

## Review Article

# Efficacy and Safety of Transcranial Direct Current Stimulation (tDCS) in the Treatment of Bipolar Depression: A Systematic Review

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### Abstract

Since standard treatments often show limited efficacy in the treatment of bipolar depressive disorder, the use of non-invasive stimulation techniques such as transcranial direct current stimulation (tDCS) (tDCS) can be promising. The aim of the present study is to systematically review studies on the effectiveness of tDCS on bipolar depression. This research was conducted to investigate the effectiveness of this method in the treatment of bipolar depression. 154 articles were retrieved from Google Scholar, PubMed, Scopus, and Web of Science databases, among which 19 articles were relevant to the topic. Finally, 13 studies were excluded and 6 studies were included for investigation. In all these studies, the anode electrode in the left dorsolateral prefrontal cortex (DLPFC-F3) and the cathode electrode in the right dorsolateral prefrontal cortex (DLPFC-F4) were selected as stimulation areas. The results of the extracted articles indicated the tDCS is a safe method. In summary, the results of the present study indicate that tDCS is a promising approach to treating symptoms of bipolar depression. The findings of the present study are significant from two aspects: firstly, they demonstrate the effectiveness of tDCS in reducing depressive symptoms in these patients; secondly, the lack of a long follow-up period to assess the durability of the treatment effects and the use of small sample sizes in experimental groups were the main limitations of the reviewed studies. Therefore, future research is encouraged to take this issue into consideration when designing interventions.

### Keywords

Bipolar disorder  
Depression  
Transcranial direct  
current stimulation  
tDCS

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### Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), bipolar disorders are described as a group of brain disorders that cause severe changes in mood, energy, and an individual's ability to function (American Psychiatric Association & Association, 2013). This disorder affects more than 1% of the world's population, regardless of nationality, ethnicity, or socioeconomic status (Grande et al., 2016). About 10 to 20% of people with bipolar disorder die by suicide, and nearly one-third of patients report at least one suicide attempt (Müller-Oerlinghausen et al., 2002). Bipolar type I, is associated with periods of depression and mania, and can be diagnosed based on the presence of a manic episode; bipolar type II is associated with periods of depression and hypomania; and Cyclothymic disorder is characterized by hypomanic and depressive

symptoms that do not meet the criteria for depressive episodes (Phillips & Kupfer, 2013). For the treatment of this disorder, few options remain besides electroconvulsive therapy (ECT), which can also lead to serious side effects, such as transitioning from depression to hypomania or mania, rapid-cycling bipolar disorder, and increased risk of suicide. Lithium treatment with a mood stabilizer is rarely enough to treat bipolar depression. Given the lack of therapeutic approaches, there is a need to develop new treatments for patients with bipolar depression (Donde et al., 2017).

Among clients with severe depression, some may also suffer from bipolar disorder. This may be due to several reasons, including the following: 1) In many cases, bipolar disorder begins with symptoms of depression and leads to mania or hypomania in later years. 2) Depression is considered to be part of the bipolar genetic spectrum; therefore, some forms of depression are likely to be a

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type of bipolar disorder, especially in people with a strong family history. 3) In some patients, periods of hypomania or even mania in the past may have been overlooked. The signs of depression in bipolar disorder include suicidal thoughts, decreased appetite, difficulty sleeping, feelings of guilt and hopelessness, and self-doubt (O'Donovan & Alda, 2020).

