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Research report

A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression

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ABSTRACT

Background: Anxiety disorders are among the most prevalent mental disorders and are usually treated with medication and/or psychotherapy. When anxiety disorders are accompanied with comorbid depression, this further complicates the treatment process. Medication compliance is a common problem due to adverse side effects and new and effective treatments that have minimal side effects are needed for the treatment of anxiety and depression. This study used a randomized, double-blind, sham controlled design to examine the effectiveness of CES as a treatment for anxiety disorders and comorbid depression in a primary care setting. The study was registered at clinicaltrials.gov, NCT01533415.

Methods: One hundred and fifteen participants, age 18 years and over, with a primary diagnosis of an anxiety disorder were enrolled from February 2012 to December 2012 The Hamilton Rating Scale for Anxiety (HAM-A) and the Hamilton Depression Rating Scale$_{17}$ (HAM-D$_{17}$) were used for baseline and outcome measures at weeks one, three, and five. Response to treatment was defined as a reduction of $\geq$ 50% or more on these measures.

Results: Analysis of covariance revealed a significant difference between the active CES group and the sham CES group on anxiety ($p=0.001$, $d=0.94$) and on depression ($p=0.001$, $d=0.78$) from baseline to endpoint of study in favor of the active CES group.

Conclusions: CES significantly decreases anxiety and comorbid depression. Subjects reported no adverse events during the study.

1. Introduction

Anxiety disorders are the most common mental disorders with lifetime prevalence rates ranging from 13.6% to 28.8% (Kessler & Wang, 2008; Michael et al., 2007). According to a World Health Organization report (Andrade et al., 2000) anxiety disorders generally develop before the age of 35 in 80–90% of cases; however, differences do appear between various anxiety disorders. Research also reveals that individuals with anxiety commonly have comorbidity (Gros et al., 2013; Kessler et al., 2010) and more than three-quarters of individuals with a lifetime anxiety disorder exhibit an additional lifetime disorder (Kessler et al., 2010; Merikangas & Swanson, 2010). It has also been shown that about 50–60% of depressed individuals also meet the lifetime criteria of an anxiety disorder (Kaufman & Charney, 2000) and that anxiety disorders can be causal factors for later developing depression (Starr & Davila, 2012; Wittchen et al., 2000). Patients who have an anxiety disorder with comorbid depression have an increased number of suicide attempts compared to those without comorbid depression (Dolnak, 2006).

Medication is the standard treatment for anxiety disorders and includes selective serotonin reuptake inhibitors (SSRIs), serotonin–noreepinephrine reuptake inhibitors (SNRIs), benzodiazepines, buspirone, and tricyclic antidepressants (TCAs) (Bespalov et al., 2010). While these medications can be helpful, compliance is often compromised due to the adverse effects these medicines have on the patient including but not limited to weight gain, gastrointestinal and sexual difficulties, insomnia, and severe headaches (Lingam & Scott, 2002; Swanson et al., 2000). Due to the non-compliance issue, new and effective treatments that have minimal side effects are needed for the treatment of anxiety and depression. Cranial electrotherapy stimulation (CES) can be used as an adjunct to the pharmacological approach and psychotherapy or as an alternative therapy (Kirsch & Nichols, 2013). CES is a noninvasive brain stimulation prescriptive medical treatment (Nardone et al., 2014) that uses the application of pulsed, low amplitude electrical current to the head via electrodes placed on the earlobes; usually less than 1 mA at 0.5 Hz from either a 9 V, AAA, or AA batteries (D. Kirsch, personal communication, March 24, 2014).

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CES received clearance by the Food and Drug Administration (FDA) for the treatment of depression, anxiety, and insomnia in 1979 (Kirsch & Nichols, 2013). Although the mechanisms of action are not precisely known, studies have shown that CES alters the levels of various neurotransmitters in the brain (Ferdjallah et al., 1996; Liss & Liss, 1996; Shealy et al., 1998, 1989) and changes in brainwave activity (Kennerly, 2006; Electromedical Products International, Inc., 2013). According to Gilula and Kirsch (2005) it is believed that the effects of CES are mediated through the limbic system, reticular activating system (RAS), and the hypothalamus.

