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ORIGINAL RESEARCH

# Home-Based Transcranial Direct Current Stimulation for Menstrual Pain and Premenstrual Symptoms: A Randomized Controlled Trial

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**Background:** Primary dysmenorrhea (PD) and premenstrual syndrome (PMS) are common gynecological conditions that impair quality of life and productivity. Current treatments are mostly pharmacological and often come with side effects. Transcranial direct current stimulation (tDCS) has emerged as a promising non-invasive neuromodulation technique for pain and mood symptoms.

**Methods:** We conducted a double-blind, randomized, sham-controlled clinical trial to evaluate the effects of home-based, self-administered dual-target tDCS on menstrual pain, mood symptoms, functional capacity, and quality of life in women with PD and PMS. Forty participants were randomized to receive either active or sham tDCS over five days in a menstrual cycle. Primary and secondary outcomes were assessed at baseline, post-intervention, and one-cycle follow-up.

**Results:** No significant group-by-time interaction was found for menstrual pain (VAS) ($F(2,64)=1.09$, $p=0.34$). Menstrual pain decreased over time in both groups ($F(2,64)=7.93$, $p<0.001$). At follow-up (T2), mean VAS was 23.44 ± 29.31 in the active group vs 39.43 ± 31.10 in the sham group (Cohen's d = −0.53; 95% CI −37.2;5.2). Exploratory analyses suggested improvements in negative mood (Estimate = 3.50, SE = 1.41; 95% CI 0.74–6.26) and psychological quality of life (Estimate = 0.36, SE = 0.15; 95% CI 0.07–0.65). No serious adverse events were reported, and most adverse effects were mild.

**Conclusion:** Home-based self-administered tDCS may be a safe and potentially beneficial non-pharmacological approach for managing menstrual pain and emotional symptoms in women with PD and PMS. Larger trials with longer follow-up periods are warranted to confirm these preliminary findings and to better understand possible longer-term effects.

**Keywords:** transcranial direct current stimulation, neuromodulation, menstrual pain, home-based therapy

## Introduction

Primary dysmenorrhoea (PD), defined as menstrual pain without identifiable pelvic pathology, affects more than half of reproductive-age women and is frequently accompanied by symptoms such as fatigue, nausea, dizziness, and headache.[1,2] Symptoms usually begin soon after menarche and can be severe in up to 20% of affected individuals.[1] PD often co-occurs with premenstrual syndrome (PMS), a constellation of emotional, behavioural, and physical manifestations that significantly impair quality of life (QoL), academic performance, and work productivity, generating notable socioeconomic burden.[3,4]

Neuroimaging evidence indicates that women with PD exhibit structural and functional alterations in brain regions involved in nociception and emotion regulation, including the superior temporal gyrus, orbitofrontal cortex, postcentral gyrus, and dorsolateral prefrontal cortex (DLPFC).[1,5] These alterations resemble those observed in other chronic pain conditions and support the role of central sensitization mechanisms involving spinal, limbic, and cortical pathways.[6,7]

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Available treatments for PD and PMS are primarily pharmacological and often limited by contraindications and adverse effects, highlighting the need for non-pharmacological, accessible interventions.[8]

Transcranial direct current stimulation (tDCS) has emerged as a promising neuromodulation technique capable of modulating cortical excitability, reorganizing pain-related networks, and influencing cognitive–emotional processing. Analgesic effects have been consistently reported when stimulating the primary motor cortex (M1),[9–14] while DLPFC-targeted tDCS has shown beneficial effects on anxiety, depressive symptoms, and affective components of pain.[15–17] The DLPFC is particularly relevant to menstrual pain because of its role in top-down emotional regulation, modulation of viscerosensory processing, and attenuation of pain-related distress, mechanisms observed across chronic pain, fibromyalgia, endometriosis, and central sensitization models.[15–17]

Although early studies[9,18] have investigated tDCS in PD and PMS, these trials were small, clinic-based, and operationally demanding, relying exclusively on supervised stimulation sessions. Preliminary evidence suggests improvements in menstrual pain, emotional symptoms, and QoL; however, the limited sample sizes, absence of follow-up, and lack of real-world applicability reduce confidence in their generalizability.

At the same time, a rapidly growing body of evidence has demonstrated that home-based and wearable neuromodulation systems are feasible, safe, and capable of sustaining high adherence. Remote tDCS study[19] validated key components of home-use protocols, including device authentication, remote monitoring, automated compliance tracking, and patient safety procedures. These advances support the expansion of remote neuromodulation but have not yet been tested in the context of PD or PMS, leaving a critical gap in knowledge.

Furthermore, neuromodulation trials commonly exhibit strong placebo and sham responses, reinforcing the need for adequately controlled designs to distinguish true neuromodulatory effects from non-specific improvement.[20]

Given these gaps, this randomized, sham-controlled trial aimed to evaluate the feasibility, safety, adherence, and preliminary clinical effects of a home-based, self-administered dual-target tDCS protocol (M1 + DLPFC) for managing menstrual pain, premenstrual symptoms, functional capacity, and QoL in women with PD and PMS. We hypothesized that one menstrual cycle of stimulation would be associated with reduced pain severity and improved emotional and functional outcomes compared with sham.

