Clinical effectiveness of active Alpha-Stim AID versus sham Alpha-Stim AID in major depression in primary care in England (Alpha-Stim-D): a multicentre, parallel group, double-blind, randomised controlled trial

Richard Morriss, Shireen Patel, Clement Boutry, Priya Patel, Boliang Guo, Paul M Briley, Deborah Butler, Michael Craven, Ashley Duncan, Christopher Griffiths, Fred Higton, Rebecca McNaughton, Neil Nixon, Vibhore Prasad, Kapil Sayal, David Smart, Azhar Zafar, Joe Kai

Lancet Psychiatry 2023; 10: 172–83

Published Online January 29, 2023 https://doi.org/10.1016/S2215-0366(23)00007-X

See Comment page 156

Institute of Mental Health (Prof R Morriss MD, P M Briley PhD, N Nixon MD, Prof K Sayal PhD) **and Faculty of Medicine and Health Sciences** (V Prasad PhD, Prof J Kai PhD), **University of Nottingham, Nottingham, UK; NIHR ARC East Midlands** (Prof R Morriss, S Patel MSc, C Boutry MSc, P Patel MSc, B Guo PhD, D Butler, A Duncan MSc, F Higton PhD, R McNaughton) **and NIHR MindTech Medical Technology Co-operative** (M Craven PhD), **University of Nottingham, Nottingham, UK; Northamptonshire Healthcare NHS Foundation Trust, Northampton, UK** (C Griffiths PhD)**; General Practice Alliance Foundation, Northampton, UK** (D Smart MBChB, A Zafar MSc)

Correspondence to: Prof Richard Morriss, Institute of Mental Health, University of Nottingham, Nottingham NG7 2TU, UK **richard.morriss@nottingham.ac.uk**

Summary

Background Randomised sham-controlled trials of cranial electrostimulation with the Alpha-Stim Anxiety Insomnia and Depression (AID) device have reported improved anxiety and depression symptoms; however, no adequately powered sham-controlled trials in major depression are available. We investigated whether active Alpha-Stim AID is superior to sham Alpha-Stim AID in terms of clinical effectiveness for depression symptoms in major depression.

Methods The Alpha-Stim-D trial was a multicentre, parallel group, double-blind, randomised controlled trial, recruiting participants from 25 primary care centres in two regions in England, UK. Eligible participants were aged 16 years or older with a current diagnosis of primary major depression, a score of 10–19 on the nine-item Patient Health Questionnaire, and had been offered or prescribed and reported taking antidepressant medication for at least 6 weeks in the previous 3 months. Main exclusion criteria were contraindications to Alpha-Stim AID device use, having persistent suicidal ideation or self-harm, neurological conditions, a substance use disorder or dependence, an eating disorder, bipolar disorder, or non-affective psychosis, or receiving psychological treatment in the past 3 months. Eligible participants were randomly assigned (1:1, minimised by region, anxiety disorder, and antidepressant use) to 1 h daily use of active (100 μA) or sham Alpha-Stim AID treatment for 8 weeks. Randomisation was via an independent web-based system, with participants, outcome assessors, and data analyst masked to treatment assignment. The primary outcome was change from baseline in score on the 17-item Hamilton Depression Rating Scale (HDRS-17, GRID version) at 16 weeks after randomisation, with participants analysed by intention to treat (ITT; all randomly assigned participants). Safety was assessed in all randomly assigned participants. The trial is registered with the ISRCTN registry (ISRCTN11853110); status completed.

Findings Between Sept 8, 2020, and Jan 14, 2022, 236 eligible participants were randomly assigned to active or sham Alpha-Stim AID (n=118 each). 156 (66%) participants were women, 77 (33%) were men, and three (1%) self-reported as other gender; 200 (85%) were White British or Irish; and the mean age was 38·0 years (SD 15·3; range 16–83). 102 (86%) participants in the active Alpha-Stim AID group and 98 (83%) in the sham group were followed up 16 weeks after randomisation. In the ITT population, mean change in GRID-HDRS-17 at 16 weeks was –5·9 (95% CI –7·1 to –4·8) in the active Alpha-Stim AID group and –6·5 (–7·7 to –5·4) in the sham group (mean change difference –0·6 [95% CI –1·0 to 2·2], p=0·46). Among the 236 participants, 17 adverse events were reported in 17 (7%) participants (nine [8%] participants in the active Alpha-Stim AID group; and eight [7%] participants in the sham group). One serious adverse event of suicidal ideation leading to hospitalisation was reported in the sham group, which was judged to be unrelated to the device.

Interpretation Active Alpha-Stim AID was safe and acceptable, but no more clinically effective than sham Alpha-Stim AID in major depression.

Funding National Institute for Health Research Applied Research Collaboration East Midlands and Electromedical Products International.

Introduction

Globally in 2015, depression was the leading cause of years lost to disability.[1] As of 2019, approximately 280 million people had depression worldwide, with 5% of adults having current major depression.

The two main forms of treatment for depression are antidepressant medications and psychological treatments. However, first-line use of antidepressants is effective in only 37% of people who are offered them, according to a report in 3671 adult outpatients in the USA.[2] Additionally,

For more on **estimates on depression from the Global Health Data Exchange database** see https://www.who.int/news-room/fact-sheets/detail/depression

Research in context

Evidence before this study

The Alpha-Stim Anxiety Insomnia and Depression (AID) device provides cranial electrotherapy stimulation (CES) with a microcurrent that has Conformité Européenne approval and is supported by the US Federal Drug Administration for home use for people with anxiety and depression. People can purchase the device privately. We conducted a systematic search of PubMed, the Cochrane Library, PsycINFO, Embase, and Google for articles in English published from database inception to July 31, 2022, with the terms: cranial electrical stimulation OR cranial electric stimulat* OR electrotherap* OR fisher wallace stimulat* OR alpha-stim AND depression OR depressive disorders. We found only one published randomised controlled trial of active versus sham CES in 30 adults with primary major depression (Mischoulon et al), which showed no significant difference between the active and sham treatments on depression symptoms. A Veterans Administration systematic review of five randomised trials of CES versus sham in people with anxiety and depression concluded that there was a low strength of evidence for modest improvement in anxiety and depression after treatment with active CES, with no serious adverse effects. A second meta-analysis included five randomised controlled trials in 242 children and adults treated with Alpha-Stim CES, none of whom had a diagnosis of major depression. The analysis found a moderate benefit of active Alpha-Stim CES versus sham for depression symptoms, but quality of evidence was not assessed for bias. There is a scarcity of evidence from controlled trials on the effectiveness of CES in people with primary major depression.

Added value of this study

This study is the first large multicentre randomised controlled trial to report on the clinical effectiveness of Alpha-Stim AID, or any other type of CES device, in adults (age ≥16 years) with primary major depression, using depression symptoms as the primary outcome. Fixed daily doses of CES at 100 μA delivered by Alpha-Stim AID for 8 weeks were no more clinically effective than sham Alpha-Stim AID in treating depression or anxiety symptoms in people with moderate to moderately severe primary major depression who had not responded to the prescription or offer of at least one course of antidepressants. Both active and sham Alpha-Stim AID treatment regimens were associated with clinically important decreases in the primary depression score and clinically important improvements in related secondary outcomes 8 weeks after the end of treatment. The remotely delivered intervention was well tolerated and safe with few side-effects, and treatment completion (≥28 h) was reported in 73% of the overall population.