Many studies have explored the use and effectiveness of CES. Gilula & Kirsch (2005) indicate that at the time of their writing, there were over 160 published human research studies reporting positive results. Electromedical Products International, Inc., the manufacturer of the Alpha-Stim CES devices, maintains an active list of CES research and review articles that includes 23 randomized controlled trials; 8 open clinical trials; 5 mechanistic studies; 13 case studies; and 25 combined articles on meta-analyses, commentaries, and reviews (Electromedical Products International, 2013). Klawansky et al. (1995) reviewed 18 randomized controlled trials on the effectiveness of CES and performed a meta-analysis of the effectiveness of CES for treatment of anxiety using 14 of these studies that met the acceptance criteria for inclusion in the meta-analysis. Using effect sizes to compare outcome measures, CES was shown to be significantly more effective than sham treatment (mean Cohen's $d=0.62$ for the 14 studies).

The latest known published and registered clinical trial (clinicaltrials.gov) using CES in the treatment of anxiety was performed by Bystritsky et al. (2008). They conducted a pilot study to explore if CES was an effective treatment for patients with a DSM-IV diagnosis of GAD. Participants were excluded if they had a primary diagnosis of any other Axis I disorder other than GAD. Their study utilized a 6 week open label design with 12 participants. Diagnosis of GAD was confirmed using the Mini-International Neuropsychiatric Interview. Using the Hamilton Rating Scale for Anxiety (HAM-A) score for a baseline to week 6, a response to treatment was defined as a 50% reduction in HAM-A scores and a Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2 ("much improved" or "very much improved") at the end of week 6. Medications such as SSRIs or SNRIs were permitted in the study provided they had been on a stable dose for at least 3 months and were still symptomatic. Participants taking benzodiazepines on a PRN basis were permitted to enter the study provided their frequency of use did not exceed 2 times per week. Results showed a significant decrease in HAM-A anxiety scores ($t=3.083$, $p=0.01$, $d=1.52$) from baseline to endpoint of the study. At the end of 6 weeks, 6 participants (50% of the intent-to-treat sample and 67% of those completing the study) had a 50% decrease in HAM-A scores and a CGI-I score of 1 or 2. Subjects also had significantly lower depression scores from baseline to endpoint of the study on the HAM-D_{17} ($t=3.01$, $p<0.01$, $d=0.41$). Bystritsky et al. (2008) concluded that CES appears to reduce symptoms of anxiety for individuals with a diagnosis of GAD and also for those individuals with GAD and comorbid depression. The authors recommended that future CES anxiety research include a larger sample size, utilization of sham CES treatment and requiring subjects to have a more severe anxiety level for inclusion in the study. The objective of this study was to address two of the recommendations by Bystritsky et al. (2008). We used a much larger sample size (108 versus 12 in the Bystritsky et al. (2008)) pilot study and a randomized, double-blind, sham-controlled design versus the open label pilot study design in the Bystritsky et al. (2008) study. Patients rarely present without comorbid disease in a primary care treatment setting. More often than not, patients will present with a combination of anxiety disorders such as GAD and Panic disorder, OCD, or other forms of anxiety. Anxiety disorders can be further complicated when coupled with depression.

This study examined the effects of CES on participants with any anxiety disorder. Comorbidity such as depression was included as long as the anxiety disorder was the primary diagnosis. Diagnoses for anxiety and depression were confirmed using the Structured Clinical Interview for Axis I Disorders (SCID-I). As in the Bystritsky et al. (2008) study, this study also used the HAM-A and the Hamilton Depression Rating $Scale_{17}$ (HAM-D_{17}) for baseline measurements and outcome measures (weeks 1, 3, and 5). Response to treatment was defined as a reduction of 50% or more on these measures.

