ORIGINAL ARTICLE

Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder

A Sham-Controlled Randomized Trial

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Context: Daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) has been studied as a potential treatment for depression, but previous work had mixed outcomes and did not adequately mask sham conditions.

Objective: To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder.

Design: Prospective, multisite, randomized, active sham-controlled (1:1 randomization), duration-adaptive design with 3 weeks of daily weekday treatment (fixed-dose phase) followed by continued blinded treatment for up to another 3 weeks in improvers.

Setting: Four US university hospital clinics.

Patients: Approximately 860 outpatients were screened, yielding 199 antidepressant drug–free patients with unipolar nonpsychotic major depressive disorder.

Intervention: We delivered rTMS to the left prefrontal cortex at 120% motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 minutes (3000 pulses per session) using a figure-eight solid-core coil. Sham rTMS used a similar coil with a metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations.

Main Outcome Measure: In the intention-to-treat sample (n=190), remission rates were compared for the 2 treatment arms using logistic regression and controlling for site, treatment resistance, age, and duration of the current depressive episode.

Results: Patients, treaters, and raters were effectively masked. Minimal adverse effects did not differ by treatment arm, with an 88% retention rate (90% sham and 86% active). Primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters (14.1% active rTMS and 5.1% sham) ($P=.02$). The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% confidence interval, 1.32-13.24). The number needed to treat was 12. Most remitters had low antidepressant treatment resistance. Almost 30% of patients remitted in the open-label follow-up (30.2% originally active and 29.6% sham).

Conclusion: Daily left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham.

Trial Registration: clinicaltrials.gov Identifier: NCT00149838

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MORE EFFECTIVE TREATments are needed for major depressive disorder (MDD), which is common, disabling, and costly.[1-4] After acute-phase pharmacotherapy, psychotherapy, or both, most depressed patients either do not improve or achieve only partial symptomatic improvement.[5-9] In addition to efficacy and durability concerns, pharmacologic and other somatic treatments often have treatment-limiting adverse effects (eg, sexual dysfunction).[10-17] Nonetheless, across all of medicine, antidepressants are the most commonly prescribed class of medications.[18]

Transcranial magnetic stimulation (TMS) is a brain intervention that modulates activity in discrete cortical regions and associated neural circuits by noninvasively inducing intracerebral currents.[19,20] Repetitive TMS (rTMS) refers to TMS applied repeatedly during a session.[21-23] Transcranial magnetic stimulation can map brain function and connectivity,[24-31] can probe cortical excitability,[32-38] and is a unique research tool to address key questions about brain-behavior relationships. However, this study focused on its therapeutic potential for unipolar MDD, a domain that has been the subject of numerous single-site, small-sample studies and 2 recent multisite studies.[39,40] Most reviewers have concluded that

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Antidepressant medication–free outpatients	Other current Axis I disorders (except simple phobia and nicotine addiction)
Aged 18-70 y	Past failure to respond to an adequate trial of electroconvulsive therapy
DSM-IV diagnosis of major depressive disorder, single episode or recurrent	Previous treatment with TMS or VNS
Current episode duration ≤5 y	Personal or close family history of seizure disorder
Hamilton Scale for Depression 24-item score ≥20	Neurologic disorder
Stable during a 2-wk medication-free lead-in period	Ferromagnetic material in body or close to head
Moderate level of treatment resistance as defined by the ATHF; insufficient clinical benefit to 1-4 adequate medication trials or intolerant to ≥3 trials	Pregnancy
	Taking medications known to lower seizure threshold (eg, theophylline)

Abbreviations: ATHF, Antidepressant Treatment History Form; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

