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REVIEW ARTICLE

Efficacy of Transcranial Direct Current Stimulation Associated With Antidepressants in the Treatment of Major Depressive Disorder: A Systematic Review

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Highlights:
(1) Overall, no significant effect of tDCS as a complement to antidepressant therapy on quality of life.
(2) tDCS possibly provides changes in electroencephalographic signals during REM sleep.
(3) tDCS is a safe and easy-to-apply resource.

ABSTRACT

Introduction: Transcranial direct current stimulation (tDCS) is a low-intensity neuromodulation technique that can produce a clinically significant response in patients with major depressive disorder (MDD). It seems to be a useful additional strategy to antidepressant therapy to potentiate improvements in sleep, psychomotor symptoms, and quality of life in people with MDD. *Objective*: Evaluate the efficacy of combining tDCS with antidepressants in the treatment of MDD. *Materials and Methods*: This is a systematic review, which was searched in the Embase, SCOPUS, Medline/PubMed, and Science Direct databases. Randomized clinical trials investigating the efficacy of tDCS associated with antidepressants compared to antidepressants associated or not with placebo were included. The outcomes analyzed were sleep, psychomotor symptoms, and quality of life of people with MDD. The *Revised Cochrane risk-of-bias tool for randomized trials* 2.0 was used to assess the risk of bias. *Results*: Three randomized clinical trials were analyzed, totaling 211 participants, with a risk of bias ranging from low to uncertain. Electroencephalographic signs in REM sleep significantly improved in favor of tDCS associated with antidepressants, but there was no significant difference in psychomotor symptoms and quality of life. *Conclusion*: There is initial evidence with a low risk of bias that tDCS associated with antidepressant medication is effective in changing electroencephalographic signals during REM sleep, but is not effective in treating psychomotor symptoms and quality of life in people with MDD.

Keywords: Transcranial Direct Current Stimulation; tDCS; major depressive disorder; depression; antidepressants.

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INTRODUCTION

Major depressive disorder (MDD) is a disease that leads to emotional changes in the individual, developing a feeling of chronic, continuous, and exacerbated sadness, which generates a sense of frustration and marked dissatisfaction, causing suicidal ideation or the actual practice of the act[1]. People with MDD may experience psychomotor symptoms, such as psychomotor slowness or agitation, and sleep disorders, among other symptoms, interfering with basic activities such as eating and sleeping, leisure, and work activities, impacting the quality of life[2].

MDD represents an increase in global health expenditure, affecting more than 300 million people. The impact of MDD is exacerbated by the lack of response from first-line antidepressant therapies, in which a third of people with MDD are expected to improve their sleep, psychomotor symptoms, and quality of life after initial treatment. However, a failure in the therapeutic response to the antidepressant drug leads to a worsening of the individual's state of health[3]. Therefore, to improve these symptoms, additional non-pharmacological treatment strategies are necessary. In this sense, transcranial direct current stimulation (tDCS) has been used as a promising resource for MDD[1,3].

tDCS is a low-intensity, non-invasive neuromodulation technique that has shown positive therapeutic effects in people with MDD[3,4]. People with MDD suffer from an alteration in neurotransmitter substances, causing hypoactivity in the dorsolateral prefrontal lobe, a region considered a target for mood control, which is why tDCS is applied with a weak, direct current through electrodes on the surface of the scalp to cause transformations in the activity of the cerebral cortex and alter its local excitability [5–7]. Stimulation has the potential to increase the activity of the dorsolateral prefrontal lobe, which is inhibited after neurotransmitter alterations, and can be effective in improving sleep, psychomotor symptoms, and quality of life[6].

Although several previous studies have investigated the efficacy of tDCS added to antidepressant therapy on the depressive symptoms of people with MDD[8], no recent evidence abstracts were found that specifically evaluate the effect of adding tDCS with antidepressant drugs when compared to antidepressants alone on the recovery of sleep, psychomotor symptoms and quality of life of people with MDD. Therefore, this study aims to evaluate the effectiveness of combining tDCS with antidepressants in the treatment of MDD.

MATERIALS AND METHODS

This is a systematic review study that follows the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) recommendation[9]. The protocol for the construction stages of this systematic review was submitted to the *International Prospective Register of Systematic Reviews* (PROSPERO), under number CRD42023412389.

