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ALPHA-STIM® RESEARCH ABSTRACTS

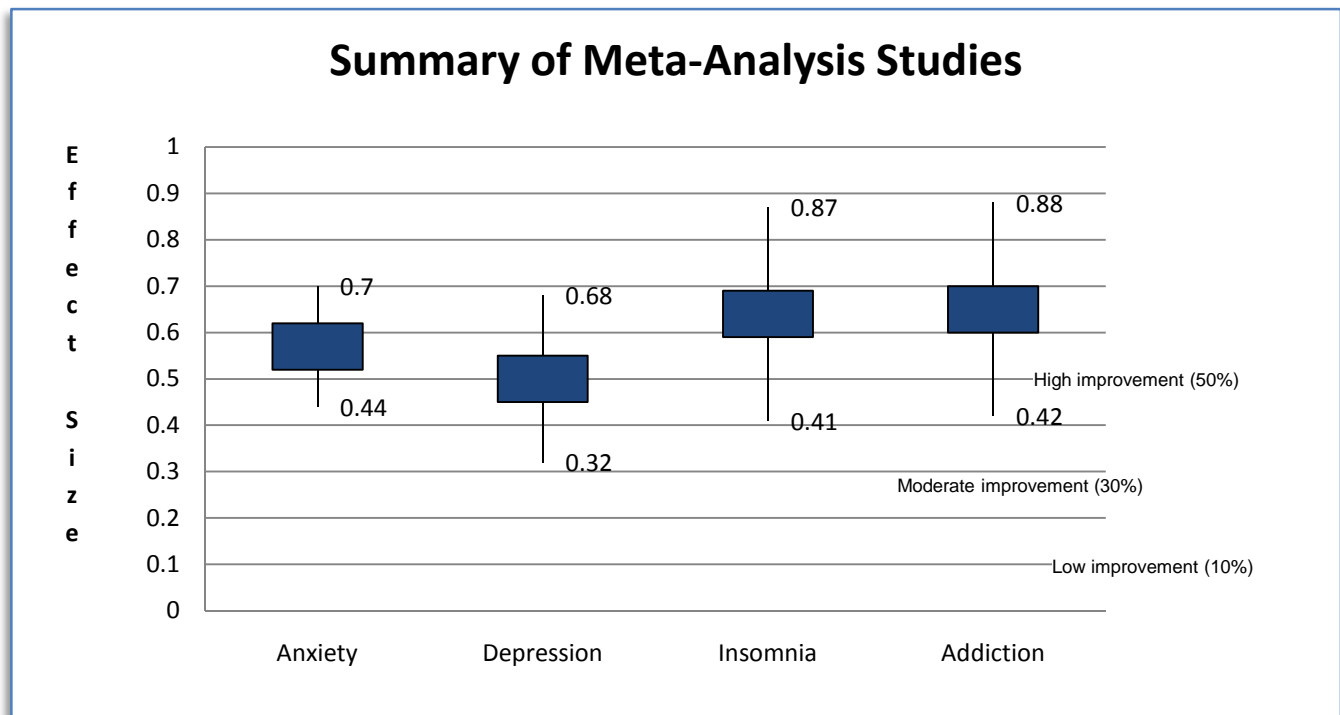
Alpha-Stim 100, Alpha-Stim SCS, and Alpha-Stim PPM microcurrent electrical therapy (MET) and cranial electrotherapy stimulation (CES) technology are FDA approved and regulated medical devices for the treatment of Anxiety, Depression, Insomnia and Pain.