# Methods

## Study Design

This double-blind, randomized, sham-controlled clinical trial was conducted at the Federal University of Rio Grande do Norte (UFRN), Brazil, from May 2023 to December 2024. The study complied with the Declaration of Helsinki and national regulations. Written informed consent was obtained, and ethical approval was granted by the UFRN ethics committee (approval no. 5.508.364). The trial is registered at the Brazilian Clinical Trials Registry (ReBEC; RBR-56w7h2p).

## Participants

Participants were enrolled through spontaneous inquiries made via social media platforms and the university's official channels. All assessments and follow-ups were conducted at the Physiotherapy Department at UFRN. The inclusion criteria were as follows: women aged 18 to 45 years; a medical diagnosis of PD based on the guidelines of The Society of Obstetricians and Gynaecologists of Canada,[21] a mean pain score of $\geq 40$ on the Visual Analogue Scale (VAS); recurrent pain for at least three consecutive menstrual cycles; at least a mild diagnosis of PMS according to the Premenstrual Symptoms Screening Tool (PSST); a regular menstrual cycle of 28 to 32 days; no history of brain surgery, intracranial metal implantation, or endometriosis; and no presence of chronic abdominal pain unrelated to the menstrual cycle, inflammatory bowel disease/irritable bowel syndrome, or a metal implant or pacemaker. Participants were excluded if they met any of the following criteria: presence of pelvic inflammatory disease or genitourinary infections during the study, pregnancy, breastfeeding, or dependence on alcohol, nicotine, or other drugs or participation in any concurrent non-pharmacological intervention during the study period. Participant flow through the study is shown in Figure 1.

