General Psychiatry

Acute effect of twice-daily 15 mA transcranial alternating current stimulation on treatment-resistant depression: a case series study

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INTRODUCTION

Major depressive disorder (MDD) is a principal cause of disability worldwide and is often associated with high morbidity and mortality rates. Although there are several therapies available for the treatment of depression, about one-third of patients with MMD will not respond to two or more antidepressant drugs with different mechanisms; the patients are then referred to as having treatment-resistant depression (TRD).[1] Patients with TRD have a poorer quality of life, greater economic burden and increased suicidal behaviours.[1] Therefore, new antidepressant treatments that are effective, safe, long-lasting and tolerable are needed. Ketamine infusion, intranasal esketamine and transcranial magnetic stimulation (TMS) have been used to treat early stage TRD.[2] A recent review suggests that electroconvulsive therapy (ECT) may be superior to ketamine for reducing depression severity in the acute treatment of TRD.[3] Another review found that ECT was more effective in treating TRD than repetitive TMS (rTMS).[1]

As neurostimulation treatments, ECT and rTMS are recommended for individuals insufficiently responsive to pharmacotherapy and psychosocial interventions.[4] Despite being the most effective strategy for patients with TRD–and in some situations, a first-line choice in the acute setting–ECT treatment is limited by its side effects, high costs and administrative impediments.[5] rTMS is a non-invasive, focal and cortical stimulation technique that has demonstrated moderate efficacy with few safety concerns for patients with MDD who have either failed or not tolerated antidepressant treatments during the acute episode and maintenance phase of the illness.[6] But, like ECT, rTMS requires specialised equipment, a particular setting, and well-trained operators to carry out the procedure. The risks of headache and potential seizure also reduce the acceptability of rTMS.[7]

Similar to the electrical current used in ECT, alternating current is also utilised in transcranial alternating current stimulation (tACS),[8] a unique form of non-invasive brain stimulation. tACS has shown efficacy and safety in chronic insomnia,[9] MDD[7] and other treatment-resistant psychiatric conditions such as clozapine-resistant schizophrenia and treatment-resistant obsessive-compulsive disorder.[10] Currently, however, there is no consensus on tACS procedures and parameters for different brain disorders in clinical

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Depression is a major cause of disability worldwide, and about one third of depressive patients have treatment-resistant depression (TRD). New treatments for depression that are safe, tolerable, and effective are urgently needed.

WHAT THIS STUDY ADDS

⇒ Our case series study found that 40 sessions of twice-daily 15 mA, 77.5 Hz transcranial alternating current stimulation (tACS) via the forehead and both mastoids given 5 days a week during a 4-week treatment offers therapeutic potential for the acute treatment of TRD by reducing the severity of the depressive symptoms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More exploration of twice-daily 15 mA tACS for TRD in large clinical studies could strengthen our preliminary results indicating that it is a promising alternative intervention with practical treatment implications for TRD.

practice and research.[7 11] The electrical current frequency and amplitude, treatment sessions and electrode locations have varied widely.[7 11] One of our recent studies revealed that a single session of 77.5 Hz tACS with a current amplitude of 15 mA via the forehead and both mastoids given 5 days a week for 4 weeks, totalling 20 sessions, (referred to as a once-daily protocol) is effective in reducing depressive symptoms in first episode and drug-naïve MDD.[7] However, whether15 mA, 77.5 Hz tACS is effective for treating TRD remains unclear.

Due to the refractory nature of TRD, we hypothesised that more sessions of tACS may effectively treat TRD. Therefore, in this initial study, we used the same amplitude and frequency of tACS as our previous studies[7] but changed the treatment course from once a day to twice a day. In doing so, the patients received 40 sessions (twice-daily tACS), instead of 20 sessions, during the 4-week treatment phase. Accordingly, this study aimed to examine the acute therapeutic potential of twice-daily tACS in TRD.

METHODS

Study design

Our study was a 4-week case series prospective study performed at Xuanwu Hospital, Capital Medical University in Beijing, China between September 2019 and January 2022. It comprised a 2-week screening/baseline period followed by a 4-week treatment phase of twice-daily tACS (twice per day, 5 days a week).

