Annals of Depression and Anxiety

Austin Publishing Group

Open Access Full Text Article

Research Article

Transcranial Direct Current Stimulation in Treatment-Resistant Major Depression

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Received: September 08, 2014; **Accepted:** September 16, 2014; **Published:** September 18, 2014

Abstract

Despite the progress made in the field of drug therapy, a large part of patients with Major Depressive Disorder (MDD) (up to 60%) do not respond to current pharmacologic interventions and developed a Treatment-Resistant Depression (TRD). Transcranial Direct Current Stimulation (tDCS) is a non-invasive and non-convulsive form of brain stimulation recently used as treatment TRD with encouraging results. The present study aimed to explore the efficacy and tolerability of tDCS on TRD. Twenty-two patients with TRD have received 15 tDCS treatments over the course of 3 weeks (one treatment per week day), and a clinical evaluation with the 17-item Hamilton Rating Scale for Depression (HRSD-17) at baseline and at the end of the study. At the end of the study the patients have shown statistically significant improvement on HDRS scores, in particular on melancholic features and feelings of guilt, and have improved their sleep-wake rhythm; a decrease in anxious levels has also been reported. Our results in favour of antidepressant efficacy enabled us to propose tDCS as a valid therapeutic strategy for treatment of drug-resistant depression. In this perspective, further researches and clinical trials are needed to better elaborate and improved tDCS protocols towards an efficacious antidepressant intervention in therapy-resistant depression.

Keywords: Transcranial direct current stimulation (tDCS); Treatment-resistant depression (TRD); Augmentation

Introduction

Major Depressive Disorder (MDD) is a highly prevalent mental illness, usually associated with substantial symptom severity and related significant functional impairment [1]. Despite the progress made in the field of drug therapy, a large part of patients with MDD (up to 60%) do not respond to current pharmacologic interventions, even when standard antidepressant therapies are correctly delivered [2]. These subjects are defined as suffering from treatment-resistant depression (TRD), a condition characterised by the lack of response to at least two antidepressants, used in sequence for an adequate period of time at therapeutic doses, monitoring patient's compliance [3-5]. An alternative treatment strategy to improve outcomes for TRD has recognized as Transcranial Direct Current Stimulation (tDCS), a non-invasive and non-convulsive form of brain stimulation in which a weak, direct current (typically 1–2 mA) is applied using two surface scalp electrodes [6]. The common rationale of tDCS protocols dedicated to the treatment of depression is to modulate the excitability of the prefrontal cortex [7]. The early studies, conducted on animals, suggested that tDCS could determine polarity-dependent alterations in cortical activity, with anodal stimulation increasing cortical excitability and cathodal stimulation producing cortical inhibition [8]. Latest studies have shown that the effects of tDCS are not limited to the time of application: a single session can generate long-lasting effects for up to 90 minutes, indicating that tDCS not only changes neuronal membrane potential but also determines synaptic permanent alterations [9].

Given the efficacy of tDCS on MDD [4,10-12], several studies have focused on the effects of this method in TRD episodes. A placebo-controlled cross-over study [13] has illustrated that prefrontal tDCS, applied for a period of 2 weeks, failed to exert any significant therapeutic outcome in treatment resistant depression compared with placebo; in contrast to clinical depression scores, subjective mood ratings showed an increase in positive emotions and a trend towards a reduction of negative emotions after real tDCS. These results were later confirmed by a clinical trial study conducted on TRD patients in which anodal stimulation to the left DLPFC and cathodal stimulation to the right DLPFC was not efficacious [7]. On the contrary, the findings from another paper have supported the effectiveness of tDCS in mild to severe depressed patients as well as in patients with TRD [14].

On the basis of existing literature, the present study aims to evaluate the efficacy of tDCS treatments in a sample of patients affected by treatment-resistant depression.

Methods

Subjects

The study was carried out at the Psychiatry Unit of the University Hospital of Messina, Italy. Twenty-two inpatients, 10 men and 12 women, aged 22 to 70 years, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for unipolar Major Depressive Disorder without psychotic features, were experiencing a Major Depressive Episode, and had a score of 21 on the 17-item Hamilton Rating Scale for Depression (HRSD-17), were included in this study.

Concomitant medications, such as various classes of antidepressants (e.g., selective serotonin reuptake inhibitors,

Citation: Bruno A, Lorusso S, Abenavoli E, Gattuso C, Scimeca G, Isgrò S, et al. Transcranial Direct Current Stimulation in Treatment-Resistant Major Depression. Ann Depress Anxiety. 2014;1(4): 1019.

Table 1: Demographic and clinical features.

