Adjunctive Use of Repetitive Transcranial Magnetic Stimulation in Depressed Adolescents: A Prospective, Open Pilot Study

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ABSTRACT

Objective: Depression is often a serious and debilitating illness in adolescents. Unfortunately, a significant number of adolescents do not respond to antidepressant medications or psychotherapy. Repetitive transcranial magnetic stimulation (rTMS) is a novel treatment intervention shown to benefit depression in adults. This study considered rTMS as an adjunctive treatment in adolescents with major depressive disorder.

Method: This prospective, open, multicenter trial of active adjunctive rTMS was conducted with 8 adolescents with *DSM-IV-TR* major depressive disorder (MDD) that had not responded sufficiently to 2 adequate antidepressant medication trials. All subjects were maintained on a stable dose of a selective serotonin reuptake inhibitor during the trial. Thirty daily rTMS treatments were given 5 days per week over 6 to 8 weeks. rTMS was applied to the left dorsolateral prefrontal cortex (120% of motor threshold; 10 Hz; 4-second trains; 26-second intertrain interval; 75 trains) for a total of 3,000 stimulations per treatment session.

Results: Seven of 8 adolescents completed all 30 treatments. rTMS was well tolerated, and no significant safety issues were identified. Suicidal ideation was present at baseline in 3 of the adolescents, and it improved during treatment. The primary outcome measure was the Children's Depression Rating Scale-Revised (CDRS-R); results improved significantly from baseline (mean [SD]) (65.9 [6.6]) to treatment 10 (50.9 [12]), $P < .02$. The CDRS-R scores continued to improve through the rTMS treatment series at treatment 20 (40.1 [14]), $P < .01$; treatment 30 (32.6 [7.3]), $P < .0001$; and at 6-month follow-up (32.7 [3.8]), $P < .0001$.

Conclusions: This prospective open trial suggests that rTMS is a safe, feasible, and potentially effective adjunctive therapy for treatment-resistant MDD in adolescents.

Trial Registration: clinicaltrials.gov Identifier: NCT00587639

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A large percentage of adolescents suffering from major depressive disorder (MDD) do not adequately benefit from currently available medications, psychotherapy, and/or social support treatments. In fact, it is estimated that current treatment approaches, considered separately, fail to provide adequate clinical improvement in 40% of adolescents with MDD. Moreover, these treatment approaches produce complete remission in only 30% of adolescent patients.[1–4] Unfortunately, adolescents with persistent symptoms of depression are more likely to experience inpatient psychiatric hospitalization, psychosocial maladjustment, and suicidality.[5] Consequently, they are more likely to receive additional psychopharmacologic agents that generally offer little additional benefit and increase the risk of adverse effects.

Repetitive transcranial magnetic stimulation (rTMS) is a novel therapy that was cleared by the United States Food and Drug Administration in the autumn of 2008 for the treatment of MDD in adults who fail to achieve satisfactory improvement from 1 prior adequate antidepressant trial. The current literature describes a total of approximately 1,300 adult subjects safely treated with rTMS. Two recent sham-controlled, randomized clinical trials (combined sample of about 500 patients) using the same device and treatment parameters demonstrated the safety and efficacy of rTMS monotherapy applied to the left dorsolateral prefrontal cortex (L-DLPFC) in depressed adults.[6,7] By contrast, rTMS has been applied to a much smaller number of adolescent depressed patients in 3 separate studies using varying clinical characteristics, devices, and stimulus dosing.[8–10] These studies demonstrated significant improvement in 7 of 10 patients with no evidence of significant treatment-related adverse events beyond scalp discomfort and mild headaches.[11] In recent years, rTMS treatment parameters have changed with regard to increased numbers of stimulations per session and the percentage of motor threshold at which the stimulations are applied.

