Title

Home-based transcranial direct current stimulation treatment for major depressive disorder: a fully remote phase 2 randomized sham-controlled trial

Authors

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Abstract

Transcranial direct current stimulation (tDCS) has been proposed as novel treatment in major depressive disorder (MDD). Present study is fully remote, multisite, double-blind, placebo-controlled, randomized superiority trial of 10-week home-based tDCS in MDD. Participants were 18 years or older, with MDD in current depressive episode of at least moderate severity as measured by Hamilton Depression Rating Scale (HDRS) (mean 19.07±2.73). 174 participants (120 women) were randomised to active (n=87) (mean age 37.09±11.14 years) or sham (n=87) (mean age 38.32±10.92 years) treatment. tDCS sessions were 5 sessions per week for 3 weeks then 3 sessions per week for 7 weeks in 10-week trial, followed by 10-week open label phase. Each session was 30 minutes, anode over left dorsolateral prefrontal cortex (DLPFC) and cathode over right DLPFC, active tDCS 2-mA, and sham tDCS 0-mA with brief ramp up and down to mimic active stimulation. In primary outcome, depressive symptoms showed significant improvement as measured by HDRS rating: active 9.41±6.25 point improvement (10-week mean 9.58±6.02) and sham 7.14±6.10 point improvement (10-week mean 11.66±5.96) (95% CI 0.51, 4.01, *P* = 0.012). There were no differences in discontinuation rates. In summary, 10-week home-based tDCS treatment with remote-supervision in MDD showed high efficacy, acceptability and safety.

ClinicalTrials.gov registration: NCT05202119

Introduction

Major depressive disorder (MDD) is common, is a leading cause of disability worldwide, and the most significant precursor in suicide.[1] MDD is characterized by a prolonged low mood or an inability to experience usual feelings of pleasure which is accompanied by disturbances in sleep, appetite, psychomotor functioning and energy levels as well as in cognitive functioning. First-line treatments are antidepressant medications and psychological therapies. However, over a third of MDD individuals do not achieve a full clinical remission despite full treatment trials.[2,3]

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation that applies a weak (0.5-2 mA) direct current via scalp electrodes.[4] Anodal stimulation shifts membrane potentials towards depolarization and increases cortical excitability, whilst cathodal stimulation tends to shift membrane potentials towards hyperpolarization, decreasing potential cell firing and inhibiting cortical excitability.[5] tDCS modulates resting state potential, thereby modulating cortical tissue excitability, rather than directly triggering an action potential which is in contrast to repetitive transcranial magnetic stimulation (rTMS).[6] Neurophysiological effects typically persist beyond the immediate stimulation period.[7] Anodal tDCS can enhance cortical excitability, which is dependent on N-methyl-D-aspartate (NMDA) receptor and calcium channel activity, demonstrating a sustained increase in synaptic transmission that is long-term potentiation-like, while cathodal tDCS decreases excitability and facilitates long-term depression-like changes.[8] Neural recordings demonstrate measurables effects on cortical electric fields.[9] Neurophysiological measures reveal network-level modulatory effects, in which anodal tDCS applied to left dorsolateral prefrontal cortex is associated with significant changes in connectivity in default mode network, self-referential network and frontal-parietal networks in comparison with sham tDCS,[10] and can extend into deeper limbic brain regions, including amygdala,[11] which are key regions in MDD neurocircuitry and reflect potential mechanisms of effect.[4]

tDCS is applied through a flexible cap or band that is worn over the forehead. The anode electrode is typically placed over the left dorsolateral prefrontal cortex (DLPFC) and cathode over the right DLPFC, suborbital or frontotemporal region.[6] In an individual patient data meta-analysis, active tDCS relative to sham tDCS was associated with a significantly greater rate of clinical response (30.9% vs. 18.9%; number needed to treat (NNT) 9) and remission (19.9% vs. 11.7%; NNT 13) from 572 MDD participants in 9 studies.[12] tDCS is safe and well tolerated with no significant differences in attrition rate and adverse events between active and sham stimulation groups, offering a potential novel first-line treatment for MDD.[4] However, a course

of tDCS treatment involves daily sessions for several weeks and most studies had been conducted in a research clinic requiring daily visits.[6,12]

As it is portable and safe, tDCS could be provided at home.[4] We developed a protocol that provides tDCS at home with real-time remote supervision by videoconference.[13] In MDD, we found significant improvements in depressive symptoms, high acceptability and feasibility,[13] as similarly observed in additional open-label trials.[14,15] However, all participants had the active tDCS device as well as real-time visits by videoconference in our protocol, which were associated with meaningful experiences of support and containment.[16] There have been three randomised controlled trials of home-based tDCS in MDD[17–19], but none were fully remote because all had included in person study appointments, two trials were likely underpowered due to small sample sizes (n=11[18] and n=58[19]), and all were limited to 6-week trial duration, finding no significant effects of active relative to sham tDCS[17–19]. However, Nikolin et al.[20] recent meta-analysis reports that active tDCS effects continue to increase up to 10 weeks as compared to sham stimulation.

In the present study, we sought to investigate clinical efficacy and safety of a 10-week course of home-based tDCS treatment for MDD in a large, double-blind, randomized superiority trial conducted in UK and USA. All participants had MDD determined by a structured diagnostic interview and all were in a current depressive episode of at least moderate severity. Participants could be taking stable antidepressant medication for at least 6 weeks, or in psychotherapy for at least 6 weeks, or treatment-free, reflecting the range of forms of MDD from first episode and recurrent MDD to treatment resistant depression. All study visits were remote and we were able to monitor participant tDCS use in real-time. The primary objective was to investigate clinical efficacy at the 10-week end of treatment course between active and sham tDCS treatment arms.

Results

Participant Data

Recruitment was from May 12, 2022 to March 10, 2023 (ClinicalTrials.gov NCT05202119). From 2,234 individuals who had an initial telephone screen, 368 individuals provided written informed consent and had an assessment by Microsoft Teams videoconference. In total, 174 MDD participants (120 women (69%)) were enrolled, mean age 37.63 years (standard deviation (SD) 11.00), 145 (72.4%) white ethnicity. All had MDD diagnosis based on DSM-5 criteria[21], assessed by structured clinical interview[22], and were in current depressive episode

of at least moderate severity as measured by score of a minimum of 16 in 17-item Hamilton Depression Rating Scale (HDRS)[23]. Mean HDRS was 19.07 (SD 2.73), and the median number of depressive episodes was 3 (interquartile range (IQR) 1, 5) (Table 1). Sex of participants was based on self-report. There were no exclusions of participants based on sex or gender.

Inclusion criteria included being treatment-free or taking stable antidepressant medication or in psychotherapy for at least 6 weeks prior to enrolment. Having persistent depressive symptoms of at least moderate severity and meeting MDD criteria while taking antidepressant medication for at least 6 weeks have been clinical criteria for treatment resistant depression in previous medication trials.[24,25] Treatment status was as follows: treatment-free: 57 (32.8%); taking antidepressant medication: 109 (62.6%); in psychotherapy: 26 (14.9%); taking medication and in psychotherapy: 18 (10.3%) participants.

Participants were randomly allocated to active tDCS treatment (87 MDD, mean age 37.09 years (SD 11.14)) or sham tDCS (87 MDD, mean age 38.32 years (SD 10.92)) (Figure 1, Table 1, Supplementary Tables 2-5). One participant did not continue and had not started any treatment; therefore, the modified intention to treat (mITT) sample was 173 participants. There were no significant differences in discontinuation rates between groups (total 25 participants (14.3%): 13 (14.9%) in active group and 12 (13.7%) in sham group (p = 0.99)) (Supplementary Table 6). Based on *a priori* blinded interim analysis, recruitment ended early (Supplementary Notes - Interim Analysis).

Primary Outcome

A significant improvement was observed in change in depressive symptomatology as measured by HDRS score from baseline to week 10 end of treatment in active tDCS treatment arm: HDRS decrease 9.41 points (SD 6.25) (estimated week 10 mean 9.58 (SD 6.02)), as compared to sham tDCS treatment arm: HDRS decrease 7.14 points (SD 6.10) (estimated week 10 mean 11.66 (SD 5.96)) (95% CI 0.51 to 4.01, p = 0.012) (Figure 2).

Secondary Outcomes

Based on HDRS ratings, active tDCS treatment arm was associated with a significantly greater clinical response rate of 58.3% as compared to sham 37.8% (p = 0.017) (Post hoc Odds Ratio (OR) 2.31 (lower bound (LB) 1.17, upper bound (UB) 4.55), and active treatment arm was

associated with significantly greater remission rate of 44.9% relative to sham 21.8% (p = 0.004) (Post hoc OR 2.93 (LB 1.41, UB 6.09)).

Based on Montgomery-Åsberg Depression Rating Scale (MADRS)[26] ratings, active tDCS treatment arm showed a significant improvement from baseline to week 10, mean improvement 11.31 (SD 8.81) (estimated week 10 mean 12.46 (SD 9.40)), as compared to sham treatment, mean improvement 7.74 (SD 8.47) (p = 0.006) (estimated week 10 mean 15.30 (SD 9.28)). In clinical response, active treatment arm was associated with significantly greater response rate of 64.2% as compared to sham 32.3% (p < 0.001) (Post hoc OR 3.76 (LB 1.83, UB 7.74)). In clinical remission, active treatment arm was associated with significantly greater remission rate of 57.5% relative to sham 29.4% (p = 0.002) (Post hoc OR 3.26 (LB 1.53, UB 6.94)).