	Total sample (n. 22)
Age, years (mean, SD)	48.2 (16.3)
Gender, M/F	10/12
Educational level, years (mean, SD)	11.18 (4.3)
First episode (n, %)	6 (27.3)
Recurrent episodes (n, %)	16 (72.7)
Duration of current episode, years (mean, SD)	3.2 (1.1)
Number of failed antidepressant trials (mean, SD)	3.8 (1.2)

tricyclic antidepressants), benzodiazepines, and antipsychotics were permitted provided that subjects had been on a stable dose of their medications for at least 4 weeks prior to entering the study and were able to maintain those stable dosages for the duration of the protocol. Subjects taking anticonvulsants were ineligible for the study, as certain agents have been found to disrupt the effects of anodal tDCS [15]. Moreover, patients with any other major psychiatric disorder, significant concurrent medical illnesses, organic brain disorder, mental retardation, a history of seizures, pregnant or lactating women, or a current diagnosis of alcohol/drug dependence were excluded.

All the patients provided written informed consent after a full explanation of the protocol design which had been approved by the local ethics committee; the study was conducted according to the Declaration of Helsinki.

Study design

Fifteen treatments, each lasting 20 min, were administered over the course of 3 weeks (one treatment per week day). Transcranial direct current stimulation treatment was delivered using a battery-operated, constant current stimulator (BrainSTIM; E.M.S. s.r.l., Italy) and transmitted by two rubber electrodes (7 cm x 5 cm = 35 cm^2), each covered by a saline-soaked sponge and affixed to the head with a head band. The anode was directed over the left DLFPC and the cathode was placed over the right supraorbital region, corresponding to electrodes F3 and Fp2, respectively, according to the 10–20 EEG system. Stimulation was delivered at 2 mA for 20 min.

Experienced clinical raters administered the HRSD-17 at baseline and at the end of the study (after 15 sessions). The primary outcome for the study was change from baseline to endpoint on the HRSD-17; secondary outcomes included response (HRSD total score reduction ≥ 50% versus baseline) and remission (HRSD total score ≤ 7) [16,17].

Blood pressure, heart rate, and a routine set of laboratory investigations (blood profile, PT, PTT, fibrinogen, basal glucose, cholesterol, triglycerides, uric acid, azotemy, AST, ALT, alkaline phosphatase, total and direct bilirubin, GGT, iron, ESR) were performed on all patients on admission and at the end of the study.

Statistical analysis

Data obtained from the study underwent check and quality control and, subsequently, descriptive and inferential statistical analysis. Due to the small sample size, the analyses were carried out by nonparametric tests. Continuous data were expressed as mean ± S.D. and the within group differences in efficacy ratings between baseline and final test were analyzed by the Wilcoxon rank sum test. To measure the magnitude of a treatment effect, effect size was provided by using Cohen's d statistic and was considered small when lower than 0.50, moderate when ranging from 0.50 to 0.79, and large when equal to or greater than 0.80. Taking into account that multiple correlations increase the risk of Type 1 errors, a Bonferroni correction

Table 2: 17-item Hamilton Rating Scale for Depression (HRSD-17).

	Baseline (T0)		Week 3 (T1)		Wilcoxon test T0 vs T1		Cohen's d
HDRS-17	Mean	SD	Mean	SD	Z	p	
1. Depressed mood	3.55	0.51	2.45	1.34	-3.440	.001	1.1
2. Feelings of guilt	1.68	1.09	0.82	0.85	-3.134	.002	0.8
3. Suicide	1.50	1.22	1.09	0.92	-2.251	.024	0.4
4. Insomnia early	1.82	1.22	1.00	1.15	-3.448	.001	0.7
5. Insomnia middle	1.18	0.73	0.27	0.63	-3.397	.001	1.3
6. Insomnia late	1.09	0.68	0.27	0.63	-3.448	.001	1.2
7. Work and activities	2.64	1.00	1.82	1.30	-3.557	<.0001	0.7
8. Retardation: psychomotor	1.18	0.96	0.64	0.79	-3.464	.001	0.6
9. Agitation	1.00	0.98	0.91	1.02	-1.414	.157	0.1
10. Anxiety: psychological	2.55	0.80	1.82	1.14	-3.176	.001	0.7
11. Anxiety somatic	1.73	0.98	1.55	1.01	-2.000	.046	0.2
12. Somatic symptoms: gastorintestinal	0.45	0.51	0.00	0.00	-3.162	.002	1.2
13. Somatic symptoms general	0.73	0.46	0.55	0.51	-2.000	.046	0.4
14. Genital symptoms	0.27	0.46	0.27	0.46	0	1.000	0
15. Hypochondriasis	1.64	1.00	1.55	0.91	-1.414	.157	0.1
16. Loss of weight	0.09	0.29	0.00	0.00	-1.414	.157	0.4
17. Insight	1.18	0.73	1.00	0.76	-2.000	.046	0.2
Total score	24.27	2.23	16.00	3.46	-4.114	<.0001	2.8

was applied, and a significance value of $p < .002$ was chosen. The statistical analysis was performed with SPSS 16.0 software (SPSS Inc, Chicago, Ill).

Results

Table 1 shows demographic and clinical data of the sample. The subjects included in the study were characterized by a mean age of 48.2 years (SD = 16.3), a level of education of 11.18 years (SD = 4.3), and a mean current episode duration of 3.2 years (SD = 1.1).

