Neuropsychopharmacology

ARTICLE

Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial

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Treatment-resistant depression (TRD) is prevalent and associated with a substantial psychosocial burden and mortality. There are few prior studies of interventions for TRD in adolescents. This was the largest study to date examining the feasibility, safety, and efficacy of 10-Hz transcranial magnetic stimulation (TMS) for adolescents with TRD. Adolescents with TRD (aged 12–21 years) were enrolled in a randomized, sham-controlled trial of TMS across 13 sites. Treatment resistance was defined as an antidepressant treatment record level of 1 to 4 in a current episode of depression. Intention-to-treat patients ($n = 103$) included those randomly assigned to active NeuroStar TMS monotherapy ($n = 48$) or sham TMS ($n = 55$) for 30 daily treatments over 6 weeks. The primary outcome measure was change in the Hamilton Depression Rating Scale (HAM-D-24) score. After 6 weeks of blinded treatment, improvement in the least-squares mean (SE) HAM-D-24 scores were similar between the active (−11.1 [2.03]) and sham groups (−10.6 [2.00]; $P = 0.8$; difference [95% CI], − 0.5 [−4.2 to 3.3]). Response rates were 41.7% in the active group and 36.4% in the sham group ($P = 0.6$). Remission rates were 29.2% in the active group and 29.0% in the sham group ($P = 0.95$). There were no new tolerability or safety signals in adolescents. Although TMS treatment produced a clinically meaningful change in depressive symptom severity, this did not differ from sham treatment. Future studies should focus on strategies to reduce the placebo response and examine the optimal dosing of TMS for adolescents with TRD.

Neuropsychopharmacology (2021) 46:462–469; https://doi.org/10.1038/s41386-020-00829-y

INTRODUCTION

Forty percent of adolescents with major depressive disorder (MDD) fail to respond to treatment with an antidepressant medication or evidence-based psychotherapy [1, 2], resulting in what is commonly referred to as treatment-resistant depression (TRD) [1, 3, 4]. Despite the prevalence of TRD in adolescents, few interventions for this condition have been systematically and prospectively evaluated. Research focused on adolescent TRD is limited, with only 1 prior large study to date [1, 4]. The Treatment of Resistant Depression in Adolescents (TORDIA) study suggested that adding cognitive behavioral therapy and switching to an alternative antidepressant are reasonable next steps after 1 medication failure [1, 5, 6]. However, few additional studies are available to guide next-step interventions. Adolescents with TRD frequently receive multiple psychotropic medications (eg, dopamine-serotonin receptor antagonists, dopamine-serotonin reuptake inhibitors, and mood stabilizers) [7–9], yet remission rates are low and many youth experience adverse effects [7, 10–12]. Although electroconvulsive therapy (ECT) has been studied for TRD, access for adolescents is limited [13]. Thus, new treatments are urgently needed for adolescents with TRD.

Transcranial magnetic stimulation (TMS) is efficacious and well tolerated in adults with MDD [14–16]. In adolescents, TMS has been adopted slowly despite its availability over the past 2 decades [17, 18]. Case reports and unblinded studies with a total of 96 patients suggest potential utility of TMS in adolescents with TRD [19]. In these initial trials, standard 10-Hz dosing was frequently used with effectiveness and tolerability similar to what has been demonstrated in adults [19, 20]. However, the inherent biases in uncontrolled studies have limited further clinical development of TMS for depression in adolescents and off-label use.

The present study represents the largest multicenter, double-blind, randomized controlled trial of TMS for TRD in adolescents to date. The study design was harmonized with 2 prior landmark studies of left prefrontal 10-Hz TMS in adults (18–70 years of age) with MDD who did not respond to prior antidepressant treatment for a meta-analysis approach [14, 16]. These two prior data sets were important to consider given that they provide substantial evidence of safety and effectiveness of TMS. This approach was clinically justified given the biological and clinical continuity of MDD from adolescence to adulthood. Further, TMS most likely has a shared mechanism of action across adolescence and adulthood.

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Received: 1 July 2020 Revised: 8 August 2020 Accepted: 17 August 2020
Published online: 12 September 2020

There is a substantial unmet need in treatment options for adolescent patients with TRD. The rationale for this methodology was based on US Food and Drug Administration (FDA) guidance, "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" (2016), to ensure that medical devices used in adults were safe for use in pediatric patients [20–22]. The FDA also has acknowledged interest in supporting an approach to medical device development that leverages existing data from adults [22].

The focus of the study was to demonstrate the absence of any new safety signal in adolescents and demonstrate clinically meaningful effects. The TMS treatment protocol had been studied extensively in adults [15, 23]. Further, the proposed analytic plan for the present study capitalized on a meta-analytic approach that evaluated data from adolescents in combination with data from 2 prior studies of adults [14, 16]. The approach was based on the rationale that differences in responses to TMS between adolescents and adults with depression were not clinically meaningful. Although the pathophysiology of MDD in adolescents is continuous with adults, placebo response rates tend to be higher in adolescents compared to adults [24–26]. This sample-size sparing approach also minimized the number of adolescents exposed to sham treatment and related study procedures [21]. We hypothesized that 1) adolescents who received 10-Hz, left prefrontal TMS, delivered over the 30 sessions would have greater improvement in depressive symptoms compared to those who received sham and 2) acute treatment with 10-Hz, left prefrontal TMS would be feasible, safe, and tolerable in adolescents with TRD.

