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Home-based transcranial direct current stimulation in bipolar depression: an open-label treatment study of clinical outcomes, acceptability and adverse events

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Abstract

Background Current treatments for bipolar depression have limited effectiveness, tolerability and acceptability. Transcranial direct current stimulation (tDCS) is a novel non-invasive brain stimulation method that has demonstrated treatment efficacy for major depressive episodes. tDCS is portable, safe, and individuals like having sessions at home. We developed a home-based protocol with real-time remote supervision. In the present study, we have examined the clinical outcomes, acceptability and feasibility of home-based tDCS treatment in bipolar depression.

Results Participants were 44 individuals with bipolar disorder (31 women), mean age 47.27 ± 12.89 years, in current depressive episode of at least moderate severity (mean Montgomery Asberg Depression Rating Scale (MADRS) score 24.59 ± 2.64). tDCS was provided in bilateral frontal montage, F3 anode, F4 cathode, 2 mA, for 30 min, in a 6-week trial, for total 21 sessions, a follow up visit was conducted 5 months from baseline. Participants maintained their current treatment (psychotherapy, antidepressant or mood stabilising medication) or maintained being medication-free. A research team member was present by video conference at each session. 93.2% participants ($n = 41$) completed the 6-week treatment and 72.7% of participants ($n = 32$) completed the 5 month follow up. There was a significant improvement in depressive symptoms following treatment (mean MADRS 8.77 ± 5.37) which was maintained at the 5 month follow up (mean MADRS 10.86 ± 6.90), rate of clinical response was 77.3% (MADRS improvement of 50% or greater from baseline), and rate of clinical remission was 47.7% (MADRS rating of 9 or less). Acceptability was endorsed as "very acceptable" or "quite acceptable" by all participants. No participants developed mania or hypomania.

Conclusions In summary, home-based tDCS with real-time supervision was associated with significant clinical improvements and high acceptability in bipolar depression. Due to the open-label design, efficacy findings are preliminary.

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Keywords Transcranial direct current stimulation, Bipolar disorder, Depression, Neuromodulation, Non-invasive

Introduction

Bipolar disorder is characterized by recurrent episodes of mania or hypomania along with depression which can often be progressive with much heterogeneity between individuals. Bipolar disorder impacts approximately 1–5% of the population and is associated with increased premature mortality, in which life expectancy is reduced by 9–17 years due to comorbid medical illnesses and suicide (Dome et al. 2019). Bipolar disorder is linked to substantial functional impairment across diverse domains, including responsibilities in work or school, household duties and maintenance of relationships (Sanchez-Moreno et al. 2009). Depressive episodes often have a greater impact on functional impairment than hypo(manic) symptoms in bipolar disorder (Rosa et al. 2010), and the severity of depressive symptoms demonstrates a robust association with the level of functional impairment (Simon et al. 2007). The economic costs are estimated to be more than £6.43 billion in the UK due to direct health care costs and indirect costs (Simon et al. 2021).

The most common treatments are a combination of medications, including mood stabilisers and antipsychotic medication, and talking therapy (Grande et al. 2016). Lithium is an effective treatment option, but can be associated with adverse drug reactions and poses specific risks with increased plasma levels, including declines in renal function and hypothyroidism (Shine et al. 2015). Psychotherapy is frequently recommended in bipolar depression and is associated with improvements in symptoms and psychosocial functioning (Miklowitz et al. 2021; Swartz and Swanson 2014).

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that is a potentially novel treatment for bipolar depression. tDCS delivers a low intensity electrical current 0.5–2.0 mA to the scalp using non-focal sponge electrodes (Woodham et al. 2021). The current can shift membrane potentials which increasing the likelihood towards depolarization at the anode and hyperpolarization at the cathode (Nitsche and Paulus 2000). tDCS primes neuronal clusters but does not cause the direct firing of neurons in contrast to repetitive transcranial magnetic stimulation (rTMS) (Mutz et al. 2019) which triggers an action potential and electroconvulsive therapy (ECT) which causes a generalised seizure (Woodham et al. 2021).

Meta-analyses demonstrate that a course of tDCS for the treatment of a major depressive episode is associated with significant improvement in depressive symptoms and clinical response in both unipolar and bipolar depression (Hsu et al. 2024; Mutz et al. 2018, 2019). In an individual patient level analysis, there is evidence that longer courses of treatment showed stronger effects (Nikolin et al. 2023). As tDCS requires daily sessions over several weeks, this is time intensive and potentially costly in terms of travel. Providing the treatment at home could improve engagement, compliance and clinical efficacy. However, only a single trial has investigated home-based tDCS in bipolar depression (Lee et al. 2022). This recent randomised controlled trial (RCT) of home-based tDCS in bipolar depression did not observe a significant effect in efficacy for active tDCS relative to sham tDCS (Lee et al. 2022). The RCT though was likely underpowered due to the small sample size ($n=64$) and participants had several sessions in clinic with research team members (Lee et al. 2022). Moreover, a recent meta-analysis of RCTs in bipolar depression, which had included this RCT (Lee et al. 2022), reported significant improvement in depressive symptoms following active relative to sham tDCS (standardised effect size −1.17, 95% confidence interval (CI) -1.65 to -0.69) (Hsu et al. 2024). Furthermore, the meta-analysis observed larger effect sizes when the length of treatment was increased from 6 to 10 weeks (Hsu et al. 2024). In support, our multisite, randomised, placebo sham-controlled trial demonstrated high efficacy, acceptability and safety for a 10-week home-based treatment protocol in unipolar depression ($n=174$ participants) and participants liked having the treatment sessions at home (Woodham et al. 2023).

In the present study, we sought to investigate a fully remote, home-based protocol of tDCS treatment with real-time remote supervision in bipolar depression. The current study investigated the efficacy, acceptability and safety of a 6-week course of home-based, remotely supervised tDCS treatment for bipolar depression.

