

The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study

Results From a Factorial, Randomized, Controlled Trial

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Importance: Transcranial direct current stimulation (tDCS) trials for major depressive disorder (MDD) have shown positive but mixed results.

Objective: To assess the combined safety and efficacy of tDCS vs a common pharmacological treatment (sertraline hydrochloride, 50 mg/d).

Design: Double-blind, controlled trial. Participants were randomized using a 2 × 2 factorial design to sertraline/placebo and active/sham tDCS.

Setting: Outpatient, single-center academic setting in São Paulo, Brazil.

Participants: One hundred twenty antidepressant-free patients with moderate to severe, nonpsychotic, unipolar MDD.

Interventions: Six-week treatment of 2-mA anodal left/cathodal right prefrontal tDCS (twelve 30-minute sessions: 10 consecutive sessions once daily from Monday to Friday plus 2 extra sessions every other week) and sertraline hydrochloride (50 mg/d).

Main Outcome Measures: In this intention-to-treat analysis, the primary outcome measure was the change in Montgomery-Asberg Depression Rating Scale score at 6 weeks (end point). We considered a difference of at least 3 points to be clinically relevant. The analysis plan was previously published. Safety was measured with an adverse effects questionnaire, the Young Mania Rating Scale,

and cognitive assessment. Secondary measures were rates of clinical response and remission and scores on other scales.

Results: At the main end point, there was a significant difference in Montgomery-Asberg Depression Rating Scale scores when comparing the combined treatment group (sertraline/active tDCS) vs sertraline only (mean difference, 8.5 points; 95% CI, 2.96 to 14.03; $P = .002$), tDCS only (mean difference, 5.9 points; 95% CI, 0.36 to 11.43; $P = .03$), and placebo/sham tDCS (mean difference, 11.5 points; 95% CI, 6.03 to 17.10; $P < .001$). Analysis of tDCS only vs sertraline only presented comparable efficacies (mean difference, 2.6 points; 95% CI, -2.90 to 8.13; $P = .35$). Use of tDCS only (but not sertraline only) was superior to placebo/sham tDCS. Common adverse effects did not differ between interventions, except for skin redness on the scalp in active tDCS ($P = .03$). There were 7 episodes of treatment-emergent mania or hypomania, 5 occurring in the combined treatment group.

Conclusions and Relevance: In MDD, the combination of tDCS and sertraline increases the efficacy of each treatment. The efficacy and safety of tDCS and sertraline did not differ.

Trial Registration: clinicaltrials.gov Identifier: NCT01033084

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THESE IS A TREMENDOUS NEED for effective, safe, affordable therapies for major depressive disorder (MDD), a disabling, highly prevalent condition,¹ the standard treatments for which are only moderately effective and have significant drawbacks such as adverse effects and high cost.²⁻⁴ Although invasive and noninvasive brain stimulation therapies may be effective,⁵⁻⁷ the cost and

adverse effects of some of them such as repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy limit their availability and applicability.⁸

Novel nonpharmacological options might have a better cost-benefit profile in certain scenarios.⁹ Research has focused on novel approaches that induce changes in cortical excitability using a simple method of brain stimulation—transcranial direct current stimulation (tDCS), a

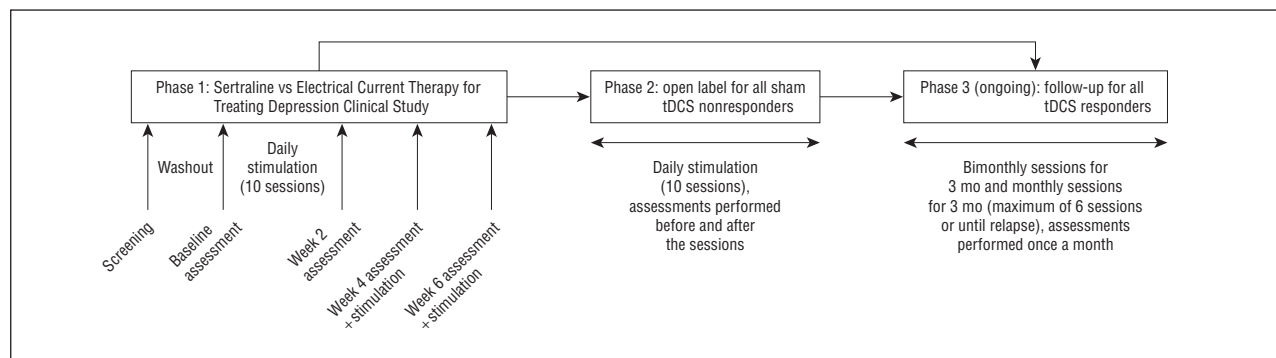


Figure. Overview of the study. tDCS indicates transcranial direct current stimulation.

