https://doi.org/10.1093/brain/awab252 BRAIN 2022: 145; 83–91 | 83

BRAIN
CLINICAL TRIAL

Transcranial alternating current stimulation for treating depression: a randomized controlled trial

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Treatment of depression with antidepressants is partly effective. Transcranial alternating current stimulation can provide a non-pharmacological alternative for adult patients with major depressive disorder. However, no study has used the stimulation to treat first-episode and drug-naïve patients with major depressive disorder.

We used a randomized, double-blind, sham-controlled design to examine the clinical efficacy and safety of the stimulation in treating first-episode drug-naïve patients in a Chinese Han population. From 4 June 2018 to 30 December 2019, 100 patients were recruited and randomly assigned to receive 20 daily 40-min, 77.5 Hz, 15 mA, one forehead and two mastoid sessions of active or sham stimulation ($n = 50$ for each group) in four consecutive weeks (Week 4), and were followed for additional 4-week efficacy/safety assessment without stimulation (Week 8). The primary outcome was a remission rate defined as the 17-item Hamilton Depression Rating Scale (HDRS-17) score $\leqslant 7$ at Week 8. Secondary analyses were response rates (defined as a reduction of $\geqslant 50\%$ in the HDRS-17), changes in depressive symptoms and severity from baseline to Week 4 and Week 8, and rates of adverse events. Data were analysed in an intention-to-treat sample.

Forty-nine in the active and 46 in the sham completed the study. Twenty-seven of 50 (54%) in the active treatment group and 9 of 50 (18%) in the sham group achieved remission at the end of Week 8. The remission rate was significantly higher in the active group compared to that in the sham group with a risk ratio of 1.78 (95% confidence interval, 1.29, 2.47). Compared with the sham, the active group had a significantly higher remission rate at Week 4, response rates at Weeks 4 and 8, and a larger reduction in depressive symptoms from baseline to Weeks 4 and 8. Adverse events were similar between the groups.

In conclusion, the stimulation on the frontal cortex and two mastoids significantly improved symptoms in first-episode drug-naïve patients with major depressive disorder and may be considered as a non-pharmacological intervention for them in an outpatient setting.

Received February 04, 2021. Revised May 08, 2021. Accepted June 15, 2021

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Keywords: drug-naïve; efficacy; first-episode; major depressive disorder; transcranial alternating current stimulation

Abbreviations: CGI-I/S = Clinical Global Impressions improvement/severity scale; HDRS-17 = 17-item Hamilton Depression Rating Scale; MDD = major depressive disorder; tACS = transcranial alternating current stimulation; tDCS = transcranial direct current stimulation; TMS = transcranial magnetic stimulation; YMRS = Young Mania Rating Scale

Introduction

Depression is a highly prevalent mental disorder that places a heavy burden on society and increases the risk of suicide.[1] Despite antidepressants and psychotherapies being available, they are only partially effective in treating depression,[2,3] and >20% of patients fail to respond to antidepressants and psychotherapy interventions.[4–6] Transcranial magnetic stimulation (TMS), as level A evidence (definite efficacy),[7,8] has recently received attention as a non-pharmaceutical treatment for patients with depression who have failed antidepressant treatment.[9] However, the findings of the TMS procedure in different trials have shown inconsistent results,[7,10] and the risk of seizure has been reported to be small.[11] Another widely used non-invasive cranial electrotherapy stimulation, transcranial direct current stimulation (tDCS), as a level B of evidence (probable efficacy),[12,13] showed a better effect than placebo in reducing depressive symptoms in patients with unipolar depression, but also produced 3% (2 in 72) new-onset mania/hypomania.[14] Both TMS and tDCS may have the potential for cognitive improvements.[15]