Materials and methods

Study design and tDCS protocol

Ethical approval was provided by the London Fulham Research Ethics Committee the study was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants electronically. All sessions were conducted by Microsoft Teams video conference. The study was a single-site, open-label, single arm acceptability and feasibility trial of home-based tDCS treatment for bipolar depression (ClinicalTrials.gov number: NCT05436613). The protocol consisted of a 6-week course of active tDCS,

which was provided 5 times a week for 3 weeks and then twice a week for 3 weeks, for a total of 21 sessions, with a minimum of 15 sessions (70%) required for study completion.

A bifrontal montage was applied with the anode positioned over left dorsolateral prefrontal cortex (DLPFC) (F3 position according to international 10/20 EEG system) and cathode over right DLPFC (F4 position). Each electrode was a 23cm^2 conductive rubber electrode covered by saline soaked sponges. Simulation was 2 mA for a duration of 30 min with a gradual ramp up over 120 s at the start and ramp down over 15 s at the end of each session. The Flow Neuroscience tDCS device was used for all participants.

Participants were taught to use the tDCS device under the remote supervision of a research team member via video conference. A member of the research team was present at each session, maintaining a discrete presence with their camera on, and the participant had both their camera and microphone enabled, facilitating communication with the researcher. Interaction between the participant and team only occurred if the participant required support. Participants were permitted to read, use handheld mobile devices, tablets, laptops or desktop computers during the sessions, while sitting quietly.

Inclusion and exclusion criteria

Participants were recruited using online advertisements and referrals from general practitioners, psychiatrists, and community mental health teams. Inclusion criteria: (1) adults aged 18 years or older; (2) diagnosis of bipolar disorder and in a current depressive episode, defined by Diagnostic Statistic Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013), determined by a structured assessment using the Mini-International Neuropsychiatric Interview (MINI; Version 7.0.2) (Sheehan et al. 1998); (3) having at least a moderate severity of depressive symptoms as measured by a minimum score of 18 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979); (4) taking a stable dosage of mood-stabilizing medication for a minimum of two weeks or not taking any medication for a minimum of two weeks. Exclusion criteria: (1) symptoms of mania or hypomania as measured by a score of 8 or greater on the Young Mania Rating Scale (YMRS) (Young et al. 1978); (2) any concurrent psychiatric disorders as defined by DSM-5 Axis I or II; (3) having a significant risk of suicide; (4) a history of seizure which resulted in a loss of consciousness; (5) a history of neurological disorder or history of migraines; (7) any exclusion criteria which prevents tDCS administration, including superficial scalp or skin conditions (e.g. psoriasis or eczema), if contact with the scalp is not possible, having metallic implants including intracranial electrodes, surgical clips, shrapnel or pacemaker.

Clinical assessments

Clinical assessments were conducted at baseline, week 2, and week 6, and a follow up assessment was made at month 5 following the initial tDCS session (week 18). Assessments were conducted using the following scales: clinician-rated measures of depressive symptoms, MADRS and Hamilton Depression Rating Scale (HDRS-17) (Hamilton 1960); self-report measure of depressive symptoms: Patient Healthy Questionnaire-9 (PHQ-9) (Kroenke et al. 2001); clinician-rated measure of anxiety symptoms: Hamilton Anxiety Rating Scale (HAMA) (Hamilton 1959); clinician-rated measure of manic symptoms, YMRS (Young et al. 1978); self-report measure of disability and impairment: Sheehan Disability Scale (SDS) (Sheehan 1893); self-report Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al. 1993). Clinical response was defined as an improvement of 50% or greater in MADRS or HAMD score from baseline. Clinical remission was defined as a MADRS score less than 10 and a HAMD score of less than 8. The same researcher was present at each visit and completed ratings for each participant throughout the study as much as possible with clinical supervision from the principal investigator.

Safety, tolerability and acceptability

Safety and tolerability were evaluated by monitoring of adverse events before and after each treatment session using the tDCS Adverse Events Questionnaire (AEQ) (Brunoni et al. 2011). We developed an acceptability questionnaire based on Sekhon et al. (2017) framework model (Woodham et al. 2022) The acceptability questionnaire consisted of five questions that were centred on acceptability sub-facets: (1) overall acceptability: 'How acceptable did you find the tDCS sessions and how do you feel about the sessions overall?'; (2) subjective efficacy: 'How helpful were the tDCS sessions for improving your depressive symptoms?'; (3) adverse effects: 'How likely do you think there will be negative side effects from the tDCS sessions?'; (4) ethical perspectives: 'How ethical do you think the tDCS sessions are?'; (5) overall burden: 'How much effort is required for the tDCS sessions?'. Responses were assessed on a 7-point Likert style scale along with open-ended responses. Acceptability data were acquired at baseline and week 6. An additional question and four open-ended questions were asked at week 6: (6) retrospective attitude: 'Would you recommend the tDCS sessions to others?'; (7) Positive aspects: 'What were the most successful parts of the study?'; (8) Negative aspects: 'What were the least successful parts of the study?'; (9) Possible improvements: 'How do you

think the study could have been improved?'; (10) Further comments: 'Do you have anything you would like to add, or any further comments?'. Participants completed the questionnaire in a semi-structured interview recorded on video using Microsoft Teams.

Statistical analysis

An intention-to-treat analysis (ITT) was completed including all participants who completed at least one session of tDCS. Last observation carried forward (LOCF) method was used for missing data on clinical assessments. Due to the open label nature and small sample size of the trial, LOCF method was deemed suitable for handling missing data as it is a conservative and widely used method for handling missing data that results in a single reproduceable dataset. Six repeated-measures ANOVAS were calculated with HDRS-17, MADRS, HAMA, YMRS, PHQ-9 and SDS. The dependent variables were the total scores, and the assessment time-points were the within-subject factor, consisting of four levels: week 0, baseline (t_0), week 2, after session 10 (t_1), week 6, end of treatment period (t_2) and week 18, end of follow up (t_3). Completers analyses were conducted including participants who completed the minimum number of stimulations and the week 6 and week 18 study visits. Statistical analyses were conducted using IBM SPSS for Windows version 29.0. All analyses were performed using two-tailed significance values of $p=0.05$. The Greenhouse-Geisser correction was utilized in cases where Mauchley's assumption of sphericity was violated. Post-hoc pairwise comparisons were performed with Bonferroni corrections. For the acceptability questionnaire, the median and interquartile range were computed for each response at every time point and the nonparametric Friedman's ANOVA was performed to assess significant differences over time for each response for participants with data at all three timepoints ($n=32$), and nonparametric Wilcoxon signed-rank test was used to assess differences between two time points, considering the Likert scale, uncertain difference between anchors, and the limited range of response choices.

