The Management of Anxiety, Insomnia and Depression with Cranial Electrotherapy Stimulation (CES): Theory and Practice

Jeff Marksberry, MD, FAIS
Science and Education Director

© Copyright 2013 EPI, Mineral Wells, Texas, USA ALL RIGHTS RESERVED

Cranial Electrotherapy Stimulation (CES)

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

The application of low level current of <1 milliampere applied across the head for treatment of anxiety (including PTSD), depression and insomnia with additional applications such as ADHD being studied.

2011 Military Service Member and Civilian Postmarketing Surveys: Alpha-Stim® CES Compared to WebMD Drug Surveys

<table>
<thead>
<tr>
<th>Condition</th>
<th>Service Member</th>
<th>Civilian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>85%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>65%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Depression</td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Percent of Patients Reporting Improvement
Traditional View of Synaptic Activity

But only 2% of neuronal communication occurs at the chemical synapse.


Models of Receptor Activation

19th & 20th Century
The Current Theory: Structural Matching; Chemical/Molecular Physical Communication

The 3D nature of the ligand matches the receptor. Physical proximity induces receptor conformational changes which triggers the cascade of events prompting cell function

21st Century
The New Proposed Theory: Physical/Atomic Electromagnetic Communication

Proximity favors co-resonance specific bioelectrical signals with frequencies that perfectly match the resonance of the receptor to amplify molecular conformational changes at all steps of the cascade including cell function, even from long distances (like tuning in a radio).


Alpha-Stim® Waveform On Oscilloscope

It is the waveform that differentiates devices.

Through periodic, but slow, reversal of the polarization of the DC current, the Alpha-Stim waveform is able to inject a spectrum of low frequencies into the neuronal tissue to match frequencies with different receptors, thus activating them in a way similar to chemical ligands.
Saul H. Rosenthal, MD, Psychiatrist and CES Researcher
Studied Medical Students at UT Austin Who Reported:
- Relaxed
- Alert
- Tranquil
- Not Worrying
- Bright and Happy
- Increased Energy
- Improved Sleep
- No Confusion, Memory Loss or Disorientation

Feelings Experienced During CES Treatment Stages
Dosage equals time inversely proportional to current level (i.e., less current requires longer treatment time per session)

Alert
Some patients feel light right away

Light Feeling
20 minutes to 1 or more hours

Sleepy
Heavy, Groggy, Euphoric (never stop here)

Putative Mechanism of CES
CES engages the serotonergic (5-HT) raphe nuclei of the brainstem. 5-HT inhibits brainstem cholinergic (ACh) and noradrenergic (NE) systems that project supratentorially. This suppresses thalamo-cortical activity, arousal, agitation, alters sensory processing and induces EEG alpha rhythm. 5-HT can also act directly to modulate pain sensation in the dorsal horn of the spinal cord, alter pain perception, cognition and emotionality within the limbic forebrain.

Legend:
- Blue arrows: inhibitory interactions
- Purple arrows: excitatory interactions
- Suppressed pathways/interactions
- ACh: acetylcholine
- LDT: laterodorsal tegmental nucleus of the brainstem
- PPN: pediculo-ponitne nucleus of the brainstem
- NE: norepinephrine
- LC: locus ceruleus
- 5-HT: serotonin

QEEG Changes in 30 Subjects Treated with 20 Minutes of CES

There is an increase in alpha activity with a simultaneous decrease in delta.

Blue = decrease  Red = increase

Presented at the International Society for Neuronal Regulation conference, September 18-21, 2003, Houston, Texas

Effects of Cranial Electrotherapy Stimulation on fMRI Brain Activity in the Resting State

Regional deactivation associated with 0.5 Hz (blue) and 100 Hz (yellow)

Regions positively associated with current intensity for 0.5 Hz


Effects of CES on Cerebrospinal Fluid and Plasma Neurochemicals

Beta-endorphins

98% in plasma
219% in CSF

Serotonin

15 - 40% in plasma
50 - 200% in CSF


Beta-endorphins

98% in plasma
219% in CSF

Serotonin

15 - 40% in plasma
50 - 200% in CSF

Safety Considerations

Primary Contraindications

- Interference with pre-1998 implants (e.g., pacemakers and defibrillators) – No longer applicable?
- Pregnancy – possible miscarriage and potential unsubstantiated legal arguments in case of developmental defects

Adverse Effects from CES

From 144 human studies encompassing 10,556 people where 8,792 received active CES:
- 9 headaches (0.10%, 1:977)
- 6 cases of skin irritation (0.07%, 1:1,465)

These are both mild and self-limiting.