The complete Annotated Abstracts and their associated research articles, as well as other information available at:

<http://www.alleviahealth.com/asresearch.htm>

Annotated Abstracts of Meta-Analysis Studies:

Due to varying methodologies and measures, the myriad of studies do not lend themselves to a simple consolidation of results. Therefore, a statistical method called “meta-analysis” is used to combine results from different studies of the same treatment in a meaningful way and allow an objective measure of the efficacy of CES. This meta-analysis calculates the percentage of patients improving versus the percentage not improving to obtain the treatment effect size r , which is equal to the % of patient improvement to be expected on a scale of 0 to 100. For example, an overall average effect size $r = 0.15$ means that there was an average of only 15% improvement among patients when measured across combined studies, while $r = 0.75$ means that there was an average of 75% improvement in patients found in the combined studies, etc. In this scale, an r effect size of 0.10 is small, while r of 0.30 is moderate, and r of 0.50 or above is considered to be high. All obtained data were converted to Z_r scores for the purpose of combining the effects from the various studies.



Meta-Analysis of CES Anxiety Studies

Kirsch D. L. & M. F. Gilula (2007). CES in the treatment of anxiety disorders - Part 2. Statistical considerations in the meta-analysis of cranial electrotherapy stimulation (CES) treatment of anxiety disorders. *Practical Pain Management*, April 22-39.

A total of 38 studies satisfied the criteria for inclusion in this meta-analysis; a subset of 17 studies utilized a double-blind design.

A meta-analysis of all 38 studies with only one data point (comparison) per study, using the average of the data points reported per study, resulted in an effect size $r = 0.57$ (99% confidence intervals: 0.44-0.70). A separate assessment of the 17 double-blind studies yielded an identical $r = 0.57$, but gave a narrower range of expected values (99% confidence intervals; 0.49-0.65).

The analysis showed that the overall effect of CES for anxiety disorders is large. There is also a notable effect that duration of use enhances such outcomes. The range of the confidence intervals suggests that 99 times out of 100, the effect size in future meta-analyses of anxiety studies would be expected to indicate a 40 % to 70 % improvement. That range is considered to represent a moderate to very strong clinical improvement.

Meta-Analysis of CES Addiction Studies

Kirsch D. L. & M. F. Gilula (2007). CES in the treatment of addictions: a review and meta-analysis. *Practical Pain Management*, November/December 73-79.

A total of 15 studies satisfied the criteria for inclusion in this meta-analysis; a subset of 10 studies utilized a double-blind design.

A meta-analysis of all 15 studies with only one data point (comparison) per study, using the average of the data points reported per study, resulted in an effect size $r = 0.65$ (99% confidence intervals: 0.42-0.88), pointing to a moderate to very strong clinical effect. The range of the confidence intervals further predicts that 99 times out of 100, the effect size in future meta-analyses of addiction studies would be expected to indicate a 42 % to 88 % improvement, across a wide range of measured outcomes such as depression, anxiety, anger, fatigue, mental confusion, or P300 speed as an evoked potential in the EEG.

The studies reviewed here also suggest that within as little as three weeks of daily treatment, CES can go a long way towards reestablishing normal short term memory after the typical memory loss suffered by substance abusers. In contrast, it usually takes at least two years of total sobriety to show signs of significant recovery without CES intervention.

Meta-Analysis of CES Depression Studies

Kirsch D. L. & M. F. Gilula (2007). CES in the treatment of depression, part 2. *Practical Pain Management*, June 32-40.

A total of 20 studies involving 937 subjects satisfied the criteria for inclusion in this meta-analysis; a subset of 8 studies utilized a double-blind design.

A meta-analysis of all 20 studies with only one data point (comparison) per study, using the average of the data points reported per study, resulted in an effect size $r = 0.50$ (99% confidence intervals: 0.32-0.68). The range of the confidence intervals further predicts that 99 times out of 100, the effect size in future meta-analyses of depression studies would be expected to indicate a 32 % to 68 % improvement.

In this review and meta-analysis, a moderate to strong effect size of CES is revealed, which exceeds the results seen in antidepressant drug studies submitted to the FDA for marketing approval. Additionally, CES has no adverse metabolic interactions with the various hepatic isoenzymes responsible for metabolizing SSRIs, other antidepressants, and various other commonly prescribed medications.

Meta-Analysis of CES Insomnia Studies

Kirsch D. L. & M. F. Gilula (2007). CES in the treatment of insomnia: a review and meta-analysis. *Practical Pain Management*, October 28-39.

