Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Trial - SELECT TDCS: Design, rationale and objectives
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Abstract  

Background: Despite significant advancements in psychopharmacology, treating major depressive disorder (MDD) is still a challenge considering the efficacy, tolerability, safety, and economical costs of most antidepressant drugs. One approach that has been increasingly investigated is modulation of cortical activity with tools of non-invasive brain stimulation — such as transcranial magnetic stimulation and transcranial direct current stimulation (tDCS). Due to its profile, tDCS seems to be a safe and affordable approach.

Methods and design: The SELECT TDCS trial aims to compare sertraline vs. tDCS in a double-blinded, randomized, factorial trial enrolling 120 participants to be allocated to four groups to receive sertraline + tDCS, sertraline, tDCS or placebo. Eligibility criteria are moderate-to-severe unipolar depression (Hamilton Depression Rating Scale \( N \geq 17 \)) not currently on sertraline treatment. Treatment will last 6 weeks and the primary outcome is depression change in the Montgomery–Asberg Depression Rating Score (MADRS). Potential biological markers that mediate response, such as BDNF serum levels, Val66Met BDNF polymorphism, and heart rate variability will also be examined. A neuropsychological battery with a focus on executive functioning will be administered.

Discussion: With this design we will be able to investigate whether tDCS is more effective than placebo in a sample of patients free of antidepressants and in addition, we will be able to secondarily compare the effect sizes of sertraline vs. tDCS and also the comparison between tDCS and combination of tDCS and sertraline.

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1. Introduction

Major Depressive Disorder (MDD) is a psychiatric condition whose core features are depressed mood and anhedonia (lack of pleasure from activities once considered joyful). Auxiliary symptoms include: excessive guilt, sleep disturbances, low self-esteem, and weight changes. MDD is one of the main causes of disability and absenteeism worldwide and has high lifetime prevalence (up to 20%) [1,2], being even higher in patients with
concomitant somatic illness or other psychiatric conditions [3]. Also, MDD presents high rates of relapse (nearly 80%) and of treatment-resistance (nearly 33%) [4,5].

Depression treatment is based on antidepressant drugs that also present side effects leading to drug discontinuation and treatment withdrawal such as sexual dysfunction and weight gain [6]; and they usually take more than two (usually four to eight) weeks for full efficacy [7], increasing the time span of MDD. Therefore, considering the burden, severity, and prevalence of the disease, new therapeutic regimens for MDD are needed.

Along those lines, non-invasive brain stimulation techniques are novel and promising treatments that have desirable characteristics such as lack of significant systemic effects and potential for better control of dosage. Repetitive transcranial magnetic stimulation (rTMS) has been recently approved in several countries for depression management, but it is costly and non-portable. Transcranial direct current stimulation (tDCS), on the other hand, is more economical and portable [8], being based on the application of weak direct currents via scalp electrodes in a simple and painless manner. The effects are polarity-dependent: anodal stimulation increases and cathodal stimulation decreases cortical excitability [9]. In MDD, the anode electrode is placed over the left dorsolateral prefrontal cortex area whose activity is impaired in depression [10]. In fact, although rTMS is advantageous considering the high temporal and spatial resolution, it is much more expensive and complicated to operate than tDCS, which is also portable and battery driven. In addition these two techniques have different mechanisms of action and it is still not clear which one would be more advantageous in terms of efficacy for treating MDD. Such aspects have instigated tDCS research in recent years [11].

Indeed, some pilot clinical trials suggested that tDCS has good antidepressant efficacy (Table 1): in a first sham-controlled trial, Fregni et al. [12] showed antidepressant efficacy of tDCS after 5 sessions. Later on, Boggio et al. [13] enrolled 40 patients and confirmed such positive effects in another double-blinded, sham-controlled trial; while Ferrucci et al. demonstrated depression improvement in an open-label clinical trial with 14 patients. Also, Rigonatti et al. [14] compared a subgroup of Boggio et al. [13] against 20 patients taking fluoxetine. Both groups had similar efficacy after 6 weeks of treatment, but a fast, sustained response occurred in tDCS group at week 2. Finally, Loo et al. [15] did not show tDCS efficacy in one double-blinded, controlled study recruiting 40 patients after 5 days of stimulation; but found positive results after 10 days of stimulation.

