J Compr Ped. 2024 May; 15(2): e142787. https://doi.org/10.5812/jcp-142787.

Published online: 2024 March 30. **Research Article**

Effectiveness of Combined Treatment of Transcranial Direct Current Stimulation and Treatment as Usual on Depression, Anxiety and Anger in Adolescents with Bipolar Disorder

Forugh Riahi [1], Ashraf Tashakori [1], Maryam Izadi Mazidi [1], Saeideh Farjadnia [1, *]

[1] Department of Psychiatry, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[*] *Corresponding author:* Department of Psychiatry, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Email: saeidehfarjadnia@gmail.com

Received 2023 November 22; **Revised** 2024 February 10; **Accepted** 2024 March 2.

Abstract

Objectives: Bipolar disorder (BD) is a prevalent psychological disorder associated with depressive symptoms. Transcranial direct current stimulation (tDCS) is a portable and non-invasive technique for brain stimulation. The present study was conducted to determine the effectiveness of the combined treatment of tDCS and routine medication on the symptoms of depression, anxiety, and anger in BD adolescents.

Methods: In this double-blind randomized clinical trial study, forty adolescents with BD referred to the outpatient clinic of child and psychiatry of Golestan Ahvaz Teaching Hospital were included. Eligible patients aged 12 - 18 years were randomly divided into 2 groups receiving routine medications plus active tDCS (intervention group) or routine medications plus sham tDCS (control group). Transcranial direct current stimulation intervention with an intensity of 2 mA was applied to the dorsolateral prefrontal cortex in two sessions for 20 minutes each day, for 5 consecutive days. Data were collected at baseline, one week, and one month after the start of the intervention using the Hamilton Depression Rating Scale (HDRS-21), Hamilton Anxiety Rating Scale (HDRS), and State-Trait Anger Expression Inventory.

Results: Based on our findings, age and gender were not considerably different between the two groups ($P = 0.592$, $P = 0.1$, respectively). In both groups, scores of depression (control: 12.25 ± 3.97, intervention: 0.75 ± 1.44, mean [SD]), anxiety (13.55 ± 2.58, 25.0 ± 0.55), and anger (52.65 ± 8.27, 47.25 ± 4.86) improved significantly one month after treatment ($P < 0.0001$). After one month of treatment, the severity of bipolar symptoms in the intervention group (slightly: 10%, moderately: 50%, and markedly: 40%) improved significantly compared to the control group (slightly: 15%, moderately: 10%, and markedly: 0%) ($P < 0.0001$). The improvement rate of HDRS in the intervention group was 81.29% and 95.24% at one week and one month after treatment, while these values were 8.41% and 23.04% in the control group, respectively ($P < 0.0001$). All patients tolerated the treatment well without serious side effects. There was no significant difference between the side effects observed in both groups ($P = 0.185$).

Conclusions: The combination of tDCS with routine medications can reduce depressive symptoms and improve bipolar symptoms. Therefore, tDCS add-on could be an effective, safe, and tolerable intervention for bipolar depression.

Keywords: Bipolar Disorder, Depression, Anxiety Transcranial Direct Current Stimulation (tDCS)

1. Background

Bipolar disorder (BD) is one of the most severe debilitating brain disorders that affects about 1% – 3% of the world's population (1). Mood disorders and affective disorders are prevalent signs of BD, which lead to disturbances in mood stability and function (2, 3). Bipolar disorder is characterized by chronic episodes of mania or hypomania alternating with depression and is often misdiagnosed at first (4, 5). In comparison to manic episodes, depression is much more common and longer in BD patients (6).

Pharmacological treatments for BD episodes are standard but have limitations, including insufficient efficacy and common adverse events (AEs) (7). Transcranial direct current stimulation (tDCS) is a safe non-invasive brain stimulation method for the modulation of cortical activity and excitability (8, 9). Transcranial direct current stimulation delivers weak, direct currents to the brain through electrodes placed

on the scalp. Repetitive transcranial magnetic stimulation and tDCS are typically applied to the dorsolateral prefrontal cortex (DLPFC), a brain region whose metabolism increases after successful antidepressant treatment (10, 11). Antidepressant effects of non-invasive brain stimulation may be due to stimulation factors including modulation of DLPFC and other brain structures involved in the pathophysiology of depression through increasing synaptic plasticity and metabolic activity as well as changes in excitability (12, 13).