technique based on the application of weak, direct electrical current to the brain through relatively large electrodes that are placed over the scalp, in which anodal and cathodal stimulation increases and decreases cortical excitability, respectively.¹⁰ Recent animal and human models have confirmed that tDCS induces significant long-lasting neuroplastic effects that are likely mediated by N-methyl-D-aspartate receptors.^{11,12} The neuromodulatory properties of tDCS can be further enhanced or diminished with pharmacological intervention.¹³ In fact, tDCS antidepressant effects are based on the finding that the left dorsolateral prefrontal cortex (DLPFC) is hypoactive in depression and, therefore, anodal tDCS would be able to restore prefrontal activity by increasing activity in this area.¹⁴

Although several studies that used tDCS to treat MDD in the 1960s showed mixed results (for a review, see the article by Nitsche et al¹⁵), tDCS parameters have been optimized using neurophysiological markers. A recent pilot trial has demonstrated significant reduction of depression scores,¹⁶ which has been replicated in a phase 2, randomized controlled trial.¹⁷ Positive results have also been obtained in open-label, noncontrolled trials.¹⁸⁻²¹ Nevertheless, 2 randomized controlled trials using tDCS generated nonsignificant results, possibly owing to issues such as broad eligibility criteria (inclusion of Axis II disorders, high degree of treatment resistance), low “dose” (alternated stimulation sessions), and lack of statistical power^{22,23}; however, another trial showed significant tDCS effects.²⁴ In fact, a recent meta-analysis of tDCS for depression suggested that the technique might be effective for depression, but further trials are necessary.²⁵ In addition, to our knowledge, no trial has yet directly compared tDCS combined with or against a pharmacological treatment, which are key aspects in determining the role of this intervention in the therapeutic arsenal for depression.

Considering the burden of MDD and the limited number of tDCS antidepressant trials, we conducted a large, controlled, randomized trial to assess safety and efficacy of tDCS: the Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study (SELECT TDCS). Our aim was to evaluate the safety and efficacy of tDCS and sertraline hydrochloride, a selective serotonin reuptake inhibitor (SSRI), in patients with MDD. Our hypothesis was that tDCS combined with sertraline has greater efficacy compared with each intervention alone as greater response rates were observed when nonpharmacological interventions (such as electroconvulsive therapy and rTMS) were

combined with antidepressant drugs.^{26,27} Further, using our 2 × 2 factorial design, we assessed whether the combination of these interventions was additive or synergistic. Finally, we performed anodal stimulation over the left DLPFC and cathodal stimulation over the right DLPFC (bifrontal montage), aiming not only to increase MDD left hypoactivity but also to modulate the potential left-right prefrontal imbalance observed in this disorder.²⁸

METHODS

The study design and rationale have previously been published and discussed.²⁹ No significant changes occurred from the original protocol. The methods are reported per CONSORT guidelines with the suggested amendments for reporting nonpharmacological treatments³⁰ and factorial trials.³¹

STUDY OVERVIEW

This study was conducted at the University Hospital, University of São Paulo, São Paulo, Brazil, with a period of active recruitment from March 1, 2010, to September 23, 2011. Local institutional review board approval was obtained, and all participants signed informed consent forms.

This study comprised 3 phases: the first was a phase 2/3, factorial, randomized controlled trial in which 120 participants were randomized using a 2 × 2 design to sertraline/placebo and active/sham tDCS, constituting 4 groups: sham tDCS and placebo (hereafter referred to as *placebo*), sham tDCS and sertraline (*sertraline only*), active tDCS and placebo (*tDCS only*), and active tDCS and sertraline (*combined treatment*). This phase entailed a short-term treatment period in which twelve 30-minute tDCS sessions were given to subjects: 10 consecutive tDCS sessions from Monday to Friday and 2 sessions during the follow-up visits, scheduled 2 and 4 weeks after the initial 10-session treatment. Participants were allowed 2 nonconsecutive missed visits; in such cases, extra tDCS sessions were performed to complete the total number of sessions. A research assistant not directly involved in other aspects of the trial performed a 1:1:1:1 permuted block randomization, and the allocation was concealed using a central randomization method.

