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"Flow" Transcranial Direct Current Stimulation (tDCS) for Depression Treatment in a Primary Healthcare General Practice—An Open-Label Cohort Study Measuring Montgomery-Åsberg Depression Rating Scale (MADRS-S) Outcomes

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Abstract

Background: Flow FL-100 is a transcranial direct current stimulation (tDCS) device self-administered by a patient at home in combination with a software application delivered wellbeing behaviour therapy training. tDCS has evidence of effectiveness in treating symptoms of depression. **Purpose/Aim:** This post marketing study evaluated the effect of Flow on depression for primary care general practice patients with depression symptoms. **Methods:** Open-label patient cohort design with no control group. Inclusion criteria were aged 18 years or over and reporting depression symptoms. Participants self-administered five 30 minute tDCS sessions per week for the first three weeks, and then 3 sessions per week following this. Three, six and ten week assessment with participant self-report measure: Montgomery-Åsberg Depression Rating Scale (MADRS-S). **Results:** MADRS-S remission rates were between 29% - 30% at three weeks, 33% - 34% at six-weeks and 50% at 10-weeks treatment. There was a significant improvement in MADRS-S with large effect sizes at all time points. **Conclusions:** Flow tDCS can be delivered through a primary healthcare general practice service and patients will choose to use. Flow tDCS provides an effective depression treatment in addition and as an alternative to antidepressants and psychotherapy. tDCS has evidence as an effective depression treatment, and the widespread availability of tDCS in primary care general practice should be considered.

Keywords

Depression, Transcranial Direct Current Stimulation, Wellbeing, General Practice

1. Introduction

Defined as experiencing a low mood and loss of pleasure or interest in activities, depression can include symptoms such as poor concentration, feelings of low self-worth, hopelessness, suicidality, disrupted sleep, and fatigue [1]. Around one in six (16%) of the general population experiences depression in Great Britain (GB) [2]. As the most prevalent mental illness, depression is the largest contributor to global disability [1]. The symptoms of depression symptoms can have a severe negative impact on everyday functioning and quality of life [1] [3] and is the most common mental illness in deaths by suicide [4].

Non-invasive brain neurostimulation (NIBS) techniques to treat depression include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) [5]. TMS is an effective and established depression treatment, but requires daily out-patient visits over approximately 5 weeks [6]. Transcranial direct current stimulation (tDCS) is non-invasive brain stimulation by weak electrical currents (0.5 - 2.5 mA) [7]. Electrode placement for treating depression is typically with the anode over the left dorsolateral prefrontal cortex (DLPFC) (F3) and cathode over the right DLPFC (F4) [8]. Possible tDCS mechanisms of action include significant gray matter increases in brain regions functionally connected with the stimulation target, including the bilateral DLPFC, bilateral posterior cingulate cortex, subgenual anterior cingulate cortex, the right hippocampus, thalamus and left caudate brain regions; tDCS leads to neurostructural changes and plasticity effects may propagate over brain networks [9]. tDCS is safe [10] and generally reported by patients as acceptable and well-tolerated (most commonly reported side effect of a temporary headache), with mild and transient physical sensations that usually do not prevent use: burning sensations (16.2%), skin redness (12.3%), scalp pain (10.1%), itching (6.7%), and tingling (6.3%) [7] [11] [12].

Meta-analyses of randomised sham-controlled trial (RCTs) show tDCS can significantly improve depressive symptoms and clinical response, with remission being significantly better than placebo sham stimulation [10] [13]-[15]. tDCS is effective as standalone treatment or in combination with other anti-depression treatments [10]. The UK's National Institute for Health and Care Excellence (NICE) reported that tDCS could particularly benefit people whose symptoms have not improved with existing interventions, or who find side effects of antidepressants intolerable or unacceptable [16].

A specific product delivering tDCS is called "Flow". It combines tDCS (delivered by Flow FL-100 device) and software app-based wellbeing behaviour training (physical exercise, nutrition, mindfulness, sleep, and behavioural activation). In a 24-participant open-label single-arm feasibility study of Flow FL-100, a sig-

nificant improvement in depressive symptoms after six weeks of treatment was maintained at 3 and 6 months [17]. An open-label 31 participant cohort design with no control group study of Flow found depression reliable improvement and remission rates were 58.1% and 32.3% and significant improvement in depression, functioning, and health related quality of life [18]. A RCT of Flow FL-100 found significant improvement in depression symptoms relative to sham after 10-weeks treament [19]. Qualitative studies on the experience of Flow tDCS found most patients reported improved depression symptoms, and that it was acceptable and they would recommend it to others [20]-[22].

