ORIGINAL ARTICLE

Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression

A.R. Brunoni, A.H. Moffa, B. Sampaio-Junior, L. Borrione, M.L. Moreno, R.A. Fernandes, B.P. Veronezi, B.S. Nogueira, L.V.M. Aparicio, L.B. Razza, R. Chamorro, L.C. Tort, R. Fraguas, P.A. Lotufo, W.F. Gattaz, F. Fregni, and I.M. Benseñor, for the ELECT-TDCS Investigators*

ABSTRACT

BACKGROUND

We compared transcranial direct-current stimulation (tDCS) with a selective serotonin-reuptake inhibitor for the treatment of depression.

METHODS

In a single-center, double-blind, noninferiority trial involving adults with unipolar depression, we randomly assigned patients to receive tDCS plus oral placebo, sham tDCS plus escitalopram, or sham tDCS plus oral placebo. The tDCS was administered in 30-minute, 2-mA prefrontal stimulation sessions for 15 consecutive weekdays, followed by 7 weekly treatments. Escitalopram was given at a dose of 10 mg per day for 3 weeks and 20 mg per day thereafter. The primary outcome measure was the change in the 17-item Hamilton Depression Rating Scale (HDRS-17) score (range, 0 to 52, with higher scores indicating more depression). Noninferiority of tDCS versus escitalopram was defined by a lower boundary of the confidence interval for the difference in the decreased score that was at least 50% of the difference in the scores with placebo versus escitalopram.

RESULTS

A total of 245 patients underwent randomization, with 91 being assigned to escitalopram, 94 to tDCS, and 60 to placebo. In the intention-to-treat analysis, the mean (±SD) decrease in the score from baseline was 11.3±6.5 points in the escitalopram group, 9.0±7.1 points in the tDCS group, and 5.8±7.9 points in the placebo group. The lower boundary of the confidence interval for the difference in the decrease for tDCS versus escitalopram (difference, –2.3 points; 95% confidence interval [CI], –4.3 to –0.4; P=0.69) was lower than the noninferiority margin of –2.75 (50% of placebo minus escitalopram), so noninferiority could not be claimed. Escitalopram and tDCS were both superior to placebo (difference vs. placebo, 5.5 points [95% CI, 3.1 to 7.8; P<0.001] and 3.2 points [95% CI, 0.7 to 5.5; P=0.01], respectively). Patients receiving tDCS had higher rates of skin redness, tinnitus, and nervousness than did those in the other two groups, and new-onset mania developed in 2 patients in the tDCS group. Patients receiving escitalopram had more frequent sleepiness and obstipation than did those in the other two groups.

CONCLUSIONS

In a single-center trial, tDCS for the treatment of depression did not show noninferiority to escitalopram over a 10-week period and was associated with more adverse events. (Funded by Fundação de Amparo à Pesquisa do Estado de São Paulo and others; ELECT-TDCS ClinicalTrials.gov number, NCT01894815.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Brunoni at the Interdisciplinary Center for Applied Neuromodulation and Service of Interdisciplinary Neuromodulation, LIM-27, University of São Paulo, Av. Prof. Lineu Prestes, 2565, 3o andar, CEP 05508-000, São Paulo, Brazil, or at brunoni@usp.br.

*A complete list of the investigators in the Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) is provided in the Supplementary Appendix, available at NEJM.org.

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Major depressive disorder is a highly prevalent condition.[1] There is interest in the effectiveness and safety of new and nonpharmacologic treatments for depression. In 2009, transcranial magnetic stimulation was approved by the Food and Drug Administration for the treatment of major depressive disorder.[2] The procedure has had mixed results in various trials,[3] is associated with a small risk of seizure,[4] and is costly.

Transcranial direct-current stimulation (tDCS) is a noninvasive brain-stimulation technique that is less costly than transcranial magnetic stimulation and has not been associated with seizures.[5] In this procedure, weak, direct current is applied through electrodes that are placed on the scalp to induce alterations in cortical activity and excitability.[6] In patients with major depressive disorder, tDCS-induced currents are applied to the dorsolateral prefrontal cortex, which is considered to be a target for mood regulation.[7]

We previously conducted a trial involving patients with major depressive disorder,[8] which showed the superiority of tDCS plus sertraline over tDCS only, sertraline only, and placebo. However, that trial was not designed to compare tDCS with pharmacotherapy directly. Furthermore, small, placebo-controlled clinical trials testing the efficacy of tDCS in patients with major depressive disorder have shown inconsistent results.[9]