The other 2 phases are an open-label, crossover phase in which sham tDCS nonresponders receive 10-day active tDCS (clinicaltrials.gov Identifier NCT01149889) and a 6-month follow-up phase in which tDCS responders receive maintenance tDCS alone or combined with sertraline if they were in the combined treatment group (clinicaltrials.gov Identifier NCT01149213). The outcomes of these phases will be available in 2013 (**Figure**).

PARTICIPANTS

We included patients with unipolar, nonpsychotic MDD per DSM-IV criteria and confirmed by psychiatrists using the Mini-International Neuropsychiatric Interview. Only those with a 17-item Hamilton Depression Rating Scale score greater than 17, with low suicide risk, and aged between 18 and 65 years were included. Exclusion criteria were other Axis I disorders, including alcohol or substance harmful use or dependence (although anxiety disorders as a comorbidity were allowed); any Axis II disorders; previous neurological conditions (epilepsy, traumatic brain injury, stroke, etc); any severe, life-threatening Axis III disorders; and specific contraindications for tDCS (eg, metallic plates in the head).

Participants were recruited by media advertisements and physician referrals. They were prescreened by brief telephone and e-mail interviews, and those meeting general criteria had additional on-site screening. All subjects were free of antidepressant, antipsychotic, and anticonvulsant medications for at least 5 half-lives of the drug (≥ 2 weeks for venlafaxine hydrochloride and paroxetine hydrochloride owing to withdrawal symptoms and 5 weeks for fluoxetine hydrochloride) before study onset. Benzodiazepines were tolerated but tapered to a maximum of 20-mg/d diazepam (or equivalent). Notably, because sertraline was our active drug comparator, participants using or who had used sertraline in the current depressive episode were excluded but those who had used sertraline in past episodes were not necessarily excluded.

INTERVENTIONS

For each session, the tDCS (Chattanooga Ionto device; Chattanooga Group) montage comprised placement of the anode over the F3 area and the cathode over the F4 area (corresponding to the left and right DLPFC, respectively, according to the International 10-20 electroencephalography system). Rubber electrodes were inserted in 25-cm² saline-soaked sponges and fixed with a headband. The montage used is referred to as bifrontal stimulation.¹⁸ We applied a direct current of 2 mA (current density = 0.80 A/m²) for 30 min/d for 10 days, followed by 2 extra tDCS sessions every other week until the study end point (total charge density of 1728 coulombs/m²).

For sham conditions, the device was turned off after 1 minute of active stimulation, a blinding method previously described as reliable,³² mimicking the common adverse effects of mild scratching and discomfort that are experienced immediately after stimulation onset.³³ The raters and patients were blinded to the treatment, and contact between participants was avoided to enhance study blinding.

Two certified nurses administered the tDCS intervention. They initially completed a 3-week tDCS practical course and thereafter administered several tDCS applications under direct supervision. To guarantee that the interventions remained standardized throughout the trial, maintenance courses were performed at regular intervals. Importantly, this intervention is quite straightforward to apply, as shown in the study and online media by DaSilva et al.³⁴ Finally, because the nurses were not blinded to the intervention, their interaction with the participants was minimal. Accordingly, they did not participate in assessment of the outcomes or in any other aspect of the trial.

The pharmacological intervention was a fixed dose of sertraline hydrochloride, 50 mg/d, an effective, relatively inexpensive SSRI with minimal adverse events according to a recent meta-analysis.³⁵ Sertraline was also chosen because it was shown that an SSRI could greatly enhance tDCS effects, facilitating tDCS-induced plasticity.³⁶ Placebo pills had the same size, color, and taste as the active drug.

To assess whether blinding was effective, we asked participants at the end point to guess whether they received treatment and to rate the confidence of their guess on a Likert scale. Finally, we assessed pharmacological adherence by pill count (an acceptable level of adherence was considered if $<10\%$ of the pills were returned). Nonpharmacological adherence was not verified as all tDCS applications were performed on-site. Importantly, both interventions were started simultaneously on the first day of treatment.

ASSESSMENTS

The primary efficacy outcome was the Montgomery-Asberg Depression Rating Scale (MADRS) score at 6 weeks. Secondary outcomes were clinical response (categorical, defined as $>50\%$ reduction of the baseline MADRS score), clinical remission (categorical, defined as a MADRS score ≤ 10), and scores on the 17-item Hamilton Depression Rating Scale, clinician-rated Clinical Global Impression–Severity of Illness scale, and Beck Depression Inventory. Treatment-resistant depression was quantified per the Massachusetts General Hospital staging method.³⁷

To assess safety, we used the Systematic Assessment for Treatment Emergent Effects questionnaire (for sertraline) and a tDCS questionnaire based on previously reported adverse events,³³ cognitive assessments (Mini-Mental Status Examination, Montreal Cognitive Assessment, Digit Span forward and backward tests, Stroop tests, and Trail Making A and B tests), and, to measure treatment-emergent mania or hypomania, the Young Mania Rating Scale.