2. Methods

2.1. Design

This study used a 5 week double-blind parallel group design to test CES treatment on various anxiety disorders. The study was registered at Clinicaltrials.gov NCT01533415. Participants were recruited through the clinicaltrials.gov website, advertisements placed in newspapers in three metropolitan areas of Central Virginia, and referral through local and regional general medical and psychiatric practices and Centra Health. The study was approved by the respective institutional review boards of the University and the regional health system (Centra Health). All participants signed the informed consent form prior to participating in the study. The study included 115 individuals with a primary diagnosis of an anxiety disorder.

Of concern in any clinical research is that of attrition. In an attempt to minimize the effects of attrition, each participant was carefully screened through initial phone contact where the study was described along with clarifying the inclusion and exclusion criteria for participation. If a participant matched inclusion criteria through initial phone contact, an interview was scheduled to confirm a primary diagnosis of anxiety which took place in a private practice setting. Each participant who was selected to participate in the clinical phase of the study paid a $30 entry fee which covered administrative costs for staff such as scheduling and data collection. The fee was also instituted to minimize attrition by securing a monetary commitment similar to copayment usually required in a clinical treatment setting.

2.2. Participants

Eligible participants included males and females between the ages of 18–65. Participants needed to meet DSM-IV criteria for an anxiety disorder which was confirmed using the SCID-I. Participants with comorbid depression ($n=23$) were required to have an anxiety disorder as a primary diagnosis. Participants needed to be in good medical health or, if having chronic medical conditions, these conditions needed to be stable. The participants were required to score on the lower end of mild on the HAM-A, >15. Scores on the HAM-D_{17} were allowed to range through the very severe range provided the HAM-A was the dominant score. Participants taking antidepressants were allowed to participate as long as the medication and dose were stable for at least 3 months prior to entering the study and the individual was still exhibiting symptoms of anxiety. The dose and type of medication were required to remain stable throughout the remainder of this study. The use of benzodiazepines was only acceptable provided they were prescribed PRN and were not taken more than two times per week. Potential participants were excluded if they met DSM-IV criteria for an Axis I diagnosis, other than an Anxiety Disorder, as the primary diagnosis and if the participant was

clinically judged by the investigator to be at risk for suicide or has attempted suicide one or more times within the past twelve months. Participants exhibiting a psychiatric condition that would require inpatient or partial psychiatric hospitalization were also excluded as well as those with current abuse of alcohol or other substances. Other exclusion criteria included a history of seizure disorders, significant history of medical disease which could impair reliable participation in the study or necessitate the use of medication not allowed by the protocol. Participants were excluded if they had a pacemaker, were pregnant or planning to become pregnant, or nursing. Participants exhibiting a history of poor treatment adherence were also excluded.

2.3. Outcome measures

Baseline and follow up measurements included the HAM-A and HAM-D_{17}. The HAM-A consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scores range from 0 to 56 where 14–17 indicates mild anxiety, 18–24 indicates moderate anxiety and scores of 25 and over indicate severe anxiety. The Hamilton Depression Scale is a test measuring the severity of depressive symptoms in individuals. It is often used as an outcome measure of depression in research. In the 17-item version, nine of the items are scored on a five-point scale, ranging from 0 to 4. The remaining eight items are scored on a three-point scale. For the 17-item version, scores can range from 0 to 54. Scores from 0 to 6 indicate no depression, scores between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression. Both instruments have demonstrated reliability and validity in the literature and have been used extensively for measuring symptoms of anxiety and depression in clinical trials (Beck & Steer, 1991; Kobak, 2010).

