intervention period of CES, and the addition of a sham group need to be used in future studies of CES in CSBP.

5.5. Holubec (2009)

Holubec JT. Cumulative response from cranial electrotherapy stimulation (CES) for chronic pain *Practical Pain Management*. 2009; 9(9): 80-83.

Device

Alpha-Stim®

Key Variable

Pain

Objective

Investigate the effect of a specified treatment course with CES with pain. Consecutive treatments were performed to determine cumulative results.

Design

This study was an open label trial involving patients entering a pain clinic who were offered a complementary CES treatment. Patients that accepted the treatment were given a pain questionnaire and rated intensity on a 1 – 10 scale. The patients were asked to repeat this once the treatment was over. The patients also had the chance to come back for consecutive treatments for up to 5 days.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the last post-treatment scores in pain.

Key Inclusion Criteria

All patients who entered the pain clinic who entered the pain clinic and did not meet the exclusion criteria

Key Exclusion Criteria

- Pregnant
- Presence of implanted pacemaker, pump or stimulator device.

Protocol Summary

Patients entering the Regional Pain Care Center of North Texas were offered the chance to receive a complementary CES treatment for their pain. Less than 1% of patients refused the treatment. Patients that participated filled out a pain questionnaire and rated their pain from 1 – 10 both before and after the CES treatment. Patients were able to adjust the current to a comfortable level and treated for 20 minutes. Most patients chose between 200 and 300 microamps. Patients were also given the chance to come back for consecutive treatments for up to 5 days to test for cumulative improvement.

Device Application Protocol

The study was open label so each patient received active treatment. Each patient determined their own comfort level and treated for 20 minutes.

Study Blinding

This study was an open clinical trial.

Outcome Measures

Change in pain level from baseline to post treatment.

Results

The percent improvement in pain was calculated after each round of treatments. Fewer patients participated on the following day as more patients became pain free. The graph below shows the percent improvement over the 5 treatments.

Cumulative Decrease in Pain after 1-5 Alpha-Stim CES Treatments

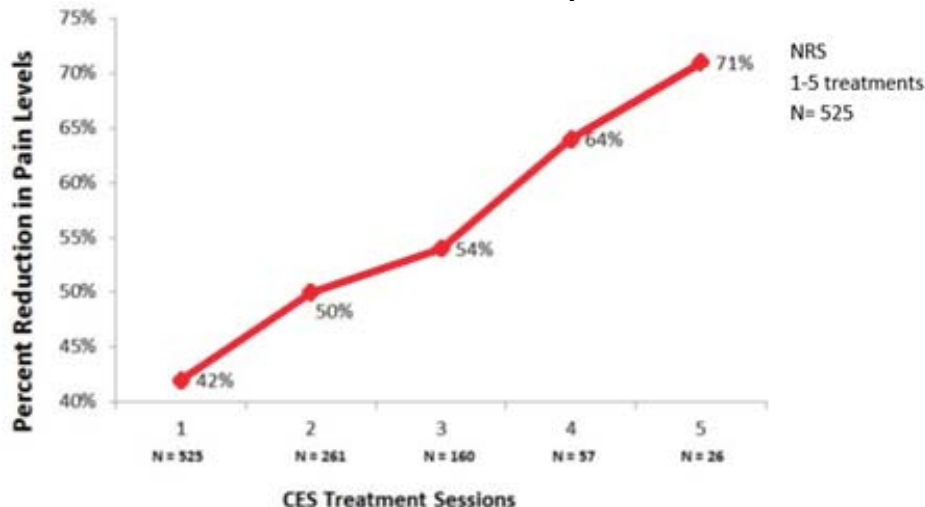


Figure 38. Cumulative improvement in pain after 1-5 CES treatments

Subjects

The sample consisted of 525 consecutive patients who entered the Regional Pain Care Center of North Texas.

Data Analysis

This was an open label study in which standard statistical methods were not used.

Quality of the Research

This open label trial was conducted to measure the effectiveness of CES for pain. Subjects were enrolled as they entered the pain clinic for their normal appointment. Once they agreed to be included in the study pain measurements were taken before and after the treatment. Patients were given the chance to come back on consecutive days for up to 5 days. This study is not equivalent to a randomized controlled, double blind trial but it does provide important information regarding the role of CES in pain management. This study also illustrates the cumulative effect seen with continued use.

Conclusion

One to five 20-minute CES treatment sessions produced a reduction in pain ranging from 42% to 71% in the approximately 80% of patients who responded. No negative side effects were observed by any member of the clinic staff or reported by the patients. 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.

Author Affiliations

Jerry T. Holubec, DO is an anesthesiologist in Allen, Texas specializing in pain management since 1986. He is board certified by the American Board of Anesthesiology and the American Board of Pain Management. He serves as adjunct faculty of the Texas College of Osteopathic Medicine, and is a member of the American Osteopathic Association, Texas Osteopathic Medical Association, Texas Medical Association, International Association for the Study of Pain, American Society of Interventional Pain Physicians, American Society of Regional Anesthesia, American Society of Anesthesiology, Texas Society of Anesthesiologists, and is a Founding Member of the Texas Pain Society.

5.6. Bystritsky (2008)

Bystritsky A, Kerwin L and Feusner J. A pilot study of cranial electrotherapy stimulation for generalized anxiety disorder. *Journal of Clinical Psychiatry*. 2008; 69: 412-417.

Device

Alpha-Stim®

Key Variables

Anxiety, Depression

Objective

To evaluate the effect of a specified treatment course with CES on the anxiety and depression levels in general anxiety disorder (GAD) patients.

Design

An IRB approved 6 week open label study. Baseline measurements were done just prior to the first CES treatment and outcome variables measurements were done at endpoint of study right after the final CES treatment.

Primary Effectiveness Endpoint

The primary outcomes endpoint was the change from baseline to endpoint of the 6 week study on the Hamilton Anxiety Scale (HAM-A) and Clinical Global Impression-Improvement Scale (CGI-I).

Secondary Outcomes Measures

The secondary outcomes endpoint was the change from baseline to endpoint of the 6 week study on the Four-Dimensional Anxiety and Depression Scale – Anxiety subscale (FDADS-A), and Hamilton Depression Scale¹⁷ (HAM-D17).

Key Inclusion Criteria

- Male or female outpatients age 18-64 years who had a current diagnosis of GAD.
- Mini-International Neuropsychiatric Interview (MINI) was conducted at screening to confirm GAD diagnosis.
- Must have a score of > 16 on the HAM-A and a score 20) so as to include milder and more numerous cases of GAD in order to improve the generalizability of these results to clinical practice.

Key Exclusion Criteria

- Has a primary diagnosis meeting DSM-IV criteria for any Axis I disorder other than GAD.
- Met DSM-IV criteria for mental retardation or any pervasive developmental disorder or had a neurologic impairment.
- Has a current diagnosis or recent (6-month) history of drug or alcohol dependence or abuse.
- Has current suicidal ideation and/or history of suicide attempt.
- Has any personality disorder of sufficient severity to interfere with participation in the study.
- Has presence or history of a medical disease that might put the patient at risk or compromise the study.
- Pregnant or breastfeeding women and those of childbearing potential who were not practicing a reliable form of contraception.

Protocol Summary

Baseline measures were done, prior to start of treatment period, and outcomes measures were done at end point of study, 6 weeks. No change was made in the medical management of the patients during the study. After instruction on how to use the CES device, participants subsequently self-administered CES at home for 60 consecutive minutes each day between the hours of 3:00 PM and 7:00 PM for a total of 6 weeks. Subjects recorded each treatment session in daily treatment logs, which were reviewed at 3 weeks and 6 weeks study visits. All subjects chose 300 μ A as their preferred level of current. Those treated with benzodiazepines (alprazolam and lorazepam) took them on an as-needed basis no more than twice per week.

Pre-specified Measures of Success

Response to treatment was defined as a reduction of 50% or more on the HAM-A and a CGI-I score of 1 or 2 (very much improved or much improved, respectively).

Outcome Measures

The Hamilton Anxiety Rating Scale was used to measure the severity of anxiety symptoms and to identify the response to CES. It has established reliability and validity in the literature (Maier et al., 1988). The Hamilton Depression Rating Scale¹⁷ (HAM-D17) was used to measure the severity of depression symptoms and identify the response to CES. It has established reliability and validity in the literature (Cusin et al., 2009). The Clinical Global Impressions Improvement Scale (CGI-I) was used to measure subjects' response to CES treatment (Guy, 2000). The Four-Dimensional Anxiety and Depression scale was used to measure anxiety (Bystritsky et al., 1996). All scales have established reliability and validity.

Results

Subjects

Fifteen (15) subjects expressed interest in the study and engaged in an initial telephone screen. 20% of participants (N = 3) were deemed ineligible to participate because of age (N = 1) and psychiatric comorbidity (N = 2). 12 subjects enrolled and received CES treatment. The mean and SD age of the sample was 42.83 ± 10.27 years. Of the 12 individuals enrolled in the study, 9 females and 3 males, 5 participants had been taking psychotropic medications (venlafaxine, N = 2; prazosin, N = 2; lorazepam, N = 1) for at least 3 months prior to enrollment and continued throughout the study. Two of these had failed 2 previous adequate trials of SSRIs.

Baseline Measurements: Group Equivalence

There were no statistically significant differences at baseline on any of the outcome measures. Nine (9) subjects completed the testing at the endpoint of the study, week 6. Data were analyzed using a 1 sample paired t test to compare baseline to endpoint means on outcome variables with significance levels set at $p = .05$, 2-tailed. At the end point of the study, subjects had significantly lower scores from baseline to endpoint of study on the anxiety outcome measures, HAM-A ($p = 0.01$, $d = -1.52$) and FDADS-A ($p = 0.39$, $d = -.75$), and on the outcome depression measure, HAM-D17 ($p = 0.01$, $d = -.41$). See Figures 39 and 40 respectively.

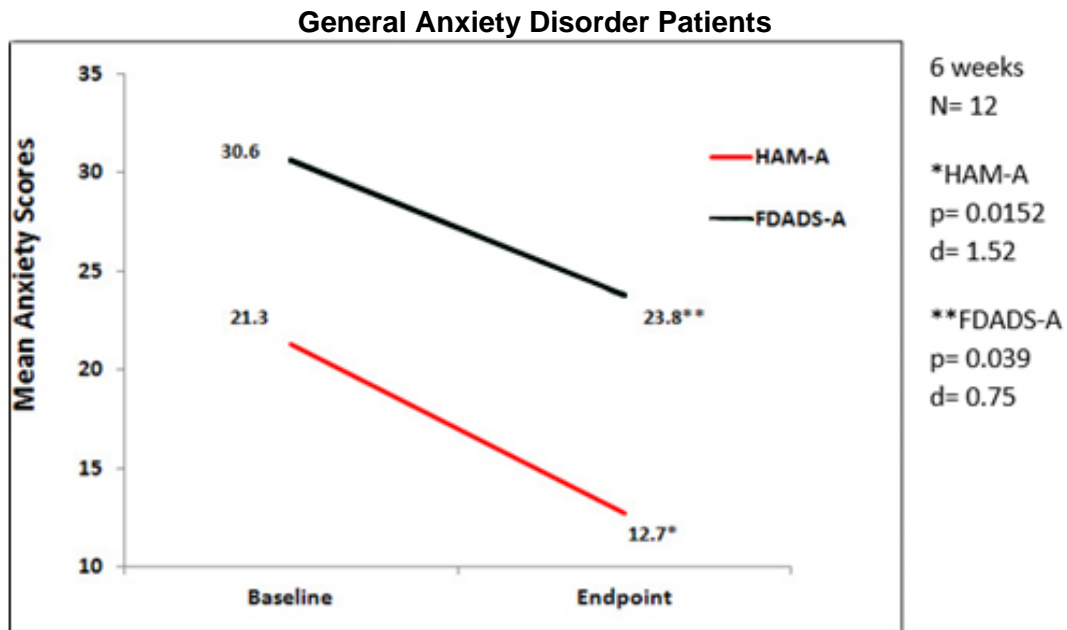


Figure 39. Mean anxiety scores on HAM-A (*p=0.01, d=1.52) and FDADS-A (** p=0.039), d= 0.75).

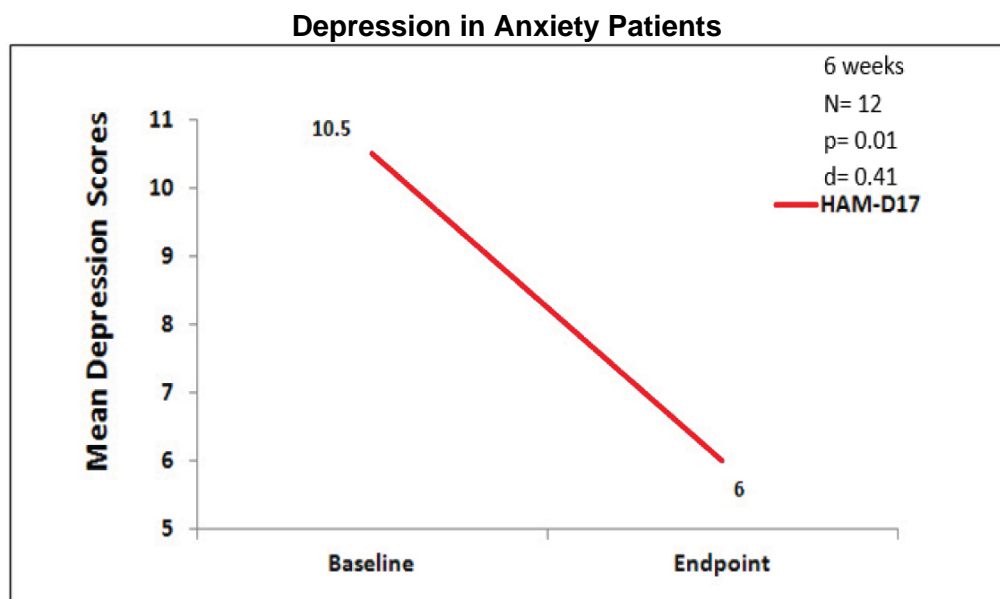


Figure 40. Mean depression scores on Ham-D17 (p = 0.01, d = -.41).

Side-Effects

Three subjects withdrew from the study after baseline measures because of the side-effects of headache (N=2) or dizziness (N=1). These side-effects are suggestive of a central nervous system effect by CES. This study was done in preparation for a large randomized control trial on the effect of CES on generalized anxiety disorder.

Quality of Research

The quality of the research of this small open label pilot study is excellent. Pre-specified criteria for success were set for outcome measures at endpoint of study. The Mini-International

Neuropsychiatric Interview was conducted at screening to confirm GAD diagnosis using DSM-IV criteria. Patients were eligible for the study if they met a cut-off score of > 16 on the HAM-A and a score < 17 on HAM-D17. All subjects followed the same specific CES treatment protocol related to duration and frequency of treatments, time during the day of treatments and use of an Alpha-Stim CES device with a setting at 300 μ A. This study has the limitations of an open label small pilot study, such as the small number of subjects. The authors also state because the small N of the study, the placebo effect associated with GAD could be a confounding variable. The value of this study is that it forms a basis for a large randomized controlled trial on the effect of CES on GAD. This study is also valuable because the findings are consistent with the findings of RCT studies that showed CES significantly decreases anxiety.

5.7. Lu (2005)

Lu XY, Wang AH, Li Y, Zhang JS and Liu BX. Safety and effectiveness of cranial electrotherapy stimulation in treating children with emotional disorders. *Chinese Journal of Clinical Rehabilitation*. 2005; 9(8): 96-7.

Device

Alpha-Stim®

Key Variables

Anxiety, Depression

Objective

The purpose of this 3 week open label study was to evaluate the safety and effectiveness of CES for the treatment of children with mixed anxiety and depression disorder (MAD).

Design

This study was an open label clinical study that included 32 children who participated in a CES course of treatment.

Primary Effectiveness Endpoints

The primary effectiveness endpoints were the change from baseline in the last post-treatment scores on the Zung Self-rating Anxiety Scale (SAS) and the Zung Self-rating Depression Scale (SDS) after 3 - 15 days of treatment.

Key Inclusion Criteria

1. Male and female children, 9 - 17 years old, with mixed anxiety and depression.
2. Diagnosis of MAD was done by a physician with a specialty in child psychosis using the Chinese Classification of Mental Disorders 3 (CCMD-3) criteria, after consultation and evaluation by a psychologist.

Key Exclusion Criteria

1. Pregnancy, planning to become pregnant or nursing.
2. Presence of implanted pacemakers, pumps or electrical stimulators.
3. Use of any anxiety or depression drug therapy or participating in psychotherapy.
4. Anxiety or depression state caused by schizophrenia or other physical diseases.

Protocol Summary

The current level of the Alpha-Stim® CES device was adjusted to a comfortable level for each subject, between 200 to 600 μ A, and the frequency was set at 0.5 Hz. Baseline measures were done prior to the first CES treatment. A course of treatment was daily 20 minute CES treatments for 5 days. Endpoint measures were done after the final CES treatment.

Device Application Protocol

The length of treatment, 20 minutes, was also pre-set on the device.

Study Blinding

The “performers, evaluators and data statisticians” were blinded regarding the type of treatment that subjects were receiving.

Pre-Specified Criteria for Success
Significance was set at $p < 0.05$.

Results

Subjects

Thirty-two (32) children participated in the study; 15 males and 17 females. Ages ranged from 9 to 17 years with a mean of 13 years old.

Data Analysis

Data were analyzed using t-tests and descriptive statistics.

Anxiety

Compared to baseline scores, the SAS standard score of all subjects significantly decreased and returned to a normal value (< 50) after the treatment ($p < 0.01$). Figure 41.

