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A Pilot Study of Safety and Efficacy of Cranial Electrotherapy Stimulation in Treatment of Bipolar II Depression

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Abstract: This double-blind, sham-controlled study sought to investigate the effectiveness of cranial electrotherapy stimulation (CES) for the treatment of bipolar II depression (BD II). After randomization, the active group participants ($n = 7$) received 2 mA CES treatment for 20 minutes five days a week for 2 weeks, whereas the sham group ($n = 9$) had the CES device turned on and off. Symptom nonremitters from both groups received an additional 2 weeks of open-label active treatment. Active CES treatment but not sham treatment was associated with a significant decrease in the Beck Depression Inventory (BDI) scores from baseline to the second week ($p = 0.003$) maintaining significance until week 4 ($p = 0.002$). There was no difference between the groups in side effects frequency. The results of this small study indicate that CES may be a safe and effective treatment for BD II suggesting that further studies on safety and efficacy of CES may be warranted.

Key Words: Bipolar, depression, cranial electrical stimulation

(*J Nerv Ment Dis* 2015;203: 00–00)

Bipolar disorder is a serious mental illness characterized by recurrent episodes of major depression and periods of mania or hypomania (American Psychiatric Association, 2000). Bipolar patients spend three times as many days depressed than hypomanic or manic (Joffe et al., 2004; Kupka et al., 2007). It is a debilitating disorder which results in a 9.2-year reduction in life expectancy and is in the top 10 leading causes of disability in the world (World Health Organization, 2001). In a Danish cohort longitudinal study, the absolute risk of suicide for bipolar females was 4.78% and 7.77% for males (Nordentoft et al., 2011). Hence, it is imperative to find effective and tolerable treatments for bipolar depression.

Despite major research efforts and investments, currently available treatments for bipolar depression are not efficacious and mood episodes are often recurrent (Perlis et al., 2006). Current pharmacological treatments for bipolar depression include the second-generation anti-psychotics, quetiapine and lurasidone, and a combination of olanzapine and the anti-depressant fluoxetine (Vieta and Valentí, 2013; Köhler et al., 2014). Modestly effective, these drugs cause severe weight gain and metabolic syndrome (Fagiolini et al., 2005). Other methods of treatment include anticonvulsant medications such as lamotrigine, valproic acid, and lithium, which are also marginally effective (Calabrese et al., 2008; Reid et al., 2013), though they have possible side effects of increased suicidal thoughts (Sidor and Macqueen, 2011). Antidepressants in bipolar depression can only be used with extreme caution because of the significant risk of mania and cycle acceleration (Post et al., 2003; Koszewska and Rybakowski, 2009; Offidani et al., 2013; Baldessarini et al., 2013). Hence, finding an effective treatment for bipolar depression would greatly improve the lives of many who suffer from bipolar disorder.

Cranial electrotherapy stimulation (CES) is a noninvasive treatment modality, which was cleared by FDA for treatment of a variety of symptoms including anxiety, depression, insomnia, and pain (Bystritsky et al., 2008; Kirsch and Nichols, 2013). However, CES efficacy has not been examined for the treatment of depression in bipolar disorder. There are two available devices, the Alpha-Stim and Fisher Wallace stimulators, which differ in the frequency of the current and the location of the electrodes (Bystritsky et al., 2008). The Alpha-Stim device is applied to the ear lobes and delivers a current between 10 μA and 500 μA at 0.5 Hz frequency (Bystritsky et al., 2008). The Fisher Wallace CES device delivers an alternating current of 5, 500, or 15,000 Hz through electrodes placed on the temples with 1–4 mA of current.

A review of CES treatments over the last 30 years done by Shealy and Thomlinson (2008) showed that out of approximately 30,000 patients with chronic pain who also had symptoms of depression, about 50% showed clinical improvement of depressive symptoms when treated with CES with 1–2 mA, with minimal side effects. However, many of these were uncontrolled, open-label studies and allowed unwitnessed patient self-treatment at home (Shealy and Thomlinson, 2008).

More recently, a double-blind, placebo-controlled trial testing CES efficacy in the treatment of various anxiety disorders and comorbid depression found association of CES with the decrease of symptoms in the first week of treatment in both active and sham groups (Barclay and Barclay, 2014). When the treatment was continued for another 4 weeks, the experimental group showed progressive symptom reduction, whereas the placebo group demonstrated a leveling effect at week 3. The change in scores of anxiety and depression from baseline to the endpoint were significantly different between the groups (Barclay and Barclay, 2014).

In this context, we conducted a pilot randomized double-blind controlled study of the treatment of CES for bipolar II depression. We chose to evaluate CES efficacy and safety for the treatment of bipolar II depression because this group of patients spends more time depressed compared with bipolar I patients (Mantere et al., 2008). Further, bipolar II depression is more difficult to treat than unipolar depression and has been reported to respond poorly to ECT treatments (Ghaemi et al., 2004; Hallam et al., 2009).