2.4. Study device

The device used in this study was the Alpha-Stim 100. The Alpha-Stim 100 is manufactured by Electromedical Products International (2013), Inc. located in Mineral Wells, TX. The device provides electrical stimulation by generating bipolar, asymmetric, rectangular waves with a frequency of 0.5 Hz and a current intensity that was preset and locked by the manufacturer at its lowest therapeutic dose at 100 μA, a subsensory level. The sham CES devices were identical to the active device, except the ear clip electrodes did not emit electricity. The manufacturer supplied 20 devices for the study. Of the 20 devices, 10 were active CES devices and 10 were sham CES devices. Participants could not change any of the device settings that regulate current and frequency. During the study, each participant was required to treat themselves daily for one hour. Participants were provided treatment logs to document the day, time, and duration of treatment. Follow up measurements took place using the HAM-A and HAM-D_{17} at the end of weeks 1, 3, and 5. At those intervals, the participants met with researchers to assess current symptoms in the same manner as the baseline intake and to determine if subjects had experienced any adverse events.

2.5. Power and sample size calculations

A priori sample size calculations to obtain an effect size of greater than 0.25 are pragmatically important and recommended as the minimum for establishing projected sample requirements (Ferguson, 2009; WWC, 2014) and Cohen(1998) recommends $d=0.50$. Based on the meta-analysis on the effectiveness of CES by Klawansky et al. (1995) who reported a mean effect size of $d=0.62$ for anxiety based on 14 studies and effect sizes for anxiety from CES anxiety studies by Bystritsky et al. (2008) of $d=1.52$ and Voris (1995) who reported $d=1.60$, we expected an effect size from 0.60 to 0.80 for anxiety; 0.80 is considered a large effect by Cohen (1998). We estimated an effect size of $d=0.50$ for depression based on Bystritsky et al. (2008) who reported an effect size of $d=0.41$. The requirements for an effect size of $d=0.50$ for an advanced analysis of variance with covariates (ANCOVA) with fixed effects, main effects and interactions, $p=0.05$, two groups and at least one covariate was 107 participants (Faul, et al., 2007, 2009). The number of participants who were accepted into the study was 115. Some subjects did not complete scheduled follow up measures and at the end of the study there were 57 patients in the active CES group and 51 in the sham CES group at the end of the study, for a total of 108 subjects.

2.6. Participant selection

There were 115 participants selected and who agreed to participate out of 125 participants who initially responded to the study announcement. Participants were enrolled from February 2012 to December 2012. Ten individuals were not selected because they either did not meet the full inclusion criteria or did not demonstrate a willingness to commit to five weeks of daily treatment. The participants were randomized into two groups; an active CES group and a sham CES group. The active CES group had 60 participants (52%) and the sham CES group had 55 participants (48%). Throughout the study, neither the investigators, research staff, nor the participants knew which devices were active or sham. Because people entered and completed the study at different times, a nonparticipating clinician held the research key and was able to determine if a given device was active or sham. If it was found that a participant received a sham device, participants were given the option to obtain treatment with an active device for an additional 5 weeks. Randomization took place through the blind assignment of devices as people passed through the baseline intake phase. In order to maintain randomization, all experimental devices were kept in two separate boxes. As participants entered the study they were given a device and the serial number was recorded on their case chart along with their demographic data. Each participant was number coded. As participants completed the study, the device was collected and placed in a box separate from the other devices. The serial number was given to the non-participating clinician who determined if the device was an active or sham device. As new participants entered the study, they were given a device from the original box until all devices were used. Once all the devices were used, random selection of devices continued in the same manner to ensure the each device had an equal chance of being used in the study. No participant reported any adverse effects verbally or in their treatment log during the study (See Fig. 1, Flow Diagram).

2.7. Statistical methods

Data were entered into a Microsoft Excel (Microsoft Corporation, Redmond, Wash.) spreadsheet and converted into IBM/SPSS (IBM/SPSS, Chicago, IL). The primary analysis was an analysis of covariance (ANCOVA) of the change in scores from baseline to endpoint of study on the HAM-A and HAM-D_{17} using the baseline measure as a covariate to determine any different between the active CES and sham CES groups.