MATERIALS AND METHODS

Study design

The study was a randomized, sham-controlled trial of 10 Hz, left prefrontal TMS for adolescents with TRD across 13 sites (Fig. 1; ClinicalTrials.gov identifier: NCT02586688). Institutional review board (IRB) approval was obtained through the Copernicus Group and each site IRB prior to any research related activities. The acute phase of the trial (phase I) provided 30 sessions of TMS over 6 weeks as monotherapy. An overview of the full protocol including recruitment, screening and eligibility criteria is described in the Supplementary Materials and methods. The study conformed to Consolidated Standards of Reporting Trials (CONSORT) guidelines [27].

After 1 week of screening, patients were randomly assigned in a 1:1 ratio. Patients in phase I who were assigned to sham treatment had schedules, clinical assessments, and treatment approaches that were identical to those of patients receiving active TMS. Patients, treaters, and raters were blind to treatment assignments. The sham coil was identical in appearance to the active coil, had an acoustically matched profile, and created a mild percussive sensation to further simulate active treatment.

Participants

Patients aged 12–17 years provided informed consent or assent (as dictated by the institutional review board), and a parent provided written, informed consent. Patients aged 18–21 years provided informed consent.

Eligible participants met the following criteria: (1) aged 12–21 years; (2) met *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) [28] criteria for diagnosis of unipolar MDD in a current major depressive episode (episode duration ≥4 weeks and ≤3 years) without psychotic features; and (3) had a HAM-D-24 score of 2 or more for item 1 and a total score of 20 or more at screening [29]. *Treatment resistance* was defined as an antidepressant treatment record (ATR) level of 1 to 4 in the current episode or 1 to 4 failed antidepressant trials in a prior episode administered at an adequate dose and duration as defined within the ATR [3, 30]. Patients who were previously intolerant of 4 or more antidepressant medications were eligible for enrollment. For eligibility at the baseline visit, patients had a HAM-D-24 score of at least 18 and improvement in symptom severity that was 25% or

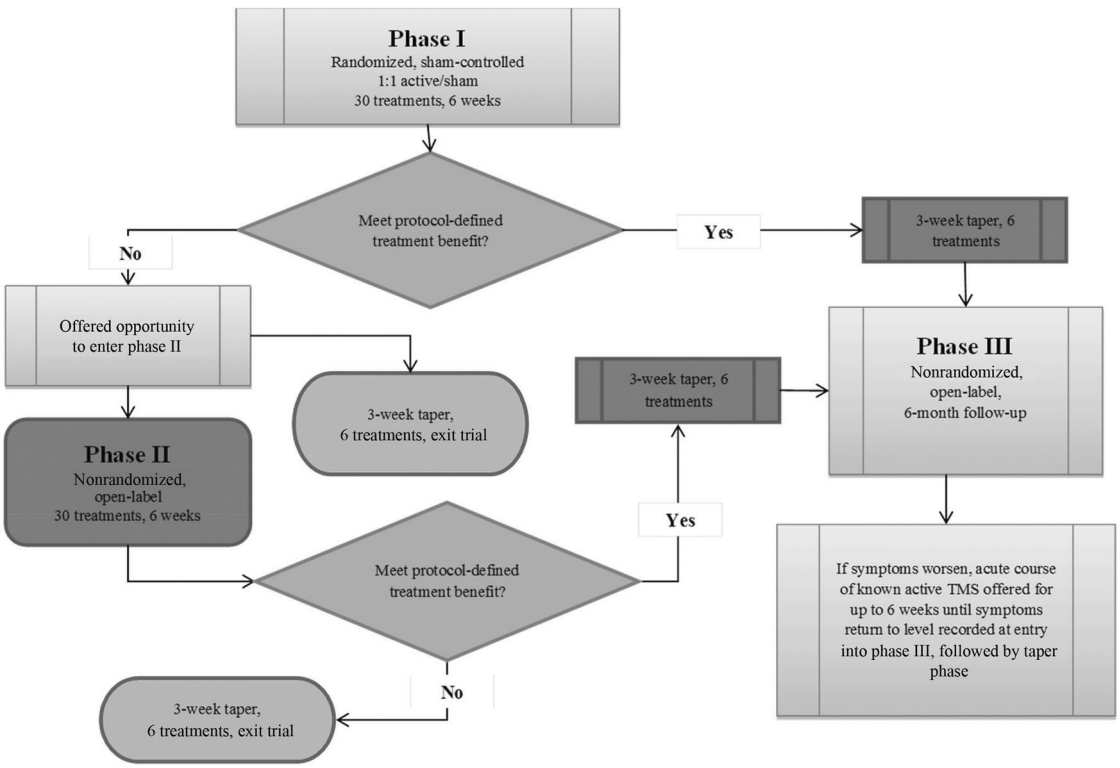

Fig. 1 Flowchart showing 3 phases of the study. TMS indicates transcranial magnetic stimulation.

less. The diagnosis of MDD was based on physician evaluation according to *DSM-5* criteria and a structured interview with the Mini International Neuropsychiatric Interview (MINI) for Children and Adolescents (MINI-KID) if they were aged 12–17 years [31] or the MINI if they were aged 18 to 21 years [32].