In recent years, tDCS has shown effectiveness for the treatment of BD in some studies, is relatively inexpensive, and is assumed to be safe (8, 13, 14). This method is a safe and painless way to modulate brain activity that does not increase the risk of seizures and is able to selectively stimulate or inhibit specific areas of the brain (15).

2. Objectives

Considering the importance of finding new methods to reduce the symptoms of depression in bipolar patients, as well as the lack of sufficient studies on the use of tDCS in bipolar patients, the present study was conducted with the aim of investigating the effect of tDCS on depression symptoms in adolescents with bipolar disorder referred to the psychiatry department of Golestan Hospital, Ahvaz.

3. Methods

3.1. Study Participants

Forty adolescents with BD referred to the outpatient clinic of child and adolescent psychiatry of Golestan Ahvaz Teaching Hospital in 2022 were enrolled in this double-blind randomized clinical trial study. Inclusion criteria were patients with bipolar disorder based on DSM-5 diagnostic criteria, aged between 12 and 18 years, and in the depression phase (presence of MDD symptoms). The presence of other psychiatric disorders, psychotic patients, a history of seizures except seizures with fever, and patients requiring ECT were excluded from the study. The diagnosis of BD was made based on DSM-5 criteria, requiring the patient to meet the diagnostic criteria for at least one episode of hypomania (in bipolar type II) or a fully syndromic manic episode (in bipolar type I) and a major depressive episode. All patients received routine drug regimens (mood stabilizers including lithium and sodium valproate, antipsychotics such as quetiapine and risperidone at a low dose based on the patient's needs) at least two weeks before the start of the study, and drug doses remained unchanged during the study. According to Cochran's formula, the sample size of each group was 20 using Gpower software considering $\alpha = 0.05$ and $\beta = 0.2$.

3.2. Interventions and Measurement

The eligible subjects were allocated into two groups of 20 patients each using a four-block randomization method. The control group received placebo treatment, and the intervention group received tDCS treatment. The tDCS device was a two-channel device manufactured by Mind Alive Inc. company from Canada. The tDCS intervention, with an intensity of 2 mA, was applied to the dorsolateral prefrontal cortex in two sessions per day for 20 minutes each day, for 5 consecutive days. At the beginning of the study, basic characteristics of the patients, including demographic data, were collected. The severity of bipolar disorder, depressive symptoms, and mood changes were evaluated at the beginning of the study (prior to the intervention), one week later, and one month after the end of the treatment.

The severity of bipolar disorder was evaluated based on clinical symptoms using the comprehensive clinical impression form on a scale of 0 to 3 as follows: Score 0 for unchanged or at the same level as the basic level, score 1 for slightly improved, score 2 for moderately improved, and score 3 for markedly improved. The Hamilton Depression Rating Scale (HDRS) was used to examine the severity of depression symptoms. Hamilton Depression Rating Scale questions are scored from 0 to 2 or 0 to 4, indicating various symptoms such as depressed mood, guilt, suicidality, insomnia, anxiety, primary insomnia, overnight insomnia, delayed insomnia, work and interests, psychiatric anxiety, retardation, restlessness, psychiatric anxiety, gastrointestinal somatic signs, general somatic signs, hypochondriasis, reproductive symptoms, weight loss, and insight. A score between 0 and 7 is considered normal, while a score of 20 or higher indicates severe depression (16).

The Hamilton Anxiety Rating Scale was used to assess the severity of anxiety on clinical scales. This questionnaire comprises 14 statements, each scored on a 5-point scale ranging from 0 to 4 based on the severity of symptoms. A score of zero indicates the absence of the symptom, while 4 indicates its maximum intensity in the patient. Additionally, to measure anger across various dimensions, the State-Trait Anger Expression Inventory–2 (STAXI-2) was employed. State-Trait Anger Expression Inventory–2 consists of three parts and 57 questions, where participants rate the intensity of their feelings on a four-point scale from 0 (never or not at all)

to 4 (always or very much). The first, second, and third parts respectively gauge the state of anger, the quality of anger, and the ways of expressing and controlling anger (17). Before the study commenced, one week and one month after the intervention, patients completed all questionnaires. The questionnaires were then re-examined, scores were calculated, and the two groups were compared. The study patients were followed up at predetermined times by the same psychiatrists: Prior to the start of the treatment, one week subsequently, and one month after the start of the intervention. It is noteworthy that the patients were unaware of the process of allocating participants to the groups, ensuring that both groups received their usual treatment methods, and tDCS was applied to both groups. The only difference was that in the control group, the electric current was deactivated, simulating a placebo effect. Furthermore, the statistical analyzer remained unaware of the designed treatment groups.