Therefore, vital questions remain: (1) is the active tDCS antidepressant response effective when compared to sham tDCS, and if so, what is the effect size? Other secondary questions are: (2) is tDCS more effective or faster than pharmacotherapy? (3) What are the possible adverse effects of tDCS therapy? (4) What are possible predictors of tDCS response?

Aiming to answer these questions, we designed the Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Study (SELECT TDCS), a phase II/III trial to address the safety and efficacy of tDCS in the treatment of MDD. In the present paper we discuss the rationale, methods, design and objectives of our ongoing trial. This paper aims to: (1) present and discuss important topics observed in a trial

Table 1

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Subjects</th>
<th>Sample size</th>
<th>Target area</th>
<th>Cathode electrode placement</th>
<th>Current strength (mA)</th>
<th>Duration/session (min)</th>
<th>Number of sessions</th>
<th>Side-effects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fregni et al. (2006)</td>
<td>Randomized, double-blinded, sham-controlled</td>
<td>MDD 10 F3</td>
<td>Contra-lateral supra-orbital</td>
<td>F3</td>
<td>35</td>
<td>20</td>
<td>5 alternate days</td>
<td>not reported</td>
<td>Reduction of depressive symptoms</td>
</tr>
<tr>
<td>Boggio et al. (2008)</td>
<td>Randomized, double-blinded, sham-controlled</td>
<td>MDD 40 F3</td>
<td>Contra-lateral supra-orbital</td>
<td>F3</td>
<td>35</td>
<td>10 consecutive days</td>
<td>mild transient effects in active and sham groups</td>
<td>not reported</td>
<td>Reduction of depressive symptoms</td>
</tr>
<tr>
<td>Ferruci et al. (2009)</td>
<td>Open trial</td>
<td>Severe MDD referred for ECT</td>
<td>Contra-lateral supra-orbital</td>
<td>F3</td>
<td>35</td>
<td>20</td>
<td>5 twice a day</td>
<td>a) 5 active days</td>
<td>Improvement in depression</td>
</tr>
</tbody>
</table>

The table shows the study design, the sample characteristics (MDD = major depressive disorder; ECT = electroconvulsive therapy); sample size, position of the anode (target area, F3 is over the left dorsolateral prefrontal cortex); parameters of current delivery (current strength, cathode placement, duration of session and number of stimulation days); and the reported side effects and results.
design combining pharmaotherapy and brain stimulation; (2) report in advance the methodology of an ongoing clinical trial using tDCS for MDD; (3) show our study protocol before trial results, thus giving additional assurance of adherence to the protocol. We believe that our manuscript can contribute to the development of the field by discussing the design and methods of a Phase II/III factorial clinical trial for tDCS.

2. Methods

2.1. Participants

We are enrolling patients aging from 18 to 65 years diagnosed with Major Depressive Disorder according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria and confirmed by the Mini-International Neuropsychiatric Interview (M.I.N.I.). Only patients with a Hamilton Depression Rating Scale (17-items) (HDRS17) >18 and low suicidal ideation are included. Exclusion criteria are other axis I disorders such as bipolar disorder, schizophrenia, alcohol and substance use disorders; and any axis II (personality and developmental) disorders. Patients with severe, life-threatening medical conditions and concomitant neuropsychiatric disorders such as dementia, epilepsy, and stroke are also excluded.

Importantly, subjects using or who used sertraline in the current acute depressive episode are also excluded, because in such cases sertraline would not be a suitable comparator. However, those who used sertraline in previous episodes and presented clinical response can be included. Other antidepressants are discontinued before trial onset for a time period of five half-lives of the drug; exceptions being venlafaxine and paroxetine, which have serious withdrawal symptoms, and, therefore, are slowly tapered off to avoid possible withdrawal symptoms that may occur [16]. Finally, patients using other classes of psychopharmacological drugs (e.g. benzodiazepines) are included with the following precautions: (1) the drug dosage must be stable in the last 8 weeks; and (2) this variable is controlled and explored during statistical analysis.