The goal of this study was to evaluate the safety and efficacy of rTMS as an adjunctive therapy in a prospective, open, multicenter pilot study in adolescents with MDD that had not responded sufficiently to 2 adequate antidepressant medication trials. Because rTMS treatment parameters have increased, we used the optimized rTMS stimulus dosing recently reported in the 2 large studies on adults.[6,7] Thus, our study utilized the highest feasible dose consistent with the present safety guidelines.[6,12–14]

METHOD

Subjects

Participants were diagnostically assessed by a board-certified child and adolescent psychiatrist. This included a comprehensive clinical evaluation and standardized diagnostic interview and utilized the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL).[15] Eight adolescents (1 male and 7 females; ages 14.6 to 17.8 years, mean age 16.5 years) were recruited over a 1-year period and enrolled from clinic and community referrals (clinicaltrials.gov Identifier: NCT00587639). At the time of enrollment, all participants were

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Clinical Points

- Previous trials of repetitive transcranial magnetic stimulation (rTMS) in depressed adolescents utilized less robust treatment dosing parameters than this study.
- rTMS treatment dosing consistent with adult protocols was found to be safe, feasible, and effective in this group of adolescents.
- Treatment benefits of rTMS in adolescents appeared durable at 6-month follow-up.

receiving active treatment for an MDD episode according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*).[16] Clinically significant depressive symptoms were defined by a Children's Depression Rating Scale-Revised (CDRS-R)[17] total score of at least 40 (t score > 63). Participants included those with treatment failure/nonresponse to 2 adequate antidepressant trials (ie, treated with stable selective serotonin reuptake inhibitor [SSRI] dose regimen for at least 6 weeks as defined by the Antidepressant Treatment History Form).[18] Participants in psychotherapy were ineligible if they had changed therapists, type of psychotherapy, or providers in the 4 weeks prior to rTMS initiation. All participants continued treatment with a stable dose of an SSRI during the rTMS course. Participants also continued previously prescribed sleep aids during treatment. Stimulants, antipsychotics, mood stabilizers, and non-SSRI antidepressants were not permitted during the active treatment phase.

Patients with comorbid secondary diagnoses of dysthymia, attention-deficit/hyperactivity disorder, or anxiety disorders were eligible for enrollment. However, patients with schizophrenia, schizoaffective disorder, bipolar spectrum disorders, substance abuse or dependence, somatoform disorders, dissociative disorders, posttraumatic stress disorder, obsessive-compulsive disorder, eating disorders, mental retardation, or pervasive developmental disorder/autism spectrum disorders were excluded from participation. Medical exclusions included preexisting seizure disorders or active neurologic conditions (eg, brain tumor, dyskinesias, or paralysis). The screening process included a urine toxicology screen for drugs of abuse and a urine pregnancy test. All participants and treaters wore ear plugs during the sessions to minimize the risk of auditory threshold changes.

Study Overview

This trial was a prospective, open, multicenter pilot trial of active rTMS in adolescents with MDD confirmed with the K-SADS-PL at 3 participating sites including Mayo Clinic, Rochester, Minnesota; University of Texas Southwestern Medical Center, Dallas; and Rush University Medical Center, Chicago, Illinois. Each site's local institutional review board approved this study. All patients provided written informed assent, and parents provided written informed consent per institutional review board–approved guidelines. Recruitment, outcomes, and potential adverse effects were monitored by a Data and Safety Monitoring Board comprising nonstudy clinicians from each of the participating sites.

rTMS Procedures

Identification of the treatment site and stimulus dosing were based on previously defined techniques and guidelines used in the previously noted adult rTMS trials.[6,7] These included identification of the motor cortex via a single pulse every 3 to 5 seconds that produced a localized contraction of the contralateral abductor pollicis brevis muscle. Once this site was defined, the resting motor threshold (MT) was determined using a computer-assisted maximum likelihood threshold-hunting algorithm (MT Assist, Neuronetics Inc, Malvern, Pennsylvania) with a single pulse every 10 seconds. This algorithm calculates the MT based on observed visible movement of the abductor pollicis brevis. After each algorithm-defined stimulus dose, the program asked the observer whether the stimulation produced visible finger movement. Responses of *yes* or *no* were recorded, and the program indicated the next stimulus setting on the computer. Through the recording of stimulus/response observations, the MT was determined by "capturing" the minimal stimulus that provided an observable movement through the superthreshold stimuli (produced observable movement) and subthreshold stimuli (no observable movement). At the end (between 15 and 20 pulse trials), the program defined the MT. Repeat MT determinations occurred once every 10 treatments to assess for possible changes that could produce safety issues due to changes in cortical excitability. This approach has been successfully used in previous clinical trials.