STATISTICAL ANALYSIS

All analyses were performed using Stata version 12 statistical software (StataCorp LP), with 2-sided significance tests at the 5% significance level. Analyses were conducted in the intention-to-treat sample according to the last observation carried forward through the time points. Missing data were considered to be at random.

Sample size was estimated using data from previous tDCS studies,^{17,18} antidepressant and rTMS meta-analyses,^{5,38,39} and rTMS studies in which antidepressant drugs were combined.^{40,41} With these data, we estimated a 3-point difference effect (effect size of Cohen $d=0.5$) for both tDCS only and sertraline only vs placebo and a combined additive effect in the combined treatment group (ie, 6-point difference, with an effect size of Cohen $d=1.0$), which, considering probabilities of 5% for type I error and 20% for type II error, resulted in an estimated sample size of 30 patients per arm for a total of 120 participants (for an extensive discussion regarding our power analysis, see the articles by Brunoni et al^{29,42}). Further, we considered a difference smaller than an effect size of 0.5 or a 3-point between-group difference not to be clinically relevant per the National Institute for Clinical Excellence guidelines.⁴³

We compared clinical and demographic characteristics between groups at baseline by 1-way analysis of variance and χ^2 test for continuous and categorical variables, respectively. To analyze the primary outcome, we generated a mixed, repeated-measures analysis of variance model with 1 dependent within-subject variable (MADRS score), 1 within-subject variable (time, 4 levels), and 1 between-subject variable (group, 4 levels). According to a priori specifications, contrast comparisons were performed to assess the effects between (1) combined treatment vs placebo, (2) combined treatment vs other active groups (tDCS only and sertraline only), and (3) tDCS only vs sertraline only.

The factorial analysis allowed us to perform 3 comparisons at the main end point: (1) the effects of each group (inside the

Table 1. Montgomery-Asberg Depression Rating Scale Scores at Different Times

Group or Factor	Baseline	Week 2		Week 4		Week 6	
	Mean (SD)	Mean (SD)	% (SD) ^a	Mean (SD)	% (SD) ^a	Mean (SD)	% (SD) ^a
Group							
Sham tDCS and placebo	30.76 (5.31)	21.37 (10.06)	−30.2 (30.7)	22.56 (9.50)	−24.1 (36.1)	24.73 (8.65)	−18.2 (29.0)
Sham tDCS and sertraline	30.50 (6.81)	22.10 (11.50)	−28.9 (30.1)	22.83 (11.03)	−25.2 (34.5)	21.67 (13.14)	−29.8 (36.7)
Active tDCS and placebo	30.76 (5.78)	20.53 (9.59)	−34.0 (26.8)	19.33 (10.41)	−37.9 (29.5)	19.07 (12.21)	−39.5 (34.2)
Active tDCS and sertraline	30.73 (6.72)	15.53 (7.90)	−48.5 (23.5)	15.70 (7.98)	−46.9 (25.7)	13.17 (8.46)	−55.6 (27.3)
<i>P</i> value ^b	.99	.01		.01		<.001	
Factor							
No sertraline	30.76 (5.51)	20.95 (9.70)	−32.1 (28.6)	20.95 (10.02)	−31.0 (33.3)	21.90 (10.88)	−28.8 (33.3)
Sertraline	30.61 (6.71)	18.81 (10.32)	−38.7 (28.6)	19.27 (10.20)	−36.1 (32.5)	17.14 (11.77)	−42.7 (34.8)
<i>P</i> value ^b	.89	.25		.36		.03	
No tDCS	30.63 (6.10)	21.73 (10.71)	−29.6 (30.9)	22.70 (10.21)	−24.7 (34.8)	23.20 (11.14)	−24.0 (33.3)
tDCS	30.75 (6.22)	18.03 (9.02)	−41.2 (25.6)	17.52 (9.38)	−42.4 (27.9)	16.11 (10.83)	−47.6 (31.7)
<i>P</i> value ^b	.91	.04		.003		.001	

Abbreviation: tDCS, transcranial direct current stimulation.

^aPercentage represents percentage of change, calculated as (score at period − score at baseline)/score at baseline.

