Protocol on transcranial alternating current stimulation for the treatment of major depressive disorder: a randomized controlled trial

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Abstract

Background: Transcranial alternating current stimulation (tACS) offers a new approach for adult patients with major depressive disorder (MDD). The study is to evaluate the efficacy and safety of tACS treating MDD.

Methods: This is an 8-week, double-blind, randomized, placebo-controlled study. Ninety-two drug-naive patients with MDD aged 18 to 65 years will receive 20 daily 40-min, 77.5-Hz, 15-mA sessions of active or sham tACS targeting the forehead and both mastoid areas on weekdays for 4 consecutive weeks (week 4), following a 4-week observation period (week 8). The primary outcome is the remission rate defined as the 17-item Hamilton depression rating scale (HDRS-17) score $\leq$7 at week 8. Secondary outcomes are the rates of response at weeks 4 and 8 and rate of remission at week 4 based on HDRS-17, the proportion of participants having improvement in the clinical global impression-improvement, the change in HDRS-17 score (range, 0–52, with higher scores indicating more depression) over the study, and variations of brain imaging and neurocognition from baseline to week 4. Safety will be assessed by vital signs at weeks 4 and 8, and adverse events will be collected during the entire study.

Discussion: The tACS applied in this trial may have treatment effects on MDD with minimal side effects.

Trial registration: Chinese Clinical Trial Registry, ChiCTR1800016479; http://www.chictr.org.cn/showproj.aspx?proj=22048.

Keywords: Major depressive disorder; Transcranial alternating current stimulation; Treatment; Trial

Introduction

Major depressive disorder (MDD) is a deliberating mental disorder with a high prevalence,[1] and it produces heavy burden and suicide.[2] The current anti-depression medications and psychotherapeutic interventions are partly effective in treating depression.[3-9] And those anti-depressants show unwanted side effects, including nausea, diarrhea, fatigue, and dizziness.[8] Therefore, in addition to anti-depressants treating MDD, non-pharmacological interventions have been proposed to treat MDD, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).[10,11] Since the Food and Drug Administration (FDA) approved TMS for the treatment of MDD in 2009,[12] the increasing interest in the effect of new non-pharmaceutical therapy for depression has been reported.[10] However, the TMS procedure in different trials not only has paradoxical consequences,[13] but also causes a risk of seizure.[14] tDCS has a chance of inducing a new-onset mania for MDD patients.[10]

Transcranial alternating current stimulation (tACS) is a kind of cranial electrical stimulation technique of delivering brain stimulation by applying a weak intensity

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000589

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Chinese Medical Journal 2020;133(1)

Received: 11-07-2019 **Edited by:** Li-Min Chen

electrical current to the scalp to modulate cortical excitability and spontaneous brain activity.[15-17] In patients with MDD, tDCS, and tACS-induced currents are applied to the frontal cortex, which is regarded to be a target for mood regulation.[18] Moreover, compared with tDCS, tACS appears advantages, including less sensation and fewer known adverse responses.[19,20] Although tACS has been suggested to be utilized for the treatment of anxiety, depression, and insomnia,[14,21] there is a lack of robust results available to support the effect of tACS treating patients with unipolar depression.[22]

Our pre-clinical experiment on the effect of tACS at a frequency of 77.5-Hz and 15-mA current treating in depression has shown that tACS has a therapeutic effect via stimulating the forehead and both mastoid areas. Therefore, we hypothesize that the tACS with 77.5-Hz and 15-mA current may treat patients with MDD. In this framework, the aim of the current study is to explore the efficacy and safety of the tACS treating MDD.

Methods

Ethics and dissemination

The study is being conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of the Xuanwu Hospital, Capital Medical University, Beijing, China (LXS[2017]-002) on July 20, 2017, then amended (LXS[2017]-002-Amendment 2) on January 17, 2018. The ethics committee's phone, email, and address as follows: 0086-10-83919270, xwkyethics@163.com, and No. 45, Changchun Street, Xicheng District, Beijing 100053, China. Investigators will obtain signed informed consent forms provided by participants before their enrollment in the study. After the study, all patients will continue to receive medical care from the investigators. The results of this study will be presented via articles and national and international conferences. So, this study will contribute to the current treatments on MDD and provide an available non-pharmacological intervention approach in the near future. Due to funding restriction, a maximum fifteen participants in each group will receive cognitive assessment, resting-state magnetoencephalography (MEG),[23] functional magnetic resonance imaging (fMRI),[24] and positron emission tomograph/magnetic resonance (PET/MR) examination after obtaining their another signed informed consent forms.