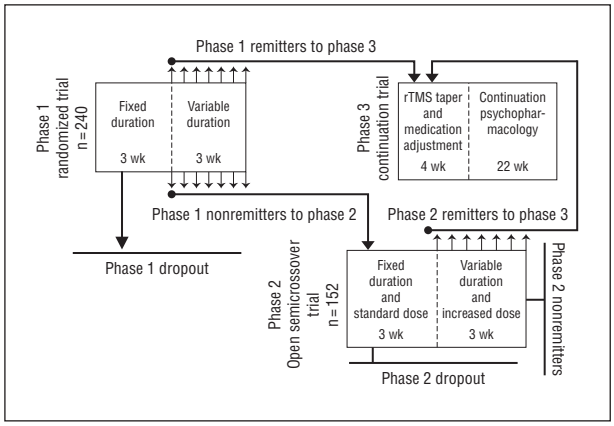

Figure 1. Overall design of the National Institute of Mental Health–sponsored Optimization of TMS [Transcranial Magnetic Stimulation] for the Treatment of Depression Study (OPT-TMS). This report describes the main safety of the randomized acute phase 1. Patients were randomized 1:1 to either active or sham repetitive transcranial magnetic stimulation (rTMS). During the 3-week fixed-treatment phase, rTMS sessions were scheduled daily in a 5-day sequence, typically Monday through Friday, for a total of 15 sessions. Each treatment lasted about 50 minutes, including 40 minutes of actual delivery of rTMS or the sham treatment. A certified, masked clinical rater who was not involved in giving TMS assessed patients weekly.

daily left prefrontal rTMS has antidepressant properties, with most meta-analyses indicating a large effect size for symptom change compared with sham treatment.[41-44] However, there is controversy about the quality of the extant research,[45] including questions about the validity of the sham-control interventions[46,47] and concern that the antidepressant effects of rTMS are not sufficiently robust to be "clinically meaningful."[48] Many of the early TMS trials[49-51] used small doses (number of stimuli per day) and administered treatment for only 2 weeks. Based primarily on 1 industry-sponsored trial in antidepressant medication–free adults,[40] the US Food and Drug Administration recently approved rTMS as a treatment for unipolar MDD in adults who have not responded to a single antidepressant medication in the current episode.

We designed this National Institutes of Health–sponsored study to (1) optimize rTMS treatment parameters to maximize the likelihood of robust antidepressant effects, (2) address key methodological limitations (eg, adequacy of masking, validity of sham treatment, and reliability of outcomes evaluation), and (3) demonstrate consistency across research sites. Specifically, we used intense rTMS treatment, including high-intensity stimulation (120% motor threshold [MT]), a high number of pulses (3000 stimuli per session), magnetic resonance imaging (MRI) adjustment for proper scalp placement,[52] and provision for extended treatment in patients showing clinical improvement using a duration-adaptive design.[53-56] Other methodological improvements included use of an active sham condition that mimicked the somatosensory experience of rTMS,[57,58] masking of rTMS administrators and patients to the acoustic signals produced by stimulation, requiring all outcome evaluators to undergo a competency certification process, continuous assessment of outcome evaluator reliability compared with a masked expert external rater, and constant assessment of potential unmasking.

METHODS

PATIENTS

Patients were recruited via public media advertisements and physician referrals. Investigators telephone-screened potential participants, and those meeting the inclusion and exclusion criteria had additional on-site screening (**Table 1**).[59] All the patients underwent baseline laboratory studies, including urine toxicology screening and electrocardiography. Individuals positive for cocaine, marijuana, PCP (phencyclidine), or opiates were excluded.

STUDY OVERVIEW

This study was conducted at 4 sites in the United States (Medical University of South Carolina [MUSC], Columbia University/New York State Psychiatric Institute, University of Washington, and Emory University), with active enrollment extending from October 15, 2004, through March 31, 2009. The institutional review board at each center approved the protocol, and all the participants provided written informed consent. An independent data and safety monitoring board reviewed participant safety and study progress. Data were processed, managed, and organized by the MUSC data coordination unit, with primary analyses conducted by independent statisticians (M.P. and T.S.) at Columbia University and cross-checked by the MUSC data coordination unit.

The study design is depicted in **Figure 1**. We report herein the main results of phase 1, the randomized, masked, acute trial, which used a duration-adaptive design.[53] There was a 2-week no-treatment lead-in phase, a 3-week fixed-treatment phase, and a variable 3-week extension for clinical improvers. Randomization to active and sham conditions was based on randomized permuted blocks stratified by site and higher or lower treatment resistance. Patients who did not show sufficient improvement at the end of the fixed 3-week period (defined as a <30% drop from baseline in Hamilton Scale for Depression [HAM-D] score) were discontinued from phase 1 and crossed over to open treatment (phase 2) without unmasking their original randomized assignment. If patients improved sufficiently (ie, ≥30% reduction in HAM-D score), treatment was contin-

