A Pilot Study of Cranial Electrotherapy Stimulation for Generalized Anxiety Disorder

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Background: Cranial electrotherapy stimulation (CES) is a noninvasive procedure that has been used for decades in the United States to treat anxiety, depression, and insomnia in the general population. Whether CES is an effective treatment for patients with a DSM-IV diagnosis of generalized anxiety disorder (GAD) has not previously been explored. The goal of this study was to evaluate the efficacy of CES in alleviating anxiety in patients with DSM-IV–diagnosed GAD.

Method: Twelve patients from 29 to 58 years of age with a DSM-IV diagnosis of GAD were enrolled from August 2005 to March 2006 through the University of California, Los Angeles (UCLA) Anxiety Disorders Program. Cranial electrotherapy stimulation treatment was administered for 6 weeks using the Alpha-Stim Stress Control System at 0.5-Hz frequency and 300-μA intensity. The primary efficacy measures were the Hamilton Rating Scale for Anxiety (HAM-A) and the Clinical Global Impressions-Improvement (CGI-I) scale. 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 ("much improved" or "very much improved," respectively).

Results: Cranial electrotherapy stimulation was associated with a significant decrease in HAM-A scores (t = 3.083, p = .01). At endpoint, 6 patients (50% of the intent-to-treat sample and 67% of completers) had a 50% decrease in HAM-A score and a CGI-I score of 1 or 2. One additional patient significantly improved in anxiety scores but did not meet criteria for response. Adverse events were generally mild in severity, mostly consisting of headache and nausea.

Conclusion: This preliminary study suggests that CES may reduce symptoms of anxiety in GAD. We hope that these preliminary results will encourage further research to explore the use of CES in clinical settings.

Trial Registration: clinicaltrials.gov Identifier: NCT00539357

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Generalized anxiety disorder (GAD) is a chronic condition characterized by excessive and uncontrollable worry, with episodes usually persisting for a decade or more.[1] It is relatively common, with a lifetime prevalence reaching 5.7%.[2] In addition, an estimated 6.6% of the population suffers milder variations; these subthreshold or milder forms of GAD are more prevalent than their clinical counterparts and are associated with higher rates of psychological distress.[3] Symptoms of GAD can interfere with the daily lives of patients and often require prolonged treatment.[4] In 2 national surveys, GAD was ranked among the 10 most impairing chronic conditions in terms of sickness, absence from work, and inability to fulfill other roles, with levels of impairment comparable to those associated with arthritis, diabetes, and ulcers.[5,6] Finding effective treatments for GAD, therefore, is an important public health imperative.

The drug classes found to be effective in treating GAD include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, the serotonin 5-HT$_{1A}$ partial agonist buspirone, and tricyclic antidepressants (TCAs).[7–10] Current treatments, while helpful, have limitations in terms of safety, tolerability, and efficacy. For example, the side-effect profiles of SSRIs and SNRIs include sexual and gastrointestinal side effects, weight gain, and insomnia, any of which can potentially interfere with patient compliance. Because of these limitations, there is a need for more effective and better tolerated treatments for anxiety.

Cranial electrotherapy stimulation (CES) is a non-invasive procedure that involves applying a pulsed, low-amplitude electrical current to the head using electrodes placed on the earlobes. Cranial electrotherapy stimulation received U.S. Food and Drug Administration (FDA) approval for the treatment of insomnia, depression, and anxiety in 1979.[11] Recent studies have examined the effect of CES on pain, headaches, fibromyalgia, smoking cessation, and opiate withdrawal.[12] Cranial electrotherapy stimulation has few adverse effects, although headache, skin irritation (e.g., burns), and light-headedness may occur following treatment.[13]

Early CES studies for anxiety ranged from uncontrolled, open trials to randomized, double-blind, controlled experiments.[14–20] Flemenbaum[12] conducted an open trial of CES in patients with anxiety, depression, and insomnia who were refractory to treatment. Twenty-five

patients underwent five 30-minute CES treatments over 3 months. Although overall improvement was moderate, most patients who benefited from treatment remained better at 6-month follow-up.[12,21] Moore and colleagues[22] reported on a randomized, double-blind, crossover study of 17 nonpsychotic patients with anxiety and insomnia. Patients in the active treatment arm of the study received CES treatments during five 30-minute sessions over 3 months. The findings were largely negative, although there was a statistically significant improvement in a patient self-assessment of insomnia.[22]