Implications of all the available evidence

The Alpha-Stim AID device for moderate to moderately severe depressive symptoms is an acceptable, safe, and well tolerated intervention. Although the previous meta-analysis suggests CES might reduce anxiety and depression symptoms in people with primary anxiety disorders, this trial and the previous small trial by Mischoulon and colleagues do not support its clinical effectiveness in the treatment of primary major depression.

antidepressants are associated with a range of side-effects such as sedation, weight gain, falls, and sexual dysfunction.[2] Psychological treatments, such as cognitive behavioural therapy, are as effective as antidepressant therapies; however, according to data from National Health Service (NHS) England, only 40% of those offered psychological treatments attend for two sessions or more, and of those treated, 49% do not progress or recover.[3]

A wider range of treatments is therefore desirable. Patient preferences for treatment vary and influence their willingness to seek treatment for depression.[4] These preferences include a desire for self-administered home-based interventions; addressing concerns about side-effects of medication; and dissatisfaction with the accessibility, duration, and required commitment with psychological treatment.[5]

Cranial electrostimulation (CES) therapy might offer promise for the treatment of depression as it can be used at home, is self-directed and easy to use, and has been found to be safe. However, its clinical effectiveness and mechanism of action are disputed.[6] In the USA, the Alpha-Stim Anxiety Insomnia and Depression (AID) device, manufactured by Electromedical Products International (Mineral Wells, TX, USA), is a CES device for the treatment of anxiety, insomnia, and depression. Alpha-Stim AID received Conformité Européenne approval (ie, was CE-marked) in 2012 as a class 2a medical device. Alpha-Stim AID is mobile phone-sized (with two AAA batteries), attached by metal clips to both earlobes, and used daily for 20–60 min. CES has been associated with an increase in alpha oscillatory brain activity, a feature of relaxed wakefulness.[7] CES might also stimulate the vagal nerve, modulating the brainstem, limbic, and cortical regions of the brain.[6] It differs from transcranial direct current stimulation, which delivers a weak direct current to the dorsolateral prefrontal cortex to treat depression.[8] The Alpha-Stim AID device is available privately in many countries, retailing at approximately US$570. However, given that depression is associated with social deprivation,[9] most people with depression are unable to afford the device.

In 2018, a systematic review by the US Veterans Administration identified five randomised controlled trials, with 198 participants in total, comparing active and sham CES for the treatment of anxiety or mixed anxiety and depression.[10] The review found low-quality evidence for the effectiveness of CES in alleviating anxiety and depression symptoms. In 2021, a meta-analysis of

five randomised and 12 non-randomised studies[11] concluded that CES with Alpha-Stim AID had small-to-medium significant effects in reducing depressive symptoms. Thus, preliminary evidence has indicated the safety and benefits of CES for depression symptoms. However, there is a scarcity of robust evidence on the clinical effectiveness of CES versus sham treatment in people with primary major depression.

The UK National Institute for Health and Care Excellence (NICE) has suggested primary health care to be the most clinically relevant setting for CES use, where most common forms of mental ill health are treated, and where other similar home-based devices, such as transcutaneous electrical nerve stimulation for pain, are used.[12] We therefore conducted a randomised trial of active versus sham CES, using the Alpha-Stim AID device in primary care settings in people with moderate to moderately severe primary major depression. We aimed to establish whether an 8-week course of active Alpha-Stim AID was superior in clinical effectiveness for depression symptoms at 16 weeks, compared with sham Alpha-Stim AID.

Methods

Study design and participants

The Alpha-Stim-D trial was a multicentre, parallel group, double-blind, non-commercial randomised controlled trial. Participants were recruited from 25 primary care practices in the East Midlands region and the Thames Valley and South Midlands region of England, UK (appendix p 23). Practices varied in registered patient list size, serving populations with a range of ethnic diversity and social deprivation. The trial design and methods are outlined in detail in a published trial protocol.[13]

See Online for appendix

Eligible participants were aged 16 years or older; had moderate to moderately severe depressive symptoms defined as a score of 10–19 on the nine-item self-rated Patient Health Questionnaire (PHQ-9);[14] had a diagnosis of a current primary major depressive episode made with the research version of the Structured Clinical Interview for DSM-5 (SCID-5-RV);[15] had been offered antidepressant medication to be prescribed for a minimum of 6 weeks (but did not accept the offer) or had been prescribed antidepressant medication for a minimum of 6 weeks, in the past 3 months; gave oral and written informed consent to participate in the study; and agreed not to purchase the Alpha-Stim AID device privately during the trial, and to return the device at the end of the study.

Participants were excluded if they had a score of 20 or higher on the PHQ-9, in consideration of patient safety; required urgent clinical care such as having persistent suicidal ideation, self-harm, or suicidal intent; had completed and benefited from psychological treatment for depression, with self-reported reduction of two or more symptoms, in the past 3 months (because psychological treatments might become effective after they stop); were planning to commence psychological treatment in the next 6 months; were involved with any other depression-related clinical trial at the time of consent or within 6 months before the study; were diagnosed with neurological conditions such as brain neoplasm, cerebrovascular events, epilepsy, dementia, and neurodegenerative disorders, or had previously received brain surgery; had a pacemaker, cochlear implant, or an implantable cardioverter device; were pregnant; had major unstable medical illness requiring further investigation or treatment; or were diagnosed with a current substance use disorder or dependence, an eating disorder, bipolar disorder, or non-affective psychosis, determined with the SCID-5-RV interview. Being on medication; having a comorbid anxiety, neurodevelopmental, or personality disorder; or having a stable physical illness not requiring urgent clinical care were not exclusion criteria.

Participants were recruited by referral from participating primary care practices. Types of referral included opportunistic referrals (during remote or face-to-face usual care consultations) based on the primary care physician's clinical knowledge of the patient; patient self-referral to primary care practice staff following social media, website, or poster advertising; or through postal invitations (Docmail) sent to patients after an electronic search of medical records (for patients who consulted with the practice regarding depression in the preceding 3 months with an offer or receipt of an antidepressant prescription). Participants indicated on a self-report questionnaire if they no longer had depression or met any of the exclusion criteria before an initial screening questionnaire. After exclusions, the study outcome assessors completed a screening interview to establish further eligibility using the PHQ-9 and SCID-5-RV. Potential participants then completed a baseline assessment with the outcome assessors, including the GRID version of the 17-item Hamilton Depression Scale (HDRS-17),[16] the seven-item generalised anxiety disorder scale (GAD-7),[17] the eight-item Work and Social Adjustment Scale (WSAS),[18] the five-level EQ-5D (EQ-5D-5L) quality of life questionnaire,[19] an adapted version of the Client Service Receipt Inventory,[20] and SCID-5-RV (anxiety disorders). All screening and baseline assessments were completed remotely by telephone or by video conferencing via Microsoft Teams as the trial was conducted during the COVID-19 pandemic. Participants received a £10 Amazon gift voucher on completion of all follow-up assessments.

Written informed consent was obtained from participants before undertaking the screening and baseline assessments. The Alpha-Stim-D trial was designed and reported in compliance with CONSORT guidelines.[21] The trial received research ethics committee approval and health research authority approval from the East Midlands–Leicester South Research Ethics Committee (research ethics committee approval reference 20/EM/0061).

Randomisation and masking

Participants were randomly assigned (1:1) to 8 weeks of treatment with either active CES with an active Alpha-Stim AID device, or sham CES with a sham Alpha-Stim AID device. The researchers conducting assessments enrolled participants into the trial before randomisation. Random assignment was done with a secure web-based randomisation system developed and managed by the Clinical Database Support Service at the University of Nottingham (Nottingham, UK), who managed the system independently of the research team and following specified standard operating procedures. Randomisation was minimised by region, by the presence or absence of one or more current SCID-5-RV anxiety disorders, given that CES with Alpha-Stim AID might be effective for anxiety disorders, and by the use of antidepressant medication (offered [declined] *vs* prescribed as reported by the participant). Further details on the randomisation procedure are provided in the statistical analysis plan (appendix p 8).