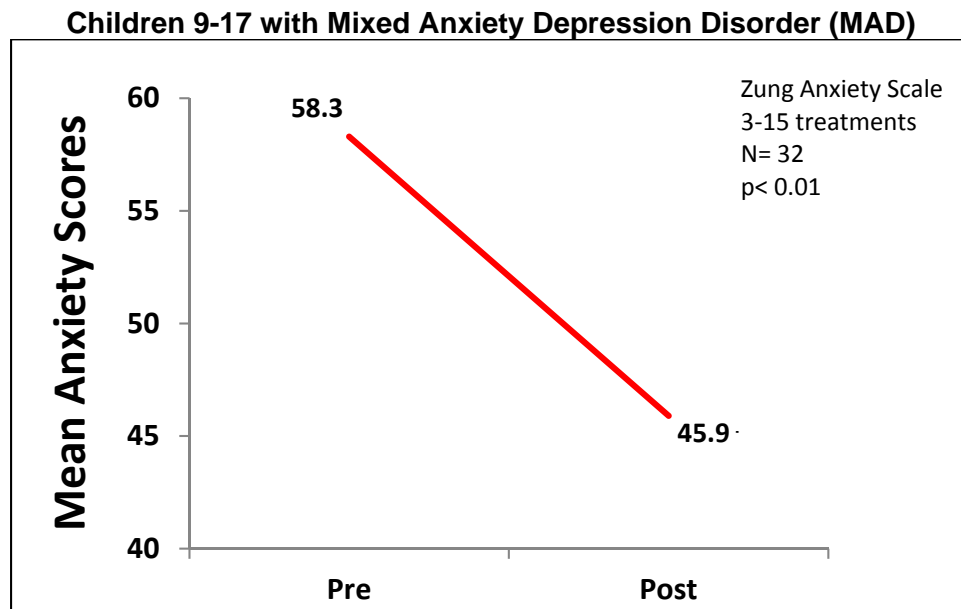


Figure 41. Subjects had a significant decrease ($p < 0.01$) in anxiety scores from baseline after CES treatments.

Depression.

Compared to baseline scores, there was a significant decrease in SDS scores at endpoint of the study ($p < 0.01$), Figure 42.

Children 9-17 with Mixed Anxiety Depression Disorder (MAD)

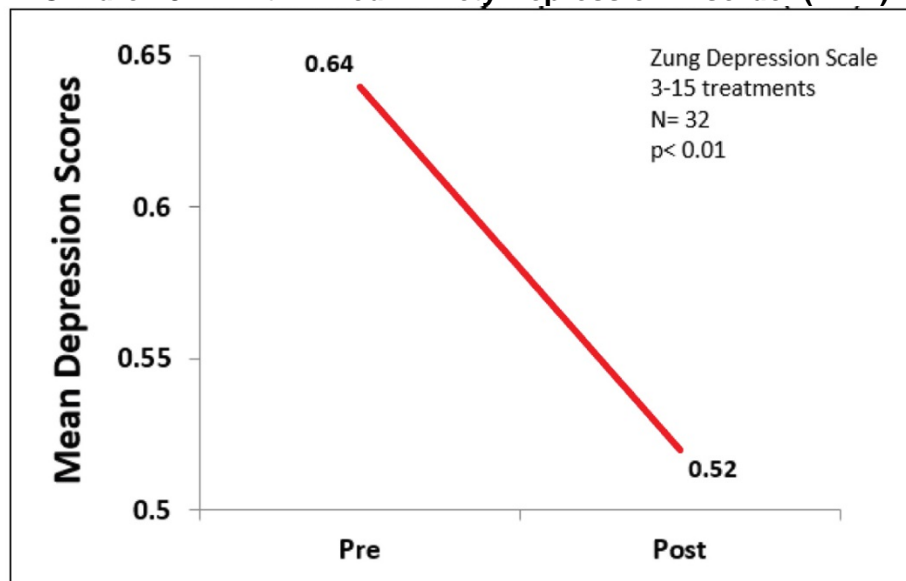


Figure 42. Subjects had a significant decrease in depression scores from baseline to endpoint of study ($p < 0.01$).

Efficacy of CES

Among the 32 children, the shortest period of treatment was 3 days and the longest was 15 days with a mean of 7 days. Investigators categorized the results as significantly effective: good self-feelings, stable emotions, and good social functions, the SAS and SDS scores recovered to normal values (SAS < 50 , SDS < 0.5). Effective: Self-feelings, emotions social functions improved some, SAS and SDS scores decreased, but did not recover to normal values; Ineffective: No improvement in self-feelings and SAS and SDS test scores did not decrease. The total effectiveness rate was 94%; Significantly effective – 40.62%, Effective – 53.12%, Ineffective – 0.062%.

Physiological indices before and after CES treatment

Skin temperature increased significantly after treatment from baseline ($p < 0.01$). There was a significant decrease in systolic blood pressure and pulse rate ($p < 0.05$). These significant changes occurred in 75% of all subjects.

Adverse Effects

Three subjects occasionally felt dizziness and experienced local irritation at the electrode site. There were no serious adverse events.

Quality of the Research

This is a good clinical study. Strengths of the study are establishing the diagnosis of MAD using specific criteria prior to inclusion in the study, use of a single-blind method, use of a pre-specified criteria for success and the operational definition for efficacy of CES using the SAS and SDS scores, and blinding of the “performers, evaluators and data statisticians” regarding the type of treatment that subjects were receiving. Limitations include variation in the number of CES treatments. While it is expected that some children may miss a CES treatment, some children had more than the number of CES treatments (5) in the protocol. The small sample size is also a limitation of the study. The positive findings of this study are consistent with other studies on anxiety and depression that used Alpha-Stim® CES technology.

5.8. Lee (2004)

Lee TK, Lee KS, Jeun SS, Hong YK, Park CK and Kim JK. The control of chronic pain using microcurrent electrical therapy and cranial electrotherapy stimulation. *From the Department of Neurosurgery, Kangnam St. Mary's Hospital, College of Medicine, and The Catholic University of Korea, Seoul, Korea. Presented at the Korea Society for Stereotactic & Functional Neurosurgery, April 14, 2004.*

Device

Alpha-Stim®

Key Variables

Pain

Objective

The purpose of this study was to investigate the efficacy of CES and MET for refractory chronic pain.

Design

This is an open label study which used CES and MET to treat pain.

Primary Effectiveness Endpoint

Pain levels

Key Inclusion Criteria

Patients from the Department of Neurosurgery at Kangnam St. Mary's Hospital who presented with chronic refractory pain.

Protocol Summary

Treatments were scheduled for 1 hour per day, 5 days a week, for 3 weeks. The current used ranged from 100 to 300 μ A, and often varied from day to day. Both CES and MET treatments were given with the Alpha-Stim® 100 device.

Outcome Measures

VAS for pain relief

Results

Although 3 patients out of 20 obtained no relief from this treatment, 6 obtained complete relief, and an additional 8 patients received significant relief of 33% – 94%. When treatment response by the length of time they had the pain was evaluated it was found that patients who had been in pain for 2 months and 4 months improved 94% and 100%.

Quality of the Research

This was an open label study with 20 patients presenting with chronic refractory pain. The researchers used a range of treatment parameters based on the patient. Follow up studies would need to be standardized and include sham and control groups.

Conclusion

The researchers concluded that the combination of CES and MET is an effective treatment for patients with chronic pain and is good for long-standing chronic pain as well as for pain of shorter duration.

5.9. Kulkarni (2001)

Kulkarni AD and Smith R. The use of microcurrent electrical therapy and cranial electrotherapy stimulation in pain control. *Clinical Practice of Alternative Medicine*. 2001; 2(2): 99-102.

Device

Alpha-Stim®

Key Variable

Pain

Objective

The purpose of this study was to assess the effectiveness of Alpha-Stim® microcurrent electrical therapy (MET), cranial electrotherapy stimulation (CES) or a combination of both therapies for the treatment of pain.

Design

This open clinical trial measured pain in 20 patients who had been refractory to previous treatments.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was change in pain levels using the VAS.

Key Inclusion Criteria

These were patients who presented at the pain clinic at Nav-Durga Hospital near Bombay, India. These pain patients had been refractory to previous treatments.

Protocol Summary

Treatments were provided for one hour daily, Monday through Friday, for 3 weeks. No pain medications were taken during the study period. MET was given via probes or self-adhesive electrodes at 600 microamperes, while the current for CES was regulated by each patient, ranging from 100 to 300 microamperes. Pain was scored on an 11 point self-rating VAS scale, with 0 being no pain and 10 being the most intense pain they had experienced to date.

Device Application Protocol

The active CES device was pre-set and locked by the manufacturer at 100 μ A which is a subsensory level. The sham CES device was pre-set and locked by the manufacturer so that it did not emit electricity. The sham device was identical to the active CES device, except it did not emit electricity. The 60 minutes length of treatment was also pre-set and locked by the manufacturer for both active and sham devices.

Results

Nine patients (45%) left the study early following reduction of their pain to a level between 0 and 1.5 on the 11 point scale. One had complete remission of her pain after only 2 treatments. Of 3 patients who received no relief, none returned for the final week of treatment. 7 patients (35%) who were treated with CES plus self-adhesive electrodes began at an average pain level of 7.7 (range 5-10) and ended with an average of 3.7 (range 0-10), or a 52% reduction in pain from an average of 12 days of treatment. 7 patients who were treated with CES plus probes fared even better beginning with a pain level of 7.1 (range 4-8) and ending at an average of 1.1 (range 1-6),

or an 85% reduction of pain from an average of 8.1 days of treatment. 5 patients (25%) were treated with CES only. They experienced an average of 50% drop in their pain level from 4.4 (range 3-7) to 2.2 (range 0.5-5) with an average of 10.6 days of treatment. No negative side effects were reported.

Conclusion

The authors concluded that CES and MET are effective treatments for chronic pain patients.

5.8. Overcash (1999)

Overcash SJ. Cranial electrotherapy stimulation in patients suffering from acute anxiety disorders. *American Journal of Electromedicine*. 1999; 16(1): 49-51.

Device

Alpha-Stim®

Key Variable

Anxiety

Objective

To evaluate the effectiveness of cranial electrotherapy stimulation (CES) on patients' anxiety levels.

Design

An open label retrospective analysis of 197 patients who were seen at a mental health clinic between January 1989 and January 1995.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the change from baseline in the last post-treatment scores on the Numerical Rating Scale (NRS) for anxiety, along with physiological measurements of electromyogram (EMG), electrodermal response (EDR), and finger temperature (FT) taken at the last therapy session.

Key Inclusion Criteria

- Subjects who had CES treatments for anxiety from January 1989 to January 1995 and had completed the baseline and final evaluation post-test measures.
- Diagnosis of anxiety was verified by a doctoral level clinical psychologist and scores on the Numerical Rating Scale for anxiety, EMG, EDR, and finger temperature assessments.

Key Exclusion Criteria

- Pregnancy
- Presence of implanted pacemakers, pumps or stimulators.

Protocol Summary

An Alpha-Stim CES treatment was done for 25 minutes at a comfortable current setting up to 500 µA at the beginning of a therapy session. Measurements of outcome variables were taken before and after treatment. The final post-treatment measurements were taken at the last treatment session.

Device Application Protocol

The CES treatments were 25 minutes long and the current was set at a comfortable level for the subjects, between 100-500 µA in the clinic. Over 80% of the time, patients were also loaned an Alpha-Stim CES device to take home and they used the device once or twice a day in a manner consistent with how they were using it during therapy sessions.

Pre-specified Criteria for Success

The level of significance was set at $p < 0.05$.

Outcome Measures

A numerical rating scale (NRS), 0-100, with 100 being the “highest amount of anxiety they can imagine” and 0 being no anxiety. The NRS has established reliability and validity for measuring anxiety (Davey, 2007). The following physiological indices of anxiety were also measured; electromyogram (EMG), Electrodermal response (EDR), and peripheral temperature.

Results

Baseline Measurements

Baseline measures on the anxiety Numerical Rating Scale. EMG. EDR and finger temperature were taken prior to the first CES treatment at the first therapy session.

Data Analysis

Data were analyzed using paired t-tests scores.

Anxiety

Subjects had significantly lower scores on the 0-10 numerical rating scale for anxiety ($p < .05$), significantly lower EMG scores ($p < .05$), significantly lower EDR scores ($p < .05$) and significantly higher finger temperature scores ($p < .05$) at post-test from baseline, with all factors indicating and cross confirming less anxiety (See Figure 43, 44, 45 and 46).

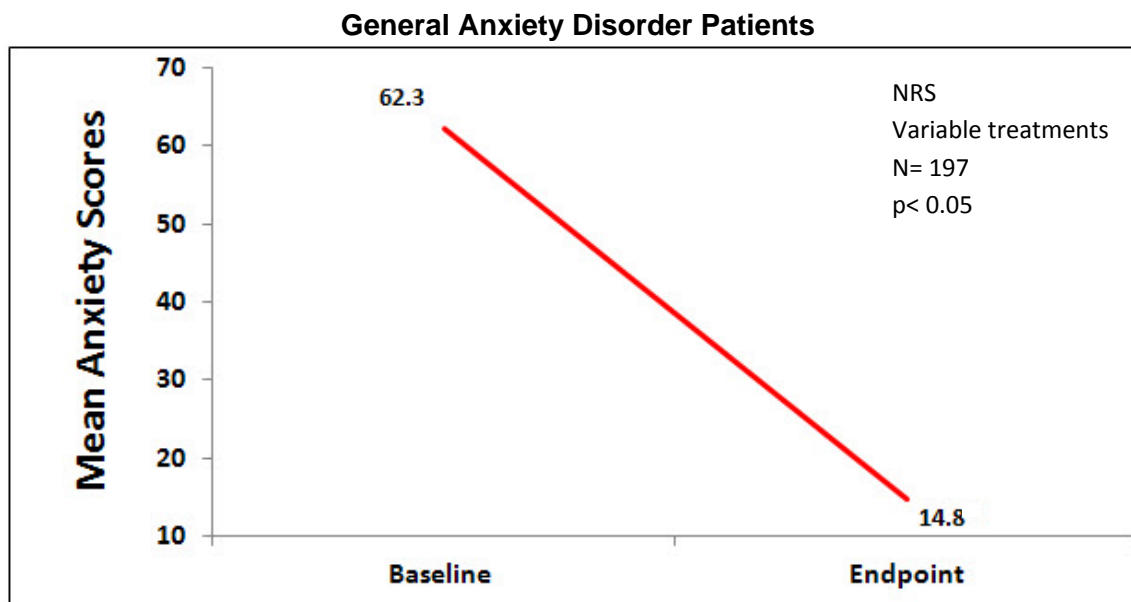


Figure 43. Mean anxiety scores over time on the 0-100 numerical rating scale (NRS).

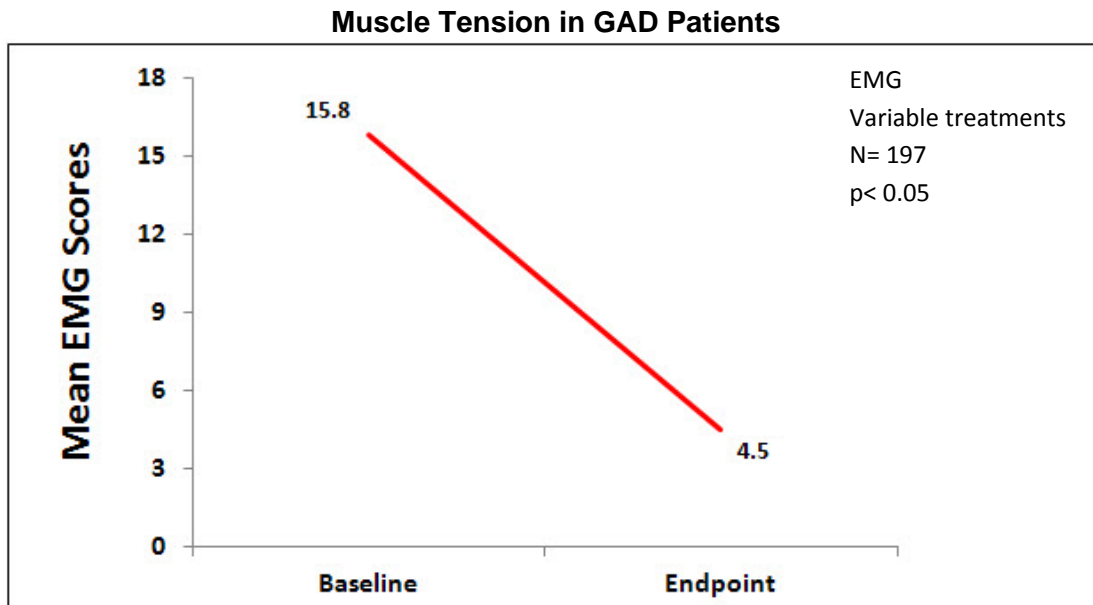


Figure 44. Mean scores over time on EMG as an objective physiological measure of anxiety.

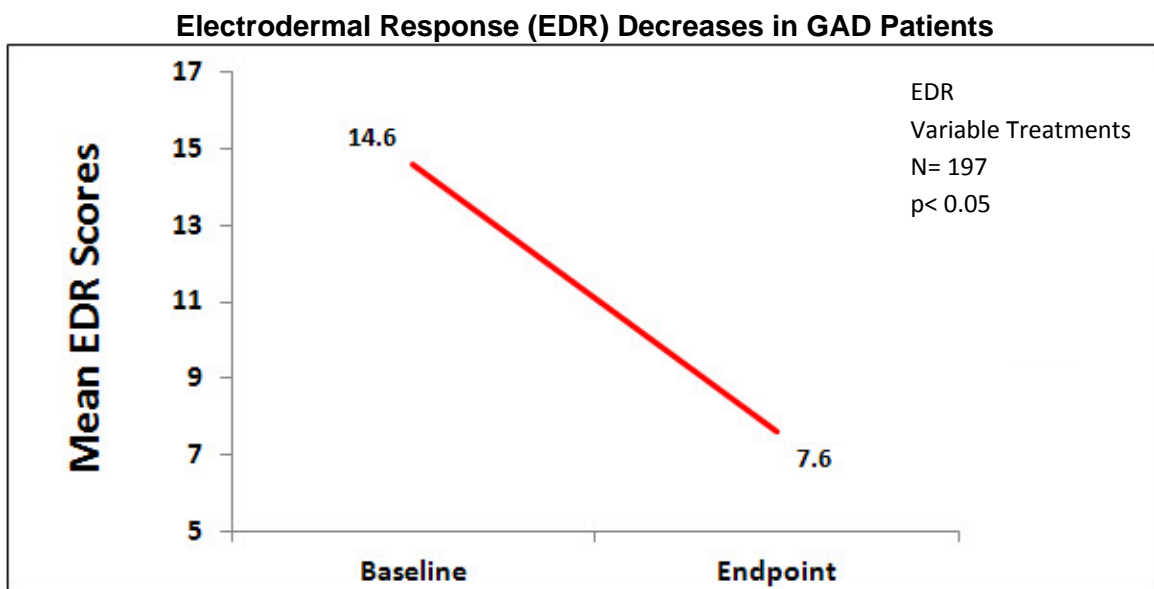


Figure 45. Mean scores over time on EDR as an objective physiological measure of anxiety.