Pharmacotherapy used for depression with evidence of effectiveness includes selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs); however, antidepressant first-line treatment is effective in only around 37% of people [23] [24]. When compared with placebo, the incremental effectiveness of antidepressants may be modest, with only one in nine patients experiences a benefit [25]. Antidepressant adverse side effects can include nausea, fatigue, weight gain, tremors, sexual dysfunction, insomnia, and gastrointestinal problems [26]; side effects can result in additional costs, for example, additional GP visits [27]. Antidepressants are not an acceptable option for some people, between 18% to 30% of people stop using SSRIs [28]. There can also be a high risk of relapse [29], withdrawal effects can be long-lasting and severe [30], and use can result in increased suicide risk [31].

Psychotherapy is recommended for depression, with recovery rates of around 50% for those who complete treatment, but 60% of people drop out after one or two sessions and, as it is delivered over multiple sessions over a period of several months, it is costly and lengthy; and there can be long wait times to access (average waiting time for a psychotherapy to start is 21 days in the UK) [24] [32] [33]. There can be induvial barriers to access, some people do not find psychotherapy to be an acceptable option due to, for example, cultural beliefs, mobility issues, travel costs, or work and caring responsibilities [34].

A choice of options for effective depression treatment in addition to antidepressants and psychotherapy that best suit people's lives, needs, and concerns is highly valuable. In this project Flow tDCS was offered through a United Kingdom (UK) primary care general practice to patients who reported symptoms of depression and outcomes were assessed in terms of feasibility and depression. Our objectives were to measure and compare change in depression symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS-S) [34] at 3, 6 and 10 weeks at approximately 60% and 75% adherence to usage protocol, and to measure and compare remission rates at 3, 6 and 10 weeks at approximately 60% and 75% adherence to usage protocol.

2. Methods

2.1. Design

The study had an open-label patient cohort design with no control group.

2.2. Approval

Approval was granted by the review panel of the NHS Trust (Ideas Forum: reference IFFLOW) leading the evaluation and by the NHS primary care provider consortium. All participants provided informed consent. The study was delivered in accordance with the Declaration of Helsinki.

2.3. Medical Records

Following informed consent, demographic and other information was extracted from data provided by participant through the Flow software application.

2.4. Setting

Participants were recruited through a primary healthcare general practice (GP). Flow was self-administered at home by participants living in the community. Flow Neuroscience AB (manufacturer of Flow device) provided GPs and other healthcare staff with training.

2.5. Inclusion/Exclusion Criteria

Inclusion criteria:

1) Aged 18 years or over

2) Patient reporting depression symptoms

Exclusion criteria:

1) Epilepsy (or having a history of seizures)

2) Having a defect in the neurocranium and/or a cranial implant

3) Having an active, implanted medical device (e.g., cardiac pacemaker, spinal cord stimulator, vagal nerve stimulator, auricular stimulator, deep brain stimulating electrodes, cochlear implant, implanted hearing aid or defibrillator) or other implanted, metallic, or electronic device

4) A neurological condition

5) A history of hypomanic/manic episodes

2.6. Procedure

From February 2023 to January 2024, patients were selected by their GP if they met the inclusion/exclusion criteria and were provided with information about the treatment and evaluation. Participants stayed on the same medication and continued any current psychological interventions they were undertaking. Informed consent was obtained prior to beginning treatment. Participants could withdraw consent or stop treatment at any point without the need to provide a reason. Following informed consent, participants collected the Flow device and instructions from the GP reception Participants were informed about Flow Neuroscience AB's website which provides information, training on use, and email support.

2.7. Intervention

Flow FL-100 is a Conformite Europeene (CE) marked Class IIa medical device

for the treatment of major depressive disorder (MDD). Flow can be purchased directly by anyone via the manufacturer's website in the European Union and other European countries. Flow has been used by >15,000 users in UK/EU and is offered by >70 private healthcare institutions.

In the treatment protocol, the patient remains awake and self-administers five sessions per week for the first three weeks and then three sessions per week for the following three weeks: 24 sessions, with a maximum of one 30-minute session per day. After the initial six-week period, patients can choose to self-administer up to three sessions per week for as long as they choose.

The anode was positioned over the left dorsolateral prefrontal cortex (DLPFC) (F3 on the international 10/20 EEG system) and the cathode over the right DLPFC (F4); stimulation is 2 mA for 30 min. On the Flow mobile phone software app, seven brief (around 20 minutes, pace of completion chosen by user) healthy lifestyle behaviour therapy training sessions are available for users to optionally engage with. These provide information about the links between behaviour and wellbeing and how to take actions to improve wellbeing and reduce depressive symptoms. They are titled: "The basics", "Choosing your actions", "Mindfulness meditation", "Exercise for your brain", "The anti-depression diet", "Therapeutic sleep", and "Looking back and planning ahead".

The Flow mobile phone software app is used to control the Bluetooth-connected Flow FL-100 tDCS headset via the user's smartphone. Flow also provides depression symptom level tracking that enables users to monitor their progress/symptoms. This is done by the completion of the nine-question Montgomery–Åsberg Depression Rating Scale Self-report (MADRS-S) [35] the user's smartphone prior to a tDCS session. Flow also provides an integrated platform for the patient's GP, with the ability to monitor patients, and customise protocols remotely.