Based on Montgomery-Åsberg Depression Rating Scale self-report scale (MADRS-s)[27], active tDCS treatment arm was associated with a significant improvement from baseline to week 10, mean improvement 9.90 (SD 8.94) (estimated week 10 mean 16.60 (SD 9.33)), as compared to sham treatment, mean improvement 6.23 (SD 9.13) (p = 0.009) (estimated week 10 mean 19.55 (SD 9.62)). In clinical response, active treatment arm was associated with significantly greater response rate of 51.8% as compared to sham 25.1% (p = 0.002) (Post hoc OR 3.22 (LB 1.15, UB 6.94)). In clinical remission, active treatment arm was associated with significantly greater remission rate of 53.8% as compared to sham 23.4% (p = 0.002) (Post hoc OR 3.83 (LB 1.61, UB 9.13)) (Table 2, Extended Data Figures 1-2).

There were no significant differences in quality of life between treatment arms as measured by EQ-5D-3L[28,29] (p = 0.33).

Exploratory Outcomes

In anxiety symptoms, there were no significant differences between active, mean Hamilton Anxiety Rating Scale (HAMA)[30] score improvement 6.62 (SD 6.09) (mean 8.24 (SD 5.65)), as compared to sham improvement 4.88 (SD 5.88) (mean 9.29 (SD 4.90)) (p = 0.08). In hypomanic symptoms, Young Mania Rating Scale (YMRS)[31] mean score was 1.27 (SD 1.40) in active treatment arm at week 10 and 1.84 (SD 1.69) in sham treatment arm, which was statistically significant (p = 0.03) (Supplementary Tables 12-13).

In neuropsychological assessments, there were no significant differences in Rey Auditory Verbal Learning Test (RAVLT)[32] total learning or Symbol Digit Modalities Test (SDMT)[33] between treatment arms (Supplementary Table 14).

Per protocol and sensitivity analyses in participants with persistent depressive symptoms and had been taking antidepressant medication at study enrolment showed significant improvements in depressive symptoms, clinical response and remission (Supplementary Tables 15 and 18).

Blinding analysis

Prior to unblinding at the week 10 end of trial, participants were asked to guess whether they thought they were receiving the active or sham tDCS device and their level of certainty, rating in a scale from '1' to '5' indicating 'very uncertain' to 'very certain'. A guess of active tDCS was made by 77.6% in the active treatment arm and 59.3% in the sham treatment arm, which was a significant difference ($p = 0.01$). The certainty of having received active tDCS was rated high by 57.6% (38 out of 66 guesses) in the active arm and 41.7% (20 out of 48 guesses) in sham arm, as measured by rating of 4 or 5, while certainty was rated low by 16.7% (11 out of 66 guesses) in active and 18.8% (9 out of 48 guesses) in sham arm, as measured by rating of 1 or 2 (Supplementary Tables 36 and 39).

Adverse events and safety

At week 10, reports of skin redness ((active 54 (63.5%); sham 15 (18.5%), $p < 0.001$); skin irritation ((active 6 (6.9%); sham 0 (0%), $p = 0.03$); and trouble concentrating ((active 12 (14.1%); sham 3 (3.7%), $p = 0.03$) were greater in active relative to sham treatment arm. There were no differences in headache, neck pain, scalp pain, itching, burning sensation, sleepiness, or acute mood changes between treatment arms. Two participants in the active group had described developing "burns" at the left anode site. In review, they seemed to be caused by using sponges that had dried out. Neither developed into residual skin lesions or scarring. Participants had not contacted the 24-hour contact number, and both had informed the research team at their following study visit, which was 1-2 weeks afterwards. There were no visible lesions at the study visits. One participant had taken a break from the sessions for 4 days and the burn had fully healed. The second participant was experiencing dry skin at the electrode site and was advised that they could take a break from the sessions until the skin had healed, however they did not take a break until after the next study visit, 3 weeks later, when they were advised to take a break from the sessions to allow the dry skin and tenderness

to heal. The participant then missed the next three stimulations, and the skin was no longer tender but was still dry at the week 10 end of study visit. There were no serious adverse events related to the device, and no participants developed mania or hypomania (Tables 3 and 4, Supplementary Tables 24-29).

Discussion

In this international, multi-site, sham-controlled randomised controlled trial (RCT) of home-based tDCS treatment for MDD, a 10-week course of active stimulation was associated with significantly greater improvements in depressive symptoms, clinical response and remission rates as compared to sham stimulation. Improvements were evident in both clinician-rated depressive symptom ratings (HDRS and MADRS) as well as in self-report ratings (MADRS-s). The clinical significance of the outcomes is highlighted by high rates of treatment response and remission which were two to three times greater in the active treatment arm as compared to the sham treatment arm. Clinical efficacy was demonstrated in a wide range of forms of MDD, from first episode MDD to those having a history of recurrent episodes as well as participants with treatment resistant depression.

Meta-analyses of clinic-based tDCS sessions report that active tDCS is associated with greater improvements in depressive symptoms, clinical response and clinical remission rates as compared to sham tDCS, particularly in first episode and recurrent MDD.[6,34–36] In a recent large trial though, Burkhardt et al.[37] had not observed any significant effects of adjunctive tDCS treatment to antidepressant medication in a 6-week trial. In the present trial, we had a comparable inclusion criteria for treatment resistant depression but longer 10-week treatment duration. Burkhardt et al.[37] inclusion criteria were MDD participants with persistent depressive symptoms of at least moderate severity while taking a selective serotonin reuptake inhibitor for a minimum of 4 weeks. Similarly, our inclusion criteria were MDD participants with persistent depressive symptoms of at least moderate severity while taking antidepressant medication for a minimum of 6 weeks at the point of screening. Our inclusion criteria meet UK National Institute of Health Care Excellence definition of treatment resistant depression,[24,25] and 63% of our sample had fulfilled these criteria. Treatment resistant depression though is negatively correlated with clinical efficacy to tDCS treatment.[6,34–36] This is a clinical definition, which can be further delineated by the number and types of failed treatment trials. Our exclusion criteria included having a history of poor treatment response to two or more antidepressant medications, which reflects increased severity of treatment resistant depression. About 12-17% of participants in Burkhardt et al.[37] trial had such a history of treatment failures, which could have impacted on their observed lack of clinical effects. The

level of depressive symptom severity and mean ages were comparable in Burkhardt et al.[37] and in the present trial, while the age of onset was younger in the present trial by about 10 years and we did not have an upper age limit.

Furthermore, clinical effects of tDCS have been found to continue increase up to 10 weeks.[20] In the present trial, we found strong clinical efficacy and safety with our 10-week home-based protocol. This is in contrast with recent home-based tDCS trials, in which all had 6-week treatment durations and two trials had small sample sizes (n=11[18] and n=58[19]).[17–19] A single-blind RCT of tDCS augmentation to antidepressant medication, consisting of hybrid clinic- and home-based tDCS sessions, reported significant improvements in depressive symptoms in the active group as measured by self-reported symptoms ratings but not in clinician-based ratings.[19] In a large RCT (n = 210), no significant effects were observed between three treatment arms: active tDCS, active tDCS combined with a digital psychological intervention (double active); and sham tDCS combined with internet browsing (double sham). In the present trial, clinical treatment effects were evident at 10 weeks. Longer treatment durations may be necessary to observe clinical efficacy,[38] and Nikolin et al.[20] meta-analysis reported that effect sizes continue to increase with longer treatment durations.

We found high safety in the present trial. Safety was monitored in real-time assessments by videoconference and the availability of a dedicated study number with 24-hour access to researchers. A recent trial had ended early due to adverse events of skin lesions which were the result of an accumulation of electrical burns in 5 participants in the active tDCS group from a total enrolment of 11 MDD participants as the trial ended early.[18] Electrical burns can be an unanticipated side effect, which are usually caused by the application of tap water to moisten sponges,[39] insufficient moistening with conductive saline solution,[40] or pre-existing skin lesions. In the present trial, we had two incidents of reported electrical burns, which both participants had reported in the study visit. Both seem to have been due to insufficient sponge moistening, neither developed into residual skin lesions or scarring, and participants were eager to continue tDCS sessions following a brief break. There were no serious adverse events related to the device and no incidents of serious suicide risk. Active stimulation though was associated with higher rates of skin redness, irritation and dry skin relative to sham.[41,42]

During the tDCS sessions, participants were asked to sit or lie down and to not engage in activities that might compromise safety or device functionality. Their activities though had not been recorded by the research team. State-dependent effects of tDCS stimulation are possible in which an interaction of external stimulation, location and internal state of the region or network has been observed.[43,44] The type of task activity during stimulation can influence

cognitive enhancement in healthy participants[45] and treatment response in clinical samples.[46] Concurrent administration of active tDCS and cognitive control training (CCT) has been associated with sustained improvements in depressive symptoms as compared to active tDCS plus sham CCT or sham tDCS plus CCT.[46] However, a 6-week trial of cognitive behavioral therapy (CBT) with three treatment arms: CBT alone, CBT plus active tDCS, and CBT plus sham-tDCS, in a sample of 126 MDD participants, reported no significant effects between groups.[47]

