

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

Transcranial magnetic stimulation (TMS) is a brain intervention that modulates activity in discrete cortical regions and associated neural circuits by noninvasively inducing intracerebral currents.<sup>19,20</sup> Repetitive TMS (rTMS) refers to TMS applied repeatedly during a session.<sup>21-23</sup> Transcranial magnetic stimulation can map brain function and connectivity,<sup>24-31</sup> can probe cortical excitability,<sup>32-38</sup> 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.<sup>39,40</sup> Most reviewers have concluded that

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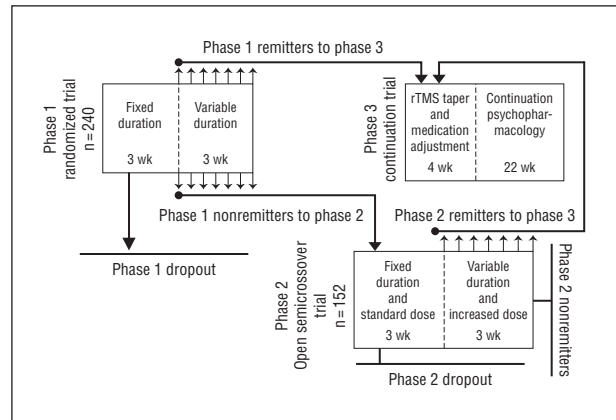
**Table 1. Study Inclusion and Exclusion Criteria**

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 $\leq 5$ y	Personal or close family history of seizure disorder
Hamilton Scale for Depression 24-item score $\geq 20$	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 $\geq 3$ 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.

daily left prefrontal rTMS has antidepressant properties, with most meta-analyses indicating a large effect size for symptom change compared with sham treatment.<sup>41-44</sup> However, there is controversy about the quality of the extant research,<sup>45</sup> including questions about the validity of the sham-control interventions<sup>46,47</sup> and concern that the antidepressant effects of rTMS are not sufficiently robust to be “clinically meaningful.”<sup>48</sup> Many of the early TMS trials<sup>49-51</sup> 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,<sup>40</sup> 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,<sup>52</sup> and provision for extended treatment in patients showing clinical improvement using a duration-adaptive design.<sup>53-56</sup> Other methodological improvements included use of an active sham condition that mimicked the somatosensory experience of rTMS,<sup>57,58</sup> 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.



**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.

## METHODS

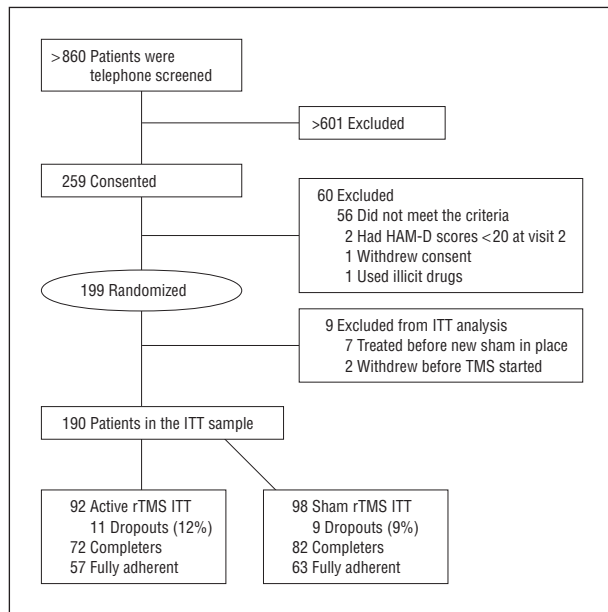
### PATIENTS

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).<sup>59</sup> 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.<sup>53</sup> 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,  $\geq 30\%$  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 pollicis brevis).<sup>60</sup> 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.<sup>61-64</sup> 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 deter-

mined whether the intended coil placement location was over the premotor or the prefrontal cortex.<sup>52</sup> 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.<sup>65</sup>

## 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.<sup>66</sup> Secondary outcome measures included the dichotomous variable of response (defined as a  $\geq 50\%$  decrease in HAM-D score from baseline at the final phase 1 visit), Montgomery-Åsberg 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<sup>a</sup>**

	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 <sup>b</sup>	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.

<sup>a</sup>Overall, there were no significant differences by arm.

<sup>b</sup>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 intra-class 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 $\chi^2$	P Value	Wald $\chi^2$	P Value	Wald $\chi^2$	P Value
Treatment (1)	5.93	.02	5.45	.02	3.05	.08
Site (3)	6.05	.11	7.14	.07	... <sup>a</sup>	... <sup>a</sup>
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) <sup>b</sup>	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.

<sup>a</sup>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.