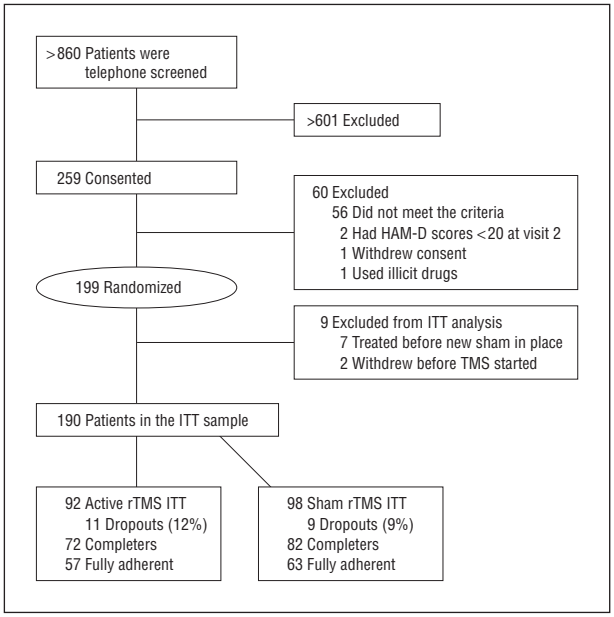

Figure 2. Enrollment flow. Patients were referred from local psychiatrists or responded to media advertisements and were telephone screened. Those meeting the broad inclusion and exclusion criteria were asked to come for an in-person screening. Some sites required full informed consent for all patients invited for an in-person visit, whereas other sites had patients sign a blanket screening consent, followed by a specific treatment consent only if they met all the study criteria. HAM-D indicates Hamilton Scale for Depression; ITT, intention to treat; and rTMS, repetitive transcranial magnetic stimulation.

ued for up to 3 additional weeks, with HAM-D assessments performed twice weekly. Improvers but nonremitters continued receiving treatment during the variable 3-week period if they showed progressive improvement, defined as at least a 2-point HAM-D score reduction at every other rating. The acute trial was terminated when patients met the stable remission criteria. The rTMS was then tapered during a 3-week period, and an antidepressant medication was started (phase 3).

rTMS TREATMENT SESSIONS

Treatment Parameters

Treatment was standardized at 120% magnetic field intensity relative to the patient's resting MT, at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds (eFigure; http://www.archgenpsychiatry.com). During the first week of the acute phase only, treatment intensity could be reduced to 110% for tolerability but then had to return to 120% from week 2 onward. Treatment sessions lasted for 37.5 minutes (75 trains) with 3000 pulses. Using an always active coil, left and right hemisphere MT was determined weekly using electromyographic measurement (3 sites) or visual monitoring (Emory University) of the resting right thumb (abductor pollicus brevis).[60] The scalp spatial coordinates of the MT and treatment positions were recorded using a mechanical coil positioning system, allowing reliable repositioning.

The standardized treatment location was over the left prefrontal cortex, determined by moving the TMS coil 5 cm anterior to the MT location along a left superior oblique plane with a rotation point about the tip of the patient's nose.[61-64] Before the first treatment session, patients underwent head MRI, with fiducials (vitamin E capsules) attached to a swim cap over the motor cortex region identified during the threshold determination and the putative prefrontal brain region. Scans were digitally transferred to MUSC, where a trained observer determined whether the intended coil placement location was over the premotor or the prefrontal cortex.[52] If the area identified by the vitamin E capsule was over the premotor cortex and, thus, too posterior, the coil was moved 1 cm anterior. This occurred in 33.2% of patients, equally distributed across the 4 sites. Ongoing analyses are determining whether the actual location correlated with clinical response.[65]

Concomitant Treatments

All the randomized patients were free of antidepressant, antipsychotic, and anticonvulsant medications for 2 weeks before baseline assessment (5 weeks for fluoxetine) and for the duration of active treatment. Patients were allowed limited use (up to 14 daily doses) of either sedatives and hypnotics or anxiolytics.

The primary efficacy outcome measure was the dichotomous variable of remission, defined as a HAM-D score of 3 or less or 2 consecutive HAM-D scores less than 10 during phase 1.[66] Secondary outcome measures included the dichotomous variable of response (defined as a ≥50% decrease in HAM-D score from baseline at the final phase 1 visit), Montgomery-Åsperg Depression Rating Scale scores, Clinical Global Impression Severity of Illness Scale scores, and patient-reported Inventory of Depressive Symptoms–Self-report scores.

Safety was assessed at every treatment visit by spontaneous adverse event reports. Additional evaluations included auditory thresholds and a neuropsychological battery at baseline, at the end of the active phase, and at 6-month follow-up.