3.3. Statistical Analysis

Statistical analysis was conducted using SPSS software version 22 (IBM, Chicago, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to assess distribution. Differences were compared using the *t*-test or Mann-Whitney U test, as appropriate. The chi-square test was utilized to ascertain correlations between qualitative variables. Additionally, analysis of covariance (ANCOVA) with squared eta partial was employed. A P-value less than 0.05 was deemed statistically significant.

4. Results

4.1. Patients' Basic Characteristics

This study involved 40 adolescents aged 12 to 18 years diagnosed with bipolar disorder. The cohort comprised 18 females (45%) and 22 males (55%). There were no significant differences in age and gender between the two groups (P > 0.05). The demographic characteristics of the participants are outlined in Table 1.

Table 1. Demographic Characteristics of the Studied Patients in the Intervention and Control Groups [a]

Variable	Control Group (n = 20)	Intervention Group (n = 20)	P-Value
Age (y)	15.70 ± 1.26	15.90 ± 1.07	0.592
Sex			
Female	9 (45.0)	9 (45.0)	1.000
Male	11 (55.0)	11 (55.0)	1.000

[a] Values are expressed as No (%) or mean ± SD.

Based on Table 2, one week and one month after the treatment, a significant improvement in the depression score was observed in the intervention group (P < 0.0001 at all times). In the control group, notable improvements in depression symptoms were seen at the end of one week and one month (P = 0.003, P < 0.0001, respectively). The results of covariance analysis, controlling for pre-test scores, showed a significant difference between the depression scores after treatment in the intervention and control groups (one week later: effect size: 0.849; P > 0.0001, one month later: effect size: 0.850; P < 0.0001). The improvement rates of HDRS in the intervention group were 81.29% and 95.24% at one week and one month after treatment, respectively, while these values were 8.41% and 23.04% in the control group.

Table 2. Depression Scores Before and After Treatment in Two Groups [a]

Time	Control Group (n = 20)	Intervention Group (n = 20)	P-Value
Before the intervention	16.90 ± 5.70	17.40 ± 6.76	0.803
One week after the intervention	15.15 ± 4.90	3.10 ± 2.36	< 0.0001
One month after the intervention	12.25 ± 3.97	0.75 ± 1.44	< 0.0001
The difference before and one week after the intervention	1.75 ± 0.51	14.30 ± 5.76	< 0.0001
The difference before and one month after the intervention	4.65 ± 1.88	16.65 ± 6.35	< 0.0001
Recovery percentage one week after the intervention	8.41 ± 2.50	81.29 ± 13.15	< 0.0001
Recovery percentage one month after the intervention	23.04 ± 4.29	96.24 ± 7.20	< 0.0001

[a] Values are expressed as mean ± SD.

According to Table 3, one week and one month after the treatment, a remarkable improvement in the anxiety score was observed in the intervention group (P < 0.0001 at all times). In the control group, significant improvements in anxiety symptoms were observed at the end of one week and one month (P = 0.011 and P < 0.0001, respectively). A significant difference was observed between the anxiety scores after treatment in the intervention and control groups (one week later: effect size: 0.871; P > 0.0001, one month later: effect size: 0.941; P < 0.0001).

After one week and one month of treatment, in the intervention group, a significant improvement was observed in the overall score of the anger questionnaire and its three subscales, i.e., trait anger, state anger,

Table 3. Anxiety Scores Before and After Treatment in Two Groups [a]

Time	Control Group (n = 20)	Intervention Group (n = 20)	P-Value
Before the intervention	18.40 ± 4.81	17.75 ± 5.69	0.699
One week after the intervention	16.80 ± 4.65	5.70 ± 3.11	< 0.0001
One month after the intervention	13.55 ± 2.58	0.25 ± 0.55	< 0.0001
The difference before and one week after the intervention	1.60 ± 0.56	12.05 ± 3.11	< 0.0001
The difference before and one month after the intervention	4.74 ± 1.22	17.50 ± 5.48	< 0.0001
Recovery percentage one week after the intervention	8.27 ± 3.11	69.73 ± 11.13	< 0.0001
Recovery percentage one month after the intervention	16.46 ± 3.12	98.84 ± 2.49	< 0.0001

[a] Values are expressed as mean ± SD.

occurrence, and control of anger (P < 0.0001 at all times). In the control group, at the end of one week and one month, there was a significant difference in the total score of the anger questionnaire (P = 0.002, P < 0.0001, respectively). Based on analysis, there is a significant difference between the anger control scores after treatment in the intervention and control groups (P < 0.0001 at all times) (Table 4).