The L-DLPFC treatment location was determined by movement of the transcranial magnetic stimulation coil 5 cm anterior to the MT location along a left superior oblique plane.[19] Spatial coordinates were recorded with a mechanical coil positioning system to ensure placement reproducibility.

Treatments consisted of 30 treatments given 5 days per week within a range of 6–8 weeks. The 6–8 week range was chosen for potential variation in patient schedules related to school and family events. Thus, each patient was offered a total of 40 treatment opportunities to complete 30 treatments. Each treatment was fixed at 120% of calculated MT, at a frequency of 10 Hz, with stimulus train duration of 4 seconds and an intertrain interval of 26 seconds, for a total of 3,000 stimulations per treatment session. rTMS was delivered using the Neuronetics Model 2100 Therapy System investigational device (Neuronetics, Inc, Malvern, Pennsylvania).

Safety Assessments

Neurocognitive testing was administered by trained psychometrists at baseline, on completion of the active rTMS treatments, and at a 6-month follow-up assessment. Analysis of the results was completed by a doctorate-level child psychologist. Neurocognitive measures included the following: The Children's Auditory Verbal Learning

Table 1. Demographic and Clinical Characteristics of Adolescents (N = 8) With Major Depressive Disorder at Enrollment

Identification	Age at First Treatment, y	Sex	Duration of MDE at Start of Treatment, mo	Severity of Current Depressive Episode (CGI-S score)	Medication	
					Failed (ATHF rating)[a]	Active (ATHF rating)[a,b]
Subject 1	17.3	Female	8	4 (moderately ill)	citalopram (3) escitalopram (3)	fluoxetine (5)
Subject 2	17.4	Male	36	4 (moderately ill)	fluoxetine (3)	citalopram (5)
Subject 3	15.5	Female	25	4 (moderately ill)	fluoxetine (4) venlafaxine (4) bupropion (2)	escitalopram (4)
Subject 4	17.7	Female	8	5 (markedly ill)	fluoxetine (4)	citalopram (5)
Subject 5	16.1	Female	5	4 (moderately ill)	bupropion (5)	sertraline (5)
Subject 6	17.8	Female	4	5 (markedly ill)	fluoxetine (5) amitriptyline (2)	escitalopram (5)
Subject 7	14.6	Female	50	5 (markedly ill)	citalopram (3) fluoxetine (4)	sertraline (4)
Subject 8	15.9	Female	27	6 (severely ill)	fluoxetine (4) bupropion (4) paroxetine (3)	sertraline (2)
Mean	16.5	NA	20.4	4.6	2.5	

[a]An ATHF Rating ≥ 3 is considered an adequate trial.
[b]Remained active during treatment course.
Abbreviations: ATHF = Antidepressant Treatment History Form, CGI-S = Clinical Global Impressions-Severity of Illness scale, MDE = major depressive episode, NA = not applicable.

Test-Second Edition,[20] which is a word list that examined auditory verbal learning and memory; the Autobiographical Memory Interview,[21] which sampled the participants' recollections across 3 broad time periods; and the Delis-Kaplan Executive Function System,[22] which measured higher-level cognitive functions in children and adults. In this study, this measure assessed flexibility of thinking and verbal fluency. Auditory threshold testing used the Earscan Audiometer device from Micro Audiometrics Corporation (Murphy, North Carolina) and occurred at baseline, on completion of the active rTMS treatment course, and at 6-month follow-up. Safety and participant comfort were assessed and recorded before and after each study visit with prompted opportunities to report adverse events.