Recruitment is being performed at two levels: (a) a convenience sample of depressed patients from primary and secondary care ambulatories (referred from general physicians and psychiatrists) and; (2) spontaneous demand through advertising in local newspapers, radio stations, and websites.

The sample size was estimated using data from previous meta-analyses: for the placebo response, we used the effect size obtained from a meta-analysis comparing pharmacological vs. non-pharmacological interventions [17]; for sertraline, a recent meta-analysis of sertraline for depression [18]; for tDCS, a recent meta-analysis of rTMS for depression [19]. Also, we estimated different degrees of sertraline-tDCS synergistic effects based on previous tRMS studies that combined the rTMS and the antidepressant drugs [20–22]. With these data, we simulated different scenarios testing the study power vs. sample size vs. depression score reduction (against sham-placebo group) in sham-sertraline group (Fig. 1a), in active tDCS – placebo group and in active tDCS – sertraline group (Fig. 1b), obtaining a study power of 80% to detect a 3-point score reduction (which is a criteria of clinical significance in MDD trials according to NICE guidelines) of tDCS and sertraline, and a study power of 80% to detect an interaction of 100–125% between tDCS and sertraline, which was obtained during two trials testing the combined effect of rTMS and antidepressant drugs [20,21].

For a detailed, statistical description of our sample size calculation, please contact the corresponding authors.
2.2. Materials

For tDCS delivery, the anode electrode is placed over the left dorsolateral prefrontal cortex that is located in F3 (according to the International EEG System 10-20) and the cathode electrode over the right dorsolateral prefrontal cortex (F4), similar positioning used in Ferrucci et al. [23] study. The rubber electrodes are involved in 25 cm² saline-soaked sponges and fixed with a headband. We use a direct current of 2 mA (current density = 0.80 A/m²) for 30 min per 10 consecutive workdays (total charge density of 1440 C/m²). After that, we apply tDCS again another two times — at week 4 and at week 6.

For sham conditions, the device is turned off after one minute of active stimulation, a blinding method that has proved to be reliable previously [24,25] as it presents the same side effects of active stimulation, which is a mild tingling that fades away just after stimulation onset. Nevertheless, other methods to minimize blinding vulnerability are used, such as blinding raters to treatment applied, avoiding contact between subjects of different groups, and keeping the statistician unaware of treatment allocation during statistical analysis (i.e., “triple-blinded study”). Blinding is tested when treatment ends by asking subjects to guess to which group they were assigned.

The pharmacological intervention is sertraline 50 mg/day (or placebo), which was chosen because sertraline is an effective antidepressant treatment with very low side effects [26] and dose up-titration is usually done after 6 to 8 weeks [27], after our study endpoint. Blinding is achieved using capsules that have the same size, color and taste of the active drug as usually done in randomized, controlled, drug trials.

2.3. Design

SELECT TDCS is a randomized, factorial, placebo-controlled trial in which 120 patients with MDD are randomly assigned to four groups: 1) the active tDCS – sertraline group; 2) the active tDCS – placebo pill group; 3) the sham tDCS – sertraline group and; 4) the sham tDCS – placebo pill group. Patients are followed for 6 weeks, and four assessments are performed: baseline, week 2, week 4, and endpoint (week 6). Adverse effects are assessed at week 1, week 2, week 4, and week 6 (endpoint); neuropsychological testing is conducted at baseline and week 6. At the end of the trial, subjects who received tDCS and achieved remission are invited to maintain tDCS bimonthly for 6 months, as part of a long-term study of tDCS for MDD; those who did not receive tDCS and did not respond are offered ten open-label daily sessions of tDCS; finally, those who showed response with sertraline or placebo and sham are referred to the outpatient psychiatry clinic of our hospital.

In our trial, patients return to the research center daily, for ten consecutive days. As this might be an issue for adherence (considering that São Paulo City has considerable traffic congestion), the patients are granted two non-consecutive visits or two consecutive visits during the initial 10-weekdays stimulation period; (2) do not return at week 4 or week 6; (3) present serious clinical or psychiatric adverse effects during the trial; (4) are lost to follow-up; (5) withdraw at their own request; (6) are excluded for safety reasons, including severe worsening of psychiatric condition and severe adverse effects; and (7) pregnancy is identified. In our previous trial with similar population missing data was minimal [25]; and missing data will be considered at random.