STATISTICAL ANALYSIS

The major goal of this study was to assess whether active, compared with sham, rTMS increased the remission rate during phase 1. Two hundred forty randomized patients were required to achieve 80% power to detect a clinically relevant odds ratio of at least 2 assuming a 10% sham remission rate and a 20% overall dropout rate. Dichotomous outcomes (remission, response) were assessed using a logistic regression model (SAS Institute Inc, Cary, North Carolina) with independent variables of treatment (active vs sham), medication resistance (low vs high), current depressive episode duration (log transformed), age (continuous), and site (categorical). The primary analysis was conducted using the intention-to-treat (ITT) population, defined as all randomized patients who started at least 1 treatment session. Secondary analyses of the primary outcome examined completer and fully adherent samples. The completer sample was defined as randomized patients who were treated according to the protocol and had fewer than 4 rescheduled, missed, or partially completed rTMS sessions during weeks 2 to 6 of phase 1. The fully adherent sample had fewer than 2 rescheduled, missed, or partially complete sessions; must not have been taking prohibited psychiatric medications or illicit drugs; and had no other protocol violations during phase 1. All the statistical tests were performed at the .05 significance level. Interactions were considered significant at the .15 significance level. Three planned interim analyses for harm with respect to depression severity (as measured using the HAM-D) were conducted for the data and safety monitoring board when 25%, 50%, and 75% of the total number of planned participants completed phase 1.

RESULTS

PATIENTS

We screened approximately 860 patients to randomize 199, all screened by a psychiatrist (**Figure 2**). Seven patients participated in the first year while the sham method

Table 2. Demographic and Clinical Characteristics of Patients by Treatment Arm[a]

	Active (n=92)	Sham (n=98)	Total (N=190)	*P* Value
Male sex, No. (%)	34 (37)	48 (49)	**82** (43)	.10
Age, y				
Mean (SD)	47.7 (10.6)	46.5 (12.3)	47.1 (11.5)	.48
Range	22-69	23-69	22-69	
Current episode duration, wk				
Mean, median (SD)	74.1, 53 (64.9)	82.2, 61 (65.4)	78.3, 56 (65.1)	.39
Range	8-280	3-260	3-280	
Baseline HAM-D score				
Mean (SD)	26.3 (5.0)	26.5 (4.8)	26.4 (4.9)	.73
Range	20-43	20-42	20-43	
Baseline MADRS score				
Mean (SD)	29.5 (6.9)	29.8 (6.4)	29.6 (6.6)	.74
Range	12-44	12-44	12-44	
Baseline IDS score				
Mean (SD)	41.0 (9.3)	40.1 (9.8)	40.5 (9.5)	.53
Range	24-63	18-65	18-65	
Failed research-quality antidepressant trials, No.				
Current				
Mean, median (SD)	1.62, 1 (1.37)	1.41, 1 (0.97)	1.51, 1 (1.18)	.22
Range	0-6[b]	0-4	0-6	
Lifetime				
Mean, median (SD)	3.34, 3 (2.68)	3.28, 3 (2.11)	3.31, 3 (2.40)	.85
Range	0-14	0-9	0-14	
ATHF rating, No. (%)				
Lower antidepressant resistance	53 (58)	69 (70)	**122** (64.2)	.07
Higher antidepressant resistance	39 (42)	29 (30)	**68** (35.8)	
Right motor threshold	(n=90)	(n=94)	(N=184)	
Mean (SD)	56.5 (13.2)	57.2 (12.1)	56.9 (12.6)	.71
Range	36-95	39-85	36-95	
Left motor threshold	(n=92)	(n=97)	(N=189)	
Mean (SD)	58.9 (11.3)	56.9 (9.9)	57.9 (10.6)	.18
Range	26-95	35-77	26-95	

Abbreviations: ATHF, Antidepressant Treatment History Form; IDS, Inventory of Depressive Symptoms–Self-report; HAM-D, Hamilton Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale.

[a] Overall, there were no significant differences by arm.

[b] Note that the allowed maximum duration of the length of the current episode was 5 years. Some patients were enrolled, and then later-requested records revealed the episode to be longer than 5 years.

was being developed and were not included in the ITT analysis following a blinded decision by the Executive Committee, composed of the study chairs, site principal investigators, and study statisticians. An additional 2 patients exited before receiving any treatment. Thus, 190 patients composed the ITT sample.