2.8. Measure

Participants self-completed the MADRS-S [35] at 3, 6 and 10 weeks. Assessment of MADRS-S [35] psychometric properties indicated good acceptability, all items contributed to a common underlying concept (depression), stability over time and sensitivity to change was good. [36] Remission is MADRS-S score change from 13 or over (have depression) to 12 or less (cut-off for depression).

2.9. Study Size

The study sample size was not predetermined and based on an opportunity sample.

2.10. Statistical Analysis

Paired T-tests conducted between baseline and weeks 3, 6 and 10 for approximately 60% and 75% adherence to the intervention usage protocol. Only participants who met the below eligibility criteria were included in the statistical analysis:

- Used Flow for 3 weeks and had 9 sessions minimum of tDCS and had week 3 MADRS-S data.
- Used Flow for 6 weeks and had 15 sessions minimum of tDCS and had week 6 MADRS-S data.
- Used Flow for 10 weeks and had 27 sessions minimum of tDCS and had week 10 MADRS-S data.

3. Results

Used Flow for 3 weeks and 9 sessions minimum (60% adherence)

Descriptive Data

Number of participants = 43. 33 had age data: 1 (3.03%) 18 - 20, 2 (6.06%) 21 - 30, 6 (18.18%) 31-40, 7 (21.21%) 41 - 50, 11 (33.33%) 51 - 60 and 6 (18.18%) 61 - 70. 40 had sex data: 31 (77.5%) females and 9 (22.5%) males. 39 had depressive symptoms duration data: 10 (25.64%) depressive symptoms for <6 months, 13 (33.33%) depressive symptoms for 6 - 12 months and 16 (41.03%) depressive symptoms for >12 months. 40 had "tried treatments data": 15 (37.5%) had tried medication only, 8 (20.0%) had tried talking therapy only, 13 (32.5%) had tried both medication and talking therapy, 3 (7.5%) had not tried either and 1 (2.5%) tried "something else". 28 had medication data: 24 (85.71%) are taking antidepressants, 1 (3.57%) are taking antidepressants and benzodiazepine, 1 (3.57%) is taking antidepressants, benzodiazepine and "other", 1 (3.57%) is taking antidepressants and "other", and 1 (3.57%) is taking "other". 40 had tried antidepressants data: 27 (67.5%) tried antidepressants and 13 (32.5%) have not tried antidepressants. 11 had other diagnoses data: 6 (54.55%) have anxiety syndrome, 2 (18.18%) have bipolar disorder, 2 (18.18%) have ADHD, 4 (36.36%) have chronic pain, 2 (18.18%) have PTSD, 1 (9.09%) has OCD, 1 (9.09%) has insomnia, 1 (9.09%) has long-term stress exhaustion, 5 (45.45%) have "other". 38 had work ability affected data: 34 (89.47%) did not have their work ability affected, 3 (8.82%) were on sick leave and 1 (2.63%) was on part-time sick leave. MADRS-S baseline score: below cut-off for depression (0 - 12) = 13 participants (30.23%); mild depression (13 - 19) = 18 participants (41.86%); moderate depression (20 - 34) = 12 participants (27.91%); and severe depression (≥35) = 0 participants (0%).

Outcome Data

There was a significant decrease of 11.56 (SD = 7.53) in MADRS score from baseline to week 3 follow-up in those who completed at least 9 sessions and who had week 3 MADRS-S follow-up data, with a large effect size (Cohen's d = 1.54), 95% CI [1.09, 1.98]. Mean scores showed that at 3-week follow-up, 13 (30.23%) experienced remission.

Used Flow for 3 weeks: 11 sessions minimum (73.3% adherence)

Descriptive Data

Number of participants = 41. 32 had age data: 1 (3.13%) 18 - 20, 2 (6.25%) 21 - 30, 6 (18.75%) 31 - 40, 7 (21.88%) 41 - 50, 11 (34.38%) 51 - 60 and 5 (15.63%) 61-70. 37 had sex data: 37, 29 (78.38%) females and 8 (21.62%) males. 37 had