Patients were excluded if they met any of the following criteria: (1) depression related to a medical condition or substance-induced depressive symptoms; (2) a seasonal depressive pattern as defined by *DSM-5*; (3) any lifetime psychotic disorder, intellectual disability, substance dependence or abuse (except nicotine and caffeine) in the past year; bipolar disorder, obsessive compulsive disorder, posttraumatic stress disorder, or eating disorder; (4) any history of a neurologic disorder or seizures; (5) unstable medical conditions; (6) contraindications to TMS (e.g., magnetic-sensitive metals implanted in or near the head); (7) previous exposure to TMS, ECT, or vagus nerve stimulation; or (8) a cardiac pacemaker [23, 33].

Patients treated with psychotherapy must have received stable treatment for at least 3 months before screening with no planned change in the frequency or focus of the therapeutic sessions during the study. Patients could not take psychotropic medications during the study with the exception of zaleplon, zolpidem, zopiclone, or lorazepam for up to 14 doses during phase I. If necessary, patients had at least a 1-week washout period of psychotropic medications (4 weeks for fluoxetine) before screening.

A history and physical examination, medical history, and psychiatric history were completed at the screening visit. Vital signs were collected at the baseline visit and at week 6. Screening laboratory tests included blood chemistry panel, complete blood count, thyroid function tests, urine drug screen, and urine pregnancy test. The National Institutes of Health (NIH) Toolbox Cognition Battery (NIHTB-CB) was performed at baseline and week 6 [34]. Auditory threshold assessments for left and right ears were collected at baseline and week 6. A subgroup of patients underwent structural magnetic resonance imaging (MRI) at baseline and week 6 to assess any neurostructural effects of acute TMS therapy.

Interventions

TMS treatments were delivered with the NeuroStar XPLOR TMS Therapy System (Neuronetics, Inc) in a manner consistent with prior adult [14, 16] and adolescent studies [17, 18]. The 5-cm rule was used for coil localization. The motor cortex abductor pollicis bevis muscle area was identified, and the treatment coil was placed 5 cm anteriorly for TMS treatment sessions. Stimulation was delivered at an intensity of 120% of the patient's resting motor threshold, at 10 pulses per second (10 Hz) for 4 s, and with an intertrain interval of 26 s. During the first treatment week, treatment intensity could be decreased to 110% if needed for tolerability. Each treatment session was 37.5 mins (75 trains) for a total of 3,000 pulses per session. Patients had the opportunity to complete 30 treatment sessions over 6 weeks and could not have more than 2 days between sessions during the 6-week acute treatment period.

Assessments

Raters with established interrater reliability administered all diagnostic and clinical assessments, and physicians administered the ATR. Outcome measures included assessments with the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS) in structured interviews [29, 35]; the Children's Depression Rating Scale–Revised (CDRS-R) [36]; the Clinical Global Impressions–Severity of Illness (CGI-S) scale [37]; and the Quick Inventory of Depressive Symptomatology–Adolescent (17-Item)–Self-Report version (QIDS-A_{17}-SR) [38, 39]. Clinical assessments were collected at baseline (before the first TMS sessions), at the end of treatment week 4, and at the end of treatment week 6. The Columbia-Suicide Severity Rating Scale (C-SSRS) was completed weekly during TMS sessions [40]. The Young Mania Rating Scale (YMRS) was completed at baseline and repeated as needed for any concern of treatment-emergent mania [41].

Outcome variables

The primary efficacy outcome measure was the change in the HAM-D-24 score from baseline to week 6 (ie, the last observation). Secondary efficacy outcome measures included continuous outcomes from the HAM-D, MADRS, CDRS-R, QIDS-A_{17}-SR, and CGI-S; response categorical outcomes; remitter categorical outcomes; and factor scores derived from the HAM-D. Safety outcomes included adverse event reporting, neurocognitive assessments, vital signs, and C-SSRS and YMRS assessments.

Statistical analysis

The statistical analysis plan was developed in collaboration with the FDA based on the guidance, "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" [22]. The change in HAM-D-24 from baseline to week 6 was analyzed with a mixed-effects analysis of covariance (ANCOVA). Baseline assessments with HAM-D-24, ATR medication resistance level, and treatment group were fixed effects, and site of enrollment was a random effect. Significance was predefined as a P value less than 0.05 for the treatment effect.

Alternatively, if the ANCOVA treatment effect was not statistically significant, a meta-analysis pooling with prior landmark adult (18–70 years of age) randomized, sham-controlled studies of TMS (with congruent treatment protocols and study designs) [14, 16] was performed with the overall type I error for the adolescent data controlled at 0.15, and success was defined as follows: (1) The main effect on the primary efficacy variable of mean change from baseline on the HAM-D-24 in the adolescent and adult studies of the meta-analysis would be statistically significant and decrease below the prespecified α level of 0.05. (2) There would be no statistically significant evidence of interaction between study and treatment on the primary efficacy outcome variable at the prespecified α level of 0.10 or more. (3) The study-specific treatment effect observed for the primary efficacy outcome variable in the adolescent clinical study as a stand-alone analysis would be in the range of 1.7 to 5.5 points on the HAM-D-24 and meet the maximum type I error rate of 15%.