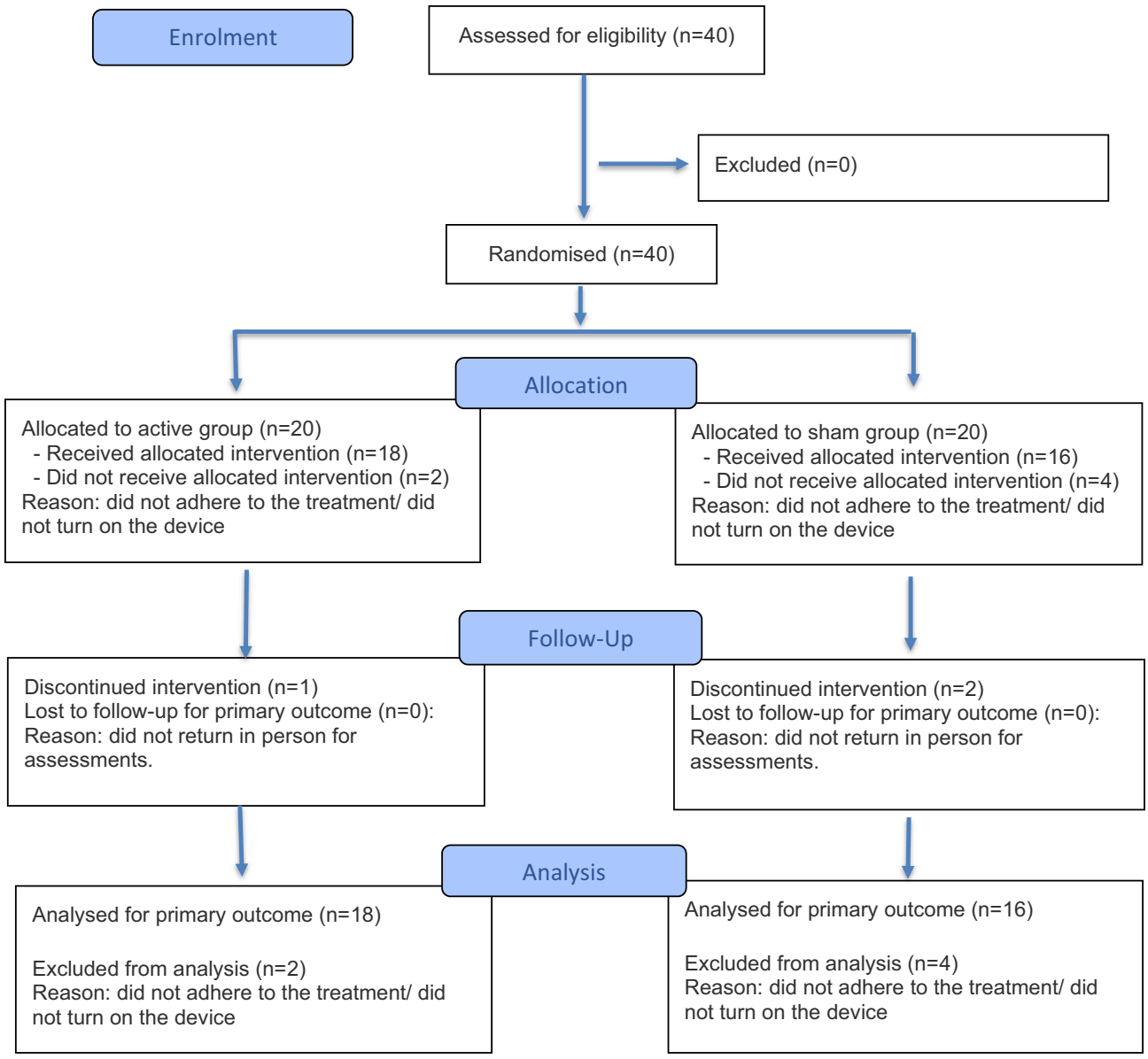


**Figure 1** CONSORT flow diagram showing participant recruitment, allocation, follow-up, and analysis.

## Randomization and Blinding

Participants were randomly assigned (1:1) to active (active-G) or sham (sham-G) groups using a computerized algorithm managed by a third party. Random codes were provided to researchers, and participants received codes in a blinded manner. Blinding was maintained until study completion. A trained physiotherapist evaluator, blinded and independent from other study phases, conducted all assessments. This double-blind design ensured both participants and evaluator were unaware of group allocation.

The sham tDCS protocol, validated in prior clinical trials, mirrored the active protocol (montage and session duration) and delivered a 30-second ramp-up to 2 mA followed by a 30-second ramp-down and taper to 0.01 mA for the remainder of the session. This procedure is designed to reproduce the initial tingling/itching sensations commonly perceived during active stimulation while minimizing ongoing stimulation. This ramp-up/ramp-down pattern was pre-programmed in the device's internal software, meaning that neither participants nor the researcher supervising the procedures could distinguish


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between active and sham modes during the session. Device logs containing stimulation mode were not accessible to participants or blinded study personnel during the trial and were reviewed only after study completion/unblinding.

## Sample Size

The sample size was based on prior research[14] using a numerical pain scale for primary outcome assessment in women with PD. Calculations were performed with G*Power (v3.1.9.4, Düsseldorf, Germany) using an F-test for repeated measures ANOVA with intra- and inter-group interactions. Assuming $\alpha = 0.05$, power = 0.80, 2 groups (active-G and sham-G), sphericity = 1, and effect size = 0.2, the required sample was 36 participants (18 per group). To account for potential attrition, 4 additional participants were recruited, totaling 40 (20 per group), ensuring adequate power to detect group differences despite dropouts.

## Intervention

The clinical trial protocol is organized into four menstrual cycles (Figure 2). In the first month, menstrual cycles were tracked using individual diaries recording menstruation onset, next cycle estimates, and PD symptoms (pain, fatigue, mood swings). Baseline assessment (T0) occurred on day one of the second cycle, alongside tDCS training by a physical therapist. Participants began tDCS five days before the next menstruation. Post-intervention assessment (T1) was on the first day of the third cycle, with a follow-up (T2) one cycle later.

The tDCS protocol followed established guidelines[22,23] using a wearable Nettle device (Samphire Neuroscience) controlled via Bluetooth app. Four medical-grade silicone electrodes covered with saline-soaked sponges were placed bilaterally over F3 (anode), F4 (cathode), and motor cortex sites C3 (anode) and C4 (cathode), per the 10–20 EEG system. A 2 mA current was applied daily for 20 minutes over five days. Importantly, all stimulation sessions were completed at home and self-administered without real-time supervision, demonstrating the practical implementation of a drug-free, non-invasive neuromodulation approach in this trial.

Four wet sponge electrodes were used (one per contact site), with an individual electrode contact area of $10.5 \pm 0.5$ cm$^2$. The skin–electrode interface consisted of single-use sponges made of natural cellulose extracted from wood pulp without non-biocompatible additives, hydrated immediately prior to application using $0.9 \pm 0.1\%$ NaCl saline solution. Prior to stimulation, the device performed an impedance/contact-quality check; sessions proceeded only when measured resistance was within the