As a primary outcome measure, we chose the Beck Depression Inventory (BDI) (Beck et al., 1996), which has been shown to contribute more than the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1967) to the prediction of outcomes in the treatment of depression (Uher et al., 2012). We hypothesized that CES would reduce depression symptom severity in the active group more than in the sham group. We also hypothesized that CES administered for 20 minutes daily for 4 weeks would be safe and well tolerated when treating bipolar II patients.

METHODS

Study Design and Treatment

This is a prospective, double-blind, randomized, sham-controlled study for the use of CES to treat the depressive phase of bipolar II disorder. The study was conducted at the Family Center for Bipolar in New York City from December 2011 to May 2014. The study was approved by Mount Sinai Beth Israel's Institutional Review Board,

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Clinical Trial Registration: clinicaltrials.gov identifier: NCT01909011.

ISSN: 0022-3018/15/20311–0000
DOI: 10.1097/NMD.0000000000000378

and all study participants signed an informed consent form before commencing the study. The trial was conducted in accordance with the Declaration of Helsinki and was registered at clinicaltrials.gov (identifier: NCT01909011).

The 12-week study design included the following three stages: double-blind phase (weeks 1–2), open-label phase (weeks 3–4), and follow-up phase (weeks 5–12). Each participant visited the study site five times per week for treatment. This study used the Fisher-Wallace Cranial Stimulator device with alternating current in three frequencies: 5 Hz, 500 Hz, and 15,000 Hz. The CES treatment was delivered by two electrodes covered with damp sponges and placed over the temples bilaterally with 2 mA of alternating current for one 20-minute session per day for the active treatment group. The use of 2 mA current was recommended by the manufacturer and has been used in other studies evaluating CES treatment effects (Shealy and Thomlinson, 2008). The sham CES treatment was performed by a trained technician who did not take part in any other aspect of the study, by turning the current on until the patient experienced a tingling sensation on the scalp, then turning it off. The treatment itself was a subthreshold for the above sensation.

Participants were randomized into one of the two treatment groups (Active CES or Sham treatment) using a method of random sequence generator. The randomization list was prepared and kept by a clinician who did not participate in any other aspect of the study. The treatment technician contacted the clinician to find out about the randomization for each new participant separately before the start of their treatment.

At the end of phase I, patients whose scores on the HAM-D were ≤7 were considered to be in remission and were moved into the follow-up phase of the trial. All other participants, who had HAM-D scores >7, were crossed over to the open-label treatment phase for another 2 weeks.

Participants

Male and female outpatients aged 23–71 years diagnosed with bipolar II disorder were recruited via advertisements and from clinician referrals. Diagnosis was established using the Structured Clinical Interview (SCID-P) (First et al., 1995) based on the Diagnostic and Statistical Manual (DSM-IV-TR) (American Psychiatric Association, 1994, 2000). To be eligible to participate in the study, participants had to be in a depressive episode at the time of their recruitment, with a score on the Hamilton Rating Scale for Depression (HAM-D 17) ≥13 and ≤28, and a Clinical Global Impressions Severity (CGI-S) score ≤5 (Guy, 1976). Patients were excluded from the study if they had a history of treatment resistant bipolar II depression, defined as the lack of response to two antidepressant trials, were in a manic or mixed episode, had a diagnosis of unipolar depression, schizophrenia, schizoaffective disorder, other (non-mood disorder) psychosis, depression secondary to a medical condition, psychotic features in this or previous episodes, amnestic disorder, dementia, delirium, mental retardation, substance dependence or abuse within the past year (except nicotine), an active suicidal plan, or history of suicide attempt within the past 12 months, as determined by the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). Additional exclusion criteria were significant current history of autoimmune or endocrine disorder affecting the brain, unstable cardiac disease, uncontrolled hypertension, sleep apnea, history of skull fracture, craniotomy, deep brain stimulation, cochlear implants, seizures, epilepsy, pregnancy, or having a pacemaker.

Study participants were allowed to take part in the study if they maintained stable dosages of their antidepressant medications for 2 weeks before entering the study and throughout the treatment period.

Assessment Measures

Mood Measures

Participants were assessed at baseline and then weekly throughout the study with the Beck Depression Inventory (BDI), the Hamilton Rating Scale for Depression HAM-D 17, and the Young Mania Rating Scale (YMRS) (Young et al., 1978).

Measures of Functioning

We used the Clinical Global Impressions scale (CGI), the Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) (Endicott et al. 1993), and the Medical Outcome Survey—Short Form (MOS-SF) (Ware and Sherbourne, 1992).

Cognitive Measures

Cognitive assessment measures included the Cognitive Failures Questionnaire (CFQ) (Wallace and Vodanovich, 2003), the Modified Mini-Mental State (3MS) (Teng and Chui, 1987) examination, and the Autobiographical Memory Inventory (AMI) (Kopelman et al., 1990) administered at baseline, week 2, week 4, and week 12.