Table 4. Changes in Anger Control Questionnaire Score Before and After Treatment in Two Groups [a]

Variables and Time	Control Group (n = 20)	Intervention Group (n = 20)	P-Value
State of anger			
Before treatment	10.20 ± 5.15	10.70 ± 5.67	0.722
1 week after treatment	8.95 ± 4.32	0.6 ± 1.31	< 0.0001
1 month after treatment	7.25 ± 3.47	0.30 ± 0.65	< 0.0001
Trait of anger			
Before treatment	12.75 ± 4.38	13.15 ± 5.05	0.791
1 week after treatment	11.40 ± 3.57	2.25 ± 2.38	< 0.0001
1 month after treatment	9.70 ± 3.49	1.55 ± 1.53	< 0.0001
Occurrence and control of anger			
Before treatment	36.55 ± 3.98	37.65 ± 4.64	0.426
1 week after treatment	36.05 ± 4.11	44.30 ± 4.20	< 0.0001
1 month after treatment	35.70 ± 3.96	45.40 ± 4.14	< 0.0001
Total score			
Before treatment	59.50 ± 11.03	61.5 ± 12.09	0.588
1 week after treatment	56.40 ± 9.43	47.15 ± 5.38	0.001
1 month after treatment	52.65 ± 8.27	47.25 ± 4.86	0.016
Difference before and one week	3.10 ± 1.87	14.35 ± 8.15	< 0.0001
Difference before and one month	6.85 ± 1.45	14.25 ± 10.62	0.011

[a] Values are expressed as mean ± SD.

According to Table 5, the results showed that after the treatment, the severity of bipolar symptoms improved significantly in the intervention group compared to the control group (P < 0.0001).

In the intervention group, one week after treatment, moderate and mild improvement was observed in 65% and 35% of patients, respectively. One month after the treatment, 10%, 50%, and 40% of patients showed mild, moderate, and marked improvement of bipolar disorder symptoms, respectively. There was a significant difference in the severity of bipolar symptoms one month after treatment in the intervention and control groups (P < 0.0001).

Table 5. Comparison of the Severity of Bipolar Symptoms of Controls After Treatment in Two Groups [a]

Time and Severity of Bipolar Disorder	Control Group (n = 20)	Intervention Group (n = 20)	P-Value
1 week after treatment			< 0.0001
0 (unchanged)	17 (85)	0 (0)	
1 (slight improvement)	2 (10)	7 (35)	
2 (moderate improvement)	1 (5)	13 (6 5)	
1 month after treatment			< 0.0001
0 (unchanged)	15 (75)	0 (0)	
1(slight improvement)	3 (15)	2 (10)	
2 (moderate improvement)	2 (10)	10 (50)	
3 (high improvement)	0 (0)	8 (40)	

[a] Values are expressed as No (%) or mean ±SD.

In our study, no serious and unbearable side effects related to tDCS were observed. In the intervention group, 2 cases of mild headache, 7 cases of itching and tingling during work, and 2 cases of local skin redness were reported. In the control group, 3 cases of itching and tingling, 1 case of local redness, and 1 case of

headache were reported. There was no significant difference between the side effects observed in the two groups (P = 0.185).

5. Discussion

As a complex psychiatric disorder, bipolar disorder requires long-term use of psychiatric drugs, and the use of new treatments, including tDCS, can improve the performance of BD patients (3, 18). The abnormality of the prefrontal cortex in BD patients is approved by postmortem studies and neuroimaging findings. Interestingly, in these patients, the sub-genual portion of the anterior cingulate cortex is smaller than in healthy individuals, as well as their mitochondria structure. Moreover, an abnormal pattern of clumping and marginalization in the intracellular distribution of mitochondria has been observed in BD patients (19, 20). Based on previous studies, the prefrontal cortex plays a vital role in many functions, including reward evaluation, risky decision-making, and impulse control. Transcranial direct current stimulation as a therapy method could bring advantages and improvements in the prefrontal cortex for BD patients (21, 22).