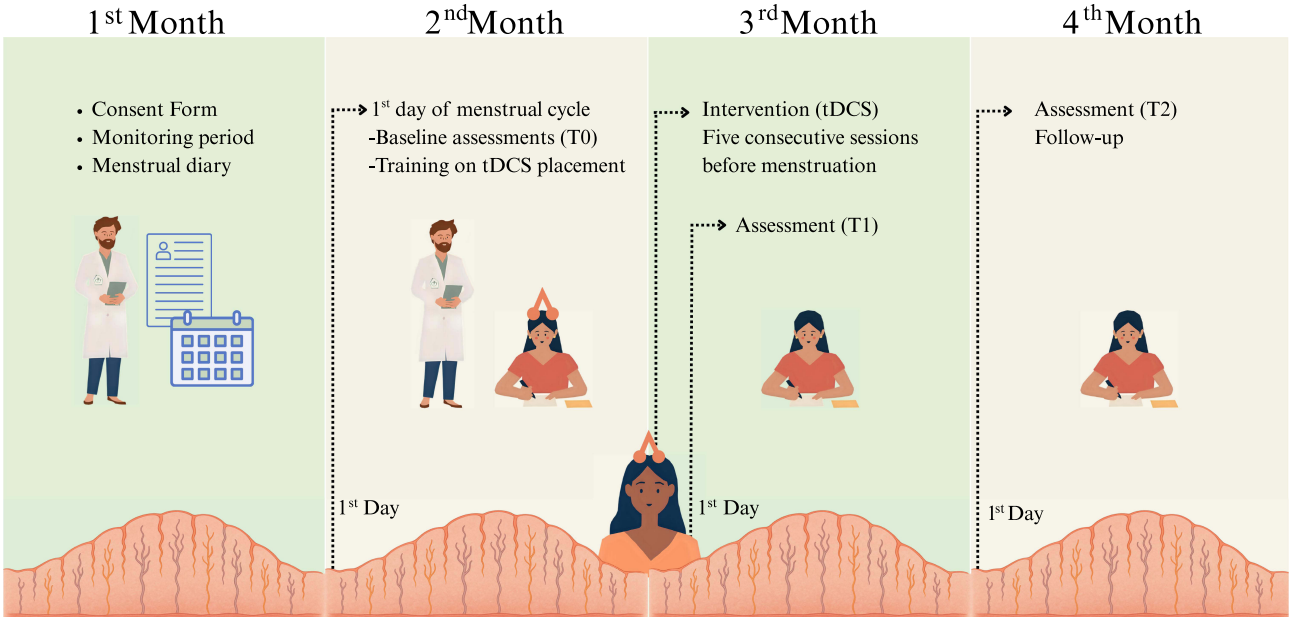


**Figure 2** Schematic representation of the clinical trial protocol and timeline.

pre-specified range (1–25 kΩ). Polarity was fixed by the device as a left-anodal configuration: when worn, the left-side electrodes delivered anodal (+) stimulation and the right-side electrodes delivered cathodal (−) stimulation.

In Active-G, current ramped up to 2 mA over 30 seconds, held for 20 minutes, then ramped down in 30 seconds. Sham-G followed the same ramp-up but tapered to 0.01 mA for 20 minutes to mimic sensations and maintain blinding. This method is standard in the field and considered to be the state of the art for tDCS research.[21] Participants applied tDCS at consistent times while continuing usual activities.

Participant training was conducted in person at the time of the baseline assessment (T0) and was delivered by a properly trained physiotherapist. During this session, participants received detailed instructions on device handling, correct electrode placement, safety procedures, and how to initiate and conduct stimulation sessions using the smartphone-controlled application. The training included practical, hands-on explanations, and was further supported by the application itself, which provides images and instructional videos demonstrating correct application. This procedure was implemented to ensure correct execution of the therapy during the self-administration phase and to minimize risks and protocol deviations.

Adverse events were recorded via diaries and a post-intervention questionnaire detailing any events and severity.

## Adherence and Dose Fidelity

Stimulation adherence was assessed using (i) participant diaries and (ii) device-generated session logs capturing time-stamped session completion and the delivered stimulation program (active vs sham waveform). These records were used to quantify the number of completed sessions and to identify protocol deviations/incorrect device use.

## Outcomes

The primary outcome of the study was menstrual pain, assessed using the VAS. The VAS represents participants' perception of menstrual pain severity on a 0–100 mm scale, where 0 indicates no pain and 100 represents unbearable pain. Commonly used severity thresholds are as follows: scores between 10 and 30 indicate mild pain, 40 to 70 signify moderate pain, and 80 to 100 denote severe pain.[24]

Secondary outcomes included mood symptoms assessed using the Positive and Negative Affect Scale (PANAS), Hamilton Anxiety Scale (HAS), Beck Depression Inventory (BDI), and PSST. Functional capacity was evaluated through the Six-Minute Walk Test (6MWT), sit-to-stand test, Timed Up and Go test (TUG), and the QoL was assessed using the World Health Organization Quality of Life Questionnaire – brief version (WHOQOL-BREF).

PANAS, a widely recognised and extensively used self-report tool, is aimed at assessing two distinct yet related states of mood: positive affect (PA) and negative affect (NA).[25] Positive affect corresponds to the pleasurable interaction with the surroundings, whereas negative affect encompasses a broad spectrum of distress, consolidating diverse negative emotional states such as anger, guilt, or anxiety. The questionnaire consists of 20 items which are rated on the 5-point Likert scale, indicating the intensity of each emotion experienced with 1 being (not at all) to 5 (extremely).

Anxiety was assessed using the HAS,[22,26] a 14-item clinician-rated instrument, with each item scored from 0 to 4, yielding a total score ranging from 0 to 56. Higher scores reflect greater anxiety symptoms. Depressive symptoms were evaluated using the BDI,[27] a 21-item self-report questionnaire that assesses cognitive and emotional aspects of depression. Each item is scored from 0 to 3, with total scores ranging from 0 to 63; higher scores indicate more pronounced depression symptoms.

The PSST[28] was used to assess symptoms of PMS. It includes 14 items on PMS-related symptoms and 5 items on their impact on daily activities and relationships. Responses are rated on a Likert scale from 0 (absent) to 4 (severe).