Table 1 Demographic and clinical data at baseline

Total number (Female)	44 (31)
Mean age (years)	47.27 ± 12.89
Age range (years)	24–76
Age of onset (years)	27.80 ± 9.28
Years of education	16.30 ± 2.46
IQ	100.66 ± 9.29
Duration of illness (years)	18.98 ± 12.47
Duration current depressive episode (weeks) (range)	49.55 ± 100.4
Previous number of episodes	18.16 ± 16.13
Clinical ratings	
MADRS	24.59 ± 2.64
HDRS-17	19.98 ± 2.62
HAMA	16.55 ± 5.26
YMRS	2.20 ± 1.49
PHQ-9	16.80 ± 4.94
SDS	20.77 ± 5.87
Treatments during trial	
Taking mood stabilizer and other medications	38 (86)
Taking antidepressant medication only	1 (2)
Taking no medication	5 (11)
Engaged in psychotherapy	12 (27)

Categorical variables are presented as number of participants with percentage in parentheses for treatments during trial. Mean values are presented with '±' standard deviation values. MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS-17, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; YMRS, Young Mania Rating Scale; PHQ-9, Patient Health Questionnaire-9; SDS, Sheehan Disability Scale

Results

Participants

A total of 44 participants were enrolled (31 women), mean age 47.27 ± (standard deviation) 12.94 years (Table 1). Participants were recruited from online advertisements (77.3%), primary care GP clinics (15.9%), and secondary care community mental health teams (6.8%). At baseline, mean MADRS and HAMD scores were 24.6±2.64 and 20.0±2.62, respectively. Mean duration of the current depressive episode was 0.95±1.93 years (range 0.3 to 12 years). 97% of participants ($n=43$) completed a minimum of 70% of sessions (15 tDCS sessions), mean 19.6±1.9 sessions; 93.2% of participants ($n=41$) completed the full 6-week course of treatment; and 72.7% of participants ($n=32$) attended the 5-month follow up visit. 86.3% of participants ($n=38$) were taking mood-stabilising medication, 2% of participants ($n=1$) were taking antidepressant medication without mood-stabilising medication, 5 participants were not taking any pharmacological interventions, and 27.3% of participants ($n=12$) were in psychotherapy (CBT or psychodynamic psychotherapy) in addition to taking medication.

In the follow up period, 24 participants continued using the tDCS device for some of the follow up period, and 16 participants continued to use the device at the 5-month visit.

Clinical assessments

For all four time points (weeks 0, 2, 6 and 18), 73% of participants ($n=32$) completed clinical questionnaires assessments at all time points and were included in the completers analysis. Data were missing from 27% of participants ($n=12$) at the end of the follow up period (week 18).

At week 6, mean MADRS score was 8.91±5.56, in which 34 participants (77.3%) showed clinical response and 21 participants (47.7%) achieved clinical remission (Fig. 1). At week 2, following 10 tDCS sessions, seven participants (15.9%) showed an early response, one

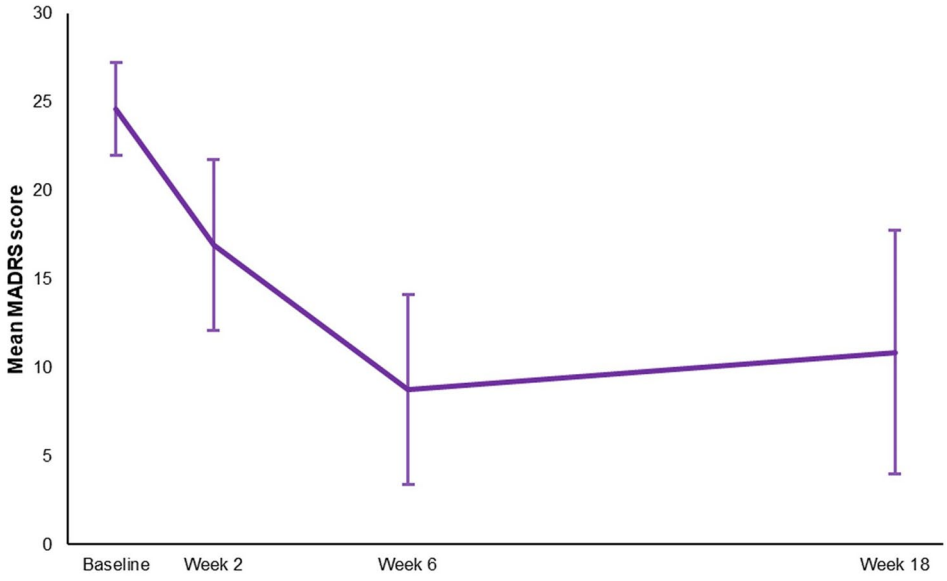

Fig. 1 Mean Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline to week-18 (intention-to-treat analysis). Error bars represent 1 standard deviation

Table 2 Clinical rating scale scores over the 6-week course of treatment and at the month 5 (18 week) follow up in the intension to treat analysis

	Baseline	Week-2	Week-6	Week-18	F-Value	*P*-Value
MADRS	24.59 ± 2.64	16.93 ± 4.82	8.77 ± 5.37	10.86 ± 6.90	120.51	$P < 0.001$
HDRS-17	19.98 ± 2.62	13.57 ± 4.14	6.77 ± 4.74	8.59 ± 5.99	98.84	$P < 0.001$
HAMA	16.55 ± 5.26	10.43 ± 4.61	6.36 ± 4.10	7.32 ± 4.85	60.72	$P < 0.001$
YMRS	2.20 ± 1.49	1.50 ± 1.15	0.80 ± 1.09	1.30 ± 1.37	12.21	$P < 0.001$
PHQ-9	16.80 ± 4.02	10.93 ± 4.94	6.52 ± 4.69	8.34 ± 5.68	56.39	$P < 0.001$
SDS	20.77 ± 5.87	16.39 ± 8.06	9.93 ± 7.85	11.66 ± 8.48	36.58	$P < 0.001$