The current study aimed to evaluate the efficacy of tDCS on depression in adolescents with BD. Our results demonstrated the efficacy of left anodal/right cathodal tDCS for 5 consecutive days, combined with common medication, in decreasing depression in adolescents with bipolar disorder compared to those who received medication alone. Also, a notable improvement in the severity of bipolar symptoms was observed in the intervention group compared to the control group. Based on our findings, at one week and one month after the treatment, a remarkable improvement was observed in the anxiety score and anger control in the tDCS group. Based on our knowledge and research, this is the first clinical trial study in Iran that evaluates the effectiveness of tDCS on depression, anxiety, and the severity of bipolar symptoms in adolescents with bipolar disorder. The effect of tDCS on bipolar depression in adults has been investigated in previous studies. Mardani et al. reported in a clinical trial that the combined intervention of tDCS with pharmacotherapy (mood stabilizers including lithium, sodium valproate, and carbamazepine) can reduce depressive symptoms in bipolar patients in comparison to pharmacotherapy alone and has a better effect than pharmacotherapy alone. However, this effect was not sustained in the three-month follow-up (22). The non-continuation of effectiveness up to 3 months after treatment in the study of men can be due to the small number of sessions and duration (10 sessions for 20 minutes each session). Additionally, although the treatment duration and protocol were different compared to our study, the target patients were type 1 bipolar patients and the drug treatment used was also different in the two studies. Despite these differences, both studies showed the high effectiveness of tDCS treatment along with standard drug treatment in reducing the symptoms of BD, and in the present study, this effectiveness lasted for a month. Contrary to our findings, the results of Lee's study showed that the active tDCS group did not show symptomatic improvement superior to that of the sham tDCS group (7). Previous studies reported that active tDCS had better symptom improvement than sham tDCS based on HDRS-17 scores (23, 24).

In a review study by Herrera-Melendez et al., it was found that tDCS potentially improved depressive symptoms in bipolar patients (25). Dondé et al. also conducted a meta-analysis indicating that different tDCS protocols and techniques can improve depressive symptoms in bipolar patients, especially after one week of treatment (26).

In another study by Brunoni et al., the effectiveness of tDCS was investigated in two groups of patients with bipolar depression or major depression. The results showed that after the fifth session of tDCS, the symptoms of depression were significantly reduced in both study groups, and the beneficial effect continued one week and one month after the treatment (27). Therefore, tDCS has been a promising treatment for reducing the symptoms of bipolar and unipolar depression.

In a meta-analysis by Mutz et al., the effectiveness of non-invasive tDCS therapy in the treatment of bipolar and unipolar depression in adults was investigated. The results of the review of ten clinical trials showed that active tDCS is an effective treatment method compared to the sham group for reducing the severity score of disease symptoms, achieving more recovery, and reducing the severity score of depression after treatment (28).

However, in this meta-analysis, bipolar depression included only 20% of the studied patients, and in only one trial was tDCS added to standard drug therapy (and most tDCS was performed as monotherapy). Also, the range of tDCS sessions varied from 5 to 22 sessions (average 10 sessions), and the treatment duration was 20 or 30 minutes. Other treatment protocol details were not similar in different studies.

McClintock et al. showed that tDCS has positive neurocognitive effects in unipolar and BD (29). The DLPFC is related to depression due to increased right DLPFC function and decreased left DLPF (30). The

possibility of dysfunction with decreased regional blood flow, impaired glucose metabolism in DLPFC, and right-sided hyperactivity during depression has been suggested (31). Therefore, right anodal/left cathodal tDCS can aid in decreasing depressive signs (30).

Although mood stabilizers are FDA-approved for the treatment of BD patients, they are not sufficient because several patients show resistance to these drugs, and on the other hand, high doses of these drugs cause disturbances in the daily functioning of patients. Applying the tDCS method facilitates the effects of drug treatment. It modulates synaptic transmission by regulating the dose of transmitters, including serotonin. Hence, it has been recommended that the combined treatment of tDCS with conventional therapy can be a useful and effective method for the treatment of depression in BD patients. Although promising results of tDCS in the treatment of major depressive disorder have been observed, few studies have been conducted on the effectiveness of different tDCS protocols in bipolar depression. Most of the previous studies have been conducted with a small sample size, with an open-label protocol, and with a mixed population of unipolar and bipolar depression (23, 32).