The outcome assessments were conducted by blinded raters at baseline and week 4. Assessment scales include the 17-item Hamilton Rating Scale for Depression (HAMD-17),[7] the Montgomery-Åsberg Depression Rating Scale (MADRS),[12] an 18-item common questionnaire on cranial electrical stimulation made by our study group,[7] and the Young Mania Rating Scale (YMRS).[7]

Participants

Patients were enrolled from the outpatient clinic of Xuanwu Hospital, Capital Medical University. The inclusion criteria were: (1) male or female, aged 18–65 years; (2) able to provide written informed consent voluntarily; (3) a diagnosis of MDD (recurrent episodes) without psychotic features in compliance with the criteria from the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revised (DSM-IV-TR) and confirmed by the Mini-International Neuropsychiatric Interview, Chinese V.5.0; (4) the depressive episode duration ≥2 years; (5) failure of response to at least two antidepressant medication trials based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; (6) ongoing antidepressant treatment at a fixed dose for at least 8 weeks prior to baseline assessment; (7) a baseline score of >20 on HAMD-17.

Exclusion criteria were: (1) axis I psychiatric disorders, including schizophrenia, bipolar disorder, manic episode, anxiety disorders (panic disorder, generalised anxiety disorder and social anxiety disorder), post-traumatic stress disorder, obsessive compulsive disorder, anorexia nervosa, bulimia nervosa, psychosis over the previous 6 months and any axis II disorders (borderline personality disorder, antisocial personality disorder, schizotypal personality disorder and narcissistic personality disorder); (2) a treatment history of ECT, modified ECT, transcranial direct current stimulation, tACS, deep brain stimulation, or TMS; (3) risk for suicide (defined as a score of ≥3 on the suicide item of HAMD-17); (4) known allergy to electrode materials; (5) inability to communicate with researchers fluently; (6) traumatic brain injury; (7) cerebrovascular or cardiovascular stents; (8) substance use disorder (abuse or dependence, as defined by DSM-IV-TR) in the previous 6 months; (9) females who are pregnant, breast feeding or have the potential for childbearing but refuse to use reliable contraceptive methods during the study.

Procedures

At baseline, demographic and clinical data on study participants were collected. Depressive symptom severity was assessed with the Chinese versions of HAMD-17[7] and MADRS[12] at baseline and week 4. Similarly, an 18-item common questionnaire on cranial electrical stimulation[7] and the YMRS[7] were administered and a 30 min electroencephalogram (EEG) with an internationally recognised 10/20 system of electrode placement method was carried out to monitor safety and identify manic/hypomanic symptoms (defined as a YMRS score >8) and potential epileptiform discharges at the 4-week efficacy assessment. The EEG was recorded by two experienced EEG technicians.

Twice-daily 15 mA tACS intervention

The tACS procedure was similar to that published in our recent report.[7] Briefly, patients sat in a comfortable chair quietly while receiving Chinese National Medical Products Administration-approved tACS (Nexalin Technology). Three Nexalin conductive electrodes were attached to the scalp. One 4.45 cm×9.53 cm electrode was placed on the scalp on the forehead, equated to Fpz, Fp1 and Fp2. The other two 3.18 cm×3.81 cm electrodes were put on each side of the mastoid area. All participants were scheduled to receive 40 sessions with stimulation at 77.5 Hz and 15 mA during four consecutive weeks. The stimulation was provided twice daily (09:00–11:00 and 14:00–17:00) from Monday to Friday, and each session lasted 40 min.

Permitted medication

Patients were required to continue taking their ongoing antidepressants throughout the treatment period. Their medication history is shown in online supplemental table 1.