A total of 20 studies satisfied the criteria for inclusion in this meta-analysis; a subset of 7 studies utilized a double-blind design.

A meta-analysis of all 20 studies resulted in an effect size $r = 0.64$ (99% confidence intervals: 0.41-0.87), which is considered high. The range of the confidence intervals further predicts that 99 times out of 100, the effect size in future meta-analyses of insomnia studies would be expected to indicate a 41 % to 87 % improvement.

WHAT IS CRANIAL ELECTROTHERAPY STIMULATION (CES)?

Cranial Electrotherapy Stimulation (CES) is a form of electromedicine. In 1966 and 1969, two international conferences were held in which Soviet block scientists shared with the rest of the world their research on CES and the related technology of electroanesthesia. These two conferences stimulated Western research interest in CES, and researchers in the United States, Europe and India started investigating CES. Research has found CES safe and effective for multiple therapeutic uses. Despite the positive findings of Western researchers, CES is just beginning to find fertile ground among Western clinicians. The approval of Alpha-Stim® SCS by the FDA in 1992 has provided official recognition of sufficient good science to apply CES as a safe and effective therapy for depression, anxiety, insomnia and pain. Even though CES has the advantage of providing treatment without the risk of serious side effects that accompany many pharmacotherapies, it remains largely unknown to most western physicians, psychiatrists and psychologists.

Cranial electrical stimulation (CES) is the deliberate application of low-level current, usually less than one milliampere to the head for a therapeutic purpose. The Alpha-Stim® Cranial Electrotherapy Stimulation (CES) uses a proprietary wave form of less than 600 Microamperes. This level of current used is significantly less than with the other two applications of current to the entire head, electroanesthesia and electroconvulsive therapy.

The United States Food and Drug Administration (FDA) has approved Alpha-Stim® CES for the treatment of insomnia, anxiety and depression (Code of Federal Regulations, title 21, vol. 8, section 882.5800). The FDA regulates the sale of CES equipment in the United States as a medical device and established the official name for all medical devices that put a low level current across the head as "cranial electrotherapy stimulation" (National Research Council, Division of Medical Science, 1974). The FDA requires a prescription by a licensed mental health or health care professional to legally obtain and use CES device in the U.S. In all other countries CES is an over-the-counter medical device that does not require a prescription. When used to treat pain, a CES device is considered by the FDA to be a transcutaneous electrical nerve stimulator (TENS) and is regulated in this category of medical device (Code of Federal Regulations, title 21, vol. 8, section 882.5890).

Acceptance of a therapy in modern western medicine is often based not just on objective evidence for its efficacy, but also on an explanation that explains the mechanism of action within already accepted medical knowledge and principles. The application of electrical currents to a site on the body which was in pain was a practice known to and used by ancient Egyptian and Greek physicians, but was not accepted in modern medical practice until the development of the gate control theory of pain. The history of the TENS unit is provided as an example of the long gap that can occur between the development of a therapeutic use for electric currents and its acceptance into orthodox medical practice. As far back as 1850, electric current was used to effectively treat pain, but until the gate control theory provided an explanation for why electricity could be used to reduce pain it was not accepted in mainstream Western medicine. The same sort of lag has occurred with Cranial Electrotherapy Stimulation (CES). The technology is not new, but despite many positive studies and FDA approval, it is relatively unknown. The reason CES has not been embraced by the medical community despite clear evidence of its efficacy may be the lack of a model for how it works.

There is currently no body of research that identifies the complete mechanism underlying CES. However, there is research that suggests some of the possible mechanisms involved. The literature on the neurochemical changes involved in CES reveals a picture of significant increases in neurotransmitters and hormones known to be involved in the regulation of sleep, pain, affect and stress responses. It has been reported that the application of low-level currents can speed healing in tissue by turning on the genetic machinery for cellular repair (Zhao, et al. 2006).