Blinding is key in randomised clinical trials in order to mitigate potential biases that can impact on the outcome. Procedures involve establishment and maintenance of blinding, measures to prevent of unblinding, and assessment of success of blinding.[48,49] In the establishment of blinding in the present trial, all participants and researchers were blind to the treatment arm allocation, and the placebo-sham, control intervention was identical in appearance to the active intervention. Furthermore, in the sham device, there was brief stimulation at the start and end of each session to mimic active tDCS sensations in order to aid in blinding and to balance potential nocebo effects across groups.[50] For maintenance of blinding, the treatment protocol and study visits were identical in both treatment arms. All participants were able to maintain their ongoing treatments throughout the trial, and all participants were able to use the active tDCS device in the subsequent open label phase of the trial in order to incorporate real-life clinical care while balancing expectations between groups and to aid in limiting attrition.[49] The tDCS treatment arms were described as ‘active’ or ‘inactive’ stimulation by researchers during the trial to maintain comparable phrasing and reduce potential negative connotations associated with the words 'placebo' or 'sham'. Outcome assessors were blind to group allocation as a second independent researcher was present for the clinical ratings.[49] Ethicality had been assessed *a priori* and worsening of symptoms was included as a withdrawal criteria. An automatic email report was sent to all research team members when unblinding occurred as a notification and to prevent potential concealment of any accidental unblinding. The timing of the blinding assessment questionnaire at the end of the blinded treatment phase, rather than at timepoints throughout the trial, reduced the influence of potential interjections.

In the blinding assessment, participants were asked to guess if they had been receiving the 'active' or 'sham' treatment and the certainty of their guess, ranging from 'very uncertain to 'very certain' in a 5-point scale. We may consider that participants who 'very uncertain' of their guess to be comparable to a guess of 'don’t know'. More participants in the active treatment arm guessed that they were receiving active tDCS (77.6%) as compared to participants in the sham treatment arm (59.3%). However, a moderate proportion were 'very uncertain' about

their guess in the active (16.7%) and sham (18.8%) treatment arms, and there was limited endorsement of being 'very certain' in active (57.6%) and sham (41.7%) treatment arms, with no significant differences between treatment arms. It is possible that participants who believed that they were in the active treatment arm were more likely to show a placebo response. Lin et al.[51] meta-analysis of antidepressant medication randomised controlled trials though found no association between blinding effects and treatment effect sizes. Consolidated Standards of Reporting Trials (CONSORT) 2010 guidance recommends specification of how blinding is established but no longer recommend reporting on how the success of blinding is assessed because healthcare providers and participants are likely to know if the primary outcome had been achieved by participants, making interpretation more difficult as responses might reflect accurate assumptions about efficacy of the intervention rather than a failure of blinding.[52] Moreover, significant clinical efficacy was maintained for active relative to sham treatment in participants who had made a guess of 'active' treatment, and the placebo response rate in the sham treatment arm in the present trial (26.9%) was lower than placebo response rates observed in a sham group (36%)[19] and double sham group (38%)[17] which had included in person study visits at the clinical research centre[17,19] and weekly online visits for 6 weeks.[19]

Limitations of the present trial include the lack of a 'don't know' option in the blinding assessment. Well executed blinding to treatment allocation should lead participants to be uncertain of which treatment they are receiving. With inclusion of a 'don't know' option, it would be possible to calculate a proposed index of blinding.[53] Differences in head sizes, individual anatomical features and the positioning of devices among users may lead to unique configurations of electric field density within the brain.[54,55] Inter-individual variations in tDCS can be partially explained due to differences in electric fields.[56] The tDCS device used in the present study has undergone electric field modelling, indicating that the device targets areas within the prefrontal cortex linked to MDD pathophysiology.[54] While participants were taught how to use the device and positioning had been observed in real-time, variations in positioning could potentially affect electric field intensity and in turn treatment outcomes.[54] All clinical rating scale assessments were performed by videoconference, although no significant differences have been found between face-to-face and videoconference HRSD ratings conducted within the same day,[57] and we sought to have a second team member to perform clinical ratings in order to maintain blinding and ensure validity. Video consultation for clinical assessment and mental health treatment has become more common in recent years and has been reported as being as effective as face-to-face visits for improving clinical outcomes and giving more flexibility to patients.[58,59] In quality of life, there was no significant difference between groups in a self-report measure. The scores on the quality of life measure though were relatively high at baseline and both treatment arms reported some improvement in quality

of life, which was not statistically significant. MDD is more common in women and the present study had consisted of a larger proportion of female participants as expected. All participants had self-reported their sex, and it had not been expected that there would be an effect of sex or gender on clinical efficacy, though this would benefit from further investigation. The ethnic diversity in the present sample was limited and history of hospital admissions was exclusion criteria, which may limit generalisability of the findings.

In summary, the 10-week course home-based active tDCS was associated greater improvements in depressive symptoms, clinical response and remission in MDD participants with at least a moderate severity of depressive symptoms as compared to sham tDCS. Efficacy was observed in participants who were taking antidepressant medication indicative of treatment resistant depression or in psychotherapy as well as those who were treatment-free. All participants had real-time remote supervision visits, and high acceptability and safety were observed in the present trial, Home-based tDCS could be a potential first line treatment for MDD that demonstrates efficacy, acceptability and safety, but consideration of continuing safety monitoring is required.

Acknowledgements

C.F. has received grants from the following funding: Research grant funding on behalf of the University of East London from Flow Neuroscience (R102696); research grant funding: NIMH (R01MH134236), Baszucki Brain Research Fund Milken Institute (BD0000009), Rosetrees Trust (CF20212104), International Psychoanalytic Society (158102845), MRC (G0802594), NARSAD, Wellcome Trust. S.S. acknowledges the following funding: Research grant funding on behalf of the University of Texas Health Science Center at Houston from Flow Neuroscience. Paid advisory boards for the following companies: Worldwide Clinical Trials and Inversago; Vicore pharma. S.S. is a fulltime employee of Intra-Cellular Therapies, Inc. He has received grants/research support from NIMH, United States (1R21MH119441-01A1), NIMH (1R21MH129888-01A1), NICHD 1R21HD106779-01A1, SAMHSA (6H79FG000470-01M003) and Fizer foundation. A.Y.'s independent research is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Principal Investigator for the following studies: 1. the Restore-Life VNS registry study funded by LivaNova; 2. ESKETINTRD3004: "An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression"; 3. The Effects of Psilocybin on Cognitive Function in Healthy Participants; 4. The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD); 5. A Double-Blind, Randomized, Parallel-Group Study with Quetiapine Extended Release as Comparator to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy. (Janssen); 6. An Open-label, Long-term, Safety and Efficacy Study of Aticaprant as Adjunctive Therapy in Adult and Elderly Participants with Major Depressive Disorder (MDD). (Janssen); 7. A Randomized, Double-blind, Multicentre, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aticaprant 10 mg as Adjunctive Therapy in Adult Participants with Major Depressive Disorder (MDD) with Moderate-to-severe Anhedonia and Inadequate Response to Current Antidepressant Therapy; 8. A Study of Disease Characteristics and Real-life Standard of Care Effectiveness in Patients with Major Depressive Disorder (MDD) With Anhedonia and Inadequate Response to Current Antidepressant Therapy Including an SSRI or SNR. (Janssen). UK Chief Investigator for the following studies: 1. Novartis MDD study MIJ821A12201; 2. Compass; COMP006 & COMP007 studies. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK) EU Horizon 2020. The views expressed are those of the authors and not necessarily those of the

NHS, the NIHR, or the Department of Health. R.M-V is the PI for the following grants: NIH (R21HD106779 and R21MH129888), Milken Institute (BD-0000000081).

Author Contributions

C.F. was the chief investigator of the study, designed the study, led its conduct, was principal investigator for the UK site, led the interpretation of data and wrote the first draft of the manuscript with R.W. S.S. was the principal investigator at the USA site until March 2023, and R.M.V. was the principal investigator at the USA site from March 2023. J.S. and A.Y. contributed to the study design, conduct, interpretation of data. R.W. was the study coordinator, and A.G., G.S., H.H., N.L. and P.L. contributed to the data acquisition in the UK study site. M.R., P.O. and S.K. contributed to the data acquisition in the USA study site. D.M. was the lead statistician, supervised the design of the statistical analysis plan, statistical analysis and report of the clinical trial results, and L.H. provided statistical support. All authors have approved the submission of the manuscript for publication.

Competing Interests

Author C.F. reports the following declaration of interests: Research grant funding on behalf of the University of East London from Flow Neuroscience (R102696); research grant funding: NIMH (R01MH134236), Baszucki Brain Research Fund Milken Institute (BD0000009), Rosetrees Trust (CF20212104), International Psychoanalytic Society (158102845), MRC (G0802594), NARSAD, Wellcome Trust. Associate Editor of Psychoradiology, Section Editor of Brain Research Bulletin.

