A double-blind randomized placebo controlled study of cranial electrotherapy stimulation for the treatment of depression in bipolar II disorder

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Abstract

Introduction: Cranial Electrical Stimulation (CES) technology has been used widely for treatment of depression, anxiety and insomnia, but to date, there have been no studies examining the efficacy of this technology to treat bipolar II depression. Our goal in this study was to evaluate the use of CES for treatment of the symptoms of depression in bipolar II disorder. We examined changes in levels of depression and quality of life during the four week treatment period.
Methods: Patients diagnosed with bipolar II disorder and currently depressed by SCID-P were recruited from the Family Center for Bipolar in NYC. Participants were randomly assigned to either a placebo group or an active group for the first two weeks of daily 20 minute CES treatment sessions. Both groups received open-label active treatment for an additional two weeks following the randomization period. Participants were assessed at baseline, and weekly during the treatment period, using the Hamilton Depression Rating Scale (HAM-D), the Beck Depression Inventory (BDI), Clinical Global Impressions Scale (CGI-S), and the Quality of Life Satisfaction and Enjoyment Questionnaire (Q-LES-Q). ANOVAs were run to compare the groups at baseline, 1st assessment and 2nd assessment; independent t-tests to analyze differences at each time period between groups, and paired t-tests to analyze the quantitative changes between each time point.
Results: The sixteen participants were 50% female, with a mean age of 47.69 (15.88), and an average level of education of 16.81 (2.401) years. Results showed a significant interaction between BDI scores and the treatment group (p =.006). There is a significant main effect of treatment group on HAM-D scores (p=.00). Groups did not differ significantly on any of the assessment measures at baseline. At week two, the active group compared to placebo had significantly higher scores on Q-LES-Q scale (p=.010) There was a significant decrease in participants' HAM-D and BDI scores in the active group from baseline to the second week (p=.004, p=.004) and baseline to the fourth week (p=.002, p=.015).The placebo group showed a significant decrease on BDI scale scores from baseline to week four (p=.012), but no significant change from baseline to week two. In the placebo group, there was a significant change from baseline to 2 weeks on HAM-D scores, (p=.015), and during the open label treatment phase from 2 weeks to 4 weeks, (p=.022). In the active group, there was a significant decrease in severity scores using CGI-S from baseline to second week, and baseline to 4th week, (p=.017), while there is no significant difference in means for the placebo group.
Discussion: Our preliminary results indicate that the active group had significantly higher reduction in depression levels compared to the placebo group. During the double-blind randomized and controlled trial of the first 2 weeks, there was a significant decrease in BDI scores for only the active group. However, the data displays improvement effects for both groups on the Hamilton Depression Rating Scale, which may be due to the difference in brain regions associated with HAM-D and BDI. Also, patients who received active treatment had decreased severity of the illness on CGI-S measures, while the placebo group had no change on the CGI-S scale. Clinical implications of this study include validating the safety and efficacy for CES in treatment of depression in bipolar II disorder.
Keywords: bipolar II depression, cranial electrical stimulation This research was funded by the Fisher Wallace Laboratories.

Introduction

- Bipolar II disorder is challenging to treat, with only marginally effective treatments.
- CES has been used for pain, anxiety, insomnia and depression (Kirsch & Nichols, 2013).
- Lack of research with controlled, randomized and double-blind trials, specifically with bipolar II patients currently depressed.
- Another study examining CES on bipolar disorder looked at chart reviews, N=7, and yielded no significant results. (Mostafa et al, 2013)
- Clinical implications include validating the safety and efficacy of Cranial Electrotherapy Stimulation for the treatment of depression.

Hypothesis

- In this study, we hypothesize that CES will reduce depression symptom severity in the active group more than in placebo group. We also hypothesize that CES administered for 20 minutes daily for four weeks is safe and well tolerated when treating bipolar II patients.

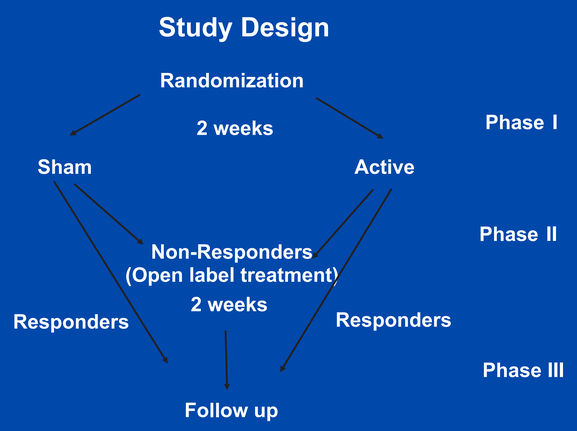
Methods

- 16 patients diagnosed with Bipolar II Disorder and currently depressed by SCID-P & HAMD were recruited by the Family Center for Bipolar in New York City and randomly assigned to active or placebo group for the first 2 weeks of tx.
- Assessments of depression: HAM-D, BDI, CGI-S, Q-LESQ
- Cognition: AMI, MMS, CFQ
- Safety: pre and post treatment blood pressure, EEGS, EKGS, side effects

Side effects were calculated by counting the incidences during active treatment (total=210) versus during non-active treatment (n=90). The number of participants who reported event were counted. A symptom was noted as having a change greater than or equal to one difference from pre treatment to post treatment. Side effects were rated from 1=none to 4=severe.

