CES in the Treatment of Anxiety Disorders

A Review and Meta-Analysis of Cranial Electrotherapy Stimulation (CES) in the Treatment of Anxiety Disorders — Part 1

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Cranial electrotherapy stimulation (CES) is the FDA-recognized generic category for medical devices using microcurrent levels of electrical stimulation applied across the head via transcutaneous electrodes for the treatment of anxiety, insomnia and depression. The spectrum of anxiety disorders are clearly bidirectionally-comorbid with insomnia and depression, and CES is also emerging as a complementary and stand-alone treatment for pain-related disorders. Certain anxiety disorders — such as panic attacks which are incipient and not chronically severe — may respond to CES as the least complex, least expensive, and most efficacious treatment modality. In truth, it is safe to assume that our healthcare culture will usually prescribe a medication such as a minor tranquilizer as the first treatment of choice for a number of anxiety disorders, including panic attacks. But nearly all of the pharmacological interventions employed for anxiety disorders tend to be dependency-provoking, expensive, and depression-facilitating by virtue of the fact that they depress the central nervous system.

Today's treatment regimen for anxiety disorders still does not regularly include CES, but there is already more than enough experimental evidence to establish CES as an adjunct to medication regimens or other interventions of anxiety disorders, both acute and chronic. When CES is widely recognized as the value modality that it is, CES will also emerge as an effective way to decrease and limit the toxic effects of many pharmacological treatment regimens.

Anxiety Disorders

Anxiety disorders are a group of mental disturbances having anxiety as a core symptom. Anxiety is found to some degree in nearly all forms of illness and is ubiquitous in pain patients. Viewed in terms of possible causation, anxiety can be etiologic or reactive, and is often masked or unrecognized and therefore untreated. When this is the case, the illness may be labeled intractable and the healthcare practitioner may move into higher dosage levels of pharmaceuticals that remain ineffective. Although mild anxiety can be an unavoidable commonplace experience in daily life, such feelings alone do not constitute an anxiety disorder. Anxiety disorders are also associated with a wide range of physical illnesses, medication side effects (including psychiatric medications), and other psychiatric disorders.

Anxiety disorders are the most common mental illness affecting 27.4 million people in the U.S. According to The Economic Burden of Anxiety Disorders, a study commissioned by the Anxiety Disorders Association of America. Anxiety disorders incur an economic burden of approximately $63.1 billion a year in 1998 dollars, with 54% of that amount spent on non-psychiatric medical treatment costs.[1] People with an anxiety disorder are three to five times more likely to seek medical attention and six times more likely to be hospitalized than non-sufferers. Post traumatic stress disorder (PTSD) and panic disorder patients have the highest rates of medical care.

These disorders are a serious societal problem because of their potential interference with work, schooling, and family life. They have also been shown to contribute to alcohol and substance abuse and other major psychiatric disorders in the United States.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) refined the classification of anxiety based upon recent discoveries about the biochemical and post-traumatic origins of some types of anxiety (see Table 1).[2] The present definitions are based on the external and reported symptom patterns of anxiety disorders — rather than exclusively and implicitly on their biochemical or physiologic etiology.

Because panic disorders and agoraphobia occur in a wide variety of anxiety disorders, the DSM-IV-TR takes care to define both at the beginning of the Anxiety Disorder section since neither can be classified (or coded in billing) as a separate disorder on its own but in combination with some other diagnostic, classifiable feature such as social phobias.[3]

Panic Disorder is defined as "a discrete period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate, (2) sweating, (3) trembling or shaking, (4) sensations of shortness of breath or smothering, (5) feeling of choking, (6) chest pain or discomfort, (7) nausea or abdominal distress, (8) feeling dizzy, unsteady, lightheaded, or faint, (9) derealization or depersonalization, (10) feeling of losing control or going crazy, (11) fear

of dying, (12) paresthesias, or (13) chills or hot flushes.

Agoraphobia is defined as: (1) anxiety about being in places or situations from which escape might be difficult or embarrassing in case one experiences panic in situations like being away from home alone, being in a crowd, standing in a line, being on a bridge, or traveling in a private or public transport. The situations are avoided or else endured with marked stress and the anxiety or phobic avoidance are not better explained by another mental disorder, including any of the listed Anxiety Disorders.

Anxiety Disorders, listed in Table 1, may be distinguished as follows:

Generalized anxiety disorder (GAD). GAD is the most commonly diagnosed anxiety disorder and occurs most frequently in young adults and children. It involves excessive anxiety and worry, and difficulty controlling worry along with one of six other features, including (1) restlessness, (2) easily fatigued, (3) difficulty concentrating, (4) irritability, (5) muscle tension, and (6) sleep disturbance.