Author A.Y. reports the following declaration of interests: Paid lectures and advisory boards for the following companies with therapies used in affective and related disorders: Flow Neuroscience, Novartis, Roche, Janssen, Takeda, Noema pharma, Compass, Astrazenaca, Boehringer Ingelheim, Eli Lilly, LivaNova, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, Sage, Novartis, Neurocentrx. Principal Investigator for the following studies: 1. the Restore-Life VNS registry study funded by LivaNova; 2. ESKETINTRD3004: “An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression”; 3. The Effects of Psilocybin on Cognitive Function in Healthy Participants; 4. The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD); 5. A Double-Blind, Randomized, Parallel-Group Study with Quetiapine Extended Release as Comparator to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult

and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy. (Janssen); 6. An Open-label, Long-term, Safety and Efficacy Study of Aticaprant as Adjunctive Therapy in Adult and Elderly Participants with Major Depressive Disorder (MDD). (Janssen); 7. A Randomized, Double-blind, Multicentre, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aticaprant 10 mg as Adjunctive Therapy in Adult Participants with Major Depressive Disorder (MDD) with Moderate-to-severe Anhedonia and Inadequate Response to Current Antidepressant Therapy; 8. A Study of Disease Characteristics and Real-life Standard of Care Effectiveness in Patients with Major Depressive Disorder (MDD) With Anhedonia and Inadequate Response to Current Antidepressant Therapy Including an SSRI or SNR. (Janssen). UK Chief Investigator for the following studies: 1. Novartis MDD study MIJ821A12201; 2. Compass; COMP006 & COMP007 studies. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK) EU Horizon 2020. Editor of Journal of Psychopharmacology and Deputy Editor, BJPsych Open. No shareholdings in pharmaceutical companies.

Author S.S. reports the following declaration of interests: Research grant funding on behalf of the University of Texas Health Science Center at Houston from Flow Neuroscience. Paid advisory boards for the following companies: Worldwide Clinical Trials and Inversago; Vicore pharma. S.S. is a fulltime employee of Intra-Cellular Therapies, Inc. He has received grants/research support from NIMH, United States (1R21MH119441-01A1), NIMH (1R21MH129888-01A1), NICHD 1R21HD106779-01A1, SAMHSA (6H79FG000470-01M003) and Fizer foundation. He has received research funding as a Principal investigator or study/sub-investigator from and/or participated as consultant/speaker for Flow Neuroscience, COMPASS Pathways, LivaNova, Janssen, Relmada, and Psychiatry education forum. Intra-Cellular Therapies (ITI) or NIH or SAMHSA or any other organizations had no role in the study's design and conduct; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. This study's content is solely the responsibility of the authors and does not necessarily represent the official views of the ITI or NIH or SAMHSA

Author R.M-V has received consulting fees from Eurofarma Pharmaceuticals, Abbott, and BioStrategies group; has research contracts with Boerhinger Ingelheim and Janssen Pharmaceuticals; has received speaker fees from Otsuka, EMS, and Cristalia, member of the

scientific boards of Symbinas Pharmaceuticals and Allergan. Author R.M-V is also the PI for the following grants: NIH (R21HD106779 and R21MH129888), Milken Institute (BD-0000000081).

Authors D.M. and L.H. work for Biomedical Statistical Consulting, who provides statistical support to MCRA, LLC who received payments from Flow Neuroscience.

Authors A.G., G.S., H.H., J.S., M.R., N.L., P.L., P.O., R.W. and S.K. declare no competing interests.

Role of the funding source

This study was funded by a grant from Flow Neuroscience to the overall study Chief Investigator and UK PI to C.F., and to the USA PI, S.S. The funder provided the tDCS devices. The funder had no role in data analysis, data interpretation, or writing of the manuscript.

Table 1. Demographic and clinical characteristics of participants at baseline

Characteristic	Active	Sham
Number of participants	87	87
Age	37.09 ± 11.14	38.32 ± 10.92
Sex		
Women	54 (62)	66 (76)
Race		
Asian	9 (10)	2 (2)
Black or African American	3 (3)	1 (1)
Native Hawaiian or Other	0 (0)	0 (0)
White	72 (83)	73 (84)
Other	3 (3)	11 (13)
Missing	0 (0)	0 (0)
Educational Level		
Less than High School/Secondary School	1 (1)	0 (0)
Some College	18 (21)	19 (22)
Diploma	9 (10)	7 (8)
Bachelor's or Professional Degree	37 (43)	37 (43)
Master's or Doctoral Degree	22 (25)	23 (26)
Prefer not to answer/Missing	0 (0)	1 (1)
Age of onset of MDD	22.08 ± 9.68	22.40 ± 8.78
Previous number of episodes	3 (1, 5)	3 (1.5, 5)
Previous number of suicide attempts	0 (0, 0)	0 (0, 0)
First episode MDD	18 (21)	10 (11)
Clinical ratings		
HDRS	19.18 ± 2.83	18.92 ± 2.63
HDRS severity:		
Moderate (HDRS score: 16-18)	45 (52)	45 (52)
Severe (HDRS score: 19-22)	29 (33)	33 (38)
Very severe (HDRS score: 23 or greater)	13 (15)	9 (10)
MADRS	24.72 ± 4.68	23.87 ± 5.49
MADRS-s	26.77 ± 6.90	25.67 ± 6.34
HAMA	15.45 ± 4.61	14.25 ± 4.57
YMRS	2.10 ± 1.72	1.92 ± 1.58
EQ-5D-3L	0.75 ± 0.13	0.75 ± 0.14
RAVLT	57.92 ± 11.15	58.51 ± 13.40
SDMT	52.26 ± 10.13	50.40 ± 10.14
Taking antidepressant medication	56 (64)	53 (61)
Selective serotonin reuptake inhibitor	40 (46)	35 (40)
Non-selective monoamine reuptake inhibitor	1 (1)	3 (3)
Other antidepressant medications	18 (21)	17 (20)
Taking combination antidepressant medications	5 (6)	3 (4)
In psychotherapy during trial	12 (14)	14 (16)
In psychotherapy and taking antidepressant medication	6 (7)	12 (14)
No antidepressant medication or psychotherapy during trial	25 (29)	32 (37)

Categorical variables are presented as number of participants with percentage in parentheses for sex, race, educational level, first episode MDD, antidepressant medication and individual medications, individual psychotherapy during trial and No antidepressant or psychotherapy during trial. Mean values are presented with '±' standard deviation values. Previous number of episodes and previous number of suicide attempts are presented as median with interquartile range in parenthesis. Diploma, a certificate that signifies a certain level of education and practical experience. HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MADRS-s, Montgomery-Åsberg Depression Rating Scale-self report; HAMA, Hamilton Anxiety Rating Scale; YMRS, Young Mania Rating Scale; RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol Digit Modalities Test. SDMT active, n=85, SDMT sham, n=85. Age of onset, active n=86, sham n=86. HDRS scores range from 0 to 52, MADRS scores range from 0 to 60, MADRS-s scores range from 0 to 54, with higher scores indicating increased depressive symptom severity. RAVLT scores range from 0 to 75. SDMT scores range from 0 to 110. Two-sided significance tests (Fisher exact test for categorical variables and t-test for continuous variables) found a significant difference between groups for race, $p = 0.012$. $p > 0.05$ for all other characteristics.

Table 2. Primary and secondary outcomes: changes in depressive severity as measured by HDRS, MADRS and MADRS-s and quality of life as measured by EQ-5D-3L following a 10-week course of active or sham tDCS sessions

Measure	Active (n = 87)	Sham (n = 86)	Difference or Odds Ratio (95% CI)	Cohen's D or NNT	P value
Primary Outcome					
Decrease in HDRS score	9.41 ± 6.25	7.14 ± 6.10	2.26 (0.51 to 4.01)	0.37	0.012
Secondary Outcomes					
HDRS					
Clinical response	44 (58.3%)	29 (37.8%)	2.31 (1.17 to 4.55)	5	0.017
Clinical remission	34 (44.9%)	17 (21.8%)	2.93 (1.41 to 6.09)	4	0.004
MADRS					
Decrease in score	11.31 ± 8.81	7.74 ± 8.47	3.57 (1.06 to 6.07)	0.41	0.006
Clinical response	47 (64.2%)	26 (32.3%)	3.76 (1.83 to 7.74)	4	0.0002
Clinical remission	42 (57.5%)	25 (29.4%)	3.26 (1.53 to 6.94)	4	0.002
MADRS-s					
Decrease in score	9.90 ± 8.94	6.23 ± 9.13	3.66 (0.93 to 6.40)	0.41	0.009
Clinical response	32 (51.8%)	15 (25.1%)	3.22 (1.50 to 6.94)	4	0.002
Clinical remission	32 (53.8%)	18 (23.4%)	3.83 (1.61 to 9.13)	3	0.002
EQ-5D-3L					
Change in score	0.07 ± 0.15	0.07 ± 0.17	0.02 (-0.02 to 0.06)	-	0.326

HDRS, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MADRS-s, Montgomery-Åsberg Depression Rating Scale-self report. EQ-5D-3L, quality of life measure[28,29] (https://euroqol.org); CI, confidence interval; NNT, number needed to treat; mean values are presented with '±' standard deviation values. HDRS, MADRS, MADRS-s change ratings are the decrease in total ratings from baseline to week 10. Between-group differences are shown for the changes in scores from baseline to week 10, and odds ratios are shown for the outcomes for clinical response and remission. Percentages for clinical response and remission outcomes are estimated based on odds ratios. HDRS scores range from 0 to 52; MADRS scores range from 0 to 60; MADRS-s scores range from 0 to 54, with higher scores indicating increased depressive symptom severity. Clinical response was defined as a decrease in the score (indicating less depressive severity) of 50% or more from baseline to week 10. Clinical remission was defined as: HDRS score of 7 or less; MADRS score of 10 or less; MADRS-s score of 12 or less. Fully Conditional Specification (FCS) approach was used to produce 20 multiply imputed completed data sets. The FCS approach accommodates nonmonotonicity in the pattern of missing data and requires regression models to be specified for each variable with missing values needing imputation. All models included age, sex, in psychotherapy at baseline, use of any antidepressants at baseline and treatment group. The resulting completed datasets were combined using Rubin's Rules. Estimated Standard Effect Size (Cohen's D) is the group difference in estimated means divided by pooled within group SD.