All subjects completed the treatment showing a good tolerability to tDCS: the most common adverse effects were headache (2 patients, 9%), and itching and redness at the site of application of the electrodes (4 patients, 18%). Adverse events were generally mild and regressed with continuation of treatment or after the end of the stimulation.

Table 2 shows the baseline, and final scores (week 3) of the efficacy measure and the effect size for the sample group.

At endpoint (week 3), within-group comparison revealed that tDCS significantly reduced HDRS items "1. Depressed mood" (p=.001), "2. Feelings of guilt" (p=.002), "4. Insomnia early" (p=.001), "5. Insomnia middle" (p=.001), "6. Insomnia late" (p=.001), "7. Work and activities" (p<.0001), "8. Retardation: psychomotor" (p=.001), "10. Anxiety: psychological)" (p=.001), "12. Somatic symptoms: gastorintestinal" (p=.002), and total score (p<.0001).

Effect sizes were large in items 1, 2, 5, 6, 12, and total scores, moderate in items 4, 7, 8, 10, and small in items 3, 11, 13, 14, 15, 16, and 17.

Regarding treatment response, at endpoint, 4 subjects (18%) met the selected response criteria in HDRS total score versus baseline, whereas no patients reported a symptomatology remission.

No clinically significant changes in blood pressure, heart rate, and in biochemical and hematological parameters were recorded, and no acute extra pyramidal effects, seizures, or cardiac events occurred.

Discussion and Conclusion

Results from the present study demonstrated that tDCS treatment, administered over the course of 3 weeks in one session per day, each lasting 20 minutes was effective and well tolerated in patients with TRD, reducing depressive symptoms. According to previous data [14] this paper supports the efficacy of tDCS on poor responder's patients to pharmacological treatment. tDCS is a relatively novel brain stimulation technique and its application is now limited by the lack of standardized protocols towards an efficacious antidepressant intervention, particularly in therapy resistant depression [13]. The anodal stimulation in our model was directed over the left DLFPC and the cathodal stimulation over the right supraorbital region. At the end of stimulation the patients have shown statistically significant improvement on HDRS scores; after three weeks they reduced melancholic features such as feelings of guilt and improved their sleep-wake rhythm; a decrease in anxious levels and in its somatic aspects has also been reported. Several studies have suggested tDCS effectiveness in reduction of depressive symptoms in MDD patients: HRS-D scores have significantly improved from the baseline and when compared to the sham groups [4,10,18]. There has also been carried out comparative studies with antidepressants; a double-blind clinical trial [10] compared the efficacy of ten tDCS sessions each lasting 20 minutes, to the administration of Fluoxetine for 6 week at the dose of 20 mg/day finding that the antidepressant effects of tDCS were as good as those of pharmacological therapy, though the first ones appear to become significant in a briefer period and to last longer than fluoxetine-induced ones. Regarding TRD, the effectiveness of tDCS is less clear and data from current literature are divergent. On one side, results from a study conducted on patients with MDD and poor response to pharmacological treatment showed that tDCS, administered twice a day for 5 consecutive days, was effective in reducing melancholic features, which represent nuclear and difficult-to-treat depressive symptoms [14]; on the other side two clinical trials [6,12,] failed to exert any significant therapeutic outcome in treatment resistant depression compared with sham tDCS sessions.

The state of current knowledge has not allowed the development of a standard tDCS protocols because of the partial understanding of tDCS methodological aspects. It is still not clear whether the efficacy of tDCS depends critically on increased cortical excitability by anodal stimulation, cortical decreased excitability by cathodal stimulation or both mechanisms. Further studies are needed to better explore the PFDLC areas of interest for depression that could thus become the target of a more direct stimulation and to elaborate modified and improved tDCS protocols towards an efficacious antidepressant intervention in therapy-resistant depression.

There are a number of limitations to this study that should be considered such as the relatively small sample size, the open label trial structure, the lack of a sham-group and of ongoing study that did not allowed us to develop conclusive indications. Moreover, need to be taken into account that it may not be excluded the differential interaction between the concomitant pharmacological treatments and the effects of tDCS.

Despite the tDCS represent an experimental technique still being validated in different applications and clinical areas, our results in favour of antidepressant efficacy enabled us to propose it as a valid therapeutic strategy for treatment of drug-resistant depression. In this perspective, further researches and clinical trials are needed to standardize the best way and to evaluate the possible use of the method in other medical and psychiatric areas.

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Ann Depress Anxiety - Volume 1 Issue 4 - 2014
ISSN : 2381-8883 | www.austinpublishinggroup.com

Citation: Bruno A, Lorusso S, Abenavoli E, Gattuso C, Scimeca G, Isgrò S, et al. Transcranial Direct Current Stimulation in Treatment-Resistant Major Depression. Ann Depress Anxiety. 2014;1(4): 1019.