On the basis of the safety of tDCS that has been observed in previous studies, and given the possibility that tDCS would be more acceptable to patients than antidepressants, we conducted a noninferiority trial, the Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS), to compare the efficacy of tDCS with that of the selective serotonin-reuptake inhibitor escitalopram in patients with major depressive disorder. The null hypothesis was that the decrease in the score (indicating less depression) on a conventional rating scale of depression in the tDCS group would be 50% or less of the difference in the decreased scores between the escitalopram group and the placebo group; that is, noninferiority would be established if tDCS, as compared with escitalopram, was associated with at least 50% of the superiority of escitalopram over placebo. As secondary aims, we investigated biomarkers that are associated with clinical depression outcomes. We also investigated the effects of tDCS versus placebo and tDCS versus escitalopram over time and assessed the adverse effects and safety of both tDCS and escitalopram.

METHODS

TRIAL DESIGN

The trial design has been published previously.[10] The trial was conducted at the University Hospital and Department and Institute of Psychiatry, University of São Paulo, with a recruitment period from October 2013 through July 2016. The trial was approved by the local ethics committee. All the patients provided written informed consent. All the authors affirm that the trial was conducted, and all analyses were performed, per the original protocol, which is available with the full text of this article at NEJM.org. The authors vouch for the accuracy and completeness of the data and analyses reported.

Soterix Medical provided five tDCS devices (1×1 tDCS-CT) free of charge, and Libbs provided escitalopram oxalate (Reconter, 10-mg pills) free of charge. These companies were not involved in any aspect of the conduct, analysis, or reporting of the trial. The funder, Fundação de Amparo à Pesquisa do Estado de São Paulo, had no role in any aspect of the trial.

In this noninferiority, parallel, placebo-controlled trial, patients were randomly assigned in a 2:3:3 ratio, with the use of a permuted-block design, according to a computer-generated list, to receive one of three regimens: sham tDCS plus placebo (placebo group), sham tDCS plus escitalopram (escitalopram group), and active tDCS plus placebo (tDCS group).

PATIENTS

We included patients 18 to 75 years of age who had unipolar depression that had been diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), criteria and confirmed by psychiatrists by means of the Mini-International Neuropsychiatric Interview (MINI).[11] Patients had to have a score of 17 points or more on the 17-item Hamilton Depression Rating Scale (HDRS-17; scores range from 0 to 52, with higher scores indicating more depression; a score of 24 or more indicates severe depression; minimal

clinically significant difference, 3 points) as well as a low risk of suicide (evaluated with the use of the MINI). The exclusion criteria were bipolar disorder, substance abuse or dependence, dementia, personality disorder, brain injury, pregnancy, specific contraindications to tDCS (e.g., cranial plates), current or previous escitalopram use, and previous or concomitant participation in other trials of tDCS. Patients who presented with an anxiety disorder (generalized anxiety disorder, specific phobia, panic disorder, or social anxiety disorder) as a coexisting condition were not excluded.

Participants were recruited by means of advertisements and physician referrals and were prescreened by means of telephone and e-mail. Persons who met the inclusion criteria underwent on-site screening. Before the onset of the trial, the patients either were not using antidepressants or underwent a drug washout and remained free of antidepressant medications for five or more drug half-lives. Benzodiazepines were allowed but were tapered to a maximum dose of 20 mg per day of a diazepam equivalent; the dose remained stable during the trial.

INTERVENTIONS

Anode and cathode electrodes were placed over the left and right dorsolateral prefrontal cortexes, respectively, with the use of the Omni-Lateral-Electrode system.[12] In a total of 22 sessions that lasted 30 minutes per day, 2 mA of direct-current stimulation were administered in each session. The first 15 sessions took place daily, except for weekends, and the remaining 7 sessions took place once a week, until week 10. The tDCS protocol that was used in this trial had more sessions than in earlier trials because recent studies have suggested that more sessions could produce greater clinical effects.[13,14]

Trained nurses administered the tDCS regimen. The same protocol was used for active and sham tDCS, but the current was turned off automatically after 30 seconds in patients receiving sham tDCS by devices that were programmed to deliver active or sham stimulation according to the randomized code.