CES Induced Vasodilation in GAD Patients

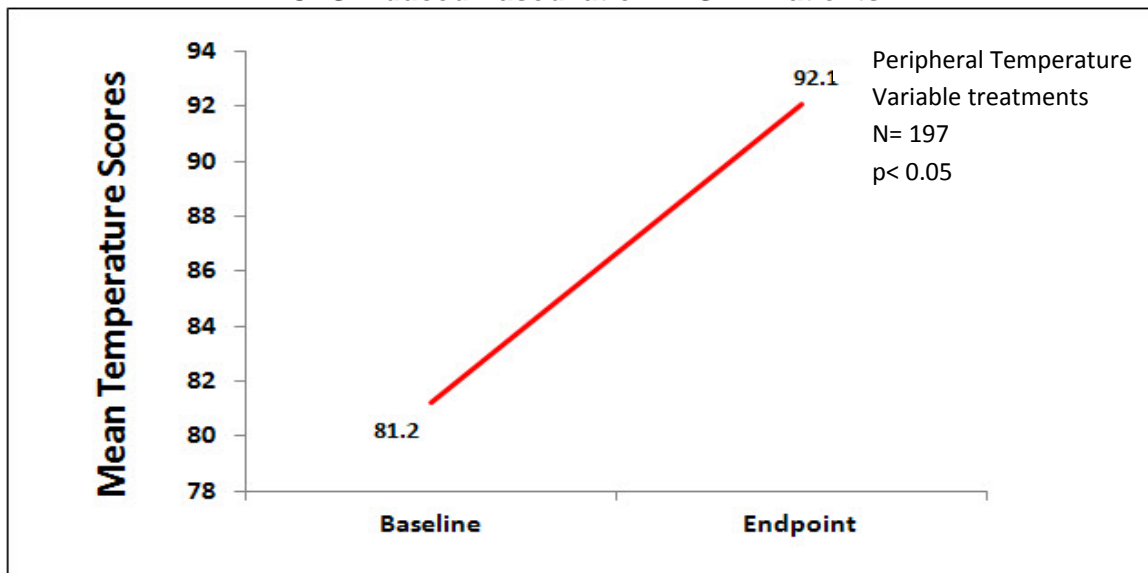


Figure 46. Mean scores over time on peripheral temperature as an objective physiological measure of anxiety.

Quality of the Research

Strengths of this study are; it was adequately powered with a large N of 197 subjects, both subjective and objective physiological measures of anxiety were used, and an analysis of the data was done comparing outcomes by the therapist's level and type of training in order to determine if the effect was from CES or from the therapist (there were no significant differences in outcomes by level of training of therapist). This was a retrospective study and it has the following limitations; lack of controls; lack of a standard protocol for CES treatments that includes number of treatments, the current level and length of treatment, and for where treatments were done – clinic, home or both places. However, the findings of this study that CES significantly decreases anxiety are consistent with other Alpha-Stim CES studies that found CES significantly decreases anxiety.

5.11. Alpher (1998)

Alpher J and Kirsch DL. Traumatic brain injury and full body reflex sympathetic dystrophy patient treated with cranial electrotherapy stimulation. *American Journal of Pain Management*, 1998; 8(4): 124-128.

Device

Alpha-Stim®

Key Variables

Pain

Objective

This study was case report on a single patient with reflex sympathetic dystrophy treated with Alpha-Stim® cranial electrotherapy stimulation (CES)

Design

This is a case report of a single patient.

Primary Effectiveness Endpoint

Pain

Protocol Summary

The patient was referred from the National Rehabilitation Hospital in Bethesda, MD to the Metropolitan Area Craniofacial Pain Center in Washington, DC for dentistry and treatment of TMD. He used Alpha-Stim® CES to overcome his anxiety for dental procedures. CES helped with his anxiety but also significantly enhanced his pain threshold. Subsequently, he was prescribed daily 20 minute treatments.

Results

After initiation of the treatment the patient returned to work and improved his family and social life. The patient estimated his treatment provided him a moderate improvement of 50-74% relief from his pain, anxiety, depression, headaches and muscle tension and marked improvement (75-99%) from insomnia. He was also able to eliminate the need for morphine and fentanyl patches. His other medications were reduced.

Conclusion

CES proved to be an effective treatment for symptoms associated with intracranial TBI and full body reflex sympathetic dystrophy (RSD) in this 60 year old male patient. The treatment provided satisfactory pain relief allowing him to improve his quality of life greatly. He was also able to reduce his medications. CES is worthy of therapeutic consideration in such cases.

5.12. Zimmerman (1987)

Zimmerman SI and Lerner FN. Biofeedback and electromedicine reduce the cycle of pain spasm pain in low back patients. *Medical Electronics*, 1989; June, 117: 108-120.

Device

Alpha-Stim®

Key Variable

Pain

Objective

The study was designed to test the effectiveness of Alpha-Stim®, biofeedback and the combination of Alpha-Stim® and biofeedback for back pain.

Design

This open label study randomized 45 patients into 3 different groups (Alpha-Stim® + biofeedback, biofeedback alone or Alpha-Stim® alone). Patients received 30 minutes of treatment, twice a week for a total of 20 treatments. This study was done for a doctoral dissertation.

Primary Effectiveness Endpoint

Daily pain levels

Secondary Effectiveness Endpoint

Trunk mobility, subjective units of disturbance (SUDS), EMG and Minnesota Multiphasic Personality Inventory

Key Inclusion Criteria

Patients responded to a public notice for a study on back pain. Patients were required to obtain a physician's referral for erector spinae spasms at a level between the third and fifth lumbar vertebrae, with associated low back pain.

Exclusion Criteria

- Pregnant
- History of heart disease
- Psychosis
- Diabetes
- Epilepsy
- Drug or alcohol abuse
- Pain medication

Protocol Summary

This open label study randomized 45 patients into 3 different groups (Alpha-Stim® + biofeedback, biofeedback alone or Alpha-Stim® alone). Patients received 30 minutes of treatment, twice a week for a total of 20 treatments.

Device Application Protocol

The patient was treated with 20 – 60 minutes of Alpha-Stim® CES and InterX Therapy for 15 – 30 minutes.

Outcome Measures

Pain, trunk mobility, EMG, subjective units of disturbance (SUDS), and Minnesota Multiphasic Personality Inventory (MMPI)

Results

All Groups improved significantly in their trunk mobility. Daily pain cards also improved across all groups, however, it was evident by the conclusion of the study that Groups I and III who received electrical stimulation noted a greater reduction in perceived pain than the biofeedback subjects in Group II. SUDS, a measure of how their physical symptoms resulted in psychological distress was measured on a 0 (no disturbance) to 100 (extreme disturbance) scale. Group I subjects demonstrated the best improvement in SUDS which were reduced from an initial mean of 89 to a final of 8.3, and Group III reported a greater improvement in SUDS than Group II. All Groups exhibited significant and equivalent reductions in their EMG after the first treatment session. All Groups also exhibited a decrease in their level of psychological distress as evidenced by changes in the MMPI. Clinically significant decrements of impairment were found to exist on 13 of 17 MMPI subscales.

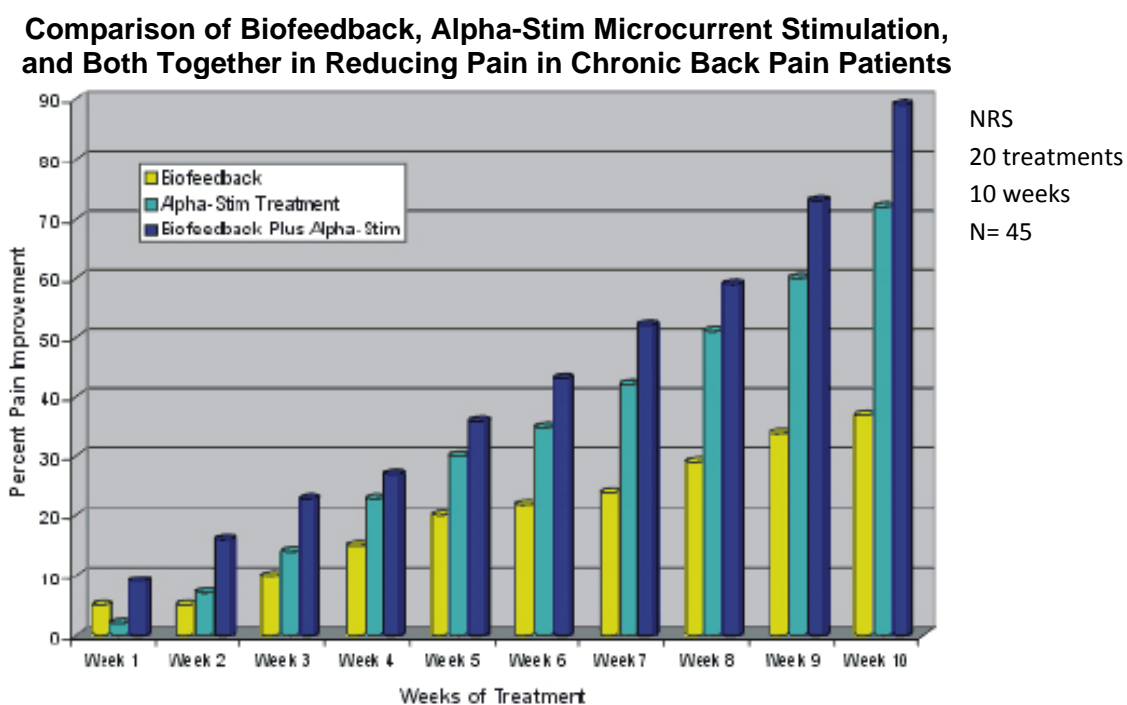


Figure 47. Comparison of biofeedback, Alpha-Stim® and biofeedback plus Alpha-Stim® for chronic back pain.

The graph shows the percent improvement in pain for the biofeedback group alone, for the Alpha-Stim® group alone, and for the biofeedback plus Alpha-Stim® microcurrent stimulation group. It can be seen that the greatest improvement for the biofeedback group was 37%, for the Alpha-Stim® group was 71% while the improvement of the combined treatment group was 89%.

Comparison of the Effects of Biofeedback, Alpha-Stim Microcurrent Stimulation, or a Combination of Both in Increasing the Mobility of Chronic Back Pain in Patients

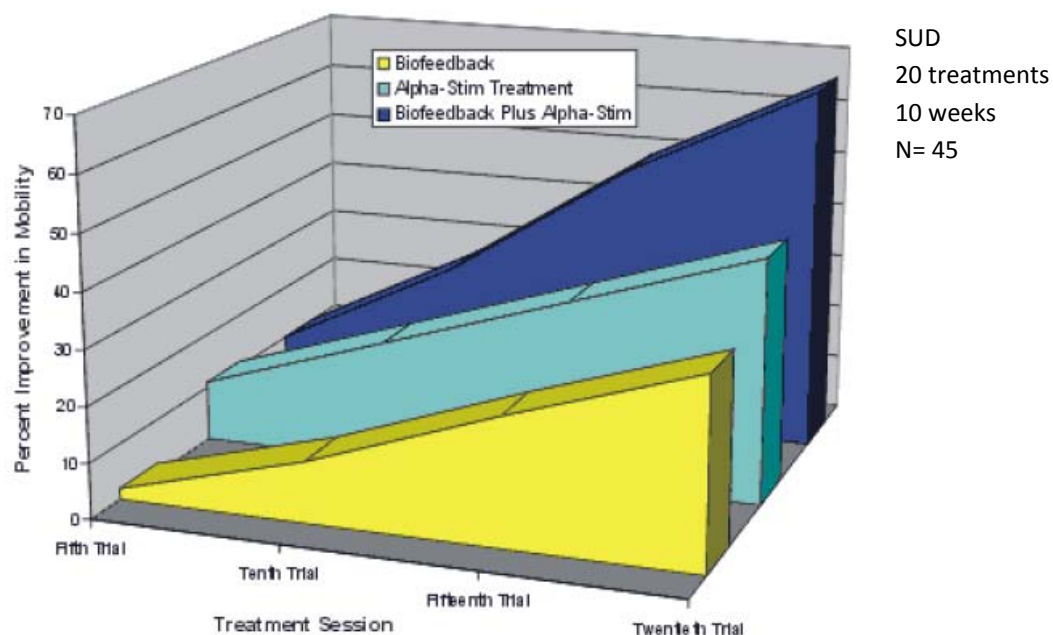


Figure 48. Comparison of biofeedback, Alpha-Stim® and biofeedback plus Alpha-Stim® for increased mobility in chronic back pain patients.

The graph shows the mobility gain from biofeedback alone and shows the potentiating effect of Alpha-Stim® when used with biofeedback therapy. It can be seen that with 20 sessions of biofeedback, there was a 22% gain in back mobility, the group that had Alpha-Stim® microcurrent stimulation gained 33%, whereas for the group that had 10 biofeedback sessions, alternated with 10 Alpha-Stim® treatments, the gain in mobility was 64%.

The Effect of Biofeedback Alone, Or Biofeedback Plus Alpha-Stim Microcurrent Stimulation in Reducing Stress in Chronic Back Pain Patients

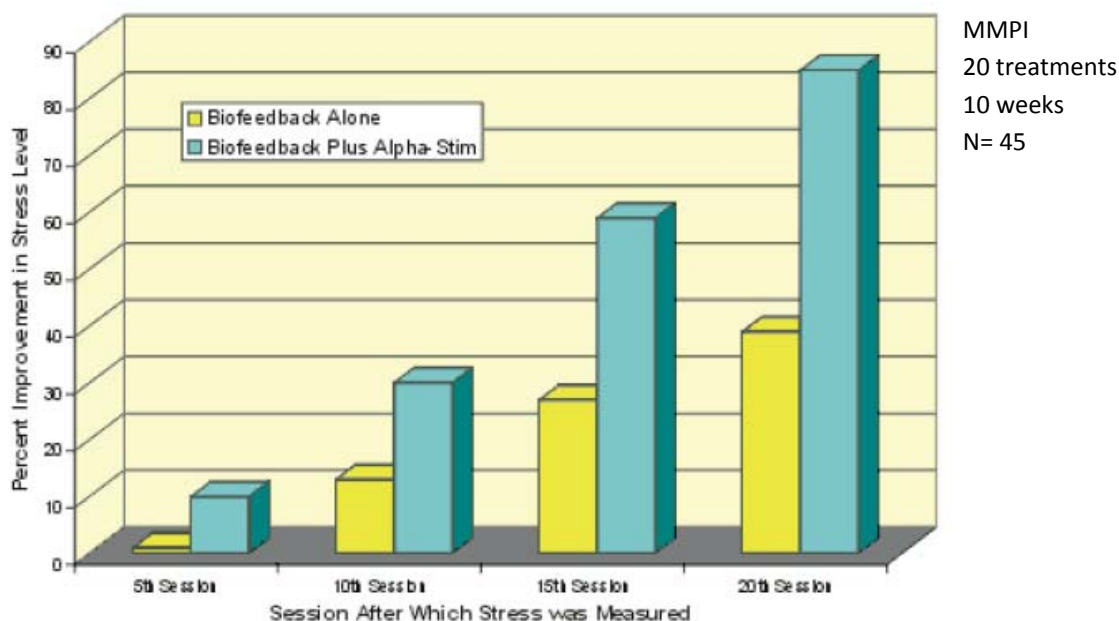


Figure 49. The effect of biofeedback alone or biofeedback plus Alpha-Stim® in reducing stress in chronic back pain patients.

The graph shows that while biofeedback therapy reduced the patients' perception of personal psychological distress by 39% by the end of the study the group receiving both biofeedback and Alpha-Stim® microcurrent stimulation perceived an 85% drop in their level of psychological distress.

Subjects

The study included 45 patients who responded to a public notice about back pain. They were then randomly divided into 3 treatment groups of Alpha-Stim® electrical stimulation and EMG biofeedback (Group I), biofeedback alone (Group II), or Alpha-Stim® electrical stimulation alone (Group III). One subject in Group II, and 2 in Group III failed to complete the study. There were no significant differences in any of the 3 groups in sex, education level, occupational level, injury site and duration of pain, or socioeconomic class. The only significant group difference was in age between Group I with a mean of 35.7 years, and Group II with a mean of 44.6 years.

Quality of the Research

This open label study was able to show the effectiveness when treating back pain using electrical stimulation, biofeedback and a combination of the two. This was a well-executed open label study but there was a significant age difference in groups I and II even though they were randomly assigned. The study not only looked at pain but took into account mobility and personality changes. A double blind randomized controlled trial would be the logical next step.

Conclusion

The authors concluded that the results suggest that the effects of each treatment modality were cumulative, or additive to the other mode of treatment, and more effective than each procedure used alone, with the exception of EMG findings. No side negative effects were reported.

6. Case Series and Case Studies

6.1 Libretto (2015)

Libretto S, Hilton L, Gordon S and Zhang W. Effects of integrative PTSD treatment in a military health setting. *Energy Psychology*. 2015; 7(2): 33-44.

Device

Alpha-Stim®

Key Variables

Anxiety, Depression, Pain, PTSD

Objective

The purpose of this IRB approved study was to examine the efficacy of the US Department of the Army integrative PTSD program, the Warrior Combat Stress Reset Program (WCSRP) at Fort Hood, Texas, USA. The examination and the article were carried out by members of The Samueli Institute.

Design

The Warrior Combat Stress Reset Program had evaluation design built into the program from the beginning. Soldiers were screened for admission then pre-evaluations were done on day 1 of the 3 week program with post-evaluations done on the final day of 3 weeks. Evaluation results were coded and saved for analysis once resources were available. In 2012, the retrospective formal analysis began and the data files were entered into a database for analysis.

The psychometric instruments used for inclusion and exclusion into the program were also used to assess outcomes. Inclusion and exclusion criteria were also flexible as this was an active treatment program rather than a research project. The program was dynamic in that it could change according to patient feedback to ensure optimal results.