Based on intention to treat analysis, using last observation carried forward (n = 44). MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS-17, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; Young Mania Rating Scale, YMRS; PHQ-9, Patient Health Questionnaire-9; SDS, Sheehan Disability Scale. Mean values are presented with '±' standard deviation values

Table 3 Clinical rating scale scores over the 6-week course of treatment and at the month 5 (18 week) follow up in the completers analysis

	Baseline	Week-2	Week-6	Week-18	F-Value	*P*-Value
MADRS	24.78 ± 3.00	16.72 ± 5.23	8.13 ± 5.48	10.81 ± 7.46	80.30	$P < 0.001$
HDRS-17	20.09 ± 2.58	13.41 ± 4.41	6.00 ± 4.64	8.50 ± 6.51	70.16	$P < 0.001$
HAMA	15.84 ± 4.46	10.37 ± 4.32	6.09 ± 4.17	7.41 ± 5.18	38.62	$P < 0.001$
YMRS	2.37 ± 1.54	1.44 ± 1.16	0.81 ± 1.18	1.50 ± 1.48	9.25	$P < 0.001$
PHQ-9	17.09 ± 4.20	11.25 ± 4.87	5.91 ± 4.74	8.41 ± 6.17	42.74	$P < 0.001$
SDS	20.28 ± 6.51	16.66 ± 8.27	8.88 ± 7.84	11.16 ± 8.87	27.57	$P < 0.001$

Data from participants who completed treatment and follow up (n = 32). MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS-17, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; Young Mania Rating Scale, YMRS; PHQ-9, Patient Health Questionnaire-9; SDS, Sheehan Disability Scale. Mean values are presented with '±' standard deviation values. Demographic data at baseline: female, $n = 26$; mean age 50.34 ± 12.53 years; age range, 24–76 years; age of onset, 29.34 ± 9.58 years; years of education, 16.34 ± 2.72; IQ, 101.13 ± 8.81; duration of illness, 20.16 ± 11.39 years; duration of current depressive episode, 54.94 ± 115.53 weeks; previous number of episodes, 21.17 ± 25.92

participant (2.3%) was in remission and mean MADRS score was 16.93±4.82. At week 18, mean MADRS score was 10.86±6.90, in which 20 out of 32 participants (62.5%) showed clinical response and 13 out of 32 participants (40.6%) achieved clinical remission. Repeated-measures analyses demonstrated significant clinical improvements in mean MADRS scores across time points in the ITT ($F_{(2,88)} = 120.51$, $p < 0.001$) (Table 2) and completers ($F_{(2,62)} = 80.30$, $p < 0.001$) analyses (Table 3). In the ITT analysis, post hoc tests revealed significant improvements between $t_{(0)}$, $t_{(1)}$, $t_{(2)}$, ($p < 0.001$) but no significant change between end of treatment week-6 ($t_{(2)}$) and

week-18 follow-up ($t_{(3)}$) ($p=0.71$) depressive symptom scores indicating that significant improvements were maintained at follow-up (Table 2). A similar pattern of results was evident in the completers analysis (Table 3).

In HDRS-17, there was a similar pattern of results. Mean HDRS-17 score was 6.77±4.74 at week 6, in which 37 participants (84.1%) showed clinical response and 31 participants (70.5%) achieved clinical remission (Fig. 2). At week 2, 12 participants (27.3%) showed an early response, 3 participants (6.8%) were in remission and mean HDRS-17 score was 13.57±4.14. At week 18, mean HDRS score was 8.59±5.99, in which 19 out of 32 participants (59.4%) showed clinical response and 18 out of 32 participants (56.3%) achieved clinical remission. Significant clinical improvements in mean HDRS-17 scores were evident across time points in ITT ($F_{(2,94)}=98.84$, $p<0.001$) and completers analyses ($F_{(2,64)}=70.16$, $p<0.001$). In the ITT analysis, post hoc tests revealed significant improvements between $t_{(0)}$, $t_{(1)}$, $t_{(2)}$, ($p<0.001$) but no significant change between end of treatment week-6 ($t_{(2)}$) and week-18 follow-up ($t_{(3)}$) ($p=0.76$) depression scores, indicating that significant improvements were maintained at follow-up (Table 2). A similar pattern of results was evident for the completers analysis (Table 3).

In HAMA, YMRS, PHQ-9 and SDS scores, there were significant improvements from baseline, which were maintained from week 2 to week 6 (Tables 2 and 3). Mean HAMA score at baseline was 16.6±5.26 (range 9–36), indicating mild to moderate severity of anxiety. Following treatment, the mean scores were 6.36±4.10 at 6-weeks and 7.32±4.85 at 18-weeks demonstrating mild anxiety (Fig. 3). Mean YMRS score at baseline was 2.20±1.49 (range 0–7), indicating an overall absence of significant manic or hypomanic symptoms. Following treatment, the mean score decreased to 0.80±1.09 at 6-weeks and 1.30±1.37 at 18-weeks demonstrating a reduction from initial manic or hypomanic symptoms (Fig. 4). Mean PHQ-9 score at baseline was 16.8±4.02, which improved following treatment (mean score at week 6=6.52±4.69) and was maintained at follow up (mean score at week 18=8.34±5.68) (Fig. 5). SDS rating of functional impairment was high at baseline (mean 20.77±5.87) and significantly improved at the end of treatment (mean score at week 6=9.93±7.85) and was maintained at follow up (mean score at week 18=11.16±8.87) (Fig. 6).

Safety, acceptability, and tolerability

The most common side effects were tingling (83.5%), skin redness (40.6%), itching (29.3%) and burning sensation, (26.5%) (Table 4, supplementary material Table 1). 90.6% of adverse events related to tDCS were rated as mild, 9% were rated as moderate and 0.4% were rated as severe. These included one report each of tingling and burning sensation and two reports each of itching and skin redness.