^b*P* values represent results for the mixed-model analysis of variance time × group interaction (for the main analysis) or time × tDCS and time × sertraline interaction (for the factorial analysis) at each week.

cell); (2) the effects (at the margins) of each factor (ie, active tDCS vs sham tDCS and sertraline vs placebo); and (3) the conditional, higher-order interaction of tDCS × sertraline. We therefore determined whether treatments were additive or nonadditive (ie, synergistic) according to 1 of 2 possible scenarios: (1) if the interaction is not significant, the factors are independent of each other and therefore the effects are additive; and (2) if the interaction is significant (ie, the effect of one factor is conditioned to the level of the other factor), then the combined effects of the 2 treatments are nonadditive (ie, synergistic).

Secondary assessments were performed similar to the MADRS analysis, but to limit type I errors, pairwise between-group analyses were corrected by the Bonferroni method; for categorical variables, we performed logistic regressions. We reported the frequency of adverse events in each group and used the χ^2 test or the Fisher exact test for comparisons. We also compared the mean changes of cognitive assessments using paired *t* tests.

Regarding predictors of response, we performed general linear models using the difference between baseline and end point scores as the dependent variable. For the independent variables, we used the factors tDCS, sertraline, and 1 predictor variable at a time.

RESULTS

PARTICIPANTS

Of approximately 850 potential volunteers, 506 were screened and 386 were excluded (eFigure, <http://www.jamapsych.com>). The groups were similar in clinical and demographic characteristics at baseline. The prevalence of hypertension was 22.5%, the prevalence of hypothyroidism was 13.3%, and 17.5% were current smokers. The sample had, on average, low treatment resistance (55.8% of patients had 0 or 1 failed treatment and only 21.7% had >2 failed episodes), with a median index episode duration of 12 weeks (interquartile range, 5-20 weeks) and a median of 3 past depressive episodes (interquartile range, 2-5 episodes). The washout had a mean duration of 18 days, and 23 participants (19.2%) were using

benzodiazepines (mean dosage, 13.4-mg/d diazepam equivalent) (eTable 1).

Nine patients dropped out within the first 2 weeks and 103 patients (85.8%) completed the entire trial (eFigure). Dropouts were balanced between groups. The reasons for dropouts were manic switch (*n* = 2, combined treatment group), suicidal ideation (*n* = 1, placebo; *n* = 1, tDCS only), more than 2 missing visits within the first 2 weeks (*n* = 2, placebo; *n* = 3, sertraline only; *n* = 1, tDCS only), and other reasons. The pharmacological and non-pharmacological procedures were implemented per the protocol (eFigure and eTable 1).

PRIMARY OUTCOME

The primary outcome was the MADRS score. We observed a significant time × group interaction ($F_{479,9} = 3.85$; $P < .001$). The combined treatment differed significantly from placebo (mean difference, 11.5 points; 95% CI, 6.03 to 17.10; $P < .001$), tDCS only (mean difference, 5.9 points; 95% CI, 0.36 to 11.43; $P = .03$), and sertraline only (mean difference, 8.5 points; 95% CI, 2.96 to 14.03; $P = .002$). No difference was observed between tDCS only and sertraline only (mean difference, 2.6 points; 95% CI, −2.90 to 8.13; $P = .35$). Other post hoc comparisons revealed that sertraline only did not reach statistical significance compared with placebo (mean difference, 2.9 points; 95% CI, −1.50 to 7.10; $P = .20$), while tDCS only was significantly superior to placebo (mean difference, 5.6 points; 95% CI, 1.30 to 10.01; $P = .01$) (**Table 1**).

In the factorial analysis, there were 2 factors: tDCS (active tDCS vs sham tDCS) and sertraline (sertraline vs placebo). This analysis is important in assessing whether the effects of these treatments are additive or synergistic. Because it showed no significant interaction ($F_{116,1} = 0.51$; $P = .48$)—only significant main effects for tDCS ($F_{116,1} = 12.85$; $P < .001$) and sertraline ($F_{116,1} = 5.15$; $P = .02$)—we conclude that the effects of the interven-

Table 2. Response and Remission Rates According to Montgomery-Asberg Depression Rating Scale Scores^a

Group	No. (%)					
	Week 2		Week 4		Week 6	
	Response	Remission	Response	Remission	Response	Remission
Sham tDCS and placebo	11 (36.7)	6 (20.0)	9 (30.0)	3 (10.0)	5 (16.7)	4 (13.3)
Sham tDCS and sertraline	10 (33.3)	5 (16.7)	8 (26.7)	4 (13.3)	10 (33.3)	9 (30.0)
Active tDCS and placebo	9 (30.0)	4 (13.3)	12 (40.0)	7 (23.3)	13 (43.3)	12 (40.0)
Active tDCS and sertraline	16 (53.3)	6 (20.0)	16 (53.3)	7 (23.3)	19 (63.3)	14 (46.7)
<i>P</i> value	.25	.89	.14	.40	<.001	.03

Abbreviation: tDCS, transcranial direct current stimulation.