In addition, our study uses an intention-to-treat (ITT) design, i.e., all patients whose baseline data were collected and performed at least 1 day of stimulation are included in our analysis; the missing observations due to non-compliance are imputed accordingly to the last observation performed. The method of LOCF has fewer assumptions as it allows MCAR (missing completely at random) and MAR (missing at random). In addition, we will compare baseline characteristics of patients with missing data and patients with no missing data. We expect based on our previous experience with similar population from 5 to 10% of missing data.

Finally, our study was approved by the Internal Review Board of the University Hospital of University of São Paulo (Hospital Universitário da Universidade de São Paulo, protocol number 873/08), where the study is being conducted, and by the National Ethics Committee (Sistema Nacional de Informações sobre Ética em Pesquisa envolvendo seres humanos, protocol number FR236964). The clinicaltrials.gov identifier is NCT01033084.

2.4. Procedures

For assessment, we are applying the following scales: HDRS17, Montgomery–Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), and Clinical Global Impression (CGI). For detecting treatment-emergent (hypo) mania the Young Mania Rating Scale (YMRS) is performed at each evaluation. All scales have already been translated and validated to Portuguese [29] and are applied at all visits. The neuropsychological assessments, which are applied at baseline and endpoint, are: the Mini-Mental Status Examination (MMSE) [30], The Montreal Cognitive Assessment (MOCA) [31], the Wechsler Adult Intelligence Scale-III digit span (forward and backward) [32], the Stroop Test (color, word, and interference) [33], and the Trail Making test (numbers and words and numbers) [34]. Finally, adverse effects are assessed at every visit through the SAFTEE questionnaire (Systematic Assessment for Treatment Emergent Effects) [35] and a tDCS adverse effects questionnaire used in a previous safety study [36].

The score change in MADRS is the primary endpoint of our study, the clinical efficacy being described in terms of effect size (i.e., difference in means divided by the standard deviation of the means). MADRS was chosen because it is less “imbalanced” than HDRS and thus better reflects the clinical symptoms of depression [37]. Also, although
categorical outcomes (i.e., percentage of responders/remitters) probably better reflects better clinical practice [38], we chose score change as the primary endpoint for increasing study power. This approach is also useful to assess improvement in refractory patients who usually present low remission rates [39]. Our secondary outcomes are: (1) clinical depression response (50% of reduction in baseline MADRS scores); (2) clinical remission (MADRS ≤ 10) and (3) the score changes of HDRS17, BDI, and CGI.

For statistical analysis, we will use the data collected according to the ITT protocol. To check equipoise between the four groups, the baseline scores are going to be compared using one-way ANOVAs (Analysis of Variance), for continuous variables; and the Chi-Square test, for categorical variables. Our main model is a mixed ANOVA with one dependent, within-subject variable (MADRS score – continuous – differences as compared to baseline), one independent, within-subject variable (time – four levels) and one independent, between-subject variable (group – four levels). Whether a statistical significance is obtained at a two-tailed p level=0.05, post-hoc analyses will be performed (contrast method) to analyze the main and interaction effects of our intervention. We will also perform exploratory analyses to identify whether the variables gender, age, number of previous depressive episodes, and duration of index episode are moderators of time x group interaction and the variables refractoriness of index episode, BDNF baseline levels, MADRS baseline levels, and BDNF Val66Met polymorphism are mediators of this interaction.

Adverse events are going to be assessed by counting the number of adverse effects in each group at each period of evaluation, expressing them as percentages. The Fisher’s exact test will be used to compare the frequency of adverse effects along the different treatment groups.