Patients received 10 mg per day of escitalopram (or matching placebo) for the first 3 weeks and 20 mg per day thereafter. The School of Pharmaceutical Sciences of the University of São Paulo produced the placebo pills. They had the same size, color, appearance, and taste as the escitalopram pills and were stored in identical bottles. Escitalopram was chosen as representative of a first-line therapy for major depressive disorder,[15] with the maximally effective dose (20 mg per day) administered close to the initial dose (10 mg per day), which thus allowed the maximum dose to be reached within weeks after the initiation of the intervention if necessary.

To assess the integrity of trial-group blinding, patients were asked to guess which intervention they had received and to rate the confidence in their prediction. Adherence to the escitalopram and placebo regimens was determined by means of pill count and was considered to be acceptable if less than 10% of the pills were returned.

OUTCOMES

All the assessments were performed by trained psychiatrists and psychologists who were unaware of the trial-group assignments. Efficacy and safety were measured during screening, at baseline, and at the end of weeks 3, 6, 8, and 10. The primary outcome was the change in the HDRS-17 score from baseline to 10 weeks.

Secondary outcomes included the changes from baseline in the Montgomery–Åsberg Depression Rating Scale (MADRS) score (range, 0 to 60, with higher scores indicating more severe depression; minimal clinically significant difference, 1.6 to 1.9 points),[16] the Beck Depression Inventory score (range, 0 to 63, with higher scores indicating more severe depression; minimal clinically significant difference, 5 points),[17,18] and several other scales that are listed in the protocol, the Supplementary Appendix (available at NEJM.org), and previous publications.[19,20] Additional secondary outcomes were early improvement (defined as a change in the score from baseline to week 3 on the HDRS-17),[21] clinical response (defined as a >50% reduction from the baseline HDRS-17 or MADRS score), and remission (defined as an HDRS-17 score ≤7 or a MADRS score ≤10) at week 10.

ADVERSE EVENTS

Adverse events were assessed with the use of the Systematic Assessment for Treatment Emergent Effects questionnaire[22] and a commonly used questionnaire regarding 39 adverse events that

have been associated with tDCS.[23] At the end of weeks 3 and 10, patients were asked to fill out these questionnaires, describing the presence of an adverse event, its severity, and their opinion regarding its relationship to the trial regimen. We report data on all mild, moderate, and severe adverse events that were considered by the patients to be at least remotely associated with the intervention.

The Young Mania Rating Scale (range, 0 to 60, with higher scores indicating a greater degree of manic features; minimal score to define new-onset mania or hypomania, 8 points) was used at the end of weeks 3 and 10 to assess mania or hypomania during the trial.[24] Other events that were considered by the investigators to be potentially serious adverse events were hospitalization for a psychiatric cause, suicidality or attempted suicide, or events leading to major incapacity or a life-threatening condition. A brief neuropsychological evaluation consisting of seven tests (listed in the trial-design publication[10] and Table S12 in the Supplementary Appendix) was performed at baseline and at 10 weeks to determine whether tDCS was associated with cognitive impairment.

BIOLOGIC MARKERS

Several biologic markers were investigated as predictors and mediators of clinical response. Two of these biologic markers have been analyzed so far: heart-rate variability and motor cortical excitability (see the Supplementary Appendix). Other planned analyses have not yet been done.

STATISTICAL ANALYSIS

The sample size was estimated on the basis of results from our previous study, the Sertraline versus Electrical Current Therapy for Treating Depression Clinical Study (SELECT-TDCS),[8] with the use of an attrition rate of 13%[25] and a noninferiority margin of 50% of the comparative efficacy of placebo versus escitalopram. The noninferiority margin was based on our hypothesis that tDCS would be associated with at least 50% of the difference in efficacy of escitalopram as compared with placebo (see the Supplementary Appendix).[26]

For our primary hypothesis, we compared the decrease in the HDRS-17 score (the baseline score minus the score at 10 weeks, with a decrease in score indicating less depression) among the three groups. A modified t-test was used to assess whether the difference in the scores between the tDCS group and the placebo group was more than 50% of the mean difference between the scores in the escitalopram group and the placebo group.[25] The noninferiority margin was based on the point estimate of 50% of the difference in the mean change in the HDRS-17 score in the comparison of placebo with escitalopram. This approach was chosen because our hypothesis was that tDCS would be associated with at least 50% of the effectiveness of escitalopram. If the lower boundary of the confidence interval around the mean difference between the scores in the tDCS group versus the escitalopram group exceeded this value, then noninferiority could be claimed (see the statistical analysis plan provided with the protocol). After the noninferiority assessment, t-tests were used for superiority analyses, comparing the decrease in the HDRS-17 score for escitalopram versus tDCS, for escitalopram versus placebo, and for tDCS versus placebo.

