Case study
The PSYLECT study: opportunities and pitfalls of digitizing a clinical trial in a LMIC

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Brief description of the research project

The *Portable Transcranial Electrical Stimulation and Internet-based Behavioral Therapy for Major Depression Study* (PSYLECT) is a randomized, sham-controlled clinical trial with digital features that recruited 210 patients with unipolar depression. These patients will be randomized to one of three groups: sham, home-use transcranial electric stimulation (tES) and digital placebo intervention, active, home-use tES and digital placebo, and active, home-use tES and app-based behavior therapy. These patients will be followed up for 6 weeks, and, at the endpoint, we will compare which group achieved superior efficacy. Both interventions are designed to be performed at home and self-delivered, and were developed together with Flow Neurosciences™. Previously to the trial, we translated the iBT questionnaires to Portuguese and validated it in our local population. The trial started in May 2021 and finished in October 2022.

Background

Major depressive disorder (MDD) remains a leading cause of disability-adjusted life years, despite traditional pharmacological and psychotherapeutic options[1]. MDD affects more than 300 million people worldwide, with a chronic and recurrent course[2], particularly in LMIC. First-line treatments for MDD present significant caveats, as antidepressant medications are associated with modest efficacy[3] and adverse effects[4], while in-person cognitive-behavioral therapy lacks wide-range availability, and involves higher costs and logistical burdens[5]. Transcranial electrical stimulation (tES), is a non-invasive brain stimulation technique with excellent acceptability and moderate effectiveness for MDD. Thus, it could be a first-line intervention, especially in patients with low-drug resistance[6,7]. However, such an approach is hampered by the limited scalability of tES treatment. The relative scarcity of skilled personnel and the logistical burdens and transportation costs associated with daily visits to external facilities are probably associated with its suboptimal utilization in clinical practice. In this context, recent technological advancements are progressively allowing tES to be performed remotely, operated by patients themselves, therefore reducing costs and enhancing scalability. This could represent important gains in vulnerable groups with depression, such as in LMIC. Concomitantly, growing attention has also been directed towards the combination of tES and neurobehavioral or psychotherapeutic interventions[8,9]. They can also be delivered remotely, in an internet-based and self-directed manner, especially using interactive smartphone apps[10]. Meta-analyses that evaluated the effect of app-based interventions in MDD found superiority of these interventions over control conditions, with small to large effect sizes[10–12], and higher retention rates when there was human feedback and mood assessments through the apps[13]. Moreover, the recent research interest in mental health apps for the treatment of MDD is occurring within a larger framework encompassing the rapid development of digital mental health technologies, in great part, boosted by the social distancing restrictions imposed by the COVID-19 pandemic[14,15]. Therefore, the expansion of digital mental health interventions and their good usability enables better access to healthcare, cost reduction, personalized approaches, and adherence to treatment. While a few studies evaluating the combination of tES with psychotherapy have been performed in research facilities, to the best of our knowledge, no controlled trial has investigated the synchronous combination of portable transcranial electrical stimulation (ptES) and a remotely delivered, self-directed and internet-based behavioral intervention (iBT), for the treatment of MDD, in adult patients.

Digital clinical trial

Considering that the intervention (ptES + iBT) can be deployed fully at home, we designed a digital trial[16] to enhance its scalability. Therefore, we use social media and digital marketing strategies to advertise our trial and screen potential participants by telemedicine. All evaluations of the study, except the first and the last ones, are performed virtually. During the initial visit, participants are instructed on how to operate the device and install the accompanying app in their smartphones. Regarding data collection and protection, our staff was trained on how to use RedCap and has taken classes on data protection law (the GDPR-Brazilian equivalent, LGPD). Communication with patients is centered on WhatsApp, a very popular app in Brazil, and randomization, allocation and blinding through the development of applications that carry out the intervention according to an encrypted code. Compared to previous studies performed by our group[17–19], we observed (as 60% of the sample has already been recruited) that the external validity / generalizability of these participants is higher compared to previous ones. Since tES sessions needed to be performed on-site (at the clinical center) before, the participation in our previous studies was restricted to those who had flexible working hours or lived near the clinical center. Additionally, the adherence to the study has been very high, as fewer than 5% of participants have dropped out so far.

Ethical issues

1. Selection process

We found that recruitment rates increased five times compared to our previous studies, due to online advertising, stimulating us to further increase trial scalability. Here, we found that a critical choke point is the screening process. Only 30% of screened patients meet eligibility criteria and can be invited to participate in the study. Moreover, during the initial interview, which is done on-site, about 30% of them are excluded as the online interview misses important information. Therefore, we considered options to enhance screening accuracy. In this context, we considered collecting more information by questionnaires that volunteers answer when subscribing to the study to train an algorithm for this purpose. However, here there is the ethical challenge of using screening data prior to the informed consent, which is only offered to the participant at a later step of the study. Ultimately, a new study, recruiting participants to collect data to allow future participants to be excluded in further trials, would have to be conducted. Nonetheless, the collection of new data that could enhance the algorithm would still not be allowed. Therefore, one possible solution is to collect the consent form as soon as the participant volunteers to participate in the trial. Additionally, usually more severe patients are not included in a study. However, more severe patients are also those in a more vulnerable socioeconomic position. An algorithm that is trained aiming to enroll less severe patients could use such information to enhance its accuracy, essentially digitizing exclusion. The same issue could occur whether the algorithm is trained to enroll participants that are less likely to drop out of the study. This could be related to people who have less digital literacy, which are usually people who are less educated or have a lower socioeconomic status. It is important to highlight that the selection process which eliminates people who are unlikely to be successful in the use of the tool means that the success rate of the trial will ultimately be higher than what will be obtained if administered outside the trial setting.