The 6MWT[29] was used to assess aerobic capacity, reflecting daily activity demands. It measures the maximum distance an individual can walk in six minutes at a self-paced speed. The TUG[30] was conducted to assess lower limb muscle strength, including power, speed, agility, and dynamic balance. Participants were instructed to rise from a seated position upon the examiner's signal, walk a distance of three meters in a comfortable space, turn around, walk back to the chair, and sit down again. In addition, the 30-Second Chair Stand Test[31] was conducted to assess lower limb strength. Participants were instructed to sit in the middle of a chair with a 43 cm seat height and backrest, keeping their feet flat on the floor and their arms crossed over their chest. Upon the command to "start," they were required to fully stand up from

the chair and return to a seated position as many times as possible within 30 seconds. The score was determined by the total number of complete stands performed within the allotted time.

The WHOQOL-BREF is a 26-item instrument designed to assess QoL across four domains: physical, psychological, social relationships, and environment. These encompass aspects such as pain, energy, sleep, mobility, emotional well-being, cognition, self-esteem, social support, sexual activity, safety, finances, healthcare access, and transportation. Higher scores reflect better QoL.[32]

## Statistical Analyses

All analyses were performed using R statistical software (R Core Team 2014. R: A Language and Environment for Statistical Computing, version v4.3.2)., with 2-sided significance tests set at the 5% significance level. Missing data was treated by intention-to-treat analysis. At baseline, clinical and sociodemographic characteristics were compared using t-tests or Mann–Whitney tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. The normality of the distributions and homogeneity of variance were assessed using the Shapiro–Wilk and Levene tests, respectively.

The effects of tDCS intervention on the primary (VAS) and secondary variables were assessed using mixed, repeated-measures analysis of variance (ANOVA). The dependent variables were the scores for each outcome. At the same time, the fixed independent predictors included: Time (T0, T1 and T2), group (active and sham) and time x group interaction. Post-hoc analyses were conducted using Bonferroni correction when statistically significant effects were found. Results are presented as mean differences (MD) with 95% confidence intervals and effect sizes (Cohen's *d*), when applicable.

The association between groups, time points, and PSST symptoms, as well as anxiety (absent or mild as negative and moderate or severe as positive), was assessed using the Cochran-Mantel-Haenszel test. The results were interpreted based on the common odds ratio, with 95% confidence intervals, and statistical significance was determined using a chi-square test. The significance level of $p < 0.05$ was set.

# Results

Sample characteristics are described in Table 1. Race, ethnicity and income distributions were comparable between groups. Hair description was diverse in both groups, supporting fit of the wearable headband across common hair types. Hair type was recorded because it can influence scalp-electrode contact and comfort during unsupervised use.

**Table 1** Sample Characteristics at Baseline

| Variable | Sham-G (N=16) | Active-G (N=18) | p-value |
|---|---|---|---|
| Age (years) | 23.9±3.28 | 24.8±3.02 | 0.41 |
| Age of menarche (years) | 12.1±1.48 | 11.91.02 | 0.70 |
| BMI (Kg/cm$^2$) | 23.5±3.50 | 24.1±4.84 | 0.71 |
| Income | | | 0.19 |
| Up to 1 MW | 6 (37.5%) | 2 (11.1±%) | |
| 2 - 3 MW | 6 (37.5%) | 11 (61.1%) | |
| More than 4 MW | 3 (18.8%) | 5 (27.8%) | |
| Not responded | 1 (6.25%) | 0 (0.00%) | |
| Education | | | 0.85 |
| Elementary | 1 (6.25%) | 0 (0.00%) | |
| Secondary | 5 (31.2%) | 5 (27.8%) | |
| College | 10 (62.5%) | 13 (72.2%) | |
| Marital Status | | | 1.00 |
| Single | 14 (87.5%) | 15 (83.3%) | |
| Married | 2 (12.5%) | 3 (16.7%) | |

(*Continued*)

**Table 1** (Continued).

| Variable | Sham-G (N=16) | Active-G (N=18) | p-value |
|---|---|---|---|
| Race | | | 0.72 |
| Caucasian | 7 (43.8%) | 11 (61.1%) | |
| Asian | 1 (6.25%) | 1 (5.56%) | |
| Mixed | 6 (37.5%) | 6 (33.3%) | |
| Black | 1 (6.25%) | 0 (0.00%) | |
| Not responded | 1 (6.25%) | 0 (0.00%) | |
| Hair Description | | | 0.46 |
| Straight | 4 (25.0%) | 7 (38.9%) | |
| Wavy | 6 (37.5%) | 8 (44.4%) | |
| Curly | 6 (37.5%) | 3 (16.7%) | |

**Notes**: Sample characteristics at baseline. Data are presented as mean and standard deviation (SD) for continuous variables and counts and frequency (%) for categorical variables. P-values are based on t-tests for continuous variables and chi-square tests for categorical variables.
**Abbreviations**: BMI, body mass index; MW, Brazilian minimum wage; SD, standard deviation.

No significant differences were observed between groups in any of the demographic characteristics. The mean age was 24.8 ± 3.28 for the active-G and 23.9 ± 3.28 for the sham-G (Table 1). Age of menarche was 11.9 ± 1.02 for the active-G, and 12.1 ± 1.48 for the sham-G. Most of the participants had a college education level with 72.2% in the active-G, and 62.5% in the sham-G (Table 1).