Demographic and clinical features were not statistically significantly different between the 2 treatment arms (**Table 2**). Current episode treatment resistance did not differ between groups, with an average of 1.5 failed research-quality adequate treatment trials (by Antidepressant Treatment History Form criteria), which translates approximately to 3 to 6 clinical antidepressant medication trials. During their lifetime, patients had failed 3.3 research-adequate treatment trials (approximately 9 clinical attempts). The group, on average, was moderately treatment resistant.

RATER CERTIFICATION

Only 13 of 18 proposed raters qualified for the trial (Appendix). Because all key ratings were obtained locally at the site by the clinical rater and by an external expert, 2 data sets were available for analysis. The overall intraclass correlation was 0.92 for the reliability assessment between the expert and the site clinical rater for ratings of baseline and end of phase 1 HAM-D scores. We report site clinical rater ratings.

INTEGRITY OF THE BLIND

The eTable details the guesses for patients, treaters, and raters at the end of the active phase with respect to treatment assignment.

PRIMARY OUTCOME: REMITTERS

For the primary analysis of remission in the ITT sample (n=190), there was a significant effect of treatment (odds ratio, 4.2; 95% confidence interval, 1.32-13.24; *P*=.02). There were 18 remitters (9.5% [14.1% in the active arm and 5.1% in the sham arm]). No covariates were significant. **Table 3** and **Table 4** list the completer and fully adherent remission rates. The ITT number needed to treat based on phase 1 results was 12.

Table 3. Remission Status (Primary Outcome)

	ITT (n=190)		Completers (n=154)		Fully Adherent (n=120)	
	Active (n=92)	Sham (n=98)	Active (n=72)	Sham (n=82)	Active (n=57)	Sham (n=63)
Remission						
No. (%)	13 (14)	5 (5)	10 (14)	4 (5)	6 (11)	2 (3)
95% CI	8.5-22.7	2.3-11.4	7.8-23.7	2.0-11.9	5.0-21.2	1.0-10.8
No remission						
No. (%)	79 (86)	93 (95)	62 (86)	78 (95)	51 (89)	61 (97)
95% CI	77.3-91.5	88.6-97.7	76.2-92.2	88.1-98.0	78.8-95.0	89.2-99.0
Logistic regression model (*df*)	Wald χ^2	*P* Value	Wald χ^2	*P* Value	Wald χ^2	*P* Value
Treatment (1)	5.93	.02	5.45	.02	3.05	.08
Site (3)	6.05	.11	7.14	.07	. . .[a]	. . .[a]
Age (1)	0.06	.81	0.20	.66	0.13	.73
Duration (1)	1.90	.17	3.62	.06	1.18	.27
Medication resistance (1)	2.12	.15	2.27	.13	2.55	.13
Treatment						
Odds ratio (95% CI)[b]	4.18 (1.32-13.24)		4.92 (1.29-18.76)		Not significant	

Abbreviations: CI, confidence interval; ellipses, not applicable; ITT, intention to treat.

[a] The 8 remitters in this analysis sample were distributed unequally among the sites (6 at the Medical University of South Carolina, 1 at the University of Washington, and 1 at Emory University); therefore, site was excluded from the fully adherent model to perform maximum likelihood estimation of the regression parameters.

[b] Adjusted odds ratios are reported only for significant ($P<.05$) variables in the regression model; odds ratios are adjusted for site (categorical), age (continuous), duration of current depressive episode (log transformed), and medication resistance (low vs high).

Table 4. Patients Who Remitted by Treatment Phase in the ITT Sample

	Remitters in Phase 1 Fixed (Weeks 1-3) (n=8)	Remitters in Phase 1 Variable (Weeks 4-6)		
		Week 4 Day 2 (n=2)	Week 4 Day 5 (n=3)	Week 5 Day 2 (n=5)
Active TMS remitters, No. (n=13)	6	2	3	2
Sham TMS remitters, No. (n=5)	2	0	0	3

Abbreviations: ITT, intention to treat; TMS, transcranial magnetic stimulation.

SITE DIFFERENCES

Most remitters (15 of 18 [83.3%]) and less treatment-resistant individuals (81 of 122 [66.4%]) were at 2 of the 4 sites. Although site and treatment resistance were not statistically significant covariates in the primary model, multicollinearity between the 2 covariates was detected. When either variable was removed from the primary model, the remaining variable was significant (site: $P=.04$; Antidepressant Treatment History Form: $P=.03$). This relationship between site and treatment resistance did not affect the primary study results. However, it did influence interpretation of the site and treatment resistance regression estimates.