During the follow up period, common side effects were the same as during the trial (Supplementary Table 1). Two participants had experiences of dry skin and two participants who had continued to use the tDCS device reported experiencing hypomanic symptoms and had stopped using the device. Neither participant contacted the study team, and at the 5 month follow up visit

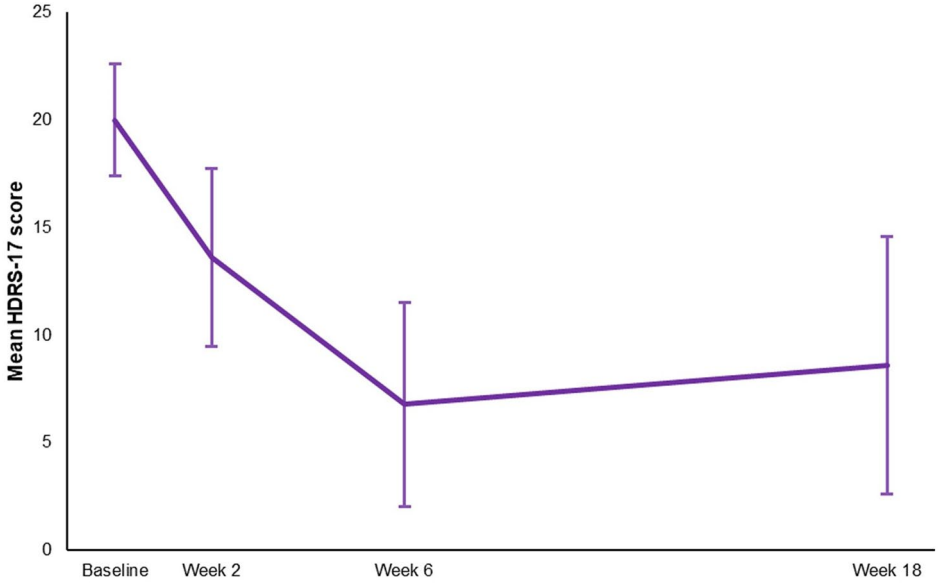

Fig. 2 Mean Hamilton Depression Rating Scale (HDRS-17) scores from baseline to week-18 (intention-to-treat analysis). Error bars represent 1 standard deviation

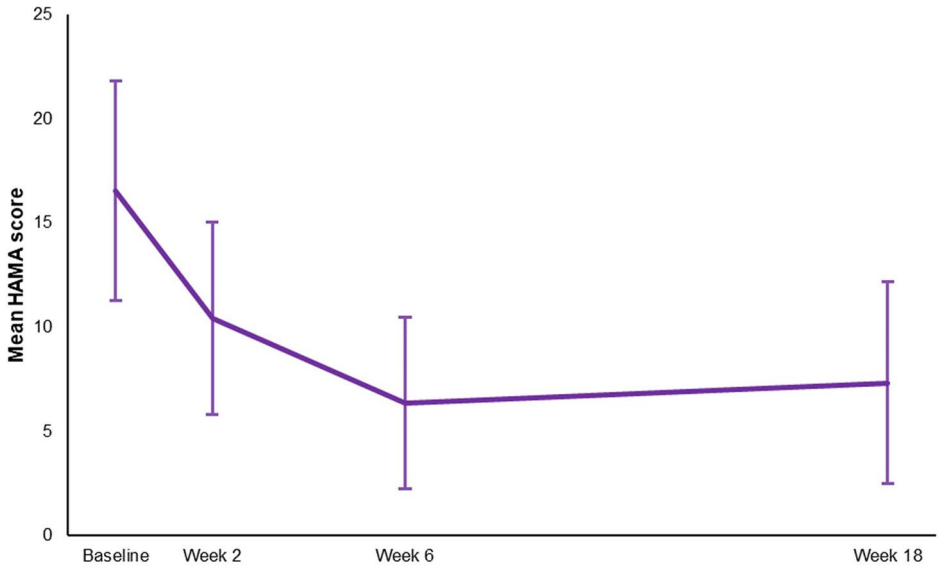

Fig. 3 Mean Hamilton Anxiety Scale (HAMA) scores from baseline to week-18 (intention-to-treat analysis). Error bars represent 1 standard deviation

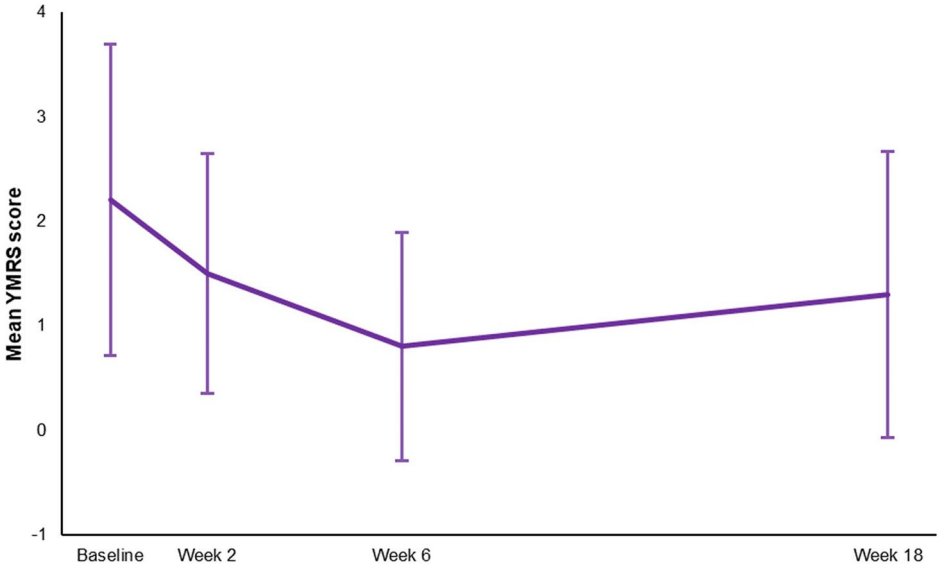

Fig. 4 Mean Young Mania Rating Scale (YMRS) scores from baseline to week-18 (intention-to-treat analysis). Error bars represent 1 standard deviation

hypomanic symptoms were not present for either participant, as indicated by YMRS assessment.