Participants, researchers rating outcome measures and conducting the outcome assessments, primary care staff, the chief investigator (RM), and the trial statistician (BG) were masked to treatment allocation. The sham Alpha-Stim AID devices were identical to the active device in look, sound, and feel. The study administrator or another member of the study team at the University of Nottingham (not involved in assessment outcomes) was informed of the allocation by email. They conveyed device allocation directly to The Microcurrent Site (Huntingdon, UK; device distributors in the UK) who were provided with the name and address of the participants (but were masked to any baseline clinical or demographic information about the participants). The company then distributed the allocated device to the participant. Participants were not directly informed of their allocation by the researchers or the manufacturer. After the collection of all outcome data, participants were asked which device they thought they had received.

Procedures

Participants in both groups were advised to use the either active or sham Alpha-Stim AID device for 60 min daily for 8 weeks. The active device used in this study was the Alpha-Stim AID 100 manufactured by Electromedical Products International (Mineral Wells, TX, USA). The device provides electrical stimulation by generating bipolar, asymmetric, rectangular waves with a frequency of 0·5 Hz and a current intensity that is pre-set and locked by the manufacturer at its lowest therapeutic dose of 100 µA (a subsensory level for most participants). This dose has been found to be effective in five previous randomised trials of CES that used current or earlier models of the Alpha-Stim device in participants with anxiety or depression symptoms.[11] 60 min daily was used in previous trials of Alpha-Stim AID[11,22] and an 8-week treatment duration was suggested by NICE in their technology appraisal of Alpha-Stim CES for generalised anxiety disorder.[12] A light indicates the machine is on and a counter records the total minutes of machine use during treatment with the device. In the sham Alpha-Stim AID device, the only difference was that the ear clip electrodes did not emit electricity.

Participants were not able to change any of the device settings that regulated current, frequency, and time on the active or sham devices. The manufacturers (Electromedical Products International) tested the active and sham devices before they were shipped to the distributors in the UK (The Microcurrent Site) to ensure that sham devices were not emitting a current. In addition, three patient and public involvement volunteers with lived experience of depression tested the device before the first participant was randomly assigned, confirming that the dose of 100 µA was subsensory and that there were no obvious indicators from the device itself that would unmask a participant. The patient and public involvement volunteers were recruited by study investigators independently of the device manufacturer or distributor.

Participants received an instructional video and a written leaflet with the device, which were identical for the active and sham groups, and they were instructed to use the device while at rest or doing light activity, but we did not record which they did or whether they followed these instructions. Participants were advised to contact the primary care practice staff or study team (outcome assessors) with any queries. Participants were provided with treatment logs to document the date, time, and duration of treatment, and any feedback they had about the experience of using the device, including any side-effects. Treatment logs were reviewed by the outcome assessors after 16 weeks. A primary care physician, nurse, or supervised health-care assistant from the primary care practice telephoned the participants within 72 h of starting active or sham Alpha-Stim AID treatment to discuss any uncertainties, record and discuss side-effects, and check participants' mental state to ensure that participants were not at risk of self-harm or suicide. If the staff member had concerns related to the participant's safety, then the primary care physician and research team were informed.

Adherence was measured with the time counter that is part of the display output of the machine, which provides the total amount of time used. Participants were considered adherent if they had used the device for a minimum of 28 h (ie, at least 50% of the intervention time), given that 75% of improvement in depression symptoms with Alpha-Stim AID was previously shown to occur in the first 4 weeks of the intervention.[23]

Participants were advised to contact the study site immediately in the event of any adverse events. Side-effects reported in treatment logs were also considered adverse events. All adverse events and serious adverse events were reported to the chief investigator (RM) and

assessed for seriousness, expectedness, and causality according to the European Medicines Agency ICH E2A clinical safety data management guideline.[24] Adverse events were closely monitored and reported in accordance with the regulatory procedures of the East Midlands–Leicester South Research Ethics Committee and University of Nottingham.

Outcome data from assessment scales (GRID-HDRS-17,[16] PHQ-9,[14] GAD-7,[17] WSAS,[18] and EQ-5D-5L[19]) were collected at baseline and at 4 weeks, 8 weeks, and 16 weeks after randomisation. The adapted version of the Client Service Receipt Inventory[20] was completed at baseline and 16 weeks. All data were collected by study researchers by telephone or via Microsoft Teams. Gender was self-reported as a UK NHS-protected charactersitic (male, female, or other when the particpant did not self-identify as male or female).

The three Alpha-Stim patient and public involvement and engagement representatives informed all aspects of the design and conduct of the trial including taking a lead role in the production of the instructional video and all promotional materials.

Outcomes

The primary clinical outcome was change on the GRID-HDRS-17 from baseline to 16 weeks after randomisation. Secondary clinical outcomes were changes from baseline to 16 weeks on the PHQ-9 depression scale, the GAD-7, the WSAS, and the EQ-5D-5L including a visual analogue scale of overall health.[19] As a secondary clinical outcome we also assessed change in health-care service use between baseline and 16 weeks, established with the adapted version of the Client Service Receipt Inventory. A health economics analysis will be reported separately. Exploratory outcomes were response, defined as a 50% decrease in baseline score on the GRID-HDRS-17 at 16 weeks, and remission, defined as a score of 7 or less on the GRID-HDRS-17 at 16 weeks.[25] Safety was assessed on the basis of participant-reported adverse events and adherence (as a measure of device tolerability) during the trial.

Choice of primary outcome measure

The HDRS-17 was selected as the primary outcome measure because it is an internationally used clinician-administered depression assessment scale that is preferred by regulatory bodies in Europe and the USA. The HDRS-17 contains 17 items relating to symptoms experienced in the past week. A score of 0–7 is generally accepted to be within normal range (clinical remission) and a score of 20 or more indicates moderately severe depression. The GRID version was chosen because of superior inter-rater reliability compared with other structured versions of the HDRS-17.[16] The 16-week timepoint was chosen to establish whether any benefits of active Alpha-Stim AID were maintained after the treatment period, given that a treatment effect only at the end of treatment would be unlikely to be important in clinical practice.

Statistical analysis

A between-group difference of 3 points on the GRID-HDRS-17 scale at follow-up is internationally accepted as a minimum clinically important difference for depression disorders.[26] We compared the score change from baseline in the active Alpha-Stim AID group with that in the sham Alpha-Stim AID group. Assuming a standard deviation of 6·4 for the mean change difference between groups, observed in a randomised trial of a similar patient population,[27] a sample size of 86 per group was required to detect a between-group mean change difference of 3 points at 16 weeks follow-up with 90% power and a two-tailed significance level of 5%, assuming an intragroup correlation (Pearson's r) between the baseline and follow-up measures of 0·1 and an intragroup correlation between follow-up measures at 4, 8, and 16 weeks of 0·85. To allow for up to 25% missing primary outcome data due to anticipated dropout, we planned to recruit 230 participants (115 per arm). Stata sampsi code was used to calculate the sample size.

The analysis was conducted on an intention-to-treat (ITT) basis with all randomly assigned patients included in the analysis. Treatment effects on GRID-HDRS-17 score were quantified with the ANCOVA approach by means of multilevel modelling with patients as level 2 analytical unit, arm, follow-up time, and their interaction, and baseline measure and minimisation factors included as fixed-effects covariates.[28] The treatment differences at each follow-up time with 95% CIs were derived from the multilevel modelling. Missing values were imputed with an analytical model by means of the Markov chain Monte Carlo approach for multilevel data under the missing at random assumption.[28] Secondary outcomes were analysed in a similar way in the ITT population. All randomly assigned participants were included in the safety analysis (safety dataset). Adverse events and adherence are reported by gender.