Primary Effectiveness Endpoint

Each patient was given a battery of 21 validated psychometric instruments which assessed PTSD symptoms, anxiety, depression and pain as well as other health outcomes. The assessment included the Beck Depression Inventory, Beck Anxiety Inventory, the Oswestry Pain Index and the Post Traumatic Growth Inventory.

Secondary Effectiveness Endpoint

Patient satisfaction

Key Inclusion Criteria

The evaluation team performed a retrospective analysis which included 764 de-identified patient files. These soldiers attended the reset program from August 2008 to March 2013. Admission to the reset program was flexible as it is a working treatment program. The general reset admission criteria included active-duty status, at least one deployment, moderate to severe PTSD symptoms, Axis II characteristics low and adequate readiness for intensive outpatient treatment.

Key Exclusion Criteria

Exclusion criteria included immediate suicidal or homicidal ideation, active substance abuse or unresolved legal or Uniform Code of Military Justice actions.

Protocol Summary

The WCSRP is an intensive 3 week program broken down into 3 stages with several different CAM modalities used throughout the duration of the program. Stage 1 was designed to reduce hyperarousal, improve sleep, emotional reactivity and avoidance. In this stage Alpha-Stim® CES was used in the clinic and often assigned as homework for participants. State 2 targeted further sleep disturbances, pain, headaches, avoidance and residual post-concussion symptoms. Several CAM modalities including Alpha-Stim® CES were typically useful in this stage. Stage 3 focused on trauma and specific triggers.

Device Application Protocol

The Alpha-Stim® CES treatments were initially carried out by the staff until patients were comfortable applying the treatment themselves.

Outcome Measures

The evaluation team included several tables in their report which illustrate the efficacy of the program. Table 9 shows the reduction in symptoms from 2008 to 2013. Patient satisfaction with the available CAM modalities was also surveyed during that time. These results are shown on Table 10.

Outcome measure	Pre-Tx mean	Post-Tx mean	Mean difference	P-value	N
PTSD	64.6	54.9	-10.2	<0.0001	586
Depression	30.3	21.5	-9.0	<0.0001	562
Anxiety	27.0	20.9	-6.3	<0.0001	567
Pain	34.3	32.1	-2.4	<0.0001	537

Table 9. Overall Health Outcomes (2008 – 2013)

Modality	2008	2009	2010	2011	2012	2013
Alpha-Stim® CES	n/a	74.1%	78.4%	76.4%	83.2%	100%
Individual Treatment	97.7%	92.6%	89.3%	91.6%	92.5%	87.5%
Acupuncture	n/a	76.5%	72.1%	72.7%	72.5%	75.0%
EFT	n/a	40.0%	40.9%	58.9%	50.9%	37.5%
Group Processing	95.5%	84.8%	65.5%	79.2%	85.6%	100%
Massage	n/a	95.2%	86.7%	90.2%	91.5%	100%
Yoga	n/a	57.7%	43.1%	41.2%	46.5%	62.5%

Table 10. Patient Satisfaction with Program Components

Analysis

In order to test the hypothesis that the soldiers treated in the reset program had fewer combat stress/PTSD symptoms compared to before participating in the program, the change in instrument scores of each patient was computed. Sample paired t-test was applied to compare pre- and post-intervention outcomes. Longitudinal models were used to estimate the effects of the CAM therapies. Since satisfaction and symptom relief ratings for CAM therapies were measured repeatedly, the evaluation team was able to use generalized estimating equations (GEE) to account for correlations. A 95% confidence interval was used to assess the results.

Average scores from 2008 to 2013 decreased:

Anxiety (N=567): 27.0 to 20.9 (-6.3, $p<0.0001$)

Depression (N=562): 30.3 to 21.5 (-9.0, $p<0.0001$)

Pain (N=537): 34.3 to 32.1 (-2.4, $p<0.0001$)

Results

Effectiveness

All health related outcomes showed statistically significant improvements from pre to posttreatment, as seen in Table 8. The trend toward increasing effectiveness over the years is interpreted as reflecting the addition of more CAM services.

CAM Outcomes

On average, 1.7 to 2 point improvement in the NRS score for pain, anxiety and mood was shown from pre to post CAM treatment. The results are statistically significant and no adverse events were noted in the CAM treatments.

Patient Satisfaction

Soldiers rated satisfaction with treatment modalities and the overall program on a 5-point Likert-type scale ranging from “extremely helpful” to “not helpful.” A large majority of soldiers found Reset helpful or very helpful in addressing hyperarousal and their individual issues. Dropouts numbered less than 10 soldiers out of 1,400 over the life of the program.

Conclusion

The WCSRP appears to be very successful in meeting its stated goals and objectives. The improvements in health were both statistically and clinically significant. The improvements in PTSD, anxiety, depression and pain from pre to post treatment suggest the CAM sessions may have a positive impact on conventional behavior health treatment effectiveness.

6.2. Bauer (1983)

Bauer W. Electrical treatment of severe head and neck cancer pain. *Archives of Otolaryngology*. 1983; 109(6):3 82-383.

Device

Alpha-Stim®

Key Variables

Pain

Objective

The purpose of this study was to determine the effectiveness of Alpha-Stim® CES to reduce pain secondary to head and neck cancer.

Design

This is a case series which includes 3 patients from the Division of Otolaryngology, Case Western Reserve University School of Medicine, and the Veterans Administration Medical Center in Cleveland, Ohio. These patients each had a form of head or neck cancer and pain secondary to that diagnosis.

Primary Effectiveness Endpoint

Pain

Key Inclusion Criteria

These 3 patients were all being seen by the Division of Otolaryngology, Case Western Reserve University School of Medicine, and the Veterans Administration Medical Center in Cleveland, Ohio and each had significant pain reduction upon using the Alpha-Stim®.

Protocol Summary

Each of the 3 patients had severe pain which was not being controlled by medication. Patient 1 had received morphine sulfate and sedatives, patient 2 had received codeine, zomax and Elavil and patient 3 had received codeine and meperidine. Once the medications failed the patients were treated with Alpha-Stim®.

Results

Patient 1 received 3 daily, 10 minute Alpha-Stim® treatments and was completely pain free for one week. Patient 2 received 6 minutes of Alpha-Stim® treatment and was pain free for 50 hours. Further treatment continued to give relief. Patient 3 received 8 hours of relief after the first treatment and 24 hours after the second.

Conclusion

The author noted that the longevity of the results was especially encouraging. In every case pain relief lasted at least 8 hours, and in case 2, the effect lasted more than 3 weeks. There was no indication of side effects, and usually there was no sensation of the electrical stimulus. The positive results are unquestionable, and this form of electrical stimulation should not be confused with [other forms of] TENS.

7. Chapter Review

7.1 Bioelectromagnetic and Subtle Energy Medicine

Kirsch DL and Marksberry JA. The Evolution of Cranial Electrotherapy Stimulation for Anxiety, Insomnia, Depression and Pain and Its Potential for Other Indications. Bioelectromagnetic and Subtle Energy Medicine, 2nd Edition. CRC Press, Boca Raton FL, 2015.

This chapter was written for the reference book Bioelectromagnetic and Subtle Energy Medicine at the request of the editor, Paul Rosch MD, FACP. The 20 page review chapter covers the history of Cranial Electrotherapy Stimulation (CES), the mechanism of action, the clinical role of CES, clinical research on the indicated uses, post-marketing data as well as clinical considerations and guidelines. This review chapter focuses on the published clinical research regarding CES and discusses the safety, precautions and efficacy of the treatment. There is also discussion on the implementation of CES into the clinical practice and how this modality may be used concurrently with psychotherapy or pharmacotherapy. The chapter provides compelling research to support the safety and efficacy of CES for the treatment of anxiety, insomnia and depression.

8. Reports of Post-Marketing CES User Surveys

8.1. Kirsch (2015)

Kirsch DL, Price LR, Nichols F, Marksberry JA and Platoni KT. Cranial electrotherapy stimulation: treatment of pain and headache in military population. *Practical Pain Management*, 15(8):57-64, 2015.

Device

Alpha-Stim®

Key Variables

Pain and headaches

Objective

The purpose of this study was to determine the efficacy of CES for the treatment of pain and headaches in the military population

Design

This was a post marketing study focused on active duty and veteran Service Members

Primary Effectiveness Endpoint

Improvement in pain and headaches

Key Inclusion Criteria

The survey was sent to subjects who had prescriptions on file from the DoD and VAMC with Electromedical Products International, Inc., the manufacturer of Alpha-Stim® from 2007 to 2011.

Protocol Summary

The survey asked about results with anxiety, insomnia, depression, PTSD, pain and headaches and required the subjects to treat for at least 3 weeks. The survey also asked about safety and side effects of the treatment.

Outcome Measures

Pain and headache improvement self reports

Results

The graph below shows the level of improvement subjects reported for pain. The groups were also broken up into patients who used medications and Alpha-Stim® together or just Alpha-Stim®. In the “total group” (N=73), 45.1% of patients reported CES was effective (>25% improvement) for pain.

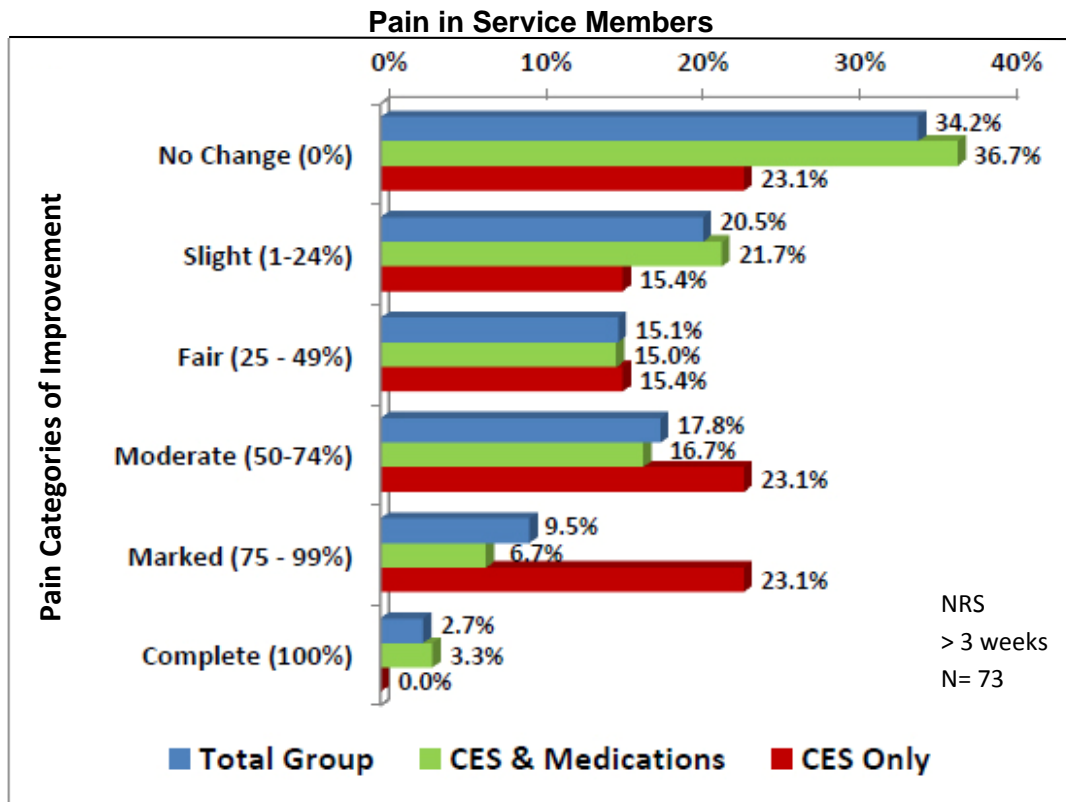


Figure 50. Percent improvement in pain

The graph below shows the level of improvement subjects reported for headaches. The groups were also broken up into patients who used medications and Alpha-Stim® together or just Alpha-Stim®. In the “total group” (N=70), 58.5% of patients reported CES was effective (>25% improvement) for pain.

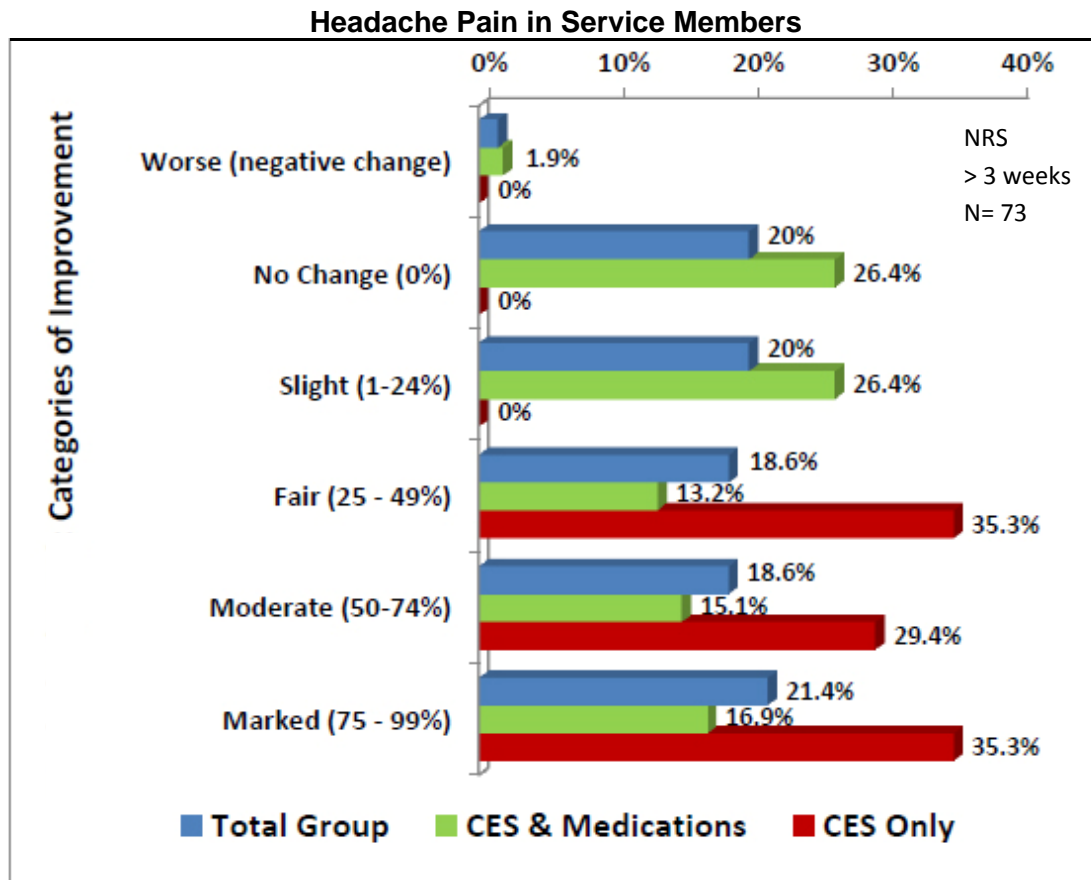


Figure 51. Percent improvement in headaches

Conclusion

The findings of this study provide additional evidence that CES is a safe and effective treatment for pain and headaches. Results in this study are consistent with the findings on randomized, sham-controlled trials on the use of CES for the treatment of pain in a military population.

8.2. Comparison of Three Alpha-Stim® Post-Marketing Surveys (N=5,917)

Peer-reviewed outcomes conducted on Alpha-Stim® from 2,500 patient surveys published in 2001 correlated well with 47 physicians' reports on 500 patients. This data revealed that at least 25% improvement was reported by 9 out of 10 in this group of 3,000 patients (Kirsch, 2002; Smith, 2001). In another survey of 152 military Service Members and veterans conducted on Alpha-Stim® in 2011 the outcomes, while still positive, were lower than prior surveys of civilians (Kirsch et al., 2014). However, the findings of a third survey conducted in 2013 of 2,861 Service Members, veterans and civilians were closer to the original survey of civilians in 2001. Service Members and veterans who use CES are most likely to suffer from more extreme trauma and therefore it is not surprising that they reported less effectiveness from CES treatments than a civilian-only cohort. However, the effects of CES reported by this Service Member and veteran cohort were clinically important with 66.7% reporting $\geq 25\%$ improvement in anxiety, 65.2% in insomnia, 54% in depression, and 45.1% in pain. Figure 52 provides a detailed summary of all 3 of the post marketing surveys conducted, totaling 5,917 Service Member, veteran and civilian self-reports. A report on each of the three post-marketing surveys is included on the following pages. Also, included is a report from US Department of Veterans Affairs on Veterans' preference of 5 complimentary medical devices for used in treatment of anxiety, insomnia, depression and pain in which veterans chose Alpha-Stim® 73% of the time over the 4 other types of devices.