There was a significant increase in endorsement of acceptability as being "quite acceptable" at baseline and "very acceptable" post treatment and at follow up ($t_{(0)}$ Mdn=6, IQR=1; $t_{(2)}$ Mdn=7, IQR=0, $t_{(3)}$ Mdn=7, IQR=1) (X^2_F (2)=15.7, p=<0.001). Ratings for perceived effectiveness were endorsed as being "quite helpful" at baseline and post treatment, and "very helpful" at follow up with no significant change over time ($t_{(0)}$ Mdn=6, IQR=0.75; $t_{(2)}$ Mdn=6, IQR=1, $t_{(3)}$ Mdn=7, IQR=1) (X^2_F (2)=4.17, p=<0.13). Ethicality remained high at "very ethical" for all three time points, with no significant changes over time ($t_{(0)}$ Mdn=7, IQR=1; $t_{(2)}$ Mdn=7, IQR=0, $t_{(3)}$ Mdn=7, IQR=0) (X^2_F (2)=4.2, p=<0.12). The impact of side-effects showed a significant decrease from being "a bit unaffected/quite unaffected" at baseline to being "very much unaffected" post-treatment and "very much unaffected/quite unaffected" at follow up ($t_{(0)}$ Mdn=2.5, IQR=2.75; $t_{(2)}$ Mdn=1, IQR=1, $t_{(3)}$ Mdn=1.5, IQR=3.25) (X^2_F (2)=15.7, p=<0.001). There was also a significant decrease in the perceived amount of effort required which improved from "some more effort than usual" at baseline to "a little bit more effort than usual" post treatment and "a little bit less effort than usual" at follow up ($t_{(0)}$ Mdn=2, IQR=1; $t_{(2)}$ Mdn=3, IQR=3, $t_{(3)}$

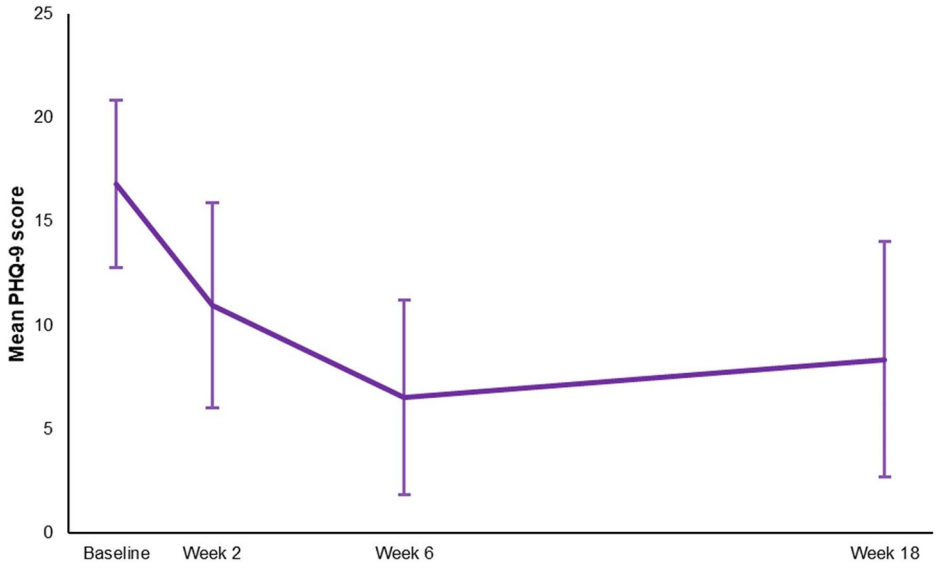

Fig. 5 Mean Patient Health Questionnaire-9 (PHQ-9) scores from baseline to week-18 (intention-to-treat analysis). Error bars represent 1 standard deviation

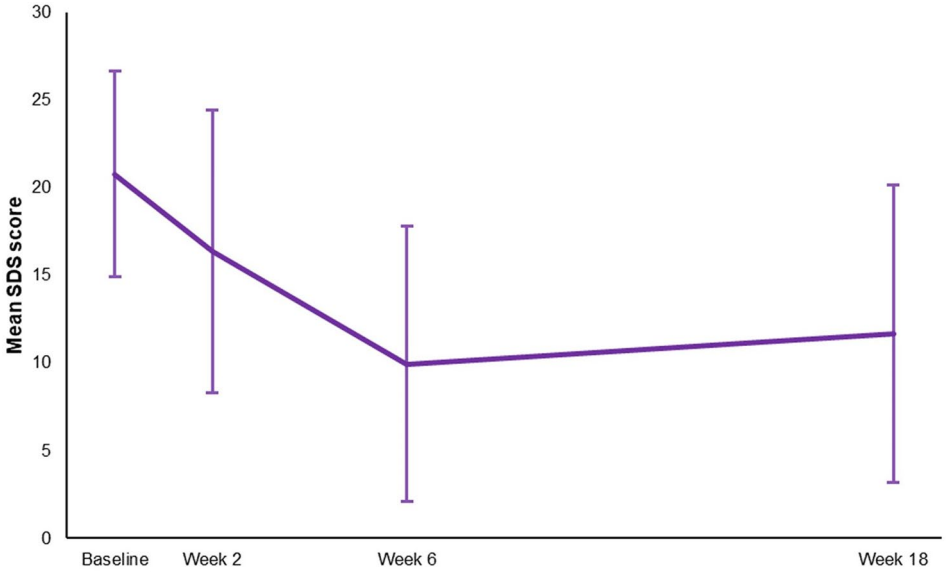

Fig. 6 Mean Sheehan Disability Scale (SDS) scores from baseline to week-18 (intention-to-treat analysis). Error bars represent 1 standard deviation

Mdn=5, IQR=3.75) (X^2_F (2)=33.9, p=<0.001). At post treatment and at follow up participants "would very strongly recommend" tDCS to others with no significant differences over time ($t_{(2)}$ Mdn=7, IQR=1, $t_{(3)}$ Mdn=7, IQR=1) (Z = -0.52, p=0.61) (Fig. 7).