A sample size of 50 patients per treatment arm was expected to provide more than 85% power to detect a statistically significant difference between treatment groups at an α level of 0.05 for the stand-alone efficacy analysis. For the combined, meta-analytic approach, a sample size of 50 patients per treatment arm and an α level of 0.10 to test the study by treatment interactions would allow detection of a statistically significant study by treatment interaction if the mean treatment group difference, in favor of active, was greater than the upper bound of 5.5 points or less than the lower bound of –0.8 points. In the absence of a statistically significant interaction between study and treatment, the lower bound of the observed treatment group difference must be greater than 1.7 in favor of active treatment to combine data from the adult studies for a meta-analysis of data from the adolescent clinical study. The analytic plan, assumptions, and type I error rate of 15% were justified based on results from the HAM-D-24 outcome in adult studies, the large data set available for adults ($N = 491$), and the premise that adolescent and adults would have a similar response to TMS [14, 16–18].

RESULTS

Participants

Of the 177 patients considered, 65 did not meet the inclusion criteria and 112 were randomly assigned for acute TMS treatment

Table 1. Key demographics and clinical variables at baseline.

Variable	Treatment group		*P*-value[b]
	Sham ($n = 55$)[a]	Active ($n = 48$)[a]	
Sex, No. (%)			0.61
Female	37 (67.3)	30 (62.5)	
Male	18 (32.7)	18 (37.5)	
Age, *y*			0.34
Mean (SD)	17.1 (2.22)	17.6 (2.28)	
Median (range)	17.4 (12.1–21.4)	17.6 (12.2–21.8)	
Age group, No. (%), y			0.74
12–14	11 (20.0)	8 (16.7)	
15–17	24 (43.6)	19 (39.6)	
18–21	20 (36.4)	21 (43.8)	
Race, No. (%)			0.35
White	47 (85.5)	43 (89.6)	0.53
Black or African American	5 (9.1)	1 (2.1)	
Asian	1 (1.8)	3 (6.2)	
American Indian, Alaskan Native, Native Hawaiian, or other Pacific Islander	0 (0.0)	0 (0.0)	
Other	2 (3.6)	1 (2.1)	
Ethnicity, No. (%)			0.62
Hispanic or Latino	3 (5.5)	1 (2.1)	
Not Hispanic or Latino	52 (94.5)	47 (97.9)	
Motor threshold (SMT)	($n = 55$)	($n = 46$)	0.24
Mean (SD)	0.92 (0.199)	0.97 (0.192)	
Median (range)	0.95 (0.35–1.27)	0.94 (0.42–1.30)	
Primary diagnosis, No. (%)			NA
Major depressive disorder	55 (100.0)	48 (100.0)	
Not major depressive disorder	0 (0.0)	0 (0.0)	
Major depressive disorder episodes, No. (%)			0.55
1	13 (23.6)	9 (18.8)	
>1	42 (76.4)	39 (81.2)	
Duration of current episode, mo			0.92
Mean (SD)	13.8 (8.36)	13.9 (9.01)	
Median (range)	12.9 (1.5–33.9)	13.2 (1.8–36.2)	
<24, No. (%)	50 (90.9)	43 (89.6)	>0.99
≥24, No. (%)	5 (9.1)	5 (10.4)	
ATR medication resistance level, No. (%)			0.75
0[c]	4 (7.3)	2 (4.2)	
1	30 (54.5)	22 (45.8)	
2	15 (27.3)	17 (35.4)	
3	4 (7.3)	5 (10.4)	
4	2 (3.6)	1 (2.1)	
5[c]	0 (0.0)	1 (2.1)	
Secondary psychiatric diagnosis, No. (%)			0.24
None	19 (34.5)	22 (45.8)	
Any	36 (65.5)	26 (54.2)	
Treatment history, No. (%)			
Prior ECT	0 (0.0)	0 (0.0)	NA
Prior inpatient hospitalization for depression	9 (16.4)	9 (18.8)	0.75
Prior psychotherapy	10 (18.2)	7 (14.6)	0.62
Mania or hypomania by YMRS (total score >20)	0 (0.0)	0 (0.0)	NA
HAM-D-24 total score			0.57
Mean (SD)	29.5 (6.69)	28.8 (5.75)	
Median (range)	28.0 (18.0–54.0)	28.5 (19.0–43.0)	
HAM-D-17 total score			0.47
Mean (SD)	21.5 (4.41)	20.9 (4.43)	
Median (range)	21.0 (12.0–37.0)	21.0 (11.0–31.0)	
MADRS total score			0.39
Mean (SD)	32.3 (7.16)	31.1 (6.41)	
Median (range)	33.0 (12.0–56.0)	32.0 (17.0–42.0)	
CDRS-R total score			0.59
Mean (SD)	62.6 (10.03)	61.5 (10.03)	
Median (range)	63.0 (41.0–89.0)	61.0 (40.0–84.0)	
CGI-S total score			0.77
Mean (SD)	5.1 (0.68)	5.1 (0.72)	
Median (range)	5.0 (4.0–7.0)	5.0 (4.0–7.0)	
QIDS-A_{17}-SR total score			0.76
Mean (SD)	20.8 (7.54)	20.4 (6.80)	
Median (range)	21.0 (1.0–36.0)	20.0 (6.0–35.0)	