One of the most common and popular non-invasive brain stimulation methods is transcranial direct current stimulation (tDCS), which applies a weak current (0.5 to 2 milliamps) from two electrodes (anode and cathode) placed on a conductive rubber pad soaked in sodium chloride and positioned over specific areas of the cerebral cortex, resulting in changes in cognitive, perceptual, and behavioral functions. The current sent by the anode increases neuronal activity, while the current sent by the cathode decreases neuronal activity (Dondé et al., 2018; Nitsche et al., 2008). On the other hand, tDCS modulates the long-term effects of use-dependent plasticity, in which synapses are strengthened through a process similar to long-term potentiation (LTP) (Rroji et al., 2015). A review of studies shows that the tDCS method is effective in treating various psychiatric disorders (Alizadehgoradel, 2023; Alizadehgoradel et al., 2020; Alizadehgoradel, Taherifard, & Vanderhasselt, 2023; Jafari et al., 2021; Arshadi et al., 2022). Studies using functional imaging techniques have shown frontal asymmetry in unipolar depression, characterized by reduced activity in the left DLPFC and increased activity in the right DLPFC (Zhang et al., 2022). In the treatment of patients with unipolar depression, tDCS studies of bifrontal montage with an excitatory electrode (anode) fixed on the left DLPFC or F3 and an inhibitory electrode (cathode) on the right DLPFC (F4), or right lateral frontal orbito (F8), or the right superior cortex (Fp2) were employed (Brunoni et al., 2016). The rationale for this electrode placement stems from the fact that functional imaging studies have shown hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) (Kennedy et al., 1998) and relative hyperactivity in the right DLPFC (Grimm et al., 2008), suggesting frontal asymmetry in unipolar depressed patients. Recent evidence has reported mild side effects of this method, such as mild headache, skin inflammation, tingling/itching of the scalp, or drowsiness (Donde et al., 2017).

According to the research literature review, based on the specific mechanisms of bipolar depression, no evidence is available to guide the choice of electrode montage and other stimulation parameters (for example, current intensity, number and duration of sessions). Unipolar and bipolar disorders have a complex and distinct neurobiological basis; they are multigenic and multifactorial (Hou et al., 2016), which cause dysfunctional synaptic plasticity and disorder in the regulation of the subcortical brain network (Rodríguez-Cano et al., 2017). Due to the lack of studies on the effectiveness of tDCS in treating bipolar disorder in Iran, the present study was conducted with the following objectives: (1) to clarify the stimulation montages and target areas for treating symptoms of

bipolar depression, (2) to determine the safety and side effects of tDCS in patients with bipolar disorder, and (3) to provide research and practical recommendations for future studies.

## Method

### Participants

In order to study the impact of transcranial stimulation on the symptoms of bipolar depression, relevant articles were searched in various databases including Google Scholar, PubMed, Scopus, and Web of Science from 2007 to 2023.

Articles meeting the following criteria were included in the study:

- 1-Studies that used the transcranial direct current stimulation (tDCS) method.
- 2- Studies with sample populations comprising individuals with bipolar disorder and prominent depressive symptoms.
- 3- Studies that examined the effects of electrical stimulation in different brain areas on depressive symptoms.
- 4- Studies that examined the effects of different stimulation poles (anode, cathode, or both) on reducing depressive symptoms.
- 5- Studies that were published in English or Persian.
- 6- Studies available in full-text format.

Articles that met the following criteria were excluded from the study:

- 1- Studies that used similar methods such as high definition (HD)-tDCS.
- 2- Studies where individuals with bipolar disorder presented only manic symptoms or lacked prominent depressive symptoms.
- 4- Studies that focused solely on cognitive aspects or sleep quality in individuals with depressive symptoms without assessing the severity of depression.

### Procedure

Initially, titles were screened based on the keywords of interest, and abstracts were reviewed. Similar articles were excluded during this process. In the next step, articles that did not align with the primary objectives or employed complementary methods were excluded. In cases of ambiguity between two articles, a third source was consulted for further investigation.

The quality of the selected studies was assessed using the PEDro scale, with results presented in Table 1.