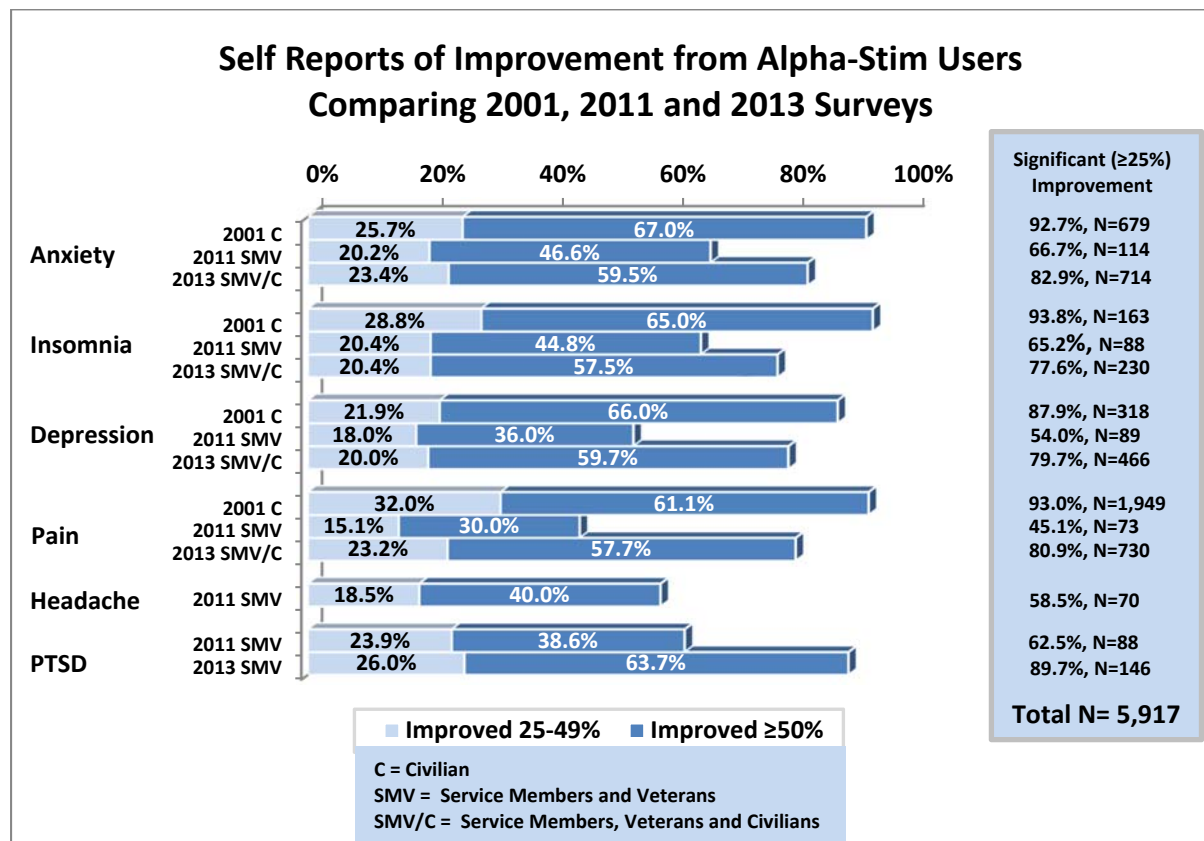


Figure 52. Comparison of Three Alpha-Stim® Post-marketing Surveys. 2001, 2011, and 2013.

Determining Clinical Significance

The Dworkin and colleagues (2008) criteria were used to determine meaningful clinical improvement for the surveys. While the criteria were developed for clinical pain trials, we have also found it useful for mental health research because it identifies a group of individuals that improve, but do not meet the ≥ 50 standard. Between 25 – 49% improvement was defined as moderate clinical importance and $\geq 50\%$ or greater was defined as the substantial clinical importance category.

8.3. Alpha-Stim® 2007- 2013 Post-Marketing User Survey of Civilians

Conducted by Larry Price, Professor and Director, Interdisciplinary Initiative for Research Design and Analysis, Texas State University, San Marcos, Texas.

Self-report data on the perceived effectiveness of Alpha-Stim® was acquired from 2,861 respondents through a mail survey. Data collection occurred between January 2007 and July 2013. The primary focus of the survey was to acquire information regarding the effectiveness of using Alpha-Stim® for the treatment of anxiety, insomnia, depression, pain and PTSD. Eighteen percent (513) of the respondents exhibited nonresponse on at least one of the questions, diagnosis or improvement and were not included in the analyses. The final sample size used in the descriptive analyses after screening the data for overt errors in coding, aberrant or out of range values and item nonresponse was N=2,348, providing a useable response rate of 82% for the diagnosis and improvement questions. One reason for the excellent response rate was that the user survey was included on the warranty card in the Alpha-Stim® device kit with instructions to complete the survey and return the warranty card after using the Alpha-Stim® device for at least 30 days.

Characteristics of Sample

The mean age for the analytic sample was 50 years (standard deviation of 14.5 years). The sample consisted of 69% females and 30% males with 1% not reporting their sex. The average number of months respondents reported using Alpha-Stim® on a continuous basis according to prescribed protocol was 106 days. However, the median (*i.e.*, exact center of the distribution) of the numbers of days of use was 1 month or 30 days. The mean days of use were higher than the median statistics due to extremely long continued use by a small number of consumers (*e.g.*, 23 respondents reported using Alpha-Stim® 3 years or longer and 85 reporting 1 year or longer) who found Alpha-Stim® technology effective for their condition..

Safety of CES

Over 99.9% of respondents reported that they considered Alpha-Stim® to be effective (*e.g.*, either yes or no) for treating their identified medical problem. Out of 1,498 respondents to the question, “Do you consider Alpha-Stim® to be safe?” one person marked “no” but gave no reason for this response.

Effectiveness of Alpha-Stim® CES

This survey included civilians, Service Members and Veterans for the analysis of the perceived effectiveness of anxiety, insomnia, depression and headache. PTSD data included Service Members and Veterans only. The 2011 Alpha-Stim® Service Members and Veterans Survey revealed that Service Members and Veterans rated their perceived effectiveness of Alpha-Stim® lower than civilians in a previous survey. This is most likely due to Service Members and Veterans having more complex, serious injuries and medical conditions than civilians as a group. In the 2013 survey, Service Members and Veterans effectiveness ratings for PTSD was high with 63.7% reporting clinical improvement of $\geq 50\%$ and 26% of respondents reporting improvement between 25-49%. This is a total effectiveness rate for PTSD of 89.7%.

Dworkin and colleagues (2008) criteria for determining the importance of clinical improvement was used in this survey: $\geq 50\%$ was improvement of substantial clinical importance. Improvement of moderate clinical importance was defined in this survey as 25-49% as this category was also used in the validated Likert Scale that was used for the survey.

Respondents were asked to respond regarding their perceived improvement since beginning treatment in the form of a rating scale. Improvement was measured according to (a) a negative change (*i.e.*, condition worsened), (b) no change, (c) slight improvement (1-24%), (d) fair improvement (25-49%), (e) moderate improvement (50-74%), (f) marked improvement (75-99%), or (g) complete recovery (100%). Participants evaluated the effectiveness of CES for the following categories of diagnoses; anxiety, insomnia, depression, pain, PTSD (See Figure 53).

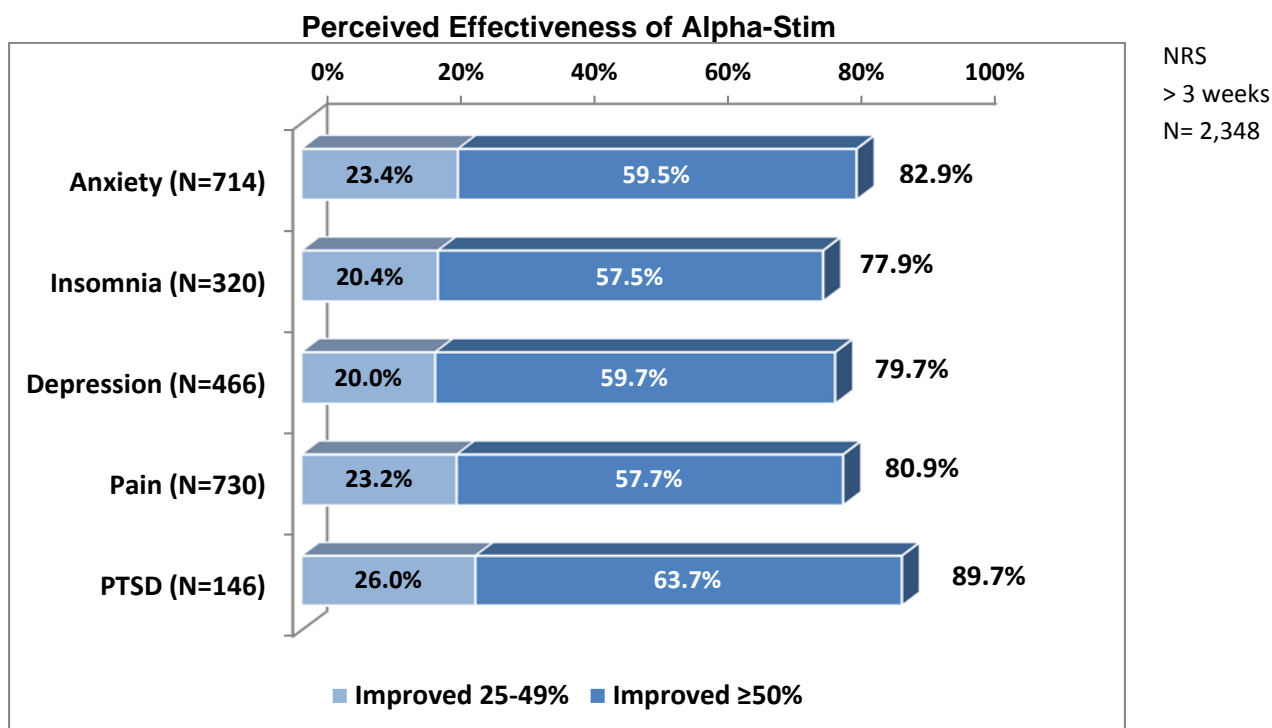


Figure 53. Perceived effectiveness of Alpha-Stim® for anxiety, insomnia, depression, pain and PTSD (N= 2,348). PTSD includes Service Members and Veterans only. Anxiety, insomnia, depression and pain categories include civilians, Service Members and Veterans. The dark blue indicates improvement of substantial clinical importance (≥50%). The light blue indicates improvement of moderate clinical importance (25-49%). The total percent of respondents for ≥ 25% improvement is shown at the end of each bar.

Overall (includes the diagnostic categories of anxiety, insomnia, depression, pain and PTSD), 60% of respondents reported having either moderate, marked or complete improvement (≥ 50%) from use of Alpha-Stim® CES from baseline or starting treatment, while 23% percent reported fair improvement (25-49%). Sixteen percent (16%) of respondents reported slight improvement (1-24%). Approximately 2% reported no change in improvement while 3 individuals out of 2,348 respondents reported that their condition became worse.

The final question asked whether Alpha-Stim® was more effective than anything else they had used for their respective medical condition. Thirty-six percent (36%) of the respondents reported that Alpha-Stim® was more effective than anything else they had used for anxiety, 35% for pain, 17% for depression and 11% for insomnia.

Note: The criteria developed by Dworkin and colleagues (2008) to evaluate the importance of clinical improvements were used for the following reason. In addition to ≥ 50% improvement that was termed improvement of substantial clinical importance, it includes a category of

improvement called improvement of moderate clinical importance (30-49%). The reporting of the moderate clinical importance category is recommended because it provides a more complete picture of the response to treatment.

8.4. Alpha-Stim® 2011 Post-Marketing User Survey of Service Members and Veterans

Conducted by Larry Price, Professor and Director, Interdisciplinary Initiative for Research Design and Analysis, Texas State University, San Marcos, Texas.

The primary purpose of this non-probability, purposive sampling survey study was to examine Service Members' and veterans' perceptions of the effectiveness and safety of CES for anxiety, PTSD, insomnia, depression, pain and headache. A secondary purpose of the study was to investigate if there was a difference in perceived effectiveness of those respondents who were taking prescription medications for their condition and those that used CES only. Email addresses for potential participants were obtained from prescriptions for Alpha-Stim® CES devices written by DOD or VA practitioners that were on file at Electromedical Products International, Inc., Mineral Wells, Texas, the manufacturer of the device. Service Members and Veterans (N=1,514) who had obtained an Alpha-Stim® CES device through the Department of Defense or Veterans Affairs Medical Center from 2006-2011 were invited to participate in the web based survey via email. One hundred fifty-two participants (152) returned questionnaires. Seven (7) questionnaires did not include any effectiveness and safety data. Thus, the valid sample size was N=145 for the analysis of the effectiveness and safety questions. All participants used CES at home following a DOD or VA CES protocol.

Data were analyzed using descriptive statistics. Improvement of substantial clinical importance was defined as $\geq 50\%$. Improvement of moderate clinical importance was defined as 25-49% (Dworkin et al., 2008).

Characteristics of Respondents

Seventy-two percent (72%) of respondents were active duty Service Members and 28% were Veterans. The sample was 75% male. Subjects ranged in age from 19-67 years with a mean of 38 years. Eighty-two percent (82%) were still using Alpha-Stim® CES. Seventy-three percent (73%) were currently taking at least one prescription drug for their condition. The length of time respondents reported using Alpha-Stim® ranged from 3 months to 3 years. The median length of time respondents used Alpha-Stim® CES was 9 months.

Safety of Alpha-Stim® CES

Ninety-nine percent (99%) of subjects in this survey considered CES technology to be safe. Ninety-nine percent (99%) of participants did not report any problems related to using CES self-directed at home following a DOD or VA CES Protocol. One respondent reported not being shown how to use the CES device properly.

Effectiveness of Alpha-Stim® CES

Participants (total group) reported clinical improvement of $\geq 25\%$ from using CES as follows: anxiety (66.7%), PTSD (62.5%), insomnia (65.3%), depression (53.9%), pain (45.1%) and headache (58.5%). The majority of these participants reported $\geq 50\%$ clinical improvement (See Figures 54 and 55). Those individuals who were not taking any prescription medication rated CES more effective than those individuals in the prescription medication group. The use of prescription medication was the highest for drugs used for anxiety (45.9%), depression (44.8%), pain (38.7%) and insomnia (27.5%). The most striking finding was that 100% of those respondents who were using Alpha-Stim® for headache reported improvement of $\geq 25\%$ and 64.7% of these respondents reported improvement of $\geq 50\%$.

Conclusions

Service Members and Veterans perceived CES as a safe and effective treatment for anxiety, PTSD, insomnia, depression, pain and headache when used either as an adjunct to pharmaceutical therapy or as a stand-alone therapy. In addition, the findings support that Service Members and Veterans can successfully use self-directed CES at home following a DOD or VA CES protocol.

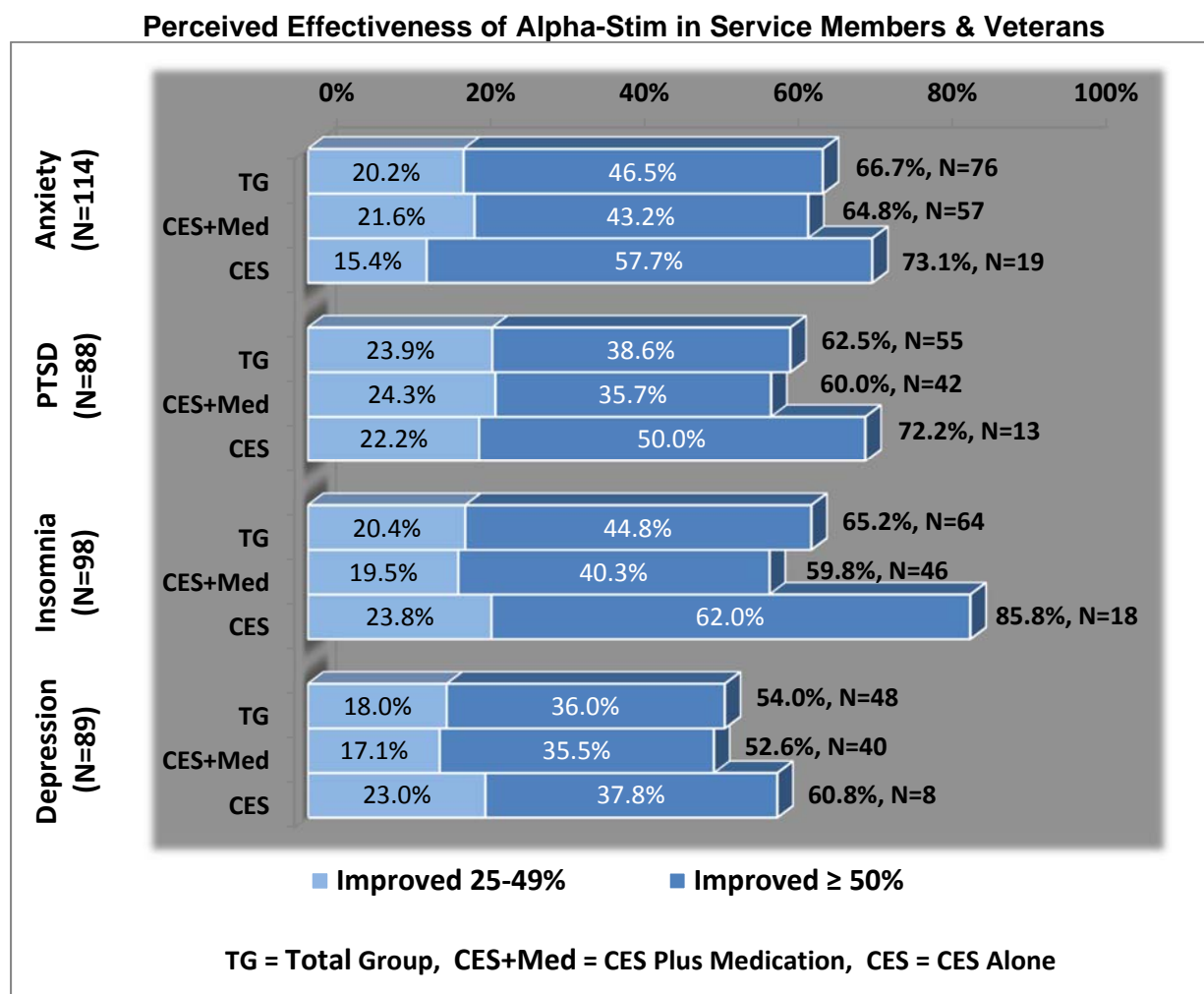


Figure 54. Service Members and Veterans perceived effectiveness of Alpha-Stim® for anxiety, insomnia and depression.

Kirsch DL, Price LR, Nichols F, Marksberry JA and Platoni KT. Efficacy of Cranial Electrotherapy Stimulation for Anxiety, PTSD, Insomnia, and Depression: US Military Service Members and Veterans Self Reports. *The Army Medical Department Journal*. October-December 2014:46-54.

8.5. Veterans at a VA walk-in pain clinic chose Alpha-Stim® CES (73%) over 4 other devices for the treatment of anxiety, insomnia, depression and pain.

Psychological services for veterans have been expanded to include complementary and alternative medicine (CAM) approaches in interdisciplinary pain management programs. A study by Tan and colleagues (2010) reported that benefits included a significant decrease in self-reported pain ($p < 0.01$) and a decrease in anxiety, improved sleep and an increased sense of emotional well-being although these last 3 did not meet the level of significance. The purposes of the study were to evaluate the walk-in pain CAM clinic and to determine Veterans' preference for the CAM modalities.