depressive symptoms duration data: 9 (24.32%) had depressive symptoms for <6 months, 13 (35.14%) depressive symptoms for 6-12 months and 15 (40.54%) depressive symptoms for >12 months. 37 had "tried treatments data": 13 (35.14%) had tried medication only, 8 (21.62%) had tried talking therapy only, 12 (32.43%) had tried both medication and talking therapy, 3 (8.11%) had not tried either and 1 (2.70%) tried "something else". 25 had medication data: 21 (84%) were taking antidepressants, 1 (4%) were taking antidepressants and benzodiazepine, 1 (4%) were taking antidepressants, benzodiazepine and "other", 1 (4%) were taking antidepressants and "other", and 1 (4%) is taking "other". 37 had tried antidepressants data: 24 (64.86%) participants had tried antidepressants and 13 (35.14%) had not tried antidepressants. 11 had other diagnoses data: 11 participants, 6 (54.55%) had anxiety syndrome, 2 (18.18%) had bipolar disorder, 2 (18.18%) had ADHD, 4 (36.36%) had chronic pain, 2 (18.18%) had PTSD, 1 (9.09%) had OCD, 1 (9.09%) had insomnia, 1 (9.09%) had long-term stress exhaustion, 5 (45.45%) had "other". 35 had work ability affected data: 32 (91.43%) did not have their work ability affected, 2 (5.71%) were on sick leave and 1 (2.86%) were on part-time sick leave. MADRS baseline score: Below cut-off for depression (0 - 12) = 0 participants (0%) mild depression (13 - 19) = 7 participants (17.07%) moderate depression (20 - 34) = 24 participants (58.54%); and severe depression (≥35) = 9 participants (21.95%).

Outcome Data

There was a significant decrease of 11.13 (SD = 7.62) in MADRS-S scores from baseline to week 3 follow-up, with a large effect size (Cohen's d = 1.46), 95% CI [1.00, 1.90]. Mean scores showed that at 3-week follow-up, 12 (29.27%) of participants who completed at least 11 sessions and who had 3 week MADRS-S data experienced remission.

Used Flow for 6 weeks: 15 sessions minimum (62.5% adherence)

Descriptive Data

Number of participants = 33. 25 had age data: 25, 1 (4%) 18 - 20, 1 (4%) 21 - 30, 4 (16%) 31 - 40, 8 (32%) 41 - 50, 6 (24%) 51 - 60 and 5 (20%) 61 - 70. 30 out of 33 participants had sex data: 30, 24 (80%) females and 6 (20%) males. 29 had depressive symptoms duration data: 29, 7 (24.14%) depressive symptoms for <6 months, 11 (37.93%) depressive symptoms for 6 - 12 months and 11 (37.93%) depressive symptoms for >12 months. 30 had "tried treatments data": 10 (33.33%) had tried medication only, 7 (23.33%) had tried talking therapy only, 12 (40%) had tried both medication and talking therapy, and 1 (3.33%) tried "something else". 22 had medication data: 18 (81.82%) were taking antidepressants, 1 (4.55%) were taking antidepressants and benzodiazepine, 1 (4.55%) were taking antidepressants, benzodiazepine and "other", 1 (4.55%) were taking antidepressants and "other", and 1 (4.55%) were taking "other". 30 had "tried antidepressants data": 21 (70%) of participants has tried antidepressants and 9 (30%) have not tried antidepressants. 10 had other diagnoses data: 6 (60%) had anxiety syndrome, 2 (20%) had ADHD, 3 (33.33%) had chronic pain, 2 (20%) had PTSD, 1 (10%) had

OCD, 2 (20%) had insomnia, 2 (20%) had long-term stress exhaustion, 1 (10%) had bipolar disorder, 1 (10%) had alcohol/drug addiction, 5 (50%) had "other". 28 had work ability affected data: 28 participants, 25 (89.29%) did not have their work ability affected, 1 (3.57%) was on sick leave and 2 (7.14%) were on part-time sick leave. MADRS-S baseline scores: below cut-off for depression (0 - 12) = 0 participants (0%); mild depression (13 - 19) = 5 participants (15.15%); moderate depression (20 - 34) = 19 participants (57.58%); and severe depression (≥35) = 9 participants (27.27%).

Outcome Data

There was a significant decrease of 13.48 (SD = 9.51) in MADRS-S score from baseline to week 6 follow-up, with a large effect size (Cohen's d = 1.42), 95% CI [0.93, 1.90]. Mean scores showed that at 6-week follow-up, 11 (33.33%) experienced remission.

Used Flow for 6 weeks: 18 sessions minimum (75% adherence)

Descriptive Data

Number of participants = 32. 24 had age data: 24, 1 (4.17%) 18 - 20, 1 (4.17%) 21 - 30, 4 (16.67%) 31 - 40, 7 (29.17%) 41 - 50, 6 (25%) 51 - 60 and 5 (20.83%) 61 - 70. 29 out of 32 participants had sex data: 23 (79.31%) females and 6 (20.69%) males. 28 had depressive symptoms duration data:7 (25%) depressive symptoms for <6 months, 10 (35.71%) depressive symptoms for 6 - 12 months and 11 (39.29%) depressive symptoms for >12 months. 29 had "tried treatments data": 10 (34.48%) had tried medication only, 7 (24.14%) had tried talking therapy only, 11 (37.93%) had tried both medication and talking therapy, and 1 (3.45%) tried "something else". 32 had medication data: 21 participants, 17 (80.95%) were taking antidepressants, 1 (4.76%) were taking antidepressants and benzodiazepine, 1 (4.76%) was taking antidepressants, benzodiazepine and "other", 1 (4.76%) was taking antidepressants and "other", and 1 (4.76%) was taking "other". 29 had tried antidepressants data: 20 (68.97%) of participants has tried antidepressants and 9 (31.03%) have not tried antidepressants. 9 out of 32 participants had other diagnoses data: 9 participants, 5 (55.56%) had anxiety syndrome, 1 (11.11%) had ADHD, 3 (33.33%) had chronic pain, 2 (22.22%) had PTSD, 1 (11.11%) had OCD, 2 (22.22%) had insomnia, 2 (22.22%) had long-term stress exhaustion, 1 (11.11%) had bipolar disorder, 1 (11.11%) had alcohol/drug addiction, 5 (45.45%) had "other". 27 had work ability affected data: 24 (88.89%) did not have their work ability affected, 1 (3.70%) was on sick leave and 2 (7.41%) were on part-time sick leave. MADRS-S baseline score: below cut-off for depression (0 - 12) = 0 participants (0%); mild depression (13 - 19) = 5 participants (15.62%); moderate depression (20 - 34) = 18 participants (56.25%); and severe depression (≥35) = 9 participants (28.13%).