Several studies in the 1990s looked at the effects of CES on affective disorders and anxiety in alcoholic or drug-addicted patients. Krupitsky et al.[23] conducted a double-blind sham-controlled experiment on 20 recovering alcoholics with depression and anxiety. This was one of the few studies of long-term CES therapy, during which patients received twenty 30-minute treatments over the course of 29 days. Cranial electrotherapy stimulation subjects had decreased anxiety and depression after 10 treatments and continued to improve after 20 procedures.[23] Philip and colleagues[24] looked at the effects of CES on anxiety and insomnia in 21 patients undergoing a washout period during an antidepressant trial. They found that anxiety and insomnia improved among patients receiving active treatment, while the placebo group had increased anxiety and decreased sleep duration.[24] Another small double-blind study found that CES significantly reduced anxiety and depression in patients with head injuries following 3 weeks of 45-minute treatments. Patients served as their own control, although a crossover design was not employed.[25]

To our knowledge, Klawansky and coworkers[26] performed the only meta-analysis of CES, in which they reviewed randomized controlled trials of CES for anxiety, "brain dysfunction," headache, and insomnia. A total of 8 trials on anxiety were combined and analyzed using effect sizes to compare outcome measures. Overall, CES was significantly more effective than sham treatment (effect size = 0.62). The placebo effect may have been a factor since many patients (30%) who received sham therapy also improved.[26]

Although many studies on CES have been published in the last 30 years, most have used relatively small samples in which only a dozen or so patients received the active treatment. In addition, the frequency and duration of CES treatment have not been established for different conditions. While short-term CES (e.g., 1–5 treatments of 23–30 minutes each) may help with acute anxiety, some researchers argue that chronic conditions may require longer periods of treatment and that effective therapy for patients with clinical depression or anxiety disorders may result only from daily CES for 2–4 weeks.[27] Given the largely positive results of preliminary studies on people with acute anxiety, CES is worthy of further exploration as a therapy for chronic anxiety disorders. In addition, CES is relatively inexpensive, can be self-administered by patients, and has few side effects.

The objective of this study was to preliminarily explore whether CES treatment is an effective therapy for patients with DSM-IV–diagnosed GAD. Our primary hypothesis was that CES treatment would have a beneficial effect on GAD symptoms, resulting in a reduction in Hamilton Rating Scale for Anxiety (HAM-A)[28] scores from baseline to week 6 of the treatment. Response to treatment was defined as a reduction of 50% or more on the HAM-A and a Clinical Global Impressions-Improvement (CGI-I)[29] score of 1 or 2 ("much improved" or "very much improved," respectively) at endpoint.

METHOD

Study Design

This study utilized a 6-week open-label design to test CES in the treatment of GAD. Participants were recruited from August 2005 to March 2006 from the University of California, Los Angeles (UCLA) Anxiety Disorders Program at the Semel Institute for Neuroscience and Human Behavior. Permission from UCLA's Institutional Review Board was obtained to conduct this study. All eligible subjects provided written informed consent prior to the initiation of any study-related procedure.

Patient Selection

Male or female outpatients aged 18 to 64 years were eligible if they had a current diagnosis of GAD. The Mini-International Neuropsychiatric Interview[30] was conducted at screening to confirm GAD diagnosis. Patients were eligible if they had a score ≥ 16 on the HAM-A and a score < 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[31] at baseline. We included patients with lower HAM-A scores than have typically been used in GAD clinical trials (i.e., HAM-A > 20)[3] so as to include milder and more numerous cases of GAD in order to improve the generalizability of these results to clinical practice.

Patients were excluded if they had a primary diagnosis meeting DSM-IV criteria for any Axis I disorder other than GAD, as were patients who met DSM-IV criteria for mental retardation or any pervasive developmental disorder or had a neurologic impairment. Also excluded were those with a current diagnosis or recent (6-month) history of drug or alcohol dependence or abuse, current suicidal ideation and/or history of suicide attempt, or any personality disorder of sufficient severity to interfere with participation in the study. Other exclusion criteria included the 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 were also excluded from the study.