A mixed-model analysis of variance was conducted to assess a reduction in symptoms over time. Logistic regression was performed to assess the rates of response and remission between groups. The chi-square test or Fisher's exact test was used to compare the frequency and severity of adverse events, new-onset mania or hypomania, and serious adverse events between groups. The number of adverse events between groups at 10 weeks was compared with the use of the Kruskal–Wallis test. General linear models were used to assess predictors of response. These exploratory analyses were not corrected for multiple comparisons (see the protocol).

For biomarker analyses, 78 analyses were performed, and 3 or 4 positive results were expected by chance (see the Supplementary Appendix). For the clinical, demographic, neuropsychological, psychological,[27] and adverse-event analyses, 4 or 5 positive results were expected by chance, because 85 analyses were performed.

We performed noninferiority analyses in the intention-to-treat and per-protocol populations.[28] Analysis was also performed in the population of patients who had high adherence to the trial visits (patients who had <2 missing visits). Missing data were considered to be missing at random and were imputed with the use of regression models, in which baseline depression and main demographic characteristics were used as variables.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=60)	Escitalopram (N=91)	tDCS (N=94)
Female sex — no. (%)	41 (68)	61 (67)	64 (68)
Age — yr			
Current	40.9±12.9	41.8±12.5	44.6±11.8
At onset of depression	25.7±11.3	26.4±12.0	26.4±11.7
Type of depression — no. (%)			
Recurrent	44 (73)	59 (65)	59 (63)
Chronic	29 (48)	46 (51)	42 (45)
Severe	22 (37)	25 (27)	28 (30)
Melancholic	22 (37)	37 (41)	34 (36)
Atypical	18 (30)	25 (27)	30 (32)
Any anxiety disorder — no. (%)†	38 (63)	46 (51)	56 (60)
Family history of psychiatric disorder — no. (%)	39 (65)	57 (63)	64 (68)
History of treatment for depression			
No. of treatment failures			
In current episode	1.0±1.4	0.9±1.5	1.0±1.2
Over lifetime	4.9±4.3	4.5±3.9	4.8±3.8
Treatment resistance — no. (%)	19 (32)	25 (27)	30 (32)
Current use of benzodiazepines — no. (%)	17 (28)	20 (22)	31 (33)
HDRS-17 score‡§	22.7±4.3	21.7±3.5	21.8±3.9
MADRS score§¶	28.1±6.8	26.2±6.0	27.4±7.0
Beck Depression Inventory score§‖	31.1±11.1	29.4±8.8	30.9±9.2

* Plus–minus values are means ±SD. No significant between-group differences were observed.
† Any anxiety disorder was defined as generalized anxiety disorder, specific phobias, social anxiety disorder, or panic disorder.
‡ Scores on the 17-item Hamilton Depression Rating Scale (HDRS-17) range from 0 to 52, with higher scores indicating more depression; a score of 24 or more indicates severe depression (minimal clinically significant difference, 3 points).
§ The variables include depression characteristics, such as recurrence (>3 previous episodes), chronicity (current episode with ≥12-month duration), severity, and treatment resistance (≥1 treatment failure in the current episode or >4 treatment failures over the patient's lifetime).
¶ Scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating more severe depression (minimal clinically significant difference, 1.6 to 1.9 points).
‖ Scores on the Beck Depression Inventory range from 0 to 63, with higher scores indicating more severe depression (minimal clinically significant difference, 5 points).

RESULTS

PATIENTS

Of 1479 patients screened, 245 were enrolled and underwent randomization. A total of 60 patients were assigned to receive placebo, 91 to receive escitalopram, and 94 to receive tDCS. Of these 245 patients, 202 received all 22 planned sessions of actual or sham tDCS and completed the week-10 assessment (55 patients in the placebo group, 75 in the escitalopram group, and 72 in the tDCS group) (Fig. S1 in the Supplementary Appendix). Withdrawal rates did not differ significantly among the three groups ($\chi^2=4.77$, $P=0.09$). The reasons for withdrawal are described in Table S1 in the Supplementary Appendix. The characteristics of the patients are described in Table 1, and in Tables S2, S12, and S14 in the Supplementary Appendix.