^aRemission was defined as a Montgomery-Asberg Depression Rating Scale score of 10 or less, and response was defined as a score change greater than 50% from baseline. All remitters were responders, but not all responders were remitters. *P* values represent results for the logistic regression of time × group interaction.

tions were additive. Analyses of the main effects revealed a difference of 7.08 points (95% CI, 3.16 to 11.01; *P* < .001) for the factor tDCS and a difference of 4.48 points (95% CI, 0.57 to 8.39; *P* = .02) for the factor sertraline.

SECONDARY OUTCOMES

MADRS Score at Week 2

We observed a significant between-group difference for MADRS score at week 2 (*P* = .04). The combined treatment (mean change, −48.5%) differed significantly from placebo (mean change, −30.2%; *P* = .02), sertraline only (mean change, −28.9%; *P* = .01) and tDCS only (mean change, −34.0%; *P* = .05). Other post hoc comparisons were not significant; thus, only the combined treatment group experienced a significant improvement at 2 weeks. Notably, for the factorial analysis, we observed a main effect for tDCS ($F_{116,1} = 4.26$; *P* = .04; mean change, −41.2% for active tDCS vs −29.6% for sham tDCS) but not for sertraline ($F_{116,1} = 1.42$; *P* = .24; mean change, −38.7% for sertraline vs −32.1% for placebo) or the interaction (*P* = .11), suggesting that the initial antidepressive effect was driven primarily by tDCS.

Remitters and Responders

There was a significant association in response rates between placebo (16.7%) vs tDCS only (43.3%; odds ratio = 8.6; 95% CI, 2.5-29.1; *P* < .001) and vs combined treatment (63.3%; odds ratio = 3.8; 95% CI, 1.1-12.7; *P* = .03); however, this was not observed vs sertraline only (33.3%; odds ratio = 2.5; 95% CI, 0.7-8.5; *P* = .14). Also, compared with placebo (13.3%), the combined treatment (46.7%; odds ratio = 5.7; 95% CI, 1.6-20.3; *P* = .007) and tDCS only (40.0%; odds ratio = 4.3; 95% CI, 1.2-15.6; *P* = .02) effected significant remission, whereas sertraline only did not (30.0%; *P* = .12) (**Table 2**).

Other Depression Measures

Results similar to those reported for the MADRS score were observed for the 17-item Hamilton Depression Rating Scale, clinician-rated Clinical Global Impression–Severity of Illness scale, and Beck Depression Inventory. These results are shown in eTable 2.

SAFETY OUTCOMES

Skin redness was more common in the active group at the end of week 2 (eTable 3). Other adverse events were not different between active and sham tDCS. For all groups and assessments, the end point to baseline comparisons revealed no change or improvement in cognitive performance (eTable 4), ie, tDCS had no hazardous cognitive effects. Five episodes of hypomania (Young Mania Rating Scale score >8) and 2 episodes of clinical mania developed: 5 (including 2 manic episodes) in combined treatment, 1 in tDCS only, and 1 in sertraline only. The frequency of adverse effects did not differ per group (*P* = .17, Fisher exact test), but we will further discuss their the clinical implications.

PREDICTOR VARIABLES

Our exploratory analysis shows that age, sex, and other demographic variables were not predictors of response. We found that baseline severity and treatment resistance to more than 1 failed antidepressant trial (*P* = .01 for both) presented main effects, being that these variables were associated with a lower response. In addition, for baseline severity, there was a 3-way interaction: tDCS, sertraline, and baseline severity (*P* = .01); post hoc analyses showed that patients in the combined treatment group with more severe depression had a greater response. We also observed an interaction between tDCS and melancholic depression (*P* = .03) (greater response in patients with melancholic depression receiving active tDCS compared with sham tDCS) and a 3-way interaction with benzodiazepine use (*P* = .03)—this drug was associated with a lower response in the sertraline-only and tDCS-only groups (eTable 5).

INTEGRITY OF BLINDING

Although participants correctly guessed both sertraline and tDCS use, considering only those who were almost or absolutely sure of the assigned intervention group, only sertraline—but not tDCS—use was guessed correctly. The blinding analysis is shown in eTable 6.