Sensitivity analyses of the primary outcome included a per-protocol analysis (excluding participants with protocol violations—ie, used the device for <28 h; completed follow up >10 days after follow-up was due; or received the device >7 days after baseline), an analysis with observed data only, and a complier average causal effect (CACE) analysis, all with the same analytical model as for the primary analysis. CACE estimation was performed with latent class modelling to explore the effect of treatment on the primary outcome estimates in those participants who complied with the intervention (≥28 h) and those who would have complied if assigned to treatment (ie, predicted subgroups of patients with similar characteristics to those who complied). In a post-hoc ITT analysis, we stratified the primary outcome data by gender. Further details on the analysis are provided in the statistical analysis plan (appendix pp 1–17). Stata (version 17) was used for data analysis and Blimp

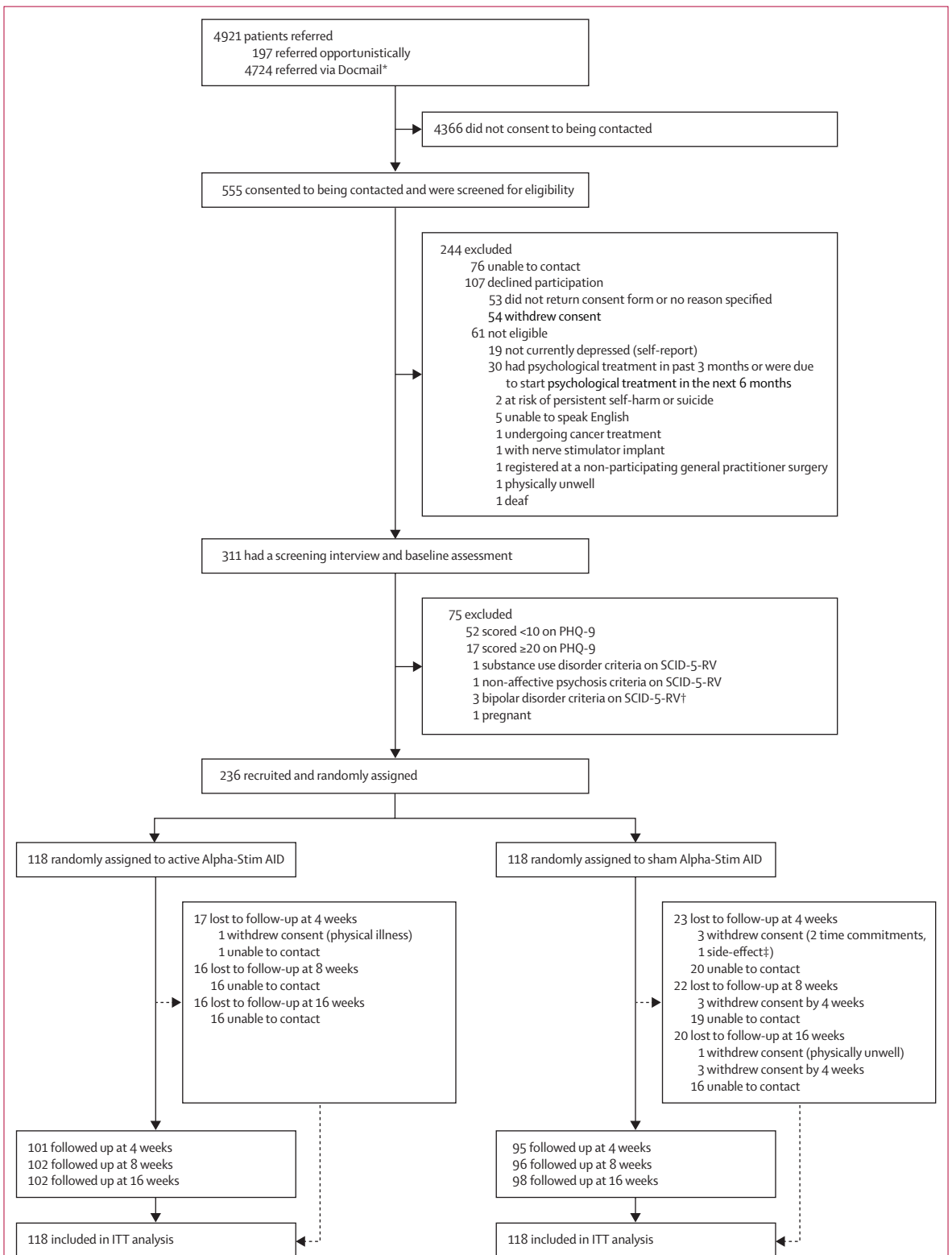

Figure 1: **Trial profile**
PHQ-9=nine-item Patient Health Questionnaire. SCID-5-RV=Structured Clinical Interview for DSM-5, Research Version. Alpha-Stim AID=Alpha-Stim Anxiety Insomnia and Depression device. ITT=intention to treat. *Platform used to collate patient self-referrals and invite letters. †Including two individuals who met the criteria for manic disorder on SCID-5-RV. ‡Headache, which was recorded as an adverse event.

software (version 3.1.24; University of California, Los Angeles, CA, USA) was used for missing value imputation.[29]

An independent trial oversight committee fulfilled the functions of both a trial steering committee and a data monitoring and ethics committee. The study was prospectively registered with the ISRCTN registry, ISRCTN11853110, on Aug 14, 2020, before any participant was recruited.

	Active Alpha-Stim AID (n=118)	Sham Alpha-Stim AID (n=118)
Age, years	37·1 (15·1)	38·9 (15·5)
Gender		
Male	43 (36%)	34 (29%)
Female	74 (63%)	82 (69%)
Other	1 (1%)	2 (2%)
Ethnicity		
White British or Irish	106 (90%)	94 (80%)
White European or other White ethnicity	5 (4%)	7 (6%)
Asian	2 (2%)	8 (7%)
African	2 (2%)	4 (3%)
Chinese	0	2 (2%)
Other ethnicity	3 (3%)	3 (3%)
Marital status		
Married or in a partnership	45 (38%)	50 (42%)
Single or separated	71 (60%)	64 (54%)
Prefer not to say	2 (2%)	4 (3%)
Highest qualification		
Higher degree	17 (14%)	23 (19%)
First degree	28 (24%)	23 (19%)
Other higher qualification	11 (9%)	10 (8%)
A-level*	21 (18%)	22 (19%)
O-level or GCSE*	15 (13%)	15 (13%)
Other qualification	19 (16%)	16 (14%)
No qualification	4 (3%)	6 (5%)
Prefer not to say	3 (3%)	3 (3%)
Occupational status		
Paid employment or self-employment	67 (57%)	63 (53%)
Student or training	26 (22%)	23 (19%)
Home maker	2 (2%)	4 (3%)
Unemployed	15 (13%)	18 (15%)
Retired	5 (4%)	5 (4%)
Other	1 (1%)	3 (3%)
Prefer not to say	2 (2%)	2 (2%)
Physical disability		
Yes	35 (30%)	29 (25%)
No	80 (68%)	85 (72%)
Prefer not to say	3 (3%)	3 (3%)
Comorbidities†		
Any anxiety disorders	91 (77%)	84 (71%)
General anxiety disorder	81 (69%)	68 (58%)
Panic disorder	33 (28%)	27 (23%)
Social anxiety disorder	29 (25%)	43 (36%)
Agoraphobic disorder	15 (13%)	17 (14%)

(Table 1 continues on next page)

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 8, 2020, and Jan 19, 2022, 4921 potential participants were referred to the study, 555 provided verbal or written consent to be contacted, and 311 were identified as potentially eligible. 75 were excluded after the screening interview and baseline assessment (figure 1). In total, 236 participants were enrolled from 25 primary care practices and were randomly assigned to receive active Alpha-Stim AID (n=118) or sham Alpha-Stim AID (n=118). 160 (68%) participants were from primary care practices in the East Midlands and 76 (32%) were from the Thames Valley and South Midlands region. The mean age was 38·0 years (SD 15·3; range 16–83 years), with five participants aged 16–18 years. 156 (66%) of the 236 participants were female, 77 (33%) were male, and three (1%) self-reported as other gender (table 1). 200 (85%) participants defined their ethnicity as White British or Irish. Of the 236 participants, 205 (87%) were prescribed and reported taking antidepressant medication for a minimum of 6 weeks in the 3 months before study enrolment, and 31 (13%) had been offered antidepressant medication but did not take it.