Panic disorders with or without agoraphobia. The chief characteristic of panic disorder is the occurrence of panic attacks and the fear of their recurrence. In clinical settings, agoraphobia is usually not a disorder by itself, but is typically associated with some form of panic disorder. As previously described, those with agoraphobia are afraid of places or situations in which they might have a panic attack and be unable to leave or to find help or emotional security. About 25% of people with panic disorder may develop obsessive-compulsive disorder (OCD).

Phobias include specific phobias and social phobia that are found in both children and adults. A phobia is an intense and irrational fear of a specific object or situation that evokes profound negative responses and compels the person to avoid it. Some phobias are related to activities or objects that involve some risk (e.g., flying or driving) but many are focused on harmless animals or other objects.

Specific Phobia used to be called Simple Phobia. Exposure to the phobic stimulus usually provokes an immediate anxiety response which may take the form of a situational panic attach. The person usually recognizes that the fear is unreasonable or excessive and the stimulus is either avoided or tolerated with extreme anxiety or stress. Specific phobias can be tied to specific animals or natural situations such as heights, storms, or water. Many of the specific phobias originate in childhood.

Social phobia, also called Social Anxiety Disorder, involves a fear of being humiliated, embarrassed, judged, or scrutinized. It manifests as a fear of performing certain functions in the presence of others (e.g., public speaking) or can include most social situations and normal developmental activities such as dating.

Obsessive-compulsive disorder (OCD). This disorder is marked by unwanted, intrusive, persistent thoughts characteristically coupled with repetitive behaviors that reflect the patient's response to, or attempts to control the escalating intrusive ideas. OCD affects between 2-3% of the population. The disorder may have either obsessions, compulsions, or both. The person attempts to control, ignore, or suppress the unwanted thoughts and behaviors and almost always recognizes at some point in the illness that they are excessive or unreasonable. The symptoms may cause marked distress, waste a lot of time, and generally interfere with, and obstruct, the person's quality of life.

TABLE 1: SUMMARY OF DSM-IV-TR ANXIETY DISORDER CLASSIFICATIONS

300.01	Panic Disorder Without Agoraphobia
200.21	Panic Disorder With Agoraphobia
300.22	Agoraphobia Without History of Panic Disorder
300.29	Specific Phobia (specific type such as Animal Type, etc.)
300.23	Social Phobia
300.3	Obsessive-Compulsive Disorder
309.81	Posttraumatic Stress Disorder
308.3	Acute Stress Disorder
300.02	Generalized Anxiety Disorder
293.84	Anxiety Disorder Due to a General Medical Condition
___.__	Substance-Induced Anxiety Disorder
300.00	Anxiety Disorder Not Otherwise Specified

Stress Disorders

These include **Post Traumatic Stress Disorder** (PTSD) and **Acute Stress Disorder** as well as **Combat Stress Disorder**. Stress disorders are symptomatic reactions to traumatic events in a person's life. The challenges of civilian life can frequently produce stress disorders. These events involve the threat of either real death or serious injury which becomes recorded in the individual's memory in some way and then re-experienced over and over again in waking imagery or in dreams. Repetitive internal replay of the distress produces both psychological and physiological effects which cause the individual, as with some soldiers, to make many different attempts at avoiding the memories and dreams. The interest in life and any sense of a positive future become very weak. Life can become a series of different alarm and arousal states that include (1) difficulty falling or staying asleep, (2) irritability or outbursts of anger, (3) difficulty concentrating, (4) hypervigilance, and (5) exaggerated startle response.

Anxiety Disorders Due To Known Medical Conditions. These disorders can include intense anxiety, panic attacks, or obsessions, and compulsions. The severity of the anxiety disorder is often directly proportional to the physiological consequences and life pattern disruption of the general medical condition.

Substance-Induced Anxiety Disorder. These include the same features as the disorders accompanying medical conditions but also include complicating factors such as substance intoxication or withdrawal states, as well as toxicity states related to the use of prescribed medications. Most prominent conditions include the use and abuse of substances that can involve the sympathetic nervous system while producing hyperstimulated physiologic responses and emotional states of anxiety (e.g., caffeine, amphetamines).