Study design, randomization, and blinding

This is a single-center, double-blind, randomized, placebo-controlled intervention trial. Ninety-two participants with MDD will be recruited, and randomized to either the active or sham treatment group with a ratio of 1:1. The concealed randomization will be established using a computer-generated random number sequence and maintained by an offsite statistician who will not be involved in the enrolment nor the assessment of the study. The randomization sequence is computed in permuted blocks of four. Each participant will have a number before the first treatment via opening a sealed, opaque envelope to determine the instrument selection in whole trial. A total of 12 tACS devices (six sham and six active) have the same size, color, appearance, weight, and odor. Two of them (one sham and one active) will be intended to be used as a backup in case any one of the other ten devices does not work. To maintain double-blindness, all devices will be coded by the statistician. Persons involving in the study (including the investigators, trial monitors, trained nurses, electroencephalogram (EEG) technicians, raters, and participants) will be blinded to treatment assignment during double-blinded treatment until the end of follow-up. Blinding will be broken in case of an emergency. Participants will undergo a 4-week intervention (week 4), and another 4-week follow up (week 8). All procedures will strictly follow the consolidated standards of reporting trials guidelines [Figure 1] and standard protocol items: recommendations for interventional trials checklist [Supplementary File 1, http://links.lww.com/CM9/A150].

Study participants

Participants will be recruited from the university hospital by our investigators, other physicians' referral and advertisement. The patient inclusion criteria are: (1) aged 18 to 65 years old; (2) unipolar, non-psychotic MDD; (3) meeting with the criteria of MDD in diagnostic and statistical manual of mental disorders, 4th ed., text revision (DSM-IV-TR),[25] and confirmed with the mini-international neuropsychiatric interview (MINI) in Chinese version.[26] (4) drug-naive and having the 17-item Hamilton depression rating scale (HDRS-17) scores >17 at baseline; (5) being able to speak, read, and understand the examinations required for the study; (6) all research content will be understood and informed consent will be signed.

Exclusion criteria are: (1) a recent or past history of DSM-IV-TR axis I diagnoses besides unipolar major depression verified by MINI 5.0 version; (2) anti-social personality disorder of axis II; (3) patients who have received any anti-psychotics or/and anti-depressants and/or anxiolytics before the enrollment; (4) having severe or unstable physical diseases; (5) a history of organic brain disorders, neurological disorders, or any other medical illness; (6) a history of a cochlear implant, cardiac pacemaker, and any brain devices or/and implants; (7) a history of electroconvulsive therapy, TMS, tDCS, and other neuromodulation treatments; (8) active current suicidal intent or plan as shown by a score of ≥3 on the suicide item of HDRS-17; (9) skin integrity at the electrode placement site is impaired or allergic to electrode gel or adhesive; (10) pregnancy or lactation; (11) currently participating in any other clinical trial; (12) situations in which the investigators believe that they are not suitable for this study.

Principal investigators (HXW, YPW) will decide to terminate the trial, and the criteria for the termination are: (1) severe adverse events (AEs); (2) missing two consecutive tACS sessions; (3) other diseases for which treatment may affect the assessment of the tACS; (4) non-attendance at weeks 4 and 8.

For maximizing compliance over the trial, the investigators will fully explain the study schedule, requirements, and potential risks and benefits to all interested participants.