Transcranial alternating current stimulation (tACS) is another method of cranial electrotherapy stimulation, which provides brain stimulation by applying changing intensity electrical currents to the scalp to regulate cortical excitability and spontaneous brain activity.[16–20] Compared with tDCS, tACS appears to have an advantage because it involves less sensory experience[21] and has fewer known adverse effects.[22] Although tACS is regarded as a promising method for treating patients with depression,[23] the evidence for the effectiveness of tACS in depression remains limited.[24] A few studies have assessed tACS as a treatment for depression, but provided uncertain interpretations due to lack of methodological rigour.[25,26] Through electrodes placed on the forehead and mastoid regions, tACS (with a frequency of 77.5 Hz) has an antinociceptive effect by increasing the levels of beta-endorphin and neurotransmitters (including serotonin) in the CSF, brainstem, hypothalamus and cortex.[27,28] Some of these changes are believed to be the neurobiological mechanisms for improving depressive symptoms.[29,30] Therefore, we think that tACS with a frequency of 77.5 Hz may have a therapeutic effect on adults with major depression.

Our pilot study with a frequency of 77.5 Hz and 15 mA current over the frontal region and both mastoid regions ($n = 30$ in the sham and active groups) showed that tACS had good feasibility

and acceptability in patients with first-episode drug-naïve major depressive disorder (MDD).[20] To the best of our knowledge, no other clinical studies have tested the efficacy of tACS in patients with first-episode drug-naïve MDD. Moreover, depressive patients have different illness courses, such as a first-episode versus recurrent episode, acute versus chronic illness and treatment response versus treatment-resistance. Each different group of patients have different treatment responses and distinct prognoses.[31,32] Therefore, our current study aimed to use a larger sample size of patients with first-episode drug-naïve MDD in a Chinese Han population to examine the efficacy and safety of tACS, with a frequency of 77.5 Hz and a current of 15 mA over the frontal region and both mastoid regions. We hypothesized that active tACS would have significantly more antidepressive effects than sham tACS. We also posited that there was no significant difference in the incidence of adverse events between the two groups.

Materials and methods

This 8-week, double-blind, randomized, sham-controlled trial was performed at Xuanwu Hospital, Capital Medical University (Beijing, China) from 4 June 2018 to 30 December 2019. The protocol was approved by the Ethics Committee of Xuanwu Hospital [Approval No. LXS (2017) 002-Amendment 2] and reported in accordance with CONSORT guidelines.[33] The study was registered on the Chictr.org.cn website before the start of enrolment (ChiCTR1800016479, http://www.chictr.org.cn/showproj.aspx?proj=22048). There was no change in the protocol during the study period. All participants gave informed written consent before any research procedures. The study included a 4-week tACS intervention phase (Week 4) and another 4-week efficacy/safety assessment phase without tACS intervention (Week 8). The assessments were performed at baseline, Week 4 and Week 8.

Participants

Participants were recruited through physician referrals, posters and flyers. The inclusion criteria were: (i) 18–65 years old, Han Chinese; (ii) met the diagnostic criteria of unipolar, non-psychotic MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR)[34]; (iii) a 17-item Hamilton Depression Rating Scale (HDRS-17) total score higher than 17 points at baseline; (iv) acute episode; and (v) no previous psychoactive drug treatment.

The exclusion criteria were: (i) a current or history of comorbid Axis I psychiatric disorders (including hypomanic or manic episode, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, psychotic disorder, anorexia nervosa, bulimia nervosa, generalized anxiety disorder) and antisocial personality disorder in Axis II as assessed via the Mini-International Neuropsychiatric Interview (MINI) Chinese version 5.0[35]; (ii) a current or history of organic brain disorders or neurological disorders; (iii) acute suicidal risk as shown by a score of 3 or 4 on the suicide item of HDRS-17; (iv) previous or current exposure to electroconvulsive therapy (ECT), modified electroconvulsive therapy (MECT), TMS, tDCS, tACS or other neurostimulation treatments; (v) cochlear implant, cardiac pacemaker and implanted device or metal in the brain; (vi) previous or current psychotropic treatment; (vii) previous or current any psychotherapy; (viii) pregnant or lactating; (ix) participation in a concurrent clinical trial; and (x) refusal to sign the informed consent to participate in the trial.

The reasons for participants being lost to follow-up were: (i) missed two consecutive tACS sessions for any reason; (ii) severe adverse events; (iii) any medication treatment that may affect mood changes; and (iv) inability to complete on-site assessments at Weeks 4 and 8.