Outcome Data

There was a significant decrease of 13.69 (SD = 9.59) in MADRS-S scores from baseline to week 6 follow-up, with a large effect size (Cohen's d = 1.43), 95% CI [0.93, 1.92]. Mean scores showed 11 (34.38%) experienced remission.

Used Flow for 10 weeks: 27 sessions minimum (75% adherence)

Note: all participants who used for 10 weeks had a minimum of 75% adherence.

Descriptive Data

Number of participants = 18. 13 had age data: 1 (7.69%) 18 - 20, 1 (7.69%) 31 - 40, 6 (46.15%) 41 - 50, 2 (15.38%) 51 - 60 and 3 (23.08%) 61 - 70. 17 had sex data: 12 (70.59%) females and 5 (29.41%) males. 17 out of 18 participants had depressive symptoms duration data: 4 (23.53%) depressive symptoms for <6 months, 5 (29.41%) depressive symptoms for 6-12 months and 8 (47.06%) depressive symptoms for >12 months. 17 had "tried treatments data": 6 (35.29%) had tried medication only, 5 (29.41%) had tried talking therapy only, 6 (35.29%) had tried both medication and talking therapy. 12 had medication data: 12 participants, 8 (66.67%) were taking antidepressants, 1 (8.33%) was taking antidepressants and benzodiazepine, 1 (8.33%) was taking antidepressants, benzodiazepine and "other", 1 (8.33%) was taking antidepressants and benzodiazepine, 1 (8.33%) was taking antidepressants and "other", and 1 (8.33%) was taking "other". 17 had tried antidepressants data: 17 participants, 11 (64.71%) of participants has tried antidepressants and 6 (35.29%) have not tried antidepressants. 17 had other diagnoses data: 4 (66.67%) had anxiety syndrome, 1 (16.67%) had chronic pain, 2 (22.22%) had PTSD, 1 (16.67%) had OCD, 1 (16.67%) had insomnia, 2 (33.33%) had long-term stress exhaustion, 1 (16.67%) had bipolar disorder, 1 (16.67%) had alcohol/drug addiction, 4 (66.67%) had "other". 16 had work ability affected data: 15 (93.75%) did not have their work ability affected and 1 (6.25%) was on part-time sick leave. MADRS-S baseline score: below cut-off for depression (0 - 12) = 0 participants (0%); mild depression (13 - 19) = 4 participants (22.22%); moderate depression (20 - 34) = 10 participants (55.55%); and severe depression (≥35) = 4 participants (22.22%).

Outcome Data

There was a significant decrease of 12.22 (SD = 9.16) in MADRS-S score from baseline to week 10 follow-up, with a large effect size (Cohen's d = 1.33), 95% CI [0.68, 1.97]. Mean scores showed that at 10-week follow-up, 9 (50%) experienced remission. Table 1 compares MADRS-S scores and remission rates for each group.

Table 1. MADRS-S scores and remission rates.

Group	Baseline MADRS-S	Follow-up MADRS-S	Mean change MADRS-S	Remission rate
3 weeks 60%	27.42	15.86	11.56	30.23%
3 weeks 73.3%	27.03	15.90	11.13	29.27%
6 weeks 62.5%	28.55	15.06	13.48	33.33%
6 weeks 75%	28.47	14.78	13.69	34.38%
10 weeks 75%	27.56	15.33	12.22	50%

4. Discussion

This study found that Flow FL-100 tDCS and software application delivered wellbeing behaviour therapy training can be offered by primary care providers as an addition and alternative to existing treatments for depression. Patients will choose to use Flow tDCS when they are offered it, and they generally follow the protocol. Flow was found to reduce depression symptoms, adding evidence to support the effectiveness of tDCS [10] [13]-[15] [17]-[19].