PRIMARY OUTCOME

As compared with baseline, the mean depression scores, as measured by the HDRS-17, decreased (with greater decreases indicating less depression) by 11.3±6.5 points in the escitalopram group, by 9.0±7.1 points in the tDCS group, and

by 5.8±7.9 points in the placebo group. The mean difference between the placebo group and the escitalopram group (i.e., placebo minus escitalopram) was −5.5 points (indicating a greater decrease in the escitalopram group), and the difference between the tDCS group and the escitalopram group was −2.3 points (95% confidence interval [CI], −4.3 to −0.4). The noninferiority of tDCS to escitalopram could therefore not be claimed, because the lower boundary of the confidence interval (−4.3) was lower than the prespecified noninferiority margin of 50% of the difference between the placebo group and the escitalopram group (−2.75; P=0.69 by the modified t-test for noninferiority) (Table 2 and Fig. 1).

SUPERIORITY ANALYSES

Escitalopram was superior to placebo (difference in mean scores, 5.5 points; 95% CI, 3.1 to 7.8; P<0.001), as was tDCS (difference, 3.2 points; 95% CI, 0.7 to 5.5; P=0.01). Similarly, in the per-protocol analyses, escitalopram was superior to placebo (difference, 5.6 points; 95% CI, 3 to 8.3; P<0.001) and to tDCS (difference, 2.9 points; 95% CI, 0.5 to 5.2; P=0.02). We also found that tDCS was superior to placebo (difference, 2.5 points; 95% CI, 0.1 to 5.0; P=0.048).

Among the 122 patients who had high adherence to the trial visits (31 patients in the placebo group, 47 in the escitalopram group, and 44 in the tDCS group), escitalopram was superior to placebo (difference in mean scores, 5.0 points; 95% CI, 1.8 to 8.1; P<0.001). Treatment with tDCS was also superior to placebo (difference, 4.1 points; 95% CI, 0.9 to 7.3; P=0.01), and the efficacies of tDCS and escitalopram did not differ significantly (difference, −0.9 points; 95% CI, −3.7 to 1.9; P=0.53).

OTHER SECONDARY OUTCOMES

There was a significant time-by-group interaction across weeks 0, 3, 6, 8, and 10 with regard to the HDRS-17 score (P<0.01 for all comparisons). Pairwise comparisons between the trial groups at week 10 corroborated the primary-outcome findings. Escitalopram was superior to placebo at all time points after baseline, whereas tDCS was superior to placebo only at weeks 8 and 10 (Fig. 2, and Table S3 in the Supplementary Appendix).

The results regarding changes from baseline in the other scales were similar to those for HDRS-17, except for the Beck Depression Inventory score, for which tDCS was not superior to placebo (Table 2, and Tables S4 through S7 in the Supplementary Appendix). At week 10, the rates of response (defined as a >50% reduction in the baseline HDRS-17 or MADRS score) with tDCS and with escitalopram were significantly superior to the response rate with placebo, but the remission rates did not differ significantly between groups (Table 2, and Tables S8 and S9 in the Supplementary Appendix).

Neuropsychological assessments showed either an improvement in cognitive performance or no changes in performance from baseline to 10 weeks in each of the three trial groups (Table S12 in the Supplementary Appendix). The Montreal Cognitive Assessment and Trail Making Tests A and B showed significant improvement in all three groups, whereas verbal fluency improved in only the two active-treatment groups.

ADVERSE EVENTS AND SAFETY

There were no significant differences among the groups in the overall frequency and intensity of adverse events (Table 3, and Tables S10 and S11 in the Supplementary Appendix). Patients who received tDCS had significantly more itching, tingling, skin redness, and burning sensation at the skin sites under the electrodes, as well as tinnitus and nervousness, than did those in the other two groups. Sleepiness and obstipation were significantly more frequent with escitalopram than with tDCS.

Two patients, both of whom received tDCS, had new-onset mania during the conduct of the trial. One patient had a Young Mania Rating Scale score of 11 at week 3 and a score of 3 at week 10, and the other had scores of 22 and 11 at these respective time points. These episodes did not result in hospitalization, discontinuation from the trial, or specific treatment. These two patients were followed for 6 months after the trial and did not present with further manic or hypomanic symptoms.