ATR antidepressant treatment record, *CDRS-R* Children's Depression Rating Scale–Revised, *CGI-S* Clinical Global Impressions–Severity of Illness, *ECT* electroconvulsive therapy, *HAM-D-17* 17-item Hamilton Depression Rating Scale, *HAM-D-24* 24-item Hamilton Depression Rating Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *NA* not applicable, *QIDS-A_{17}-SR* Quick Inventory of Depressive Symptomatology–Adolescent (17-Item)–Self-Report version, *SMT* standardized motor threshold, *YMRS* Young Mania Rating Scale.

[a]Unless indicated otherwise.

[b]*P*-value from χ^2 test or Fisher exact test for categorical variables and from *t*-test for continuous variables.

[c]Patients with ATR medication resistance level of 0 or 5 did not meet the study inclusion criteria and were documented as protocol deviations.

in phase I (54 in the active treatment group; 58 in the sham group) (Supplementary Fig. S1). In total, 103 patients met criteria for modified intent to treat (mITT) of at least 1 treatment and a posttreatment HAM-D-24 rating (Supplementary Fig. S1). The patients in the active and sham groups had no statistically significant differences in demographic or clinical variables (Table 1). There were 2 patients in the active group and 4 patients in the sham group with an ATR medication resistance level of 0. Although these patients did not meet inclusion criteria, they were included in the analyses given the importance of the safety data and following the modified intent-to-treatment principal as pre-specified for the efficacy analyses. Sensitivity analyses which excluded these patients (with ATR = 0) showed similar results to the primary analysis.

Clinical outcomes

There were no statistically significant differences in clinical outcomes between the active TMS and sham TMS groups (Tables 2 and 3 and Fig. 2). The observed average total HAM-D-24 score in the treatment group decreased from 28.8 to 18.1 in the group treated with active TMS and from 29.5 to 19.2 in the sham group. Since the *P* value for treatment effect was greater than 0.05, a prespecified, meta-analysis with adult study data was performed with a linear mixed-effects model. The interaction of treatment and study was not significant ($P > 0.15$), which was consistent with the prespecified hypothesis that the observed treatment effect would be in the same direction across studies. The treatment effect (active-sham) was estimated to be –1.4 ($P = 0.15$). However, the study-specific stand-alone effect for the adolescent clinical study was not between –5.5 and –1.7 ($P < 0.15$), and so primary analyses indicated that the study did not meet its primary end point.

Secondary analyses showed no statistically significant difference between response rates in the active and sham groups. Response rates were 41.7% in the active group and 36.4% in the sham group ($P = 0.6$) (Supplementary Table S1). The high placebo response rate (36.4%) was consistent with results from antidepressant randomized controlled trials with adolescents but much larger than randomized controlled trials of TMS for MDD in adult

Table 2. Primary efficacy outcomes in the 6-week acute treatment phase[a].

Treatment group	HAM-D-24 total score		
	Baseline[b]	Week 6[b]	Change from baseline[c]
Active ($n = 48$)[d]			
Mean (SD)	28.8 (5.75)	18.1 (10.91)	
Median (range)	28.5 (19–43)	18.5 (0–38)	
LS mean (SE)			–11.1 (2.03)
95% CI			–15.2 to –7.1
Sham ($n = 55$)[d]			
Mean (SD)	29.5 (6.69)	19.2 (11.03)	
Median (range)	28.0 (18–54)	21.0 (0–43)	
LS mean (SE)			–10.6 (2.00)
95% CI			–14.8 to –6.8
Difference (95% CI); *P*-value			–0.5 (–4.2 to 3.3); $P = 0.80$

HAM-D-24 24-item Hamilton Depression Rating Scale, *LS* least-squares.
[a]All comparisons are based on the last observation carried forward for missing data.
[b]Summary statistics are based on observed outcomes and are not adjusted for antidepressant medication resistance or site.
[c]Primary analysis is based on analysis of covariance for each time point, fixed effects for baseline measures, antidepressant medication resistance level (0 or 1 vs 2–4 in current episode), treatment, and random effect for site.
[d]Number of patients was the same at baseline and at week 6.

Table 3. Meta-analysis of primary efficacy outcomes in the 6-week acute treatment phase[a, b, c].