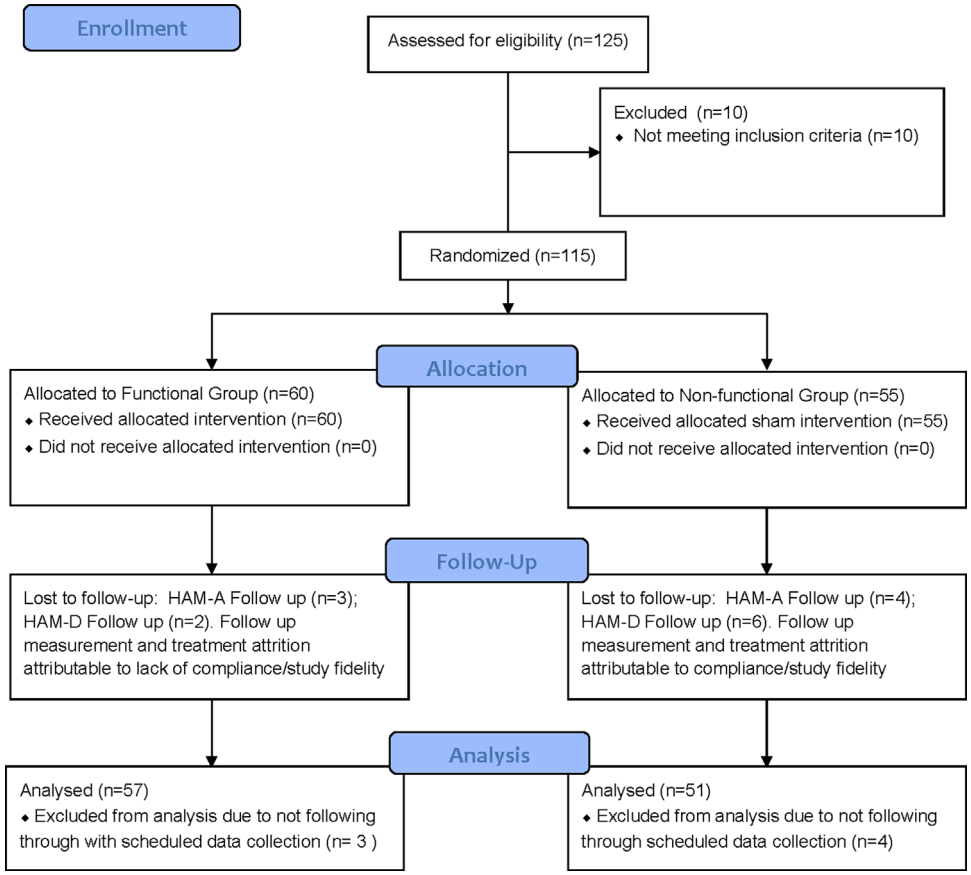

Fig. 1. Flow diagram.

3. Results

3.1. Group equivalence

The mean age of participants was 42.3 years (SD=14.6) with no significant difference between active and sham groups for age ($p=0.711$). The duration of use of prescription medications to treat mental health conditions was 17.2 years on average (SD=12.7) and the number of sessions missed (sham or active) was 1.15 days on average (SD=2.9). The use of prescription medications and days of treatment missed were not significantly different between the two groups ($p=0.934$ and $p=0.727$ respectively).

Additional differences in the active group and sham group for key demographic and clinical conditions were examined by conducting t-tests and chi-square analyses. Chi-square analyses showed no significant relationships out of the nine comparisons run between the proportion of participants who were in the active and sham groups: Gender, Prescribed Medication, Specific Phobia, Post Traumatic Stress Disorder, Panic Disorder, Obsessive Compulsive Disorder, Generalized Anxiety Disorder, Anxiety Disorder NOS, and Depression. Pre-test differences on the HAM-A and HAM-D_{17} assessment measures were examined to determine group differences at baseline. An analysis of means, standard deviations, and t-test results showed that the active CES group performed descriptively better (HAM-A mean, 9.62; HAM-D_{17} mean, 4.87) on the pretests as compared to the sham CES group (HAM-A mean, 5.44; HAM-D_{17}, 2.833) but these differences were not statistically significant ($p<0.001$).