Patients were permitted to continue taking an SSRI or SNRI if they had been on a stable, therapeutic-range dose for at least 3 months and were still symptomatic. Patients who had been using as-needed benzodiazepines were permitted to enter the study if the frequency of use did not exceed 2 times per week.

Study visits were conducted at baseline and at the end of 3 and 6 weeks of treatment. Patients who met all of the eligibility criteria at baseline were enrolled and administered CES treatment.

Each subject received the CES device, called the Alpha-Stim Stress Control System (SCS), 3 batteries, a bottle of Alpha Conducting Solution, an adequate supply of felt electrodes, and logs to record their treatments. At week 3, subjects received 3 new batteries, a new bottle of Alpha Conducting Solution, and new felt electrodes.

The Alpha-Stim SCS is FDA-approved for anxiety and was provided by the manufacturer, Electromedical Products International (Mineral Wells, Tex.). The Alpha-Stim SCS provides cranial electrical stimulation by generating bipolar, asymmetric, rectangular waves with a frequency of 0.5 Hz and a current intensity that can be adjusted continuously to provide between 10 μA and 500 μA. At the initial visit, the investigator applied conducting solution to the electrodes and clipped them on the subject's earlobes. The investigator then adjusted the current until the patient felt a mild tingling sensation and/or dizziness, at which point the current was reduced to just below the reported threshold of sensation. If the patient experienced no sensation, the investigator increased the current incrementally until the patient perceived a sensation and then reduced it to slightly below that threshold. Once the current intensity was found, the patient was instructed to use it consistently throughout the duration of the 6 weeks of treatment.

For the treatment, each participant subsequently self-administered stimulation at his or her place of residence for 60 consecutive minutes each day between the hours of 3:00 p.m. and 7:00 p.m. Treatment was administered daily for a total of 6 weeks. Subjects recorded each treatment session in daily treatment logs, which were reviewed at each assessment. Assessments took place every 3 weeks during the treatment period.

Assessments

Psychiatric assessments included the HAM-A, the Clinical Global Impressions-Severity of Illness (CGI-S)[29] scale, the CGI-I scale (beginning at week 2), and the HAM-D-17. In addition, patients completed the Patient Global Impressions-Improvement (PGI-I)[32] scale and the Four-Dimensional Anxiety and Depression Scale (FDADS).[33]

The FDADS is a self-rated measure of anxiety and depression that has been tested in the general population as well as in clinical samples and demonstrates sound psy-

chometric properties with good internal consistency and test-retest reliability. The scale has demonstrated validity relative to other measures of anxiety and depression.[33–36] Safety measures included the initial and final physical and routine laboratory evaluations (i.e., electrolytes, hematology, and urinalysis) and subjective reports on the Matson Evaluation of Drug Side Effects Scale.[37]

Statistical Methods

The primary efficacy measures included the CGI-I scale and the HAM-A. 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, and symptom remission was defined as a CGI-I score of 1 or 2 and a score ≤ 7 on the HAM-A. Data were entered anonymously into an Excel (Microsoft Corporation, Redmond, Wash.) spreadsheet and analyzed by the UCLA Semel Institute Biostatistics Core. The analysis was done on the intent-to-treat sample using last observation carried forward. A 1-sample paired t test was used to compare endpoint to baseline means on the HAM-A, with a significance level set at α = .05, 2-tailed.

RESULTS

Fifteen subjects expressed interest in the study and engaged in an initial telephone screen. Twenty percent of participants (N = 3) were deemed ineligible to participate. Reasons for ineligibility included age (N = 1; 6.7%) and psychiatric comorbidity (N = 2; 13.3%). Twelve subjects enrolled and received CES treatment. The mean ± SD age of the sample was 42.83 ± 10.27 years. Of the 12 individuals enrolled in the study, 9 (75%) were female and 3 (25%) were male. Five participants (41.7%) had been taking psychotropic medications (venlaflaxine, N = 2; alprazolam, 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. Those treated with benzodiazepines (alprazolam and lorazepam) took them on an as-needed basis no more than twice per week. During the initial, variable current-intensity setting, all 12 patients chose 300 μA as just below the sensation threshold.

Overall, 75% of patients (N = 9) completed the study. All were compliant with CES treatment according to their treatment logs. Three subjects discontinued after baseline due to adverse events including dizziness (N = 2) and headache (N = 1). The patient-by-patient results are presented in Table 1.