Feature	Change in HAM-D-24 total score from baseline to week 6	*P*-value
Active treatment group		
LS mean (SE)	–8.5 (0.85)	
95% CI	–10.1 to –6.8	
Sham treatment group		
LS mean (SE)	–7.1 (0.83)	
95% CI	–8.7 to –5.5	
Difference (95% CI)	–1.4 (–3.3 to 0.5)	
Treatment effect		0.15
Study		<0.001
Treatment-by-study interaction		0.36

HAM-D-24 24-item Hamilton Depression Rating Scale, *LS* least-squares.
[a]All comparisons are based on the last observation carried forward for missing data.
[b]Analysis is based on linear mixed-effects model for change from baseline and includes treatment group (fixed), baseline HAM-D-24 score (fixed), antidepressant medication resistance level (0 or 1 vs 2–4 in current episode, fixed), study (adolescent vs adult, fixed), treatment-by-study interaction (fixed), antidepressant medication resistance level-by-treatment interaction (fixed), and site nested within study (random).
[c]The *P*-value for the adolescent study was greater than 0.015, and therefore the analysis was post hoc and not controlled at the prespecified level.

patients. Although the difference between the active and sham groups in the adolescent clinical study was not statistically significant, the difference increased among the subgroup of patients with greater ATR medication resistance (Supplementary Table S2). This difference was not statistically significant, but there was increased separation between the active and sham groups as the ATR level increased. Secondary analyses of all other clinical outcomes (MADRS, CDRS-R, QIDS-A_{17}-SR, and CGI-S) did not reveal any statistically significant differences between the active and sham treatment groups. Remission rates were 29.2% in the active group and 29.0% in the sham group ($P = 0.95$). Secondary analyses of remission rates with all other clinical outcomes (MADRS, CDRS-R, QIDS-A_{17}-SR, and CGI-S) did not reveal any statistically significant differences between active and sham treatment groups. Exclusion of the 6 patients with an ATR medication resistance level of 0 did not change the above findings of the efficacy analyses. There were no significant differences in efficacy outcomes with respect to various age groups within the sample.

Safety outcomes

Acute TMS treatment was well tolerated by all patients. In total there were five serious adverse events. One patient in screening developed suicidal ideation and this was classified as definitely not related to the study device. One patient receiving sham treatment during week 1 developed suicidal ideation and this was classified as definitely not related to the study device. In the patients treated with active TMS, one developed suicidal ideation during week 2 (classified as probably not related to the study device), one developed worsening depression during week 4 (classified as definitely not related to the study device), and another had a suicide attempt during week 6 (classified as definitely not related to the study device).

Sixty patients reported at least 1 adverse event (Supplementary Table S3). Notable events that were more common in the active group than in the sham group included headaches (31.5 vs 17.2%), eye pain (5.6 vs 0.0%), nausea (11.1 vs 5.2%), and facial twitching (7.4 vs 1.7%). Four patients dropped out of the study due to reported adverse events. There were no seizures during the study. Treatment groups did not differ with regard to suicidality as measured on the C-SSRS. There were no clinically significant changes in height, weight, or vital signs and no marked changes in auditory thresholds from baseline to posttreatment. There were no significant changes in NIHTB-CB individual or composite scores from baseline to posttreatment. In a subset of patients ($n = 11$) that underwent serial structural MRI scans, no clinically significant structural changes were observed.

DISCUSSION

This study was the first blinded, randomized, sham-controlled clinical study of the effectiveness of high-frequency TMS for TRD in adolescents. High-frequency TMS demonstrated safety and tolerability in adolescents. With rigorous assessments there was no evidence of treatment-emergent suicidality. There was also no evidence of negative neurocognitive effects or structural brain changes [20]. Patients in both the active and the sham treatment groups experienced improvement in depressive symptoms. There was no statistically significant difference between the study groups, and this was likely secondary to a high placebo response. This high placebo response is well characterized in studies of antidepressants in adolescents with depression [26, 42]. For example, summary data from published and unpublished clinical trials of antidepressants for children and adolescents demonstrated placebo response rates ranging from 33 to 57% (average, 46%). Conversely the response rates to active medication ranged from 47 to 69% (average, 59%) [43]. In a recent study of a novel antidepressant medication in adolescents with MDD, the placebo response rate was 58.3%, which is greater than the sham response rate in the present study [44]. Prior work underscores that more study sites and lower baseline depressive symptom severity are associated with higher placebo response rates in clinical trials of