Differences on the HAM-A and HAM-D_{17} baseline measures for other participant characteristics were also examined. Results of the analysis showed no significant differences between the active and sham groups on baseline measures for gender, medication prescribed and all but two of the diagnosed disorders variables, panic disorder diagnosis variable on the HAM-A, $t(111)=-2.820$, $p=0.006$ and the depression disorder diagnosis on the HAM-D_{17}, $t(111)=2.478$, $p=0.015$.

3.2. Measurement attrition

To examine whether or not there was a significant relationship between individuals who provided and did not provide data (at each data point) and group assignment (active or sham), chi-square analyses was utilized to determine if the proportion of measurement attrition was equivalent among groups. The study found the proportional differences were not significant between active and sham groups for each data point (1, 3, and 5 weeks).

3.3. Effect of CES on anxiety and depression

The analyses examined whether the outcome measures for anxiety scores and depression scores differed significantly between the active CES and sham CES groups. A repeated measures ANCOVA was used to analyze the change in scores on the HAM-A (anxiety) and HAM-D_{17} (depression) from baseline to endpoint of the study. Outcome measures were done at weeks 1, 3 and 5. The covariate was the baseline score on the anxiety or depression measures. Levene's test for homogeneity of variances for the two outcome measures for each treatment condition was not significant ($p>0.05$) and it can assumed the variability in the two conditions is similar and one can proceed with analysis of outcomes. In addition, Mauchly's test of sphericity was done and this condition was not met ($p<0.05$). The corrections required to meet this assumption were applied to all multivariate *F*-tests used to analyze outcomes.

The active CES group had significant lower anxiety scores on the HAM-A than the sham CES group from baseline to endpoint of the study ($F=43.404$, df=1, $p=0.001$, $d=0.94$) and significantly lower depression scores on the HAM-D_{17} than the sham CES group ($F=17.050$, df=1, $p=0.001$, $d=0.78$). In the active CES group, 83% had a decrease of $\geq 50\%$ in anxiety scores from baseline to endpoint on the HAM-A ($p<0.001$). The HAM-A decrease in the active CES group of 32.8% (19.89–13.37) was more than three (3) times the mean decrease on the HAM-A for the sham CES group of 9.1% (21.98–19.98) from baseline to endpoint of the study (See Fig. 2).

In the active CES group, 82% had a decrease of $\geq 50\%$ in depression scores from baseline to endpoint on the HAM-D_{17}. The mean decrease on the HAM-D_{17} in the active CES group of 32.9% (9.64–6.47) was more than twelve (12) times the mean decrease on the HAM-D_{17} for the sham CES group of 2.6% (10.22–9.96) from baseline to endpoint of study (See Fig. 3).

Table 1 shows the means and standard deviations from baseline to endpoint of study for weeks 1, 3, and 5.

4. Discussion

This study used a 5 week randomized, double-blind, sham controlled design to test the effectiveness of CES treatment on various anxiety disorders and comorbid depression within a primary care setting. This required participants to return to the clinic for re-evaluation at intervals throughout the duration of the study. While most participants were compliant, a few did not return at designated times but did show up for other evaluations. This loss of data was minimal and did not appear to affect the overall results.

Each participant was required to pay $30.00 to enter the study to mimic the expectation of treatment as seen within a primary