In this relatively large controlled clinical trial, we evaluated 2 antidepressant treatments simultaneously—a traditional SSRI (sertraline) and a novel nonpharmacological option (tDCS). The combination of sertraline and tDCS led to a significantly greater effect compared with placebo and was also clinically relevant per the National Institute for Clinical Excellence guidelines.⁴³ By factorial analysis, the effects of sertraline and tDCS were additive. Our findings at 2 weeks showed that the combined treatment accelerated clinical improvement as compared with the other groups. Further, adverse effects were low, although active tDCS was significantly associated with skin redness. Moreover, no hazardous cognitive effects were observed. There were 7 episodes of treatment-emergent mania or hypomania, 5 of which occurred in the combined treatment group.

Remarkably, tDCS induced greater effects in melancholic depression, similar to the findings observed in rTMS.⁴⁴ This might be related to focal brain stimulation over the left DLPFC, which is associated with some important symptoms of melancholic depression such as psychomotor retardation. Further, benzodiazepine use, even in low dosages, induced lower effects in the tDCS-only group. Benzodiazepines indeed decrease cortical excitability,⁴⁵ which could have decreased anodal tDCS effects both over local and remote areas.⁴⁶ Interestingly, this hazardous effect was not observed in the combined treatment group, possibly because the excitability-enhancing effects of the SSRI in subcortical circuits³⁶ counteracted the inhibitory effects of the benzodiazepines. Of note, patients with greater baseline severity showed greater response to the combined treatment, suggesting that this combined therapy strategy is particularly effective in this subgroup of patients. Finally, the negative association with treatment refractoriness was also observed in 2 TMS studies.^{47,48}

The findings that the combined treatment was associated with a faster, greater response could indicate that each intervention has a distinct but additive mechanism of action. Considering that MDD is associated not only with lateralized (left vs right) cortical DLPFC dysfunction but also with limbic subcortical dysfunction,⁴⁹ we hypothesize that tDCS could act primarily in cortical activation, whereas SSRIs would act primarily on the downregulation of limbic hyperactivity. In fact, a recent systematic review compared neuroimaging findings from psychological vs pharmacological interventions, suggesting that the former were related to top-down (frontal activation) effects, whereas the latter were associated with bottom-up effects.⁵⁰ Analogously, we propose that participants with MDD in the combined treatment group were exposed to both bottom-up and top-down regulation and that such differential and combined activation translated clinically to the increased response. Future studies could explore this hypothesis using neuroimaging methods to further understand the mechanism when combining interventions.

The factorial design is an important aspect of the SELECT TDCS. We not only compared tDCS against sertraline and placebo, we also investigated the effects of tDCS and sertraline combined. Notably, the absence of a statistically significant interaction suggests that their clinical effects are additive. Nevertheless, power analysis was planned to show a moderate (3-point difference) effect size for the interaction. Therefore, we cannot exclude that this interaction, although small (<3-point difference), would be significant in a study with a larger population.

Also, our cohort was antidepressant free, avoiding the confounding factors of other pharmacological interventions and increasing the internal validity of our study.

The 13% attrition, which was lower than in antidepressant trials,⁵¹ can be partly explained by the requirement of daily 10-day visits. This early attrition could have been higher if we had granted no rescheduling of missing visits.

At the end point, patients correctly guessed the interventions (ie, tDCS and sertraline), but they were only moderately confident in their choices. However, considering only the subsample of those who were very or extremely confident in their choices, their guesses were not accurate for tDCS (only for sertraline). In addition, responders were more confident in their choices but were not accurate. These analyses suggest that patients' guesses were driven by clinical improvement (an issue often observed⁵²) rather than blinding failure. In fact, tDCS blinding was as reliable as that for sertraline.

The pharmacological and nonpharmacological "doses" chosen are worth comment. When designing this trial, evidence indicated antidepressant effects with 5 to 10 daily tDCS sessions,²⁵ although a recent trial²⁴ suggests that such effects might be enhanced with longer treatment. Likewise, 50 mg/d of sertraline hydrochloride may have been low for some participants, which might explain its low antidepressant effect observed in our trial. There are also negative MDD clinical trials for sertraline.⁵³ Nevertheless, our aims were to assess the combined tDCS and antidepressant effects and to provide pragmatic insight for the relative efficacy of tDCS, having sertraline, an SSRI used worldwide, as a clinical index. We also used this dose considering the risk of treatment-emergent mania or hypomania in the combined treatment group.

Finally, it should be noted that although sertraline had an efficacy comparable to that of tDCS, sertraline only was not different when compared with placebo, while tDCS only was significantly different from placebo. Although this finding may seem contradictory, it may indicate a small difference in efficacy between tDCS and sertraline that was not detected in our study as we considered only clinically meaningful differences when calculating sample size.

