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Preliminary study on the efficacy of intermittent theta burst stimulation (iTBS) in adolescents with affective disorders, with and without antidepressants

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To the editor:

A wide range of affective disorders affects people of all ages globally and contributes significantly to the global disease burden.[1] In China, a nationwide survey found a 3.21% prevalence of affective disorders in children and adolescents, with major depressive disorder (MDD) at 2.00% and bipolar disorder at 0.86%.[2] Adolescent MDD has a lifetime prevalence of 11.0%, but treatment options are limited.[3] While antidepressants are commonly prescribed, their potential side effects—such as weight gain, gastrointestinal issues, drowsiness, and suicide risk—raise concerns.[4] This highlights the urgent need for alternative treatments for affective disorders in adolescents.

Intermittent theta burst stimulation (iTBS) is an example of repetitive transcranial magnetic stimulation (rTMS), which enhances synaptic transmission and cortical excitability by simulating cortical rhythm.[5] The Stanford group demonstrated that a 5-day accelerated iTBS protocol (10 sessions per day) led to immediate, significant reductions in depressive symptoms.[6] Given the time constraints faced by adolescents, short-term, effective treatment options like iTBS could be beneficial. However, research on iTBS for affective disorders in adolescents remains limited. Moreover, adolescents with affective disorders who are not receiving medication require greater attention, as prompt and effective physical therapy can reduce treatment duration and costs for patients and their families.[7] It is important to explore whether iTBS is more effective in adolescents with affective disorders who are on medication compared with those who are not. Currently, no research has addressed this question, and this study aimed to provide a scientific basis for determining the most appropriate treatment, including medication and/or physical therapy, for adolescents with affective disorders in the future.

STUDY DESIGN AND PARTICIPANTS

This study enrolled participants diagnosed with unipolar or bipolar depression at Tianjin Anding Hospital between August 2023 and January 2024. All eligible patients underwent iTBS interventions, with baseline assessments conducted 72 hours before the first treatment. Follow-up evaluations were conducted 2 days after the initial iTBS and after each subsequent maintenance treatment, totalling six evaluations. Of the 86 individuals assessed for eligibility, 30 were enrolled (18 under medication, 12 non-medication).

All participants or their legal guardians provided written informed consent. The inclusion criteria were as follows: (1) age between 12 and 18 years; (2) diagnosed with a current episode of unipolar or bipolar depression disorder, with no psychotic symptoms and manic episodes occurring in the first 6 months of enrolment, based on the Mini-International Neuropsychiatric Interview-Kid V.5.0 Edition (M.I.N.I. KID V.5.0 revision)[8]; (3) a Montgomery-Åsberg Depression Rating Scale (MADRS) score greater than 22[9]; (4) use of an antidepressant medication (either a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor) at a fixed and minimally effective dose as defined by the Antidepressant Treatment History Form criteria[10]; (5) no concurrent

treatment, such as psychological and behavioural therapy; (6) in the medicine-used group, use of two antidepressants simultaneously for at least 1 month; and (7) commitment to the study schedule and active participation in the assessment process.

The excluded criteria were as follows: (1) diagnoses of other mental disorders besides unipolar or bipolar depression disorder, including schizophrenia, major neurocognitive disorder and alcohol or substance dependence; (2) use of antipsychotics, mood stabilisers, anticonvulsants, γ-aminobutyric acid receptor agonists (such as benzodiazepines and gabapentin), N-methyl-D-aspartate receptor partial agonists, stimulants, tricyclic antidepressants or bupropion during iTBS treatment; (3) serious medical conditions, including neurological diseases, traumatic brain injuries, surgeries and infectious diseases; (4) contraindications to iTBS treatment and magnetic resonance imaging (MRI) scans; (5) received rTMS or electroconvulsive therapy (ECT) in the past 6 months; (6) history of epilepsy; (7) unable to communicate, understand or follow instructions normally, and therefore unable to cooperate with treatment and evaluation; (8) pregnancy; and (9) a Young Mania Rating Scale score greater than 5.