Veterans Preference for CAM Device

Thirty-two (32) Veterans who participated in a total of 197 visits to a walk-in pain clinic could choose among one of 5 CAM portable devices for pain, anxiety, insomnia and depression. The CAM choices were cranial electrotherapy stimulation (CES) using the Alpha-Stim® (AS) medical device, 3 biofeedback devices: Stress Eraser (SE), EmWave (EM), Respire (RR) or an audio-visual entrainment device called the David Pal. Individuals could choose a different device if they wished to do so at subsequent treatments. Seventy-three percent (73%) selected the Alpha-Stim® device (CES), 11% choose the Stress Eraser, 6% chose EmWave, 6% chose Respire and 4% choose David Pal.

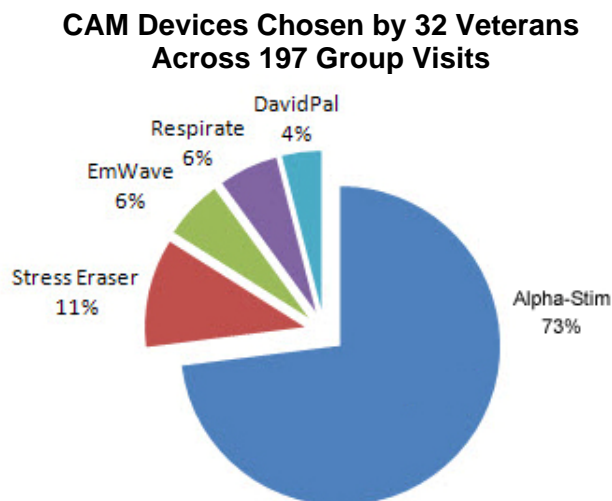


Figure 55. CAM devices chose by 32 Veterans across 197 group visits

Study outcomes were as follows:

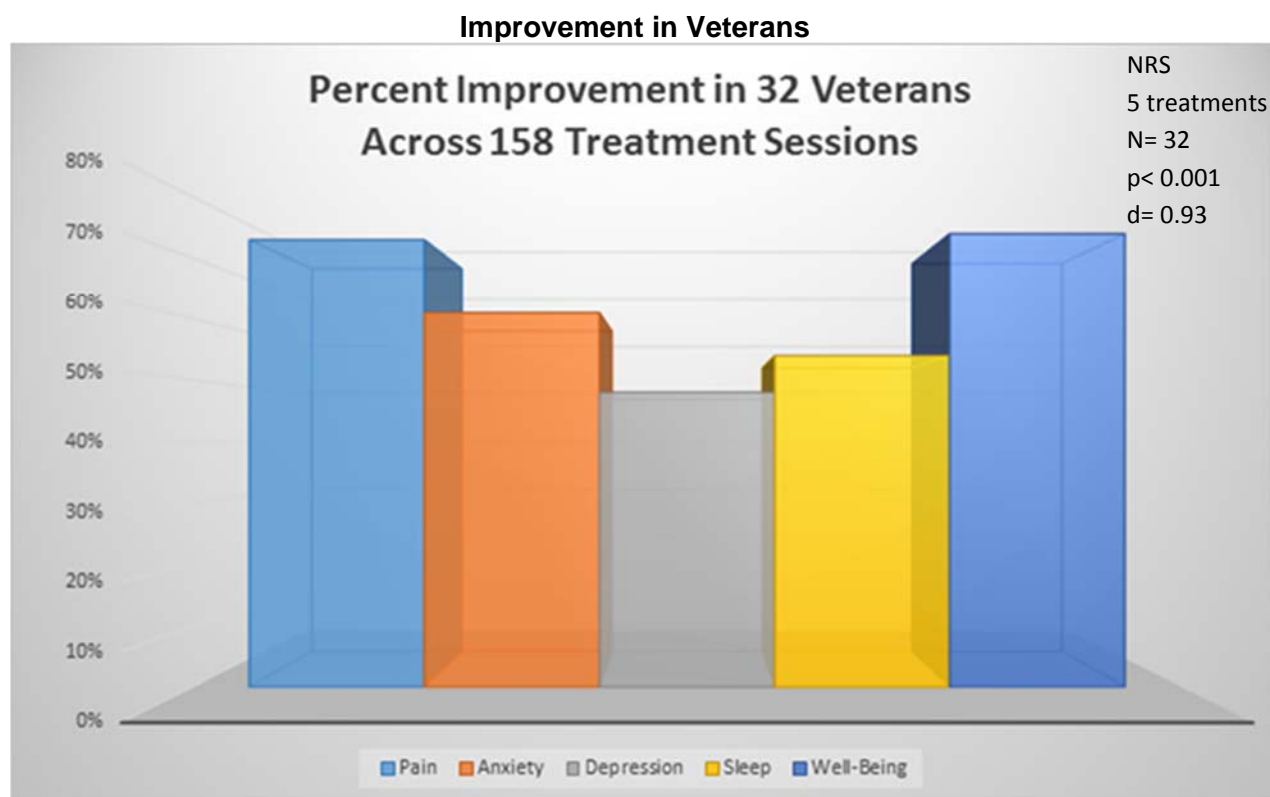


Figure 56. Improvement in 32 Veterans after an average of 5 treatments (158 total treatments)

Attendance and Device Preference

32 Veterans participated during the review period, resulting in a total of 197 visits to one or more of the 32 CAM groups offered from March 1, 2009 to May 22, 2009. Among the 5 CAM portable devices made available to the Veterans (the option of switching devices between sessions was permitted), the majority opted for the Alpha-Stim® (73%). The average number of Veterans who attended each CAM group session was significantly higher than the average number attending Pre-CAM groups: CAM average 6.16 (SD = 1.99; range, 2 to 9); Pre-CAM average 2.97 (SD = 1.49; range, 1 to 7); [two-sample t test, $t(63) = -7.303$, $p < .001$].

Benefits Reported From Session Monitoring

Veterans reported substantial “improvements since last session” especially in pain and sense of well-being (73% and 74%, respectively). “Yes” responses to progress (improvement) were also quite substantial (83% for relaxation, 77% for mood, and 80% for well-being post session). Because of the limited data for the devices other than Alpha-Stim®, the investigators said comparing the efficacy of the various devices was not possible.

Pain Reduction

A paired t-test indicated an average decrease of 1.02 units (SD = 1.10) on the 0–10 Numerical Rating Scale of pain intensity during the study period, which was statistically significant $t(196) = -12.99$, $p < .001$, and represented a large effect size of .93.

Changes in Standardized Measures of Patient Functioning

Monthly administration of 4 brief, standardized assessment tools, PHQ-2 I(depression), OASIS (anxiety), MOS SPI-I (Sleep) and MHI-5 (emotional well-being), was used as a supplement to the session rating forms to assess and monitor progress on 4 outcome domains in addition to pain intensity: anxiety, depression, sleep quality, and sense of well-being. Statistical analysis was performed using SPSS version 17.0. T-tests examined changes in these additional outcome measures. Although the change scores were not statistically significant, perhaps because of the low sample size, or the use of the PHQ-2 to measure depression and OASIS to measure anxiety, the effect sizes for improvements in well-being, sleep, anxiety, and depression were promising (1.54, 0.73, 0.44, and 0.37, respectively).

Conclusions

The authors concluded that the CAM therapies used in the study could be used alone or in conjunction with other psychological therapies and potentially could be used as a self-management approach for chronic pain management. The Alpha-Stim® was the most passive device (all the individual had to do was put on the ear-clips and set the current level) while the other 4 devices required the patient to learn a new skill, such as breathing in a certain manner. When asked why they chose Alpha-Stim®, the most common responses were “feeling relaxed, improved sleep and a sense of well-being.”

Reference

Tan G, Dao TK, Smith DL, Robinson A and Jensen MP. Incorporating complementary and alternative medicine (CAM) therapies to expand psychological services to veterans suffering from chronic pain. *Psychological Services*. 2010; 7(3): 148–161.

PART III: SAFETY OF CRANIAL ELECTROTHERAPY STIMULATION

1. Clinical Data to Date: CES Safety

CES is non-invasive and side-effects are mild and self-limiting. A FDA commissioned review of the safety of CES by the National Research Council (1974) stated, “significant side effects or complications attributable” to the application of electric current of approximately one milliampere or less for “therapeutic effect to the head” (*i.e.*, cranial electrotherapy stimulation) were “virtually nonexistent” (p.42). The Alpha-Stim® device uses 50% of this amount of current at the highest CES setting. A review of 14 Alpha-Stim® CES studies using human subjects revealed that incidence of adverse events was < 1% and all were mild and self-limiting.

Table 11 lists all adverse events reported in the studies. The 14 Alpha-Stim® CES studies in this table include 2,600 subjects of which 2,389 (in CES group, sham/open label group or control/open label group) had treatment while the balance were in the sham or control groups only (N=211). No serious adverse events have been reported during the 33 years that Alpha-Stim® CES had been on the market. (EPI Safety data submitted to FDA, February 10, 2012). The most common non-serious adverse events (less than $\leq 1\%$) were skin irritation at the site of the electrodes, dizziness and headache. Both dizziness and headache occur when the current is set to high for the individual and these symptoms disappear when the current is decreased.

Principal Investigator Year	N	Subject Description	Adverse Events
Tan, Gabriel 2011	105	Neuropathic Pain	<p><u>Alpha-Stim® CES group:</u> Ears pulse, tingle, sting, itch, ear clips too tight – 12; Legs, tingling, burning, electric shot in feet – 1; Spasms, leg spasms – 1; Burning in buttocks – 1; Ringing in ears – 1; Drowsy, sleepy, fell asleep, relaxing – 7; Dizzy, lightheaded, feeling crooked – 3; Nausea, stomach rolled – 1; Headache, slight headache – 2; Metallic or unusual taste in mouth – 1; Increased pain – 1.</p> <p><u>Sham CES group:</u> Ears pulse, tingle, sting, itch, ear clips too tight – 6; Head tingles – 1; Legs tingling, electric shot in feet – 1; Spasms, leg spasms – 2; Drowsy, sleepy, fell asleep, relaxing – 4; Dizzy, lightheaded, feeling crooked – 1; Nausea, stomach rolled – 2; Shaky – 1; Heart racing, chest pain – 2; Headache, slight headache – 3; Metallic or unusual taste in mouth – 1; Increased pain – 1.</p> <p>There were no serious study-related adverse events in any phase of this study (p. 292).</p>
Rintala, Diane 2010	13	Parkinson's Disease	<p><u>Alpha-Stim® CES group:</u> Pulsing, tickling, tingling in ears – 3; Tender ears – 1; Pins and needles sensation in bladder – 1.</p> <p><u>Sham CES group:</u> Drowsiness – 1; Warm ears – 1; Headache – 1.</p> <p>No serious study-related adverse events occurred during this study (p. 4).</p>

Eidelman, William 2009	1,000	Cigarette smokers	Three (3) subjects out of 1,000 individuals (0.3%) were unable to tolerate the CES treatment due to vertigo (p. 83).
Holubec, Jerry 2009	525	Chronic Pain	No negative adverse events were observed by any member of the clinic staff or reported by patients (p. 83).
Mellon, Ronald R. 2009	21	Security and patrol staff of a rural jail	After the third CES session, one subject reported increased levels of agitation secondary to treatment and was removed from the study (p. 11).
Bystritsky, Alexander 2008	12	Generalized anxiety disorder	Two subjects dropped out of the study because of dizziness and one dropped out of study because of headache, (p. e3).
Strentzsch, Julie A. 2008	42	Chronic mentally ill patients in a partial hospitalization program	<u>Alpha-Stim® CES Group</u> : One subject from the active CES group reported increased auditory hallucinations but remained in the study with no further problems (p. 56). <u>Sham CES Group</u> : Two subjects from the sham group reported headaches from treatment (p. 56).
Kirsch, Daniel L. 2002	500	Anxiety, depression, insomnia, pain, and stress patients	Adverse events: 6 (1.2%) reported dizziness, and 2 (0.4%) reported nausea, both of which normally occur when the current is set too high, 3 (0.6%) reported skin irritation, 1 each (0.2%) reported, anger, a metallic taste, a heavy feeling, or intensified tinnitus (p.44).
Kulkarni, AD 2001	20	Chronic pain patients	No negative adverse events were reported by patients (p.102).
Lichtbroun, Alan 2001	60	Fibromyalgia patients	Subjects experienced no significant adverse events (p.76).
Schroeder, MJ 2001	12	"Normal" subjects	No adverse events were reported (p. 2081).
Winick, Reid 1999	33	Dental patients	No detectable adverse effects were noted in any of the subjects undergoing CES treatment (p.54).
Overcash, Stephen 1999	197	Acute anxiety disorder patients	There was no reported side-effects (either short or long term) from CES (p. 51).

Table 11. Adverse events reported in 14 Alpha-Stim® studies. Note: To be included in the table of studies, the study must have been done using Alpha-Stim® CES, must include a specific statement on adverse events and must be a primary source.

The total number of adverse events in the 14 Alpha-Stim® CES studies above are shown by category in Table 12 below.

Adverse Event	CES < 1%	Sham < 1%
Ears tender, tingle, sting, itch, ear clips too tight*	16	7
Vertigo*	14	1
Drowsy, sleepy, relaxing	7	5
Headache*	3	3
Skin Irritation, earlobes	3	0
Nausea*	3	0
Agitation/Anger	2	0
Tinnitus	2	0
Metallic taste in mouth	2	1
Increased pain	1	1
Legs tingling, burning	1	1
Leg spasms	1	2
Head tingles	0	1
Pins and needles in bladder	1	0
Burning in Buttocks	1	0
Auditory hallucinations	1	0
Heavy feeling*	1	0
Heart racing, chest pain	0	2
TOTAL	59	24

Table 12. Adverse events from 14 Alpha-Stim® studies by category. Comments: Vertigo, headache and nausea occur when the current is set too high for the individual. These symptoms disappear when the current is decreased. Tingling, stinging and itching of ears are a response to the current and will disappear when the current is decreased. Feelings of drowsy, sleepy, relaxing and heaviness indicate a central nervous system response to CES treatment.

During the five year period between 2007 and 2011, 58,030 Alpha-Stim® CES devices were sold. Based on the 5 years sales figure of 58,030 minus returns (there were 75 returns in 2011), an individual home Alpha-Stim user survey, and an Alpha-Stim® practitioner survey, during 2007-2011 there was a total of 8,248,920 Alpha-Stim® CES treatments (1,982,520 individual user treatments, plus 6,266,400 in-office treatments by practitioners). There were 14 reported adverse events during this time frame. Every reported adverse effect was mild and self-limiting. Adverse effects from using Alpha-Stim® CES reported to EPI in 2007-2011 were < 1%. This is consistent with a review of Alpha-Stim® CES studies where adverse effects reported were also < 1%. There were no Medical Device Reports (MDR's) reported to FDA during this time.

Reported Adverse Events 5 year Summary 2007-2011	N
Skin irritation at electrode site	11
Tinnitus	2
Panic attack	1
TOTAL	14

Table 13. Adverse events summary 2007-2011 reported to Electromedical Products International, Inc.

A comparison of the side-effects of drugs prescribed for anxiety, insomnia and depression with CES is shown in Table 14.

Anxiolytics	Antidepressants	Anti-Insomnia	CES
<p><u>Benzodiazepines</u> are most commonly associated with cognitive side effects including sedation, impairment in attention, delay in psychomotor performance, and memory deficits. depression, delirium, and paradoxical reactions and physiological dependence can occur.</p> <p><u>Non-Benzodiazepines</u> The most commonly reported side effects include dizziness, headache, nervousness, light-headedness, diarrhea, nausea, paresthesia, excitement, and insomnia.</p> <p>Yujuan Choy. Managing side effects of anxiolytics. <i>Primary Psychiatry</i>, 14(7):68-76. 2007.</p>	<p>Dry mouth, drowsiness, insomnia, blurred vision, headache, constipation, diarrhea, appetite increase, appetite decrease, nausea, vomiting, urinary problems, sexual problems, palpitations, orthostatic dizziness, vertigo, sweating, increased temperature, tremor, disorientation, yawning, and weight gain</p> <p>James M. Ferguso). SSRI Antidepressant medications: adverse effects and tolerability. <i>Primary Care Companion Journal of Clinical Psychiatry</i>, 3(1): 22–27, 2001.</p>	<p>Prescription drugs used specifically for improving sleeping include benzodiazepines and non-benzodiazepines (See column I, anxiolytics side-effects).</p> <p>Common side-effects include: headache, dizziness and drowsiness throughout the day, memory loss, drug dependence, and insomnia rebound.</p> <p>Insomnia - Medications, University of Maryland Medical Center, http://www.umm.edu/patient/articles/what_drug_treatments_insomnia_000027_8.htm#ixzz2VFsUz4fQ</p>	<p>No serious adverse events reported in over 30 years that CES has been on the market. Minor side effects that are self-limiting (< 1%): dizziness, headache and local skin irritation at the electrode site. Data submitted to US FDA by EPIL, February 10, 2012</p>

Table 14. Comparison of side effects of anxiolytics, anti-depressants, anti-insomnia drugs and Cranial Electrotherapy Stimulation (CES)

2. Summary

Alpha-Stim® CES has over a 30-year history of no serious adverse events. All adverse events that were reported were $\leq 1\%$, mild and self-limiting. The following research findings provide evidence that CES has a positive risk-to-benefit profile:

- The findings of the US FDA commissioned report on the safety of CES by the National Research Council in 1974 that stated, “significant side effects or complications attributable” to the application of electric current of approximately one milliampere or less for “therapeutic effect to the head” (*i.e.*, cranial electrotherapy stimulation) were “virtually nonexistent.” (p.42).
- The mild and self-limiting adverse events reported in the 14 Alpha-Stim® studies (See Table 11) were $<1\%$.
- The data from 2007 through 2015 which shows reports of only 25 adverse events (See Table 13) were reported to Electromedical Products International, Inc. during that same time.

PART IV: SUMMARY OF REPORT

This scientific and clinical literature examination report presented scientific and clinical data on the safety and effectiveness of the Alpha-Stim® CES device under normal conditions of use for the treatment of anxiety, insomnia, depression, and pain.