All assessments were made by the study psychologist, a trained psychiatry resident and a doctorate-level psychology student who were all blinded to the treatment allocation of the study participants. A standard 64-channel EEG was recorded for 5 minutes before the first CES session and for 5 minutes after the first CES session, and was repeated at the 12th week to evaluate acute and long-term effects of CES on EEG. As a safety measure, EKG was recorded at baseline and repeated at week 12.

At each treatment session, patients reported the number of hours slept the previous night, any changes in medical state since the last treatment, and medication intake. To evaluate the side effects of the treatment, participants were asked to rate drowsiness, blurred vision, dizziness, and headache on a 4-point Likert scale ranging from 1 (none) to 4 (severe) before and after each treatment. Changes in mood state were assessed by patients' report on the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) before and after the treatment.

Statistical Analysis

Demographic and clinical data were compared between active and sham arms using *t*-test for continuous and Fisher's exact test or chi-square test for categorical variables. To evaluate the change in scores from baseline to the end of week 1, week 2, week 4, and week 8, paired samples *t*-tests were performed for the BDI, HAM-D 17, Q-LES-Q-SF, CGI-S, GAF, and YMRS scales. Independent samples *t*-tests were used to compare the mean change in scores from baseline to week 1 and week 2 between groups. Repeated measures analysis of variance (ANOVA) was used for within-group and between-group comparisons on the medical outcomes scale (MOS-SF) physical functioning, role limitations due to physical health, and bodily pain subscales, as well as for the cognitive measures (CFQ, AMI, and 3MS). After assessment of trends, paired samples *t*-tests were used to examine the change in scores for the medical outcomes measure from baseline to the end of week 1, week 2, and week 4, as well as for the cognitive measures from baseline to week 2, week 4, and week 12. Differences in the phase I pretreatment and posttreatment positive and negative affect ratings were compared between the groups using repeated measures analysis (ANOVA). Two missing pretreatment BDI scores were extrapolated from a regression analysis of BDI assessments.

The frequency of side effect incidences was assessed by a change of one or more points from pretreatment to posttreatment side effect scores. The percent of incidences out of total treatments were assessed as well; there were 210 total active treatment sessions and 90 nonactive treatment sessions. The total percentage of participants experiencing a symptom at least once during active treatment was also assessed.

Blood pressure was measured pre- and posttreatment daily for 20 treatments. The mean aggregates per week were calculated for systolic and diastolic pressure for active and sham groups for a total of 4 weeks.

The data displayed the weekly mean per group ±SD for systolic and diastolic pressure.

Two-sided significance was considered at the 0.05 level. SPSS version 11.0 was used to analyze the data.

RESULTS

Participants

The 16 participants were 50% female, with a mean age of 47.62 (SD = 15.88) and an average level of education of 16.81 (SD = 2.401) years. Seventy-five percent of our participants were Caucasian, whereas 12.5% were African-American and 6% were labeled as other; one participant declined to identify their race. One out of the 16 participants had attempted suicide in their lifetime, according to the C-SSRS. The active treatment group participants were older (mean age 52.57 (11.43)) than those in the sham group (43.78 (18.26)), but the difference between groups was not significant. There was no significant difference between the groups in gender, race, relationship status, employment, current symptom severity, number of previous depressive or hypomanic episodes, comorbid anxiety disorders, comorbid personality pathology, past drug abuse or dependence, and medication use, supporting successful randomization (Table 1).

Of the 16 subjects, 10 received antidepressants, 8 received mood stabilizers, 10 were on benzodiapines, and 5 were prescribed antipsychotics. The following comorbidities were identified by the SCID: Panic Disorder $n = 2$, Generalized Anxiety Disorder $n = 6$, Obsessive Compulsive Disorder $n = 1$, Avoidant Personality Disorder $n = 3$, Obsessive Compulsive Personality Disorder $n = 5$, Borderline Personality Disorder $n = 5$, Narcissistic Personality Disorder $n = 3$, and Histrionic Personality Disorder $n = 1$. There was no difference between the groups in either comorbidities or concomitant medications.

Efficacy of CES

The results of the analysis are reported in Table 2 and Figures 1–5. On repeated measures ANOVA, there was no significant difference between the active and the sham groups on any of the mood