Mean ± SD HAM-A scores decreased significantly from baseline (21.25 ± 5.82) to endpoint (12.67 ± 5.47) (t = 3.083, p = .01; Table 1). At endpoint, 6 patients (50% of the intent-to-treat sample and 67% of completers) had a 50% decrease on HAM-A and a score of 1 or 2 on the CGI-I and were therefore considered responders to treatment. One additional patient improved but did not meet

Table 1. Results and Analysis of Treatment With Cranial Electrotherapy Stimulation for Generalized Anxiety Disorder

	Gender	Age, y	HAM-A Score at Baseline	HAM-A Score at Endpoint	FDADS-Anxiety Score at Baseline	FDADS-Anxiety Score at Endpoint	CGI-I Score at Endpoint
Individual Results							
1	F	47	17	24	26	36	5[a]
2	F	42	24	15	40	27	3[a]
3	F	32	16	19	26	20	4[a]
4	M	55	16	17	18	20	3
5	F	43	30	7	34	24	2[b,c]
6	M	29	34	10	55	39	2[b]
7	F	37	18	11	35	19	2
8	M	33	22	8	44	19	2[b]
9	F	54	19	6	21	14	2[b,c]
10	F	58	24	12	20	21	2[b]
11	F	32	18	8	23	18	2[b]
12	F	52	17	15	25	29	3
Group Analysis							
Mean ± SD		42.83 ± 10.27	21.25 ± 5.82	12.67 ± 5.47	30.58 ± 11.24	23.83 ± 7.57	
Paired t test[d]				t = 3.083		t = 2.35	
p Value[d]				.01		.039	

[a]Patient dropped out of the study because of side effects.
[b]Patient was a responder.
[c]Patient achieved remission.
[d]Baseline versus endpoint comparison.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, F = female, FDADS-Anxiety = Four-Dimensional Anxiety and Depression Scale–Anxiety subscale, HAM-A = Hamilton Rating Scale for Anxiety, M = male.

criteria for response. Two patients (16.7% of the intent-to-treat sample and 22.2% of completers) met criteria for symptom remission.

Mean ± SD HAM-D-17 scores changed significantly from 10.50 ± 15.01 at baseline to 6.00 ± 3.64 at endpoint (t = 3.01, p = .01). A significant change was also found from baseline (30.58 ± 11.24) to endpoint (23.83 ± 7.57) on the FDADS-Anxiety subscale scores (t = 2.35, p = .039; Table 1).

DISCUSSION

Results of the current study suggest that CES may improve anxiety symptoms associated with GAD. The response rate of 50% in the intent-to-treat sample is modest for an open-label study, although the response rate was higher (67%) for those who did not discontinue due to side effects. Preliminary clinical studies with CES have demonstrated efficacy in several conditions frequently associated with anxiety and depression including chronic pain, insomnia, and fibromyalgia.[13,20] Furthermore, some studies have already documented improvement in anxiety and depression in a nonclinical population.[12] Our pilot study furthers this line of research by suggesting possible efficacy of CES in a clinical sample of patients meeting criteria for GAD.

The exact mechanism of action of CES is unclear. Several preliminary studies have shown that CES alters various neurotransmitters or hormone levels in the brain.[38] One study demonstrated increased catecholamine levels in men and women and increased thyroxine production in men following long-term treatment with CES.[27] In a different study, platelet monoamine oxidase-B (MAO-B) activity and plasma concentration of γ-aminobutyric acid (GABA) increased following CES, in conjunction with clinical improvement in anxiety and depression.[26] Other studies in normal volunteers and in treatment-resistant depression found that CES was associated with significant elevations in cerebrospinal fluid and plasma serotonin, respectively.[39–41]

Alternatively, CES may work by stimulating brain cells primarily via electrical pathways and may effectively reset the brain to a prestress homeostasis.[13] Cranial electrotherapy stimulation has been found to alter electroencephalographic (EEG) readings during and after treatment. In studies of macaque monkeys, alpha EEG waves were slowed following CES, which was associated with a reduction in adverse reactions to stressful stimuli.[27] Schroeder and Barr[42] published a double-blind study on EEG changes in 28 healthy male subjects who underwent sham CES, 0.5-Hz CES, and 100-Hz CES treatment in random order. Both active CES treatments resulted in a downward shift in the alpha mean frequency. The authors noted that these changes from CES treatment were similar, although of greater magnitude, to EEG changes in trained meditators and may be associated with a relaxed state. In addition, the attenuation of the beta band with 100-Hz treatment may be of additional benefit, as this band is associated with arousal, problem solving, and stress.[42] These EEG changes may be associated with reduced anxiety states, although it is still unclear which is cause and which is effect.