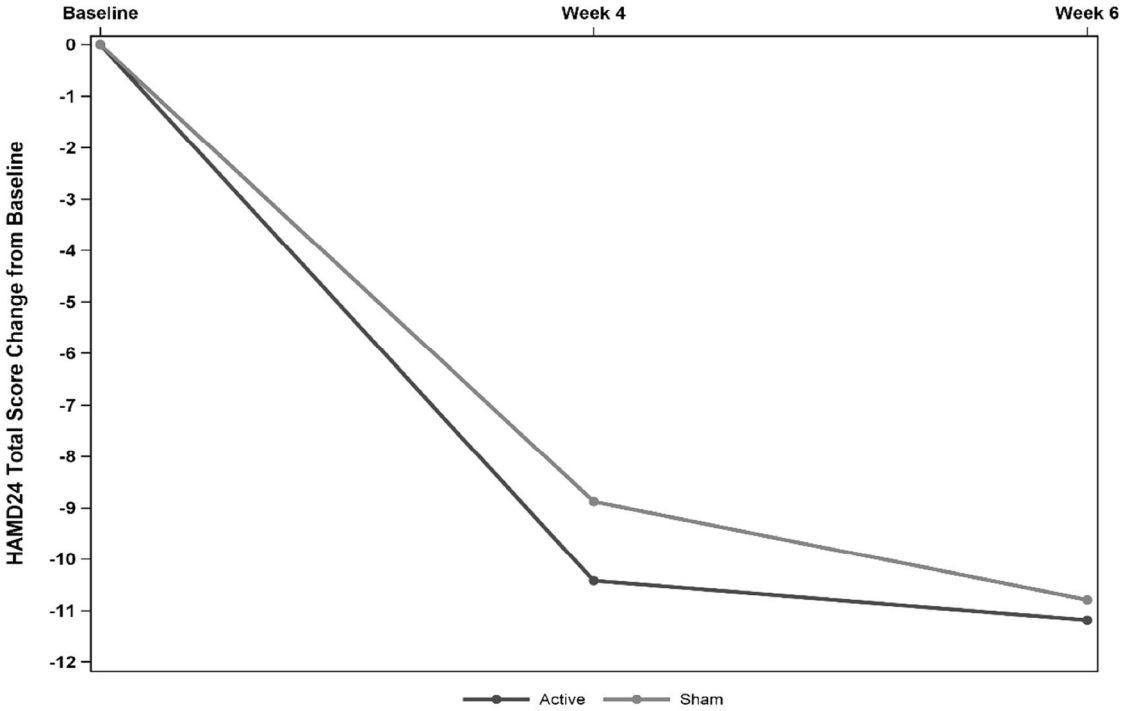

Fig. 2 Primary efficacy outcome. Week 4 and Week 6 primary effiacy outcomes (HAMD24) in depressed adolescents treated with active 10 Hz TMS or sham treatment.

antidepressants for children and adolescents [43]. In the present study, the placebo response rate was likely further enhanced by the technologic aspects of the intervention [21]. Notably, the 36.4% sham response rate in the current study is much larger than what has been observed in most prior studies of TMS in adults with MDD [14, 16]. One exception is a large study of United States Veterans with a different TMS device reporting a sham remission rate of 37.4% highlighting the challenges of studying TMS interventions in populations that are prone to large placebo effects [45]. In the present study the response rate to active TMS was 41.7%, but the true effect of TMS was masked by the large placebo response.

It is important to consider that this sample of adolescent patients with TRD was maintained with monotherapy TMS (active or sham) for a 6-week trial. In clinical practice, the majority of the adolescents in this sample would be treated with 1 or more psychotropic medications and, in many cases, a mixed serotonin-dopamine antagonist [7, 9]. Given the demonstrated favorable adverse-effect profile of TMS compared with mixed serotonin-dopamine antagonists, further study and consideration are warranted, particularly for patients at risk for obesity and metabolic syndrome [10–12, 20]. Otherwise, in some respects TMS appeared to be more tolerable for adolescents than for adults [20, 23]. For example, the rates of site pain (3.7 vs 35.8%) and headache (31.5 vs 58.2%) were lower for the adolescent patients than for adults in prior trials of TMS [14, 16].

Although active TMS (compared with sham TMS) did not show statistically significant benefit in the primary analysis, secondary analysis suggested that TMS provides a clinically meaningful benefit in adolescents with TRD. A larger proportion of adolescents with TRD treated with active TMS (41.7%) compared with sham TMS (36.4%) responded to treatment. When the study sample was stratified by ATR medication resistance level, meaningful benefit was observed on the HAM-D-24 among patients with an ATR level of 2 or more. The observed group difference was −2.2 HAM-D-24 points in this subgroup. The magnitude of this difference is similar to results of landmark TMS studies of adults that culminated in FDA clearance for TMS [16]. As demonstrated in prior work, an increase in the severity of illness and symptoms in adolescents with TRD would be expected to dampen the placebo response in adolescents receiving TMS [43].

Further efforts should use larger sample sizes and innovative designs to reduce the nonspecific effects of TMS in adolescent populations [21]. As with pharmacologic interventions, neurodevelopmental considerations are also often lacking in clinical trials of adolescent depression [26]. For example, few dose-finding studies of adolescents with TRD have compared 1-Hz, 10-Hz, continuous theta burst, intermittent theta burst, and bilateral approaches, but they are critical to advance the study of TMS for youth [21, 46]. Compared with adults, adolescents with TRD may need more pulses or sessions of TMS for an antidepressant effect or a different dosing strategy [21]. Sham lead-in periods or discontinuation trials could be considered to mitigate the nonspecific effects of TMS on depressive symptoms in adolescents. Finally, narrow phenotypes in adolescent depression deserve consideration. Bipolar depression [47, 48], suicidality [49, 50], high levels of medication resistance [51], or neurobiologic constructs in adolescents [52, 53] are considerations for future studies aimed at demonstrating a greater clinical effect. Prior general guidance from antidepressant studies for children and adolescents with depression is also important to consider. As feasible, future studies should limit the number of trial sites. A highly trained and specialized treatment research network focused on TMS studies should also be developed. Training and expertise in clinical screening and rating are critical [43].

Future efforts should also focus on novel means of identifying placebo responders before randomization. One recent effort sought to develop a rating score system to predict the probability of placebo response in adolescents with MDD. A logistic mixed-model analysis identified an equation with optimal discriminatory ability to index the probability of placebo response. This model included age, sex, race, symptom severity, and recurrence of episodes. The positive predictive value of this Adolescent Placebo Impact Composite Score was 74.5% in an adolescent with a score

equal to or less than a specified cut point [44]. Although these findings should be replicated and prospective studies should be performed, this tool is an example of novel approaches to future studies.

