Home-Based Transcranial Direct Current Stimulation (tDCS) Compared to Duloxetine in the Treatment of Fibromyalgia: A Randomized Non-Inferiority Clinical Trial

(FIBROSTIM)

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PROTOCOL

Home-Based Transcranial Direct Current Stimulation (tDCS) Compared to Duloxetine in the Treatment of Fibromyalgia: A Randomized Non-Inferiority Clinical Trial (FIBROSTIM)

Study Design

A randomized, non-inferiority, double-dummy, factorial, controlled, parallel-group clinical trial will be conducted.

Sampling

Recruitment and Informed Consent Process

Participants will be selected from the database of the Pain and Neuromodulation Laboratory, which contains records of 2,700 patients who participated in the 2023-0210 study — "Mapping factors associated with symptom worsening and quality of care in primary care for fibromyalgia: a Brazilian population-based study." These patients were recruited through large-scale media outreach. Among the questions assessed in the Mapping project, one asked about interest in participating in future studies — "Are you interested in participating in future studies of the Pain and Neuromodulation Laboratory?" (Response options: yes or no). Only participants who answered "yes" will be contacted.

A member of the research team will contact participants via WhatsApp to invite them to participate, following the message in Appendix 1. It will be communicated that, in order to join the study, participants must first read and accept the online Informed Consent Form and then complete an online form (Appendix 2).

If additional recruitment is needed to meet the required sample size, the study will be advertised in accordance with the HCPA's communication guidelines. Appendix 3 contains the text that will be used for recruitment advertising if necessary (Recruitment Cover Letter – standard template).

Inclusion Criteria:

Participants will be right-handed women aged 18 to 75, with reading and writing proficiency, diagnosed with fibromyalgia according to the American College of Rheumatology (ACR) criteria established between 2010 and 2016. They must report a pain score of four or higher on the Numeric Pain Scale (NPS) on most days over the past 30 days. To be included in the study, patients must maintain the doses of medications to which they are refractory, except for analgesics. Doses of other medications must remain unchanged during the study period.

Exclusion Criteria:

Women who live more than 200 km from Porto Alegre, are pregnant, have decompensated systemic diseases, chronic inflammatory rheumatologic diseases, untreated hypothyroidism, a current or ongoing history of cancer, history of alcohol or drug abuse in the past 6 months, or decompensated

psychiatric conditions with suicidal risk and a defined plan (based on a validated Suicide Risk Assessment Scale score) will be excluded.

Additional exclusion criteria include the use of duloxetine doses greater than 60 mg/day. Contraindications to TMS and tDCS include metal implants in the brain, implanted medical devices in the brain, cardiac pacemakers, cochlear implants, neurological pathologies, history of traumatic brain injury or neurosurgery.

Interventions

The study includes 28 sessions of transcranial direct current stimulation (tDCS), either active or sham, combined with 60 mg duloxetine or placebo. Participants will be randomized according to the flowchart in Figure 2. All participants will receive a video-based educational intervention on fibromyalgia (https://youtu.be/riH7VcgpbSk) and daily exercise instructions.

Transcranial Direct Current Stimulation (tDCS)

Participants will be randomized to receive 28 sessions of active anodal tDCS (2 mA) or sham, with the anode over the left M1 and the cathode over the right supraorbital area, for 20 minutes, combined with pain neuroscience education and physical exercises.

Sham protocol: the same montage as active tDCS will be used, with current applied for 30 seconds at the beginning, at 10 minutes, and at the end of the session. Sessions will be self-administered at home, daily for 4 weeks. Electrodes (35 cm2) will be placed using neoprene caps (sizes S to XL), adjusted according to head circumference.

Monitoring: the device records session time, duration, and adherence, interrupting the session if impedance exceeds 1 mA (5-second interval) or if current varies >10%. Developed in partnership with HCPA's Biomedical Engineering, the device is licensed by UFRGS/HCPA and registered with ANVISA (No. 80079190028). Instructions are provided in Appendices 5 and 6.