In this study, no serious or intolerable side effects related to tDCS leading to discontinuation of treatment or emotional switch leading to treatment were observed. Adverse effects observed included itching during stimulation, tingling, localized redness of the skin, and mild headache. Also, since the side effects were mild, they had no effect on blinding.

In other studies, the complications were not serious and existed for a short time (33-35). The reported side effects of tDCS include headache, itching, tingling, burning, and local redness at the site of stimulation, which is due to skin irritation (36).

This investigation had several limitations. First, the sample size of the study was small because patients were selected from one psychiatry department of a hospital and the number of BD patients who visited the hospital was insufficient. The second limitation was the small number of sessions and duration of tDCS treatment and the short follow-up period. Third, targeted sampling is another limitation because some patients come from a long distance and they were reluctant to cooperate. The strength of this study is that it is the first clinical trial study in Iran that evaluates the effectiveness of tDCS on depression, anxiety, and severity of bipolar symptoms in BD adolescents.

5.1. Conclusions

The results of the present study showed that the combination of tDCS and routine medications can reduce the symptoms of depression, mood disorders including anxiety and anger in adolescents with bipolar disorder and also improve the severity of bipolar symptoms. It is also well tolerated by patients and does not cause serious side effects. Therefore, tDCS adjuvant therapy can be an effective, safe, and tolerable non-pharmacological intervention for patients with bipolar disorder. It is recommended that more multicenter studies with a higher sample size and objective tools such as electroencephalography or functional magnetic resonance imaging (fMRI) should be performed.

Acknowledgements

The authors would like to thank all the patients participated in this study for their cooperation.

Footnotes

Authors' Contribution: Study concept and design: F.R and S.F.; Analysis and interpretation of data: M.IM. and A.T.; Drafting of the manuscript: S.F and F.R. Critical revision of the manuscript for important intellectual content: F.R., M.I, and S.F.; All authors have approved the final version of the manuscript.

Clinical Trial Registration Code: This trial was registered in the Iranian clinical trial system with the patented number of IRCT20100520003979N11 .

Conflict of Interests: There is no conflict of interests

Ethical Approval: This study is approved under the ethical approval code of IR.AJUMS.HGOLESTAN.REC.1400.043 .

Funding/Support: This research was supported by Grant no. U-00075 from Ahvaz Jundishapur University of Medical Sciences.

Informed Consent: The written informed consent was obtained from each patient.

References

1. Dome P, Rihmer Z, Gonda X. Suicide Risk in Bipolar Disorder: A Brief Review. *Medicina (Kaunas).* 2019;**55**(8). [PubMed ID: 31344941]. [PubMed Central ID: PMC6723289]. https://doi.org/10.3390/medicina55080403.
2. Asbaghi E, Rafieinia P, Hosseini SM, Sabahi P. [The effectiveness of rTMS on working memory and symptoms of bipolar disorder]. *Neuropsychol.* 2017;**3**(8):29-50. Persian.
3. D'Urso G, Toscano E, Barone A, Palermo M, Dell'Osso B, Di Lorenzo G, et al. Transcranial direct current stimulation for bipolar depression: systematic reviews of clinical evidence and biological

underpinnings. *Prog Neuropsychopharmacol Biol Psychiatry*. 2023;**121**:110672. [PubMed ID: 36332699]. https://doi.org/10.1016/j.pnpbp.2022.110672.

4. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet*. 2013;**381**(9878):1663-71. [PubMed ID: 23663952]. [PubMed Central ID: PMC5858935]. https://doi.org/10.1016/S0140-6736(13)60989-7.
5. Goes FS. Diagnosis and management of bipolar disorders. *BMJ*. 2023;**381**. e073591. [PubMed ID: 37045450]. https://doi.org/10.1136/bmj-2022-073591.
6. Hu ZY, Liu X, Zheng H, Zhou DS. Commentary: Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression: A Randomized Clinical Trial. *Front Hum Neurosci*. 2018;**12**:480. [PubMed ID: 30574077]. [PubMed Central ID: PMC6291661]. https://doi.org/10.3389/fnhum.2018.00480.
7. Lee J, Lee CW, Jang Y, You JS, Park YS, Ji E, et al. Efficacy and safety of daily home-based transcranial direct current stimulation as adjunct treatment for bipolar depressive episodes: Double-blind sham-controlled randomized clinical trial. *Front Psychiatry*. 2022;**13**:969199. [PubMed ID: 36203828]. [PubMed Central ID: PMC9530445]. https://doi.org/10.3389/fpsyt.2022.969199.
8. Zhang L, Li Q, Du Y, Gao Y, Bai T, Ji GJ, et al. Effect of high-definition transcranial direct current stimulation on improving depression and modulating functional activity in emotion-related cortical-subcortical regions in bipolar depression. *J Affect Disord*. 2023;**323**:570-80. [PubMed ID: 36503046]. https://doi.org/10.1016/j.jad.2022.12.007.
9. Schlaug G, Renga V. Transcranial direct current stimulation: a noninvasive tool to facilitate stroke recovery. *Expert Rev Med Devices*. 2008;**5**(6):759-68. [PubMed ID: 19025351]. [PubMed Central ID: PMC3176333]. https://doi.org/10.1586/17434440.5.6.759.
10. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry*. 2000;**48**(8):830-43. [PubMed ID: 11063978]. https://doi.org/10.1016/s0006-3223(00)01036-2.
11. Jin J, Al-Shamali HF, McWeeny R, Sawalha J, Shalaby R, Marshall T, et al. Effects of Transcranial Direct Current Stimulation on Cognitive Deficits in Depression: A Systematic Review. *Psychiatry Clini Psychopharmacol*. 2023;**33**:330-43.
12. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry*. 2015;**72**(6):603-11. [PubMed ID: 25785575]. [PubMed Central ID: PMC4456260]. https://doi.org/10.1001/jamapsychiatry.2015.0071.
13. Sampaio-Junior B, Tortella G, Borrione L, Moffa AH, Machado-Vieira R, Cretaz E, et al. Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2018;**75**(2):158-66. [PubMed ID: 29282470]. [PubMed Central ID: PMC5838572]. https://doi.org/10.1001/jamapsychiatry.2017.4040.
14. Yokoi Y, Narita Z, Sumiyoshi T. Transcranial Direct Current Stimulation in Depression and Psychosis: A Systematic Review. *Clin EEG Neurosci*. 2018;**49**(2):93-102. [PubMed ID: 28929795]. https://doi.org/10.1177/1550059417732247.
15. Zhang Y, Song W. Transcranial direct current stimulation in disorders of consciousness: a review. *Int J Neurosci*. 2018;**128**(3):255-61. [PubMed ID: 28918680]. https://doi.org/10.1080/00207454.2017.1381094.
16. Strik JJ, Honig A, Lousberg R, Denollet J. Sensitivity and specificity of observer and self-report questionnaires in major and minor depression following myocardial infarction. *Psychosom*. 2001;**42**(5):423-8. [PubMed ID: 11739910]. https://doi.org/10.1176/appi.psy.42.5.423.
17. Spielberger CD. The experience and expression of anger: Construction and validation of an anger expression scale. *Anger Hostility Cardiovascular Behavi Disord*. 1985:5-30.
18. Mutz J. Brain stimulation treatment for bipolar disorder. *Bipolar Disord*. 2023;**25**(1):9-24. [PubMed ID: 36515461]. [PubMed Central ID: PMC10210071]. https://doi.org/10.1111/bdi.13283.
19. Scaini G, Valvassori SS, Diaz AP, Lima CN, Benevenuto D, Fries GR, et al. Neurobiology of bipolar disorders: a review of genetic components, signaling pathways, biochemical changes, and neuroimaging findings. *Braz J Psychiatry*. 2020;**42**(5):536-51. [PubMed ID: 32267339]. [PubMed Central ID: PMC7524405]. https://doi.org/10.1590/1516-4446-2019-0732.
20. Clark L, Sahakian BJ. Cognitive neuroscience and brain imaging in bipolar disorder. *Dialogues Clin Neurosci*. 2008;**10**(2):153-63. [PubMed ID: 18689286]. [PubMed Central ID: PMC3181872]. https://doi.org/10.31887/DCNS.2008.10.2/lclark.
21. Ashcroft J, Patel R, Woods AJ, Darzi A, Singh H, Leff DR. Prefrontal transcranial direct-current stimulation improves early technical skills in surgery. *Brain Stimul*. 2020;**13**(6):1834-41. [PubMed ID: 33130252]. https://doi.org/10.1016/j.brs.2020.10.013.
22. Mardani P, Zolghadriha A, Dadashi M, Javdani H, Mousavi SE. Effect of medication therapy combined with transcranial direct current stimulation on depression and response inhibition of patients with bipolar disorder type I: a clinical trial. *BMC Psychiatry*. 2021;**21**(1):579. [PubMed ID: 34789181]. [PubMed Central ID: PMC8596350]. https://doi.org/10.1186/s12888-021-03592-6.
23. Brunoni AR, Ferrucci R, Bortolomasi M, Scelzo E, Boggio PS, Fregni F, et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: findings from a naturalistic study. *Eur Psychiatry*. 2013;**28**(6):356-61. [PubMed ID: 23182847]. https://doi.org/10.1016/j.eurpsy.2012.09.001.
24. Dell'Osso B, Zanoni S, Ferrucci R, Vergari M, Castellano F, D'Urso N, et al. Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. *Eur Psychiatry*. 2012;**27**(7):513-7. [PubMed ID: 21621982]. https://doi.org/10.1016/j.eurpsy.2011.02.008.
25. Herrera-Melendez AL, Bajbouj M, Aust S. Application of Transcranial Direct Current Stimulation in Psychiatry. *Neuropsychobiol*. 2020;**79**(6):372-83. [PubMed ID: 31340213]. https://doi.org/10.1159/000501227.
26. Donde C, Amad A, Nieto I, Brunoni AR, Neufeld NH, Bellivier F, et al. Transcranial direct-current stimulation (tDCS) for bipolar depression: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;**78**:123-31. [PubMed ID: 28552295]. https://doi.org/10.1016/j.pnpbp.2017.05.021.
27. Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;**35**(1):96-101. [PubMed ID: 20854868]. https://doi.org/10.1016/j.pnpbp.2010.09.010.
28. Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. *Neurosci Biobehav Rev*. 2018;**92**:291-303. [PubMed ID: 29763711]. https://doi.org/10.1016/j.neubiorev.2018.05.015.
29. McClintock SM, Martin DM, Lisanby SH, Alonzo A, McDonald WM, Aaronson ST, et al. Neurocognitive effects of transcranial direct current stimulation (tDCS) in unipolar and bipolar depression: Findings from an international randomized controlled trial. *Depress Anxiety*. 2020;**37**(3):261-72. [PubMed ID: 31944487]. https://doi.org/10.1002/da.22988.