Clinical Assessments

Subjects were evaluated at screening, baseline, every other week during treatment, and at treatment end with the following measures: (1) the CDRS-R[17] is a validated, 17-item, semistructured clinician rating tool to assess severity of depression, with parents providing input into 14 of the items; (2) the Quick Inventory of Depressive Symptoms-Adolescent version (QIDS-A17)[23] is a 17-item, self-report instrument; (3) the Clinical Global Impressions-Severity of Illness (CGI-S) and the Clinical Global Impressions-Improvement (CGI-I)[24] scales are standardized assessments that rate illness severity and change over time; (4) the Suicide Severity Rating Scale[25] is a semistructured instrument that elicits information about recent suicidal behavior, attempts, and ideation, the potential method employed, medical lethality, precipitants, and surrounding circumstances; (5) a Subjective Reaction Questionnaire (completed by all patients and guardians) assesses patients' experience with the rTMS process; and (6) an Adverse Event Monitoring Form documents the specifics regarding potential adverse events, severity, and relationship to the study.

Statistical Analysis

Measurements were presented as mean change with standard deviation (± SD) from baseline. Analyses were conducted to assess change in scores between endpoints compared with the baseline using the Wilcoxon signed rank test. Data analysis was generated using SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

The primary aim of this study was to assess whether adjunctive rTMS is a safe and feasible treatment approach in adolescents. This question was evaluated by neurocognitive and auditory assessments that occurred at baseline, immediately following treatment 30, and again 6 months posttreatment. These results were analyzed using comparative statistics from baseline to each subsequent treatment as individuals and as a group.

Feasibility was determined by patient and family self-reports as well as by adherence to the protocol treatment guidelines of 30 treatments within 40 treatment opportunities. Tolerability assessments occurred daily—before and after each treatment session—using a pretreatment and posttreatment form on which any potential changes in medication/pain/discomfort status were recorded. A subjective reaction questionnaire was provided to each adolescent on completion of the final treatment.

A secondary aim of this study was to evaluate whether rTMS reduced symptoms of depression measured by 4 clinical scales (ie, the CDRS-R, QIDS-A17, CGI-S, and CGI-I). Suicidality was serially assessed using the Suicide Status Rating Scale-Short Form.

RESULTS

A total of 8 adolescents (1 male, 7 females; mean age = 16.5 years; range, 14.6 to 17.8 years) enrolled in the study. Demographic and clinical details are listed in Table 1. All participants met diagnostic criteria for MDD (mean episode

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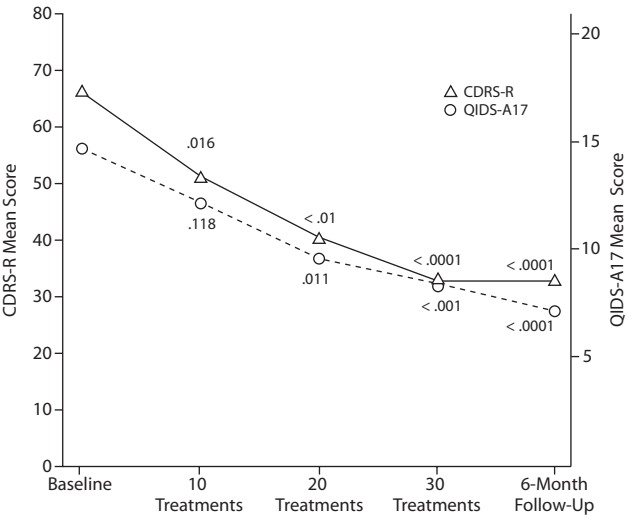
Table 2. CDRS-R vs QIDS-A17 Depression Severity Scale Comparison

Illness Category	CDRS-R	QIDS-A17
Not depressed	< 20	0–5
Borderline depressive symptoms	20–29	Not a category
Mild depression	30–39	6–10
Moderate depression	40–59	11–15
Severe depression	≥ 60	16–20
Very severe depression	Not a category	> 21

Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised, QIDS-A17 = Quick Inventory of Depressive Symptomatology-Adolescent Version.