INTERVENTION

The Aim Magnetic Stimulation Robot (AIM-III) and Mag TD (Yiruide Medical Equipment New Technology Co, Ltd, Wuhan, China) with an active, 70-mm figure-of-eight, air-cooled coil were used to deliver the iTBS stimulation. Using the Magnetization Prepared Rapid Gradient Echo sequence, 3D T1-weighted structural images were acquired. The dorsolateral prefrontal cortex (DLPFC) target location was identified through cortical coregistration using each participant's MRI; the coordinates for targeting the left DLPFC were identified at the location (−41, 16, 54).[11] The resting motor threshold (RMT) was defined as the minimal intensity needed to elicit responses greater than 50 µV in at least 5 of 10 stimulations.

The iTBS protocol involved 50-Hz bursts at 5 Hz, with 2 seconds on and 8 seconds off, delivering 1800 pulses per session at 70% of the RMT. Participants received 10 accelerated intermittent theta burst stimulation (aiTBS) sessions over 2 days (five sessions per day) and eight maintenance sessions over 4 weeks (two sessions per day). Each aiTBS session had 1800 pulses with 50 min intervals. For maintenance, participants received 3600 pulses weekly. Both groups followed the same pre-treatment protocol throughout the iTBS treatment. A treatment flowchart is shown in figure 1.

ASSESSMENTS

The MADRS score was used to assess depression severity, focusing on 10 factors: chief complaint, observed depression, nervousness, sleep disturbances, appetite loss, concentration difficulties, lethargy, lack of emotions, pessimism and suicidal ideation. Overall illness severity was measured using the Clinical Global Impression Severity Subscale (CGI-S).[12] The Patient Rated Inventory of Side Effects evaluated eight biological dimensions—gastrointestinal, cardiovascular, skin, neurological, eye/ear, genitourinary, sleep and sexual function—along with the side effect severity.

STATISTICAL ANALYSIS

Following iTBS treatment, a positive response was defined as a 50% reduction in MADRS score from baseline, with remission indicated by a MADRS score below 8.[13] Continuous variables were presented as means or medians and interquartile ranges, depending on the distribution, while categorical variables were expressed as proportions. Baseline demographical and clinical characteristics were compared using independent samples t-tests or Mann-Whitney U tests for continuous variables, and the χ^2 test for categorical variables. Response and remission rates between medicine-used and non-medicine-used groups were compared using Fisher's exact test, and odds ratios

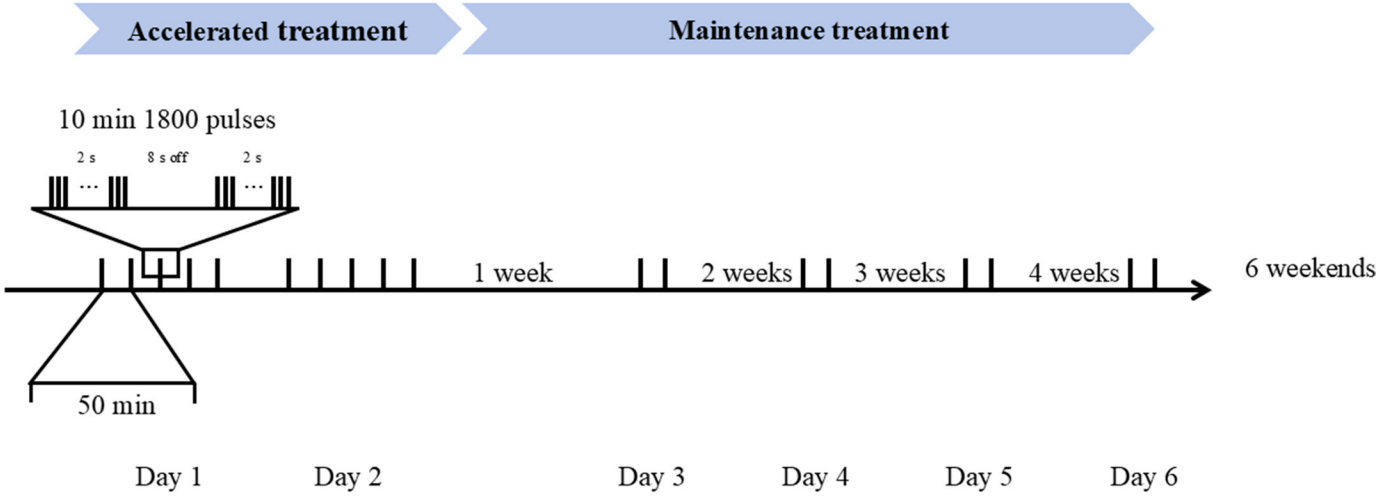

Figure 1 Treatment flowchart.