Table 3. Unanticipated adverse events at 10 weeks

Event category	Active tDCS (N=87)	Sham tDCS (N=86)	Difference (95% CI)	P Value
Ear and labyrinth disorders	2 (2.3%)	2 (2.3%)	0.0 (-6.2 to 6.0)	0.99
Eye disorders	3 (3.4%)	1 (1.2%)	2.3 (-3.3 to 8.9)	0.62
Gastrointestinal disorders	2 (2.3%)	1 (1.2%)	1.1 (-4.5 to 7.0)	0.99
General disorders and administration site conditions	3 (3.4%)	2 (2.3%)	1.1 (-5.2 to 8.0)	0.99
Infections and infestations	1 (1.1%)	1 (1.2%)	0.0 (-5.5 to 5.3)	0.99
Injury, poisoning and procedural complications	2 (2.3%)	0 (0.0%)	2.3 (-2.2 to 8.1)	0.49
Nervous system disorders	7 (8.0%)	8 (9.3%)	-1.3 (-10.4 to 8.0)	0.79
Psychiatric disorders	4 (4.6%)	4 (4.7%)	-0.1 (-7.5 to 7.3)	0.99
Skin and subcutaneous tissue disorders	17 (19.5%)	7 (8.1%)	11.4 (1.0 to 22.3)	0.05
Vascular disorders	1 (1.1%)	0 (0.0%)	1.1 (-3.3 to 6.4)	0.99
Number of participants with adverse events at week 10				
>=1 Mild adverse event	21 (24.1%)	14 (16.3%)	7.9 (-4.5 to 20.3)	0.25
>=1 Moderate adverse event	13 (14.9%)	18 (9.3%)	5.6 (-4.5 to 16.1)	0.35
>=1 Severe adverse event	3 (3.4%)	1 (1.2%)	2.3 (-3.3 to 8.9)	0.62
Serious adverse events during the trial				
Hospitalisation for hypertension	1 (1.1%)	0 (0.0%)	1.1 (-3.3 to 6.4)	0.99
Death	0	0	___	___
New onset mania or hypomania	0	0	___	___

An adverse event was present if the participant rated that it was at least possibly associated with the intervention. Participants rated the severity of the adverse events as mild, moderate, or severe, which were assessed by the investigator. Adverse event categories are displayed as number of participants with percentage in parentheses. Difference between groups is displayed as a percentage. P values represent difference between groups using two-sided Fisher exact test. Analyses were completed on all participants who completed at least one tDCS session. The serious adverse event was not related to the intervention.

Table 4. Anticipated adverse events at 10 weeks as measured by tDCS Adverse Events Questionnaire.[41]

	Active (N=87)				Sham (N=86)				
Adverse event category	**Total**	**Mild**	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**P Value**
Headache	36 (42.4%)	24 (28.2%)	11 (12.9%)	1 (1.2%)	29 (35.8%)	18 (22.2%)	9 (11.1%)	2 (2.5%)	0.43
Neck Pain	2 (2.4%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	4 (4.9%)	1 (1.2%)	3 (3.7%)	0 (0.0%)	0.44
Scalp pain	18 (21.2%)	14 (16.5%)	3 (3.5%)	1 (1.2%)	10 (12.3%)	7 (8.6%)	3 (3.7%)	0 (0.0%)	0.15
Itching	43 (50.6%)	37 (43.5%)	3 (3.5%)	3 (3.5%)	35 (43.2%)	28 (34.6%)	7 (8.6%)	0 (0.0%)	0.08
Burning sensation	37 (43.5%)	32 (37.6%)	4 (4.7%)	1 (1.2%)	31 (38.3%)	25 (30.9%)	6 (7.4%)	0 (0.0%)	0.43
Skin redness	54 (63.5%)	42 (49.4%)	11 (12.9%)	1 (1.2%)	15 (18.5%)	13 (16.0%)	2 (2.5%)	0 (0.0%)	<0.001*
Sleepiness	10 (11.8%)	5 (5.9%)	4 (4.7%)	1 (1.2%)	12 (14.8%)	9 (11.1%)	2 (2.5%)	1 (1.1%)	0.65
Trouble concentrating	12 (14.1%)	8 (9.4%)	3 (3.5%)	1 (1.2%)	3 (3.7%)	2 (2.5%)	1 (1.2%)	0 (0.0%)	0.03
Acute mood change	7 (8.2%)	3 (3.5%)	3 (3.5%)	1 (1.2%)	6 (7.4%)	5 (6.2%)	1 (1.2%)	0 (0.0%)	1.00

Values are number of participants with percentage in parentheses. An adverse event was present if the participant rated that it was at least remotely possible that it was associated with the intervention. Participants rated the severity of the adverse events as mild, moderate, or severe. P values represent group differences of the total number of events per event category with two-sided Fisher exact test.*Exact p-value for skin redness = 0.000000003.

Figure Legend

Figure 1.

Consolidated Standards of Reporting Trials (CONSORT) diagram: enrolment, group allocation, follow-up and analysis are presented. MDD, major depressive disorder; tDCS, transcranial direct current stimulation; mITT, modified intention-to-treat.

Figure 2.

Change in depressive severity ratings over time. Shown are the estimated mean 17-item Hamilton Rating Scale for Depression (HDRS) rating scores from baseline to week 10 in the modified intention-to-treat analysis sample (n=173) for the active tDCS and sham tDCS treatment arms. Error bars represent $\pm$ 1 standard error (SE). HDRS scores range from 0 to 52 with higher values indicating more severe depressive symptoms. A significant improvement was observed in the change in HDRS ratings from baseline to week 10 in the active tDCS treatment arm, HDRS decrease 9.41 $\pm$ 6.25 (SD) (mean week 10 HDRS 9.58 $\pm$ 0.70 (SE)), as compared to sham tDCS treatment arm, HDRS decrease 7.14 $\pm$ 6.10 (SD) (mean week 10 HDRS 11.66 $\pm$ 0.69 (SE)) (95% CI 0.5 to 4.0, $p = 0.012$). The difference in change scores was also significant at week 4 (95% CI 0.2 to 3.4, $p = 0.03$) with a greater score decrease in the active treatment arm. Fully Conditional Specification (FCS) approach was used to produce 20 multiply imputed completed data sets. The FCS approach accommodates nonmonotonicity in the pattern of missing data and requires regression models to be specified for each variable with missing values needing imputation. All models included age, sex, in psychotherapy at baseline, use of any antidepressants at baseline and treatment group. The resulting completed datasets were combined using Rubin's Rules. * = $p < 0.05$.

Extended Data Figure 1.

Estimated mean MADRS rating scores from baseline to week 10 in the modified intention-to-treat analysis sample (n=173) in active tDCS and sham tDCS treatment arms. Error bars represent + 1 standard error (SE). MADRS scores range from 0 to 60 with higher values indicating more severe depressive symptoms. A significant improvement was observed in the change in MADRS ratings from baseline to week 10 in the active tDCS treatment arm, MADRS change 11.31 + 8.81(standard deviation (SD)) (mean week 10 MADRS 12.46 + 1.09 (SE)) as compared to sham tDCS treatment arm, MADRS change 7.74 + 8.47 (SD) (mean week 10

MADRS 15.30 + 1.07 (SE)) (95% CI 1.1 to 6.1, p = 0.006). The difference in change scores was also significant at week 4 (95% CI 1.2 to 5.5, p = 0.003) and week 7 (95% CI 1.1 to 5.8, p = 0.005) with a greater score decrease in the active treatment arm. Fully Conditional Specification (FCS) approach was used to produce 20 multiply imputed completed data sets. The FCS approach accommodates nonmonotonicity in the pattern of missing data and requires regression models to be specified for each variable with missing values needing imputation. All models included age, sex, in psychotherapy at baseline, use of any antidepressants at baseline and treatment group. The resulting completed datasets were combined using Rubin's Rules. ** = p <0.01.

Extended Data Figure 2.