Figure 1. Mean CDRS-R and QIDS-A17 Scores of Adolescents (n = 7) With MDD During Adjunctive rTMS Treatment and at 6-Month Follow-Up



Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised, MDD = major depressive disorder, QIDS-A17 = Quick Inventory of Depressive Symptomatology-Adolescent Version, rTMS = repetitive transcranial magnetic stimulation.

duration = 20.4 months; range, 4 to 50 months). Seven of the 8 adolescents completed the treatment series within the protocol parameters. One adolescent (subject 8) discontinued treatment after a total of 10 trains (ie, 5 minutes of treatment) due to scalp discomfort. Therefore, the data analysis and outcomes are reported on the 7 participants who completed the study. Adverse events are reported for all 8 patients enrolled in the study. During the study, none of the adolescents experienced serious or significant treatment-related adverse events (eg, seizures or suicide attempts). The most commonly reported adverse event was temporary scalp discomfort, which occurred in 3 of 8 participants.

Given concerns related to the possibility of headaches and scalp discomfort with rTMS, we monitored these reactions with a visual analog scale after each treatment. No worsening of headaches was reported. An unexpected finding of decreased headache frequency and intensity was noted as the treatment course progressed.

Six of 7 participants completed neuropsychological testing at all 3 time points. One patient did not receive 6-month follow-up testing due to loss of psychometric support at the study site. Cognitive testing performed at baseline, treatment conclusion, and at 6-month follow-up showed no statistically significant decline in measures of immediate memory, level of learning, immediate recall, delayed recall, and auditory/verbal fluency. A trend was noted in the baseline to posttreatment Autobiographical Memory Interview[21] results showing a decrease in scores at treatment completion and at 6-month follow-up driven by 2 subjects. No clinical concerns regarding cognitive functioning were raised by participants or their family members. All participants completed auditory threshold assessments at the 3 time points with no evidence of significant threshold shifts in any subject at any time point compared with baseline.

With regard to suicidal ideation and behaviors, there was no evidence of worsening suicidal ideation or behaviors in this group of adolescents. However, 3 adolescents reported suicidal ideation ratings at baseline (ie, 2 indicated nonspecific suicidal thoughts and 1 described suicidality as a passive death wish). Expressions of suicidal ideation decreased as treatment progressed, commensurate with mood improvement. At treatment completion, only 1 adolescent rated any suicidal ideation as a passive death wish (previously nonspecific suicidal thoughts), and at 6-month completion that same adolescent described self-cutting behavior following the break-up of a significant relationship that occurred 20 weeks after acute treatment. One adolescent was psychiatrically hospitalized 5 weeks after treatment concluded and immediately following the death of a "best friend" via a tragic motor vehicle accident. This hospitalization was reported to the institutional review board and was deemed unrelated to the rTMS treatments. At 6-month completion, this participant denied any suicidal ideations or behaviors. During this study, there was no evidence of exacerbated suicidal ideation or behavior, individually or as a group.

Of the 7 adolescents completing the protocol, all patients and their family members stated that, if prescribed, they would again utilize rTMS to treat their depression. On the Subjective Reaction Questionnaire, all participants rated the experience of rTMS as better than the experience of depression and stated that the treatments were "not frightening." Adolescents and their parents (total of 14 respondents) assessed the rTMS experience as follows: rTMS rated as preferable to medications by 12 of 14 (86%), whereas 2 of 14 (14%) rated rTMS as equal to medications; 12 of 14 (86%) rated rTMS as preferable to psychotherapy, while 1 (7%) rated it equal to psychotherapy, and 1 participant (7%) stated that psychotherapy was better than rTMS. The main complaints about the treatment experience included having an "uncomfortable seat," "boredom," and "issues with parking."

Mean baseline score on the CDRS-R was 65.9 (SD = 6.6), indicating severe depression, whereas the baseline QIDS-A17 mean score of 14.7 was just below the cutoff for severe depression (Table 2 presents a comparison of depression

Table 3. CDRS-R and QIDS-A17 Ratings of Adolescents (n = 7) With MDD During Adjunctive rTMS Treatment and at 6-Month Follow-Up