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with 95% confidence intervals were calculated. The distribution of missing data over time was analysed using Kaplan-Meier estimation and a log-rank test. Changes in scores at each treatment time point were assessed using paired t-tests or Wilcoxon signed-rank tests. A linear mixed model with random intercepts and slopes was used to examine variability across time points, considering time, group and their interactions. All analyses were conducted with SPSS V.22.0, using a significance level of 0.05.

CHARACTERISTICS OF THE STUDY PARTICIPANTS

The participant flow diagram is demonstrated in online supplemental figure 1. A total of 86 individuals were assessed for eligibility, of whom 44 were found to be ineligible or declined participation, and 12 had received either rTMS or ECT within the previous 6 months. Consequently, 30 participants were included in our study. Among them, 18 had taken one or more antidepressant medications in the past month, while 12 had not used any antidepressants. Among the 30 participants, all completed a 2-day accelerated stimulation process, 26 participants completed the 1-week stimulation sessions (medicine-used: 16/18 (88.9%); non-medicine-used: 10/12 (83.3%)), 25 participants completed the 2-week stimulation sessions (medicine-used: 16/18 (88.9%); non-medicine-used: 9/12 (75.0%)), 22 participants completed the 3-week stimulation sessions (medicine-used: 14/18 (77.8%); non-medicine-used: 8/12 (66.7%)) and 21 participants completed the 4-week stimulation sessions (medicine-used: 13/18 (72.2%); non-medicine-used: 8/12 (66.7%)).

Baseline sociodemographic and clinical data are summarised in online supplemental table 1. Among all the individuals in the study group, 73.3% were female, and the mean (standard deviation) age was 15.75 (1.78) years. All participants were right-handed and of Han nationality. Family history of mental illness was reported in 3.3% of the participants. Median MADRS total scores and CGI-S scores were 27 and 4 at baseline. There were no statistically significant variations in sociodemographic and baseline clinical characteristics between the subgroups of medicine-used and non-medicine-used. Additionally, no serious adverse reactions occurred among all patients; common adverse reactions included discomfort at the stimulation site and headache, with only one patient reporting a mild headache.

THE CLINICAL ASSESSMENTS BETWEEN GROUPS

The variations in MADRS total score, MADRS score reduction and CGI-S score are summarised in figure 2, showing significant differences over time. Starting from the second week, variations emerged between the groups regarding the MADRS score and MADRS score reduction. Clinical scores at each time point are presented in online supplemental table 2. Response rates and remission rates did not exhibit significant discrepancies across the groups (online supplemental table 3).

CHANGES IN CLINICAL SCALES IN MIXED LINEAR REGRESSION MODEL

The analysis using a linear mixed model indicated a significant decrease in MADRS scores and CGI-S scores at the 4-week follow-up appointment. It also revealed notable variances in the mean MADRS total score (F=4.164, p=0.002) and reduced scores for decreased sleep (F=3.228, p=0.009), difficulty concentrating (F=4.367, p=0.001) and pessimistic thinking (F=2.866, p=0.017) factors across different groups over time (online supplemental table 4).

This preliminary investigation aimed to evaluate the impact of aiTBS and iTBS maintenance over a 4-week period on the levels of depressive symptoms in adolescents with affective disorders, both with and without the use of antidepressants. The treatment regimen in this study involved 18 000 pulses during the 2-day accelerated treatment period, which is the shortest and largest dose regimen among total treatments in the ongoing aiTBS study involving adolescents. The treatment was safe and well tolerated in this sample of adolescents.