Search strategy and study selection

The following databases were used: Embase, SCOPUS, Medline/PubMed, and Science Direct. The last search was carried out in July 2023. Keywords and synonyms were used according to the databases, identified in the Health Sciences Descriptors (*Descritores em Ciências da Saúde*, DeCS), Medical Subject Headings (Mesh) and Embase Subject headings (Emtree), using the Boolean operators "AND" and "OR". The search was carried out using the words found in the titles, subjects, and abstracts of the articles, according to chart 1.

Chart 1 – Databases and keywords.

Database	Keywords
Embase	'depression'/exp AND 'antidepressant agent'/exp AND 'transcranial direct current stimulation'/exp AND 'controlled clinical trial'/exp
Scopus	(TITLE-ABS-KEY (tdcs) OR TITLE-ABS-KEY ("transcranial direct current stimulation") AND TITLE-ABS-KEY (depression) OR TITLE-ABS-KEY ("major depressive disorder") OR TITLE-ABS-KEY ("antidepressive agents")).
Medline/Pubmed	(((tDCS) OR (transcranial direct current stimulation)) AND (depression)) AND (major depressive disorder)
Science Direct	(tDCS OR "transcranial direct current stimulation") AND depression OR "major depressive disorder

Eligibility criteria

This research was structured using the PICOT *(Population, Intervention, Control, Outcome, and Type of study)* strategy:

- Population: individuals over the age of 18, of both genders, with a diagnosis of MDD according to DSM-5;
- Intervention: at least one group with tDCS associated with an antidepressant of any class;
- Comparison: at least one group with antidepressant alone or in association with placebo tDCS;
- Outcome: sleep, psychomotor symptoms, and quality of life;
- Type of study: randomized clinical trials (RCTs).

Research protocols, studies with other associated populations, and antidepressants associated with another drug that would increase the positive response to the outcome in question were excluded.

Risk of bias assessment

The Cochrane Collaboration recommendations were used to assess the risk of bias for all randomized clinical trials using the RoB 2.0 tool (*Revised Cochrane risk-of-bias tool for randomized trials)*[10]*, composed of five domains: Bias in the randomization process; Deviations from the intended intervention; Bias due to missing data; Bias in the measurement of outcomes; and Bias in the reporting of outcomes. The risk of bias was assessed by two independent researchers. A third reviewer was activated in cases of inconsistencies between the reviewers and made the final decision*.

Data extraction and analysis

Data extraction from the included studies was carried out using a standardized form adapted from the Cochrane Collaboration Checklis[11], extracted by two independent reviewers. In cases of disagreement, a third independent reviewer assessed and made the final decision. The results were analyzed according to the outcomes of interest: sleep, psychomotor symptoms, and quality of life.

RESULTS

Of the 4,822 studies identified in the initial search, 3 randomized clinical trials met all the inclusion criteria. The search and selection flowchart are described in Figure 1.

The data of the participants analyzed in the included RCTs, as well as the tDCS prescription parameters and the instruments used to assess the outcomes of interest are described in Table 1. Concerning the characteristics of the participants analyzed, the sum of the samples from the included studies made up a total of 211 participants. Ages ranged from 18 to 65, out of which 129 were female and 82 were male. One study [12] included participants with a diagnosis of resistant MDD, all diagnosed according to the DSM-5. Two trials[13,14] used scores ≥ 15 and 20 on the HAM-D scale as inclusion criteria. One RCT[12] recruited patients with a score ≥ 25 on the MADRS.

Regarding the assessment tools used in the studies analyzed, the quality of life outcome was assessed using the general health status and social function domains of the *Short Form Health Survey* (SF-36) questionnaire[14]; for the outcome psychomotor symptoms (psychomotor retardation), one RCT[12] used the Salpêtrière Retardation Rating Scale (SRRS); and for the outcome of sleep/insomnia, one study[13] used polysomnography. The evaluation period from baseline and last reassessment ranged from five days to six weeks.

Regarding the characteristics of the antidepressants, SSRI-class antidepressants were used in the three studies and one of these trials[13] used a selective serotonin and noradrenaline reuptake inhibitor (SSNRI) class antidepressant. One RCT[12] used a constant dose of 10 to 20 mg/day of escitalopram; one study[13] used escitalopram at a dose of 20 mg/day or duloxetine hydrochloride at a dose of 60 mg/day. One trial[14] did not report the type of SSRI and stable dose used. The duration of antidepressant use ranged from five to six weeks.