Identification	Depression Rating	Baseline	Treatment 10	Treatment 20	Treatment 30	6-Month Follow-Up
Subject 1	CDRS-R	58	29	27	21	28
	QIDS-A17	11	4	5	4	6
Subject 2	CDRS-R	67	35	24	25	28
	QIDS-A17	15	8	4	5	7
Subject 3	CDRS-R	75	57	41	36	42
	QIDS-A17	15	13	10	11	10
Subject 4	CDRS-R	71	61	40	41	40
	QIDS-A17	18	16	12	11	8
Subject 5	CDRS-R	61	52	53	33	30
	QIDS-A17	13	15	12	7	5
Subject 6	CDRS-R	70	71	42	34	32
	QIDS-A17	15	17	8	6	5
Subject 7	CDRS-R	59	51	54	38	29
	QIDS-A17	16	12	16	14	9
Mean	CDRS-R	65.9	50.9	40.1	32.6	32.7
	QIDS-A17	14.7	12.1	9.6	8.3	7.1
Mean ± SD change from baseline	CDRS-R	NA	15.0 ± 12	25.7 ± 14	33.3 ± 7.3	33.1 ± 3.8
	QIDS-A17	NA	2.6 ± 3.7	5.1 ± 3.7	6.4 ± 2.8	7.6 ± 2.1
P Value	CDRS-R	N/A	.016	< .01	< .0001	< .0001
	QIDS-A17	N/A	.118	.011	< .001	< .0001

Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised, MDD = major depressive disorder, NA = not applicable, QIDS-A17 = Quick Inventory of Depressive Symptomatology-Adolescent Version, rTMS = repetitive transcranial magnetic stimulation.

Table 4. Clinical Global Impressions-Severity of Illness[a] Ratings of Adolescents (n = 7) With MDD During Adjunctive rTMS Treatment and at 6-Month Follow-Up

Identification	Baseline	Treatment 10	Treatment 20	Treatment 30	Follow-Up
Subject 1	4	2	2	1	2
Subject 2	4	3	2	1	1
Subject 3	4	4	4	3	3
Subject 4	5	5	3	3	2
Subject 5	4	3	3	1	1
Subject 6	5	6	2	2	1
Subject 7	5	5	5	4	2
Mean	4.4	4.0	3.0	2.1	1.7
Mean ± SD change from baseline	NA	0.4 ± 1.0	1.4 ± 1.1	2.3 ± 1.0	2.7 ± 1.0
P Value	NA	.2894	.016	< .001	< .001

[a]CGI-S ratings: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, MDD = major depressive disorder, NA = not applicable, rTMS = repetitive transcranial magnetic stimulation.

severity scores on these scales). Total scores on the CDRS-R, QIDS-A17, and CGI-S were significantly improved for all clinical measures from baseline to treatment 20, treatment 30, and at 6-month follow-up (Figure 1). The CDRS-R scores improved significantly at treatment 10 (mean = 50.9, SD = 12, $P < .02$), treatment 20 (mean = 40.1, SD = 14, $P < .003$), treatment 30 (mean = 32.6, SD = 7.3, $P < .0001$), and at 6-month follow-up (mean = 32.7, SD = 3.8, $P < .0001$). Improvement from baseline in the self-reported QIDS-A17 became significant at treatment 20 (mean = 9.6, SD = 3.7, $P < .0106$) and remained significant at treatment 30 (mean = 8.3, SD = 2.8, $P < .001$), and at 6-month follow-up (mean = 7.1, SD = 2.1, $P < .0001$; combined CDRS-R and QIDS-A17 results are detailed in Table 3). Clinician ratings of illness severity and improvement showed significant improvement as a group and individually. At baseline, the mean CGI-S score was 4.4, indicating moderate to marked depression. Significant improvement was noted at treatment 20 (mean = 3.0, SD = 1.1, $P < .016$), treatment 30 (mean = 2.1, SD = 1 $P < .001$), and at 6-month follow-up (mean = 1.7, SD = 1.0, $P < .001$) (Table 4). On completion of treatment 30, the CGI-S ratings of 6 of 7 adolescents were 3, mildly ill (n = 2); 2, borderline mentally ill (n = 1); or 1, normal, not at all ill (n = 3). At 6-month follow-up, improvement persisted with ratings of 3, mildly ill (n = 2); 2, borderline mentally ill (n = 2); or 1, normal, not at all ill (n = 3). CGI-I scores were 2 (much improved) or 3 (very much improved) in 5 of 7 participants.