Externally applied electrical currents using the CES device may influence brain activity via a pathway involving cranial nerves. Clinical trials of vagus nerve stimulation demonstrated that stimulation of the vagus nerve could lead to activation of the brain, symptomatically improving depressed, treatment-resistant patients.[43] Cranial electrotherapy stimulation, by generating an electrical current through the earlobe, may similarly influence the activity of the afferent branches of the facial, glossopharyngeal, and/or vagus nerves.

Some of the signals from these afferent nerves eventually reach the ventral posteromedial nucleus of the thalamus. Animal studies indicate that 42% to 46% of CES current enters the brain, with the highest levels of current recorded in the thalamus.[44] The thalamus is a region that seems to be important in the pathophysiology of anxiety. Evidence of this comes from positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies in GAD patients, which show changes in thalamic activity (as well as in other regions) with medication treatments.[45–47] A single photon emission computed tomography (SPECT) study in other anxiety disorders including obsessive-compulsive disorder, posttraumatic stress disorder, and social anxiety disorder also found decreases in thalamic activity with treatment with the medication citalopram.[48] Therefore, CES could hypothetically exert anxiolytic effects by affecting the thalamus and/or its afferent pathways. Future neuroimaging studies examining the brain regions and circuits associated with CES treatment will be needed to understand its mechanism of action.

Three patients dropped out of the study because of side effects of dizziness or headache (suggestive of the presence of a central nervous system effect). In the majority of subjects, however, the treatment was well tolerated. The efficacy and overall tolerability of CES demonstrated in this pilot study suggest that the clinical use of CES and its putative mechanism of action deserve further investigation.

This study had the limitations of a small, pilot, open trial. The efficacy of the intervention could be attributed to a powerful placebo effect, which is often found in GAD patients. Multiple pharmaceutical studies report placebo response rates in GAD ranging from about 40% to 60%.[49–61] Our clinical database indicates the rate of placebo response to be 35% to 45%. The preliminary efficacy of 50% in the intent-to-treat sample in this study therefore does not exclude the possibility of a placebo effect. Since 5 subjects were taking concomitant psychotropic medications, it is possible there was an interaction between the CES and medication treatments; however, the sample size did not permit a stratified analysis of outcomes.

The efficacy of CES needs to be evaluated in larger, controlled studies using sham devices. A sham device is available, and its use has been previously reported.[27] Future studies will also need an objective measure of compliance and will need to exclude those taking concurrent medications. The presence of side effects in this study indicates that there may also be a need for studies optimizing parameters such as stimulus intensity, frequency, and electrode placement to achieve the best efficacy and tolerability in anxiety disorders. Whether this treatment could be effective for more severe forms of anxiety also needs further clarification. Nevertheless, we believe that CES treatment clearly warrants investigation in further studies.

Drug names: alprazolam (Xanax, Niravam, and others), buspirone (BuSpar and others), citalopram (Celexa and others), lorazepam (Ativan and others), venlafaxine (Effexor and others).