Detailed mean values, standard deviations, mean differences (MD), 95% confidence intervals (CI), and effect sizes (Cohen's d) for all primary and secondary outcomes across time points are provided in Supplementary Tables 1 and 2. The results illustrate the clinically relevant reduction in menstrual pain in the active-G and shows that no significant group-by-time interactions were observed for most functional and quality-of-life measures.

## Primary Outcome

Significant reduction in menstrual pain was observed only in the active-G between baseline and T2 (Estimate: 26.22, SE: 6.78, p = 0.001) (Figure 3). Both groups showed clinically relevant improvements at follow-up, with the sham-G exhibiting a 24.43% decrease and the active-G a 52.79% reduction in VAS scores. However, no significant effect of group (F = 1.07, p = 0.30) or group-by-time interaction (F = 1.09, p = 0.34) was found.

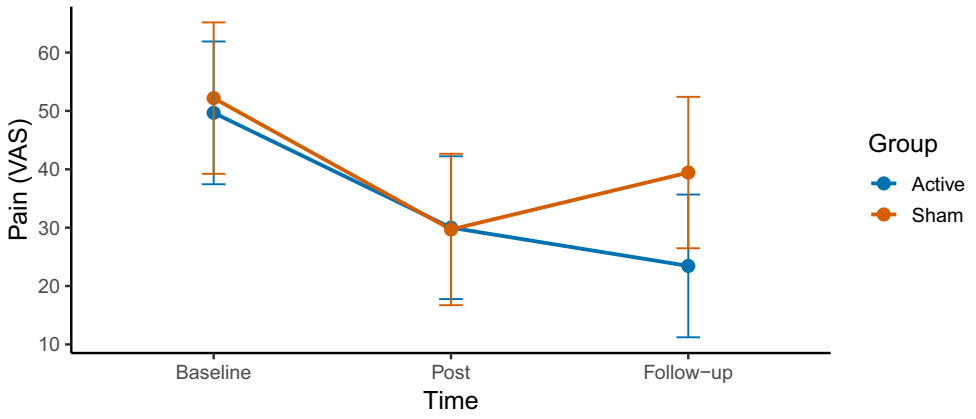


**Figure 3** Results on menstrual pain reduction using Visual Analogue Scale (VAS) between groups across time.


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## Secondary Outcomes

The secondary outcomes are presented in four subsections (premenstrual and emotional symptoms, functional aspects, quality of life and adverse events and adherence).

### Premenstrual and Emotional Symptoms

For symptoms assessed using the PSST, the estimated common odds ratio was 0.44 (95% CI: 0.17 to 1.17). However, no significant differences were observed between groups ($\chi^2 = 1.96$, $p = 0.16$).

The evaluation of positive affect revealed no significant differences for group ($F = 2.33$, $p = 0.14$, $\eta^2 = 0.052$), time ($F = 0.66$, $p = 0.52$, $\eta^2 = 0.005$), or the group-by-time interaction ($F = 0.52$, $p = 0.60$, $\eta^2 = 0.004$). The evaluation of negative affect showed a significant effect of time ($F = 4.84$, $p = 0.012$, $\eta^2 = 0.029$). In the active-G, a significant difference was observed between baseline and post-intervention (Estimate: 3.50, SE: 1.41, $p = 0.04$), as well as between baseline and follow-up (Estimate: 3.17, SE: 1.24, $p = 0.039$). However, no significant differences were found for group ($F = 0.03$, $p = 0.86$, $\eta^2 = 0.001$) or the group-by-time interaction ($F = 0.45$, $p = 0.63$, $\eta^2 = 0.003$).

A significant effect of time was observed for the Hamilton Anxiety Score ($F = 3.89$, $p = 0.03$, $\eta^2 = 0.03$), with a significant difference in the active-G between the baseline and post-intervention assessments (Estimate: 4.39, SE: 1.84, $p = 0.05$). No significant group-by-time interaction ($F = 0.74$, $p = 0.48$, $\eta^2 = 0.005$) or between-group difference ($F = 0.15$, $p = 0.70$, $\eta^2 = 0.004$) was observed. For the depression score (BDI), no significant differences were observed between groups ($F = 0.29$, $p = 0.60$, $\eta^2 = 0.007$), over time ($F = 0.81$, $p = 0.42$, $\eta^2 = 0.70$), or in the group-by-time interaction ($F = 0.26$, $p = 0.70$, $\eta^2 = 0.001$). In the assessment of anxiety levels (no anxiety or mild vs moderate or severe) using the HAS, the estimated common odds ratio was 0.85 (95% CI: 0.39–1.87), with no significant difference between the groups ($\chi^2 = 0.039$, $p = 0.843$).

### Functional Aspects

A significant effect of time was observed for the 6MWT ($F = 4.43$, $p = 0.02$, $\eta^2 = 0.053$). In the active-G, a significant main effect of time was found between baseline and post-intervention (Estimate: −52.59, SE: 20.7, $p = 0.04$) and between post-intervention and follow-up (Estimate: 61.82, SE: 19.8, $p = 0.01$). No significant group-by-time interaction ($F = 0.81$, $p = 0.44$, $\eta^2 = 0.010$) or between-group difference ($F = 0.41$, $p = 0.53$, $\eta^2 = 0.008$) was observed.