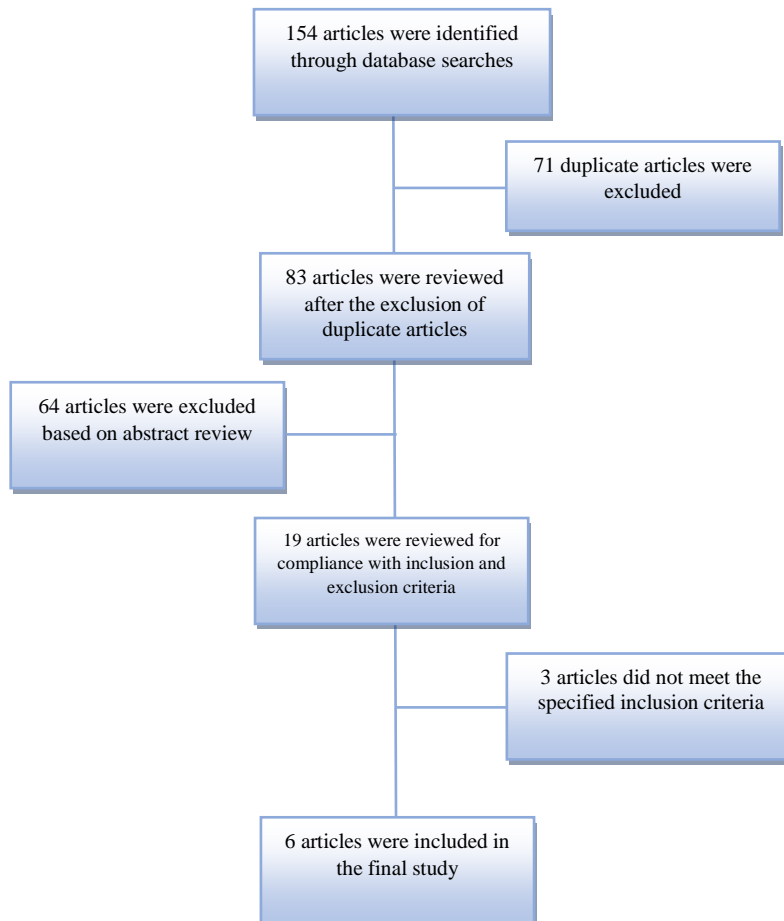
To extract the necessary data from the selected articles, the findings were summarized and presented in Table 2. This information includes the purpose of the experiment, the number of participants and their average age, clinical symptoms, grouping method, electrode placement, intensity and duration of stimulation, measurement tool for the variables being evaluated, and results.

## Results

Following the application of the inclusion and exclusion criteria, 6 articles were selected for final review from a total of 154 articles (Brunoni et al., 2011; Brunoni et al., 2013; Lin et al., 2021; Mardani et al., 2021; McClintock et al., 2020; Sampaio-Junior et al., 2018). The mean PEDro scale score of the articles was 9, and all articles were considered valid. Data from the articles meeting the inclusion criteria were extracted and summarized in Table 2.

In all reviewed articles, the anode was placed over the left dorsolateral prefrontal cortex (DLPFC-F3), and the cathode over the right DLPFC (DLPFC-F4) except in one study (Brunoni et al., 2011; Brunoni et al., 2013; Lin et al., 2021; Mardani et al., 2021; Sampaio-Junior et al., 2018). In one study, the cathode was placed over F8 (McClintock et al., 2020). The Hamilton Rating Scale for Depression (HAM-D) was used to evaluate depression

severity in four articles (Brunoni et al., 2011; Lin et al., 2021; Mardani et al., 2021; Sampaio-Junior et al., 2018), the Beck Depression Inventory (BDI) was employed in two articles (Brunoni et al., 2011; Lin et al., 2021), and cognitive effects of depression were evaluated in one study (McClintock et al., 2020). In all but one study, stimulation lasted 20 minutes at 2 milliamperes; in one study, it was 30 minutes at 2.5 milliamperes (McClintock et al., 2020). No drugs or complementary methods were used in any of the selected studies, but the previously prescribed drugs of the participants were not discontinued. In all of the studies, tDCS was reported to be effective in reducing the severity of depression. In two of the studies, this method was effective in conjunction with drug therapy, in one study it was evaluated along with cognitive effects such as attention and memory, and in three studies, it was effective solely in reducing the symptoms of depression.