SUBGROUP ANALYSES

In post hoc analyses, significant interactions were found between the assigned group and smoking status (nonsmokers had a greater decrease in the HDRS-17 score than smokers in the analysis of tDCS vs. placebo), self-directedness (patients with higher scores had a greater decrease in the HDRS-

Table 2. Outcomes at 10 Weeks.*

Outcome	Placebo (N=60)	Escitalopram (N=91)	tDCS (N=94)	tDCS vs. Placebo		tDCS vs. Escitalopram		Escitalopram vs. Placebo	
				Difference or Odds Ratio (95% CI)	P Value	Difference or Odds Ratio (95% CI)	P Value	Difference or Odds Ratio (95% CI)	P Value
Primary outcome									
Decrease in HDRS-17 score	5.8±7.9	11.3±6.5	9.0±7.1	3.2 (0.7 to 5.5)	0.01	–2.3 (–4.3 to –0.4)	0.02	5.5 (3.1 to 7.8)	<0.001
Secondary outcomes									
Decrease in MADRS score	6.6±9.3	13.4±9.3	11.0±9.4	4.4 (2.1 to 7.2)	0.006	–2.4 (–5.7 to –1.1)	0.04	6.8 (5.4 to 10.6)	<0.001
HDRS-17 — no. (%)									
Response	13 (22)	43 (47)	39 (41)	2.6 (1.2 to 5.4)	0.01	0.8 (0.4 to 1.4)	0.43	3.2 (1.5 to 6.8)	<0.001
Remission	8 (13)	27 (30)	23 (24)	2.1 (0.9 to 5.1)	0.10	0.8 (0.4 to 1.5)	0.42	2.7 (1.1 to 6.5)	0.02
MADRS — no. (%)									
Response	14 (23)	47 (52)	38 (40)	2.2 (1.1 to 4.6)	0.03	0.6 (0.3 to 1.1)	0.13	3.5 (1.7 to 7.2)	<0.001
Remission	12 (20)	37 (41)	30 (32)	1.9 (0.9 to 4.0)	0.11	0.7 (0.4 to 1.2)	0.21	2.7 (1.3 to 5.8)	<0.001

* Plus–minus values are means ±SD. Change in the score was calculated as the score at baseline minus the score at 10 weeks, with greater decreases indicating less depression. Between-group differences are shown for the outcomes regarding decreases in scores from baseline to week 10, and odds ratios are shown for the outcomes regarding response and remission. Scores on the HDRS-17 range from 0 to 52, with higher scores indicating more depression; a score of 24 or more indicates severe depression (minimal clinically significant difference, 3 points). Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression (minimal clinically significant difference, 1.6 to 1.9 points). Response was defined as a decrease in the score (indicating less depression) of 50% or more from baseline to week 10. Remission was defined as a score of 7 or fewer points on the HDRS-17 or as 10 or fewer points on the MADRS at 10 weeks. Results for the primary-outcome scale were obtained with the use of t-tests and for the secondary outcomes with the use of mixed-model analyses of variance and logistic regressions.

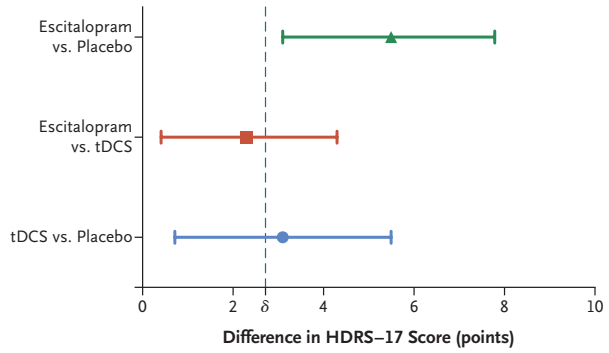

Figure 1. Comparative Efficacy of the Trial Groups.
Shown are the results of the intention-to-treat analysis of the differences in the decreased scores (defined as the baseline score minus the score at 10 weeks, with a greater decrease indicating less depression) between escitalopram and placebo, escitalopram and transcranial direct-current stimulation (tDCS), and tDCS and placebo. The x axis represents the difference in the scores on the 17-item Hamilton Depression Rating Scale (HDRS-17). Scores range from 0 to 52, with higher scores indicating more depression, and a score of 24 or more indicates severe depression; the minimal clinically significant difference is 3 points. The dashed line at δ indicates the noninferiority margin, which was defined as 50% of the difference in the decreased scores between the escitalopram group and the placebo group (2.75, green line). The lower boundary of the 95% confidence interval (error bars) for the difference in decrease between the scores in the tDCS group and the escitalopram group (4.3, red line) was lower than the noninferiority margin of 2.75, so noninferiority could not be claimed.