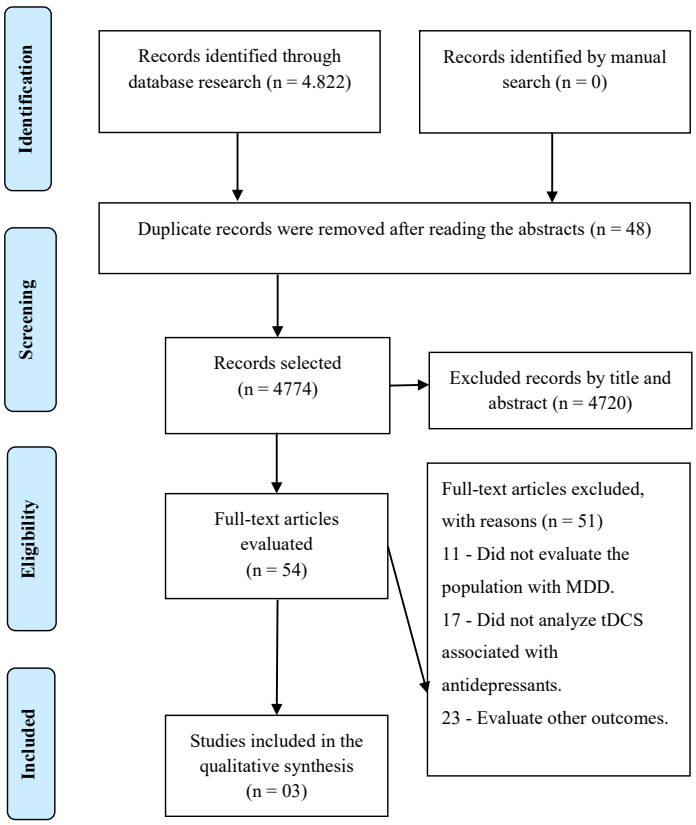

Figure 1 – Flowchart of the search and selection of studies according to Prisma.

Regarding the characteristics of tDCS, an intensity of 2mA was used in the 3 included RCTs, with a variation in time per session of 20 to 30 minutes. In two studies[13,14], the electrodes were located bifrontal in areas F3 and F4, and another RCT (12) was located in areas F3 and FP2, according to the 10/20 electroencephalogram system. The frequency of the sessions varied from 1 to 2 times a day, with a total of 10 to 24 sessions. The placebo tDCS had a rise time variation of 15 to 30s up to intensity 2 mA and then a fall time with a variation of 10-30s to intensity 0 mA maintained for a time variation of 20 to 30 minutes.

Table 1 – Description of the characteristics of the included studies

Author/Date	Type of study	Participants		Intervention	Outcome/instrument
Burkhardt et al., 2023	RCT Triple-blind, placebo-control	EXP:	n = 77; 48 (62%) women; 40.2±13.6 years old	tDCS (int.2mA, rise time 15s, and fall time 30s, 30 minutes, for 24 sessions, in 6 weeks) + SSRI (stable dose, for 35.9 ± 61.2 weeks before randomization and for 6 weeks of intervention)	Quality of life (General state of health and Social function domains of the SF-36).
		CG:	n = 73; 41 (56%) women; 40±13.3 years old	tDCS placebo (int. 2mA, with rise for 15s, followed by int. 0mA for 30s; 30minutes; for 24 sessions, in 6 weeks) + SSRI (stable dose, for 25.6 ± 42.0 weeks before randomization and for 6 weeks of intervention)	
Bennabi et al., 2015	Double-blind, placebo-controlled pilot RCT	EXP:	n = 12; 10 (83.3) women; 60.4±12 years old	tDCS (int. of 2mA; 30 minutes per session; 2x a day; 10 sessions, for 5 days) + Escitalopram (10 to 20 mg/day)	Psychomotor retardation (SRRS)
		CG:	n = 11; 5 (45.5) women; 59.9±15.4 years old	tDCS placebo (int. 2mA, followed by gradual reduction to 0mA; 2x a day; 30 minutes; for 5 days) + Escitalopram (10 to 20 mg/day)	
Li et al., 2022	Double-blind, placebo-controlled RCT	EXP:	n = 19; 13 (68.4%) women; 44.79±15.25 years old	tDCS (int. 2mA, up/down time 30s, 20 minutes per session; 5x a week, for 10 sessions, for 2 weeks) + Escitalopram (20 mg/day) or duloxetine hydrochloride (60 mg/day)	Sleep/insomnia (Polysomnography)
		CG:	n = 18; 9 (50%) women; 43.61±11.89 years old	tDCS placebo (int. 2mA, up/down time 30s, followed by gradual reduction to 0mA, 20 minutes per session; 5x a week, for 10 sessions, for 2 weeks) + Escitalopram (20 mg/day) or duloxetine hydrochloride (60 mg/day)	