TABLE 1. Demographic and Clinical Characteristics

Characteristic	Active Group ($N = 7$) N (%) or Mean ± SD	Sham Group ($N = 9$) N (%) or Mean ± SD	t/χ^2	p
Age	52.57 ± 11.43	43.78 ± 18.26	1.178	0.259
Gender				
Male	5 (71.4)	3 (33.3)		0.315
Race			0.938	0.626
White	6 (85.7)	6 (66.7)		
Black	1 (14.3)	1 (11.1)		
Other	0 (0.00)	1 (11.1)		
Years of school	16.43 ± 2.29	17.11 ± 2.57	−0.551	0.590
Single/separated/divorced	3 (42.9)	7 (77.8)		0.329
Employed or student	3 (42.9)	2 (22.2)		0.596
Symptom severity			1.778	0.411
Mild	1 (14.3)	1 (11.1)		
Moderate	6 (85.7)	6 (66.7)		
Severe without psychosis	0 (0.00)	2 (22.2)		
Past depressive episodes				0.315
0–10	2 (28.6)	6 (66.7)		
>11	5 (71.4)	3 (33.3)		
Past hypomanic episodes				1.000
0–10	5 (71.4)	7 (77.8)		
>11	2 (28.6)	2 (22.2)		
Comorbid anxiety disorders	1 (14.3)	5 (55.5)		0.145
Comorbid personality disorders	6 (85.7)	7 (77.8)		1.000
Borderline	1 (14.3)	4 (44.4)		0.308
Narcissistic	3 (42.9)	0 (0.00)		0.063
OCPD	2 (28.6)	3 (33.3)		1.000
Avoidant	1 (14.3)	2 (22.2)		1.000
Histrionic	1 (14.3)	0 (00)		0.438
Past hospitalizations	3 (42.9)	4 (44.4)		1.000
Medications				
Antidepressant	5 (71.4)	5 (55.6)		0.633
Mood stabilizers	3 (42.9)	5 (55.6)		1.000
Benzodiazepines	4 (57.1)	6 (66.7)		1.000
Antipsychotics	2 (28.6)	3 (33.3)		1.000
Other	5 (71.4)	7 (77.8)		1.000
Past drug abuse	0 (0.00)	1 (11.1)		1.000
Past drug dependence	1 (14.3)	1 (11.1)		1.000

TABLE 2. Paired Samples *t*-Tests and Independent Samples *t*-Test Comparing Active and Sham Groups

	Treatment Effect Over Time				Active Treatment vs. Placebo											
	Baseline—Week 1		Baseline—Week 2		Baseline				Week 1				Week 2			
Scales	95% CI	*p*	95% CI	*p*	Mean (SD)	Mean Diff. Between Groups at Baseline	*t*	*p*	Mean (SD)	Mean Diff. Baseline - Week 1 (SD)	*t*	*p*	Mean (SD)	Mean Diff. Baseline - Week 2 (SD)	*t*	*p*
Primary outcomes																
BDI																
Active	[1.21–20.8]	0.033	[6.6–19.4]	0.003	30.58 (10.54)				19.57 (6.73)	−11.01 (10.59)			17.57 (11.31)	−13.01 (6.95)		
Sham	[0.91–17.5]	0.034	[−1.2–8.7]	0.119	29.65 (13.06)	0.93	0.873	0.397	20.44 (8.85)	−9.20 (10.78)	−0.334	0.743	25.89 (11.60)	−3.76 (6.44)	−2.753	0.016
HAM-D																
Active	[3.61–8.67]	0.001	[3.4–11.2]	0.004	18.14 (4.74)				12.00 (3.56)	−6.14 (2.73)			10.86 (6.18)	−7.29 (4.19)		
Sham	[0.9–11.1]	0.027	[1.4–9.7]	0.015	20.67 (5.22)	−2.52	−0.998	0.335	14.67 (4.47)	−6.00 (6.65)	−0.053	0.958	15.11 (3.86)	−5.56 (5.39)	−0.699	0.496
Secondary outcomes																
CGI-S																
Active	[0.1–1.1]	0.03	[0.2–1.5]	0.017	4.57 (0.53)				4.00 (0.58)	−0.57 (0.53)			3.71 (0.76)	−0.86 (0.69)		
Sham	[−0.3–0.7]	0.347	[−0.5–0.7]	0.681	4.44 (0.53)	0.13	0.475	0.642	4.22 (0.44)	−0.22 (0.67)	−1.129	0.278	4.33 (0.50)	−0.11 (0.78)	−1.99	0.066
Q-LES Q																
Active	[−24.3–(−2.7)]	0.023	[−37.9–0.9]	0.058	35.00 (17.78)				48.50 (12.97)	13.50 (10.27)			53.50 (16.05)	18.50 (18.53)		
Sham	[−23.5–3.3]	0.117	[−11.8–14.8]	0.797	31 (15.35)	4	0.451	0.66	41.13 (18.83)	10.13 (16.01)	0.449	0.661	29.50 (17.24)	−1.50 (15.86)	2.174	0.050
GAF																
Active	[−7.1–7.1]	1.00	[−7.6–0.8]	0.093	55.14 (7.20)				55.14 (3.89)	0.00 (7.64)			58.57 (6.68)	3.43 (4.54)		
Sham	[−13.2–2.3]	0.144	[−9.6–5.1]	0.504	50.11 (5.93)	5.03	1.536	0.147	55.56 (7.49)	5.44 (10.09)	−1.185	0.256	52.33 (7.68)	2.22 (9.54)	0.307	0.763
YMRS																
Active	[−2.3–1.6]	0.2	[−2.7–0.4]	0.121	0.71 (0.95)				1.57 (2.23)	0.86 (1.57)			1.86 (2.19)	1.14 (1.68)		
Sham	[−2.3–1.6]	0.705	[−1.1–0.2]	0.169	1.00 (1.23)	−0.06	−0.114	0.911	1.11 (2.03)	0.11 (2.03)	0.802	0.436	1.22 (1.09)	0.22 (1.20)	1.282	0.221