Discussion

The present 6-week course of home-based tDCS with real-time supervision was associated with significant clinical improvements in bipolar depression, which were maintained at 5-month follow up from baseline. Participants experienced high rates of clinical response and remission, high treatment acceptability, and mild adverse effects. Depressive rating in scores at each time-point showed a consistent decrease in both clinician-rated and self-rated measures. Moreover, anxiety symptoms and disability measures were significantly improved at the end of treatment.

Adverse events related to tDCS were mild over 90% of the time and transient. The most common side effects were tingling, skin redness, itching and burning sensation, which are typical with tDCS (Brunoni et al. 2011). There were no serious adverse events associated with the device, nor were there any instances of

Table 4 Total incidence of side effects out of 860 sessions during the 6-week treatment phase of the trial

Side effect	Incidence	Percentage
Headache	19	2.2%
Neck pain	0	0.0%
Scalp pain	24	2.8%
Tingling	718	83.5%
Itching	252	29.3%
Burning sensation	228	26.5%
Skin redness	349	40.6%
Sleepiness	17	2.0%
Trouble concentrating	3	0.3%
Acute mood change	6	0.7%
Other	18	2.1%
Tinnitus	1	0.1%
Pressure on right eye	1	0.1%
Vibration	3	0.3%
Improved concentration	1	0.1%
stinging	1	0.1%
Sore feeling	2	0.2%
vivid dreams	2	0.2%
Dizziness	2	0.2%
Bruise	1	0.1%
Dry skin	3	0.3%
Throbbing in left eye	1	0.1%

Adverse events were recorded using the tDCS Adverse Events Questionnaire (Brunoni et al. 2011). An adverse event was present if the participant rated that it was at least remotely possible that it was associated with the intervention

treatment-emergent affective switching. Remote real-time supervision during stimulation allowed for close monitoring of adverse events and ensuring that the device was used correctly. However, this is resource intensive and reduces flexibility for patients. Monitoring of side effects with an online daily report has also been effective in a home-based trial (Alonzo et al. 2019) as well as periodic monitoring visits in two large home-based trials (Borrione et al. 2024; Woodham et al. 2023). Safety reporting for home-based tDCS treatments is an important consideration as reports of skin burns at the electrode site have been reported (Kumpf et al. 2023; Woodham et al. 2023), which can occur with insufficient moistening with conductive saline solution (Kortteenniemi et al. 2019) or application of tap water to moisten sponges (Frank et al. 2010; Palm et al. 2008). If participants encounter potential challenges in managing side effects independently, it could lead to the exacerbation of adverse events and eventual discontinuation of treatment.

In bipolar depression, Lee et al. (2022) recently reported an RCT of daily home-based active or sham tDCS as an adjunct treatment to mood-stabilising medication. No significant differences in depressive symptoms were found between groups after 6-weeks of treatment. However, the trial had included five in person clinical visits, and only 59.3% of participants completed the full course of treatment, and missed in person assessments were an exclusion criterion. In the present study, the protocol was fully remote with real-time visits during each session and the discontinuation rate was 6.8%.

While there is no definitive consensus regarding optimal scheduling or dosage, the present study used parameters established through meta-analyses, which demonstrated highly effective treatment outcomes using a minimum of 20 sessions, lasting 30 min each, with electrical current set at 2 mA (Brunoni et al. 2016; Mutz et al. 2018, 2019; Woodham et al. 2022), but increased session frequency has been correlated with improved clinical outcomes (Moffa et al. 2020). As far as we are aware, the present study is the first to employ remote supervision for home-based tDCS for bipolar depression. A significant advantage of employing a home-based tDCS protocols is that participants had the autonomy to schedule their sessions according to their preferences, thereby enabling them to maintain a consistent regimen at a convenient time. This may have contributed to the low attrition rate which was notably lower than clinic-based tDCS protocols, in which the attrition rate might reach 10.1% (Brunoni et al. 2016; Mutz et al. 2019). Furthermore, the present study found significant improvements in disability and functional outcomes, which has been observed with TMS (Tavares et al. 2017).

Limitations of the study include the absence of a sham tDCS treatment arm as all participants received active tDCS with an open-label design. The large observed effects could be in part due to a placebo effect, and the provision of real-time supervision for each session likely played a role in the improvement of depressive symptoms (Papoutsi and Fu 2021). Thematic analysis of feedback from our unipolar depression tDCS pilot trial indicated that the presence of the same researcher at each visit was rapport building and helped participants feel connected and safe (Rimmer et al. 2024), which likely contributed to the high response and remission rates. Furthermore, the study did not control for the types of medication. Participants were required to maintain a stable dosage of mood stabilizing medication for at least two weeks or abstain from medication for the same duration. Mood stabilizers such as lithium and lamotrigine, exert their effects through the modulation of cortical excitability, a mechanism shared with voltage-gated sodium channels (Lee et al. 2022). A reduction in cortical excitability could be associated with a reduction in tDCS efficacy (Romero Lauro et al. 2014). Variations in head sizes, individual anatomical characteristics, and device placement among users may have resulted in different configurations of electrical field density within the brain. Individual differences in tDCS effects may arise partially due to discrepancies in electric fields. The tDCS device