Study procedures

Participants were prescreened via brief face-to-face unstructured interviews and those who met the general criteria were invited for additional on-site screening. According to DSM-IV-TR, all participants were confirmed on MINI to suffer from a current episode of major depression.[34,35] The reliability and validity of the MINI Chinese version 5.0 are consistent with the English version.[35,36] At the baseline visit, demographic and clinical data were collected, including age, sex, marital status, the highest level of education, occupation, disease duration, family history of depression, substance use and medical histories including neurological disorder, psychiatric disorder and traumatic brain injury. Depressive severities were assessed at baseline, Week 4 and Week 8 by HDRS-17 and the Clinical Global Impressions (CGI) scale.

The Chinese version of HDRS-17 has been validated with psychometric properties.[37] The CGI includes the severity scale (CGI-S) and the improvement scale (CGI-I), both of which are 7-point rated scales.[38] Adverse events were recorded at Weeks 4 and 8. The frequency and severity of treatment-emergent adverse events were assessed with a self-reported common adverse effects questionnaire that includes 18 items.[20] To monitor manic/hypomanic symptoms during the study, the Young Mania Rating Scale (YMRS)[14] was administered at baseline, Week 4 and Week 8.

On the request of the local ethics committee, two EEG technicians recorded for at least 30 min[39] on a 23-channel EEG according to the International 10/20 system of electrode placement before the first stimulation, after the 4-week stimulation and at the end of Week 8 for safety.[19] The EEG technicians were blinded to the treatment arm. Those patients with epileptiform activities before stimulation were excluded from the study. For those patients who showed epileptiform activities after randomization and 4 weeks of treatment, the principal investigator and an EEG technician conducted a re-evaluation of the EEG. For those patients who continued to exhibit epileptiform activities, a thorough evaluation of epileptic seizures, including EEG and brain imaging, was provided.

Blinding was separately evaluated on the final day of Week 8 by participants and raters. Participants were asked by investigators whether they believed they were in the active or sham group during the study (yes, no), and raters independently assessed whether the subject belonged to the active or sham group (yes, no).

Randomization, concealment and blinding

Investigators randomly assigned eligible participants to receive active or sham tACS with a ratio of 1:1 according to a computer-generated list of random numbers. An independent statistician prepared a randomization sequence with a block size of four. Before the first treatment, the nurse assigned each participant a number by opening an opaque, sealed envelope with the corresponding code for group allocation, and fixed it to the same tACS device during the 4-week tACS treatment phase. The statistician also coded the tACS device. All the instruments applied in the study were the same in size, colour, appearance, weight and odour. The other two devices (one sham and one active) were available as a backup if any other devices did not work. At the end of the study, blindness was evaluated by separately asking participants and raters to determine which group they were randomly assigned to. All study staff (including investigators, nurses, EEG technicians, and raters) and patients were blinded to the group allocation.