30. Brunoni A, Nitsche M, Loo C. *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders*. London, England: Springer Nature; 2016.
31. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *Br J Psychiatry*. 2016;**208**(6):522-31. [PubMed ID: 27056623]. [PubMed Central ID: PMC4887722]. https://doi.org/10.1192/bjp.bp.115.164715.
32. Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, et al. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. *Brain Stimul*. 2012;**5**(3):242-51. [PubMed ID: 21962978]. https://doi.org/10.1016/j.brs.2011.08.005.
33. Guarienti F, Caumo W, Shiozawa P, Cordeiro Q, Boggio PS, Bensenor IM, et al. Reducing transcranial direct current stimulation-induced erythema with skin pretreatment: considerations for sham-controlled clinical trials. *Neuromodulation*. 2015;**18**(4):261-5. [PubMed ID: 25209456]. https://doi.org/10.1111/ner.12230.
34. Aparicio LVM, Guarienti F, Razza LB, Carvalho AF, Fregni F, Brunoni AR. A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials. *Brain Stimul*. 2016;**9**(5):671-81. [PubMed ID: 27261431]. https://doi.org/10.1016/j.brs.2016.05.004.
35. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. *N Engl J Med*. 2017;**376**(26):2523-33. [PubMed ID: 28657871]. https://doi.org/10.1056/NEJMoa1612999.
36. Riahi F, Pourshams M, Tashakori A, Hassani SM. The Effect of transcranial Direct Current Stimulation (tDCS) on the Reduction of Negative Symptoms in Schizophrenic Patients in Ahvaz Golestan Hospital. *NeuroQuantology*. 2022;**20**(20):2497.