COMPARISON WITH RECENT NONINVASIVE BRAIN STIMULATION TRIALS

Although our sample presented a relatively low degree of refractoriness and short duration of the index episode, our results were comparable to other pilot tDCS trials.^{16,17} Like-

wise, compared with a larger trial²⁴ that enrolled patients receiving antidepressant therapy, similar results were observed. Finally, our results were comparable to previous open trials, eg, the study by Ferrucci et al¹⁸ that showed a 30% improvement in Beck Depression Inventory score after 5 days of tDCS (our improvement was 34.0% at week 2) and the study by Dell'Osso et al²⁰ that showed a 30% response rate in Hamilton Depression Rating Scale score 1 week after tDCS. Although we did not evaluate clinical effects earlier than 2 weeks, their results are similar to our findings. Disparate protocols were used between these trials and ours regarding the number of sessions (5 sessions,^{16,22} 5 sessions twice daily,^{18-20,54} 10 sessions,^{17,23} and 15 sessions²⁴), position of the reference electrode (supraorbital^{16,17,22-24} and F4 area^{18-20,54}), and dose (1 mA^{16,22} and 2 mA^{17-20,54}); thus, the comparisons are not straightforward.

Although tDCS has a different mechanism of action than rTMS, they both induce increases in DLPFC excitability. The efficacy of tDCS appeared to be greater compared with recent rTMS trials.^{7,55} However, our primary end point was at 6 weeks vs 4 weeks in the study by O'Reardon et al⁵⁵ and 5 weeks in the study by George et al.⁷ These studies and ours showed increased efficacy over time. Both tDCS and rTMS appear to be associated with a sustained and progressive response over time.⁵⁶ In addition, these studies had samples more refractory than ours, which was more similar to levels 1 and 2 of the Sequenced Treatment Alternatives to Relieve Depression pragmatic trial that enrolled patients with 0 or 1 failed response to antidepressants² and presented response and remission rates comparable to those in our trial.

CLINICAL IMPORTANCE

We observed comparable efficacies of sertraline and tDCS, which is notable because antidepressant drugs can have adverse effects and contraindications that might not apply to tDCS. Conversely, tDCS treatment is less practical than taking a pill. Even if tDCS becomes available for in-house use, it would still require 20- to 30-minute daily sessions for several weeks. Further, it is unknown whether tDCS as a maintenance treatment is effective; indeed, our ongoing follow-up tDCS trial might provide some insights into this issue.

The sertraline-tDCS combination changed the response time and the magnitude of response compared with each treatment alone, similar to rTMS^{40,41} and electroconvulsive therapy,²⁷ which elicit greater response combined with pharmacotherapy. Further research using tDCS in inpatient settings is warranted.

As previously observed,^{33,57,58} we noted low rates of common tDCS adverse events and slightly increased rates of some effects (eg, skin redness) in the active group compared with the sham group. We also confirmed that tDCS is not associated with hazardous cognitive effects.⁵⁹

A notable clinical finding was treatment-emergent hypomania or mania in the combined treatment group, particularly 1 severe manic episode that required pharmacological intervention.⁶⁰ Arul-Anandam et al⁶¹ and Gálvez et al⁶² also reported hypomania after tDCS. Hypomania or mania induction following tDCS is possibly higher than

with rTMS⁶³ and is perhaps similar to that with antidepressants,⁶⁴ warranting careful reporting of such events in future trials. Conversely, one study¹⁹ described the efficacy of tDCS in patients with depression and bipolar disorder, although all were taking mood-stabilizing drugs that might have prevented hypomania.

CONCLUSIONS

Noninvasive brain stimulation is becoming an established therapy for the treatment of depression. Treatment with rTMS is already approved by regulatory agencies for clinical use in many countries, including the United States, Israel, Canada, and Brazil. Based on compelling preliminary data, we conducted a phase 2/3 factorial trial that determined the efficacy of a simple but powerful method of noninvasive brain stimulation—tDCS—alone and combined with sertraline. Because tDCS devices are relatively inexpensive, further health economics studies should analyze whether it would be a cost-effective alternative for regions with low resources where the prevalence of MDD is high, such as most developing nations.

In addition to confirming the clinical efficacy of tDCS and demonstrating that tDCS has effects similar to those of sertraline in antidepressant-free patients with MDD, we observed that tDCS and sertraline combined have greater response compared with each intervention alone, although the increased risk of mania or hypomania should be considered.

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