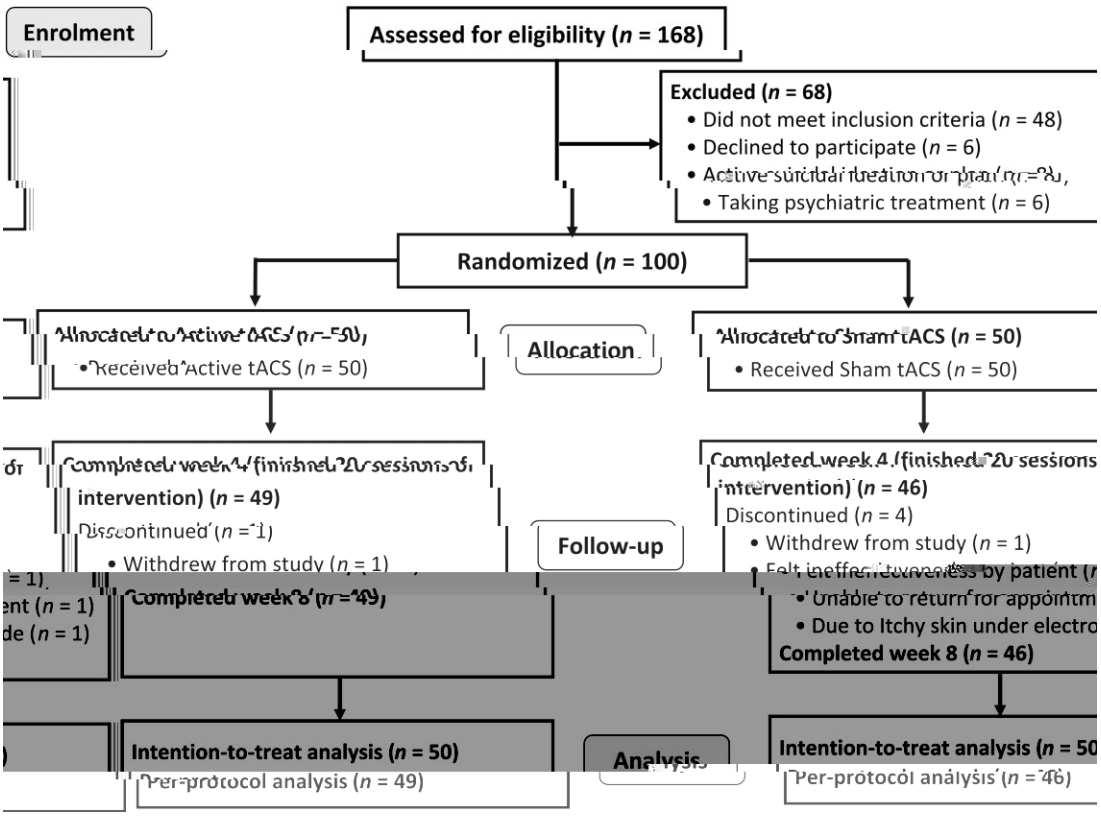

Figure 1 CONSORT diagram of study flow.

Transcranial alternating current stimulation intervention

Participants sat comfortably on reclining chairs to receive FDA-approved tACS (Nexalin Technology, Inc), which was administered by trained nurses in accordance with standardized instructions. Patients were advised to relax, drink water or even sleep, with minimal communication with the nurses. Three Nexalin conductive electrodes were placed overhead. In the 10/20 international placement system, a 4.45 × 9.53 cm electrode was placed on the forehead corresponding to Fpz, Fp1 and Fp2. Two 3.18 × 3.81 cm electrodes were placed on the mastoid region of each side. The tACS stimulation waveform includes ramp-up and ramp-down periods of 180 and 12 s, respectively. It was a square-wave with an average amplitude of 15 mA and was equally distributed from the frontal region to the mastoid areas (amplitudes are reported as zero-to-peak).

All participants were treated for a total of 20 sessions with stimulation at 77.5 Hz and 15 mA. Sham tACS had no active stimulation. From Monday to Friday, each session lasted 40 min at a fixed daytime interval.[19,20] During the entire intervention period, each participant was assigned to the same tACS device regardless of active or sham.[19,20]

Outcomes

Trained investigators and raters were blind to the participants' assignments and performed the assessments. Efficacy and safety were evaluated at baseline, Week 4 and Week 8. The primary outcome was the rate of clinical remission, defined as the HDRS-17 total score $\leqslant 7$ at Week 8.[14] The secondary outcomes were: (i) the remission rate at Week 4; (ii) rates of response defined as a $\geqslant 50\%$ reduction in HDRS-17 total score from baseline to Week 4 and Week 8; (iii) change of HDRS-17 score and its subscales from baseline to Week 4 and Week 8; (iv) changes from baseline to Week 4 and Week 8 in CGI-S and CGI-I scores; and (v) incidence of adverse events, including treatment-emergent adverse events, YMRS (manic or hypomanic episode defined as YMRS score >8)[14] and epileptiform activities revealed by EEG recordings.

Statistical analyses

The sample size was estimated with a power of 80% and a two-tailed α level of 5%. According to our pilot study of tACS in treating adult patients with drug-naïve MDD, we found that the remission rates at the end of the 8-week study period in the active and sham groups were 50 and 20%, respectively.[20] Thus, the minimum sample size required for each group was 39. Considering the attrition rate of 20% and a block size of 4, each group required 50 participants with a total sample size of 100. Data were analysed in the intention-to-treat (ITT) sample with worst-case imputation.