1. Anxiety

There are 20 human studies using Alpha-Stim CES technology that support the efficacy of CES for treatment of anxiety. Nine (9) double-blind, sham-controlled, randomized clinical trials on anxiety using the Alpha-Stim CES technology had significant findings in favor of the treatment group (Barclay, 2014; Kolesos, 2013; Mellon, 2008; Strentzsch, 2008; Cork, 2001; Lichtbroun, 2001; Winick, 1999; Voris, 1995; Gibson 1987). Five (5) additional single-blind randomized clinical trials on anxiety found significant findings in favor of the treatment group (Hill, 2015; Lu, 2014; Lee, 2013; Kim, 2008; Chen, 2007). Six (6) open label and retrospective analysis also reported that CES significantly decreased anxiety (Mellen, 2016; Gong, 2016; Libretto, 2015; Bystritsky, 2008; Lu, 2005; Overcash, 1999).

2. Insomnia

Two (2) double-blind, sham-controlled, randomized clinical trials using Alpha-Stim CES technology found that CES significantly decreased insomnia in favor of the treatment group (Taylor, 2013; Lichtbroun, 2001). A small, double-blind, sham-controlled, randomized, 5-day pilot study of military Service Members using Alpha-Stim CES technology reported mixed results (Lande, 2013). Men had significantly improved sleep on day 1 and day 4 of the study while the findings for women were not significant. The study was done in preparation for a grant submission and the mixed findings are mostly likely the result of an underpowered study with a small N and the very short CES treatment period of 5 days. For research, the CES protocol for the treatment of insomnia should be a minimum of 6 weeks.

3. Depression

Two (2) double-blind, sham-controlled, randomized clinical trials using Alpha-Stim CES technology found significant findings for depression in favor of the treatment group (Barclay, 2014; Mellon, 2009). In addition, Chen (2007) in a single-blind, sham-controlled, randomized clinical trial reported that CES significantly decreased depression in the treatment group when compared to the sham group. Six (6) open label studies and retrospective analysis reported that CES significantly decreased depression from baseline to the endpoint of the study (Gong, 2016; Libretto, 2015; Amr, 2013; Bystritsky, 2008; Lu, 2005).

4. Pain

This report references eleven (11) double-blind, sham controlled, randomized clinical trials (Lee, 2013; Taylor 2013; Taylor 2013; Tan 2011; Rintala 2010; Tan 2006; Cork 2004; Lichtbroun 2001; Sizer 2000; Heffernan 1997; Roth 1986), and nine (9) open-label studies and retrospective analysis (Keizer 2016; Libretto 2015; Kirsch 2011; Holubec 2009; Lee 2004; Kulkarni 2001; Alpher 1998; Zimmerman 1987; Bauer 1983). These studies consistently show Alpha-Stim® provides significant pain relief with few side effects.

5. Safety

Based on the research and reports of adverse effects to Electromedical Products International, Inc. on CES, all adverse events were mild, self-limiting and $\leq 1\%$.

6. Surveys

The favorable findings of 2 Alpha-Stim® post-marketing user surveys, 2011 and 2013, are consistent with the findings of RCTs and open label studies that found CES was an effective treatment for anxiety, insomnia and depression. A study by Tan and colleagues (2010) on veterans preferences of complementary medical devices for anxiety, insomnia, depression and pain found that veterans chose to use the Alpha-Stim® CES device 73% of the time over the other 4 devices.

7. Conclusions

The strengths and limitations of each study are addressed in the “Quality of the Research” section of the abstracts. For the double-blind, sham-controlled RCT studies, most of the independent investigators chose to use the Alpha-Stim® double-blind, sham-controlled RCT research protocol. Active and sham devices were pre-set and locked at the designated levels in the protocol, Zero (0) for sham (no electricity emitted) and 100 μA for active was set and locked by Electromedical Products International, Inc. The devices were randomized at the factory and packed in the order that they should be given to subjects. Thus, one can have increased confidence in these studies because of the rigor and specificity of the research design. Studies using Alpha-Stim® CES devices for treatment of anxiety, insomnia, depression and pain included different populations as well as different research designs such as open label. However, the findings that CES significantly decreases anxiety, insomnia, depression and pain are consistent across all studies. This consistency increases the confidence that a reviewer can have evaluating the outcomes of these studies (Shadish, Cook and Campbell, 2002).

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APPENDIX A: PATENTS (See attached)

- 1. 2013 Alpha-Stim® Utility Patent**
- 2. 2013 Ear Clip with Pole Patent**
- 3. 2013 PEP Probe Electrode Pad Patent**
- 4. 2014 Ear Clip Patent for Russia**
- 5. 2014 Probe Electrode Pad and Probe Electrode Patent for China**

APPENDIX B: SUMMARY TABLES OF CES STUDIES ON ANXIETY, DEPRESSION, INSOMNIA AND PAIN

Table 15.	RCT CES Anxiety Studies using Alpha-Stim® CES Technology
Table 15.1	Open Label, Survey and Retrospective CES Anxiety Studies using Alpha-Stim® Technology
Table 16.	CES Depression Studies using Alpha-Stim® Technology
Table 17	CES Insomnia Studies using Alpha-Stim® Technology
Table 18	RCT CES Pain Studies using Alpha-Stim® CES Technology
Table 18.1	Open Label, Survey and Retrospective CES Pain Studies using Alpha-Stim® Technology

Table 15. Alpha-Stim CES RCT Anxiety Studies

Principal Investigator	Total N	Subjects	Study Type	Measurement Scales/Outcomes
Hill N, 2015	17	College Students	RCT, DB, IRBA	State Trait Anxiety Inventory (STAI), Skin Conductance (SC), Electromyogram (EMG): STAI scores showed a decrease over time as subjects were exposed to stress inducing pictures. There was no significant difference in the treatment and active groups. HR was significantly reduced in the treatment group ($p < .001$). EMG showed a trend for improvement with the treatment over time ($p < .098$).
Barclay H, et al., 2014	115	Anxiety Patients	RCT, DB, IRBA	Hamilton Anxiety Rating Scale (HAM-A): In the active treatment group, 83% had a decrease of $\geq 50\%$ in scores from baseline to endpoint on the HAM-A ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.94$) from baseline to endpoint of study. The mean decrease on the HAM-A in the treatment group of 32.8% (19.89 to 13.37) was more than three (3) times the mean decrease on the HAM-A for the sham group of 9.1% (21.98 to 19.98) from baseline to endpoint of the study.
Lu, 2014	120	Anxiety Patients	RCT	Hamilton Anxiety Scale (HAM-A): The treatment group which consisted of daily Paxil and CES improved significantly more than the control group which received Paxil alone. Both the control and the treatment group showed improvement in HAM-A scores with each consecutive measurement. The comparison of HAM-A scores showed no significant changes between control and treatment groups at baseline, week 2 or week 4 but there was a significant difference in the two groups at week six ($p < 0.01$).
Lee S, 2013	50	Preoperative Patients	RCT, DB, IRBA	Likert Anxiety Scale: CES group had significantly lower scores from baseline on Likert anxiety scale than the control group, which had usual care ($p = 0.016$). There was also reduction in withdrawal scores for patients during injections ($p = 0.049$).
Kolesos ON, et al., 2013	40	Dental Preoperative Patients	RCT, IRBA	Modified Dental Anxiety Scale (MDAS): The CES group ($M=10.20$), the relaxation group ($M=10.70$) and the combined treatment group ($M=9.40$) had significantly lower anxiety ($p < 0.01$) than the control group ($M=18.30$). Each of the 3 treatment groups significantly decreased dental anxiety ($p < 0.05$) from pre-test to post-test. There was no statistically significant difference among the 3 active treatment groups on dental anxiety.
Mellen R, 2008	22	Sheriff Officers	RCT, DB, IRBA	Brief Symptom Inventory (BSI): 1. Somatization: measures bodily complaints ($P < .008$), 2. Obsessive/Compulsive: repetitive thoughts and actions ($P < .020$), 3. Interpersonal Sensitivity: difficulties with interpersonal relationships ($P < .077$), 4. Depression: sad mood, loss of energy, difficulty sleeping or sleeping too much ($P < .015$), 5. Anxiety: excessive worry, ($P < .015$). Hostility: feelings of anger toward others and the world ($P < .077$), 7. Phobia: excessive fearful reactions toward objects, insects and such ($P < .177$), 8. Paranoia: excessive fears that are not supported by evidence ($P < .066$), 9. Psychoticism: these individuals can appear unusual and emotionally distant ($P < .050$).

Strentzsch J, 2008	45	Chronic Mentally Ill	RCT, DB, IRBA	State Anxiety Inventory (SAI): The active CES group had significantly lower scores on the State Anxiety Index (SAI), indicating less state anxiety, than the sham group ($P=.02$, $d = -.41$) or control group.
Kim H et al., 2008	60	Preoperative Patients	RCT, IB	Likert Anxiety Scale: CES group had significantly lower scores from baseline on Likert anxiety scale than control group at end point of study ($p < 0.05$, $d = -.88$).
Chen Y et al., 2007	60	Children with Mixed Anxiety and Depressive Disorder (MAD)	RCT, IB	Zung Anxiety Scale (SAS); The ANOVA showed that on SAS, the main effect between CES group and sham comparator group was significant ($F = 83.21$ $P < 0.01$). Changes in EEG of Occipital Lobes via brain electrical activity mapping (BEAM): on left and right $\alpha 1$ revealed the main effect of group was significant ($F = 5.98$, $P < 0.05$; $F = 6.39$, $P < 0.05$); on left and right $\alpha 2$, the main effect of group was also significant ($F = 7.54$, $P < 0.01$; $F = 6.72$, $P < 0.05$).
Cork R et al., 2004	70	Fibromyalgia Patients	RCT, DB, IRBA	Profile of Mood States (POMS): The active CES group had significantly decreased anxiety scores ($p<0.01$), tender points ($p<0.01$) and pain ($p<0.01$) compared to sham group. There was no significant difference between groups on pain as measured by the McGill Pain Questionnaire, or functional impairment.
Winick, 1999	33	Dental Patients	RCT, DB, IRBA	Visual Analogue Scale: The active CES group had lower anxiety scores (VAS) from baseline to endpoint of the study than the sham group as measured by the investigator ($p<.02$) and subjects ($p<.02$). Findings using an inverse Likert scale corroborated these findings for both the investigator evaluation ($p < .01$) and subjects' evaluation ($p < .01$).
Voris, 1995	105	Outpatient Psychiatry	RCT, DB, IRBA	Spielberger's State Anxiety Inventory: The active CES group had significantly lower anxiety scores on the State Anxiety Inventory (SAI) compared to sham group ($p=.0001$, $d = -1.60$) and control groups. The active CES group had significantly lower scores on EMG ($p=.0001$, $d = -1.08$) and increased scores on finger temperature ($p=.0141$, $d = .50$) than sham and control groups, indicating less anxiety.
Gibson, 1987	64	Anxiety Patients	RCT, SB, IRBA	State Trait Anxiety Inventory (STAI): Subjects responded on the STAI significantly ($P<.001$) better than controls and equally to either relaxation therapy alone with a means of 52.88 pretest to 32.19 post, CES alone: 52.31 pre to 30.06 post, or both relaxation therapy and CES together: 53.69 pre to 30.44 post. The control group only dropped from 53.25 to 51.94.
RCT- Randomized Controlled Study, IB – Investigator Blind, DB – Double Blind, OL – Open Label, IRBA- IRB approved study, SB – Single Blind				

N = 841 for Anxiety RCT Studies

Table 15.1 Alpha-Stim CES Open Label, Survey and Retrospective Anxiety Studies

Principal Investigator	Total N	Subjects	Study Type	Measurement Scales/Outcomes
Mellen, 2016	10	Domestic Violence	OL	Brief Symptom Inventory (BSI), Behavioral Rating Inventory of Executive Function (BRIEF-A): All three BSI global scales and 2 of 3 scales in the BRIEF-A found significant reductions in anxiety levels for the 10 sheltered residents. The 9 clinical measures of the BSI did not achieve statistical significance; however, the trend lines indicated positive changes in all nine of the clinical variables suggesting movement toward more normalized functioning in each category.
Gong, 2016	74	Functional Constipation Secondary to Mental Illness	OL	Self-Rating Anxiety Score (SAS): After treatment, the participants in the experiment group had significantly lower scores of SAS, SDS, and Wexner constipation score than the control group (all $P < 0.05$). The number of successful expulsion in the experiment group was larger than the control group ($P = 0.016$).
Libretto, S 2015	567	Active Duty Service Members with PTSD	Retrospective IRBA	Beck Anxiety Inventory. This retrospective case series evaluated the efficacy of the Fort Hood Combat Stress Reset program. Anxiety was measured using the BAI at day 1 and at 3 weeks. From 2008 to 2013 the average initial score went from 27.0 to 20.9 (-6.3 , $p < 0.0001$).
Price, LR, 2014	146	Service Members and Veterans with PTSD	Survey	7 point Likert scale. Of the total group, 63.7% reported fewer PTSD symptoms and clinical improvement of $\geq 50\%$ (improvement of substantial clinical importance category), while 26.0% reported clinical improvement of PTSD symptoms between 25-49% (improvement of moderate clinical importance). In the total group, 89.7% of respondents reported $\geq 25\%$ fewer PTSD symptoms and clinical improvement with the majority of these respondents reporting $\geq 50\%$ improvement in PTSD.
Price LR, 2013	714	Civilians, Service Members and Veterans with Anxiety	Survey	7 point Likert scale. Of the total group, 59.5% reported less anxiety and clinical improvement of $\geq 50\%$ (improvement of substantial clinical importance), while 23.4% reported clinical improvement of anxiety between 25-49% (improvement of moderate clinical importance). In the total group, 82.9% of respondents reported $\geq 25\%$ less anxiety and clinical improvement with the majority of these respondents reporting $\geq 50\%$ improvement.
Lu, X-y, et al., 2005	32	Children with Emotional Disorders (Anxiety)	OL	Zung Anxiety Scale (SAS); From baseline of 58.30 ± 11.50 to post test 45.91 ± 10.36 ($p > 0.01$). 13 cases had significant effect (41%), 17 cases had effect (53%), and the effect was invalid in 2 cases (6%); the total effective rate was 94%. Skin temperature rose ($P < 0.01$); systolic blood pressure dropped and the pulse slowed down after the treatment, and the differences were significant ($P < 0.05$). 26 cases followed up (81%), of which 24 cases had long lasting efficacy with relieved or eliminated symptoms, and 2 cases had relapse of symptom where drugs were needed to control their symptoms.
Kirsch D, et al., 2014	202	Service Members and Veterans with Anxiety (includes PTSD)	Survey	7 point Likert scale: Anxiety (N=114). Of the total group, 46.5% reported less anxiety and clinical improvement of $\geq 50\%$ while 20.2% reported clinical improvement of anxiety between 25-49%. In the total group, 66.7% respondents reported $\geq 25\%$ improvement in anxiety. In the CES only group (no medications), 57.7% reported decreased anxiety and clinical improvement of $\geq 50\%$ while 15.4% reported clinical improvement of anxiety between 25-49% for a total of 73.1% of respondents who reported less anxiety and clinical improvement $\geq 25\%$. In the CES and medications group, 43.2% of respondents reported decreased anxiety and clinical improvement $\geq 50\%$ while 21.6% reported decreased anxiety 25-49% improvement for a total of 64.8% of respondents who reported decreased anxiety and clinical improvement $\geq 25\%$. PTSD (N=88). Of the total group, 38.6% reported less anxiety and clinical improvement of $\geq 50\%$ while 23.9% reported clinical improvement of anxiety between 25-49%. In the total group, 62.5% respondents reported $\geq 25\%$ improvement in anxiety. In the CES only group (no medications), 50.0% reported decreased anxiety and clinical improvement of $\geq 50\%$ while 22.2% reported clinical improvement of

				anxiety between 25-49% for a total of 72.2% of respondents who reported less anxiety and clinical improvement $\geq 25\%$. In the CES and medications group, 35.7% of respondents reported decreased anxiety and clinical improvement $\geq 50\%$ while 24.3% reported decreased anxiety 25-49% improvement for a total of 60.0% of respondents who reported decreased anxiety and clinical improvement $\geq 25\%$.
Overcash, 1999	197	Anxiety Patients	OL Retro-spective Analysis	Numerical Rating Scale (NRS) for Anxiety: Subjects had significantly lower scores on the 0-10 numerical rating scale for anxiety ($p < .05$), significantly lower EMG scores ($p < .05$), significantly lower EDR scores ($p < .05$) and significantly higher finger temperature scores ($p < .05$) at post-test from baseline, with all factors indicating and cross confirming less anxiety. ⁷
OL – Open Label, PTSD – Post Traumatic Stress Syndrome, PSS-I PTSD Symptom Scale Interview, IRBA – IRB approved				