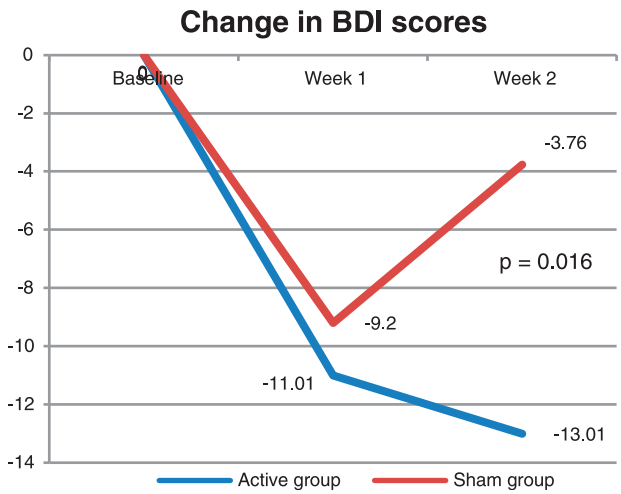

FIGURE 1. Change in BDI scores from baseline to week 1 and week 2.

or functioning scale scores. In further analyses, in the active group, a paired *t*-test from baseline to end of phase I revealed a significant effect (CI 6.58–19.43, $p = 0.003$), whereas no significant difference was found from baseline to end of phase I in the sham group. The mean change from baseline to end of phase I was significantly different between the groups ($p = 0.016$). In both the active and the sham groups, a paired *t*-test from baseline to week 1 produced near-identical significant effects that did not differ between the groups, suggesting a strong placebo response in the first week of CES treatment. The mean change from baseline in the active group maintained significance until week 4 ($p = 0.002$) and was reduced to a trend ($p = 0.09$) by week 8. The mean change in the sham group was significant from baseline to week 4 ($p = 0.013$) and week 8 ($p = 0.048$). In contrast, for HAM-D, paired *t*-tests revealed significant decreases in participants' HAM-D scores in both the active and the sham group from baseline to end of phase I. The mean change was not significantly different between the groups; however, the significant difference from baseline was still present at week 8 for both groups.

For CGI-S, paired *t*-tests in the active group revealed a significant change from baseline to end of phase I while no difference between the two time points was found for the sham group. The mean change from baseline to end of phase I approached significance between groups ($p = 0.066$). Finally, for Q-LES-Q-SF scores, paired *t*-tests

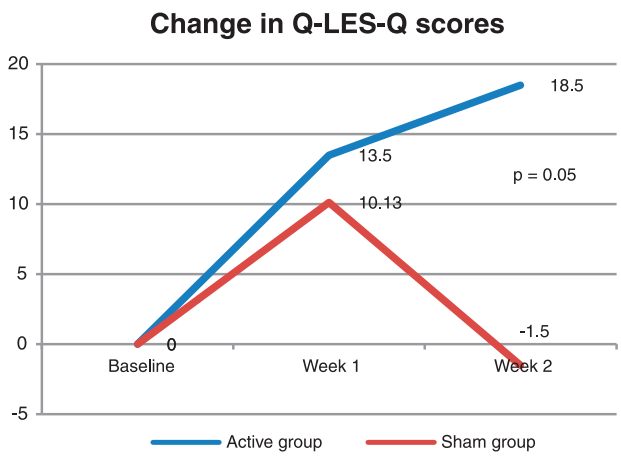

FIGURE 2. Change in Q-LES-Q scores from baseline to week 1 and week 2.

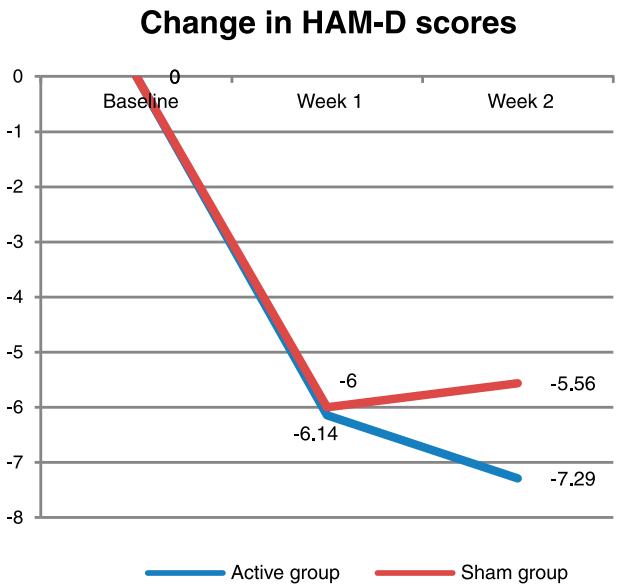

FIGURE 3. Change in HAM-D scores from baseline to week 1 and week 2.

of change from baseline to end of phase I approached significance for only the active group ($p = 0.058$).