SECONDARY OUTCOME: RESPONDERS

The responder analysis had similar results. All remitters were also responders, but not all responders were remitters. There were 19 responders (10.0%) (15% active and 5% sham) in the ITT sample, 14 (9.1%) (14% active and 5% sham) in the completer sample, and 7 (5.8%) in the fully adherent sample. Similar to the remission analyses, logistic regression detected a main effect of treatment condition for the ITT ($P=.009$) and completer ($P=.02$) samples but not for the fully adherent sample ($P=.14$). In the ITT sample, the odds ratio of responding to rTMS vs sham was 4.6 (95% confidence interval, 1.47-14.42).

Table 5 gives the results of the 4 continuous outcomes. Patients undergoing active TMS compared with sham TMS exhibited significantly greater decreases in Montgomery-Åsberg Depression Rating Scale, Clinical Global Impression Severity of Illness Scale, and Inventory of Depressive Symptoms–Self-report scores.

REMITTERS/PHASE 2

Phase 2 (open label) included 43 of 144 remitters (29.9%) (19 of 63 [30.2%] from the phase 1 active TMS arm and 24 of 81 [29.6%] from the phase 1 sham arm). Phase 2 rates do not differentiate between placebo and treatment response.

SAFETY

The main spontaneous adverse events are given in **Table 6**, and none significantly differed by treatment arm. Many patients receiving sham rTMS also reported headache, site discomfort, and facial twitching, common adverse effects associated with active rTMS that have raised concerns in

Table 5. Continuous Outcomes

	Observed[a]				Modeled[b]		
	Baseline		End of Phase 1				
	Mean (SD)	Patients, No.	Mean (SD)	Patients, No.	95% CI Effect Estimate[c]	Cohen d[d]	*P* Value[e]
HAM-D: active TMS	26.26 (4.95)	92	21.61 (9.26)	83	–4.23 to 0.10	–0.42	.06
HAM-D: sham TMS	26.51 (4.83)	98	23.38 (7.43)	91			
MADRS: active TMS	29.48 (6.91)	92	24.59 (11.44)	83	–6.10 to –0.76	–0.51	.01
MADRS: sham TMS	29.81 (6.42)	98	27.75 (9.06)	91			
CGI-S: active TMS	4.62 (0.70)	90	3.96 (1.14)	82	–0.68 to –0.09	–0.55	.01
CGI-S: sham TMS	4.63 (0.69)	98	4.30 (0.87)	90			
IDS: active TMS	40.98 (9.27)	86	32.56 (15.40)	78	–10.04 to –2.62	–0.66	.001
IDS: sham TMS	40.07 (9.81)	94	36.70 (13.91)	88			

Abbreviations: CGI-S, Clinical Global Impression Severity of Illness Scale; CI, confidence interval; HAM-D, Hamilton Scale for Depression; IDS, Inventory of Depressive Symptoms–Self-report; MADRS, Montgomery-Åsberg Depression Rating Scale; TMS, transcranial magnetic stimulation.

[a] Individuals whose scores were missing at the end of phase 1 or who dropped out of the study before the end of phase 1 were considered as missing observations. For example, 16 participants' HAM-D scores were missing at the end of phase 1 (9 in the active TMS arm and 7 in the sham TMS arm).

[b] All 4 continuous outcomes (HAM-D, MADRS, IDS, and CGI-S) were analyzed using linear modes (procedure GENMOD; SAS Institute Inc, Cary, North Carolina). The modeled differences between active and sham TMS at the end of phase 1 were adjusted for baseline values, age, log (Skid P), categorized Antidepressant Treatment History Form, and site variables. For each of the 4 models, we reported the 95% CI for the modeled difference between active and sham TMS at the end of phase 1, the effect size of the modeled difference, and the modeled difference corresponding *P* value.

[c] The 95% CI for the arm differences between the modeled scores. For example, based on the model, we can say with 95% confidence that, at the end of phase 1, active TMS decreases the patient's MADRS score by at least 0.76 points to at most 6.10 points on average.

[d] Cohen d was based on the modeled means for each treatment arm and observed baseline standard deviations. For example, based on the model, at the end of phase 1, the MADRS score of patients receiving active TMS was approximately half of baseline SD lower than the MADRS score of patients receiving sham TMS.