REFERENCES

1. Regier DA, Rae DS, Narrow WE, et al. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. Br J Psychiatry Suppl 1998;34:24–28
2. Kessler RC. The epidemiology of pure and comorbid generalized anxiety disorder: a review and evaluation of recent research. Acta Psychiatr Scand Suppl 2000;406:7–13
3. Rucci P, Gherardi S, Tansella M, et al. Subthreshold psychiatric disorders in primary care: prevalence and associated characteristics. J Affect Disord 2003;76:171–181
4. Brawman-Mintzer O, Lydiard RB. Biological basis of generalized anxiety disorder. J Clin Psychiatry 1997;58(suppl 3):16–25; discussion 26
5. Kessler RC, Keller MB, Wittchen HU. The epidemiology of generalized anxiety disorder. Psychiatr Clin North Am 2001;24:19–39
6. Kessler RC, Wittchen HU. Patterns and correlates of generalized anxiety disorder in community samples. J Clin Psychiatry 2002;63(suppl 8):4–10
7. Rickels K, Zaninelli R, McCafferty J, et al. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2003;160:749–756
8. Rickels K, Rynn M. Pharmacotherapy of generalized anxiety disorder. J Clin Psychiatry 2002;63(suppl 14):9–16
9. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. J Clin Psychopharmacol 2004;24: 488–496
10. Laakmann G, Schule C, Lorkowski G, et al. Buspirone and lorazepam in the treatment of generalized anxiety disorder in outpatients. Psychopharmacology 1998;136:357–366
11. Electrosleep and cerebral electrotherapy. Med Lett Drugs Ther 1971;13: 81–82
12. Flemenbaum A. Cerebral electrotherapy (electrosleep): an open-clinical study with a six month follow-up. Psychosomatics 1974;15:20–24
13. Kirsch DL, Smith RB. The use of cranial electrotherapy stimulation in the management of chronic pain: a review. NeuroRehabilitation 2000;14: 85–94
14. Long RC. Electrosleep therapy: some results with the use of electrically induced sleep in the treatment of psychiatric patients. J Kans Med Soc 1966;67:81–85
15. Arian E. [Electrosleep; clinical experiences]. Minerva Med 1957;48: 1828–1833
16. Buckman C, Pinsley I, Fenichel M. Electrosleep therapy in psychoses. Dis Nerv Syst 1957;18:106–108
17. Solomon S, Elkind A, Freitag F, et al. Safety and effectiveness of cranial electrotherapy in the treatment of tension headache. Headache 1989;29: 445–450
18. Schmitt R, Capo T, Frazier H, et al. Cranial electrotherapy stimulation treatment of cognitive brain dysfunction in chemical dependence. J Clin Psychiatry 1984;45:60–63
19. Schmitt R, Capo T, Boyd E. Cranial electrotherapy stimulation as a treatment for anxiety in chemically dependent persons. Alcohol Clin Exp Res 1986;10:158–160

20. Jenkins JB, Spensley J. Electrosleep therapy. Nurs Times 1971;67: 1310–1312

21. Flemenbaum A. Cerebral electrotherapy (electrosleep): a review. Curr Psychiatr Ther 1975;15:195–202

22. Moore JA, Mellor CS, Standage KF, et al. A double-blind study of electrosleep for anxiety and insomnia. Biol Psychiatry 1975;10:59–63

23. Krupitsky EM, Burakov AM, Karandashova GF, et al. The administration of transcranial electric treatment for affective disturbances therapy in alcoholic patients. Drug Alcohol Depend 1991;27:1–6

24. Philip P, Demotes-Mainard J, Bourgeois M, et al. Efficiency of transcranial electrostimulation on anxiety and insomnia symptoms during a washout period in depressed patients: a double-blind study. Biol Psychiatry 1991;29:451–456

25. Smith RB, Tiberi A, Marshall J. The use of cranial electrotherapy stimulation in the treatment of closed-head-injured patients. Brain Inj 1994;8: 357–361

26. Klawansky S, Yeung A, Berkey C, et al. Meta-analysis of randomized controlled trials of cranial electrostimulation: efficacy in treating selected psychological and physiological conditions. J Nerv Ment Dis 1995;183:478–484

27. Jarzembski WB. Electrical stimulation and substance abuse treatment. Neurobehav Toxicol Teratol 1985;7:119–123

28. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55

29. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222

30. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33; quiz 34–57

31. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62

32. Guy W. Patient assessment in clinical trials. Prog Neuropsychopharmacol Biol Psychiatry 1982;6:601–606

33. Bystritsky A, Waikar SV, Vapnik T. Four-Dimensional Anxiety and Depression Scale: a preliminary psychometric report. Anxiety 1996;2: 47–50

34. Bystritsky A, Wagner AW, Russo JE, et al. Assessment of beliefs about psychotropic medication and psychotherapy: development of a measure for patients with anxiety disorders. Gen Hosp Psychiatry 2005;27: 313–318

35. Bystritsky A, Stoessel P, Yager J. Psychometric discrimination between anxiety and depression. J Nerv Ment Dis 1993;181:265–267