RCT: Randomized clinical trial; EXP: Experimental group; CG: Control group; int.: intensity; SSRI: Selective serotonin reuptake inhibitors; SF--36:Short Form Health Survey; SRRS: Salpêtrière Retardation Assessment; tDCS: transcutaneous direct current stimulation; MDD: Major Depressive Disorder;

All the included studies compared tDCS associated with an antidepressant with placebo tDCS also associated with an antidepressant. Concerning the quality of life outcome, one trial[14] showed that there was no significant difference between the groups in the domains of general health status (MD 0.4; 95% CI -0.6 to 1.4; p = 0.47) and social function (MD -0.1; 95% CI -0.8 to 0.6; p = 0.70). As for psychomotor symptoms, an RCT[12] showed that there was no difference (F (2,28) = 0.11; p = 0.63) between the groups in the assessment of psychomotor retardation. Concerning sleep, one study [13] showed a difference between the groups favoring tDCS in improving EEG signals during nocturnal REM sleep assessed by polysomnography.

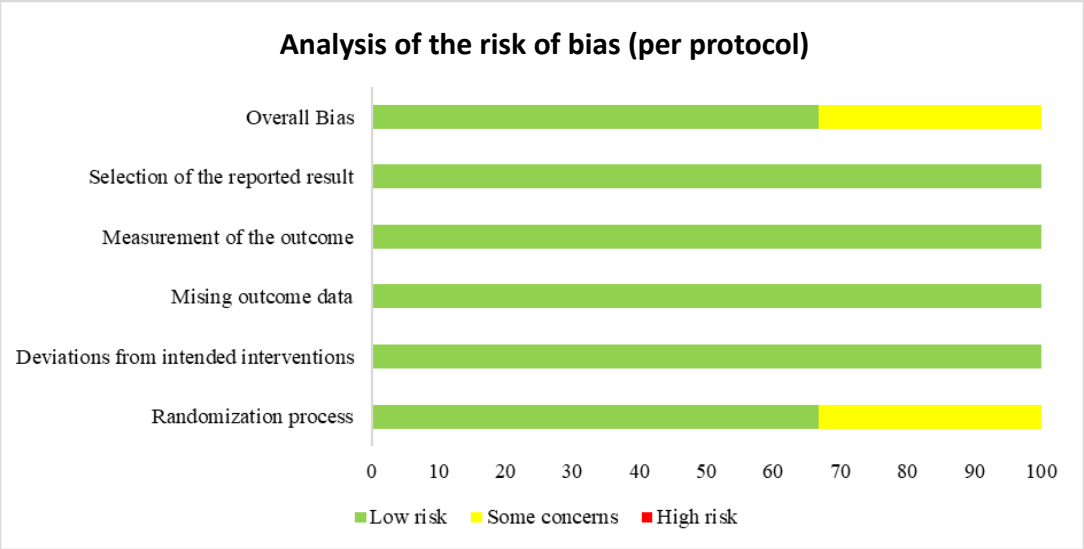

Figure 2 – Analysis of the risk of bias (per protocol) by RoB 2 of the included studies

In the analysis of the risk of bias in the included trials, the pooled analysis showed a low risk of bias (Figure 2). One RCT[12] presented an uncertain risk of bias, while two studies[13,14] presented a low risk of bias (Table 2).

Table 1 – Analysis of the risk of bias by outcome

Outcome	Weight	D1	D2	D3	D4	D5	Total	Key
Psychomotor symptoms	1	!	+	+	+	+	!	+ Low risk
Sleep	1	+	+	+	+	+	+	! Uncertain
Quality of life	1	+	+	+	+	+	+	- High risk

D1: Randomization process; D2: Deviations from intended interventions; D3: Missing outcome data; D4: Measurement of the result; D5: Selection of the reported result

DISCUSSION

The results of this systematic review showed initial evidence that tDCS associated with antidepressant therapy is not effective as an additional treatment for psychomotor symptoms and quality of life of people with MDD. However, positive electroencephalographic changes can be seen

during REM sleep in these people. This analysis consisted of three randomized clinical trials, one study for each outcome, with a risk of bias ranging from uncertain to low risk.