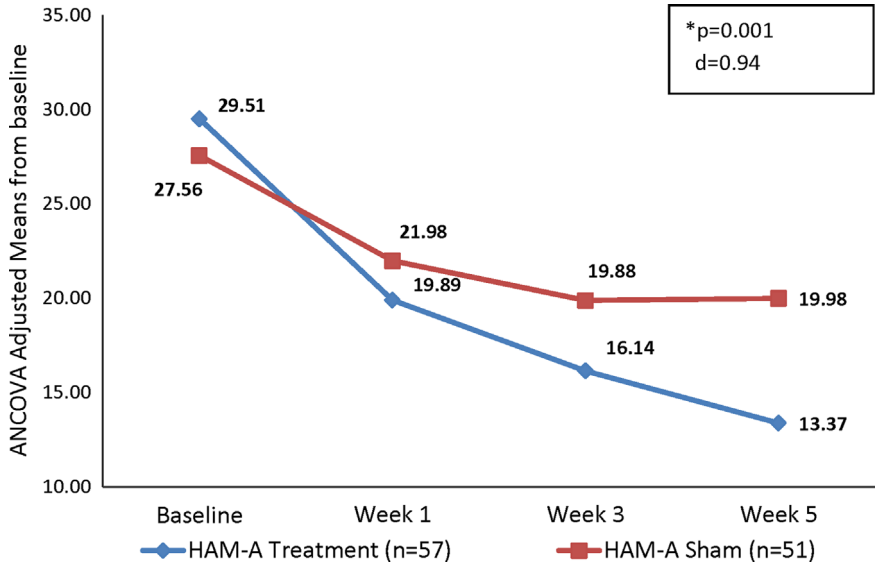

Fig. 2. Adjusted means from baseline for HAM-A scores.

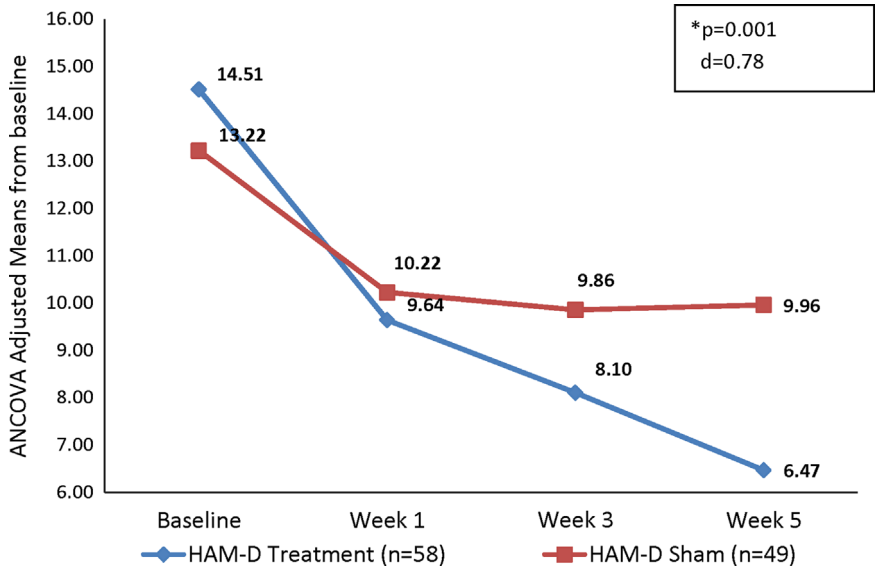

Fig. 3. Adjusted means from baseline for HAM-D_{17} scores.

Table 1
Participant demographics.

Sample characteristics	Functional ($n=60$)		Non-functional ($n=55$)		Total ($n=115$)	
	Count	Percent	Count	Percent	Count	Percent
Gender						
Male	23	62.2%	14	37.8%	37	32.2%
Female	37	47.4%	41	52.6%	78	67.8%
Prescribed medicine						
Yes	38	52.1%	35	47.9%	73	63.5%
No	22	52.4%	20	47.6%	42	36.5%
Specific phobia						
Yes	2	33.3%	4	66.7%	6	5.2%
No	58	53.2%	51	46.8%	109	94.8%
Post-traumatic stress disorder						
Yes	7	53.8%	6	46.2%	13	11.3%
No	53	52%	49	48%	102	88.7%
Panic disorder						
Yes	16	55.2%	13	44.8%	29	25.2%
No	44	51.2%	42	48.8%	86	74.8%
Obsessive compulsive disorder						
Yes	5	38.5%	8	61.5%	13	11.3%
No	55	53.9%	47	46.1%	102	88.7%
General anxiety disorder						
Yes	29	47.5%	32	52.5%	61	53.0%
No	31	57.4%	23	42.6%	54	47.0%
Anxiety disorder						
Yes	5	8.3%	3	5.5%	8	7.0%
No	55	51.4%	52	48.6%	107	93.0%
Depression						
Yes	12	52.2%	11	47.8%	23	20.0%
No	48	52.2%	44	47.8%	92	80.0%