### Table 2

Schedule of SELECT TDCS.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening visit</th>
<th>Baseline visit</th>
<th>Daily stimulation</th>
<th>D2</th>
<th>D4</th>
<th>Endpoint visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial week</td>
<td>Pre-trial</td>
<td>Day 0</td>
<td>0–2 weeks</td>
<td>Week 2</td>
<td>Week 4</td>
<td>Week 6</td>
</tr>
<tr>
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<tr>
<td>Non-structured interview</td>
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<tr>
<td>Drug washout</td>
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<tr>
<td>Informed consent</td>
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<td><strong>Diagnostics</strong></td>
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<tr>
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<tr>
<td>HDRS/MADRS</td>
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<td></td>
<td></td>
<td>X</td>
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<tr>
<td>BDI/IDS</td>
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<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>CGI – P/CGI – C</td>
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<td></td>
<td>X</td>
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<td>X</td>
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<tr>
<td>YMRS</td>
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<tr>
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<td>X</td>
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<td>X</td>
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<tr>
<td>tDCS questionnaire</td>
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<tr>
<td><strong>Neuropsychological evaluation</strong></td>
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<tr>
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<td>Stroop test</td>
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<td>Digit span</td>
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<td>X</td>
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<td>Trail making</td>
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<td>BDNF polymorphism</td>
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<td></td>
<td></td>
<td>ME</td>
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<td></td>
<td>X</td>
<td>ME</td>
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<tr>
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<td></td>
<td>X</td>
<td>X</td>
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<td><strong>Procedures</strong></td>
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<td>Stimulation session</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
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</table>

In the screening visit we check the eligibility criteria and perform a non-structured interview for the diagnosis of major depression and exclusion of other axis I diagnosis. We also collect the written informed consent from the patient and perform a drug washout of 5 half-lives of the drug, whether he/she is on antidepressant drugs. In the baseline visit we perform the structured questionnaire M.I.N.I. (Mini-International Neuropsychiatric Inventory) and the depression severity scales of Hamilton, Montgomery, Beck and Inventory of Depressive Symptoms (HDRS, MADRS, BDI, and IDS, respectively) as well as the Clinical Global Impression (Patient and Clinician Versions). The neuropsychological evaluation are also performed using the Montreal Cognitive Assessment (MOCA), Mini-Mental Status Examination (MMSE), the digit span, the Stroop Test and the trial making test. Finally, we measure Heart Rate Variability (HRV) and collect blood samples for Brain Derived Neurotrophic Factor (BDNF) serum and genetic analysis. Safety is checked at every visit starting on week 1 through the SAFTEE questionnaire (Systematic Assessment for Treatment Emergent Effects) and the tDCS adverse effects questionnaire.

3. Discussion

The SELECT TDCS trial is the largest clinical trial to date testing the efficacy of tDCS. Considering previous rTMS studies, only two studies had higher samples than ours, of 301 and 127 patients respectively [22,40]. Thus, the large sample size of SELECT TDCS decreases type I and type II errors and allows a study sample more heterogeneous than “proof-of-principle” trials, (i.e., with different degrees of refractoriness and comorbidity with anxiety disorders) thereby increasing external generalizability as tDCS is tested in different contexts.
In our study, we are delivering 2 mA for 30 min daily per ten consecutive workdays. Such dose is higher than applied in Loo et al. study [15] (1 mA×20 min three times a week per 2 weeks), in Boggio et al. study [25] (2 mA×20 min daily per 10 days) and in Ferrucci et al. study [23] (2 mA×20 min twice daily per 5 days). Although this is a topic under dispute, some evidence suggests that increased tDCS doses is associated with greater magnitude of behavioral effects [41,42]; greater long-lasting effects [15,43]; and also that increased tDCS frequency leads to increased magnitude of effects [43]. In fact, one possible explanation of the negative results of Loo et al. [15] is the lower dose delivered when compared to other studies (see Table 1). In addition, in our study we use a bilateral frontal stimulation (anode on F3 and cathode on F4) — similar to Ferrucci et al. [23] but different from others that used a cathode on the contralateral supra-orbital prefrontal cortex. Theoretically, this could be more advantageous in modulating left/right imbalance observed in MDD [44] given that DLPFC is a critical area as shown by other non-invasive brain stimulation studies [45]. Therefore, our DC dose delivery might be more “potent” than used in other trials, which can translate in more antidepressant efficacy as well as more adverse effects such as hypomania [46,47] and mania [48].

In addition, the present study is associated with a follow-up study in which responders are offered to receive tDCS stimulation every other week for additional 6 months, as to provide preliminary data for using tDCS as a maintenance treatment for MDD. Although literature on remission maintenance with non-invasive brain stimulation for MDD is scarce, one study using bimonthly or weekly rTMS in such context showed encouraging results [49].