Participants in each group subject to analysis had broadly similar characteristics. There was a slightly higher remission rate at six weeks compared to three weeks, indicating an advantage of six weeks treatment over three weeks treatment. There was a higher remission rate at ten weeks compared to three or six weeks, indicating an advantage of ten weeks treatment over three or six weeks treatment. In the three and six week results there was very little difference in remission rates between 60%/62.5% and 73.3%/75% adherence, 75% adherence at 6 weeks showing greatest remission and mean change in MADRS-S. This study showed that tDCS can be combined with other treatments, and previous research has shown this can possibly enhance overall outcomes [10].

This present study shows that the use of Flow may lead to relatively quick (three-week) improvement in depression symptoms for some participants. The time course of response of SNRIs and SSRIs is around 2 to 4 weeks to achieve significant benefits; but it may take longer to achieve most of the improvement [37]. Therefore, Flow might be considered as a treatment where a relatively quick relief of symptoms is required, future studies with a larger participant sample are needed to explore this further.

tDCS is an alternative treatment for those experiencing depression symptoms who have failed to respond to medication or psychotherapy or who find medication side effects or factors related to psychotherapy unacceptable (waiting times, travel costs, time required, other commitments preventing attendance). The NHS "Mental health and wellbeing plan" states: "We know there are limitations to the current treatment offer. More needs to be done… to diversify the range of treatments available" [38]. Primary care general practice are well-placed to offer tDCS treatment as most people first seek help for depression through a GP and many patients are treated by their GP for long-term or recurrent depression.

Many participants did not experience remission following the use of Flow. It is not effective for everyone. GPs need to prepare their patients for this potential outcome and ensure that patients receive ongoing support, and suggest other ways of maintaining well-being, preventing depression and potential treatments if tDCS does not provide relief from depression symptoms. Patients need to know that they may need to make changes to their lifestyle to enhance wellbeing or try other treatment options.

There were several limitations of the study. There was no control group. Treatment with Flow tDCS was open-label and adjunct to any existing depression or other treatments or therapies. There was a small sample size at ten weeks

treatment. The sample was over-represented by females, and so the results are less generalisable to males. This study collected outcome measures after three, six and ten weeks treatment, with no later follow-up data collection; it is recommended that future studies employ additional follow-up data collection points: 18, 26, and 36 weeks.

5. Conclusion

Flow tDCS and software application delivered wellbeing behaviour therapy training can be fully and effectively integrated into a primary care depression treatment pathway. GPs will offer and primary care patients will choose to use Flow, providing evidence of the acceptability of and demand for tDCS. Flow tDCS can be effective against depression symptoms when offered through general practice primary healthcare services for patients with depression symptoms. Availability through free-to-access universal healthcare systems such as the UK's NHS would address inequality of access issues.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] World Health Organisation (2023) Depressive Disorder (Depression)—Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/depression.

[2] Office for National Statistics Cost of Living and Depression in Adults, Great Britain: 29 September to 23 October 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/mentalhealth/articles/costoflivinganddepressioninadultsgreatbritain/29septemberto23october2022

[3] Lépine, J.P. and Briley, M. (2011) The Increasing Burden of Depression. *Neuropsychiatric Disease and Treatment*, **7**, 3-7. https://doi.org/10.2147/NDT.S19617

[4] Vigo, D., Thornicroft, G. and Atun, R. (2016) Estimating the True Global Burden of Mental Illness. *The Lancet Psychiatry*, **3**, 171-178. https://doi.org/10.1016/S2215-0366(15)00505-2

[5] Atkinson-Clement, C., Junor, A. and Kaiser, M. (2024) A Large-Scale Online Survey of Patients and the General Public: Preferring Safe and Noninvasive Neuromodulation for Mental Health. https://doi.org/10.1101/2024.01.10.24301043

[6] Griffiths, C., Da Silva, K.M., Leathlean, C., Jiang, H., Ang, C.S. and Searle, R. (2022) Investigation of Physical Activity, Sleep, and Mental Health Recovery in Treatment Resistant Depression (TRD) Patients Receiving Repetitive Transcranial Magnetic Stimulation (RTMS) Treatment. *Journal of Affective Disorders Reports*, **8**, Article 100337. https://doi.org/10.1016/j.jadr.2022.100337

[7] Grycuk, L., Moruzzi, F., Bardjesteh, E., Gaughran, F., Campbell, I.C. and Schmidt, U. (2021) Participant Experiences of Transcranial Direct Current Stimulation (TDCS) as a Treatment for Antipsychotic Medication Induced Weight Gain. *Frontiers in Psychology*, **12**, Article 694203. https://doi.org/10.3389/fpsyg.2021.694203

[8] Fregni, F., El-Hagrassy, M.M., Pacheco-Barrios, K., *et al.* (2021) Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders. *International Journal of Neuropsychopharmacology*, **24**, 256-313. https://doi.org/10.1093/ijnp/pyaa051