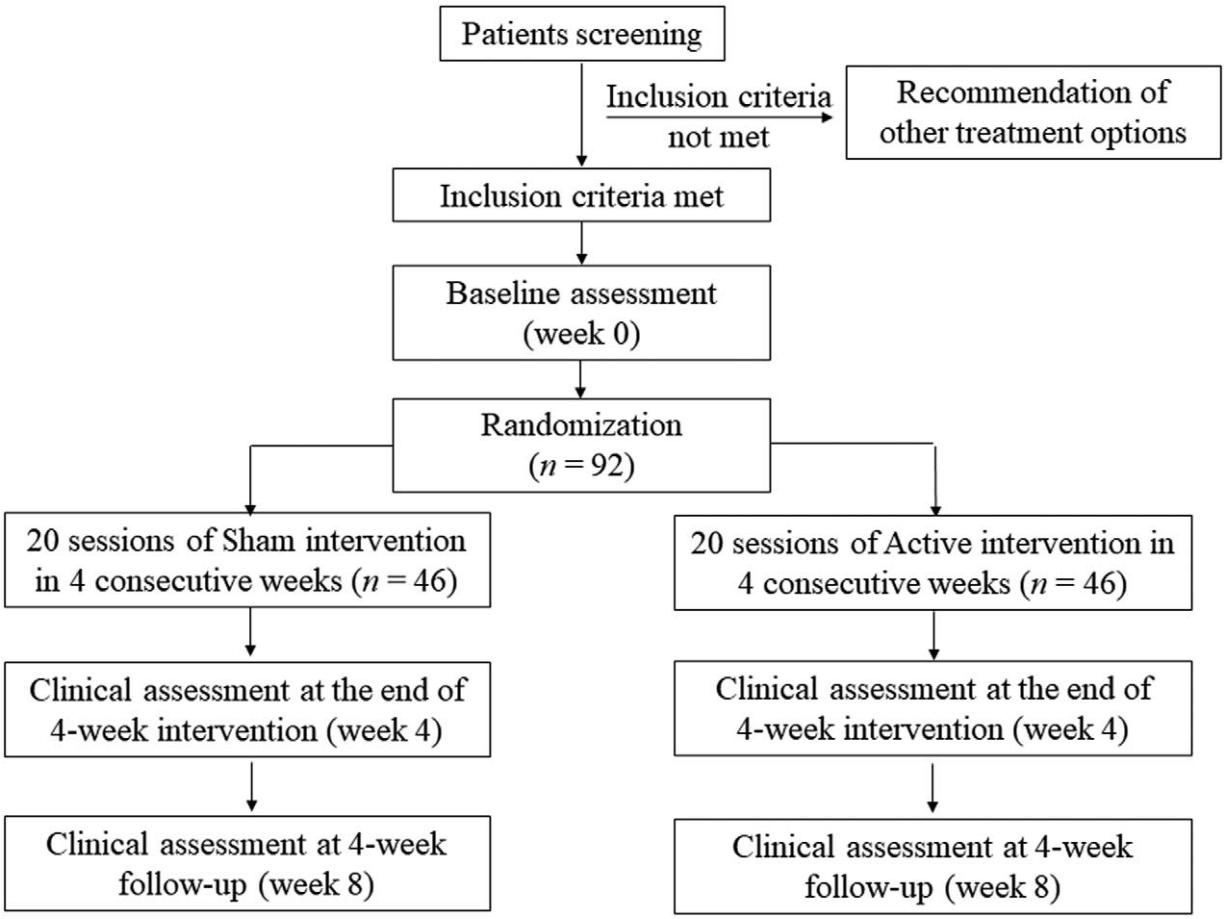

Figure 1: Study design (randomized controlled trials) and assessment time points (consort chart).

All participants will receive a call from the trial monitors for their exact appointments before their assessments at weeks 4 and 8. For preventing dropouts, we will keep contact with participants and provide them transportation allowance and free relative examination.

Sample size calculation

The sample size was estimated conservatively by assuming a 50% remission rate at the end of 8 weeks in the active group and a 10% in the sham group, which is based on our pilot study of the effect of tACS in adults with MDD. Thus, each group will be recommended to have a minimum sample size of 20, with a power to 80% and a two-tailed α level of 5%. Considering the 20% attrition rate and a block size of four, 26 participants will be required for each group with the total sample size of minimal 52. Ninety-two participants are expected to be enrolled in the study based on our funding.

TACS intervention

Trained nurses will perform the intervention and instruct participants to receive active or sham tACS intervention (Nexalin Technology, Inc., Houston, TX, USA) under the same instructions during all sessions for 4 weeks. Participants will be encouraged to turn off their smartphones, drink water, and relax, even fall asleep. Communication with the trained nurses will be restricted. The FDA-cleared tACS devices applied in the study have three electrodes, which will be positioned to the scalp: one 4.45 × 9.53 cm electrode will be placed over the forehead (Fpz, Fp1, and Fp2, in the 10/20 international placement system) and two 3.18 × 3.81 cm placed over the mastoid areas. Each participant will receive 20 sessions of intervention in 4 consecutive weeks at the fixed time frame once daily from Monday through Friday, with weekends off. Each session lasts 40 min with the default current level of 15-mA and a patented frequency of 77.5-Hz in the active group and no stimulation in the sham group. Then, participants will have another 4 weeks of observational follow-up.

Participants will be guided to refrain from any anti-depressive treatment for intervening MDD during the study, and can willingly withdraw from this study at any time and choose any other medical treatments, such as anti-depressants.