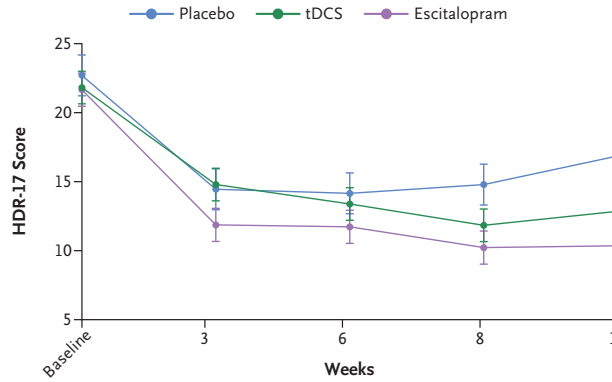

Figure 2. Change in Depression Score over Time.
Shown are the mean scores (intention-to-treat analysis) in the trial groups from baseline to 10 weeks. I bars represent ±1 SD. HDRS-17 scores range from 0 to 52, with higher scores indicating more depression, and a score of 24 or more indicates severe depression; the minimal clinically significant difference is 3 points. Treatment with escitalopram was superior to placebo at all time points except baseline (P=0.008 for the comparison at week 3, P=0.01 at week 6, and P<0.001 at weeks 8 and 10). Treatment with tDCS was superior to placebo at weeks 8 and 10 (P<0.001 for both comparisons). Treatment with escitalopram was superior to tDCS at weeks 3 (P<0.001) and 10 (P=0.004).

17 score in the escitalopram group or the tDCS group than did those with lower scores), and cooperativeness (higher scores were associated with a greater decrease in the placebo group than were lower scores) (Tables S13, S15, S16, and S17 in the Supplementary Appendix).

BIOLOGIC MARKERS

Increased cortical inhibition in tests of motor-cortex excitability was associated with lower degrees of decrease in the HDRS-17 scores in the escitalopram group and the tDCS group. No associations between heart-rate variability at baseline and a decrease in the HDRS-17 score were found. However, increased heart-rate variability was associated with the degree of decrease in the HDRS-17 score, regardless of the trial group (see the Supplementary Appendix).

INTEGRITY OF BLINDING

Patients correctly guessed their trial-group assignment to escitalopram but not to active tDCS. The unblinding with regard to escitalopram appeared to be associated with adverse events (Table S18 in the Supplementary Appendix).

DISCUSSION

In this three-group trial involving patients with major depressive disorder, tDCS did not show noninferiority to escitalopram in the intention-to-treat and per-protocol analyses in reducing depression. In secondary-outcome superiority analyses, escitalopram was superior to tDCS and placebo, and tDCS was superior to placebo.

Two patients receiving tDCS had mania that began during the trial, and tDCS was associated with higher rates of local adverse events than escitalopram. These adverse events included skin redness and tingling and nervousness and tinnitus. All these adverse events had been previously reported in trials of tDCS.[29,30] Escitalopram was associated with higher rates of sleepiness and obstipation than was tDCS or placebo. The total number of adverse events was similar among the three groups. There were no cases of suicide, psychiatric hospitalization, or other serious adverse events during the trial.

The inclusion of a placebo group is a strength of this trial design because it allowed an estimate of the relative efficacies of escitalopram and tDCS, as compared with placebo, and allowed for the calculation of a noninferiority margin.

Table 3. Adverse Events and Serious Adverse Events.*

Event	Placebo (N=55)	Escitalopram (N=75)	tDCS (N=72)	P Value	
				tDCS vs. Placebo	tDCS vs. Escitalopram
Severity of reported adverse event at 10 wk — no. (%)					
No adverse event reported	6 (11)	11 (15)	12 (17)	0.37	0.76
≥1 mild adverse event	35 (64)	51 (68)	50 (69)	0.56	0.95
≥1 moderate adverse event	37 (67)	46 (61)	46 (64)	0.62	0.83
≥1 severe adverse event	20 (36)	32 (43)	30 (42)	0.58	0.85
Median no. of reported adverse events at 10 wk (interquartile range)					
Mild	1 (0–5)	1 (0–6)	1 (0–8)	0.23	0.41
Moderate	1 (0–4)	1 (0–5)	1 (0–6)	0.72	0.62
Severe	0 (0–3)	0 (0–5)	0 (0–3)	0.89	0.51
Serious adverse event during the trial — no. (%)					
New-onset hypomania or mania	0	0	2 (3)	0.34	0.25
Suicide	0	0	0	—	—
Hospitalization for psychiatric cause	0	0	0	—	—