Research on iTBS for improving depressive symptoms in adolescents is limited. Dhami *et al* reported a significant reduction in depressive symptoms with 1800 pulses, five times per week for 2 weeks, suggesting that 10 bilateral TBS sessions could be effective for adolescent MDD, similar to our study.[14] In our research, the MADRS score decreased by an average of 8.4 points after 2 days of accelerated treatment and 12.6 points after 4 weeks of maintenance treatment, both showing significant improvement from baseline. Compared to adults, the use of iTBS in adolescents with affective disorders remains underexplored.

In our study, depressive symptoms improved during the treatment period, with a more pronounced effect in the group not using antidepressants. To our knowledge, this is the first study to compare the efficacy of iTBS in adolescents with affective disorders on versus off antidepressants. From the second week of maintenance treatment, a noticeable difference in symptom alleviation emerged between the two groups (figure 2). While iTBS was effective, its impact appeared stronger in those not on antidepressants. Previous research suggests that add-on TMS is more effective than TMS monotherapy, which contrasts with our findings.[15] However, earlier studies focused on adults, and differences in brain structure and function between adults and adolescents may explain the discrepancies. Additionally, prior studies included patients with past antidepressant use, whereas our participants in the non-medicine-used group had never used medication, potentially making them more receptive to iTBS. In addition, the duration of the disease in the medicine-used group is longer than that in the non-medicine-used group, which may also be a factor affecting its efficacy. Adolescence is a period of emotional change, and teens