In the functional assessment, no significant differences were observed in the TUG between groups ($F = 0.06$, $p = 0.81$, $\eta^2 = 0.001$) or over time ($F = 0.28$, $p = 0.72$, $\eta^2 = 0.002$). The group-by-time interaction was also not significant ($F = 0.35$, $p = 0.67$, $\eta^2 = 0.004$). In the 6MWT, a significant main effect of time was observed ($p = 0.013$, $\eta^2 = 0.127$). Post-hoc analyses revealed significant improvements from baseline to post-intervention ($p = 0.046$) and from post-intervention to follow-up ($p = 0.016$) in the active-G, while no significant changes were observed in the sham-G. No significant effect of group ($p = 0.525$) or group-by-time interaction ($p = 0.451$) was found. In the Chair Stand Test, no significant differences were found between groups ($F = 0.73$, $p = 0.40$, $\eta^2 = 0.02$), over time ($F = 0.04$, $p = 0.95$, $\eta^2 = 0.0002$), or for the group-by-time interaction ($F = 0.29$, $p = 0.73$, $\eta^2 = 0.002$).

### Quality of Life

None of the quality-of-life dimensions showed a significant group-by-time interaction: physical domain ($F = 0.01$, $p = 0.96$, $\eta^2 = 0.0001$), social relations domain ($F = 0.02$, $p = 0.97$, $\eta^2 = 0.0001$), environment domain ($F = 0.09$, $p = 0.89$, $\eta^2 = 0.0007$), and psychological domain ($F = 0.33$, $p = 0.70$, $\eta^2 = 0.003$). However, a significant between-group difference was observed in the psychological domain during the post-intervention assessment ($F = 5.99$, $p = 0.02$, $\eta^2 = 0.12$; Estimate: 0.36, SE: 0.15, $p = 0.02$), whereas no significant differences were found in the other domains ($p > 0.05$). No significant differences were observed over time for the physical ($F = 0.85$, $p = 0.40$, $\eta^2 = 0.009$), psychological ($F = 0.97$, $p = 0.38$, $\eta^2 = 0.008$), social relations ($F = 2.00$, $p = 0.15$, $\eta^2 = 0.02$), or environment ($F = 1.65$, $p = 0.20$, $\eta^2 = 0.01$) domains. Further details, including F-values, effect sizes, mean squared errors, and p-values, are provided in the supplementary material.

**Table 2** Instances of Adverse Events Recorded by Participants are Summarised as Frequency. Others Encompass Dizziness and Nausea

| Symptom | Sham-G (N=16) | Active-G (N=18) |
|---|---|---|
| Headache | 1 (6.25) | 2 (11.12) |
| Tingling | 4 (25.00) | 6 (33.34) |
| Skin Irritation/erythema | 0 (0) | 0 (0) |
| Itching | 5 (31.25) | 4 (22.23) |
| Burning sensation | 2 (12.50) | 1 (5.56) |
| Other | 2 (12.50) | 1 (5.56) |

**Note**: Data are presented as count and frequency (%).

### Adverse Events and Adherence

Table 2 summarizes the adverse effects associated with device use. The severity profile shows a predominance of mild side effects (headache, tingling, itching, burning sensation, dizziness, and nausea), with only one participant reporting a moderate symptom (tingling). Interestingly, four participants in the sham-G (25.00%) and six participants in the active-G (33.34%) reported tingling. Importantly, no serious adverse events were observed, and both active and sham stimulation were generally well tolerated. Adherence to the intervention was high in both groups, with 18 participants in the active-G and 16 in the sham-G completing the protocol as planned.

## Discussion

This study demonstrated a clinically relevant reduction in menstrual-related pain following five sessions of tDCS in women affected by PD and PMS. Pain intensity decreased over time in both intervention groups. Although the active tDCS group showed a greater magnitude of pain reduction from baseline to post-intervention and during one subsequent menstrual cycle compared with the sham group, the absence of significant between-group interaction effects indicates that these findings should be interpreted cautiously and considered exploratory rather than evidence of clinical efficacy. Similar time-dependent reductions in pain have been reported in previous tDCS studies in women with PD and CPP, supporting the plausibility of neuromodulation as a potential adjunctive approach.[7,9,18,33]

A reduction in PMS symptoms was observed within the active group; however, because no significant interaction effects were detected, these improvements may reflect nonspecific factors rather than a treatment-specific effect. The magnitude of symptom change observed in both groups suggests a potential contribution of placebo response, expectancy effects, regression to the mean, or the natural variability of menstrual symptoms, which are common in short-term interventions targeting cyclical pain conditions.[34,35] No significant between-group differences were observed for depressive symptoms or quality of life, indicating that five sessions of tDCS may be insufficient to produce measurable superiority over sham stimulation for mood-related outcomes in this population.