2. Issues arising during the trial

Another opportunity that also brings ethical challenges is using bots ("chatbots") for interacting with participants virtually. On one hand, this would improve scalability, considering that most questions from participants can be answered using decision trees (e.g., concerns regarding missing a session, or simple troubleshooting). On the other hand, participants might feel alienated if they do not have prompt access to the research team, which could in turn decrease adherence. In addition, ancillary care obligations that could require greater attention (perhaps human) to issues that participants may be facing might not be easily capturable by a chat box.

3. Ethical issues that may arise if successful and the tool is to become available population wide

Also, performing a digital trial brings the opportunity of collecting active and passive data using apps and wearables. Although using such an approach provides data granularity, this also brings ethical issues regarding the extent and how the data is being used. Participants and patients using apps that collect sensitive and personal data should be clearly informed regarding the extent and

which type of data are being collected, and should be provided several options regarding privacy access.

Conclusion and recommendations

This is the first digital trial using portable tES devices combined with an app-based behavioral therapy system in a LMIC. We noticed ethical challenges in terms of recruiting participants to our study and using the data they provided to develop algorithms that could lead to their trial exclusion. To address this issue, we amended our informed consent term to guarantee that, even at the initial stage, participants would consent that the data they provide could be used for the specific process of screening. A second aspect is that advertising our study only in social media could exclude people with low digital literacy. Therefore, we are also using traditional media (newspapers and radio) and scheduling on-site screening visits to those who are not comfortable with the digital process of screening.

References

1. Collaborators GBD. … national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis …. 2018; Available from: https://leicester.figshare.com/articles/journal_contribution/Global_regional_and_national_incidence_prevalence_and_years_lived_with_disability_for_354_diseases_and_injuries_for_195_countries_and_territories_1990-2017_a_systematic_analysis_for_the_Global_Burden_of_Disease_Study_2017_/10200149/files/18383459.pdf
2. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry* 2007;68 Suppl 8:17–25.
3. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163(11):1905–17.
4. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2008;22(4):343–96.
5. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342(20):1462–70.
6. Razza LB, Palumbo P, Moffa AH, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. *Depress Anxiety* [Internet] 2020; Available from: http://dx.doi.org/10.1002/da.23004
7. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. *Int J Neuropsychopharmacol* [Internet] 2020; Available from: http://dx.doi.org/10.1093/ijnp/pyaa051
8. Sathappan AV, Luber BM, Lisanby SH. The Dynamic Duo: Combining noninvasive brain stimulation with cognitive interventions. *Prog Neuropsychopharmacol Biol Psychiatry* 2019;89:347–60.
9. Dedoncker J, Baeken C, De Raedt R, Vanderhasselt M-A. Combined transcranial direct current stimulation and psychological interventions: State of the art and promising perspectives for clinical psychology. *Biol Psychol* 2021;158:107991.
10. Li J, Theng Y-L, Foo S. Game-based digital interventions for depression therapy: a systematic review and meta-analysis. *Cyberpsychol Behav Soc Netw* 2014;17(8):519–27.
11. Josephine K, Josefine L, Philipp D, David E, Harald B. Internet- and mobile-based depression interventions for people with diagnosed depression: A systematic review and meta-analysis. *J Affect Disord* 2017;223:28–40.
12. Linardon J, Cuijpers P, Carlbring P, Messer M, Fuller-Tyszkiewicz M. The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials. *World Psychiatry* 2019;18(3):325–36.

13. Torous J, Lipschitz J, Ng M, Firth J. Dropout rates in clinical trials of smartphone apps for depressive symptoms: A systematic review and meta-analysis. *J Affect Disord* 2020;263:413–9.
14. Psychiatry TL, The Lancet Psychiatry. Digital psychiatry: moving past potential [Internet]. *The Lancet Psychiatry*. 2021;8(4):259. Available from: http://dx.doi.org/10.1016/s2215-0366(21)00096-1
15. Torous J, Bucci S, Bell IH, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. *World Psychiatry* 2021;20(3):318–35.
16. Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. *NPJ Digit Med* 2020;3:101.
17. Brunoni AR, Moffa AH, Sampaio-Junior B, et al. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. *N Engl J Med* 2017;376(26):2523–33.
18. Sampaio-Junior B, Tortella G, Borrione L, et al. Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression: A Randomized Clinical Trial. *JAMA Psychiatry* 2018;75(2):158–66.
19. Valiengo L da CL, Goerigk S, Gordon PC, et al. Efficacy and Safety of Transcranial Direct Current Stimulation for Treating Negative Symptoms in Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry* [Internet] 2019; Available from: http://dx.doi.org/10.1001/jamapsychiatry.2019.3199

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