Regarding binary outcomes, the relative risk and risk difference were calculated to compare the relative and absolute benefits between the active and sham groups. The HDRS-17 total score and other continuous variables were expressed as the mean difference with a 95% confidence interval (CI). The baseline characteristics between the two groups were compared using χ^2 tests or Fisher's exact tests for categorical variables, and Mann-Whitney U-tests for continuous variables.[40] We performed logistic regression analyses to evaluate the treatment efficacy of the primary outcome. For the secondary analyses, general linear model and logistic regression were used for continuous and binary outcomes. The linear mixed-

Table 1 Baseline demographics and historical characteristics

Characteristics	All (n = 100)	Active (n = 50)	Sham (n = 50)	P-value[a]
Age at the enrolment, years, mean (SD)	40.0 (12.6)	38.3 (12.2)	41.6 (12.8)	0.10
Sex, n (%)				0.36
Male	26 (26.0)	11 (22.0)	15 (30.0)	
Female	74 (74.0)	39 (78.0)	35 (70.0)	
Marital status, n (%)				0.26
Married	27 (27.0)	11 (22.0)	16 (32.0)	
Single	73 (73.0)	39 (78.0)	34 (68.0)	
Educational level, n (%)				1.00
Had high school education	93 (93.0)	47 (94.0)	46 (92.0)	
Over high school education	7 (7.0)	3 (6.0)	4 (8.0)	
Occupational status, n (%)				0.44
Unemployed or retired	7 (7.0)	2 (4.0)	5 (10.0)	
Employed	93 (93.0)	48 (96.0)	45 (90.0)	
BMI, kg/m^2, mean (SD)	23.5 (2.4)	23.8 (2.5)	23.3 (2.3)	0.48
Duration, months, mean (SD)	9.0 (4.0)	9.6 (3.8)	8.5 (4.3)	0.08
HDRS-17 total score, mean (SD)	27.0 (3.3)	27.3 (3.7)	26.6 (2.9)	0.09
CGI-S, mean (SD)	5.1 (0.6)	5.1 (0.6)	5.1 (0.7)	0.95
YMRS, mean (SD),	0.4 (0.6)	0.5 (0.7)	0.4 (0.5)	0.58
Family history of depression, n (%)	0 (0)	0 (0)	0 (0)	–
History of alcohol, smoking, drug, n (%)	0 (0)	0 (0)	0 (0)	–
History of neurological disorder, n (%)	0 (0)	0 (0)	0 (0)	–
History of other psychiatric disorder, n (%)	0 (0)	0 (0)	0 (0)	–
History of traumatic brain injury, n (%)	0 (0)	0 (0)	0 (0)	–

BMI = body mass index; SD = standard deviation.
[a]P-values were obtained using chi-square tests or Fisher's exact tests for categorical variables, and Mann-Whitney U-tests for continuous variables.

effects model was used to evaluate the differences in symptom changes between the two groups at Weeks 4 or 8, including the interaction between group (active versus sham) and time (baseline, Week 4 and Week 8).

All hypotheses were tested at a significance level of 0.05, using unpaired, two-tailed tests. SAS, v.9.4 (SAS Institute Inc.) was used.

Data availability

The data supporting the results of this study and the trial protocol are available from the first or corresponding author on reasonable request. The data are not publicly available due to their containing private information about the study participants.

Results

Baseline characteristics of participants

In total, 168 individuals were screened and 68 were excluded for different reasons. Of those excluded from the study, 48 did not meet inclusion criteria, six refused to participate in the study, eight had active suicidal ideation or plan and six were taking psychiatric treatment (one TMS, three psychotherapy, one paroxetine and one fluoxetine). A total of 100 first-episode, drug-naïve adult patients (ITT sample) were included in the study and randomized 1:1 into two groups. During the treatment phase, four in the sham group (one each due to voluntary withdrawal, unable to return for appointment, lack of efficacy and skin irritation under an electrode) and one in the active group (voluntary withdrawal) dropped out of the study. Thus, 49 in the active tACS group and 46 in the sham group completed the entire trial (Fig. 1). Baseline demographic and clinical features of study participants are presented in Table 1. No significant difference was found between the two groups.