At baseline, 100 (42%) of the 236 participants scored 10–14 on the PHQ-9 and 136 (58%) scored 15–19 on the PHQ-9. 175 (74%) participants met the criteria for an anxiety disorder on the SCID-5-RV. The mean scores on the GRID-HDRS-17 were 17·4 (SD 5·5) in the active group and 16·4 (5·4) in the sham group. The mean score on the WSAS for the overall population was 24·5 (7·8), which was in the impaired range (ie, ≥20), although most participants were employed or in full-time education.

The numbers of patients followed up at 16 weeks with data on the primary outcome were 102 (86%) of 118 in the active Alpha-Stim AID group and 98 (83%) of 118 in the sham Alpha-Stim AID group. Five participants withdrew from the trial (four from the sham group and one from the active group) but were included in the ITT analysis. Reasons for withdrawal were physical illness, feeling physically unwell (unrelated to the device), time commitments, and a side-effect (tinnitus, recorded as an adverse event). The last participant completed the 16-week follow-up on May 24, 2022, at which point data collection was completed.

At 16 weeks after randomisation in the ITT population, mean GRID-HDRS-17 score was 11·1 (SD 6·3) in the active Alpha-Stim AID group, compared with 10·0 (6·7) in the sham Alpha-Stim AID group (appendix p 19). The mean change in GRID-HDRS-17 score at 16 weeks was –5·9 (95% CI –7·1 to –4·8) in the active group versus

–6·5 (–7·7 to –5·4) in the sham group (table 2). Both groups showed a clinically important decrease (≥3 points) in mean depression symptoms on the GRID-HDRS-17 at 4 weeks that was maintained at 8 and 16 weeks. Comparing the score change from baseline in the active group with the score change from baseline in the sham group, no significant difference was noted at 16 weeks (mean change difference 0·6 [95% CI –1·0 to 2·2], p=0·46). Additionally, the differences were not significant in the observed data analysis, per-protocol analysis (81 protocol deviations affecting 78 participants who were excluded), and CACE analysis at 16 weeks (figure 2). The change in GRID-HDRS-17 score did not differ significantly between the groups at 4 and 8 weeks (table 2), and there were no significant differences by gender (appendix pp 20–21). We observed no significant differences in treatment response and remission rates at 16 weeks between the active and sham groups.

For the secondary outcomes, we observed clinically important improvements in the sham Alpha-Stim AID group on the PHQ-9, GAD-7, and EQ-5D-5L at 4 weeks, which were maintianed at 8 and 16 weeks. We observed clinically important differences in these measures by 8 weeks in the active Alpha-Stim AID group. The improvements in WSAS did not reach the minimum clinically important threshold at any timepoint in either group. Compared with the active Alpha-Stim AID group, participants in the sham Alpha-Stim AID group showed significantly greater (but clinically small) reductions in self-rated depression at 4 and 16 weeks, in generalised anxiety at 4 weeks, and in overall health at 16 weeks. The change in WSAS score did not differ significantly between the groups at any timepoint.

Minimum treatment adherence with active or sham Alpha-Stim AID of 28 h was observed in 152 (73%) of 209 participants for whom data were available: 79 (72%) of 109 participants in the active group and 73 (73%) of 100 in the sham group (table 3).

A total of 17 adverse events were reported in 17 (7%) of the 236 randomly assigned participants. The number of adverse events reported was similar between the active Alpha-Stim AID group (nine events) and sham Alpha-Stim AID group (eight events; table 3). Adverse events were reported at slightly higher frequency in men than in women. The most commonly occurring adverse event was headache. In the active Alpha-Stim AID group, one adverse event was of moderate severity that required action (increased anxiety requiring a dose of an anxiolytic drug), one event (headache) led to withdrawal of treatment but not from the trial, and the remaining seven were mild in severity; seven (6%) of the 118 participants in the active group were judged to have an adverse event probably related to the device (headache, n=4; dizziness, n=1; rhythmic shocks, n=1; and tinnitus, n=1), all of mild severity. In the sham treatment group, one serious adverse event of suicidal ideation leading to hospital admission was reported (this event was judged not to be related to the device and the participant continued on the trial), three events were moderate in severity requiring action (headache requiring analgesic medication [n=1] and tinnitus requiring a decreased duration of each CES treatment session [n=2]), one event (headache) led to withdrawal from treatment and the trial, and three events were mild in severity; five (4%) of 118 participants in the sham group were judged to have a mild or moderate adverse event probably related to the device (headache, n=2; tinnitus, n=2; and skin irritation from electrodes, n=1).

After outcome data collection, of the participants allocated an active device, 51 (71%) of 72 respondents believed that they had received an active device. Of the participants allocated a sham device, 39 (60%) of 65 believed that they had received an active device.

	Active Alpha-Stim AID (n=118)	Sham Alpha-Stim AID (n=118)
(Continued from previous page)		
Antidepressant medication in the past 3 months		
Prescribed and took antidepressant medication (≥6 weeks)	103 (87%)	102 (86%)
Offered but declined antidepressant medication	15 (13%)	16 (14%)
Antidepressant medication‡		
Selective serotonin reuptake inhibitor	79 (67%)	66 (56%)
Serotonin-noradrenaline reuptake inhibitor	17 (14%)	8 (7%)
Noradrenaline and specific serotonergic antidepressant	8 (7%)	12 (10%)
Tricyclic antidepressant	9 (8%)	8 (7%)
Serotonin antagonist and reuptake inhibitor	2 (2%)	0
Monoamine oxidase inhibitor	1 (1%)	0
Miscellaneous antidepressant	0	1 (1%)
Atypical antipsychotic	4 (3%)	2 (2%)
Mood stabiliser	1 (1%)	0
Anxiolytic	2 (2%)	3 (3%)
β blocker	1 (1%)	2 (2%)
Baseline assessments		
GRID-HDRS-17	17·4 (5·5)	16·4 (5·4)
PHQ-9	15·2 (2·8)	15·0 (2·9)
GAD-7	11·6 (4·3)	11·6 (4·6)
WSAS	24·6 (7·6)	24·4 (8·0)
EQ-5D-5L VAS	54·4 (18·3)	56·3 (18·3)

Data are mean (SD) or n (%). Alpha-Stim AID=Alpha-Stim Anxiety Insomnia and Depression device. GCSE=General Certificate of Secondary Education. GRID-HDRS-17=GRID version of the 17-item Hamilton Depression Rating Scale. PHQ-9=nine-item Patient Health Questionnaire. GAD-7=seven-item Generalised Anxiety Disorder scale. WSAS=eight-item Work and Social Adjustment Scale. EQ-5D-5L VAS=five-level EQ-5D with visual analogue scale. *A-level, left school at age 18 years; O-level or GCSE, left school at age 16 years. †Comorbidities are not mutually exclusive. ‡Medications are not mutually exclusive.