If the current is set too high headaches, vertigo or nausea could develop and might endure for hours to days in people with a history of vertigo.

If the treatment is stopped too soon a heavy feeling accompanied by disorientation may persist for hours or even days.
Topics of Scientific Research on CES

Number of Pivotal Scientific Studies on Indicated Uses:

42 Anxiety
27 Insomnia
26 Depression

Research is done independently
Double blinding capabilities
Follow up studies show a durable effect

State (Situational) Anxiety

State anxiety can be effectively treated in a single CES treatment session.

This is demonstrated in medical and dental studies and in mechanistic studies of EEG and fMRI changes from a single CES treatment.

Results will vary based on initial anxiety level, length of treatment, comorbidities and overall patient health.

Trait (Chronic) Anxiety

May require up to 6 weeks of CES treatments to see significant reduction in trait anxiety levels.

Treatment outcome may also depend on comorbidities such as depression and insomnia.
Generalized Anxiety Disorder

- RCT with an N of 115 at Liberty University
- 83.7% of the active group reported at least 50% improvement
- P=0.001, Cohen’s d=0.93
- The mean decrease on the HAM-A in the active group (32.8%) was more than 3 times the mean decrease of the sham group.


Mean Anxiety Scores

![Graph showing mean anxiety scores from baseline to week 5 with a significant decrease at week 5 (P=0.001).](image)


PTSD in a 54 Year Old Male Veteran

Overall Decrease in Severity by 39% in One Month

<table>
<thead>
<tr>
<th>PTSD Symptom Scale – Interview (PSS-I)</th>
<th>PRE</th>
<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-experiencing (0-15)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Avoidance (0-21)</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Increased Arousal (0-15)</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

PTSD in a 38 Year Old Male Veteran
Overall Decrease in Severity by 43% in One Month

<table>
<thead>
<tr>
<th>PTSD Symptom Scale – Interview (PSS-I)</th>
<th>PRE</th>
<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-experiencing (0-15)</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Avoidance (0-21)</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Increased Arousal (0-15)</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>


CES Significantly Reduced the Symptom Burden of GAD with a Decrease in HARS Score (P=.01) Similar to that Found in Clinical Psychopharmacology Trials – APA 2009

Mean HARS Score


Situational Anxiety in Dentistry Following Real or Sham CES Treatment

3 Month Trial with 48 Severe Aggressive Patients

41% reduction in episodes of violence (P<.001); 40% reduction in episodes requiring restraint (P<.001) and seclusion (P<.05), and 42% fewer as-needed emergency medications (P<.01).
The decrease of 271 PRN med doses in 3 months saved >$12,000 for these med expenses alone.

Insomnia

Insomnia patients usually see results after one treatment.

Or it may take up to 4 weeks of treatment, especially if insomnia is associated with depression.

Recent study completed at Walter Reed showed an average increase of +46 minutes of sleep after only 5 treatments.

3 Week RCT of CES for Insomnia in Fibromyalgia Patients

Depression

Expect a minimum of 3 weeks of daily CES treatment before results are seen.

A patient who suffers from anxiety with a depression component will take up to 3 weeks to improve as well.

FDA Public Health Advisory
March 22, 2004
WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS

Today the Food and Drug Administration (FDA) asked manufacturers of the following antidepressant drugs to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality. The drugs that are the focus of this new Warning are:

Prozac (fluoxetine); Zoloft (sertraline); Paxil (paroxetine);
Luvox (fluvoxamine); Celexa (citalopram);
Lexapro (escitalopram); Wellbutrin (bupropion);
Effexor (venlafaxine); Serzone (nefazodone);
and Remeron (mirtazapine)
Example of Side Effect Profile for the Popular Antidepressant Zoloft (sertaline)

Results from a placebo-controlled clinical trial (n=2799) as cited by www.drugs.com/sfx/sertraline-side-effects.htm

- Appetite: >2%
- Abdominal Pain: >2%
- Paresthesia: 21%
- Insomnia: 8%
- Respiratory: 13%
- Drowsiness: 12%
- Fatigue: 15%
- Sexual Dysfunction: 7%
- Sweating: 6%
- Libido: 8%
- Tremor: 6%
- Constipation: >2%
- Back Pain: 25%
- Headache: >2%
- Malaise: >2%
- Flatulence: 5%
- Nervousness: 3%
- Rash: 4%
- Vomiting: 5%
- Agitation: 4%
- Anxiety: >2%
- Pain: 25%
- Nausea: 19%


Depression Study

- RCT with an N of 115 at Liberty University
- 82.2% of the active group reported at least 50% improvement
- P=0.001, Cohen’s d=0.75
- The mean decrease on the HAM-A in the active group (82.9%) was more than 12 times the mean decrease of the sham group.