Data analysis

Data were described as the mean and standard deviation (SD) for continuous variables. The percentage was used for the categorical variable. The paired sample Wilcoxon signed rank tests were used to determine the significance

Table 1 Clinical characteristics and outcomes of study participants

	Patient							
	1	2	3	4	5	6	7	Group
Sex	F	F	F	F	F	F	F	7 F
Age (years)	57	60	50	65	61	69	62	60.6 (5.6)
Duration of depressive illness since onset (years)	9	8	7	5	4	5	4	6.0 (1.9)
Depressive episodes	6	5	5	4	4	5	4	4.7 (0.7)
Current depressive episode duration (months)	5	4	6	4	3	4	5	4.4 (0.9)
HAMD-17 (total scores)								
Baseline	29	28	27	26	26	25	24	
Week 4	14*	13*	12*	13*	12*	10*	12*	
MADRS (total scores)								
Baseline	33	31	28	29	30	29	28	
Week 4	16†	14†	13†	14†	15†	13†	13†	

*Response defined as HAMD-17 score ≥50% decrease from the baseline.
†Response defined as MADRS score ≥50% decrease from the baseline.
F, female; HAMD-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale.

of changes from baseline to week 4. Statistical analyses were carried out by IBM SPSS Statistics V.26.0 (SPSS). The significance level was set at p<0.05.

RESULTS

Patient characteristics

A total of 45 participants were screened for eligibility. Thirty-eight were excluded (34 did not meet eligibility criteria, and 4 declined to participate in the study). Seven were eligible for the study and were all female (online supplemental figure 1). The mean (SD) age was 60.6 (5.6) years. The cumulative disease duration was 6.0 (1.9) years. The demographic and clinical features of the study subjects are illustrated in table 1.

Clinical outcomes

HAMD-17 total scores were significantly lower at week 4 than baseline (Z=−2.410, p=0.016), as shown in table 1 and figure 1A. The changes in the MADRS total scores were also significant, as shown in table 1 (Z=−2.414, p=0.016). All patients achieved a response (defined as HAMD-17/MADRS scores that decreased by 50% or more from the baseline), but no patients achieved remission (defined as HAMD-17 score ≤7) at week 4, as shown in table 1.

Safety

There were no serious complications with the stimulation in this case series study. The two patients had non-serious adverse reactions including headache (patient 1), tinnitus cerebri (patient 1), dizziness (patient 2) and

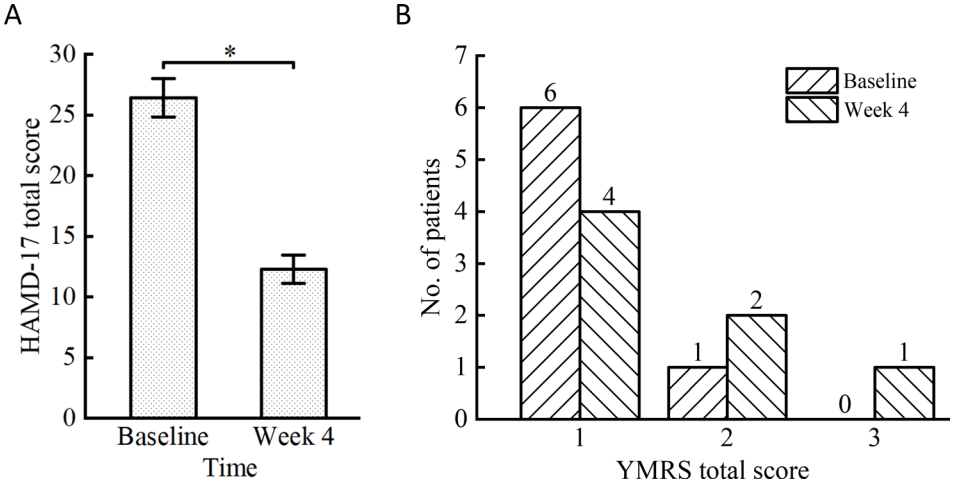

Figure 1 Clinical outcomes. (A) The mean HAMD-17 total scores significantly decreased from baseline to week 4. The error bars represent the SD. The asterisk (*) indicates a statistically significant difference with p<0.05. (B) Total YMRS scores at baseline and week 4. HAMD-17, 17-item Hamilton Rating Scale for Depression; No. number; SD, standard deviation; YMRS, Young Mania Rating Scale.

flickering (patient 1) during the twice-daily tACS treatment period. None of the subjects experienced manic symptoms, seizures, fatigue, itchiness or loss of consciousness throughout the duration of the treatment (online supplemental table 2 and figure 1B).