- ANOVAs were run to compare trends during phase I, and independent t-tests were used to analyze the quantitative differences at each time point. Paired t-tests were used to analyze the within group changes from baseline to week 1, and baseline to end of Phase I.

Study Design



Results

Table 1. Demographic and Clinical Characteristics

Characteristic	Active Tx, N=7 Mean (SD)	Placebo, N=9 Mean (SD)	p
Age	51.33(11.99)	43.78(18.26)	.279
Years of Education	15.83(1.84)	17.11(2.57)	.590
	N(%)	N(%)	
Employed or student	2(28.6)	2(22.22)	
Single/Separated/Divorced	3(42.9)	7(77.8)	.329
Sex: Male	5(71.4)	3(33.3)	.315
Comorbid personality disorders	6(85.7)	7(77.8)	1.00
Borderline	1(14.3)	4(44.4)	.308
Narcissistic	3(42.9)	0	.063
OCPD	2(28.6)	3(33.3)	1.00

Safety of CES:

- **A repeated analysis of variance was conducted on AMI, MMS, and CFQ, and no significant trends or effects were displayed. There were no changes within groups or between groups throughout the treatment.**

Blood Pressure:

- **Mean aggregates for each week, from weeks 1-4 for active and placebo were conducted.**
- **No significant changes in systolic or diastolic pressure were found.**

Table 2. Side effects associated with the use of CES

Side Effect	Percent of Patients Reporting Event		Percent of Incidences per Total Number of Treatments	
	CES (n=18)	Placebo (n=9)	CES (n=210)	Placebo (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

Discussion

Efficacy:

- **Results of the paired sample t test revealed that the active group experienced greater reduction in depressive symptoms, such as BDI, CGI-S, and Q-LES-Q.**
- **Both groups improved on HAM-D, possible explanation is the placebo effect or different brain regions being associated with HAM-D and BDI.**

Safety & Tolerability:

- **Results support our hypothesis that CES is a safe and non-invasive course of treatment.**
- **The results indicate that there was no significant difference between groups on AMI (autobiographical memory), MMS, or CFQ during phase I.**
- **Blood pressure showed no significant changes after analysis of mean aggregates per week for four weeks.**
- **This supports our hypothesis that physical functioning and limitations due to physical functioning are not negatively impacted from use of cranial electrotherapy stimulation.**
- **Implications of this study include improving treatment for depression in bipolar II disorder.**
- **Limitations of this study include the small sample size, and the specificity of the population in regards to low external validity.**
- **Future studies replicating the safety and efficacy of CES on a larger sample size would help validate our results.**

References

Kirsch D., Nichols F., (2013).
Cranial Electrotherapy Stimulation for Treatment of Anxiety, Depresion, and Insomnia. The Psychiatry Clinics of North America.

Mostafa A., El-Wasify M., Elmaadawi A., Jeannie R., Mallakh R., Cranial Electrotherapy Stimulation for the Treatment of Chronically Symptomatic Bipolar Patients. (2013) Journal of ECT.

Results (continued)

HAM-D

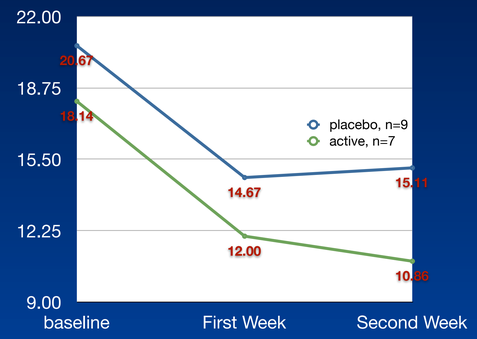


Figure 1.A: HAM-D scores during double-blind randomized control phase.

BDI

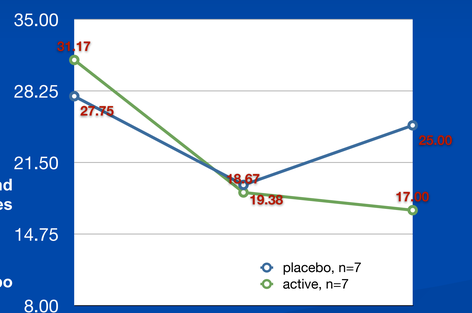


Figure 1.B: BDI scores during double-blind randomized control phase.