Along these lines, sertraline was chosen as a comparator and add-on drug. In a recent meta-analysis, Cipriani et al. [26] compared the efficacy and adverse effects of 12 antidepressants, showing that sertraline (and escitalopram) presented the most favorable profile; moreover, such drug is widely used in clinical practice. Therefore, using sertraline should be adequate for design purposes as well as for “real world” practice. Here, it should be underscored that our trial duration (6 weeks) might be relatively short considering that symptoms may improve over 2–3 months. However, recent meta-analyses for MDD suggested that clinical efficacy could be detected with 1–2 weeks of treatment [50,51] and, in addition, there are ethical issues that limit the duration of placebo-controlled trials for longer periods. In fact, a recent consensus of trialists for MDD treatment considered that current evidence favors shortening new antidepressant trials to 3 to 4 weeks from the current 6 to 8 [37].

3.1. Limitations

Some concerns regarding our study design should be underscored. One of them is adherence, as patients should return daily to our research center, and (despite being a burdensome activity for some people) São Paulo has considerable traffic congestion. Besides granting two non-consecutive missing visits, we are applying other methods for increasing adherence such as: (1) spending adequate time explain the trial to the subjects as well as side effects of treatments; (2) staff training as to promote positive, collaborative relationships between subjects and staff mem-

bers; (3) Frequent and constant contact by phone and email with subjects; and (4) Logistical support (cover transportation costs and scheduling visits according to patients schedule). Drug adherence is also being checked, as we count pills when the patient ends the study.

Another issue is the placebo response in our trial. Several aspects must be considered: (1) the placebo response in MDD trials — which ranges from 25 to 50% and increases over time [52]; (2) the placebo response of non-pharmacological interventions which, despite common sense, might not be larger than pharmacological interventions for neuropsychiatric conditions [17,53]; and characteristics of our trial that particularly influences placebo response such as: (3) daily visits during 10-weekdays, which might increase placebo response by improving patient–physician relationship [54] (on the other hand, daily visits are burdensome, which can decrease placebo response); (4) one active intervention combined with placebo/sham might potentiate the active intervention (i.e., whether sertraline associated with sham tDCS has a higher response than sertraline due to sham tDCS – the same for active tDCS and placebo pill). Here, the absence of other factorial trials of pharmacological and neuromodulation interventions hinders a definite conclusion, albeit one trial comparing rTMS and placebo pill vs. sham rTMS and venlafaxine showed similar response and remission rates than observed in literature [55] – in fact, our trial might also be useful to explore placebo response in factorial design.

3.2. Importance of our trial for clinical research on the field

To the best of our knowledge, our ongoing study is the first to apply a factorial design in non-invasive brain stimulation, comparing this intervention not only against sham (which might prove efficacy but not necessarily clinical effectiveness), but also against a pharmacological intervention [56]. This is interesting as antidepressant drugs, albeit effective, are often discontinued or taken in lower doses due to side effects such as sexual dysfunction and weight gain [6]. Thus, proving similar efficacy of antidepressant drugs is of particular clinical relevance, posing as an alternative treatment to patients who do not tolerate drug side effects, or to those who cannot take antidepressant drugs for various reasons including: pregnancy, breast feeding, renal and hepatic impairment, and polypharmacy. More importantly, this factorial design also explores tDCS-sertraline interaction effects (i.e., a potentiating effect as suggested by some rTMS trials [56]), which would also have clinical implications in treatment-resistant depression that affects up to one-third of depressed patients [4]. Finally, we will verify whether tDCS is a faster antidepressant treatment, as some studies suggested. For instance, Rigonatti et al. [14] showed that tDCS at week 2 had the same clinical efficacy of fluoxetine at week 6, and Ferrucci et al. demonstrated marked improvement of severe, treatment-resistant depression after only 5 days of tDCS treatment. Being an effective accelerating antidepressant strategy, tDCS could be applied in hospitalized patients, accelerating their improvement and diminishing hospitalization costs.

