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Supplementary Material

Article Title: A Fully Remote Randomized Trial of Transcranial Alternating Current Stimulation for the Acute Treatment of Major Depressive Disorder

Authors: Philip R. Gehrman, PhD; Eric J. Bartky, MD; Curtis Travers, MPH; and Kyle Lapidus, MD, PhD

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplemental information

Supplementary Table 1: Subgroup analyses for improvement from Baseline in BDI-II at 2 weeks

Factor	Subgroup	Statistical testing	Treatment	N	Mean	95% Confidence Interval	p-value
Sex							
	Female		Active	94	17.9	15.844 - 19.986	
			Control	85	14.2	11.723 - 16.583	
			Total	179	16.1	14.534 - 17.723	0.0197
	Male		Active	29	12.6	7.702 - 17.401	
			Control	40	14.8	10.503 - 19.097	
			Total	69	13.9	10.707 - 17.003	0.4858
		Sex (Female / Male)					0.1610
		Treatment effect					0.1153
		Interaction					0.0842
Race							
	White		Active	90	16.5	14.343 - 18.746	
			Control	95	14.1	11.790 - 16.400	
			Total	185	15.3	13.695 - 16.878	0.1294
	Non-White		Active	33	16.9	12.569 - 21.310	
			Control	30	15.2	9.989 - 20.412	
			Total	63	16.1	12.825 - 19.398	0.6013
		Race (White / Other)					0.7102
		Treatment effect					0.1546
		Interaction					0.7967

Factor	Subgroup Statistical testing	Treatment	N	Mean	95% Confidence Interval	p-value
Baseline	Beck Depression Inventory-II					
	Moderate	Active	44	11.3	8.479 - 14.021	
		Control	38	10	7.375 - 12.625	
		Total	82	10.7	8.785 - 12.556	0.5140
	Severe	Active	79	19.7	17.235 - 22.082	
		Control	87	16.3	13.515 - 19.014	
		Total	166	17.9	16.034 - 19.725	0.0696
	Baseline status (Moderate / Severe)					<.0001
	Treatment effect					0.1016
	Interaction					0.2181

Note:
Moderate (20–28) vs. severe (29–63) depression based on the subjects baseline BDI-II score at the conclusion of the lead-in period. The analysis was based on observed data and on a linear regression model was used in testing the differences in sex and baseline category by subgroups. A two-factor ANOVA was used to the test the differences between the females and male groups and initial moderate and severe groups with the factors baseline status, treatment effect and interaction.

Supplementary Table 2: Change in BDI-II at weeks 1, 2 and 4 compared to baseline.

Variable	Treatment	N	Mean	SD	Min	Median	Max
ITT Analysis							
Change in BDI-II at Week 1							
	Active Treatment	124	14.1	9.93	-9	12.5	43
	Control Treatment	125	11.5	10.68	-9	9.0	44
Change in BDI-II at Week 4							
	Active Treatment	121	19.9	11.91	-12	21.0	49
	Control Treatment	125	16.9	12.46	-17	16.0	51
Per Protocol Analysis							
Change in BDI-II at Week 1							
	Active Treatment	117	14.4	10.14	-9	13.0	43
	Control Treatment	117	11.3	10.09	-9	9.0	44
Change in BDI-II at Week 4							
	Active Treatment	97	20.0	11.87	-12	22.0	49
	Control Treatment	101	16.5	12.47	-17	16.8	51

Supplementary Table 3: Change in PHQ-9 at weeks 1, 2 and 4 compared to baseline.

Variable	Treatment	Estimate	95% confidence interval	p-value
Change in PHQ-9 at Week 1				
	Active Treatment	5.27	4.338 - 6.211	
	Control Treatment	4.5	3.533 - 5.475	
	Total	4.89	4.216 - 5.559	0.2595
Change in PHQ-9 at Week 2				
	Active Treatment	7.46	6.457 - 8.470	
	Control Treatment	6.29	5.144 - 7.432	
	Total	6.87	6.110 - 7.632	0.1286
Change in PHQ-9 at Week 4				
	Active Treatment	8.88	7.823 - 9.946	
	Control Treatment	7.72	6.559 - 8.881	
	Total	8.29	7.507 - 9.078	0.1449

Supplementary Table 4: Change in QIDS-SR at weeks 1, 2 and 4 compared to baseline.