Estimated mean MADRS-s rating scores from baseline to week 10 in the modified intention-to-treat analysis sample (n=173) for the active tDCS and sham tDCS treatment arms. Error bars represent $\pm$ 1 standard error (SE). MADRS-s scores range from 0 to 60 with higher values indicating more severe depression. A significant improvement was observed in the change in MADRS-s ratings from baseline to week 10 in the active tDCS treatment arm, MADRS-s change 9.90 $\pm$ 8.94 (standard deviation (SD)) (mean week 10 MADRS-s 16.60 $\pm$ 1.18 (SE)) as compared to sham tDCS treatment arm, MADRS-s change 6.23 $\pm$ 9.13 (SD) (mean week 10 MADRS-s 19.55 $\pm$ 1.16 (SE)) (95% CI 0.9 to 6.4, p = 0.009). The difference in change scores was also significant at week 4 (95% CI 0.3 to 4.9, p = 0.030) with a greater score decrease in the active treatment arm. Fully Conditional Specification (FCS) approach was used to produce 20 multiply imputed completed data sets. The FCS approach accommodates nonmonotonicity in the pattern of missing data and requires regression models to be specified for each variable with missing values needing imputation. All models included age, sex, in psychotherapy at baseline, use of any antidepressants at baseline and treatment group. The resulting completed datasets were combined using Rubin's Rules. * = p <0.05, ** = p <0.01.

Figure 1.

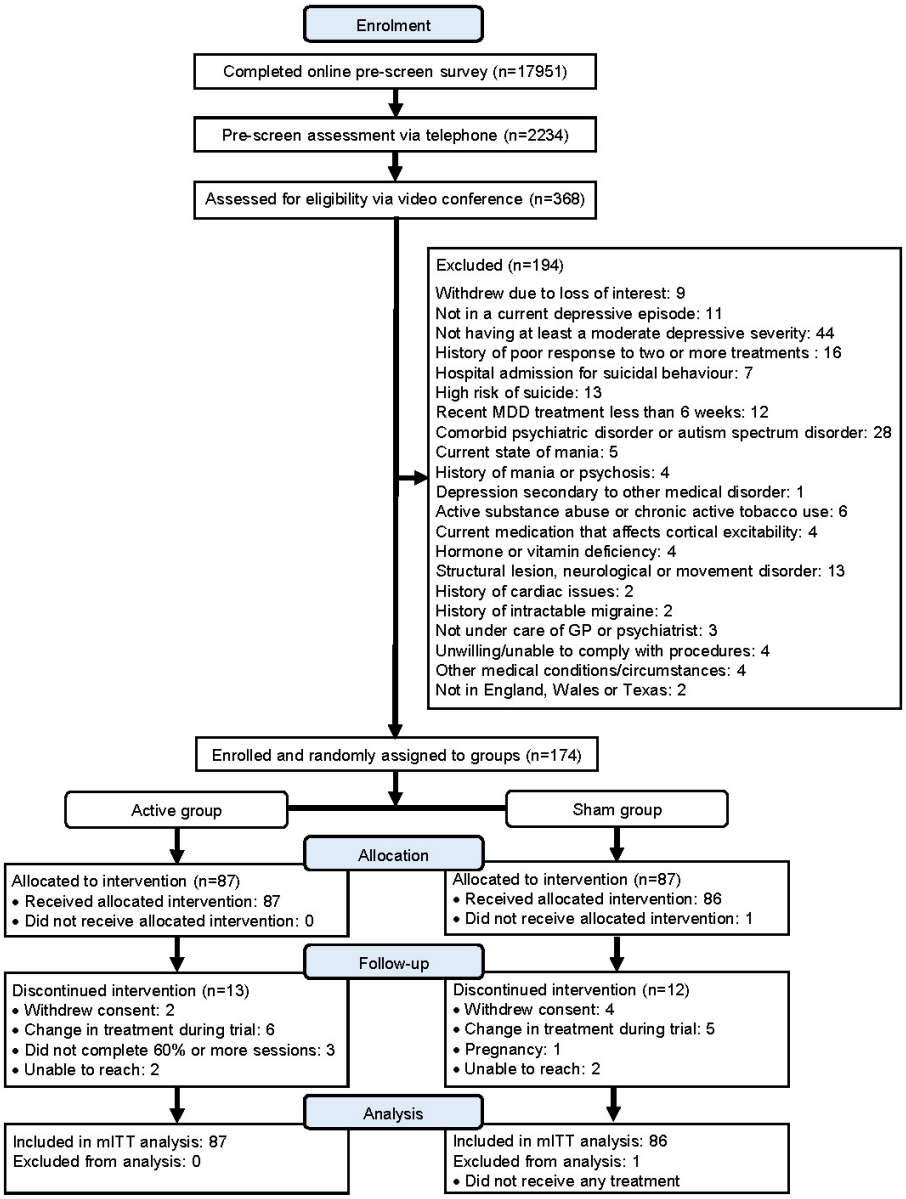
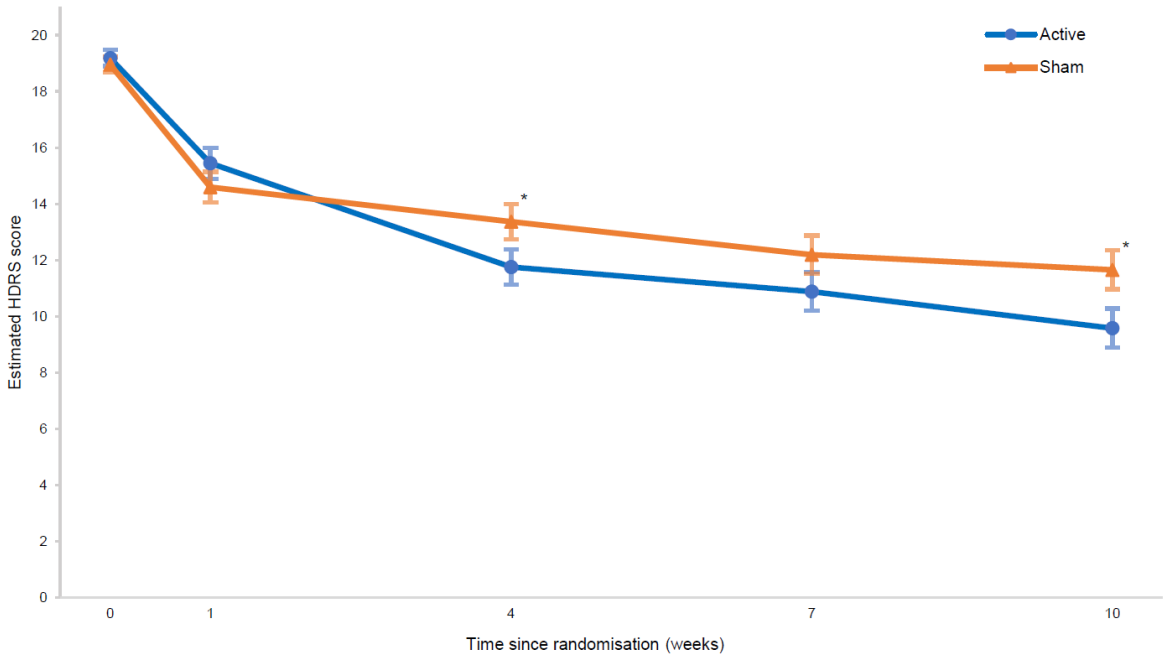
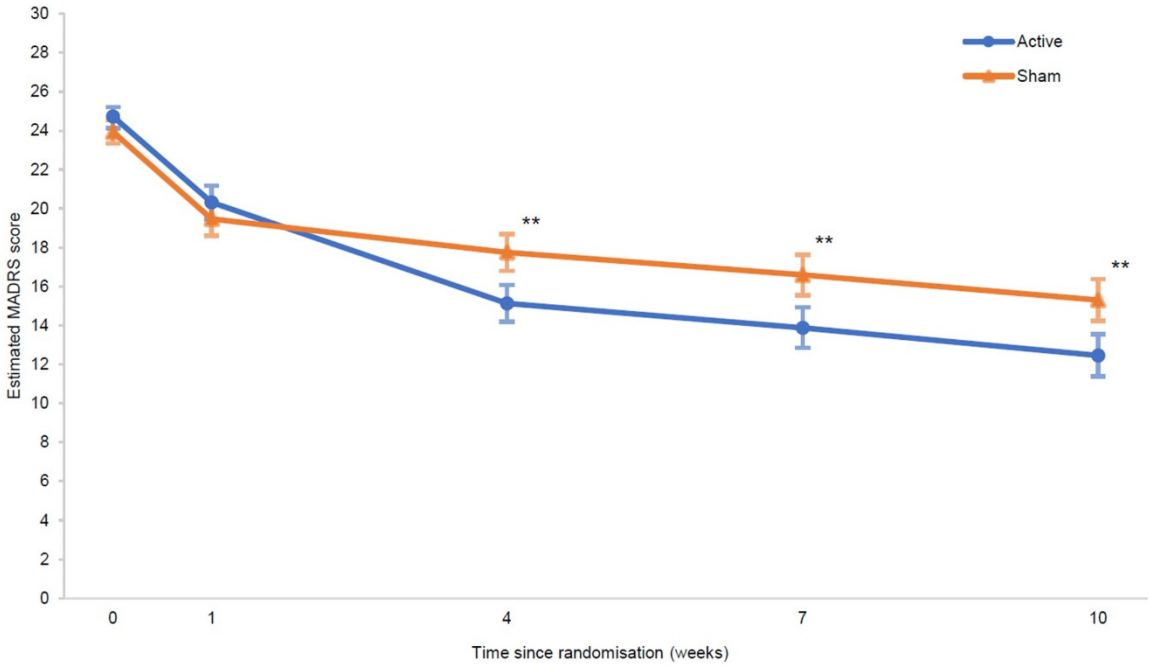