DISCUSSION

The findings of this prospective, open, multicenter trial of high frequency (10 Hz) rTMS provide promising pilot data regarding the safety, feasibility, and clinical effects in adolescents with MDD that has not adequately responded to SSRI treatment. These preliminary results also suggest that rTMS has an at least adjunctive role to pharmacotherapeutic interventions in challenging-to-treat depression in the adolescent population. This study safely utilized more aggressive treatment dosing parameters, consistent with the previously mentioned adult studies,[6,7] and provided a much larger number of rTMS sessions compared with previous adolescent trials.[8–10] Participants demonstrated a statistically significant and enduring improvement in mood that correlated with clinical and family ratings.

These data suggest that rTMS can be safely administered to adolescents without auditory threshold shifting or cognitive difficulties. Despite requiring participants to present more than 30 times for study-related assessments and treatments, 7 of 8 adolescents completed the entire treatment course. This finding suggests that rTMS is a feasible treatment modality in this patient population. The treatment was also reportedly well-tolerated, as evidenced by 86% of participants' and parents' preferring rTMS to medication.

Limitations of the study include its open design, small number of total participants (female:male ratio 7:1), and the "5-cm rule" to locate the L-DLPFC. With respect to

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the latter, it remains unclear how to optimally localize the treatment site. With regard to recruitment challenges, the low number of enrolled adolescents over a 1-year period of recruitment was very likely due to a combination of strict inclusion/exclusion criteria, limited advertising, and the inherent reluctance of adolescents and their families to commit to a new neuromodulation technique that required more than 30 study visits. Therefore, these results must be considered preliminary and in the context of clear methodological limitations.

Given the high rate of placebo response in adolescent depression trials, the data from this group of participants must be interpreted cautiously. It is encouraging, however, that the majority of this sample tolerated rTMS treatment parameters consistent with recent large trials in adults.[6,7,13] Further controlled and pragmatic trials of rTMS for depressed adolescents are essential, given our current limited treatment options. Early intervention with brain stimulation approaches such as rTMS could represent a noninvasive, durable treatment option that could alter the developmental course of pathological neurocircuitry.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Potential conflicts of interest: **Dr Croarkin** has received grant/research support from the National Alliance for Research on Schizophrenia and Depression (NARSAD). **Dr Husain** has received grant/research support from the National Institutes of Health/the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse, the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, NARSAD, the Stanley Foundation, Cyberonics, Neuronetics (past), St Jude Medical (Advanced Neuromodulation Systems), Magstim (equipment only), and Brainsway. **Dr Janicak** has been a consultant for Bristol-Myers Squibb, Neuronetics, and Sunovion; has received grant/research support from Otsuka, Neuronetics, and Sunovion; and has served on speakers/advisory boards for Bristol-Myers Squibb/Otsuka, AstraZeneca, Neuronetics, and Novartis. **Dr Kozel** has been an unpaid scientific consultant to Cephos Corporation; currently receives research and/or salary support from the Department of Defense and the NIMH; has patents pending as an inventor through the Medical University of South Carolina; and leads a monthly case discussion group sponsored by AstraZeneca. **Dr Emslie** has received grant/research support from the NIMH, Eli Lilly, Forest, GlaxoSmithKline, and Somerset; has been a consultant to Biobehavioral Diagnostics, Eli Lilly, GlaxoSmithKline, INC Research, Lundbeck, Pfizer, Seaside, and Wyeth; and has served on the speakers/advisory board for Forest. **Dr Dowd** has received grant/research support from Neuronetics, Otsuka, and Sunovion. **Drs Wall, Sim**, and **Sampson** have no potential conflicts to declare.

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Previous presentations: This work has been presented as a poster at the 21st Annual Meeting of the Society of Biological Psychiatry; May 20–22, 2010, New Orleans, Louisiana; and in an invited lecture for the 2010 Annual Meeting of the International Society for ECT and Neurostimulation; May 23, 2010, New Orleans, Louisiana.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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