Neither YMRS nor PANAS total and subscale scores changed appreciably through the study, and no significant differences were found between the active and the sham groups and within the groups at any of the time points.

Safety of CES

On repeated measures ANOVA, there was no significant difference between the active and the sham groups or within groups at any time points on AMI, 3MS, MOS-SF, and CFQ scores. The paired samples *t*-test showed significant difference in the active group reduction of subjective bodily pain from baseline to week 1 ($p = 0.041$) and week 2 ($p = 0.058$). The active group also demonstrated improved cognitive functioning from baseline to week 4 ($p = 0.045$) (Table 3). There was no significant difference between the active and the sham groups in

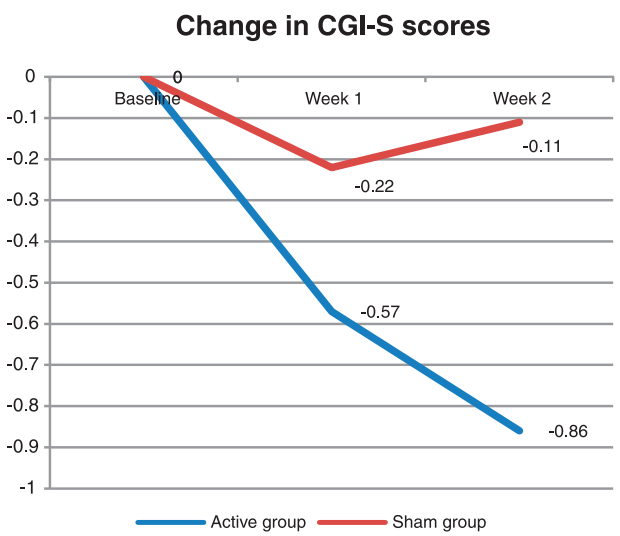

FIGURE 4. Change in CGI-S scores from baseline to week 1 and week 2.

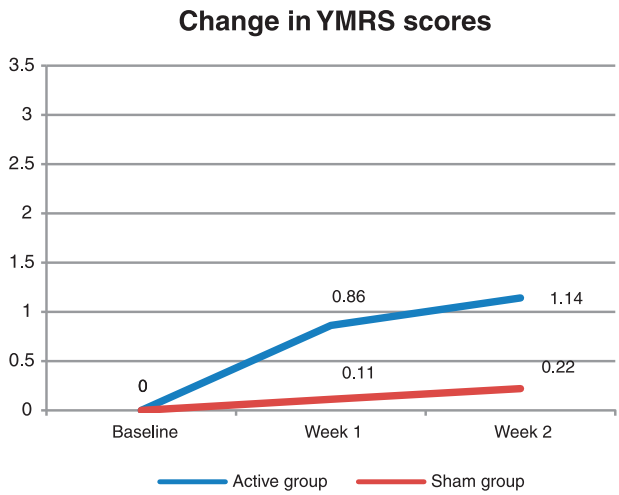

FIGURE 5. Change in YMRS scores from baseline to week 1 and week 2.

reported drowsiness, blurred vision, dizziness, or headache (Table 4). No EEG or EKG abnormalities were detected for any of the subjects.

DISCUSSION

This study sought to evaluate the efficacy and safety of cranial electrotherapy stimulation in the treatment of bipolar II depression. We hypothesized that the active group receiving CES treatment would have a significant reduction in depressive symptoms when compared to the sham group. Our findings were consistent with this hypothesis, suggesting that CES may be effective in the treatment of bipolar II depression. To our knowledge, this is the only double-blind, sham-controlled study of CES for treatment of this disorder.

Our results are consistent with two other recent studies of CES for depression and anxiety. An open-label study of CES for Generalized Anxiety Disorder showed that CES may improve anxiety symptoms associated with GAD (Bystritsky et al., 2008). A more recent double-blind, placebo-controlled trial of patients diagnosed with anxiety disorders and comorbid depression demonstrated CES to be associated with a decrease in anxiety and depression symptoms (Barclay and Barclay, 2014).

Despite the fact that the efficacy of CES has been studied and the device is broadly used, its mechanism of action has not been firmly established. In a study of CES modeling using magnetic resonance imaging, significant amounts of current were found to pass the skull and reach cortical and subcortical structures (Datta et al., 2013). Feusner and colleagues thus suggested that CES delivered through the earlobes works by stimulating afferent branches of cranial nerves, eventually reaching the brainstem, the thalamus, and finally the cortex (Feusner et al., 2012).