Enrolment
Completed online pre-screen survey (n=17951)
Pre-screen assessment via telephone (n=2234)
Assessed for eligibility via video conference (n=368)
Excluded (n=194)
Withdrew due to loss of interest: 9
Not in a current depressive episode: 11
Not having at least a moderate depressive severity: 44
History of poor response to two or more treatments : 16
Hospital admission for suicidal behaviour: 7
High risk of suicide: 13
Recent MDD treatment less than 6 weeks: 12
Comorbid psychiatric disorder or autism spectrum disorder: 28
Current state of mania: 5
History of mania or psychosis: 4
Depression secondary to other medical disorder: 1
Active substance abuse or chronic active tobacco use: 6
Current medication that affects cortical excitability: 4
Hormone or vitamin deficiency: 4
Structural lesion, neurological or movement disorder: 13
History of cardiac issues: 2
History of intractable migraine: 2
Not under care of GP or psychiatrist: 3
Unwilling/unable to comply with procedures: 4
Other medical conditions/circumstances: 4
Not in England, Wales or Texas: 2
Enrolled and randomly assigned to groups (n=174)
Active group
Sham group
Allocation
Allocated to intervention (n=87)
• Received allocated intervention: 87
• Did not receive allocated intervention: 0
Allocated to intervention (n=87)
• Received allocated intervention: 86
• Did not receive allocated intervention: 1
Follow-up
Discontinued intervention (n=13)
• Withdrew consent: 2
• Change in treatment during trial: 6
• Did not complete 60% or more sessions: 3
• Unable to reach: 2
Discontinued intervention (n=12)
• Withdrew consent: 4
• Change in treatment during trial: 5
• Pregnancy: 1
• Unable to reach: 2
Analysis
Included in mITT analysis: 87
Excluded from analysis: 0
Included in mITT analysis: 86
Excluded from analysis: 1
• Did not receive any treatment

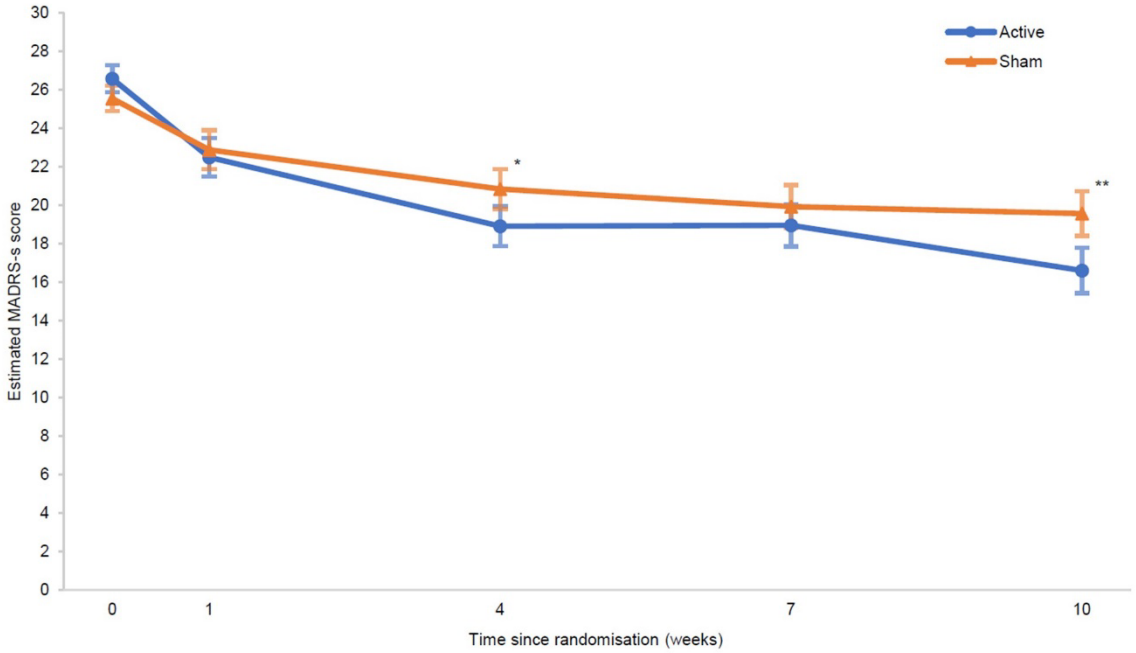
Figure 2.


Active
Sham
Estimated HDRS score
20
18
16
14
12
10
8
6
4
2
0
0
1
4
7
10
Time since randomisation (weeks)
*
*

Extended Data Figure 1.



Extended Data Figure 2.



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Methods

Ethics and study design

The study was a multisite, double-blind, placebo-controlled, randomized, superiority controlled trial (RCT) of 10-week home-based tDCS treatment in MDD followed by a 10-week open-label treatment. Participants were recruited from throughout England and Wales, UK, and Texas, USA. Recruitment sites were at University of East London, London, UK and University of Texas Health Science Center at Houston, Texas, USA, respectively.

All participants provided written informed consent. Ethical approval was provided by South Central-Hampshire B Research Ethics Committee, UK (ref. 22/SC/0023) and WIRB-Copernicus Group International Review Board, USA (ref. 1324775), ClinicalTrials.gov (NCT05202119). Research execution included local research assistants who are included as co-authors.

The study protocol is available in the Supplementary Information.

Participants

Participants were adults 18 years or older, with MDD and in current depressive episode as determined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[21] criteria and assessed in a structed clinical interview, Mini-International Neuropsychiatric Interview (MINI; Version 7.0.2).[22] Inclusion criteria included: having at least moderate severity of depressive symptoms, as measured by score of 16 or greater on 17-item Hamilton Depression Rating Scale (HDRS);[23] being treatment-free or taking stable antidepressant medication or in psychotherapy for at least 6 weeks prior to enrolment and agreeable to maintaining same treatment throughout the trial; under care of GP or psychiatrist. Exclusion criteria included: having treatment resistant depression, defined as inadequate clinical response to two or more trials of antidepressant medication at an adequate dose and duration; significant suicide risk based on Columbia Suicide Severity Rating Scale (C-SSRS) Triage and Risk Identification Screener;[60] comorbid psychiatric disorder; taking medications that affect cortical excitability (e.g., benzodiazepines, epilepsy medication); and contraindications to tDCS. Sex was determined by participant self-report, and there was no exclusion of males or females and no upper limit on how many participants of each sex or gender could enrol.[61] Full inclusion and exclusion criteria are presented in Supplementary Notes – Inclusion and exclusion criteria.

Procedures

Participants were recruited through Flow Neuroscience website, email lists and social media posts. Individuals completed an online pre-screening form, hosted by a contract research organization (CRO), followed by a telephone call with a CRO member. Individuals then provided written informed consent and had an assessment with a research team member by Microsoft (MS) Teams videoconference. All participants were registered with a primary care physician as an inclusion criterion (Supplementary Notes – Inclusion and exclusion criteria, Supplementary Table 1). Research team members completed training in clinical trial ethics and procedures, namely Good Clinical Practice, MINI interview schedule, C-SSRS, and clinical rating scales. Principal site investigators were consultant psychiatrists and reviewed eligibility of each participant and clinical assessments. Participants were compensated £30 or $60 for each study visit during the blinded phase of the trial. Participants enrolled in the UK were able to keep the tDCS device after trial completion.

Randomization

Participants were randomly assignment to sham or active tDCS treatment in 1:1 ratio, which was performed independently in UK and USA. Block randomization, which is a form of stratified random sampling, was used with permuted block sizes of four and six. This was conducted by the sponsor, Flow Neuroscience, and stored in dedicated database, which was not accessible to research team members.

Intervention

Active and sham tDCS was administered using the Flow FL-100 device. The device was headset placed over the forehead with two pre-positioned conductive rubber electrodes, each 23 cm^2. Electrodes are in a fixed position with approximate placement of anode over F3 (left DLPFC) and cathode over F4 (right DLPFC) based on international 10-20 electroencephalography system.[54]

Active stimulation was 2 mA direct current stimulation for 30 minutes with gradual ramp up over 120 seconds at start and ramp down over 15 seconds at end of session. Sham stimulation with the same device and app was used to resemble the active intervention and to control for receiving the treatment schedule. An initial ramp up from 0 to 1 mA over 30 seconds then ramp down to 0 mA over 15 seconds and repeated at session end to provide tingling sensation which mimics active stimulation.

The 10-week RCT consisted of 5 tDCS sessions per week for 3 weeks followed by 3 tDCS sessions per week for 7 weeks. tDCS parameters were based on meta-analyses which demonstrated that treatment effects are most evident for 30 min stimulus duration for at least 20 sessions at 2 mA current in MDD.[34–36]

At week 10, participants and researchers were informed of treatment arm allocation. The 10-week open-label phase consisted of active tDCS sessions for all participants. Participants who in the RCT active tDCS treatment arm were offered 3 sessions per week for 10 weeks, and participants in RCT sham tDCS treatment arm were offered the active tDCS stimulation schedule, 5 sessions per week for 3 weeks then 3 sessions per week for 7 weeks.

tDCS stimulation was provided using a study specific installation of the app which connected to headset via Bluetooth. Researchers had access to remote monitoring with real-time data use to monitor compliance. Researchers received training to use the headset and were present by videoconference for initial session to support participants who were at home, with the app-guided training to demonstrate electrode placement, consisting of video and augmented reality via device camera. All remaining tDCS sessions were completed by participants at home, without the presence of a researcher. Participants were asked to have video and microphone on during initial session. Participants were advised to sit or lie down during use, not to use the headset outdoors, close to water, whilst driving, during any activity that could lead to a significant risk of injury, while intoxicated or incapacitated, or in environments with strong magnetic fields.