Pharmacological Intervention

Duloxetine (30 mg and 60 mg) will be purchased from a commercial pharmacy and fractionated by a compounding pharmacy, which will also prepare the placebo. Capsules will be transferred into standardized jars based on dosing schedule:

- **Jar 01 (white cap):** 7 capsules of 30 mg
- **Jar 02 (green cap):** 16 capsules of 60 mg
- **Jar 03 (green cap):** 42 capsules of 60 mg
- **Jar 04 (white cap):** 7 capsules of 30 mg

Placebo and duloxetine capsules will be identical in appearance. Kits will be labeled with CAEE number, participant ID (RedCap), pharmacist and PI names, and storage/use instructions. Kits will be stored at the HCPA Pharmacy Service under controlled conditions and dispensed during visits AV1 (Jars 1 and 2), AV2 (Jar 3), and AV3 (Jar 4).

Procurement and preparation will occur in batches of 80 participants (48 placebo, 32 duloxetine), until the full sample of 610 is reached (244 duloxetine, 366 placebo).

Pain Neuroscience Education (PNE)

PNE aims to reduce fear and avoidance behaviors and improve treatment adherence. Based on scientific evidence, it explains chronic pain as a disease rather than a symptom. A video (https://youtu.be/riH7VcgpbSk) will be shared via WhatsApp, covering fibromyalgia mechanisms, related symptoms, and the importance of a multimodal treatment approach (Watson et al., 2019; Caneiro et al., 2021).

Home Exercise Program

All participants will be instructed to perform 17 simple exercises daily after each tDCS session. A video tutorial (https://youtu.be/CwkBLSYMwDQ) and printed guide (Appendix 01) will be provided. The exercises are safe, low-intensity, and focus on mobility, flexibility, and function. During the 3-week run-in phase (duloxetine titration), participants will perform 5 repetitions. Once tDCS begins, this will increase to 10 repetitions, maintained throughout the protocol and recommended for 12 months of follow-up.

Randomization

Randomization will follow a 2:1:2 ratio, generated using sealedenvelope.com. Codes will be sealed in opaque envelopes, labeled with sequential numbers. An engineer, not involved in clinical care, will open the envelope and set up the tDCS device (active or sham). The study pharmacist, also blinded, will prepare the duloxetine/placebo kits.

Blinding

Researchers will receive pre-programmed tDCS devices without knowledge of the stimulation type. The compounding pharmacy will prepare and label medication kits according to the randomization schedule. Capsules of duloxetine and placebo will be visually identical.

The pharmacist and a non-blinded researcher (not involved in data collection) will manage allocation. Labels will include the CAEE number, RedCap participant ID, pharmacist and PI names, drug/placebo identification, and storage instructions.

To assess the success of blinding, participants will complete a structured questionnaire at the end of treatment to indicate their perception of the treatment received (active or placebo) and their confidence in that assessment.

Sample size estimation and statistical analysis plan

Sample size

According to Pigeot et al.'s (2013) recommendations, the sample size was estimated using a formula composed of three factors. For the first factor, we used a standard normal distribution instead of t-quantiles. Therefore, we used z-values corresponding to a one-tailed significance level of 0.025 (z = 1.96) and a statistical power of 80% (z = 1.282), which is valid for large sample sizes.

The second factor refers to Θ, which is 1 + f, where f is the retention fraction. For this calculation, we used f = -0.5, consistent with our hypothesis that (tDCS – placebo) would be no worse than at least 50% of (duloxetine – placebo) in patients with fibromyalgia. This margin was calculated based on clinical knowledge, the minimum clinically significant difference (MCID) (Mease et al., 2011), and recent evidence regarding treatment effects for fibromyalgia. These included the BPI global score (average pain intensity and pain interference) as the primary outcome (Chiarotto et al., 2019), and other key outcomes such as the Patient Global Impression of Improvement (PGI-I) (Geisser et al., 2010), fibromyalgia-related quality of life (FIQ), self-reported executive functioning (BDEFS), and pain modulation via descending inhibitory pathways (DPIS, by CPM test), all of which were designated as primary endpoints in the present study.

We used a conservative approach to define the non-inferiority margin, considering the smallest differences in any of our five predefined outcomes. Based on a recent meta-analysis (36 studies, n = 11,930) (Farag et al., 2022), the effect sizes on pain scores (intensity and interference) for FDA-approved fibromyalgia treatments (pregabalin, duloxetine, or milnacipran) are SMD, -0.30 (95% CI, −0.32 to −0.27), −0.33 (95% CI, −0.36 to −0.30), and −0.17 (95% CI, −0.20 to −0.15), respectively. These effect sizes represent, on average, a change between 10% and 20% in pain scores. On the other hand, according to our recent meta-analysis on the effects of tDCS for fibromyalgia (16 studies, n = 813) (Teixeira et al., 2023), the impact of M1 tDCS on pain scores (including the BPI global score) was SMD = -0.81 (95% CI, -1.19 to -0.43).