Efficacy variables

The primary outcome measurement is the remission rate defined as HDRS-17 score ≤7 at week 8,[10] and the Chinese version of HDRS-17 has been validated with psychometric properties and used as a tool of assessing depressive severity in Chinese patients with depression

symptoms.[27] The secondary outcomes are: (1) the rates of response at weeks 4 and 8 and rate of remission at week 4 per HDRS-17. The clinical response is defined as a ≥50% reduction from the baseline HDRS-17.[28] (2) the proportions of participants having improvements in the clinical global impression-improvement scale at weeks 4 and 8 (ranging from 0 to 7, the range from 1 to 3 is defined as improvement, higher scores indicate higher levels of depression).[29] (3) the variations of participants on depressive symptoms at weeks 4 and 8 assessed by HDRS-17 (ranging from 0 to 52, and higher scores indicate more depression).[10] Exploratory outcomes include the possible effect of tACS on cognitive function, brain connectivity, cellular activity, and metabolism assessed by a panel of neurocognitive tools and brain imaging at baseline and at week 4. Resting-state MEG,[23] fMRI,[24] and PET/MR will be carried out on a 3.0-T MR system (Trio Tim; Siemens, Erlangen, Germany), a helmet-shaped whole-head system (VectorView; Elekta Neuromag Oy, Finland), a PET/MR system (SIGNA PET/MR; GE Healthcare, Waukesha, WI, USA), respectively. For evaluating the cognitive status of MDD, a panel of neurocognitive tools such as the repeatable battery for the assessment of neuropsychological status (RBANS),[30] which includes different domains of attention, immediate and delayed memory, language, and visuospatial/constructional. And the Chinese version of RBANS has been certified as a reliable tool for cognitive function assessment with reasonable reliability and validity, the higher scores indicate the better in neurocognitive state.

Safety variables

Vital signs will be examined at baseline, weeks 4 and 8. AEs will be collected during the trial. All AEs will be recorded in the case report form (CRF), each AE will be assessed for duration, severity, development, and causal relationship to the tACS. If serious AEs happen (death, risk of death, hospitalization, persistent or significant disability or incapacity), it is necessary to record the condition in CRF and report the issue to the local ethics committee, principal investigators, and the China FDA within 24 h. All emerging AEs will be tracked until they disappear or have no clinical significance. The treatment-emergent adverse events, the Young mania rating scale (YMRS), and the self-made common questionnaire will be applied to record adverse reactions. YMRS ranges from 0 to 60, and higher scores indicate a greater degree of manic features. Its minimal score is to define a new-onset mania or hypomania with eight points.[10] The self-made common adverse effects questionnaire consisted of 18 items will be used to evaluate whether the participant having the common AEs (ie, adverse reactions) associated with tACS in our study [Supplementary File 2, http://links.lww.com/CM9/A151]. At the request of our local ethics committee, we will record EEG at baseline, week 4, and week 8 to monitor safety. Whether the participant having an epileptic seizure after the tACS treatment will be assessed by EEG professional technicians and investigators.[31]

Planned visit schedule

The visit schedule for all assessments is presented in Table 1. Participants will be evaluated by the raters at baseline, weeks 4 and 8. Demographic characteristics, medical history, and pregnancy test will be collected at the first visit only. Cognitive assessment, MEG, fMRI, and PET/MR will be examined at baseline and week 4. Patients' compliance will be assessed at weeks 4 and 8, and blinding assessment at week 8 by patients and raters.

Data management and quality control

The trial will be performed according to the International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) Guidelines for Good Clinical Practice to assure the rigor of the study. Data will be collected in the paper-based CRFs at baseline, weeks 4 and 8 [Table 1]. The investigators, trial monitors, EEG technicians, and raters are asked to join in a series of training sessions that will cover communicating with participants on trial, handling assessments, instructing participants to relax and drink water during the tACS treatment, collecting variables, and completing CRF. Data will be entered into the EpiData system by two independent investigators, and double-entry verification will be conducted. Any inconsistent entries will be re-checked with original CRF or investigators' source data if necessary. Typos will be revised until two entered databases are the same totally. For the discontinued participants, their reasons, date, AEs, and duration of the treatment will be collected. The independent statistician will analyze the final trial dataset, including the intent-to-treat dataset (ie, all enrolled participants as belonging to the group they were randomized into) and per-protocol dataset (ie, those participants who completed the trial originally allocated).

Statistical analysis

All de-identified data from the study will be analyzed by the statistician using SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC, USA) and P value <0.05 will be considered statistically significant. All tests are two-sided. Continuous variables will be summarized as mean and standard deviation. Categorical variables will be described as frequency and percentage. Between-group comparisons will be tested by the Mann-Whitney U test for continuous variables and the Chi-square test or Fisher exact test for categorical variables. Primary outcome is based on the intention-to-treat analysis with worst case imputation. For repeated continuous outcomes, mixed linear model will be utilized.