Mean Depression Scores

Effects of 2 and 3 Weeks of CES on Depression

4 Studies that used the POMS Depression/Dejection Scale


Smith R et al. The use of transcranial electrical stimulation in the treatment of cocaine and/or polysubstance abuse. 2002

---

CES Induced Changes in Beck Depression Inventory Over 7 Months in Alcoholic Patients

May, Brad & May, Carole. Pilot project using the Alpha-Stim 100 for drug and alcohol abuse. August, 1990

---

Pain Management

- Acute
- Chronic
- Post-operative

Usually results are seen from the first treatment.

There is no risk of accommodation or addiction.

Pain relief is cumulative with continued use.
What is the first thing you think of when your computer breaks?

What is the first thing you think of treating when you have pain?

Percent Improvement in 32 Veterans Across 158 Treatment Sessions


Cumulative Improvement in Pain After 1-5 CES Treatments


Example of the CES Response Over Time in a Patient with Severe Migraine

Courtesy of COL Michael Singer, Walter Reed Army Medical Center

Stay with it!
Migraine Headaches -- Frequency and Intensity
CES Doubles Effects of Biofeedback

Following 6 Treatments
Week for 1 month
After 1 Month
Accumulated Percent Improvement


---

8 Week CES Fibromyalgia RCT Study

fMRI RCT on CES Activity in Brain Pain Processing Regions in Fibromyalgia Patients

Subjects 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.

**VA Houston CES Spinal Cord Injury Study**

Before and After Session Pain Ratings
Treatment Group (n = 18)

Before and After Session Pain Ratings
Sham Group (n = 20)

Before and After Session Pain Ratings
Sham Group and Their Open Label Treatment (n = 17)

Figures 1, 2, and 3: Daily Pain Rating for Active CES and Sham CES Groups


**3 Year, 5-Site Spinal Cord Injury Study**

- Participants in 3-Month Follow-up (n = 19)
- Participants in 6-Month Follow-up (n = 24)

- Baseline
- After Active 3 weeks
- At 3-Month Follow-up
- At 6-Month Follow-up

The Use of CES to Potentiate Anesthesia in Surgery
CES May Improve Efficacy of Meds, and May Warrant Reduced Dose

- Anesthesia Plus CES
- Anesthesia Alone


Tail Flick Latency (TFL) studies revealed a significant increase in analgesic effect of opiates: morphine 174%, fentanyl 176%, alfentanil 160%, dextromoramide 267%, limogine 336%, and morphine 392%. Results were also obtained after intracerebroventricular injection of morphine (10 micrograms; analgesic effect increase from 152% to 207% with CES) suggesting that CES potentiation of opiate-induced analgesia is centrally mediated.

There was as much as a threefold increase in β-endorphin concentration after just one CES treatment (Krupisky, 1991).

Experimental Rat Studies of CES

**Comparison of Service Members That Used Alpha-Stim With Or Without Medications**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alpha-Stim with Medications</th>
<th>Alpha-Stim Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>+9%</td>
<td>+13%</td>
</tr>
<tr>
<td>PTSD</td>
<td>+12%</td>
<td>+20%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>+13%</td>
<td>+20%</td>
</tr>
<tr>
<td>Depression</td>
<td>+9%</td>
<td>+20%</td>
</tr>
<tr>
<td>Pain</td>
<td>+9%</td>
<td>+20%</td>
</tr>
<tr>
<td>Headache</td>
<td>+15%</td>
<td>+20%</td>
</tr>
</tbody>
</table>

Summary

- CES is safe
- CES is easy to use
- CES is proven effective
- CES works quickly and lasts
- CES is FDA, CE and ISO certified
- DoD/VA is using and researching CES
- CES is available to help you NOW!
Are Your Patients in Pain? Anxious?
Depressed? Not Sleeping well?
Why Not Try Alpha-Stim?

Questions? Call 1-800-FOR-PAIN
Email Dr. Jeff Marksberry: jeff@epii.com
www.alpha-stim.com