To date, Feusner's study is the only one to investigate the neuroanatomical correlates of CES. Results of functional neuroimaging with simultaneous 0.5 Hz and 100 Hz frequency CES stimulation demonstrated deactivation in the left supplementary motor area, bilateral precentral and postcentral gyri, right posterior cingulate cortex, right lateral occipital cortex, bilateral precuneus, right and left supplementary

TABLE 3. Paired Samples *t*-Test for Medical Outcomes and Cognitive Measures Within Groups Over Time

	Baseline—Week 1				Baseline—Week 2			Baseline—Week 4			Baseline—Week 12		
	Baseline	Week 1			Week 2			Week 4			Week 12		
Measures	Mean (SD)	Mean (SD)	*t*	*p*	Mean (SD)	*t*	*p*	Mean (SD)	*t*	*p*	Mean (SD)	*t*	*p*
MOS-SF Physical Functioning													
Active	81.67 (24.01)	87.50 (23.61)	−1.56	0.180	83.33 (24.22)	−1.00	0.363	81.67 (30.11)	0.00	1.00	—	—	—
Sham	68.13 (31.28)	71.25 (23.11)	−0.46	0.657	69.38 (31.90)	−0.45	0.668	66.88 (33.16)	0.61	0.653	—	—	—
MOS-SF Role Limitations due to Physical Health													
Active	65.00 (41.83)	100 (0.00)	−1.87	0.135	80.00 (44.72)	−0.514	0.634	50.00 (50.00)	1	0.374	—	—	—
Sham	50.00 (53.45)	53.13 (41.05)	−0.15	0.885	59.38 (44.20)	−0.55	0.598	37.50 (51.76)	0.55	0.598	—	—	—
MOS-SF Pain													
Active	74.67 (25.78)	86.00 (18.50)	−2.75	0.041	87.67 (14.11)	−2.45	0.058	84.00 (14.81)	−1.77	0.137	—	—	—
Sham	49.50 (36.68)	53.88 (33.60)	−0.35	0.734	49.63 (21.31)	−0.01	0.993	52.72 (29.31)	−0.29	0.784	—	—	—
CFQ													
Active	48.50 (12.44)	40.17 (14.12)	2.18	0.081	39.67 (20.85)	2.14	0.086	39.33 (19.45)	2.66	0.045	—	—	—
Sham	54.88 (14.25)	49.13 (19.22)	1.82	0.110	58.13 (18.22)	−0.90	0.397	50.13 (19.33)	1.39	0.21	—	—	—
AMI Personal Semantic													
Active	59.21 (5.58)	—	—	—	59.36 (5.75)	−0.28	0.793	56.71 (12.83)	0.89	0.406	62.17 (0.76)	−0.16	0.885
Sham	52.28 (8.11)	—	—	—	56.00 (7.25)	−1.57	0.156	55.17 (7.88)	−1.25	0.248	54.38 (9.10)	−0.94	0.378
AMI Autobio graphical Incidents													
Active	26.00 (1.15)	—	—	—	25.29 (4.54)	0.51	0.63	23.43 (8.20)	0.93	0.39	27.00 (0.00)	−1.00	0.423
Sham	24.33 (4.61)	—	—	—	25.67 (3.04)	−0.94	0.377	25.33 (3.04)	−0.67	0.524	24.00 (4.24)	0.00	1.00
3MS													
Active	96.57 (4.69)	—	—	—	98.00 (2.24)	−1.26	0.253	97.71 (3.9)	−1.22	0.27	97.67 (2.52)	−0.56	0.635
Sham	96.44 (4.10)	—	—	—	97.56 (2.83)	−1.41	0.197	97.89 (2.80)	−1.13	0.292	95.25 (4.71)	0.64	0.544

TABLE 4. Side Effects Associated With the Use of CES

	Percent of Patients Reporting Event		Percent of Incidences per Total Number of Treatments	
Side Effect	CES ($N = 18$)	Sham ($N = 9$)	CES ($N = 210$)	Sham ($N = 90$)
Drowsiness	61	66.7	8.1	10
Blurred vision	22	22.2	4.8	7.8
Dizziness	16.7	16.7	1.9	1.1
Headache	44.4	77.8	9.5	10

motor area, right supramarginal gyrus, right superior parietal lobule, and left superior frontal gyrus. The authors suggested that even the small disruptions in brain oscillation patterns created by CES may cause significant changes in brain activity, thus interrupting brain function in the listed areas (Feusner et al., 2012). Of note, similar neuroanatomical correlates were found with antidepressant medications. In studies of resting state brain activity in depressed patients, activity in the left superior frontal gyrus was found to be deactivated after treatment with SSRIs (Fitzgerald et al., 2008). This indicates that the antidepressant effect of CES may be correlated with similar functional changes to those produced by treatment with SSRIs.

Further, Feusner and colleagues investigated the effect of CES on the Default Mode Network (DMN), the intrinsic neural network involving posterior cingulate cortex, the precuneus, and regions of the ventromedial prefrontal cortex, which show spontaneously organized neural activity in individuals who are alert but not involved in an attention requiring behavior (Raichle et al., 2001). These intrinsic neural networks have been shown to have abnormalities in populations diagnosed with depression and anxiety (Broyd et al., 2009). CES stimulation f 100 Hz significantly altered connectivity within DMN areas known to be associated with higher levels of maladaptive, depressive rumination (Hamilton et al., 2011; Feusner et al., 2012), which may explain why CES was found clinically to relieve depressive symptoms.