care setting. Because the study was not funded, this fee also helped to offset administrative costs for scheduling and data collection. The $30.00 fee is consistent with an average co-payment for third party carriers and replicated the atmosphere of a treatment setting. In this case, in an effort to maintain a primary care setting, all intakes were performed at the principal investigator's private practice location. Some of the participants were patients of other mental health professionals in the practice while the others received treatment elsewhere. All participants were told to continue their current treatment as prescribed for the duration of the study. One may consider the effects of this expectation on the results, particularly with the sham group. Initial analyses indicated a decrease in symptoms during the first week for both the active and sham groups. During subsequent weeks, symptoms continued to decrease for the experimental group. At week 3, a leveling effect took place for the sham group for both anxiety and depression scores. In the case of the anxiety scores, the mean trend line increased again by the final measurement period. It is possible that a study running 6–8 weeks would see a return to baseline for both anxiety and depression for the sham CES group. Overall change for the sham group from baseline to week 5 indicated a 28% change for anxiety scores and a 24% This fluctuation is believed to be a result of the placebo effect. The degree of the placebo effect in the sham group is within the limits of response as mentioned by Womak et al. (2001) and Walsh et al. (2002) which can be as high as 30% for clinical trials.

The $30.00 fee for the study was used because it was the average copay for treatment at the primary care practice and it was thought that this would increase participants' commitment to the study. This also causes patients to have a psychological expectation to receive something in return. It appears that the $30.00 increased the placebo effect for anxiety particularly in the sham CES group, this finding is consistent with explanations discussed by Beneditti et al. (2005) where beliefs and expectations can alter brain function effecting mental and physical health and Stewart-Williams & Podd (2004) regarding conditioning and verbal information can set up conscious expectations that can mediate the placebo effect.

This study was a randomized, double blind, sham controlled study that addressed the recommendations for future CES studies on anxiety by Bytstritsky et al. (2008). In keeping with what would normally be seen within a primary care setting, participants were required to score on the higher range of mild anxiety at baseline. Typically, these patients often present with comorbid disorders, most likely depression. When participants have comorbid conditions, the interaction between disorders can confound overall symptomology which can be difficult to account for regarding the contribution of each disorder to the other. However, even with the complexity of comorbidity, the findings of this study indicate that CES was an effective treatment for both anxiety and comorbid depression.

4.1. Limitations

A limitation of this study was the small number ($N=23$) of participants who had an anxiety disorder and comorbid depression.

4.2. Future research

Additional research is needed that includes a much larger number of participants with an anxiety disorder and comorbid depression. An important area for future research is on the effect of CES on anxiety and comorbid depression in which subjects have moderate to severe anxiety in order to be accepted into the study, all subjects have anxiety with comorbid depression and cut off scores are used for both anxiety and depression scores.

5. Conclusions

The results of this study confirm the research findings by Bytstritsky et al. (2008) that CES is an effective treatment for

anxiety and comorbid depression. Subjects reported no adverse effects from CES during the study. The large effect sizes for the effects of CES on anxiety and comorbid depression reveal a favorable risk/reward ratio supporting the use of CES for the treatment of anxiety and comorbid depression in evidence-based practice.

Role of funding source

The study, "A Randomized Clinical Trial of Cranial Electrotherapy Stimulation for Anxiety Disorders in Adults", was a non-funded study and took place in a private practice setting.

Conflict of interest

For the manuscript entitled "A Randomized Clinical Trial of Cranial Electrotherapy Stimulation for Anxiety Disorders in Adults". All authors fully contributed to the research and writing of the manuscript. Of the authors listed, there are no conflicts of interest to report in this non-funded study.

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