There are also indications that CES may have a normalizing effect on EEG. The use of CES has been found to normalize the EEG of pain patients. Human and animal research is clear that CES makes significant changes in the electrical and chemical activity of the brain and can lead to the cautious conclusion that CES has the basic effect of regulating and normalizing the neurochemical and neuroelectrical activity of the brain. Findings show that a single 20-minute session of CES has a significant effect on the cortical and subcortical activity of the human brain resulting in activity consistent with decreased anxiety and increased relaxation. Even a single session of CES can be expected to provide increased alpha relative power with concomitant decreased delta and beta relative power.

WHAT IS Microcurrent Electrical Therapy

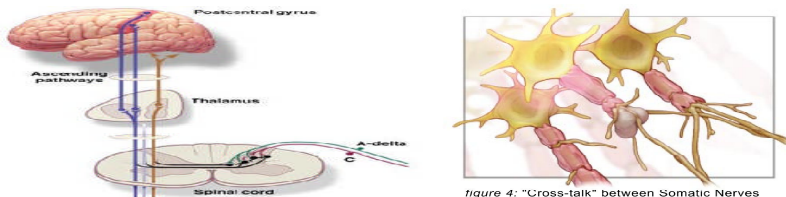
Microcurrent Electrical Therapy (MET) is a form of electromedicine. In 1995, Joseph M. Mercola and Daniel L. Kirsch coined the term "microcurrent electrical therapy" (MET) to define a new form of electromedical intervention. A growing body of research shows the effectiveness of MET to do more than control pain. MET can actually accelerate and even induce healing and can increase the amount of growth factor receptors, which increases collagen formation (Falanga et al. 1987). The first human study using direct current for wound healing was published by Assimacopoulos (1968). Wolcott et al. (1969) published frequently cited work using direct currents of 200 to 1000 μ A to treat 67 patients. The study was repeated on 76 additional patients with 106 ischemic skin ulcers by Gault and Gates (1976). Rowley et al. (1974) showed that electrically stimulated ulcers had a fourfold acceleration in healing response compared to controls. Weiss et al. (1990) found that no significant adverse effects resulting from electrotherapy on wounds have been documented. Microcurrent electrical stimulation has also been used as an effective treatment for non-tumor bone fracture for several years (Brighten 1981; Friedenber 1966; Friedenber 1981; Yasuda 1953). Becker (1985) found that repair of injury occurs in response to signals that come from the body's electrical control system. In the 1960s he demonstrated that electrical current is the trigger that stimulates healing, growth, and regeneration in all living organisms.

A mechanism for Microcurrent Electrical Therapy (MET) has been proposed by Chang et al. (1982) who found that microcurrent stimulation increased adenosine triphosphate (ATP) generation by almost 500%. Increasing the level of current to higher milliampere levels actually decreased the results. ATP provides the energy tissues require for building new proteins and increases protein synthesis and membrane transport of ions (Kirsch 2002). Microcurrent was also shown to enhance amino acid transport and protein synthesis in the treated area 30 to 40% above controls.

Trauma affects the electrical potential of cells in damaged tissues (Becker 1985). Initially the injured site has a much higher resistance to the body's normal electrical currents than the surrounding tissue, causing potentially healing bioelectricity to flow generally around the injury. The correct microcurrent application to an injured site augments the endogenous current flow. The resistance of the injured tissue is then reduced, allowing bioelectricity to enter the area to reestablish homeostasis.

When there is chronic pain the injury to peripheral neural axons can result in abnormal nerve regeneration following injury. The damaged axon may grow multiple nerve sprouts. These nerve sprouts, including those forming neuromas, can generate spontaneous activity, peaking in intensity several weeks after injury. Unlike normal axons, these structures are more sensitive to physical stimulation. After a period of time, atypical connections may develop between nerve sprouts in the region of the nerve damage, permitting "cross-talk" between efferent nerves and nociceptors.

Dorsal root (spinal) fibers may also sprout following injury to peripheral nerves. These factors can cause the perception of pain in the absence of the normal activation of the nociceptive system by noxious stimuli.