**Figure 1.** Flowchart of Eligible Articles in a Systematic Review

**Table 1.** Quality Assessment of Included Studies Using the PEDro Scale

Evaluation criteria	(Brunoni et al., 2011)	(McClintock et al., 2020)	(Mardani et al., 2021)	(Sampaio-Junior et al., 2018)	(Brunoni et al., 2013)	(Lin et al., 2021)
Study inclusion and exclusion criteria were carefully considered.	+	+	+	+	+	+
Participants were randomly assigned to study groups.	+	+	-	+	+	+
Group allocation was concealed.	+	+	+	+	-	+
Baseline data were equal in both groups.	-	+	+	-	+	-
Participants were blinded to the group allocation and intervention type.	+	+	+	+	+	-
At least one of the study's key outcomes was assessed in all participants.	+	+	+	+	-	+
The evaluator was blinded to the data and intervention type for participants in the both groups.	+	+	+	+	+	-
At least one of the outcomes being studied was assessed in more than 85% of the participants.	+	+	+	+	-	+
The therapist was blinded to the intervention type of the participants in the other group.	+	+	+	+	+	-
Acceptable results of between-group comparisons were reported for at least one of the data being studied.	+	+	+	+	-	+
For at least one outcome being studied, both point data and dispersion were reported.	+	+	+	+	+	+
Total score	10	11	10	10	7	6

**Table 2.** Extracted Data from English Studies

Authors and Year of Publication	Number of participants	Study objective	Number of sessions and intervention duration	Intensity of stimulation
(Brunoni et al., 2011)	31 participants, including 17 with major depressive disorder and 14 with bipolar disorder. - The average age ranged from 30 to 70 years, including 27 women and 7 men.	The study aimed to explore the effectiveness of transcranial direct current stimulation (tDCS) in hospitalized patients with major depressive disorder and bipolar disorder.	twice a day, with a minimum 4-hour gap, for 5 consecutive days	tDCS anodal with an intensity of 2 mA and 20 minutes
(McClintock et al., 2020)	130 participants. - Participants aged 18 years or older.	The purpose of this study is to investigate the neurocognitive effects of transcranial direct current stimulation on bipolar depression.	20 sessions over 4 weeks	Anodal tDCS with an intensity of 2.5 mA for 30 minutes
(Mardani et al., 2021)	30 participants, with 15 participants receiving medication therapy and 15 participants receiving medication therapy + tDCS. - The average age ranged from 18 to 50 years, including 17 women and 13 men.	This study was conducted to investigate the effectiveness of combined medication and transcranial direct current stimulation (tDCS) on depression and mood stabilization in patients with bipolar disorder.	2 sessions per day for 10 days	tDCS anodal with an intensity of 2 mA and 20 minutes
(Sampaio-Junior et al., 2018)	59 participants, with 29 participants in the sham stimulation group and 29 participants in the real stimulation group. -The average age ranged from 18 to 65 years, including 40 women and 19 men.	The purpose of this study is to determine the efficacy and safety of tDCS as an add-on treatment for bipolar depression.	12 sessions: One week daily, then alternate days until week 6	Anodal with an intensity of 2 mA and 20 minutes
(Brunoni et al., 2013)	Eighty-two participants. - Average age: 54 years; 54 women and 28 men.	The purpose of this study is to investigate the interaction between transcranial direct current stimulation (tDCS) and medication interventions in the course of major depressive episodes in individuals with bipolar disorder.	Five consecutive days, with 2 stimulations per day, with a 4-hour gap between each stimulation	Anodal with an intensity of 2 mA and 20 minutes:

(Lin et al., 2021)	Eighty participants, divided into two groups of patients with bipolar disorder with major depressive disorder and patients with unipolar disorder with major depressive disorder. -The average age was between 50 and 65 years old; 48 women and 32 men.	The purpose of this study is to investigate the efficacy and neural predictors of prefrontal cortex stimulation in the treatment of bipolar depression.	Five consecutive days, with 2 stimulations per day, with a minimum 3-hour gap between each stimulation	Anodal with an intensity of 2 mA and 20 minutes
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**Table 3.** Extracted Data from the Results of the Studies

Authors and Year of Publication	variables assessed	variable measurement tool	Time of assessment	Conclusion
(Brunoni et al., 2011)	Major depressive disorder (MDD) and bipolar disorder (BD)	Beck (BDI) and Hamilton-21 items (HDRS)	At the end of five consecutive days of stimulation and follow-up assessments one week and one month after the last session	After the fifth session of tDCS, depressive symptoms decreased in both groups and the beneficial effect lasted at least 4 weeks. -The simultaneous use of drugs such as anticonvulsants eliminates the increased nerve excitability. -As a result, tDCS is considered an effective treatment for bipolar disorder and depression
(McClintock et al., 2020)	Verbal learning and recall, selective attention, processing speed, and working memory	Wechsler Test of Adult Reading	Immediately before and after stimulation sessions	These findings suggest that tDCS can have positive neurocognitive effects in both unipolar and bipolar depression. The neurocognitive effects associated with tDCS need further investigation and replication.
(Mardani et al., 2021)	Depressive disorder	Go/No-Go test-Hamilton Depression Rating Scale (HDRS)	After completion of stimulation sessions and follow-up assessment three months after the last session	Combining medication and tDCS therapy may decrease depressive symptoms and improve response inhibition in individuals with bipolar disorder.
(Sampaio-Junior et al., 2018)	Severity of depression and severity of manic episodes	Montgomery-Asberg Depression Rating Scale- Clinical Global Impression (CGI)depression scale scores-Young Mania Rating Scale	At the end of weeks two, four, and six	The positive effect of some drugs simultaneously with stimulation and the negative effect of some other drugs were investigated. Transcranial stimulation was an effective, safe, and tolerable complementary intervention for this small sample of bipolar depression.
(Brunoni et al., 2013)	Mood state and severity of depression	Beck Depression Inventory (BDI)- the Hamilton Depression Rating Scale (HDRS).	Immediately after completion of five days of stimulation	The effect of medication treatments on tDCS interaction varies. For instance, benzodiazepines may reduce tDCS effects, while antidepressants can increase it.
(Lin et al., 2021)	Social, occupational, and psychological functioning-severity of manic and hypomanic episodes-severity of depression	Hamilton Anxiety Rating Scale (HAM-A)-HAM-D - The Young Mania Rating Scale (YMRS)- The Global Assessment of Functioning (GAF)	After 10 sessions and one week and four weeks later as follow-up assessments	Frontal tDCS is equally effective in patients with unipolar and bipolar disorder who do not respond to one or more drug interventions after prescription.

## Discussion

Studies have investigated the effects of transcranial direct current stimulation (tDCS) on the symptoms of bipolar disorder. One of the most prominent symptoms of this disorder is the presence of depressive symptoms in individuals; methods alleviating these symptoms differ from those for addressing bipolar disorder involving both manic and depressive states, which makes it essential to systematically review studies on the effects of tDCS in reducing depressive symptoms. Among the studies, two investigations specifically focused on the effects of transcranial stimulation on the

severity of depressive symptoms in patients with bipolar disorder, indicating consistently positive outcomes (Brunoni et al., 2011; Lin et al., 2021). After undergoing transcranial stimulation twice daily for five consecutive days, patients with bipolar disorder showed a significant decrease in depressive symptoms. The effects of the treatment lasted for at least four weeks after its initiation. However, due to the small and weak sample size, it is challenging to determine whether factors such as age, sex, or severity have an impact on the long-term effects of tDCS (Brunoni et al., 2011). Additionally, the potential effects of certain medications, such as

anticonvulsants, on the degree of irritability induced by nerve stimulation have not been investigated. In a study, after five consecutive days of enhanced stimulation, the effects of depression decreased and remained until the end of the experiment. The effectiveness was the same and effective in both single and bipolar individuals. The use of wide electrodes that can spread the current, uncontrolled trials, and awareness of the evaluator and patient of the treatment process were limitations of this study) (Lin et al., 2021)