[9] Jog, M.A., Anderson, C., Kubicki, A., *et al.* (2023) Transcranial Direct Current Stimulation (TDCS) in Depression Induces Structural Plasticity. *Scientific Reports*, **13**, Article 2841. https://doi.org/10.1038/s41598-023-29792-6

[10] Razza, L.B., Palumbo, P., Moffa, A.H., *et al.* (2020) A Systematic Review and Meta-Analysis on the Effects of Transcranial Direct Current Stimulation in Depressive Episodes. *Depress Anxiety*, **37**, 594-608. https://doi.org/10.1002/da.23004

[11] Chhabra, H., Bose, A., Shivakumar, V., *et al.* (2020) Tolerance of Transcranial Direct Current Stimulation in Psychiatric Disorders: An Analysis of 2000+ Sessions. *Psychiatry Research*, **284**, Article 112744. https://doi.org/10.1016/j.psychres.2020.112744

[12] Gordon, M.S., Dux, P.E. and Filmer, H.L. (2021) Not Quite All in Our Head: Intervention Is a Better Predictor of TDCS Mind-Wandering Effects Than Subjective Beliefs about Experimental Results. https://doi.org/10.1101/2021.11.14.468553

[13] Mutz, J., Edgcumbe, D.R., Brunoni, A.R. and Fu, C.H. (2018) Efficacy and Acceptability of Non-Invasive Brain Stimulation for the Treatment of Adult Unipolar and Bipolar Depression: A Systematic Review and Meta-Analysis of Randomised Sham-Controlled Trials. *Neuroscience & Biobehavioral Reviews*, **92**, 291-303. https://doi.org/10.1016/j.neubiorev.2018.05.015

[14] Mutz, J., Vipulananthan, V., Carter, B., Hurlemann, R., Fu, C.H. and Young, A.H. (2019) Comparative Efficacy and Acceptability of Non-Surgical Brain Stimulation for the Acute Treatment of Major Depressive Episodes in Adults: Systematic Review and Network Meta-Analysis. *British Medical Journal*, **364**, L1079. https://doi.org/10.1136/bmj.l1079

[15] Moffa, A.H., Martin, D., Alonzo, A., *et al.* (2020) Efficacy and Acceptability of Transcranial Direct Current Stimulation (TDCS) for Major Depressive Disorder: An Individual Patient Data Meta-Analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **99**, Article 109836. https://doi.org/10.1016/j.pnpbp.2019.109836

[16] NICE (2023) Flow Transcranial Direct Current Stimulation for Treating Depression. https://transformingmindsolutions.com/flow-transcranial-direct-current-stimulation-for-treating-depression/

[17] Woodham, R.D., Rimmer, R.M., Young, A.H. and Fu, C.H. (2022) Adjunctive Home-Based Transcranial Direct Current Stimulation Treatment for Major Depression with Real-Time Remote Supervision: An Open-Label, Single-Arm Feasibility Study with Long-Term Outcomes. *Journal of Psychiatric Research*, **153**, 197-205.

https://doi.org/10.1016/j.jpsychires.2022.07.026

[18] Griffiths, C., da Silva, K.M., *et al.* (2024) Flow Transcranial Direct Current Stimulation (TDCS) for Depression Treatment in a Primary Healthcare General Practice—Depression, Functioning, and Health-Related Quality of Life Outcomes. Open *Journal of Depression*, **13**, 25-39. https://doi.org/10.4236/ojd.2024.132003

[19] Woodham, R.D., Selvaraj, S., Lajmi, N., *et al.* (2023) Home-Based Transcranial Direct Current Stimulation RCT in Major Depression. https://doi.org/10.1101/2023.11.27.23299059

[20] Rimmer, R.M., Woodham, R.D., Cahill, S. and Fu, C.H. (2022) Acceptability of Community-Based Transcranial Direct Current Stimulation (TDCS) in Major Depression: Mixed Methods Analysis of Individual Experiences. https://doi.org/10.31234/osf.io/xfvwq

[21] Griffiths, C., Walker, K., Jiang, H., Noel-Johnson, A. and Zafar, A. (2023) A Qualitative Study Exploring the Experience and Value of 'Flow' Transcranial Direct Current Stimulation (TDCS) Device and Behaviour Therapy Training Software Application at Home for Symptoms of Depression. *Open Journal of Depression*, **12**, 65-86. https://doi.org/10.4236/ojd.2023.124007

[22] Griffiths, C., Walker, K. and Willis, A. (2024) A Qualitative Study Exploring the Experience and Value of Flow Transcranial Direct Current Stimulation (TDCS) and Behaviour Therapy Training Software Used at Home for Community Mental Health Team (CMHT) Patients with Symptoms of Depression. *Open Journal of Depression*, **13**, 6-23. https://doi.org/10.4236/ojd.2024.131002

[23] Rush, A.J., Trivedi, M.H., Wisniewski, S.R., *et al.* (2006) Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *American Journal of Psychiatry*, **163**, 1905-1917. https://doi.org/10.1176/ajp.2006.163.11.1905