DISCUSSION

Main findings

To the best of our knowledge, the current study was the first to use twice-daily tACS to assess its acute therapeutic potential in patients with TRD. The safety results suggest that twice-daily 77.5 Hz, 15 mA tACS, 5 days a week for 4 weeks is safe and well-tolerated. The efficacy results indicate that the twice-daily tACS has an acute effect in reducing depressive symptoms in patients with TRD. The case series data support the conduction of large, randomised, sham-controlled trials of twice-daily tACS for treating patients with TRD and assessing its usefulness as adjunctive therapy for TRD.

Our study showed that all patients with TRD had a significant reduction in depression symptoms after a 4-week treatment, and all of them achieved a clinical response. Noteworthy, the duration for most clinical trials for depression is 6–8 weeks. Although it is difficult to compare the efficacy of twice-daily tACS with other adjunctive therapies for TRD due to the minimal sample size in the current study, our results indicate that twice-daily tACS may produce an acute effect in TRD.

In a STAR*D study, about 50% of remitters on citalopram achieved remission of depressive symptoms within 6 weeks of treatment; the other half of the remitters achieved remission only after 12 weeks of treatment.[13 14] Therefore, a longer duration of the twice-daily tACS for TRD might produce a larger reduction in depression symptoms. In the current study, no patients reached remission with a 4-week treatment, suggesting that the duration of future studies of twice-daily tACS for TRD should target longer than 4 weeks. A 3-week active versus sham study of TRD with a symmetrical rectangular biphasic current of 1–4 mA, 40 V stimulations over two dorsolateral prefrontal cortex areas did not show a significant difference between the two groups,[15] also supporting the importance of longer study durations when using cranial electrical stimulations.

Limitations

It is important to consider the limitations of this study when interpreting the results. First, there was no control group in our research, and it is not possible to exclude the possibility of a placebo effect entirely. In addition to a shorter study duration than most clinical trials, the small sample size of our case-series study does not allow us to generalise the acute effect we found to all patients with TRD. However, the study showed some strengths of twice-daily tACS, and the questionnaire on cranial electrical stimulation can be used in future studies.

Implications

This case series study showed that twice-daily 15mA tACS, a unique form of non-invasive brain stimulation, offers an acute effective intervention for patients with TRD. A large randomised, sham-controlled study of twice-daily tACS in patients with TRD is warranted to support the findings observed in this case series study.

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Contributors WZ and HW conceptualised the study and drafted the original manuscript. WZ, Huang W, HL, QX, MP, XJ, LT and NP interviewed the participants and collected the data. XW, JW, KG and XZ contributed to data analysis. KG and HW critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by Xuanwu Hospital, Capital Medical University (LYS(2018)008). Participants gave informed consent to participate in the study before taking part.