Table 1: **Baseline characteristics of participants**

Discussion

Alpha-Stim AID is a safe, well tolerated, and acceptable treatment in people seeking help with treatment of

	Active Alpha-Stim AID: mean change from baseline (95% CI)	Sham Alpha-Stim AID: mean change from baseline (95% CI)	Mean change difference (95% CI)	p value
GRID-HDRS-17				
4 weeks	−5·1 (−6·3 to −4·0)	−5·9 (−7·0 to −4·8)	0·8 (−0·9 to 2·4)	0·35
8 weeks	−5·9 (−7·0 to −4·9)	−6·8 (−7·8 to −5·7)	0·9 (−0·6 to 2·3)	0·25
16 weeks	−5·9 (−7·1 to −4·8)	−6·5 (−7·7 to −5·4)	0·6 (−1·0 to 2·2)	0·46
PHQ-9				
4 weeks	−3·6 (−4·5 to −2·7)	−4·9 (−5·8 to −4·0)	1·3 (0·0 to 2·6)	0·048
8 weeks	−4·6 (−5·5 to −3·6)	−5·8 (−6·8 to −4·8)	1·2 (−0·2 to 2·6)	0·083
16 weeks	−4·0 (−5·0 to −3·0)	−5·7 (−6·7 to −4·6)	1·7 (0·2 to 3·1)	0·025
GAD-7				
4 weeks	−3·0 (−3·8 to −2·2)	−4·2 (−5·0 to −3·4)	1·2 (0·1 to 2·3)	0·031
8 weeks	−3·6 (−4·4 to −2·8)	−4·5 (−5·3 to −3·7)	1·0 (−0·2 to 2·1)	0·098
16 weeks	−3·2 (−4·1 to −2·3)	−4·4 (−5·3 to −3·4)	1·2 (−0·1 to 2·5)	0·072
WSAS				
4 weeks	−5·8 (−7·5 to −4·2)	−6·7 (−8·4 to 5·1)	0·9 (−1·3 to 3·2)	0·43
8 weeks	−6·6 (−8·2 to −5·0)	−7·8 (−9·5 to −6·2)	1·2 (−1·1 to 3·5)	0·30
16 weeks	−5·2 (−6·9 to −3·6)	−7·5 (−9·2 to −5·8)	2·3 (−0·1 to 4·7)	0·058
EQ-5D-5L VAS				
4 weeks	6·7 (3·3 to 10·0)	8·3 (4·8 to 11·7)	−1·6 (−6·4 to 3·3)	0·52
8 weeks	9·2 (6·1 to 12·2)	11·6 (8·0 to 15·2)	−2·4 (−7·1 to 2·3)	0·31
16 weeks	7·9 (4·6 to 11·1)	12·7 (9·3 to 16·1)	−4·9 (−9·7 to 0·0)	0·049
Response to treatment*, n/N (%)				
16 weeks	34/102 (33%)	40/98 (41%)	NA	0·27
Remission*, n/N (%)				
16 weeks	31/102 (30%)	41/98 (42%)	NA	0·092

Outcome scores are provided for the ITT population. Clinically important differences are as follows: for GRID-HDRS-17, ≥3 points,[26] for PHQ-9, ≥3·7 points,[30] for GAD-7, ≥3·3 points,[30] for WSAS, ≥8 points,[31] and for EQ-5D-5L VAS, ≥8 points.[32] Alpha-Stim AID=Alpha-Stim Anxiety Insomnia and Depression device. GRID-HDRS-17=GRID version of the 17-item Hamilton Depression Rating Scale. PHQ-9=nine-item Patient Health Questionnaire. GAD-7=seven-item Generalised Anxiety Disorder scale. WSAS=eight-item Work and Social Adjustment Scale. EQ-5D-5L VAS=five-level EQ-5D with visual analogue scale. NA=not applicable. ITT=intention to treat. *Response (50% decrease in baseline score on the GRID-HDRS-17) and remission (score of ≤7 on the GRID-HDRS-17) provided for the observed population at 16 weeks (figure 1).

***Table 2*: Primary and secondary outcome scores and response to treatment**

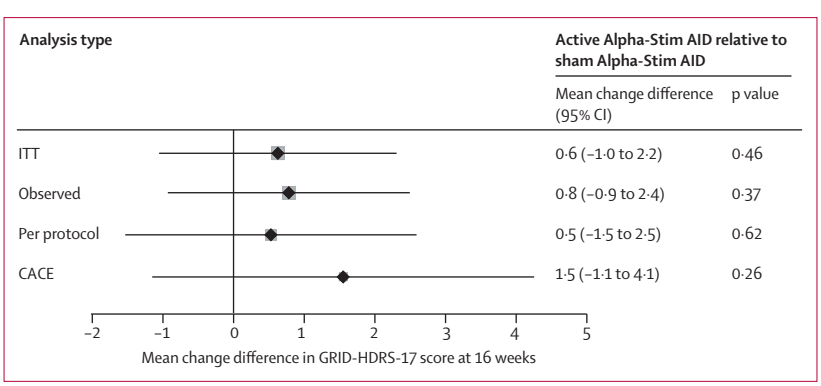

***Figure 2*: Intention-to-treat, observed, per-protocol, and CACE analysis of the primary outcome following active Alpha-Stim AID relative to sham Alpha-Stim AID**

Covariates in the ITT analysis were included in all sensitivity analyses. Alpha-Stim AID=Alpha-Stim Anxiety Insomnia and Depression device. ITT=intention to treat. CACE=complier average causal effect. GRID-HDRS-17=GRID version of the 17-item Hamilton Depression Rating Scale.

primary major depression in primary care. However, we found no evidence of an additional benefit when microcurrent, fixed-dose CES (100 μA) was delivered by the active Alpha-Stim AID device, compared with sham Alpha-Stim AID treatment, in people seeking help for primary major depression whose symptoms were not responsive to the prescription or offer of antidepressant treatment.

To our knowledge, the Alpha-Stim-D trial is the first adequately powered, multicentre, double-blind, sham-controlled, non-commercially sponsored, randomised controlled trial to assess the Alpha-Stim AID device for the treatment of depressive symptoms in people seeking help for primary major depression. Both the active Alpha-Stim AID and sham Alpha-Stim AID groups, after 8 weeks of treatment, showed a clinically important mean improvement in the primary outcome of observer-rated depression symptoms on the GRID-HDRS-17 at 16 weeks, accompanied by clinically important improvements in secondary outcomes. However, we found no significant difference between the active and sham groups in terms of the change in GRID-HDRS-17 symptoms at 16 weeks. Sham Alpha-Stim AID was statistically superior to active Alpha-Stim AID on the PHQ-9 at 4 weeks and 16 weeks, on the GAD-7 at 4 weeks only, and on the EQ-5D-5L at 16 weeks only. However, the

	Active Alpha-Stim AID			Sham Alpha-Stim AID			Total (n=236)
	Men (n=43)	Women (n=74)	Other gender (n=1)	Men (n=34)	Women (n=82)	Other gender (n=2)	
Adverse events							
Anxiety increased	2 (5%)	0	0	0	0	0	2 (1%)
Dizziness	0	1 (1%)	0	0	0	0	1 (<1%)
Headaches	1 (2%)	3 (4%)	0	2 (6%)	2 (2%)	0	8 (3%)
Mild rhythmic shocks	1 (2%)	0	0	0	0	0	1 (<1%)
Suicidal ideation leading to hospital admission	0	0	0	0	1 (1%)	0	1 (<1%)
Skin irritation	0	0	0	0	1 (1%)	0	1 (<1%)
Tinnitus	1 (2%)	0	0	1 (3%)	1 (1%)	0	3 (1%)
All events	5 (12%)	4 (5%)	0	3 (9%)	5 (6%)	0	17 (7%)
Adherence (tolerability)							
Device use <28 h	9/38 (24%)	21/70 (30%)	0	8/26 (31%)	19/72 (26%)	0	57/209 (27%)
Device use ≥28 h	29/38 (76%)	49/70 (70%)	1 (100%)	18/26 (69%)	53/72 (74%)	2 (100%)	152/209 (73%)

Data are n (%) or n/N (%) where N is number of participants with available data. Alpha-Stim AID=Alpha-Stim Anxiety Insomnia and Depression device.