[24] NHS Digital (2021) Psychological Therapies, Annual Report on the Use of IAPT Services—England, 2021-22. https://digital.nhs.uk/data-and-information/publications/statistical/psychological-therapies-annual-reports-on-the-use-of-iapt-services/annual-report-2021-22

[25] Hengartner, M.P. and Plöderl, M. (2018) Statistically Significant Antidepressant-Placebo Differences on Subjective Symptom-Rating Scales Do Not Prove That the Drugs Work: Effect Size and Method Bias Matter! *Frontiers in Psychiatry*, **9**, Article 373735. https://doi.org/10.3389/fpsyt.2018.00517

[26] Cascade, E., Kalali, A.H. and Kennedy, S.H. (2009) Real-World Data on SSRI Antidepressant Side Effects. *Psychiatry (Edgmont),* **6**, 16-18.

[27] Mark, T.L., Joish, V.N., Hay, J.W., Sheehan, D.V., Johnston, S.S. and Cao, Z. (2011) Antidepressant Use in Geriatric Populations: The Burden of Side Effects and Interactions and Their Impact on Adherence and Costs. *The American Journal of Geriatric Psychiatry*, **19**, 211-221. https://doi.org/10.1097/JGP.0b013e3181f1803d

[28] Mochcovitch, M.D., da Rocha Freire, R.C., Garcia, R.F. and Nardi, A.E. (2017) Can Long-Term Pharmacotherapy Prevent Relapses in Generalized Anxiety Disorder? A Systematic Review. *Clinical Drug Investigation*, **37**, 737-743. https://doi.org/10.1007/s40261-017-0528-x

[29] Hansen, R., Gaynes, B., *et al.* (2008) Meta-Analysis of Major Depressive Disorder Relapse and Recurrence with Second-Generation Antidepressants. *Psychiatric Services*, **59**, 1121-1130. https://doi.org/10.1176/appi.ps.59.10.1121

[30] Davies, J. and Read, J. (2019) A Systematic Review into the Incidence, Severity, and Duration of Antidepressant Withdrawal Effects: Are Guidelines Evidence-Based?

Addictive Behaviors, **97**, 111-121. https://doi.org/10.1016/j.addbeh.2018.08.027

[31] Hengartner, M.P. and Plöderl, M. (2019) Reply to the Letter to the Editor: "Newer-Generation Antidepressants and Suicide Risk: Thoughts on Hengartner and Plöderl's Re-Analysis". *Psychotherapy and Psychosomatics*, **88**, 373-374. https://doi.org/10.1159/000502485

[32] Gyani, A., Shafran, R., Layard, R. and Clark, D.M. (2013) Enhancing Recovery Rates: Lessons from Year One of IAPT. *Behaviour Research and Therapy*, **51**, 597-606. https://doi.org/10.1016/j.brat.2013.06.004

[33] Griffiths, C.A. and Griffiths, L.J. (2014) Recovery and Reliable Change Rates for Patients Scoring Severe on Depression, Anxiety or Impaired Functioning in a Psychological Therapies Service: IAPT. *Mental Health Review Journal*, **20**, 28-35. https://doi.org/10.1108/MHRJ-06-2014-0022

[34] Bandelow, B., Sagebiel, A., Belz, M., Görlich, Y., Michaelis, S. and Wedekind, D. (2018) Enduring Effects of Psychological Treatments for Anxiety Disorders: Meta-Analysis of Follow-Up Studies. *The British Journal of Psychiatry*, **212**, 333-338. https://doi.org/10.1192/bjp.2018.49

[35] Svanborg, P. and Åsberg, M. (2001) A Comparison Between the Beck Depression Inventory (BDI) and the Self-Rating Version of the Montgomery Åsberg Depression Rating Scale (MADRS). *Journal of Affective Disorders*, **64**, 203-216. https://doi.org/10.1016/S0165-0327(00)00242-1

[36] Fantino, B. and Moore, N. (2009) The Self-Reported Montgomery-Åsberg Depression Rating Scale Is a Useful Evaluative Tool in Major Depressive Disorder. *BMC Psychiatry*, **9**, 1-6. https://doi.org/10.1186/1471-244X-9-26

[37] Jakubovski, E., Johnson, J.A., Nasir, M., Müller-Vahl, K. and Bloch, M.H. (2019) Systematic Review and Meta-Analysis: Dose-Response Curve of SSRIs and SNRIs in Anxiety Disorders. *Depress Anxiety*, **36**, 198-212. https://doi.org/10.1002/da.22854

[38] Department for Health and Social Care (2023) Mental Health and Wellbeing Plan: Discussion Paper. https://www.gov.uk/government/calls-for-evidence/mental-health-and-wellbeing-plan-discussion-paper-and-call-for-evidence/mental-health-and-wellbeing-plan-discussion-paper#:~:text=the%20NHS%20Community%20Mental%20Health,support%20by%202023%20to%202024