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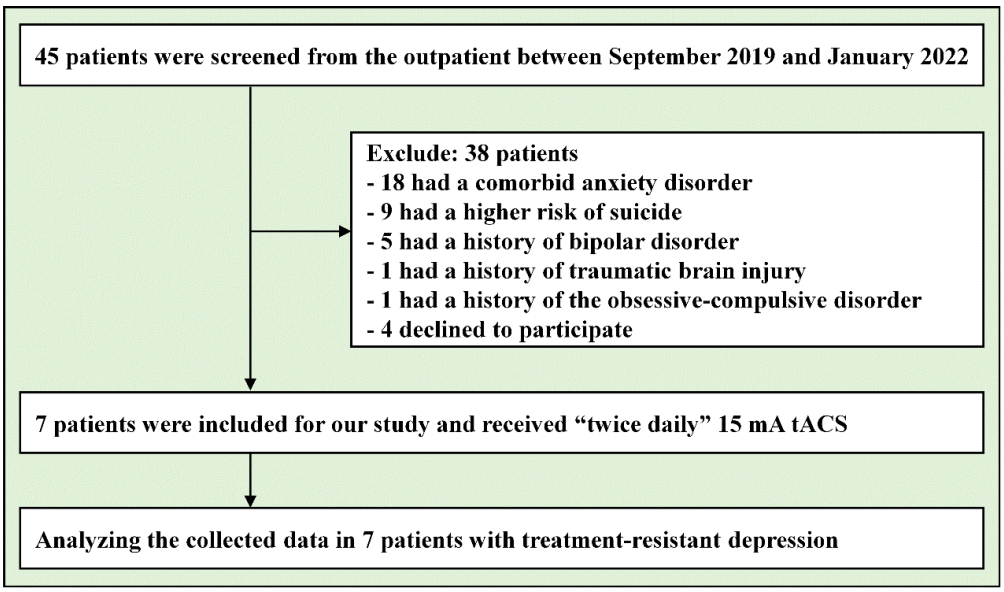

Supplementary Figure 1. Flowchart of the study. tACS, transcranial alternating current stimulation.

Supplementary Table 1. Medication history (dosage, duration) of seven patients

Patient #	Medication history (dosage, duration)
1	Paroxetine (40 mg/d, 5 months), Escitalopram (20 mg/d, 4 months), Mirtazapine (15 mg/d, 3 months), Olanzapine (5 mg/d, 3 months), Agomelatine (50 mg/d, 3 months), Milnacipran (200 mg/d,6 months)
2	Paroxetine (40 mg/d, 5 months), Escitalopram (20 mg/d, 5 months), Mirtazapine (30 mg/d, 4 months), Olanzapine (5 mg/d, 3 months), Duloxetine (60 mg/d, 4 months)
3	Paroxetine (40 mg/d, 6 months), Fluoxetine (40 mg/d, 4 months), Venlafaxine (150 mg/d, 3 months), Olanzapine (5 mg/d, 3 months)
4	Sertraline (150 mg/d, 4 months), Paroxetine (40 mg/d, 5 months), Duloxetine (80 mg/d, 3 months), Olanzapine (5 mg/d, 4 months)
5	Sertraline (150 mg/d, 3 months), Escitalopram (20 mg/d, 8 months), Duloxetine (60 mg/d, 4 months), Olanzapine (5 mg/d, 5 months)
6	Fluoxetine (40 mg/d, 3 months), Venlafaxine (150 mg/d, 6 months), Agomelatine (25 mg/d, 4 months), Duloxetine (60 mg/d, 6 months)
7	Paroxetine (40 mg/d, 3 months), Mirtazapine (15 mg/d, 8 months), Duloxetine (60 mg/d, 6 months), Quetiapine (200 mg/d, 3 months)

Supplementary Table 2. Adverse events during the study

Type of adverse event	Session (details)	Patient #
CQ-CES		
Headache	The 38th session (persisted for 10minutes, resolution with a 10-minute break)	1
Aurium tinnitus	-	-
Tinnitus cerebri	The 32nd session (persisted for 3minutes, resolution with a 20-minute break)	1
Nausea	-	-
Dizziness	The 15th session (transient, resolution with a 20-minute break)	2
Fatigue	-	-
Poor concentration	-	-
Sleepiness	-	-
Skin redness	-	-
Itches	-	-
Skin tingling	-	-
Burning sensations	-	-
Neck pain	-	-
Electric shock-like sensations	-	-
Scalp pain	-	-
Numbness	-	-
Acute mood disorders	-	-
Other (flickering)	The 31st session (transient, resolution with a 20-minute break)	1
YMRS		
Manic	Baseline: six patients scored 1 and one scored 2; Week 4: four scored 1, two scored 2, and one scored 3.	-
EEG		
Epileptic seizure	None.	-

Abbreviations: CQ-CES, 18 items common questionnaire on cranial electrical stimulation; YMRS, Young Mania Rating Scale; EEG, electroencephalogram.