Clinical outcomes

The effects of tACS on primary and secondary outcomes are presented in Table 2. For the primary analysis (n = 100), there was a significant difference in remission rate between active (54.0%) and sham (18.0%) treatment at Week 8, with a relative risk of 1.78 and a relative difference of 0.36. At Week 4, 31 (62.0%) in the active group achieved remission compared to 13 (26.0%) in the sham group. At Week 4, 35 (70%) participants in the active group and 21 (42%) in the sham group showed responses. Similarly, at Week 8, 37 (74%) participants in the active group and 19 participants (38%) in the sham group responded.

The reduction in HDRS-17 total score at Weeks 4 and 8 in the active group was significantly greater than that in the sham group with mean differences of –6.81 and –6.35 points, respectively ($P_{interaction} < 0.01$). In terms of subscale scores, all subscale scores in the active group except for genital symptoms and suicide scores were significantly lower than those in the sham group. In the active group, 96% (48/50) of participants reported feeling 'much' or 'very much' clinical improvement, compared with 70% (35/50) of participants in the sham group. At Week 8, 94% (47/50) of the active group was significantly higher than 20% (10/50) of the sham. Compared with the sham group, the active group had lower CGI-S scores at Week 4 and Week 8 ($P_{interaction} < 0.01$) (Table 2).

Adverse events and safety

Treatment-emergent adverse events did not differ significantly between the two groups (relative risk, 1.10; relative difference, 0.08). The most common nonserious adverse reactions included aurium tinnitus, tinnitus cerebri, discomfort, headache and itches, which were not statistically significant between the two groups. These adverse reactions occurred during the first two to four sessions of tACS intervention and did not persist during the acute treatment phase (Table 3). There were no significant differences between the

Table 2 Differences between active and sham treatments in primary and secondary outcome measures at Week 4 and Week 8 in the ITT sample