Anxiety Disorder Not Otherwise Specified. (NOS) This category includes conditions featuring prominent anxiety or phobic avoidance that do not meet the criteria for any of the previously described disorders. NOS disorders do not meet criteria for any specific anxiety disorder, adjustment disorder with anxiety, or adjustment disorder with mixed anxiety and depressed mood. One example might be a person who has a clinically significant social phobia because of a general medical condition such as Parkinson's disease or a dermatological disorder.

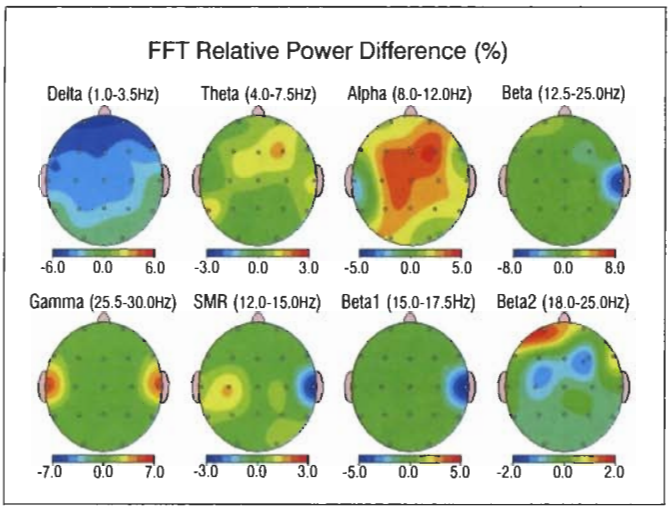

FIGURE 1. *A quantitative EEG brain map (QEEG)13 showing the changes in brain activity by traditional EEG bands of 30 volunteers after a 20 minute treatment with Alpha-Stim CES at 0.5 Hz. Blue shows a decrease in activity after CES while red shows an increase in activity. There is an increase in alpha activity (relaxation brain waves) with a simultaneous decrease in delta activity (sleep brain waves) after using CES for 20 minutes. The changes near the ears were found on raw EEG to be artifact. (Brain Map courtesy of Dr. Richard Kennerly, Psychiatric Centers of San Diego)*

All DSM-IV anxiety disorder diagnoses include criteria and indices of severity. To meet criterion for a clinically-relevant disorder, the anxiety must be severe enough to significantly interfere with the patients' occupational or educational functioning, social activities, interpersonal relationships, or other customary activities of daily living.

The anxiety disorders vary widely in frequency of occurrence in the general population, age of onset, family patterns, and gender distribution. In general, the stress disorders and anxiety disorders caused by medical conditions or substance abuse are less age and gender specific. While OCD affects males and females equally, GAD, panic disorder, and specific phobias all affect women more frequently than men. GAD and panic disorders are more likely to develop in young adults, while phobias and OCD can, and frequently do, begin in childhood.[1]

Although there is no psychiatric test that can provide definite diagnoses of anxiety disorders, there are several psychometric tests that are used to evaluate the intensity of a patient's anxiety and some of its associated features. These same tests are also used in both pharmaceutical and cranial electrotherapy stimulation (CES) research.

It is important for patients with severe anxiety symptoms to get help. Anxiety doesn't always go away by itself; it can progress to panic attacks, phobias, and, as part of a larger constellation of features known as anxiety-depressive spectral disorders, lead to episodes of depression and even suicide. In addition, many anxious patients may turn to illicit drugs or alcohol in an attempt to self-medicate their symptoms. Moreover, since children learn ways of coping with anxiety from their parents, adults who get help for anxiety disorders are better prepared to contribute to family dynamics that teach their children healthy coping patterns than adults who remain untreated and install abusive habits to their children.[1] Parents who are having difficulty coping with their own patterns of anxiety often have difficulty with effectively nurturing their children and helping them develop a healthy sense of self-esteem.

CES Protocol

A recommended CES protocol for the treatment of anxiety is to apply CES for 20 minutes to an hour each day or every other day for two to three weeks, with the patient determining their own comfortable level of current. Once symptoms subside, the treatment may be continued on a once or twice weekly schedule, or on an as-needed (PRN) basis. While many anxiety patients experience partial to complete symptomatic relief in one treatment,[7,8] for some patients a series of treatments is necessary over a two to three week period. Research has shown that by the end of the 7th to 10th treatment, anxiety symptoms have usually significantly subsided, bringing the patient back within, or even below, established norms on psychometric tests of anxiety. Some CES devices may also be used as a stand-alone treatment for anxiety and have received FDA authorization to market this claim.