Although a complete pharmacoeconomics analysis is beyond the scope of our study, it is interesting to compare sertraline vs. tDCS costs, foreseeing tDCS use in the "real world".
In our trial, the personnel costs for delivering tDCS is R$750.00\(^2\) per 88 h of work (or R$8.5/h). Each patient uses 35 min per stimulation (30 min of actual stimulation and 5 min for preparing the procedure) and receives 12 sessions; therefore the individual cost is R$59.50. However, the actual cost is in fact lower (R$20.00 to R$30.00) since we have observed that up to three participants can be stimulated simultaneously. Here we should add the costs of three tDCS devices (R$15000.00, or R$12.00 per patient), for a total of R$30.00 to R$45.00. In such analysis, tDCS is more affordable than sertraline 50 mg/day that was paid R$65.00. It should be underscored, though, that we do not consider here several other costs related to tDCS such as battery and saline replacement, infrastructure costs and for drug we did not consider higher doses, long-term costs and discontinuation costs (i.e., if one patient stops taking pills for adverse effects and another drug is prescribed, the full cost of the first drug should be counted).

4. Conclusion

SELECT TDCS is an ongoing clinical trial addressing the efficacy of transcranial direct current stimulation for patients with different degrees of treatment-resistant depression in a factorial design that uses sertraline as an add-on and comparator, thus allowing to tests different pharmacological/non-pharmacological associations. The investigation of the relationship of three biological markers with depression response will also contribute in understanding the pathophysiology of major depression as well as the mechanisms of action of this new technique of neuromodulation. Therefore, our trial can generate important findings in the fields of clinical treatment of depression and non-invasive brain stimulation.

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Appendix A. Biological markers under study in SELECT TDCS

We are also going to study biological markers related to major depression treatment response, which might also be interesting for tDCS — for instance, neuroimaging studies suggests that tDCS modulates signal transduction, which was indexed by neurotransmitter (GABA and glutamate) [57] and second-messenger (inositol) [58] densities. In the present study we are exploring the role of the following biological markers:

1) Brain Derived Neurotrophic Factor (BDNF): BDNF is a neurotrophin related to neuronal survival and synaptic strengthening [59] — roles that have raised the BDNF/neurotrophin hypothesis of MDD that states the disorder is caused by low neuronal activity (and low BDNF levels) in some key areas and amelioration of symptoms as accompanied by restoration of normal brain activity (and normal BDNF levels). In fact, in a previous meta-analysis [60], we showed that BDNF serum levels are lower in depressed patients and increase during treatment; with meta-regression analyses suggesting that degree of improvement and time period of second measurement correlates with BDNF increasing — since we will measure BDNF at week 2, we will address whether early BDNF changes are a predictor of treatment response. In addition, we will address whether BDNF increases during non-pharmacological interventions as we previously showed a trend (p = 0.08) for lower BDNF increasing in non-pharmacological (than pharmacological) treatments [60]. BDNF Val66Met polymorphism (i.e., an aminoacid substitution from Valine to Methionine due to single-nucleotide mutation at the codon 66) is suggested to adversely affect hippocampus development [61], which might be a risk factor for MDD [62]. Also, Cheeran et al. [63] demonstrated that healthy Val66Met carriers, compared to Val66Val controls, presented decreased tDCS-mediated plasticity. We will explore tDCS-depression response in Val66Met carriers, contributing to the understanding of this new neuromodulatory technique.

2) Heart rate variability (HRV): recent studies and meta-analyses substantiate that depressed patients present decreased HRV; however, antidepressant treatment also seems to decrease HRV [64–66]. Thus, either decreased HRV in depression is epiphenomena of antidepressant use or HRV not increasing after treatment is epiphenomena of antidepressant use. A third hypothesis is HRV being decreased even in patients who remitted from a depressive episode, i.e., HRV as an endophenotype for MDD. In our trial we will compare HRV changing in the four groups, distinguishing depression response from antidepressant drug response.

The importance of exploring biological markers relies on identifying novel moderators and mediators of response, thus generating new data regardless of study results. Furthermore, identifying biological markers is important to accelerate translational research, using data from basic science in clinical practice and then backwards, addressing the clinical relevance of the findings in basic science.

References