N = 1942 for Anxiety Open Label and Survey Studies

TOTAL N = 2783 for all CES Anxiety Studies

Table 16. Alpha-Stim CES Depression Studies

Principal Investigator	Total N	Subjects	Study Type	Measurement Scales/Outcomes
Gong, 2016	74	Functional Constipation Secondary to Mental Illness	OL	Self-Rating Depression Score (SDS): After treatment, the participants in the experiment group had significantly lower scores of SAS, SDS, and Wexner constipation score than the control group (all $P < 0.05$). The number of successful expulsion in the experiment group was larger than the control group ($P = 0.016$).
Libretto, S 2015	562	Active Duty Service Members with PTSD	Retro-spective IRBA	Beck Depression Inventory. This retrospective case series evaluated the efficacy of the Fort Hood Combat Stress Reset program. Anxiety was measured using the BDI at day 1 and at 3 weeks. From 2008 to 2013 the average initial score went from 30.3 to 21.5 (-9.0 , $p < 0.0001$).
Barclay H, et al., 2014	115	Anxiety Patients	RCT, DB, IRBA	Hamilton Depression Rating Scale17 (HAM-D17): In the active treatment group, 82% had a decrease of $\geq 50\%$ in scores from baseline to endpoint on the HAM-D17 ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.78$) on the HAM-D17 from baseline to endpoint of study. The mean decrease on the HAM-D17 in the treatment group of 32.9% (9.64 to 6.47) was more than twelve (12) times the mean decrease on the HAM-D17 for the sham group of 2.6% (10.22 to 9.96) from baseline to endpoint of study.
Amr, 2013	7	Bipolar Depression Patients	OL	Clinical Global Impression: Patients reported 24.8% decrease ($p < 0.001$) on the CGI and a 34% decrease ($p = 0.122$) on the Montgomery Asberg Depression Rating Scale (MADRS).
Price LR, 2013	466	Civilians, Service Members and Veterans with depression	Survey	7 point Likert scale. Of the total group, 59.7% reported less depression and clinical improvement of $\geq 50\%$ (improvement of substantial clinical importance category), while 20.0% reported clinical improvement of depression between 25-49% (improvement of moderate clinical importance). In the total group, 79.7% of respondents reported $\geq 25\%$ less depression and clinical improvement with the majority of these respondents reporting $\geq 50\%$ improvement in depression.
Kirsch D, et al., 2014	89	Service Members and Veterans with Depression	Survey	7 point Likert scale: 36% of the total group reported decreased depression and clinical improvement of $\geq 50\%$ while 18% reported clinical improvement of depression between 25-49%. 54.0% of the total group reported $\geq 25\%$ improvement in depression. In the CES only group (no medications), 38.5% reported decreased depression and clinical improvement of $\geq 50\%$ while 23.1% reported clinical improvement of depression between 25-49% for a total of 61.6% of respondents who reported decreased depression and clinical improvement $\geq 25\%$. In the CES and medications group, 35.5% of respondents reported decreased depression and clinical improvement $\geq 50\%$ while 17.1% reported decreased depression between 25-49%

				improvement for a total of 52.6% of respondents who reported decreased depression and clinical improvement $\geq 25\%$.
Mellen, 2009	21	Sheriff Officers	RCT, DB, IRBA	Beck Depression Inventory: The active CES group had significantly lower depression scores on the BDI ($p < 0.05$) and the Brief Symptom Inventory (BSI-D) ($p < 0.01$) than the sham group.
Bystritsky, 2008	12	GAD Patients	OL	Hamilton Anxiety Scale (HAM-A): subjects had significantly lower scores from baseline to endpoint of study on the anxiety outcome measures, HAM-A ($p = 0.01$, $d = -1.52$) and FDADS-A ($p = 0.39$, $d = -0.75$), and on the outcome depression measure, HAM-D17 ($p = 0.01$, $d = -0.41$).
Chen Y, et al., 2007	60	Children with Mixed Anxiety Depressive Disorder (MAD)	RCT, IB	Zung Depression Scale (SDS): The ANOVA showed that on SDS, the main effect between CES group and sham comparator group was significant ($F = 36.56$, $P < 0.01$).
Lu, X-y, et al., 2005	32	Children with Emotional Disorders (Depression)	OL	Zung Depression Scale (SDS): From baseline of 0.64 ± 0.08 to post test 0.52 ± 0.10 ($p > 0.01$). 13 cases had significant effect (41%), 17 cases had effect (53%), and the effect was invalid in 2 cases (6%); the total effective rate was 94%. Skin temperature rose ($P < 0.01$); systolic blood pressure dropped and the pulse slowed down after the treatment, and the differences were significant ($P < 0.05$). 26 cases followed up (81%), of which 24 cases had long lasting efficacy with relieved or eliminated symptoms, and 2 cases had relapse of symptom where drugs were needed to control their symptoms.
Lichtbroun, 2001	23	Fibromyalgia Patients	OL, IRBA	Numerical Rating Scale: Subjects reported a significant improvement in quality of sleep during the open label portion of the study ($p < 0.001$).
RCT – Randomized Controlled Trial, DB – Double Blind, IB – Investigator Blind, OL – Open Label, IRBA – IRB approved study				

TOTAL N = 1461 for all CES Depression Studies

Table 17. Alpha-Stim CES Insomnia Studies

Principal Investigator	Total N	Subjects	Study Type	Measurement Scales/Outcomes
Price LR, 2013	230	Civilians, Service Members and Veterans with insomnia	Survey	7 point Likert scale. Of the total group, 57.5% reported less insomnia and clinical improvement of $\geq 50\%$ (improvement of substantial clinical importance category), while 20.4% reported clinical improvement of insomnia between 25-49% (improvement of moderate clinical importance). In the total group, 77.6% of respondents reported $\geq 25\%$ less insomnia and clinical improvement with the majority of these respondents reporting $\geq 50\%$ improvement in insomnia.
Taylor A, et al., 2013	46	Fibromyalgia Patients	RCT, DB, IRBA	General Sleep Disturbance Scale (GSDS): CES group had significantly lower scores on GSDS (indicating less sleep disturbance) than sham from baseline to the end point of study ($p = 0.001$, $d = -0.30$) and completed the study with scores below the range of insomnia.
Kirsch D, et al., 2014	98	Service Members and Veterans with Insomnia	Survey	7 point Likert scale: Of the total group, 44.8% reported less insomnia and clinical improvement of $\geq 50\%$ while 20.4% reported clinical improvement of insomnia between 25-49%. In the total group, 65.2% of respondents reported $\geq 25\%$ improvement in insomnia. In the CES only group (no medications), 62% reported decreased insomnia and clinical improvement of $\geq 50\%$ while 23.8% reported clinical improvement of insomnia between 25-49% for a total of 85.8% of respondents who reported less insomnia and clinical improvement $\geq 25\%$. In the CES and medications group, 40.3% of respondents reported decreased insomnia and clinical improvement $\geq 50\%$ while 19.5% reported decreased insomnia of 25-49% improvement for a total of 59.8% of respondents who reported decreased insomnia and clinical improvement $\geq 25\%$.

Lande R, Gragnani C, 2013	57	Active Duty Service Members with Insomnia	RCT, DB, IRBA	Pittsburg Insomnia Rating Scale: The active CES group had a longer total time slept (43 minutes) from baseline than the sham CES group who average 19 minutes less total time slept. The difference between the active CES and Sham CES groups approached significance ($p = 0.079$). A gender difference was noted. Men who completed 5 sessions of CES had significant improvement in total time slept after the first CES treatment ($p = 0.04$, $d=0.41$) and on day 4 ($p = 0.03$, $d=0.49$). Men in the active CES group slept an average of 53 minutes more total time slept after the first CES treatment and an average 61 minutes more total time slept on day 4 compared to the sham CES group. There were no significant changes in total time slept among the females in this 5 day study.
Lichtbroun, 2001	23	Fibromyalgia Patients	OL, IRBA	Numerical Rating Scale: Subjects reported a significant improvement in quality of sleep during the open label portion of the study ($p<0.001$).
RCT – Randomized Controlled Study, DB – Double Blind, OL – Open Label, IRBA – IRB approved study				

TOTAL N = 454 for all CES Insomnia Studies

Table 18. Alpha-Stim® CES RCT Pain Studies

Principal Investigator	Total N	Subjects	Study Type	Measurement Scales/Outcomes
Lee, S. et.al. 2013	50	Females Undergoing Thyroid Surgery	RCT, DB, IRBA	VAS- The pain score was significantly lower at 1 and 4 hours ($P<0.05$) post-surgery in the CES group compared to the control group.
Taylor, A. et.al. 2013	46	Fibromyalgia Patients	RCT, DB, IRBA	0-10 NRS: Those individuals using the active CES device had a significant decrease in average pain ($p=0.023$) when compared to those individuals using the sham device or those receiving usual care alone over time.
Taylor, A. et al. 2013	6	Fibromyalgia Patients	RCT, DB, IRBA	Those individuals using the active device had a greater decrease in average pain ($P = .023$) than individuals using the sham device or receiving usual care alone over time. Preliminary analyses of the functional magnetic resonance imaging data on a subset of six participants from each of the two device groups show that individuals using an active CES device had a decrease in activation in the pain processing regions of the brain compared to those using a sham device.
Tan, G. et.al., 2011	39	Military, Spinal Cord Injury	RCT, IRBA	0-10 NRS: Pain Intensity: There was also significant changes on BPI intensity ($p<0.001$), BPI interference ($p<0.001$), SF-36 pain ($p<0.001$), PQAS paroxysmal pain ($p<0.001$), PQAS deep pain ($p<0.01$), and maladaptive coping ($p<0.001$). In the long term open label phase subjects reported significant linear decrease in pain at 3 months ($p<0.01$, $d=0.48$) and 6 months ($p<0.001$, $d=1.31$).
Rintala, D. et.al. 2010	13	Veterans, Parkinson's Disease	RCT, DB, IRBA	0-10 NRS: Subjects 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 ($p = .028$).
Tan, G et al. 2006	38	Military, Spinal Cord Injury	RCT, DB, IRBA	The active CES group reported significantly decreased daily pain intensity ($p = 0.03$) compared with the sham CES group. The active CES group also showed significantly decreased pain interference ($p = 0.004$). The treatment effect size was medium to large (Cohen $d = 0.76$).
Cork, R. et.al. 2004	74	Fibromyalgia patients	RCT, DB, IRBA	NRS and Tender Point: The active CES treatment group showed significantly decreased pain, tender points and anxiety compared to the sham group. This trend continued to the open label phase but also included functionality.
Sizer, P. et al.	41	Patients with	RCT, DB,	The subjects' pain levels (dependent variable), which decreased

2000		ACL reconstruction	IRBA	over time, were lower for all 10 post-operative days in the Microcurrent Group (n=25) compared to the Placebo Group (n=16). A statistically lower (p=0.004) degree of post-operative pain was experienced by the subjects receiving microcurrent.
Lichtbroun, A. et al. 1999	60	Fibromyalgia Patients	RCT, DB, IRBA	NRS- The active CES group had significant findings on 8 of the 11 variables compared to the sham group: significantly lower anxiety scores (p=0.04, d = -.60), higher quality of sleep scores (p = 0.02, d = .45), lower pain scores (p = .004, d = .65), higher feelings of well-being scores (p = .007, d = .73), higher quality of life scores (p = .000, d = .97), lower fatigue scores (p = 0.03, d = -.72 and lower anger scores (p = 0.04, d = .60) compared to sham group.
Heffernan, M. 1997	30	DJD patients	RCT, DB	Pain and EEG changes: Post stimulation spectral smoothing and pain control was found to be superior with the Alpha-Stim® (P<.01). Alpha-Stim also produced significant pain control with a five minute test dose 4.5 to 2.1, (P<.01) versus 4.3 to 4.5 (P>.01) with the Liss Stimulator and 4.6 to 4.8 (P<.01) with the control device.
Roth, P. et al. 1986	45	Patients who required orthodontic separators	RCT, DB IRBA	VAS- there were no statistically significant differences in the sham treated and placebo control patients at any rating period, showing that only the actual treatment was significantly effective in eliminating peridontal pain in these patients, and there was no placebo effect from the treatment condition.
Legend: RCT – Randomized Control Trial, DB – Double-Blind, OL – Open Label, NRS – Numerical Rating Scale, BPI – Brief Pain Inventory, SF-MPQ - McGill , Pain Questionnaire, IRBA – IRB approved study				

N = 442 for Pain RCT Studies

Table 18.1 Alpha-Stim® CES Open Label, Survey and Case Studies

Principal Investigator	Total N	Subjects	Study Type	Outcome Measure/Findings
Keizer, B. et al. 2016	1	Patient with CRPS	Case Study	The primary measurements were change in baseline pain and functionality. At the 3 month follow up the patient reported significant pain and was able to return to work full time. He was able to avoid the ketamine infusion treatment and surgery to implant a spinal stimulator.
Libretto, S 2015	537	Active Duty Service Members with PTSD	Retro-spective IRBA	Oswerty Pain Scale. This retrospective case series evaluated the efficacy of the Fort Hood Combat Stress Reset program. Anxiety was measured using the BDI at day 1 and at 3 weeks. From 2008 to 2013 the average initial score went from 34.3 to 32.1 (-2.4, p<0.0001).
Kirsch, D. et al. 2011	143	Pain Patients, Service Members and Veterans	Survey	7 point Likert scale: Pain (N=73). Thirty percent (30%) of the total group reported decreased pain and clinical improvement of ≥ 50% while 15.1% reported clinical improvement between 25-49%. A total of 45.1% of total group participants using CES reported ≥ 25% clinical improvement. In the CES only group (no medications), 61.6 % of respondents reported decreased pain and clinical improvement ≥ 25% (46.2% ≥ 50%, 15.4% between 25-49% improvement) while 41.7% of the CES and medications group reported decrease pain and clinical improvement ≥ 25% (26.74% ≥ 50%, 15 % between 25-49% improvement. Headache (N=70). Forty percent (40%) of the total group reported decreased pain and clinical improvement of ≥ 50% while 18.6% reported clinical improvement between 25-49%. Of the total group, 58.6% of participants reported ≥ 25% clinical improvement. In the CES only group (no medications), 100 % of respondents reported decreased pain and clinical improvement ≥ 25% (64.7% ≥ 50%, 35.3% between 25-49% improvement) while 45.3% of the CES and medications group reported decrease pain and clinical improvement ≥ 25% (32.1% ≥ 50% pain relief and 13.2 % reported between 25-49% improvement.
Holubec, J.	525	Chronic Pain	OL	One to five 20-minute CES treatment sessions produced a

2009		Patients		reduction in pain ranging from 42% to 71% in the approximately 80% of patients who responded.
Lee, T. et al. 2004	20	Chronic Refractory Pain	OL	VAS- Although 3 patients out of 20 obtained no relief from this treatment, 6 obtained complete relief, and an additional 8 patients received significant relief of 33% – 94%. When treatment response by the length of time they had the pain was evaluated it was found that patients who had been in pain for 2 months and 4 months improved 94% and 100%.
Kulkarni, A. et al. 2001	20	Refractory Pain Patients	OL	Nine patients (45%) left the study early following reduction of their pain to a level between 0 and 1.5 on the 11 point scale. One had complete remission of her pain after only 2 treatments. Of 3 patients who received no relief, none returned for the final week of treatment. 7 patients (35%) who were treated with CES plus self-adhesive electrodes began at an average pain level of 7.7 (range 5-10) and ended with an average of 3.7 (range 0-10), or a 52% reduction in pain from an average of 12 days of treatment. 7 patients who were treated with CES plus probes fared even better beginning with a pain level of 7.1 (range 4-8) and ending at an average of 1.1 (range 1-6), or an 85% reduction of pain from an average of 8.1 days of treatment. 5 patients (25%) were treated with CES only. They experienced an average of 50% drop in their pain level from 4.4 (range 3-7) to 2.2 (range 0.5-5) with an average of 10.6 days of treatment.
Alpher, E. et al., 1998	1	Patient with CRPS	Case Study	Patient estimated the treatment provided moderate improvement (50-74%) relief from pain, anxiety, depression, headaches and muscles tension while providing marked improvement (75-99%) in insomnia.
Zimmerman, S. et al, 1987	45	Patients with Low Back Spasms	OL	Practitioners measured daily pain levels, trunk mobility and subjective units of disturbance. The study included 3 groups: Alpha-Stim, biofeedback and Alpha-Stim with biofeedback. All Groups improved significantly in their trunk mobility. Daily pain cards also improved across all groups, however, it was evident by the conclusion of the study that Groups I and III who received electrical stimulation noted a greater reduction in perceived pain than the biofeedback subjects in Group II.
Bauer, W. 1983	3	Head and Neck Cancer pain	Case Series	Patients reported improvement in pain as well as how long the results lasted. Patient 1- received 3 daily, 10 minute treatments and was completely pain free for one week. Patient 2- received 6 minutes of treatment and was pain free for 50 hours. Patient 3- received 8 hours of relief after first treatment and 24 hours after the second.
Legend: OL – Open Label, NRS – Numerical Rating Scale, IRBA – IRB approved study, VAS – Visual Analogue Scale				

N = 1295 for Open Label and Survey Studies

TOTAL N = 1737 for all CES Pain Studies

APPENDIX C: RESEARCH POLICY

Electromedical Products International, Inc. makes every attempt to encourage research with its Alpha-Stim technology. While we do not fund research, we have developed several important ways in which we can support research in which our devices are used. They are as follows:

1. We can assist researchers by making available to them a bibliography of past and ongoing studies, both published and unpublished. This can comprise the review of the literature prior to a study, and will provide researchers with knowledge of prior subjects studied and how they fared.
2. We are in daily contact with clinicians around the world and can share research ideas that might answer the most frequently asked clinical questions that have not been researched, and the most interesting clinical observations that might be proven through research.
3. We are knowledgeable regarding the needs and requirements of Alpha-Stim studies. We can assist in preparing your study design, especially the materials and methods section.
4. We can arrange to have a statistician complete your study's statistical analysis for you at our cost, if you wish.
5. Upon receipt of an approved protocol we can lend you a reasonable number of Alpha-Stim devices set up as necessary including double-blinded (with the key provided in a sealed envelope) at no cost to you. We will also provide all the accessories, even batteries, you require to complete your study.

Alpha-Stim therapy is dosage-dependent, so the higher the current the quicker the treatment. For double-blinding, we set up the devices at only 100 μ A which has proven subsensory in many studies completed to date. To compensate for the low current, the time must be increased to one full hour. Half the devices will be modified so as not to conduct any current at all. Since the active treatments are subsensory, this method allows for double-blinding as good as a pharma study using a placebo pill. Research has also shown that there is no reliable "washout" period. In some cases, continued improvement is seen as much as two years after a series of treatments. Accordingly, only one way crossovers are possible, from the sham treated group to an active treatment. This can be done maintaining the original subsensory criteria of 100 μ A which would increase the N and allow for half the subjects to serve as their own controls. Alternatively, this optional second arm can use the original sham group in an open clinical trial where the current is raised to a comfortable level in the same way as it would be done in actual practice. This usually achieves better results while still allowing for the original sham subjects to serve as their own controls. We need a few weeks notice to build sham devices. Then we can either mark half with a dot and note which are which in the sealed study key, or we will simply mix them up and the only differentiation would be the serial number on the back of each device.

APPENDIX D: EXPERT SCIENTIFIC REVIEW (See Attached)

1. An independent review of the clinical effectiveness of the Alpha-Stim Microcurrent and Cranial Electrotherapy Stimulator by Forest Tennant, MD, FACPM, MPH, DPH.
2. Review of existing CERS on Alpha-Stim by Dr. Richard Morris, National Health Service, UK.
3. Independent CME review article comparing Alpha-Stim CES, Fisher Wallace CES, and Thync.