Outcomes	Baseline		Week 4				Week 8				P-value[b]
	Active (n = 50)	Sham (n = 50)	Active (n = 49)	Sham (n = 46)	Effect size[a] (95% CI)	P-value	Active (n = 49)	Sham (n = 46)	Effect size[a] (95% CI)	P-value	
Remission rate, n (%)[c,d]											
Risk ratio	NA	NA	31 (62.0)	13 (26.0)	1.95 (1.32, 2.88)	<0.01	27 (54.0)	9 (18.0)	1.78 (1.29, 2.47)	<0.01	NA
Risk difference	NA	NA	31 (62.0)	13 (26.0)	0.36 (0.18, 0.54)	<0.01	27 (54.0)	9 (18.0)	0.36 (0.19, 0.53)	<0.01	NA
Response rate, n (%)[d,e]											
Risk ratio	NA	NA	35 (70.0)	21 (42.0)	2.63 (1.29, 5.36)	<0.01	37 (74.0)	19 (38.0)	3.00 (1.40, 6.42)	<0.01	NA
Risk difference	NA	NA	35 (70.0)	21 (42.0)	0.28 (0.09, 0.47)	<0.01	37 (74.0)	19 (38.0)	0.36 (0.18, 0.54)	<0.01	NA
HDRS-17 total score, mean (SD)	27.3 (3.7)	26.6 (2.9)	9.0 (5.8)	15.2 (6.6)	–6.81 (–9.53, –4.09)	<0.01	10.0 (6.6)	15.7 (5.5)	–6.35 (–9.21, –3.49)	<0.01	<0.01
Subscales of HDRS-17											
Somatic anxiety[f], mean (SD)	11.4 (1.9)	11.1 (1.7)	3.8 (3.3)	6.6 (3.1)	–3.09 (–4.48, –1.70)	<0.01	4.3 (3.3)	7.3 (2.5)	–3.38 (–4.80, –1.97)	<0.01	<0.01
Psychic anxiety[g], mean (SD)	4.8 (1.1)	4.6 (1.0)	1.6 (1.5)	2.3 (1.4)	–0.90 (–1.56, –0.24)	0.01	1.6 (1.8)	2.3 (1.5)	–0.94 (–1.69, –0.19)	0.01	0.03
Core depressive symptoms[h], mean(SD)	6.4 (0.9)	6.4 (0.7)	3.0 (1.6)	4.4 (2.1)	–1.45 (–2.33, –0.66)	<0.01	3.0 (1.9)	4.2 (1.7)	–1.19 (–1.97, –0.41)	<0.01	0.01
Anorexia[i], mean (SD)	3.4 (0.8)	3.3 (0.7)	0.2 (0.4)	1.1 (1.3)	–0.99 (–1.46, –0.51)	<0.01	0.4 (1.0)	1.0 (1.1)	–0.59 (–1.12, –0.06)	0.03	0.02
Genital symptoms[j], mean (SD)	1.5 (0.5)	1.4 (0.5)	0.2 (0.6)	0.8 (0.9)	–0.66 (–1.02, –0.30)	<0.01	0.5 (0.7)	0.8 (0.8)	–0.38 (–0.41, –0.002)	0.05	0.58
Suicide[k], mean (SD)	1.4 (0.5)	1.5 (0.5)	0.5 (0.7)	0.8 (0.8)	–0.20 (–0.57, 0.17)	0.28	0.4 (0.6)	0.6 (0.6)	–0.11 (–0.45, 0.23)	0.53	0.52
CGI-S, mean (SD)	5.1 (0.6)	5.1 (0.7)	1.1 (1.4)	2.7 (1.1)	–1.63 (–2.20, –1.06)	<0.01	1.8 (1.3)	4.5 (1.0)	–2.74 (–3.25, –2.23)	<0.01	<0.01
CGI-I[d], n (%)											NA
Not improved	NA	NA	2 (4.0)	15 (32.6)	1.00		3 (6.0)	40 (80.0)	1.00		
Much or very much improved	NA	NA	48 (96.0)	35 (70.0)	7.50 (1.81, 31.10)	<0.01	47 (94.0)	10 (20.0)	13.33 (4.41, 40.29)	<0.01	
YMRS, mean (SD)	0.5 (0.7)	0.4 (0.5)	1.0 (0.8)	0.8 (1.0)	0.14 (–0.17, 0.45)	0.37	0.5 (0.6)	0.4 (0.5)	–0.01 (–0.26, 0.24)	0.96	0.80
Adverse reaction[l], n (%)											NA
Risk ratio	NA	NA	10 (20.0)	6 (12.0)	1.10 (0.93, 1.31)	0.28	10 (20.0)	6 (12.0)	1.10 (0.93, 1.31)	0.28	
Risk difference	NA	NA	10 (20.0)	6 (12.0)	0.08 (–0.06, 0.22)	0.28	10 (20.0)	6 (12.0)	0.08 (–0.06, 0.22)	0.28	
Rate of epileptiform activities, n (%)	0	0	0	0	NA	NA	0	0	NA	NA	NA

NA = not applicable.

[a]Effect size was defined as risk ratio or risk difference for categorical outcomes and mean difference from baseline for continuous outcomes (if baseline data were available) between two groups.

[b]P-value for an interaction effect between group (active versus sham) and time (baseline, Week 4, Week 8) in the linear mixed-effects models.

[c]Remission rate was defined as an HDRS-17 score $\leqslant 7$.

[d]Calculated based on 100 randomized participants using worst-case imputation.

[e]Response rate was defined as a $\geqslant$ 50% reduction of HDRS-17 from baseline.

[f]Somatic anxiety using seven items from HDRS-17 (Early insomnia, Middle insomnia, Late insomnia, Somatic anxiety, Gastrointestinal symptoms, General somatic symptoms and Hypochondria).

[g]Psychic anxiety symptoms using four items from HDRS-17 (Guilt, Agitation, Psychic anxiety and Insight).

[h]Core depressive symptoms using three items from HDRS-17 (Depressed mood, Work and interests and Retardation).

[i]Anorexia using two items from HDRS-17 (Gastrointestinal symptoms and Weight loss).

[j]Genital symptoms using one item from HDRS-17 (Genital symptoms).