In home-based neuromodulation, the treatment context itself may play a relevant role in shaping symptom perception, particularly for subjective outcomes such as pain and emotional distress. Increased comfort, autonomy, and a sense of control associated with self-administered interventions have been shown to enhance engagement and expectancy-related responses, which may partially explain symptom improvement observed in both active and sham groups. Previous studies of remotely supervised and home-based tDCS have highlighted that these contextual factors can positively influence participant experience without necessarily reflecting device-specific neurophysiological effects.[19,36]

Neuroimaging studies have demonstrated anatomical and functional connections between the DLPFC and pain-related regions such as the insula and thalamus, which are involved in sensory integration and pain modulation.[37,38] These networks are known to play a role in pain perception.[12,38,39] However, given the lack of significant between-group effects in the present study, mechanistic or neuroplastic interpretations should be regarded as hypothetical and framed as directions for future research rather than confirmed explanatory mechanisms. Although the five-session protocol aligns with commonly used parameters in neuromodulation studies, protocols for chronic pain often range from 5 to 20

sessions, and longer interventions may be required to detect robust between-group differences.40 Follow-up durations across studies vary widely, reflecting ongoing uncertainty regarding the optimal dosing and durability of tDCS effects.[40]

Although no previous study has extensively evaluated all symptoms of CPP and PMS simultaneously, there is evidence that tDCS may improve both emotional and physical symptoms.[9,18] Previous research has identified time-dependent gains in functional capacity (6MWT) in active group, suggesting benefits in daily life and social functioning. However, our study did not show significant improvements in the 6MWT or the Chair Stand Test when comparing the two groups. Future studies should include individuals with moderate to severe pain to better evaluate tDCS effects on physical function.

The results of this study indicated a reduction in scores in the psychological domain of quality of life in women with PD following the tDCS intervention. Previous studies suggest that pain and emotional disturbances contribute to functional impairment during the premenstrual and menstrual phases, as symptoms such as irritability, sadness, depressive mood, and emotional lability are known to interfere with daily activities.[1]

Apart from the effects observed in the primary and secondary outcomes, it is noteworthy that active tDCS demonstrated a favorable safety and tolerability profile. Most reported adverse events were mild and transient, including tingling, itching, and occasional headache. These findings are consistent with the existing tDCS literature and support the acceptability of this intervention in this population. Importantly, the low incidence and mild nature of adverse events may have contributed to good treatment adherence, which is a critical factor in home-based neuromodulation protocols.[19] While no direct comparison with standard care was performed in this study, these results suggest that home-based tDCS may represent a well-tolerated non-pharmacological option warranting further investigation in future trials.

Several limitations should be considered when interpreting the findings of this study. First, the homogeneity of our study population, primarily consisting of participants diagnosed with mild PMS and PD, may limit the generalizability of our findings. These participants may not fully represent the broader population of individuals with menstrual pain, especially given the lack of standardization in the definitions of PD and its associated symptoms. This lack of diversity could impact on the ecological validity of our results, as the observed effects may not be applicable to more diverse populations with comorbid conditions. Additionally, the inclusion of two distinct populations (PMS and PD) without stratified analyses may introduce heterogeneity that could obscure condition-specific effects. Although both groups share overlapping symptom profiles, the modest sample size limited our ability to perform adequately powered subgroup analyses. Future studies should consider stratified or diagnosis-specific approaches with larger samples.

Another limitation is the relatively short duration of our follow-up period (one menstrual cycle post-intervention). While we observed significant reductions in menstrual pain and emotional aspects (negative affect, anxiety, and psychological domain) immediately post-intervention and during short-term follow-up, the long-term effects of neuroplasticity induced by tDCS remain uncertain. This highlights the need for studies with longer follow-up periods to determine whether the improvements observed are sustained over time. Additionally, it is important to analyze the effects of concomitant therapies to fully ascertain whether the observed decrease in menstrual pain, emotional aspects, and improved functional capacity was solely attributed to the intervention. We did not formally assess blinding success (eg, post-intervention allocation guess and confidence ratings), which limits our ability to quantify the effectiveness of masking.

Lastly, a key limitation is that the trial was designed and powered for the primary endpoint (pain reduction), and therefore secondary outcomes such as functional capacity and QoL were underpowered. Larger trials, enrolling at least 100 participants per arm, will be necessary to determine whether the exploratory trends observed here represent reliable effects.

## Conclusion

This randomized controlled trial provides preliminary insights into the use of home-based dual-target tDCS in women with PD and PMS. Reductions in menstrual pain and emotional symptoms were observed over time, particularly in the active stimulation group; however, these findings should be interpreted as exploratory. Home-based tDCS was well tolerated, with good adherence and mostly mild adverse events. As one of the first studies to evaluate a dual-target protocol delivered at home for menstrual-related symptoms, these findings highlight the need for larger studies with expanded sample sizes and alternative stimulation protocols to further elucidate the efficacy of tDCS in this population.

## Data Sharing Statement

The authors declare that the data regarding this manuscript can be accessed as per the request of any interested body and can be accessed by emailing to the corresponding author.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Emilė Radytė, Alexander Anthony Cook and Ervinas Bernatavičius are employees and own shares in Samphire Neuroscience Ltd. Samphire-affiliated authors did not participate in participant recruitment, data collection, outcome assessment, or statistical analysis. In addition, Ervinas Bernatavičius has a patent WO2024/213900 issued to Samphire Neuroscience Ltd. Other authors declare no conflicts of interest in this work.

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