Consistent with previous reports, our results also showed a significant decrease in clinician-rated illness severity scores of the active group relative to the sham group (Amr et al., 2013). In addition, quality-of-life scores also improved significantly in the active group but not in the sham group which may be associated with the decrease in depression symptoms and an improvement in functioning. Finally, on a trend level, CES treatment was associated with improvement in cognitive functioning and a decrease in the self-report of bodily pain in the active group only. Our findings are consistent with other studies examining CES efficacy in various therapeutic areas, which include improvements in symptoms of fibromyalgia, fatigue, sleep disturbance and anxiety, improved attention, as well as a decrease in cognitive brain dysfunction and methadone cravings in chemically addicted patients (Taylor et al., 2013; Southworth, 1999; Gomez and Mikhail, 1978; Schmitt et al., 1984). There were no differences in side effects between the groups, such as drowsiness, blurred vision, dizziness, or a headache, but that was probably due to the small sample size.

In this study, we did not aim to investigate the use of CES to treat anxiety symptoms, unlike the previous study examining CES use in treatment of GAD (Bystritsky et al., 2008). Although some of our study patients had comorbid anxiety disorders, their baseline anxiety levels were low. Hence, it is not unexpected that no significant difference in anxiety levels was observed after the treatment. Furthermore, there were no significant changes in the hypomania/mania scores from baseline to the end of the treatment phase or the end of the follow-up in any group. Thus, we see no evidence of CES inducing a switch from depression to hypomania/mania.

In contrast to self-report measures, clinician-rated HAM-D scores showed significant improvement for both active and sham groups whereas the decrease of BDI scores was associated with the active CES treatment only. This result is not entirely surprising given previous reports that self-rated questionnaires assess depression more broadly compared to clinician-rated scales (Uher et al., 2012; Lindström et al., 2001; Lasalvia et al., 2002). Further, studies comparing self-report with clinician-rated scales found that the scores of self-report measures contributed more to the prediction of outcomes in the treatment of depression, provided more clinical information, and were stronger predictors of subjective quality of life (Uher et al., 2012; Lindström et al., 2001; Lasalvia et al., 2002).

Of note, the study of brain-map correlations demonstrated that the BDI is correlated with more extensive, global brain regions than the Hamilton Depression Rating Scale (Milak et al., 2010). BDI scores were more positively associated with activity in the brain regions relating to production and regulation of emotion and cognition, namely the basal ganglia, cingulate gyrus, and anterior cingulate, while negatively associated with regions such as the dorsal anterior cingulate, which shows dysfunctional regulation in depressed individuals (Milak et al., 2010). Further, these regions (Milak et al., 2010) are among those that have been intrinsically connected to the CES mechanism of action, supporting our finding that active CES treatment led to significant improvement in BDI score.

The results of our study suggest that CES may be an effective and low-risk treatment for patients struggling with bipolar depression, but they must be viewed within the study's limitations. Our data was collected from a fairly small sample size and a specific sub-population of bipolar II depressed individuals, which limits the generalizability of our findings. Replication of our findings with a larger population would validate our results. Although the active group showed significantly lower scores on the BDI scale ratings compared to the sham group, the significant treatment effect between groups was not reached on the repeated measures ANOVA, which may have been underpowered to show this effect. In addition, the study protocol required participants to come to the study laboratory five days a week for at least 1 hour per day. This may have caused a self-selection bias in our participants, the majority of whom were unemployed and single. Although we attempted to minimize the potential of unblinding by the sense of "tingling" on the skull, the actual degree of blinding/unblinding was not tested. Additionally, some patients had changes to the doses of their medication other than antidepressants during the treatment. Finally, treatment adherence and effectiveness of the CES in the "real world" ambulatory conditions may be lower than those in the controlled research clinical setting. However, this study has significant strengths—it is the first randomized double-blind study of CES in bipolar II depression, which has relatively few treatment options, and the second such study of CES overall. The research was conducted in a controlled setting at the office rather than at home, in contrast to previous reports.

CONCLUSIONS

Our study suggests that CES results in reduction of self-reported symptoms of depression and is well tolerated. Larger and more definitive future studies are necessary to test if CES is a useful treatment for this debilitating illness.

ACKNOWLEDGMENTS

The authors thank Gaiane Kazariants, PhD, Anna Buchanan, DO, and Jerald Gardner, MA, for their dedicated services and appreciate their contribution with data collection. The authors would also like to thank Allison MR Lee, MD, for her assistance with posttreatment patient evaluations.

DISCLOSURES

The study was supported by a research grant from Fisher Wallace Laboratories.

The authors declare no conflict of interest.

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