[e] *P* values for the differences between the arms for a given score based on the model.

Table 6. Spontaneous Adverse Events With rTMS[a]

	Patients Reporting, No. (%)	
	Active rTMS Group (n=92)	Sham rTMS Group (n=98)
Headache	29 (32)	23 (23)
Discomfort at the stimulation site	17 (18)	10 (10)
Insomnia	7 (7.6)	10 (10)
Worsening of depression or anxiety	6 (7)	8 (8)
Gastrointestinal	6 (7)	3 (3)
Fatigue	5 (5)	4 (4)
Muscle aches	4 (4)	4 (4)
Vertigo	2 (2)	2 (2)
Skin pain	1 (1)	1 (1)
Facial muscle twitching	0	1 (1)
Other	18 (20)	15 (15)

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

[a] Adverse events were coded in a MedDRA-modified manner similar to a recent rTMS depression trial.[40] No adverse events were significantly different by treatment arm.

the past about unblinding.[40] Five patients discontinued study participation because of adverse events, all of whom were receiving active TMS (5.4% dropout rate owing to adverse events in the active group). Four of the 5 patients dropped out because of pain or headache and received only a single TMS treatment. One patient received 14 treatments and then dropped out because of syncope.

No seizures or suicides occurred. One serious adverse event occurred before treatment: a patient's depression worsened, likely owing to medication discontinuation, and this patient was not randomized. There were 2 serious adverse events without long-term sequelae: 1 patient had syncope (active rTMS) that the investigator deemed unlikely related to the study and 1 patient had paranoid ideation (sham TMS), possibly related to the study.

COMMENT

In this National Institutes of Health–sponsored, industry-independent trial, high-intensity rTMS for at least 3 weeks was significantly more likely than sham rTMS to induce remission in antidepressant medication–free patients with moderately treatment-resistant unipolar MDD. The treatment effect seen in the primary analysis was also reflected in secondary analyses in remitted completer samples and in analyzing the number of responders. Similar treatment differences were found with continuous measures of symptom change, such as the Montgomery-Åsberg Depression Rating Scale, the Clinical Global Impression Severity of Illness Scale, and the patient-rated Inventory of Depressive Symptoms–Self-report.

This trial used a variety of methodological improvements over previous studies, including MRI adjustment for coil placement in approximately one-third of patients, an adaptive flexible duration of treatment, a novel sham device that mimicked the sensory experience of rTMS, continuous assessment of outcome evaluator reliability relative to a masked external expert rater, and constant assessment of unmasking of rTMS treaters. The treatment was relatively well tolerated, with no difference in adverse events between the active sham and the active TMS treatment arms. There were no seizures, and retention was high. For the purposes of the integrity of the blind, there were no differences in reported rates of scalp discomfort or headache, events that have differed in other TMS clinical trials between the active and sham groups.[40]

Confirming results found in an industry-sponsored trial completed after the present study was launched, we found

a significant interaction between the degree of antidepressant treatment resistance and clinical benefit, with most remitters having lower degrees of treatment resistance, although the group overall was moderately treatment resistant in the current episode and during their lifetime.[40,67]

One of the most important aspects of the study was ensuring that no one who knew the randomization status of the patient ever came in contact with the patient or interacted with the data. We developed a new active sham TMS system that simulated the rTMS somatosensory experience and effectively masked the patients, the raters, and, to a large extent, the treaters. We assessed the integrity of the blind by having patients, treaters, and clinical raters report a best guess at the end of the phase and to indicate how confident they were in this guess. No clinical rater was very confident, and their choices were driven by the patients' clinical improvement. Some patients were confident, but their confident choices were not accurate. Treaters were able to guess randomization above the chance level, but none were very confident. Future clinical trials of brain stimulation devices should work to achieve this level of blinding.

The treatment was relatively well tolerated, with no difference in adverse events between the active sham and the active TMS treatment arms. There were no seizures, and the retention rate was high at 88%. In the absence of adverse effects, it seems wise to pursue higher doses of TMS in future studies[68,69] because some studies[49,70] have found dose-dependent antidepressant effects.

An additional novel aspect of this trial was the rigorous rater certification process, with constant monitoring of ratings and the use of an independent off-site expert rater for key ratings. The intraclass correlation between the expert and site raters was high, thus ensuring that clinical ratings were truly blinded and ensuring consistency in ratings across the 4 sites for the duration of the trial.