CES Results

In the U.S., it is nearly impossible to conduct research with inpatients who are medication free, since it is considered usual and customary (if not mandatory) to provide some kind of pharmacological treatment to hospitalized patients. Accordingly, the results of CES were often accessed during a study in which CES results were combined with the pharmacologic results. However, in such studies, pharmaceuticals were used within both CES-treated and control groups.

As with most new medical treatments, CES was criticized when it first came into use in the U.S. Before it was accepted, it had to be proved that stimulation at such low intensity—at subliminal or below sensory threshold in blinded studies—could produce behavioral results or physiological effects in the brain. Both sophisticated mathematical analysis, and direct measurements of CES current passing through the head of monkeys and man, revealed that as much as half of the current applied to the outside of the head actually went through the brain with sufficient effect to cause changes in neurochemical status.[9-11]

CES caused brain wave pattern changes in every study of EEG and CES that was published.[12-16] Kennerly conducted a pilot study of 30 subjects with Alpha-Stim CES at 0.5 Hz for 20 minutes. He found a very significant decrease in delta activity (1.0 - 3.5 Hz) and a simultaneous increase in alpha activity (8.0 – 12.0 Hz) as shown in Figure 1.[13] CES was effective in relaxing patients whether or not they went to sleep.[17] In addition, it was shown that beneficial treatment effects were present above and beyond what could be accounted for by the patient's level of suggestibility, or by any placebo effect.[18] One interesting fact is that a placebo effect has never been elicited or measured in CES studies which were designed to measure the placebo effect.[19-23]

In early U.S. studies, it was found that anxiety in the substance abstinence syndrome was reduced with CES. Patients who rapidly discontinue use of various addictive substances often suffer intensively from anxiety, depression, and sleep disturbance. Because that group is susceptible to cross addiction to psychoactive medications and, because addicts are also somewhat more resistant to the effects of most of those medications, CES rapidly became a treatment of choice in both inpatient and outpatient treatment programs for this syndrome.[23-27]

TABLE 2. AGE RANGE OF PATIENTS USING CES DEVICES, AS REPORTED ON SURVEY CARDS

Age Range	3-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Number	13	37	69	159	119	62	33	8
Percent	2.6%	7.4%	13.8%	31.8%	23.8%	12.4%	6.5%	1.7%

TABLE 3. TREATMENT OUTCOME FOLLOWING CES TREATMENT OF ANXIETY

Improvement	None	1-24%	25–49%	50-74%	75-100%	Significant (>25%)
Nr. Reporting	24	63	110	156	147	413
% Reporting	5%	13%	22%	31%	29%	82%

Physician Ratings of CES Treatment Results

As part of an FDA post-market surveillance, Kirsch polled 47 physicians to assess results of 500 patients who had received the prescribed CES treatment. The prescribing physicians reported that among previously treatment resistant anxiety patients, greater than 93% had achieved significant improvement of their anxiety symptoms through the use of CES.[28]

Patient Self-Report of CES Treatment Results

Recently, reports of patients diagnosed with various anxiety disorders were examined to see how they self-rated the effects of CES treatment for their symptoms. Patients whose physicians prescribe the Alpha-Stim CES device (Electromedical Products International, Inc., Mineral Wells, TX, 76067, www.alpha-stim.com) routinely submit satisfaction surveys on warranty cards that afford information regarding their diagnosis, the length of treatment, and self-evaluation of the treatment results.

From more than 12,000 warranty cards received since the survey was instituted in 1995, the completed surveys of the last 500 anxiety patients submitted were selected for evaluation. Of these, 311 (62%) were submitted by females. Treatment ages ranged from 3 to 89 years old with the majority between the ages of 40 and 59. This demographic is shown in Table 2. Patients rated their improvement in each of the effect categories provided, as shown in Table 3.

Many of the surveys were submitted following one or two days of treatment while others were sent in after 52 to 156 weeks of treatment. A correlational analysis of the length versus results of treatment revealed an overall correlation of .63, which had strong statistical significance ($p<0.001$). When individual cards were inspected, it was found that while some patients responded at the 100% improvement level within the first week, two patients had received no treatment benefit from three months of use. In addition to the patients own general health and related symptom complexes, they may have underutilized CES in time or current level.

While 473 of the survey cards analyzed listed anxiety as the primary diagnostic factor, 39 listed stress but did not name anxiety as such, while 27 listed both stress and anxiety. For purposes of the present evaluation, stress and anxiety are combined. This combination makes sense since it is very rare to have stress without the recognition of attendant anxiety, unless the stress is so long-standing that an individual has in some way internalized much of the conscious discomfort of the anxiety. Only 175 (35%) listed anxiety alone, while 100 (20%) listed anxiety and depression, 195 (39%) listed anxiety and pain, and 30 (6%) listed anxiety and sleep problems. In addition, many listed other anxiety-related states and those, along with their self rated treatment results are shown in Table 4.