Variable	Treatment	Estimate	95% confidence interval	p-value
Change in QIDS-SR at Week 1				
	Active Treatment	5.53	4.688 - 6.377	
	Control Treatment	4.77	3.923 - 5.613	
	Total	5.15	4.554 - 5.744	0.2065
Change in QIDS-SR at Week 2				
	Active Treatment	6.72	5.842 - 7.589	
	Control Treatment	5.71	4.719 - 6.705	
	Total	6.21	5.549 - 6.870	0.1349
Change in QIDS-SR at Week 4				
	Active Treatment	7.99	7.038 - 8.946	
	Control Treatment	6.9	5.938 - 7.870	
	Total	7.44	6.761 - 8.117	0.1142

Note:
The analysis was performed on observed data (no imputation was applied)
The analysis aimed the comparison of the treatment means with a two-sample t-test. The nominal two-sided 0.05 alpha level was considered as statistically significant result.

Supplementary Table 5: BDI-II responders with at least 50% improvement in BDI-II by time point.

Visit	Response	Active Treatment (N = 126)	Control (N = 129)	p-value
Week 1				
	Yes	46 (36.51%)	38 (29.46%)	0.231
	No	80 (63.49%)	91 (70.54%)	
Week 2				
	Yes	64 (50.79%)	55 (42.64%)	0.192
	No	62 (49.21%)	74 (57.36%)	
Week 4				
	Yes	82 (65.08%)	68 (52.71%)	0.045
	No	44 (34.92%)	61 (47.29%)	

Note:
The analysis was performed on observed data (no imputation was applied).
The analysis compared the distributions under different treatments with a Chi-square test. The nominal two-sided 0.05 alpha level was considered a statistically significant result.

Supplementary Table 6. Proportion of Subjects Achieving at least 50% Improvement from Baseline in BDI-II, Stratified by Sex in the ITT Population

Gender	Timepoint	Active Arm	Control Arm	P-Value[1]
Female	Week 1	38.9% (37/95)	23.5% (20/85)	0.026
	Week 2	55.3% (52/94)	41.2% (35/85)	0.059
	Week 4	73.9% (68/92)	55.3% (47/85)	0.009
Male	Week 1	31.0% (9/29)	45.0% (18/40)	0.241
	Week 2	41.4% (12/29)	50.0% (20/40)	0.478
	Week 4	48.3% (14/29)	52.5% (21/40)	0.729

[1] Chi-square p-value.

Supplementary Table 7: Number of Patients with Adverse Events by Outcome and Description Analysis Set: Intent to Treat Population (N = 255)

Adverse Events Outcome Description	Active Treatment N=126	Control Treatment N=129	Total N=255
Subjects with at least one AE	19 (15.08%)	10 (7.75%)	29 (11.37%)
Not Resolved	2 (1.59%)	1 (0.78%)	3 (1.18%)
Arthritis	1 (0.79%)	0 (0.00%)	1 (0.39%)
Not known	1 (0.79%)	1 (0.78%)	2 (0.78%)
Resolved	16 (12.70%)	9 (7.00%)	25 (9.80%)
Agitation	0 (0.00%)	1 (0.78%)	1 (0.39%)
Allergy, Blurred vision	0 (0.00%)	1 (0.78%)	1 (0.39%)
Appetite lost	1 (0.79%)	0 (0.00%)	1 (0.39%)
Cold symptoms	1 (0.79%)	1 (0.78%)	2 (0.78%)
Eye movement disorder	1 (0.79%)	0 (0.00%)	1 (0.39%)
Feeling sad	1 (0.79%)	0 (0.00%)	1 (0.39%)
Headache	2 (1.59%)	2 (1.55%)	4 (1.57%)
Headache, Anxiety	1 (0.79%)	0 (0.00%)	1 (0.39%)
Itching	1 (0.79%)	0 (0.00%)	1 (0.39%)
Migraine	1 (0.79%)	0 (0.00%)	1 (0.39%)
Mood change	1 (0.79%)	0 (0.00%)	1 (0.39%)

Adverse Events Outcome Description	Active Treatment N=126	Control Treatment N=129	Total N=255
Not known	2 (1.59%)	2 (1.55%)	4 (1.57%)
Sinus infection	1 (0.79%)	0 (0.00%)	1 (0.39%)
Sinusitis	1 (0.79%)	0 (0.00%)	1 (0.39%)
Skin discoloration	0 (0.00%)	1 (0.78%)	1 (0.39%)
Swollen ankles	1 (0.79%)	0 (0.00%)	1 (0.39%)
Tinging, Stinging, Flashing lights	1 (0.79%)	0 (0.00%)	1 (0.39%)
Upper respiratory tract infection	0 (0.00%)	1 (0.78%)	1 (0.39%)
Unknown	1 (0.79%)	0 (0.00%)	1 (0.39%)
Skin discomfort	1 (0.79%)	0 (0.00%)	1 (0.39%)