The effects of drug supplementation on transcranial stimulation were also investigated in three studies which showed the positive effect of some drugs on the effectiveness of tDCS and negative effect of others on this stimulation method (Brunoni et al., 2013; Mardani et al., 2021; Sampaio-Junior et al., 2018). A study was conducted to evaluate the effectiveness of transcranial stimulation in conjunction with drug therapy. Following two daily stimulations for ten days, the average score of the Hamilton test decreased in both groups, i.e., drug therapy only and drug therapy with tDCS. However, after three months, the effects disappeared, and there was no significant difference between the two groups, as per the study. According to this study, drugs and their combination with tDCS can reduce depressive symptoms and improve the response ability of people with bipolar disorder. The Go/NoGo test showed that if drugs were used, errors and average response time increased, but the combination of drugs and tDCS led to a reduction in these. The limitations of this study were the small sample size, the purposive sampling method, and the lack of a sham stimulation group to investigate the effects of a placebo (Mardani et al., 2021). A study was conducted to compare two groups: the real stimulation group and the sham stimulation group. The study found that this method of stimulation was effective in reducing depressive symptoms. When used in combination with drug therapy, the results were even better. However, the study had some limitations. The sample size was small, the random distribution of participants was imbalanced, and there was no clear superiority of real stimulation over sham stimulation based on CGI scale scores (Sampaio-Junior et al., 2018). During a five-day study on enhanced stimulation, it was observed that most patients showed improvement in their condition, while 25% of individuals did not respond. The study also investigated the effects of drugs on the patients. It was found that benzodiazepines reduced the effects of tDCS, while antidepressants increased the effects. However, the study had some limitations, such as lack of control and a short period for depression. Despite these limitations, this method was shown to reduce depressive symptoms and positively impact cognitive components (Brunoni et al., 2013). A review of past studies also showed that the use of enhanced stimulation can be more effective, which is due to the greater excitability of the neurons in the stimulated areas (Agboada et al., 2020; Alizadehgoradel, Poursalmi, & Taherifard, 2023; Alizadehgoradel, Taherifard, & Vanderhasselt, 2023;

Monte-Silva et al., 2013).

In an extensive investigation, the effects of transcranial stimulation on the cognitive-neural components of people with bipolar disorder with depressive symptoms were investigated, indicating that, in addition to mood improvements, it enhanced learning, verbal recall, selective attention, information processing speed, and working memory (McClintock et al., 2020).

To elucidate the effectiveness of tDCS in treating bipolar depression, it can be stated that this disorder is associated with decreased activity in the left dorsolateral prefrontal cortex (left DLPFC) and increased activity in the right dorsolateral prefrontal cortex (right DLPFC) (Chai et al., 2011; Donde et al., 2017; Frey et al., 2007). Therefore, stimulating the left DLPFC while inhibiting the right DLPFC appears to be a logical approach for treating bipolar depression symptoms.

## Conclusion

In summary, the results of the present study indicate that tDCS is a promising approach to treating symptoms of bipolar depression. The target stimulation areas were the anode over the left dorsolateral prefrontal cortex (DLPFC-F3) and the cathode over the right dorsolateral prefrontal cortex (DLPFC-F4). As mentioned, all conducted studies had limitations, with the most important ones being the lack of follow-ups after treatment, the absence of a control group, and limited sample sizes. Therefore, future studies are encouraged to include larger sample sizes, as well as control groups and sham stimulation, to more effectively evaluate the effects of stimulation. To assess the sustained improvement effects of transcranial stimulation on reducing depression symptoms, follow-up evaluations should be conducted at specified intervals after treatment completion.

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