[k]Suicide using one item from HDRS-17 (Suicide).

[l]All adverse reactions occurred during treatment.

active and sham groups in YMRS total scores at baseline, Week 4 or Week 8 (Table 2). No patient had increase in manic/hypomanic symptoms during the study period (Supplementary Fig. 1). No deaths, seizures, neurological complications, phosphene perception or other serious adverse events were observed.

Integrity of blinding

Seventeen of 46 participants in the sham group (37%) and 25 of 49 participants in the active group (51%) correctly identified the allocation group (χ^2 = 1.90, P = 0.17). Meanwhile, the raters correctly identified 23 (50%) in the sham group and 27 (55%) in the active group (χ^2 = 0.25, P = 0.62). Neither the participants nor the researchers were able to guess their actual group beyond chance. No tactile difference between the sham and active stimulation was noted during the study.

Discussion

In this first 8-week randomized, double-blind, sham-controlled trial, we found that the active tACS at the frequency of 77.5 Hz and current of 15 mA in first-episode drug-naïve MDD patients had better remission and response rates than the sham tACS. Compared with sham treatment, almost all depressive symptom domains of active treatment were significantly improved. Meanwhile, there was no significant difference in adverse events between the two groups.

Previous studies on tACS treatment of depression have indicated that tACS may be an effective intervention for the treatment of various depression,[18,20,24–26,41] including MDD with and without

active intervention plus 4 weeks of follow-up. The longer than 4-week follow-up duration for this effect requires in-depth research. Third, we only used one frequency, one current and one fixed stimulation location. The effect of tACS with different frequencies, currents and electrode montages of tACS in the treatment of MDD is unclear.

In summary, this relatively large sample study confirmed that tACS had an antidepressant effect on depression within 8 weeks after 4 weeks, 5 days a week in patients with first-episode, drug-naïve MDD in a Chinese Han population. The tACS at a frequency of 77.5 Hz and a current of 15 mA was safe and well-tolerated, as well as did not cause disorientation, memory loss or cognitive deficits, which is one of the most common adverse reactions of ECT and MECT treating depression. The results of this study are the first step to provide evidence for the efficacy of tACS at 77.5 Hz frequency and 15 mA current targeting the frontal region and two mastoid regions in depressed patients. Future studies are warranted to investigate the role of tACS in the treatment of recurrent and refractory depression. Meanwhile, tACS with various stimulation parameters (including different frequencies, currents and

adult patients with major depressive disorder. *Zhonghua Yi Xue Za Zhi*. 2020;100(3):197–201.
21. Fertonani A, Ferrari C, Miniussi C. What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. *Clin Neurophysiol*. 2015;126(11): 2181–2188.
22. Matsumoto H, Ugawa Y. Adverse events of tDCS and tACS: A review. *Clin Neurophysiol Pract*. 2017;2:19–25.
23. Shekelle P, Cook I, Miake-Lye IM, et al. *The effectiveness and risks of cranial electrical stimulation for the treatment of pain, depression, anxiety, PTSD, and insomnia: A systematic review*. VA ESP Project #05-226; 2018. https://www.ncbi.nlm.nih.gov/books/NBK493132/.
24. 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(6):414–421.
25. 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: A three week double blind pilot study. *J Psychiatr Res*. 2015;70: 98–105.
26. McClure D, Greenman SC, Koppolu SS, Varvara M, Yaseen ZS, Galynker II. A pilot study of safety and efficacy of cranial electrotherapy stimulation in treatment of bipolar II depression. *J Nerv Ment Dis*. 2015;203(11):827–835.
27. Lebedev VP, Malygin AV, Kovalevski AV, et al. Devices for noninvasive transcranial electrostimulation of the brain endorphinergic system: Application for improvement of human psychophysiological status. *Artif Organs*. 2002;26(3):248–251.
28. White NE, Richards LM. Nexalin and related forms of subcortical electric Tm[(tre.7(Ds6.1999 .17116(I:Tm[(t8(JRl)-7589(Evaons,)7623.6RPl)-775.9Turnh)-10.8ers,)7567.6edus.)] TJ/F3 1 Tf7.4999 0 0 7.4999 70.01645 85