People with MDD show psychomotor symptoms commonly described as psychomotor retardation, characterized by slowed movements, a sluggish gait, stooped posture, and a lack of facial expressiveness[15]. In the pilot study by Bennabi et al. (2015), the use of tDCS associated with antidepressants had no impact on psychomotor retardation. However, some participants in this study used benzodiazepines, which may have influenced the neuromodulatory effects of tDCS. Another study[16] showed that benzodiazepines can alter brain excitability, which reduces the effects of tDCS, due to the reduction of GABA and glutamatergic activity by anodic and cathodic stimulation, respectively. In addition, the study by Bennabi et al. (2015) is a pilot clinical trial, with a small sample size and uncertain data on randomization. Therefore, it is unclear whether the association of tDCS with antidepressants alone is capable of improving the psychomotor symptoms of people with MDD, reinforcing the need for more robust studies on the subject.

Insomnia can be an indicator of the onset of MDD and is an important factor to evaluate[17]. The study by Li et al. (2022) showed a significant improvement in electroencephalographic signals during sleep in people with MDD after tDCS associated with Escitalopram (20 mg/day) or duloxetine hydrochloride (60 mg/day), possibly due to regional changes in cortical excitability after stimulation. Another study[18] showed that tDCS applied at an intensity of 1-2 mA can cause regional changes in cortical excitability that can last up to a few hours after stimulation. However, no clinical sleep data was collected, so the effect of tDCS associated with antidepressants on sleep quality in people with MDD is unclear. That said, further studies evaluating the effect on sleep-related clinical outcomes in this population are needed.

MDD causes a variety of disabilities, involving reduced productivity and performance at work, restricting social participation, and negatively impacting quality of life[19]. Women of different age groups affected by violence, sexual abuse, and interpersonal problems can suffer from MDD, factors that can contribute to a negative change in the perception of quality of life[20]. Other factors such as the presence of pain, admissions to psychiatric hospitals, and being in a relationship can be predictors of quality of life in people with MDD[21]. Therefore, understanding the quality of life of people with MDD encompasses understanding the different factors that can contribute to the emergence of various issues that are interconnected with the individual, which can interfere with the treatment of MDD.

Similarly, another study found no significant differences between the groups in general health status and social function related to quality of life after tDCS associated with SSRIs[14]. Similarly, other authors also found no difference in the general health status and social function domains of the SF-36 after tDCS in people with fibromyalgia and MDD[22]. This result may be associated with a failure in the therapeutic response administered, with persistence of symptoms, which makes the perception of the quality of life of people with MDD not differ significantly. Despite these results, the literature needs more studies to assess the outcome in question.

In addition to the aforementioned factors, the duration of the tDCS intervention is an important factor in its clinical effectiveness[23]. The results found for psychomotor symptoms[12] and quality of life[14] may be related to the short observation time (5 days and 6 weeks, respectively) and, therefore, the duration of the tDCS protocol. Other authors have shown that the relief of MDD symptoms depends on the number of sessions and the amount of energy provided by tDCS[23]. That said, to improve psychomotor symptoms and quality of life, a greater number of tDCS sessions may be necessary. Therefore, more studies are needed to determine the minimum effective duration of tDCS treatment associated with the use of antidepressants to achieve significant improvements in psychomotor symptoms, sleep, and quality of life.

One of the limitations of this study was the small number of articles included for analysis. Two of the studies analyzed had small samples. Fifty-one studies found in the searches were excluded, and one of the main reasons for the exclusions was the use of tDCS alone in the intervention groups. In addition, only one study was found for each outcome, which was the main factor that made it impossible to carry out a meta-analysis.

CONCLUSION

Based on this review, there is initial evidence with a low risk of bias showing that tDCS as a complement to antidepressant therapy is not effective in treating people with MDD in the outcomes quality of life and psychomotor symptoms, but with potential changes in electroencephalographic signals during REM sleep in these people. Although the parameters of tDCS for MDD are well established (intensity 2 mA), there is a variation in the location of the stimulus in the studies and the short intervention time. Furthermore, the investigation of these interventions on quality of life must take into account the various biopsychosocial aspects that can interfere with the life of the person with MDD, limiting the effects of the treatment. Therefore, these results should be considered cautiously due to the scarcity of studies, the heterogeneity of the parameters applied, and the intervention time. Although tDCS is a safe and easy-to-apply resource, new robust clinical trials with longer observation times could make a significant contribution to the growing literature on the clinical impact of tDCS in people with MDD.

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Fernanda Warken Rosa: Conceptualization; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Márcio Costa de Souza: Conceptualization; Writing – original draft; Writing – review & editing.

Roberto Rodrigues Bandeira Tosta Maciel: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

All authors approved of the final version of the text.

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