Discussion

MDD is a prevalent mental disorder, affecting a large proportion of the population.[1] Depression can not only cause individual functional impairment, but also produce a substantial economic burden to society and increase the risk of suicide.[2] Therefore, the high prevalence of depression in the general population, the heavy social-economical burden and high chance of suicide have urgently needed the requirement for effective interventions/approaches aiming to reduce depression.

The available treatment of MDD has achieved remarkable progress; however, not all patients benefit from them.[8,9]

Table 1: Schedule of enrolment, interventions, and assessments.

Week	Screening −2	Baseline 0	Treatment 4	Follow-up 8
Enrolment:				
Signed informed consent		×		
Diagnosis	×			
Randomization		×		
Interventions:				
Sham intervention group		×	×	
Active intervention group		×	×	
Assessments:				
Primary outcome				
HDRS-17	×		×	×
Secondary outcomes				
CGI-I			×	×
CGI-S	×		×	×
TEAE			×	×
EEG	×		×	×
YMRS	×		×	×
fMRI*		×	×	
Cognitive function*		×	×	
PET/MR*		×	×	
MEG*		×	×	
Pregnancy test	×			
Epileptic seizures	×		×	×
Weight	×		×	×
Temperature, blood pressure, heart rate	×		×	×
Patients' compliance			×	×
Blinding assessment				×

× Represents data collection timepoint. * A maximus of 15 participants will receive these examinations. HDRS-17: 17-item Hamilton depression rating scale; CGI-I: the Clinical global impression- Improvement scale; CGI-S: the Clinical global impression- severity scale; TEAE: the adverse events; EEG: Electroencephalography; YMRS: the Young mania rating scale; fMRI: Functional magnetic resonance imaging; PET/MR: Positron emission tomography (PET)/magnetic resonance (MR); MEG: Magnetoencephalography; T: Temperature.

Additional interventional approaches will be required. Current evidence on the efficacy of tACS intervention in MDD remains limited and unsatisfactory.[32-38] The recent study with a small sample among three groups (10, 40 Hz-tACS, and sham group) showed that tACS with 10-Hz frequency has a therapeutic intervention for treating MDD after five sessions of tACS interventions in five consecutive days.[18] This randomized, double-blind, placebo-controlled trial provides evidence for the clinical efficacy of the tACS, also investigate the possible brain activity related to the tACS intervention in MDD with resting MEG and fMRI and PET/MR. The study represents a step towards the management of MDD by means of tACS.

We acknowledge some limitations of the trial. The study is performed in a single center. It may not necessarily be possible to predict the results from the trial to other regions or ethnic groups. In addition, the intervention duration is short. In fact, at present we do not know how many times the intervention is presented to the subject will produce the optimal effect. Further, some key questions remain and could be aimed in future studies, including whether, and at what size, differences in patient characteristics or others may influence outcomes.[39]

This protocol prescribes the design and methodology of a randomized clinical trial, which aims to explore the efficacy and safety in MDD between participants receiving sham and active tACS interventions. The expected results of this study are meaningful, as it will provide a non-pharmacological intervention to treat depression in adult depressive conditions with minimal side effects.

Funding

This work is supported by the National Key R&D Program of China (No. 2017YFC1310001), the National Natural Science Foundation of China (No. 81771862), the Beijing Municipal Science and Technology Project (No. Z171100000117016), the Beijing Natural Science Foundation (No. KZ201710025017), the Beijing Hundred, Thousand, and Ten Thousand Talents Project (No. 2017-CXYF-09).

Conflicts of interest

Milestone (Beijing, China) Medical Appliances Co. Ltd. provided part grant, equipment and participants' financial compensation.

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How to cite this article: Wang HX, Wang K, Zhang WR, Zhao WF, Yang XT, Wang L, Peng M, Sun ZC, Xue Q, Jia Y, Li N, Dong K, Zhang Q, Zhan SQ, Min BQ, Fan CQ, Zhou AH, Song HQ, Yin L, Si TM, Huang J, Lu J, Leng HX, Ding WJ, Liu Y, Yan TY, Wang YP. Protocol on transcranial alternating current stimulation for the treatment of major depressive disorder: a randomized controlled trial. Chin Med J 2020;133:61–67. doi: 10.1097/CM9.0000000000000589