Table 3: **Frequency of adverse events and adherence by gender**

differences between the treatment groups were small, below the thresholds for clinically important change, and inconsistent across all timepoints. We also found no significant difference between the groups when comparing the change in WSAS score at any timepoint, and the frequency of depression response or remission at 16 weeks did not differ significantly between the groups. Thus, overall, we observed no clinically important differences in outcome between the active and sham Alpha-Stim AID treatment groups.

The intervention was well tolerated and safe for participants. We found minor differences in adverse events between the groups, and only one serious adverse event occurred in the sham group, which was judged unrelated to the treatment. An adequate course of Alpha-Stim AID treatment (≥28 h) was completed by 73% of participants overall.

The trial successfully recruited within the planned timeframe despite an initial 6-month delay in recruitment due to the COVID-19 pandemic, reflecting the substantial unmet treatment demand for a home-based, non-pharmacological, non-psychological treatment in the patient population. Retention to the primary endpoint at 16 weeks after randomisation was high (85%) with similar attrition between the groups, and the treatment completion at 73% was acceptable. The sample was representative of the age (including individuals aged 16–18 years) and gender characteristics of patients with depression in primary care, although few people who were unemployed or with a disability were recruited into the study. The sample was broadly representative of the ethnicity of the population in England. As expected, most participants had comorbid anxiety disorders and had been prescribed antidepressants. Given that both of these clinical factors might affect depression outcomes or responsiveness to CES with Alpha-Stim AID, the design and analysis of the study ensured that the treatment groups were well balanced on these variables and did not bias the overall outcome.

The study has several limitations. First, we did not set out to assess the clinical effectiveness of the Alpha-Stim AID device in subthreshold, severe, or treatment-resistant depression populations. Given that this was an effectiveness trial rather than a test of efficacy, we did not exclude all comorbidities such as personality disorder or stable medical illness, to improve the generalisability of our results to patients seeking treatment for depression in primary care. Although scores of 10–14 and 15–19 on the PHQ-9 were originally characterised as indicating moderate and moderately severe depression, more recent guidance published while the trial was recruiting suggests that these ranges should be regarded as mild and moderate severity.[33] We also did not plan to formally assess expectancy effects at the outset of the trial. We cannot rule out that a more personalised approach to Alpha-Stim AID treatment, such as increasing the dose of the CES current to the maximum tolerated dose[12] or a longer course of treatment over months, might have been more effective. However, a fixed dose of 100 μA enables adequate masking against sham treatment, and this dose was previously reported to reduce depression symptoms compared with sham treatment in patients who did not have primary major depression.[11]

The magnitude of mean clinical improvements met the minimum threshold for a clinically important change at 16 weeks in both the active and sham Alpha-Stim AID groups on the GRID-HDRS-17, and in the sham group on the PHQ-9, GAD-7, and EQ-5D-5L. Clinically important changes in PHQ-9, GAD-7, and EQ-5D-5L were observed at 8 weeks in the active Alpha-Stim AID group. The act of planning the day and devoting 1 h per day for personal relaxation for up to 8 weeks might have been of some

clinical benefit. People with depression typically have low motivation to do activities that might be rewarding to them and they put the needs of others before themselves. Structuring the day to do a relaxation task, such as Alpha-Stim AID, that increases a sense of control or pleasure might be construed as compatible with behavioural activation, an effective psychological treatment for depression.[34] However, unlike behavioural activation, with Alpha-Stim AID there was no progressive increase in activities over time.[35] Other reasons for the substantial decrease in depression over time in both groups might have been regression to the mean, benefits of support from the research team, or hope engendered by participating in a novel intervention trial. We tried to mitigate against spontaneous improvement by selecting participants who had not improved with antidepressants and restricting the amount of contact with the research team.

The results do not support a recent meta-analysis of randomised controlled trials of CES that used the same fixed dose of 100 µA CES for 1 h per day (versus sham), which improved depression symptoms,[11] nor an independent systematic review conducted by the US Veterans Administration, which showed improvement in mixed anxiety and depression symptoms when different doses and models of CES were used.[10] These previous analyses were conducted in highly heterogeneous and smaller populations with anxiety or mixed anxiety and depression. There is preliminary evidence of the effectiveness of CES in generalised anxiety disorder, as suggested by NICE,[12] but not from this trial in primary major depression. Additionally, a previous trial of CES (20 min daily at 1 mA for 3 weeks) in 30 adults with major depressive disorder found that active CES (not with Alpha-Stim AID) was no more effective than sham CES at the end of treatment.[36] The disparity might be explained by successful stimulation of the vagus nerve, which occurs after one session in some treatments for anxiety (eg, breathing exercises[37]) but not for many months after treatments for primary depression (eg, vagus nerve stimulation treatment itself[38]).

In conclusion, Alpha-Stim AID CES at a daily dose of 100 µA for 8 weeks was well tolerated and safe, but we found no evidence to support its clinical effectiveness in patients with moderate to moderately severe primary major depression.

Contributors

RM was the chief investigator and conceived and wrote the study design. SP wrote the trial protocol with input from all authors. RM and SP were responsible for study implementation and general project management. SP, CB, and PP were responsible for recruitment and follow-up visits. SP oversaw trial management. BG and RM designed and wrote the statistical analysis plan. BG did the analysis. JK contributed to the study design. JK, DS, AZ, and CG provided information on primary care. NN and PMB advised on the mechanism of action of Alpha-Stim AID and on treatment of depression. MC advised on the health economics and quality of life design. VP was involved in recruiting patients and collecting data as a general practitioner. AD oversaw randomisation. DB, FH, and RMcN recruited patient and public involvement volunteers and helped to develop materials for participants with CB. KS advised on study materials and approaches for participants aged 16–18 years. RM, BG, and SP drafted the original manuscript. All authors contributed to the interpretation of data and to re-drafts. BG, SP, CB, and PP accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. RM is guarantor of the study.

Declaration of interests

RM was chief investigator on a grant from the UK National Institute for Health and Care Research (NIHR) Applied Research Collaboration (ARC) East Midlands. RM has received other NIHR funding for research on interventions for depression and has received funding from Novartis to serve on a data management and ethics committee for two trials on the treatment of depression. SP, PP, BG, AD, and MC received funding from the NIHR to support their salaries during the conduct of the study. VP received salary support from the NIHR Clinical Lectureship scheme and a starter grant from the UK Academy of Medical Sciences. All other authors declare no competing interests.

Data sharing

The study investigators own and have complete control of the research data, which can be accessed at any time. For statistical analysis, the data will be downloaded and safely stored on a computing system maintained by the University of Nottingham. Deidentified participant data and a data dictionary will be made publicly available after publication through the University of Nottingham data repository (https://rdmc.nottingham.ac.uk/) according to NIHR policy. The study protocol has been published and the statistical analysis plan is provided in the appendix (pp 1–17).

Acknowledgments

This study was reviewed and funded by the NIHR ARC East Midlands. In addition, Electromedical Products International provided funding to cover excess treatment costs, health economic assessment, and supply of devices. The Microcurrent Site enabled the allocation of devices after randomisation, distributed the devices, and arranged the collection of devices. The views expressed are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care. We acknowledge the financial support of Electromedical Products International, and the administrative support of The Microcurrent Site. Electromedical Products International manufactured the Alpha-Stim cranial electrotherapy stimulation devices. Both companies played no part in the delivery, analysis, or interpretation of the study. RM and KS are supported by NIHR Senior Investigator Awards. MC and RM are supported by the NIHR MindTech MedTech Co-operative and the NIHR Nottingham Biomedical Research Centre. We thank all participants, clinicians who recruited participants to the trial, and the 25 primary care practices. We acknowledge the help and support of the Primary Care NIHR Clinical Research Network in the East Midlands and the Thames Valley and South Midlands. We are also grateful to our patient and public involvement members for their help. We thank Phil Nettleham, Robin Fox, and Kyle Knox for their expertise and input in developing the electronic searches, and Janet Beecham for performing some of the clinical assessments. We thank James Roe, Dan Simpkins, Safiyah Ossell, and Alison Connaughton for providing administrative support. We also thank the University of Nottingham for providing sponsorship.