For PGI, FIQ; BDEFS, DPIS the effect sizes were not reported in the published meta-analysis, so we decided to use a conservative SMD of 0.5. These effect sizes denote, on average, a change between 14% and 25% in pain scores. Additionally, the MCID for fibromyalgia is a change of 2 points in the pain score (intensity or interference) on a scale from 0 to 10, representing at least a 20% change in pain scores. Given this evidence, we used a conservative margin of 50% of the medication effect, representing 10% of pain changes (half the MCID value). This conservative approach was used in our previous non-inferiority studies on tDCS (Brunoni et al., 2017).

The third factor requires determining ε and r. ε indicates that the standard deviation is associated with the mean difference of values. Based on the previous meta-analysis, it ranges from 1.2 to 3 (Farag et al., 2022; Teixeira et al., 2023). In this study, we considered 3 (the highest reported value) as a conservative approach, due to the greater variability in responses reported in fibromyalgia patients. Additionally, r is the ratio between the relative efficacy (i.e., minus the placebo) of tDCS and the active comparator. Considering the results of the recent meta-analysis, we calculated by dividing the lower bound of the pooled mean differences, M1 tDCS = -0.43/medication = -0.30; thus, r = 1.30. The calculation was then performed as follows:

Narm ≥ (1.96 + 1.282)^2 * (1+0.5^2 + (1-0.5)^2) * [(3)/(1.30-0.5)]^2 Narm ≥ 10.51 * 1.50 * 14.06 Narm ≥ 221.7

Considering a dropout rate of 10% (like our previous home-based tDCS studies) (Brietzke et al., 2019), we determined that a total sample of 244 per arm would be required to reject the null hypothesis (non-inferiority based on BPI global score changes). The sample size calculation assumed a

$$N_{arm} \geq (t_{1-\alpha,\ 3n-3} + t_{1-\beta,\ 3n-3})^2 * (1+\theta^2 + (1-\theta)^2) * [(\varepsilon)/(r-\theta)]^2$$

fixed-sample design; however, an interim analysis is planned using the O'Brien-Fleming approach, which preserves the overall one-sided type I error rate ($\alpha = 0.025$).

Finally, the allocation ratio will be 2:2:1, also based on Pigeot et al. (2003), which recommends 1:1:kp—i.e., a similar ratio for active treatments—while kp is determined according to the retention fraction (control), which we set at 0.5. Thus, this means that 244, 244, and 122 patients are allocated to (active M1 tDCS + placebo medication), (sham tDCS + duloxetine 60 mg), and (sham tDCS + placebo medication), respectively. Therefore, the estimated total sample size will be 610 participants.

The sample size was estimated based on the composite mean of pain interference domains, which reflects the multidimensional nature of the pain phenomenon and presents the highest variability among the clinical outcomes assessed. The estimation followed the model proposed by Pigeot et al. (2013), which considers three main components: (1) the expected effect size (delta), (2) the estimated variability (standard deviation of the multidimensional mean), and (3) the significance level adjusted by the Bonferroni correction, along with the desired statistical power. As the BPI global score presented the highest variability and lowest expected effect size among the five co-primary endpoints, the estimated sample ensures sufficient power (≥80%) for all endpoints after Bonferroni correction.

The adoption of multiple primary endpoints (five) is justified by the clinical complexity of fibromyalgia, for which treatment response cannot be adequately evaluated by a single indicator. A Bonferroni correction will be applied to control the family-wise error rate (FWER), with a global one-sided significance level of $\alpha = 0.025$, equally divided among the five primary endpoints. In accordance with good clinical trial practice guidelines, each test will only be considered statistically significant if $p < 0.005$, ensuring statistical rigor and preventing type I error inflation.

Interim Analysis and Early Termination Criteria

This study includes five primary endpoints, all based on non-inferiority hypotheses, selected for their clinical relevance and the need for a multidimensional assessment of treatment response. The endpoints were chosen to capture distinct core domains affected by chronic pain, particularly in fibromyalgia. These include functional interference, global impression of improvement, quality of life, executive functioning, and the integrity of descending pain modulation mechanisms. The adoption of multiple primary endpoints is justified by the complex and multifactorial nature of fibromyalgia, for

which treatment response cannot be adequately, evaluated using a single clinical indicator. The aim is to provide a comprehensive and clinically meaningful assessment of the intervention's effects.