Blinding

Participants and research team members were blind to group allocation. We sought to have same research team member present for same participant at each study visit. A second research team member joined clinical reviews for independent ratings and would not be present whilst adverse events or stimulation was discussed in order to prevent any potential bias. Ratings were crosschecked and reviewed by principal site investigators.

At week 10, following completion of all assessments and prior to unblinding, participants were asked whether they thought they had been using the 'active' or sham' tDCS device and how certain they were, as measured by a rating on a scale from 1 ('very uncertain') to 5 ('very certain'). Once this had been completed, then the research team member accessed the online

remote monitoring system to unblind allocation and informed the participant of group allocation. At point of unblinding, an automatic email notification was sent to the principal investigator and research team members that unblinding had occurred.

Outcomes

Primary outcome was adjusted mean group difference in depressive symptom severity between active and sham treatment arms as measured by 17-item Hamilton Depression Rating Scale (HDRS)[23] at the week 10 end of treatment compared to baseline.

Depressive symptom severity was measured by clinician-rated scales, HDRS and Montgomery-Åsberg Depression Rating Scale (MADRS),[26] and self-report scale, Montgomery-Åsberg Depression Rating Scale - self-report (MADRS-s),[27] suicide ideation and attempts by C-SSRS,[60] and manic symptoms by Young Mania Rating Scale (YMRS)[31] at baseline and at weeks 1, 4, 7, 10 and 20. Anxiety symptoms were measured by Hamilton Anxiety Rating Scale (HAMA)[30] and quality of life by EQ-5D-3L,[28,29] consisting of five dimensions (mobility, self-care, usual activities, pain and discomfort) at baseline and at weeks 10 and 20.

Secondary outcomes were adjusted mean group difference in depressive symptom severity between active and sham treatment arms as measured by MADRS and MADRS-s at week 10 compared to baseline; clinical response defined as a minimum of 50% reduction from baseline in HDRS, MADRS and MADRS-s at week 10; clinical remission defined as HDRS score 7 or less, MADRS score 10 or less, and MADRS-s score 12 or less; and quality of life as measured by EQ-5D-3L at week 10.

Exploratory outcomes included correlation between adherence to stimulation and HDRS, MADRS decrease in active treatment arm at week 10; changes in anxiety symptoms from baseline to week 10; and presence of hypomanic/manic symptoms at week 10.

Exploratory outcomes in neuropsychological functioning was assessed by Rey Auditory Verbal Learning Test (RAVLT)[32] total learning sore, for memory and verbal learning, and Symbol Digit Modalities Test (SDMT)[33] for psychomotor speed and visuospatial attention, assessed at baseline, weeks 10 and 20. Order and versions were counterbalanced. Written SDMT was chosen to reduce the chance of task interference from poor internet signal. SDMT

was mailed to participants, completed by pen and paper during session, and recorded by screenshot.

Treatment acceptability was assessed by our treatment acceptability questionnaire (TAQ)[13] at baseline, weeks 10 and 20. Full description of exploratory outcomes is presented in Supplementary Tables 16, 19, 21, 23-35, 37, 38, 46-53 and Supplementary Figures 1-6, 10-12 .

Safety

Adverse events were assessed at each visit, and participants were able to contact the research team by a dedicated cell number at any time. tDCS Adverse Events Questionnaire (AEQ)[41] was administered at weeks 10 and 20.

Sample size

Sample size calculation was based on Brunoni et al.,[38] with two-sample t-test for mean difference with 80% power and one-sided Type 1 error 0.025, resulting in a sample size of 176 MDD participants. To increase power to 87.6%, sample size was increased to 216. Assuming 20% attrition rate, total sample size was 270 participants. A pre-specified interim analysis was performed when 90 MDD participants completed week 10, which included both futility assessment and sample size re-estimation.[62] The interim analysis was able to modify the trial in two ways for the primary endpoint, to declare the trial futile and stop enrolment or to specify the number of participants between 100 and 270 for powering the trial based on promising zone methodology.[63,64]

Statistical analysis

Intent-to-treat (ITT) analysis consisted of all randomized participants and classified according to intended treatment. Participants excluded prior to randomization were considered screen failures. Modified intent-to-treat (mITT) analysis set included ITT participants who received at least 1 tDCS session (active or sham) and excluded participants randomized in error. Per Protocol Analysis Set (PP) consisted of: participants in mITT analysis set, participants with a device failure within the 10-week randomised trial, and participants with deviation from the clinical investigation plan caused by the investigational device or by problems with respect to tolerability, and excluded: participants who took a new medication or treatment during the trial

which are listed as exclusion criteria, participants who do not meet the inclusion criteria or fulfilled exclusion criteria, participants who had performed less than 10 sessions during the first 3 week, and participants with major protocol violations that would be expected to confound clinical assessment (Statistical Analysis Plan (SAP), section 2).

Primary effectiveness outcome was estimated mean group difference in HDRS scores in participants randomized to active and sham treatments using a mixed model for repeated measures (MMRM). The model included the HDRS baseline value, antidepressant medication status, psychotherapy treatment, age, and sex. Missing data were categorized by the reason for missingness (missing at random or not) and differentially imputed based on that classification. If *p*-value were less than one-sided $p = 0.025$, then endpoint would be declared positive (SAP sections 3.1 to 3.1.4. sections 4 and 5).

MMRM allows for inclusion of data from all time points in the model and not only baseline and week 10 end of treatment values, and MMRM allows for inclusion of participants with missing week 10 values. The MMRM approach is a direct likelihood approach. MMRM parameters were estimated using SAS PROC MIXED (SAS Institute, Cary NC Version 9.4 or higher). In a matrix equation, the MMRM can be expressed as: $Y_i = X_i\beta + Z_iu + e_i$; where β is the vector of fixed-effect regression parameters (for the overall mean change, the treatment effect θ, a vector of post-baseline time effects τ, a vector of treatment-by-time interaction effects η, and a vector of covariate effects φ that includes baseline HDRS-17 and optionally, other a priori selected covariates). X is a design matrix for the fixed effects, Z is a design matrix used to account for other random effects u, if any were included. Key assumptions are about e, the random error vector. It is assumed that the expected values are zero, i.e., $E(e) = 0$. An unstructured covariance is assumed requiring estimation of variances at each visit and all pairwise covariances, i.e., $Var(e)=\sigma e2Vunstructured$.

If the primary endpoint is met, then secondary endpoints can be tested based on a hierarchical approach. As specified in the protocol, Hochberg[65,66] approach was used for controlling multiplicity (Supplementary Table 11). The Hochberg correction rank orders the endpoints based on the p-value size, ranking them from largest to smallest, and compares those values to a sequentially decreasing alpha-level to determine whether the null hypothesis should be rejected. Secondary outcomes were: HDRS clinical response and remission, EQ-5D-3L change, and change in ratings, response and remission in MADRS and MADRS-s (SAP sections 3.1.5 to 3.1.9).

Exploratory endpoints were analyzed through summary statistics as means and SD or percentages and odds ratios. The two groups were compared through Student's t-test or Fisher Exact Test as appropriate. Spearman correlation was used to assess the association between two continuous variables. 95% confidence intervals (CI) were presented. Percentages of participants who correctly guessed the arm that they were in were compared through Fisher Exact Test. Subgroup analyses of primary and secondary endpoints were conducted through stratification by antidepressant usage at baseline and site (SAP section 3.1.10 and section 8).

Standard deviations are provided based Cochran's[67] conversion of SE to SD weighted by sample size. Type 1 error was controlled by only testing the 3 named secondary endpoints after meeting the primary endpoint; nominal *p*-values are provided for all other evaluations.

Full description of the statistical analyses and handling of missing data can be found in Supplementary Information - SAP.

Data Availability Statement

The deidentified individual participant data and the data dictionary that support the findings of this study are available from the academic researchers or the sponsor beginning 6 months after publication because of legal reasons. However, restrictions apply to the availability of these data and so are not publicly available. The Statistical Analysis Plan is available in the Supplementary Materials. A data request and brief analysis plan will be required in accordance with Ethics Committee requirements. These will be reviewed by the lead, study steering committee and study sponsor. A data transfer agreement (DTA) will have to be completed prior to any data being shared. Following completion of the DTA, data will be shared as password-protected files. Data sharing will abide by the rules and policies defined by the sponsor, relevant institutional review boards, and local, state and federal laws and regulations. Rights and privacy of individuals participating in the research will be protected at all times. Approval will not be provided for commercial use of the data. Requests can be made to Professor Cynthia H.Y. Fu (c.fu@uel.ac.uk, cynthia.fu@kcl.ac.uk).

Code Availability Statement

The analysis code for the longitudinal model is provided in the Supplementary Information. The full code used for the data analysis will be available from the Sponsor beginning 6 months after publication of the trial results.

Methods-only references

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