Despite these design advances and the relatively unambiguous demonstration of a treatment effect in the absence of unblinding, there were several limitations. Because of the extensive work in designing a sham system, which delayed the start of the trial, the study failed to enroll the projected 240 individuals suggested by the initial power analysis. This power issue may be the reason why the treatment condition effect on remission rate in the fully adherent sample analysis was not statistically significant. Treaters were able to guess randomization assignment better than chance, without much confidence, which was not explained by covarying for clinical benefit. It may be that there were some other physical changes during treatment that these physicians were able to detect, although the sham effectively reduced differences in sound, facial twitch, and patient pain. Informal debriefing of treaters failed to reveal aspects of the delivery that may have differed by treatment arm. Nonetheless, treaters did spend a significant amount of time with patients, representing a risk of unblinding. Despite this risk, patients and raters remained effectively blinded based on their best guess results. Remember that these results apply only to medically healthy unipolar nonpsychotically depressed patients without additional psychiatric comorbidity. Moreover, these patients were antidepressant medication free. Greater rates of overall response and remission would likely be seen if TMS were delivered in combination with pharmacotherapy, as was recently demonstrated with electroconvulsive therapy.[71]

Although the treatment effect was statistically significant on a clinically meaningful variable (remission), the overall number of remitters and responders was less than one would like with a treatment that requires daily intervention for 3 weeks or more, even with a benign adverse effect profile. Several issues are important to consider when interpreting the magnitude of clinical benefit. First, this was a sample of patients who had already failed at least 1 research-quality antidepressant medication trial in the current episode and who averaged more than 3 research-quality failures in their lifetime or who had tried and were intolerant to at least 3 medications. In patients who have failed 2 medication trials, open-label studies have shown that the likelihood is slim (<20%) of producing remission with another medication trial[72] or augmentation.[72-74] In patients with 3 failed medication trials (the lifetime average of this group), remission rates with new medication trials are 10% to 20%.[72,75] Thus, the 30% remission rate in the open-label phase of this study compares favorably with current medication practice. Also, these patients were medication free. Higher remission rates might be expected if patients continued taking medications that were only partially effective.[71]

When designing this trial, it was unclear how long patients needed to be treated. Much of the early work with TMS as an antidepressant administered treatment for only 2 weeks, which is much less than is usually needed for medications (typically 6-8 weeks) or electroconvulsive therapy (3-4 weeks). We adopted a duration-adaptive design, with all patients stopping after 3 weeks of treatment unless they substantially improved. The demographics and treatment were similar to the recent industry trial, except for the modified coil position in one-third of the present patients. Although both trials allowed continued treatment for clinical improvers beyond the first fixed phase, the data analysis plan for this trial was based on the entire phase 1 period, without performing analyses at fixed periods. Thus, formal comparisons are difficult. In the present trial, the critical assessment point was at 3 weeks, and patients had to have at least a 30% HAM-D score improvement or be crossed over to active treatment. Patients who met the 30% improvement criteria continued randomized treatment for an additional 3 weeks or until the patient stopped showing a meaningful response to treatment. With this rule, no one received treatment for a full 6 weeks. Despite the more rigorous requirements for progression (30% improvement at 3 weeks vs 25% improvement at 4 weeks), this study showed a significant improvement in remission at 3 to 5 weeks, whereas the study by O'Reardon et al[40] did not find a significant difference in remission rates until the sixth week of treatment (this study—acute phase 3-5 weeks: 14.1% active and 5.1% sham; O'Reardon et al[40]—4 weeks: 9% active and 8% sham; 6 weeks: 17% active and 8% sham). The continuation algorithm was designed primarily for safety issues and may have been too conservative. Thus, 3 weeks is the minimum duration of treatment needed, and many patients need longer. Thirty percent of patients who had not clinically improved or remitted after 3 weeks of active treatment later

remitted in open-label phase 2. Future articles will discuss whether there are brain imaging,[65] genetic, electroencephalographic,[76] or other early predictors of response that might help physicians determine how long to treat a patient with TMS who is not responding. Also, many patients who remitted in this trial enrolled in a follow-up study (phase 3) that should provide information about how long the clinical benefit lasts once achieved.[77-82]

The results of this study suggest that prefrontal rTMS is a monotherapy with few adverse effects and significant antidepressant effects for unipolar depressed patients who do not respond to medications or who cannot tolerate them.

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