Limitations

While this is the first prospective, controlled trial of TMS in adolescent TRD, several limitations warrant additional discussion. First, the sample size was small and the study was underpowered [24, 25]. Second, the sample-size sparing approach to combine data from adolescents with existing data from adults necessitated the adoption of outdated study methodology. For example, the 5-cm rule was used for coil localization, but contemporary work suggests that this may be a suboptimal approach and may not find the best treatment location for all patients. In some patients the 5-cm rule localization approach may lead to stimulation of the pre-motor area rather than the prefrontal cortex [54]. Neuronavigated or scalp-based heuristics may have provided more precision for the daily treatments [17, 54, 55]. This is an area of considerable discussion and ongoing research. The 5-cm rule coil localization was necessary for harmonization of protocol for the present study design. Unfortunately, this may have been a major shortcoming of the study design that compromised the efficacy outcomes. Third, an active sham was not used, and the effect of using a sham with only some similar characteristics is unclear [14]. Fourth, at some study sites, patients watched approved television or listened to music during the TMS sessions, and this could have been a confounding factor as the study protocol did not standardize brain state during treatment sessions [21, 46]. Fifth, this must be considered an uninformative negative study in that it did not include biomarkers or other biological assessments that would help understand exactly why the study was negative. Sixth, despite the rationale for pooling the present adolescent clinical trial data with prior adult studies [14, 16] the weaknesses of this approach must be considered in the interpretation of the present finding and future endeavors with adolescents.

CONCLUSION

Left prefrontal 10-Hz TMS monotherapy in adolescents with TRD is feasible, tolerable, and safe. A statistically significant difference between 6 weeks of sham and active TMS was not observed. Further studies should examine larger samples, consider neurodevelopmental differences, and consider study design advances to dampen the nonspecific effects of sham TMS in adolescents with TRD.

FUNDING AND DISCLOSURE

The study was funded by Neuronetics. Mayo Clinic does not endorse specific products or services included in this article. Dr Croarkin has received research support from the National Institute of Mental Health, Neuronetics, and NeoSync, Inc. He has received material support from and provided consultation to Myriad Genetics. He has consulted for Procter & Gamble Co. Dr Elmaadawi receives research support from Duke University and the University of Northwestern. He receives research funding from Neurocrine, Inc, and Neuronetics. Dr Aaronson has received research support from Compass and Neuronetics and serves as a consultant to LivaNova PLC, Neuronetics, Janssen, Sage Therapeutics, and Genomind, Inc. He serves on speaker boards for Janssen and Sunovion Pharmaceuticals, Inc. Dr Holbert has received material support (equipment) from Neuronetics. He is also a speaker for Neuronetics. Ms Heart is an employee of Neuronetics. Dr Demitrack is a consultant to Neuronetics and a full-time employee of Trevena, Inc. Dr Strawn has received research support from Allergan, Neuronetics, Otsuka Pharmaceutical Co, Ltd, National Institute of Mental Health, National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, and the Yung Family Foundation. He receives royalties from Springer Publishing Co and has received honoraria from CMEology and Neuroscience Education Institute. He receives royalties from UpToDate. He has received material support from and provided consultation to Myriad Genetics. The other authors have no disclosures. The authors declare no competing interests.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the participating clinical trial sites and investigative teams: Dothan Behavioral Medicine, Dothan, Alabama; University of California, Los Angeles, Los Angeles, California; Stanford University, Palo Alto, California; Rocky Mountain TMS, Grand Junction, Colorado; Florida Clinical Practice Association, Inc, Gainesville, Florida; Anchor Neuroscience, Pensacola, Florida; Beacon Medical Group, South Bend, Indiana; Integrative Psychiatry, Louisville, Kentucky; Sheppard Pratt Health System, Baltimore, Maryland; Mayo Clinic, Rochester, Minnesota; University of Cincinnati College of Medicine, Cincinnati, Ohio; The Ohio State University, Columbus, Ohio; and Medical University of South Carolina, Charleston, South Carolina.

AUTHOR CONTRIBUTIONS

P.E.C.: conceptualization, investigation, data curation, data analysis, writing (original draft, review, and editing), and project administration. A.Z.E.: investigation, data curation, data analysis, writing (review and editing), and project administration. S.T.A.: investigation, data curation, data analysis, writing (review and editing), and project administration. G.R.S. Jr.: investigation, data curation, data analysis, and writing (review and editing). R.C.H.: investigation, data curation, data analysis, writing (review and editing), and project administration. S.V.: conceptualization, data analysis, writing (review and editing), and project administration. K.L.H.: conceptualization, investigation, data analysis, writing (review and editing), and project administration. M.A.D.: conceptualization, investigation, data analysis, writing (review and editing), and project administration. J.R.S.: investigation, data curation, data analysis, writing (original draft, review, and editing), and project administration.

ADDITIONAL INFORMATION

Supplementary Information accompanies this paper at (https://doi.org/10.1038/s41386-020-00829-y).

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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