The values shown in Table 4 include many patients who had the CES device for a week or less. Inspection of the data for the group reporting panic disorder reveals that those who had used CES for three weeks or less reported varying treatment results, while those employing it ten weeks or more reported a 99% remission of symptoms. When the treatment times for the combined group shown in Table 4 were examined, it was found that those using their device one week or less reported an average 49% improvement, while those using their device from two to three weeks reported a 62% gain, and those using it four weeks or more reported 64% improvement. Among the group of patients who had their CES device for four weeks or more, 81% claimed significant treatment response of 25% or greater (a standard of positive outcome that is commonly used in pharmaceutical studies).

TABLE 4. ANALYSIS OF TREATMENT OUTCOME FOR TREATMENT OF ANXIETY RELATED STATES

Anxiety Related State	# Responding	Age Range	Sex	Weeks Treated	Mean Improvement	Significant Improvement of >25%
Panic Disorder	14	30-69, Mean=49	50% Female	0.14 – 52, Mean=9	45%	42%
OCD	5	13-41, Mean=27	60% Female	1 – 16, Mean=6	68%	100%
Bipolar	9	33-61, Mean=49	89% Female	3 – 24, Mean=10	71%	88%
PTSD	8	39-58, Mean=51	63% Female	0.14 – 20, Mean=9	55%	71%
Cognitive Problems(ADHD)	23	7-65, Mean=37	61% Female	0.14 - 52, Mean=9	62%	81%
Phobias	9	31-72, Mean=52	78% Female	0.29 – 24, Mean=8	49%	60%
Total	54	7-72, Mean=37	63% Female	0.14-52, Mean=9	64%	73%

Meta-Analysis of CES

Meta-analysis is a statistical method of combining the results of several studies that address a set of related research hypotheses. The first meta-analysis was performed by Karl Pearson in 1904.[29] Pearson attempted to overcome the problem of reduced statistical power in studies with small sample sizes. His hypothesis was that analyzing the results from a group of studies can permit more accurate data analysis. Meta-analysis is a slightly less rigorous statistical technique but is an accepted and excellent way of teasing out important trends from a collection of different data sets. The first meta-analysis of a medical treatment was not published until 1955. Because the results from different studies investigating different independent variables are measured on different scales, the dependent variables in a meta-analysis is some standardized measure of effect size. The usual effect size indicator is either the standardized mean difference or an odds ratio in experiments with outcomes of dichotomous variables (success versus failure).

Two meta-analyses of CES previously performed were limited to the results of just eight studies, one at the Harvard School of Public Health, and the other at the University of Tulsa Graduate School. Both of these meta-analyses concluded that CES was significantly effective for the treatment of anxiety.[30,31]

Our meta-analysis of CES calculates the percent of patients improving versus the percent not improving to yield the treatment effect size r, which is equal to the amount of patient improvement given as percentage.[32] Tables 3 and 4 show that the mean effect size for all 500 patients reporting was r=.62. When the smaller groups of patients with specific types of anxiety related disorders were broken out, the effect size among those suffering from panic disorder was r=.45, OCD patients, r=.68, bipolar disorder r=.71, PTSD (r=.55) ADHD (r=.62), and phobias (r=.49). The overall mean effect size for the combined smaller groups was r=.64. These results can be compared with the accepted standardized ratings of r=.10 for small effect, r=.30 for medium effect and r=.50 for large effect.[33] Thus it can be seen that the overall effect of CES for anxiety disorders is large and that there is a notable effect of duration of use that enhances such outcomes. This explanation corresponds well to what simple visual inspection of the CES data suggests.

Conclusion

A survey of prescribing physicians reported that among previously treatment resistant anxiety patients, greater than 93% had achieved significant improvement of their anxiety symptoms through the use of CES. In another study, patients self-rating of the results from CES treatment of anxiety indicated that 82% achieved significant improvement (>25%). Finally, meta-analysis of treatment outcomes for CES—across a range of anxiety disorders—indicated that 73% of patients achieved significant improvement (>25%).

In Part 2 of this series—in the next issue of Practical Pain Management—we will see how well the efficacy of CES for anxiety holds up when subjected to an inclusionary meta-analysis. ■

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