(Source: Pain Management: Pathophysiology of Pain and Pain Assessment, 2007)

The approval of Alpha-Stim® by the FDA in 1990 has provided official recognition of sufficient good science to apply MET as a safe and effective therapy for pain. (510k No. K896948). The FDA regulates the sale of Alpha-Stim® equipment in the United States as a medical device. The FDA requires a prescription by a licensed health care professional to legally obtain and use this device in the U.S. In all other countries, it is an over-the-counter medical device that does not require a prescription. When used to treat pain, the Alpha-Stim® device is considered by the FDA to be TENS (transcutaneous electrical nerve stimulator) and is regulated in this category of medical devices (Code of Federal Regulations, title 21, vol. 8, section 882.5890).

Even though MET has the advantage of providing treatment without the risk of serious side effects that accompany many pharmacotherapies, it remains largely unknown to most western practitioners. Acceptance of a therapy in modern western medicine is often based not just on objective evidence for its efficacy, but also on an explanation that explains the mechanism of action within already accepted medical knowledge and principles. The application of electrical currents to a site on the body which was in pain was a practice known to and used by ancient Egyptian and Greek physicians, but was not accepted in modern medical practice until the development of the gate control theory of pain (Melzack and Wall 1965). The history of the TENS unit is an example of the long gap that can occur between the development of a therapeutic use for electric currents and its acceptance into orthodox medical practice.

The potential of microcurrent therapy in health care has only recently attracted serious attention. Like many biological phenomena, knowledge of the very existence of small currents in the body had to wait on the development of technology sophisticated and sensitive enough to study them (Morareidge, 2006). MET does more than just block pain. Because MET uses such a small current, typically less than 600 microamps, there is no patient discomfort or even sensation during application. In a data collection study (Wallace, 1990) 94% of the 1531 patients experienced a reduction in pain during the first treatment and 88% were pain free within 10 treatments.

Prescribing Information for Alpha-Stim® Stimulators

Caution statement for United States: Federal Law (USA only) restricts these devices to sale by, or on the order of a licensed health care practitioner. Outside of the USA they are available world wide without a prescription but consultation with a qualified health care professional is recommended for difficult and unresponsive problems.

Indications: Rx must specify the prescribed Alpha-Stim model, i.e. "Alpha-Stim 100", "Alpha-Stim SCS" or "Alpha-Stim PPM" (no substitutions; see model comparison below). Healthcare practitioners should include their degree and license number on the order form.

Contraindications: The Alpha-Stim 100, Alpha-Stim PPM or Alpha-Stim SCS may affect the operation of cardiac pacemakers (particularly demand type pacemakers). Do not stimulate directly on the eyes, or over the carotid sinus (on the neck beside the larynx).

Precautions: For external use only. Do not allow children to use or handle these devices without adult supervision. Do not operate potentially dangerous machinery or vehicles during, and in some cases, for several hours after treatment with the Alpha-Stim 100 or Alpha-Stim SCS (CES). Caution is advised in cases where other forms of analgesia (pain control) would not be used; such as to retain the beneficial aspects of pain for diagnosis or in cases where people may overuse pain-controlled areas. Safety of stimulation has not been established during pregnancy. There have been isolated reports of blood pressure being lowered by CES so care should be taken while using the Alpha-Stim 100 or Alpha-Stim SCS with high blood pressure medication.

Adverse Effects (Alpha-Stim 100 and Alpha-Stim SCS): Adverse effects are usually mild and self-limiting. Adverse effects seen in approximately 4,541 patients in controlled, open, uncontrolled conditions, and by physician survey and reasonably associated with the use of CES are dizziness (6 cases, 0.13%), skin irritation/electrode burns (5 cases, 0.11%), and headaches (9 cases, 0.20%). Prolonged CES treatment at higher than necessary currents may cause dizziness or nausea that can last from hours to days. Treatment immediately prior to going to sleep may cause difficulty sleeping due to increased alertness. It is recommended that CES be used at least 3 hours before going to sleep. Paradoxical reactions such as hyperexcited states, increased anxiety, and sleep disturbances may occur, but are rare.

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