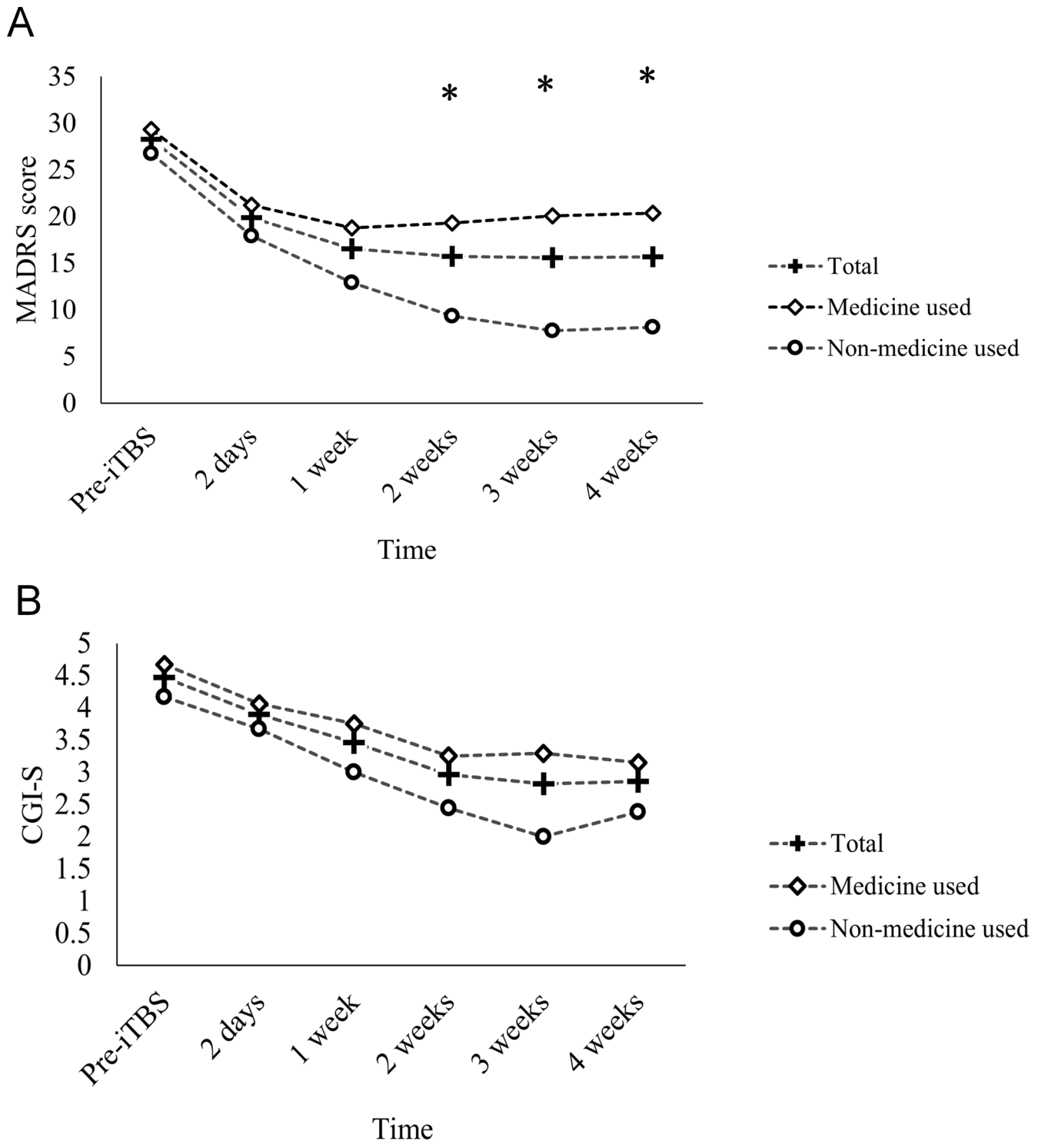

Figure 2 Changes in (A) MADRS and (B) CGI-S total scores over time. * Significant difference between groups with and without antidepressant use, p<0.05. CGI-S, Clinical Global Impression severity subscale; MADRS, Montgomery-Åsberg Depression Rating Scale.

who have been on medication for longer may develop resistance to new treatments. Although preliminary, this study offers promising insights into iTBS treatment for adolescents.

After 2 days of aiTBS treatment, MADRS scores significantly decreased, but no differences were observed between the two groups (online supplemental table 2), highlighting the importance of ongoing maintenance treatment. A brief period of high-dose accelerated therapy followed by minimal weekly maintenance is crucial for sustaining therapeutic effects. The linear mixed model showed a significant temporal trend in both MADRS scores and CGI-S. The non-medicine-used group showed greater

improvement compared to the medicine-used group, particularly in areas like sleep, concentration, pessimism and overall MADRS score. This suggests that iTBS may be more effective in addressing specific depressive symptoms in the non-medicine-used group. This research provides a scientific foundation for tailoring treatment strategies based on individual depressive symptoms in future practices.

Given that adolescents with affective disorders accompanied by psychotic symptoms are indeed more common, we carefully screened all participants using the M.I.N.I. KID to ensure that no individuals had diagnoses of schizophrenia, major neurocognitive disorder, alcohol or substance dependence or combined psychotic symptoms. Although some participants may have exhibited mild issues in other domains, these did not meet the diagnostic threshold or were far less severe compared to their current depressive episode, with their primary diagnosis and the condition most impacting their daily functioning remaining the depressive episode. Therefore, the result of 'no comorbidities' in our study reflects the absence of significant comorbidities that could confound the interpretation of our findings.

This study has several limitations. First, as a cross-sectional intervention study, it cannot draw definitive conclusions. Future randomised controlled trials with sham and placebo groups are needed to verify the effects of aiTBS and maintenance therapy on adolescent depressive symptoms. Second, while 70% RMT was used in our study, literature suggests that 90%–120% RMT may be more effective, and our study protocol is still evolving to identify optimal treatment parameters. Additionally, we plan to conduct long-term follow-ups to assess the durability of intervention outcomes. The neuronavigation method in this study used general anatomical targets based on a single Montreal Neurological Institute (MNI) coordinate rather than personalised functional magnetic resonance imaging (fMRI)-based targeting, which may affect outcome interpretation. Moreover, some adolescent participants were on multiple antidepressants, which was not the focus of this study. Future research will address the combined effects of medications. In addition, the course of the disease in the medicine-used group is longer than that in the non-medicine-used group, and we will further control the course of the disease in the future to observe its efficacy. Despite these limitations, our study offers valuable insights for optimising iTBS treatment approaches for adolescents, particularly regarding antidepressant use.

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Patient consent for publication Consent was obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by Tianjin Anding Hospital research ethics board (No. 2023-21). Participants gave informed consent to participate in the study before taking part.

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