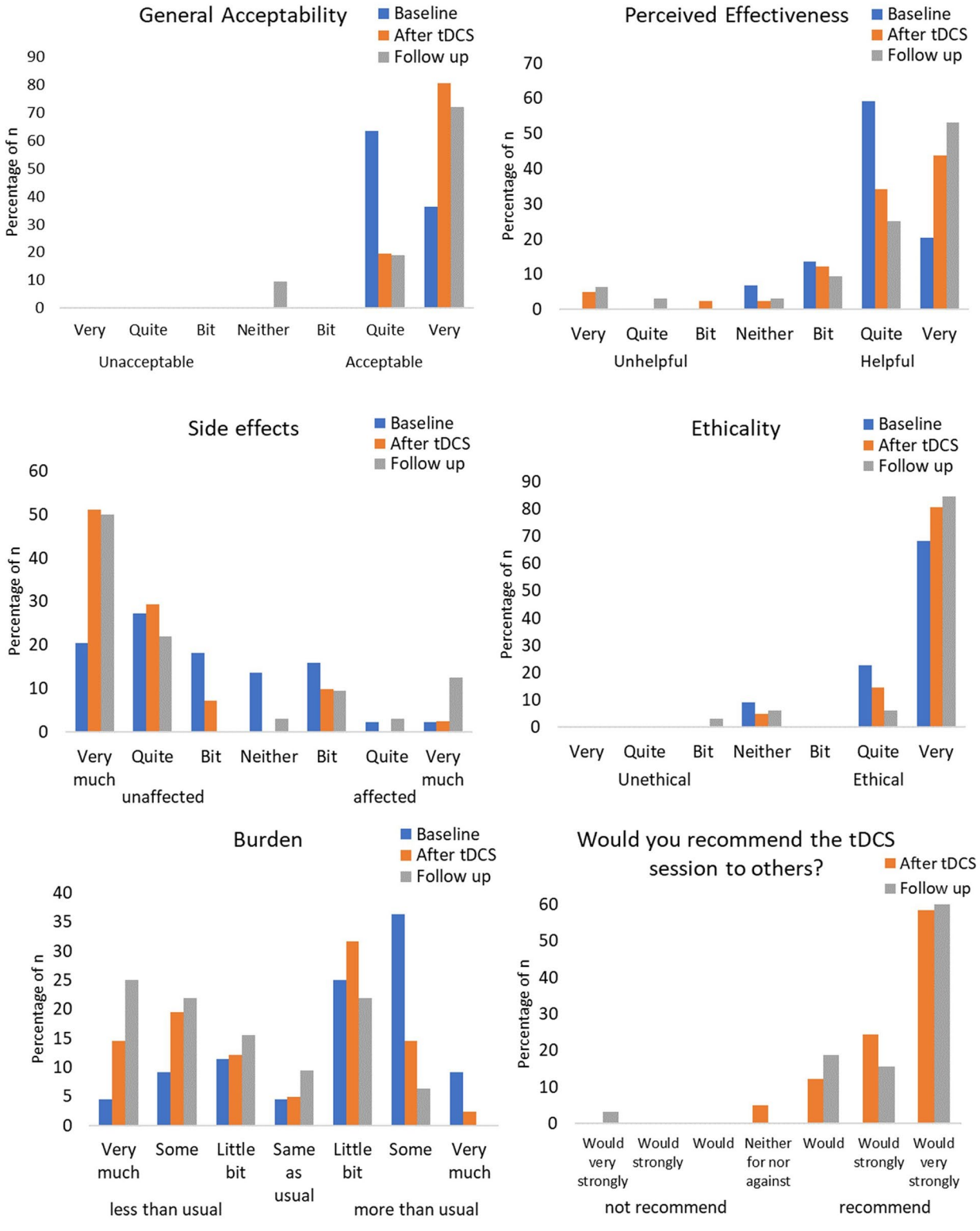

Fig. 7 Percentage of participants who endorsed each response in the acceptability questionnaire at baseline ($n=44$), end of treatment ($n=41$) and follow up ($n=32$)

used in the current study underwent electric field modelling, which indicates its targeting of areas implicated in the pathophysiology of major depressive disorder within the prefrontal cortex. However, differences in the device positioning may have influenced the intensity of the electric field and subsequently impacted treatment outcomes. Most participants were recruited from online advertisements and results may be less generalisable to patients who have not taken an interest in tDCS. Concurrent psychiatric disorders were an exclusion criteria, which may limit generalisability of the findings as bipolar disorder is consistently associated with psychiatric comorbidities (Blanco et al. 2017).

Conclusions

In summary, home-based tDCS with real-time remote supervision was associated with significant improvements in depressive symptoms in individuals with bipolar depression of moderate to severe severity. The present study demonstrated high levels of acceptability, tolerability and safety for home-based tDCS in bipolar depression. Large-scale randomised controlled trials of home-based tDCS for the treatment of bipolar depression are necessary to determine efficacy and optimal tDCS parameters.

Abbreviations

AEQ	tDCS Adverse Events Questionnaire
CI	confidence interval
DLPFC	dorsolateral prefrontal cortex
DSM-5	Diagnostic Statistic Manual of Mental Disorders, Fifth Edition
HAMA	Hamilton Anxiety Rating Scale
HDRS-17	Hamilton Depression Rating Scale
ITT	intention-to-treat
LOCF	last observation carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MINI	Mini-International Neuropsychiatric Interview
ECT	electroconvulsive therapy
PHQ-9	Patient Health Questionnaire-9
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
RCT	randomised controlled trial
rTMS	repetitive transcranial magnetic stimulation
SDS	Sheehan Disability Scale
tDCS	transcranial direct current stimulation
YMRS	Young Mania Rating Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40345-024-00352-9.

Supplementary Material 1

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Author contributions

C.F. was the chief investigator of the study, formulated the conception of the work, led its conduct, led the interpretation of data and wrote the first draft of the manuscript with A.G, R.W. and H.R. C.F., E.B., M.B., P.R., A.Y., made substantial contributions to the design of study. A.G., H.R and R.W contributed to the data acquisition and statistical analysis of the data. All authors have critically appraised the work for intellectual content and approved the submission of the manuscript for publication.

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Data availability

The anonymised datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the The Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the London Fulham Research Ethics Committee (21/LO/0910). All participants provided written informed consent for their participation. The privacy and rights of human subjects was observed at all times.

Consent for publication

Not applicable.

Competing interests

tDCS devices were provided by Flow Neuroscience. Authors AG, RW, HR, MSS, PR, EB and MB do not report any declarations of interest. CF has received funding from Flow Neuroscience. Author AY reports the following declaration of interests: Paid lectures and advisory boards for the following companies with drugs 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, 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):

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