References

1 WHO. Depression, and other common mental disorders: global health estimates. World Health Organization. 2017. https://apps.who.int/iris/handle/10665/254610 (accessed Aug 26, 2022).

2 Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006; **163:** 1905–17.

3 National Health Service Digital. Psychological therapies, annual report on the use of IAPT services 2019–20. July 30, 2020. https://digital.nhs.uk/data-and-information/publications/statistical/psychological-therapies-annual-reports-on-the-use-of-iapt-services/annual-report-2019-20 (accessed Aug 2, 2022).

4 Gelhorn HL, Sexton CC, Classi PM. Patient preferences for treatment of major depressive disorder and the impact on health outcomes: a systematic review. *Prim Care Companion CNS Disord* 2011; **13:** PCC.11r01161.

5 Waumans RC, Muntingh ADT, Draisma S, Huijbregts KM, van Balkom AJLM, Batelaan NM. Barriers and facilitators for treatment-seeking in adults with a depressive or anxiety disorder in a western-European health care setting: a qualitative study. *BMC Psychiatry* 2022; **22:** 165.

6 Brunyé TT, Patterson JE, Wooten T, Hussey EK. A critical review of cranial electrotherapy stimulation for neuromodulation in clinical and non-clinical samples. *Front Hum Neurosci* 2021; **15:** 625321.

7 Kennerly R. QEEG analysis of cranial electrotherapy: a pilot study. *J Neurother* 2004; **8:** 112.

8 Brunoni AR, Moffa AH, Fregni F, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *Br J Psychiatry* 2016; **208:** 522–31.

9 Klijs B, Mendes de Leon CF, Kibele EUB, Smidt N. Do social relations buffer the effect of neighborhood deprivation on health-related quality of life? Results from the LifeLines Cohort Study. *Health Place* 2017; **44:** 43–51.

10 Shekelle PG, Cook IA, Miake-Lye IM, Booth MS, Beroes JM, Mak S. Benefits and harms of cranial electrical stimulation for chronic painful conditions, depression, anxiety, and insomnia: a systematic review. *Ann Intern Med* 2018; **168:** 414–21.

11 Price L, Briley J, Haltiwanger S, Hitching R. A meta-analysis of cranial electrotherapy stimulation in the treatment of depression. *J Psychiatr Res* 2021; **135:** 119–34.

12 National Institute for Health and Care Excellence. Alpha-Stim AID for anxiety disorders. Medical technologies guidance [MTG56]. March 8, 2021. https://www.nice.org.uk/guidance/mtg56 (accessed Aug 25, 2022).

13 Patel S, Boutry C, Patel P, et al. A randomised controlled trial investigating the clinical and cost-effectiveness of Alpha-Stim AID cranial electrotherapy stimulation (CES) in patients seeking treatment for moderate severity depression in primary care (Alpha-Stim-D Trial). *Trials* 2022; **23:** 250.

14 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16:** 606–13.

15 American Psychiatric Association. SCID-5-RV update. April, 2017. https://www.appi.org/getattachment/c513942e-e306-429d-9c9a-dec8d86af5d6/SCID-5-RV_Updates_7-7-17.pdf (accessed Aug 26, 2022).

16 Williams JB, Kobak KA, Bech P, et al. The GRID-HAMD: standardization of the Hamilton Depression Rating Scale. *Int Clin Psychopharmacol* 2008; **23:** 120–29.

17 Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166:** 1092–97.

18 Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry* 2002; **180:** 461–64.

19 Gerhards SA, Huibers MJ, Theunissen KA, de Graaf LE, Widdershoven GA, Evers SM. The responsiveness of quality of life utilities to change in depression: a comparison of instruments (SF-6D, EQ-5D, and DFD). *Value Health* 2011; **14:** 732–39.

20 Beecham J, Knapp M. Costing psychiatric interventions. In: Thornicroft G, ed. Measuring mental health needs. London: Gaskell, 2001: 200–24.

21 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340:** c332.

22 Barclay TH, Barclay RD. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. *J Affect Disord* 2014; **164:** 171–77.

23 Morriss R, Xydopoulos G, Craven M, Price L, Fordham R. Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder. *J Affect Disord* 2019; **253:** 426–37.

24 European Medicines Agency. Clinical safety data management: definitions and standards for expedited reporting—scientific guideline. 1995. https://www.ema.europa.eu/en/ich-e2a-clinical-safety-data-management-definitions-standards-expedited-reporting-scientific (accessed Aug 26, 2022).

25 Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 1991; **48:** 851–55.

26 National Institute for Health and Care Excellence. Depression: management of depression in primary and secondary care. Clinical guideline [CG23]. 2004. https://www.nice.org.uk/guidance/cg23. (accessed Aug 26, 2022).

27 Kendrick T, Chatwin J, Dowrick C, et al. Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study. *Health Technol Assess* 2009; **13:** iii-iv, ix-xi, 1–159.

28 Carpenter JR, Goldstein H, Kenward MG. REALCOM-IMPUTE software for multilevel multiple imputation with mixed response types. *J Stat Softw* 2011; **45:** 14.

29 Enders CK, Du H, Keller BT. A model-based imputation procedure for multilevel regression models with random coefficients, interaction effects, and nonlinear terms. *Psychol Methods* 2020; **25:** 88–112.

30 Bauer-Staeb C, Kounali D-Z, Welton NJ, et al. Effective dose 50 method as the minimal clinically important difference: evidence from depression trials. *J Clin Epidemiol* 2021; **137:** 200–08.

31 Zahra D, Qureshi A, Henley W, et al. The work and social adjustment scale: reliability, sensitivity and value. *Int J Psychiatr Clin Pract* 2014; **18:** 131–38.

32 Zanini A, Aiello M, Adamo D, et al. Estimation of minimal clinically important difference in EQ-5D visual analog scale score after pulmonary rehabilitation in subjects with COPD. *Respir Care* 2015; **60:** 88–95.

33 National Institute for Health and Care Excellence. Depression in adults: treatment and management. NICE guideline [NG222]. June 29, 2022. https://www.nice.org.uk/guidance/ng222 (accessed Aug 26, 2022).

34 Ciharova M, Furukawa TA, Efthimiou O, et al. Cognitive restructuring, behavioral activation and cognitive-behavioral therapy in the treatment of adult depression: a network meta-analysis. *J Consult Clin Psychol* 2021; **89:** 563–74.

35 Jensen JS, Bielefeldt AØ, Hróbjartsson A. Active placebo control groups of pharmacological interventions were rarely used but merited serious consideration: a methodological overview. *J Clin Epidemiol* 2017; **87:** 35–46.

36 Mischoulon D, De Jong MF, Vitolo OV, et al. Efficacy and safety of a form of cranial electrical stimulation (CES) as an add-on intervention for treatment-resistant major depressive disorder. *J Psychiatr Res* 2015; **70:** 98–103.

37 Magnon V, Dutheil F, Vallet GT. Benefits from one session of deep and slow breathing on vagal tone and anxiety in young and older adults. *Sci Rep* 2021; **11:** 19267.

38 Zhang X, Qing MJ, Rao YH, Guo YM. Adjunctive vagus nerve stimulation for treatment-resistant depression: a quantitative analysis. *Psychiatr Q* 2020; **91:** 669–79.