A Bonferroni correction will be applied to control the family-wise error rate (FWER). The global one-sided significance level will be maintained at $\alpha = 0.025$, divided equally among the five primary endpoints. Accordingly, each non-inferiority test will only be considered statistically significant if the p- value is less than 0.005. This approach ensures statistical rigor and minimizes type I error inflation due to multiple confirmatory comparisons, in accordance with good clinical trial practice guidelines.

An interim analysis will be conducted after approximately 75% of the planned sample size has been accrued. The purpose is to evaluate futility, safety, and preliminary efficacy. This analysis will be carried out by an Independent Data Monitoring Committee (DMC), using a spending function based on the O'Brien-Fleming approach to preserve the global one-sided type I error rate of 0.025.

The DMC may recommend early termination of the trial based on the following criteria:

Efficacy (non-inferiority confirmed with high confidence): One or more primary endpoints (functional interference, global impression of improvement, quality of life, executive functioning) reach a p- value below the O'Brien-Fleming adjusted threshold for interim analysis (approximately $p < 0.001$), indicating robust statistical evidence of non-inferiority.

Futility (low probability of achieving the endpoint at final analysis): Based on interim data, the conditional power is less than 20% to demonstrate non-inferiority for all primary endpoints.

Safety: The occurrence of unexpected serious adverse events related to the intervention at a frequency higher than expected, with relevant clinical impact.

Critical discontinuation/adherence issues: a dropout rate greater than 40% in any group, potentially affecting the validity of the results, as judged by the DMC.

All DMC decisions will be formally recorded in meeting minutes and promptly communicated to both the study team and the ethics committee, following the procedures defined in the monitoring plan.

Statistical Analysis

Continuous and categorical variables were compared using Fisher's exact test, the chi-square test, and the t-test for independent samples. The Shapiro-Wilk normality test was applied to determine the normal distribution of continuous variables. A Linear Mixed-Effects Regression Models for Repeated Measure (LMM) assessed primary outcomes (pain severity and disability) with treatment, placebo response (responder vs. non-responder), time, and the treatment-by-time interaction as fixed

effects, and included a random intercept for patients to account for time differences. If appropriate, we then performed the Bonferroni's Test adjustment for post hoc multiple comparisons to identify differences between the groups at each time point and used a paired t test to assess the effects on each experimental group. The Generalized Linear Model (GLM) will be used to examine the treatment effect on the secondary outcomes including quality of life, HPT, PGI-I and the descending pain inhibitory system (DPIS). The treatment effect on primary and secondary outcomes might be adjusted for analgesic use. Analgesic use was included in the model to control a potential confounder affecting pain outcomes. This ensures that the observed effects of a-tDCS, duloxetine and s-tDCS are attributable to the interventions rather than variations in analgesic use, thereby enhancing the validity of the results. All analyses were adjusted for multiple comparisons using Bonferroni's Test. The modified ITT (m- ITT) analysis included those completing ≥50% of sessions, with missing data imputed using regression model coefficients. In the m-ITT, with an adjusted protocol, encompassing all patients who completed at least ten sessions. The choice of ten sessions for ITT was guided by most of the literature supporting clinical symptom improvement in chronic pain (McCoy. 2017, Caumo, 2024). This method is not as strict as classical ITT, but it suggests that A-tDCS could be useful in clinical settings with at least a minimum number of sessions. Specifically, we replaced missing values with imputed data derived from a regression model using observed data. The treatment group served as the predictor, and the outcome variable with missing values was imputed based on regression coefficients, indicating the relationship between the treatment group and the outcome. This imputation method was applied, for example, to ten patients who withdrew after ten tDCS sessions. Sensitivity analyses confirmed consistent LMM results with or without imputation.

The standardized difference means (SDM) was used to compute the effect size (ES) by dividing the mean difference between a-tDCS and s-tDCS by the pooled baseline standard deviation (SD). The ES was interpreted as small if lower than 0.20 to 0.49, moderate if between 0.50 and 0.79, and large if larger than 0.80 (Kazis ,1954). All statistical analyses were performed using two-tailed tests at the 5% significance level with SPSS, version 22.0 (SPSS, Chicago, IL).

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