36. Bystritsky A, Shapiro D. Continuous physiological changes and subjective reports in panic patients: a preliminary methodological report. Biol Psychiatry 1992;32:766–777

37. Matson JL, Mayville EA, Bielecki J, et al. Reliability of the Matson Evaluation of Drug Side Effects Scale (MEDS). Res Dev Disabil 1998; 19:501–506

38. Ferdjallah M, Bostick FX Jr, Barr RE. Potential and current density distributions of cranial electrotherapy stimulation (CES) in a four-concentric-spheres model. IEEE Trans Biomed Eng 1996;43:939–943

39. Shealy CN, Cady RK, Wilkie RG, et al. Depression: a diagnostic, neurochemical profile and therapy with cranial electrotherapy stimulation (CES). J Neurol Orthop Med Surg 1989;10:319–321

40. Shealy CN, Cady RK, Wilkie RG, et al. Cerebral spinal fluid and plasma neurochemicals: response to cranial electrotherapy stimulation. J Neurol Orthop Med Surg 1998;18:94–97

41. Shealy CN. Transcutaneous electrical nerve stimulation: the treatment of choice for pain and depression. J Altern Complement Med 2003;9: 619–623

42. Schroeder MJ, Barr RE. Quantitative analysis of the electroencephalogram during cranial electrotherapy stimulation. Clin Neurophysiol 2001; 112:2075–2083

43. Boon P, Moors I, De Herdt V, et al. Vagus nerve stimulation and cognition. Seizure 2006;15:259–263

44. Paros A, Beck SL. Folinic acid reduces cleft lip [CL(P)] in A/WySn mice. Teratology 1999;60:344–347

45. Buchsbaum MS, Wu J, Haier R, et al. Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. Life Sci 1987;40:2393–2400

46. Wu JC, Buchsbaum MS, Hershey TG, et al. PET in generalized anxiety disorder. Biol Psychiatry 1991;29:1181–1199

47. Hoehn-Saric R, McLeod DR, Funderburk F, et al. Somatic symptoms and physiologic responses in generalized anxiety disorder and panic disorder: an ambulatory monitor study. Arch Gen Psychiatry 2004;61:913–921

48. Carey PD, Warwick J, Niehaus DJ, et al. Single photon emission computed tomography (SPECT) of anxiety disorders before and after treatment with citalopram. BMC Psychiatry 2004;4:30

49. Rickels K. Use of placebo in clinical trials. Psychopharmacol Bull 1986;22:19–24

50. Watson R. The placebo effect. J Clin Nurs 2006;15:519

51. Muhlack S, Lemmer W, Klotz P, et al. Anxiolytic effect of rescue remedy for psychiatric patients: a double-blind, placebo-controlled, randomized trial. J Clin Psychopharmacol 2006;26:541–542

52. Pollack MH. Optimizing pharmacotherapy of generalized anxiety disorder to achieve remission. J Clin Psychiatry 2001;62(suppl 19):20–25

53. Wager TD. Expectations and anxiety as mediators of placebo effects in pain. Pain 2005;115:225–226

54. Trexler LD, Karst TO. Rational-emotive therapy, placebo, and no-treatment effects on public-speaking anxiety. J Abnorm Psychol 1972;79:60–67

55. Segal MM, Shapiro KL. A clinical comparison study of the effects of reserpine and placebo on anxiety. AMA Arch Neurol Psychiatry 1959;81: 392–398

56. Okada F. "Reverse placebo effects": anticipation/anxiety at the possibility of receiving placebos. Ann Pharmacother 1992;26:128

57. Mandos LA, Rickels K, Cutler N, et al. Placebo-controlled comparison of the clinical effects of rapid discontinuation of ipsapirone and lorazepam after 8 weeks of treatment for generalized anxiety disorder. Int Clin Psychopharmacol 1995;10:251–256

58. Andreatini R, Sartori VA, Seabra ML, et al. Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. Phytother Res 2002;16:650–654

59. Pollack MH, Zaninelli R, Goddard A, et al. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62:350–357

60. Rickels K, Rynn M. Overview and clinical presentation of generalized anxiety disorder. Psychiatr Clin North Am 2001;24:1–17

61. Rickels K, Rynn MA. What is generalized anxiety disorder? J Clin Psychiatry 2001;62(suppl 11):4–12; discussion 13–14