CGI-S

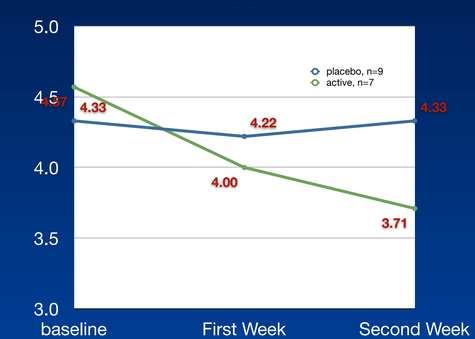


Figure 1.D CGI-S scores during double-blind randomized control phase. p approaches significance, p=.067 at week 2.

Q-LESQ

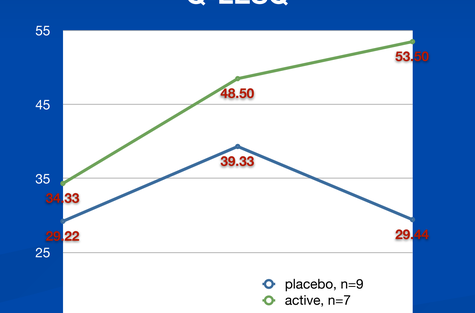


Figure 1.C: Q-LESQ scores during double-blind randomized control phase. P<.05 At week 2

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Table 3.ANOVA & T-test results

Scales	Total N	Time and treatment interaction F	Time and treatment interaction p	Active treatment vs. placebo Baseline Mean (SD)	Week 1 Mean diff.	Week 1 t	Week 1 p	Week 1 Mean (SD)	Week 2 Mean diff.	Week 2 t	Week 2 p	Week 2 Mean (SD)	Treatment effect over time Baseline - Week 1 Mean diff.	Treatment effect over time Baseline - Week 1 t	Treatment effect over time Baseline - Week 1 p	Treatment effect over time Baseline - Week 1 95% CI	Treatment effect over time Baseline - Week 2 p	Treatment effect over time Baseline - Week 2 95% CI	Treatment effect over time Baseline - Week 2 p
Primary Outcomes:																			
BDI																			
Placebo	9			27.75 (12.86)	3.42	0.52	0.62	19.38 (8.82)	-1.02	-0.26	0.802	25.00 (12.07)	-8.32	-2.44	0.172	[-1.01 - 17.76]	7.30E-0:	[-2.34 - 7.84]	0.242
Active	7			31.17 (11.43)				18.67 (6.68)				17.00 (12.28)				[1.07 - 23.93]	3.80E-0:	[7.01 - 21.33]	4.00E-03
time x tx group interaction		10.89	6.00E-0:																
HAM-D																			
Placebo	9			18.14 (4.74)	-2.52	-1	0.34	14.67 (4.47)	-2.67	-1.29	0.218	15.11 (3.86)	-4.25	1.7	0.112	[0.89 - 11.11]	2.70E-0:	[1.41 - 9.70]	1.50E-02
Active	7			20.67 (5.22)				12 (3.56)				10.86 (6.18)				[3.61 - 8.67]	1.00E-0:	[3.41 - 11.16]	4.00E-03
time x tx group interaction		*0.489*	*0.496*																
Secondary Outcomes:																			
CGI-S																			
Placebo	9			4.33 (0.5)	0.24	0.92	0.38	4.22 (0.441)	-0.22	-0.88	0.396	4.33 (0.5)	-0.62	-1.97	6.90E-	[-0.49 - 0.71]	0.681	[-0.54-0.54]	1
Active	7			4.57 (0.54)				4.00 (0.577)				3.71 (0.756)				[0.08 - 1.07]	0.03	[0.22 - 1.5]	1.70E-02
time*tx group		*5.906*	*2.90E-0.*																
Q-LES Q																			
Placebo	9			29.22 (14.84)	5.11	0.6	0.56	39.33 (18.41)	8.67	1.08	0.299	29.44 (16.13)	23.56	2.984	0.01	[-21.94 - 1.72]	8.40E-0:	[-12.2 - 11.75]	0.967
Active	6			34.33 (18.21)				48.5 (12.97)				53.5 (16.40)				[-24.54 - (-3.79)]	1.70E-0:	[-37.8 - (-.53)]	4.60E-02
time*tx group		*4.774*	*4.80E-0.*																
GAF																			
Placebo	9			50.11 (5.93)	5.03	1.54	0.15	55.56 (7.49)	-0.13	0.897		52.33 (7.68)	6.24	1.703	0.111	[-13.2 - 2.31]	0.144	[-9.55 - 5.11]	0.504
Active	7			55.14 (7.20)				55.14 (3.89)				58.57 (6.68)				[-7.06 - 7.06]	1	[-7.63 - 0.77]	9.30E-02
time*tx group		*9.40E-0*	*0.763*																
YMRS																			
Placebo	9			0.78 (1.20)	-0.06	-0.11	0.911	1.11 (2.03)	0.46	0.43	0.672	1.11 (1.05)	0.75	0.902	0.383	[-2.29 - 1.63]	0.705	[-1.1 - 0.44]	0.347
Active	7			0.71 (0.951)				1.57 (2.23)				1.86 (2.19)				[-2.31 - 0.6]	0.2	[-2.69 - 0.41]	0.121