* An adverse event was present if participants described it as being at least remotely associated with the intervention. Participants rated the severity (i.e., mild, moderate, or severe) of the adverse events. New-onset mania or hypomania was diagnosed if the participant presented with a score of 8 or more on the Young Mania Rating Scale (range, 0 to 60, with higher scores indicating a greater degree of manic features) when assessed at any point during the trial. P values represent the result of the chi-square or the Fisher's exact test comparing the frequency of adverse events between placebo and tDCS or between escitalopram and tDCS. No significant between-group differences were observed. Analyses were performed in patients who completed the trial.

Furthermore, the sample was not biased by the inclusion of patients who had treatment resistance to escitalopram. Patients in the trial had moderate-to-severe depressive symptoms, and there was a high prevalence of coexisting anxiety disorder, a combination that reflects a typical clinical population in which treatment for depression is indicated.[31]

Trial limitations include the lack of widely used or standardized tDCS treatment variables, such as amperage and duration of application of direct current, and the unblinding of escitalopram owing to its side-effect profile. Despite local skin reactions, patients did not correctly guess assignment to tDCS. The results obtained in this trial with escitalopram may not be generalizable to other antidepressant medications or to different tDCS protocols.

Because the sample size was based on continuous outcomes, the analyses of the categorical outcomes might have been underpowered. Nonetheless, tDCS was superior to placebo with regard to response rates, as measured by a 50% reduction from baseline in the HDRS-17 or MADRS score, a finding that is similar to previous results.[8,13] However, tDCS was not superior to placebo with regard to rates of remission. Furthermore, the rates of response and remission did not differ significantly between the tDCS group and the escitalopram group.

Secondary analyses revealed that tDCS was superior to placebo only at week 10 (the trial end point for the primary outcome) but not at week 3. Previous studies have also shown that the effects of tDCS are evident only several weeks after the initial 10 to 15 sessions.[8,9,13,32]

Although we used a protocol with a greater number of tDCS sessions than has been used in previous trials, the rates of clinical improvement were similar to those that have been observed in previous studies.[8,33] Future studies of tDCS could investigate different total doses of electrical stimulation in patients with major depressive disorder.

In conclusion, tDCS did not show noninferiority to escitalopram in this placebo-controlled trial involving patients with unipolar major depressive disorder. Although tDCS was superior to placebo in some secondary outcomes, it was associated with more adverse events, including new-onset mania.

Full database access is available on request. Please contact Dr. Brunoni.

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APPENDIX

The authors' full names and academic degrees are as follows: Andre R. Brunoni, M.D., Ph.D., Adriano H. Moffa, Psy.D., Bernardo Sampaio-Junior, M.D., Lucas Borrione, M.D., Marina L. Moreno, Psy.D., Raquel A. Fernandes, Psy.D., Beatriz P. Veronezi, Psy.D., Barbara S. Nogueira, Psy.D., Luana V.M. Aparicio, M.D., Lais B. Razza, Psy.D., Renan Chamorro, Psy.D., Luara C. Tort, Psy.D., Renerio Fraguas, M.D., Ph.D., Paulo A. Lotufo, M.D., Ph.D., Wagner F. Gattaz, M.D., Ph.D., Felipe Fregni, M.D., Ph.D., and Isabela M. Benseñor, M.D., Ph.D.

The authors' affiliations are as follows: the Service of Interdisciplinary Neuromodulation, Department and Institute of Psychiatry, Laboratory of Neurosciences (LIM-27) (A.R.B., B.S.-J., L.B., L.V.M.A., R.F., W.F.G.), and the Interdisciplinary Center for Applied Neuromodulation, University Hospital (A.R.B., A.H.M., B.S.-J., L.B., M.L.M., R.A.F., B.P.V., B.S.N., L.V.M.A., L.B.R., R.C., L.C.T., R.F., P.A.L., I.M.B.), University of São Paulo, São Paulo; and the Spaulding Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston (F.F.).

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