<sup>b</sup>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 <sup>a</sup>				Modeled <sup>b</sup>		
	Baseline		End of Phase 1		95% CI Effect Estimate <sup>c</sup>	Cohen d <sup>d</sup>	P Value <sup>e</sup>
	Mean (SD)	Patients, No.	Mean (SD)	Patients, No.			
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.

<sup>a</sup>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).

<sup>b</sup>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.

<sup>c</sup>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.

<sup>d</sup>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.

<sup>e</sup>P values for the differences between the arms for a given score based on the model.

**Table 6. Spontaneous Adverse Events With rTMS<sup>a</sup>**

	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.

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

the past about unblinding.<sup>40</sup> 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.<sup>40</sup>

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.<sup>40,67</sup>

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<sup>68,69</sup> because some studies<sup>49,70</sup> 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.<sup>71</sup>

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<sup>72</sup> or augmentation.<sup>72-74</sup> In patients with 3 failed medication trials (the lifetime average of this group), remission rates with new medication trials are 10% to 20%.<sup>72,75</sup> 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.<sup>71</sup>

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<sup>40</sup> 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<sup>40</sup>—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,<sup>65</sup> genetic, electroencephalographic,<sup>76</sup> 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.<sup>77-82</sup>

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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## REFERENCES

- Ustün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. *Br J Psychiatry*. May 2004;184:386-392.
- Chisholm D, van Ommeren M, Ayuso-Mateos JL, Saxena S. Cost-effectiveness of clinical interventions for reducing the global burden of bipolar disorder. *Br J Psychiatry*. 2005;187:559-567.
- Greden JF. The burden of disease for treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):26-31.
- Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747-1757.
- Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991;48(9):851-855.
- Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M; STAR\*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28-40.
- Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M; STAR\*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231-1242.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.
- Fekadu A, Wooderson SC, Markopoulou K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? a systematic review of medium to long term outcome studies. *J Affect Disord*. 2009;116(1-2):4-11.
- Baldessarini RJ, Marsh E. Fluoxetine and side effects. *Arch Gen Psychiatry*. 1990;47(2):191-192.
- Pollack MH, Rosenbaum JF. Management of antidepressant-induced side effects: a practical guide for the clinician. *J Clin Psychiatry*. 1987;48(1):3-8.
- Remick RA, Froese C, Keller FD. Common side effects associated with monoamine oxidase inhibitors. *Prog Neuropsychopharmacol Biol Psychiatry*. 1989;13(3-4):497-504.
- Thase M, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant non-responders. *J Clin Psychiatry*. 1997;58(suppl 13):23-29.
- Rush AJ, Thase ME. Strategies and tactics in the treatment of chronic depression. *J Clin Psychiatry*. 1997;58(13)(suppl 13):14-22.
- Thase ME. The need for clinically relevant research on treatment-resistant depression. *J Clin Psychiatry*. 2001;62(4):221-224.
- Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.
- Thase ME. Studying new antidepressants: if there were a light at the end of the tunnel, could we see it? *J Clin Psychiatry*. 2002;63(suppl 2):24-28.
- Olsson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66(8):848-856.
- George MS, Belmaker RH. *Transcranial Magnetic Stimulation in Neuropsychiatry*. Washington, DC: American Psychiatric Press; 2000.
- George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. *Arch Gen Psychiatry*. 1999;56(4):300-311.
- Padberg F, George MS. Repetitive transcranial magnetic stimulation of the prefrontal cortex in depression. *Exp Neurol*. 2009;219(1):2-13.
- George MS, Aston-Jones G. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology*. 2010;35(1):301-316.
- Schlaepfer TE, George MS, Mayberg H. WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry. *World J Biol Psychiatry*. August 26 2009:11-17.
- Fox P, Ingham R, George MS, Mayberg H, Ingham J, Roby J, Martin C, Jerabek P. Imaging human intra-cerebral connectivity by PET during TMS. *Neuroreport*. 1997;8(12):2787-2791.
- George MS, Bohning DE. Measuring brain connectivity with functional imaging and transcranial magnetic stimulation (TMS). In: Desimone B, ed. *Neuropsychopharmacology: Fifth Generation of Progress*. New York, NY: Lippincott Williams & Wilkins; 2002:393-410.
- Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Näätänen R, Katila T. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport*. 1997;8(16):3537-3540.
- Münchau A, Bloem R, Irlbacher K, Trimble MR, Rothwell JC. Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. *J Neurosci*. 2002;22(2):554-561.
- Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *J Neurosci*. 1997;17(9):3178-3184.
- Paus T, Castro-Alamancos MA, Petrides M. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. *Eur J Neurosci*. 2001;14(8):1405-1411.
- Schwartz ML, Goldman-Rakic PS. Callosal and intrahemispheric connectivity of the prefrontal association cortex in rhesus monkey: relation between intraparietal and principal sulcal cortex. *J Comp Neurol*. 1984;226(3):403-420.
- Shajahan PM, Glabus MF, Steele JD, Doris AB, Anderson K, Jenkins JA, Gooding PA, Ebmeier KP. Left dorso-lateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(5):945-954.
- Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P, Post RM. Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET. *J Affect Disord*. 2009;115(3):386-394.
- Paulus W, Classen J, Cohen LG, Large CH, Di Lazzaro V, Nitsche M, Pascual-Leone A, Rosenow F, Rothwell JC, Ziemann U. Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. *Brain Stimulat*. 2008;1(3):151-163.
- Ziemann U, Paulus W, Nitsche MA, Pascual-Leone A, Byblow WD, Berardelli A, Siebner HR, Classen J, Cohen LG, Rothwell JC. Motor cortex plasticity protocols. *Brain Stimulat*. 2008;1(3):164-182.
- Di Lazzaro V, Ziemann U, Lemon RN. Physiology of transcranial motor cortex stimulation. *Brain Stimulat*. 2008;1(4):345-362.
- Heide G, Witte OW, Ziemann U. Physiology of modulation of motor cortex excitability by low-frequency suprathreshold repetitive transcranial magnetic stimulation. *Exp Brain Res*. 2006;171(1):26-34.
- Ilić TV, Ziemann U. Exploring motor cortical plasticity using transcranial magnetic stimulation in humans. *Ann N Y Acad Sci*. 2005;1048:175-184.
- Wassermann EM, Wedegaertner FR, Ziemann U, George MS, Chen R. Crossed reduction of human motor cortex excitability by 1-hz transcranial magnetic stimulation. *Neurosci Lett*. 1998;250(3):141-144.
- Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G, Padberg F, Naderi-Heiden A, Abler B, Eichhammer P, Grossheinrich N, Hay B, Kammer T, Langguth B, Laske C, Plewnia C, Richter MM, Schulz M, Unterecker S, Zinke A, Spitzer M, Schönfeldt-Lecuona C. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. *Br J Psychiatry*. 2007;191:441-448.
- O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS, Sackeim HA. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007;62(11):1208-1216.
- Holtzheimer PE III, Russo J, Avery D. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull*. 2001;35(4):149-169.

42. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. 2002;5(1):73-103.
43. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. 2002;8(5):270-275.
44. Martin JLR, Barbano MJ, Schlaepfer TE, Clos S, Perez V, Kulisevsky J, Gironell A. Transcranial magnetic stimulation for treating depression [Cochrane Library on CD-ROM]. Oxford, England: Update Software; 2002;issue 2.
45. Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? *Nat Rev Neurosci*. 2007;8(7):559-567.
46. Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry*. 2001;49(5):460-463.
47. Loo CK, Taylor JL, Gandevia SC, McDermont BN, Mitchell PB, Sachdev PS. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? *Biol Psychiatry*. 2000;47(4):325-331.
48. Sackeim HA. Repetitive transcranial magnetic stimulation: what are the next steps? *Biol Psychiatry*. 2000;48(10):959-961.
49. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med*. 2009;39(1):65-75.
50. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry*. 2003;160(5):835-845.
51. Kirkcaldie MT, Pridmore SA, Pascual-Leone A. Transcranial magnetic stimulation as therapy for depression and other disorders. *Aust N Z J Psychiatry*. 1997;31(2):264-272.
52. Johnson KA, Ramsey D, Kozel FA, Bohning DE, Anderson B, Nahas Z, Sackeim HA, George MS. Using imaging to target the prefrontal cortex for transcranial magnetic stimulation studies in treatment-resistant depression. *Dialogues Clin Neurosci*. 2006;8(2):266-268.
53. Sackeim HA, Roose SP, Lavori PW. Determining the duration of antidepressant treatment: application of signal detection methodology and the need for duration adaptive designs (DAD). *Biol Psychiatry*. 2006;59(6):483-492.
54. Gallo P. Operational challenges in adaptive design implementation. *Pharm Stat*. 2006;5(2):119-124.
55. Krams M, Burman CF, Dragalin V, Gaydos B, Grieve AP, Pinheiro J, Maurer W, Gallo P. Adaptive designs in clinical drug development: opportunities, challenges, and scope reflections following PhRMA's November 2006 workshop. *J Biopharm Stat*. 2007;17(6):957-964.
56. Orloff J, Douglas F, Pinheiro J, Levinson S, Branson M, Chaturvedi P, Ette E, Gallo P, Hirsch G, Mehta C, Patel N, Sabir S, Springs S, Stanski D, Evers MR, Fleming E, Singh N, Tramontin T, Golub H. The future of drug development: advancing clinical trial design. *Nat Rev Drug Discov*. 2009;8(12):949-957.
57. Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H, Reeves ST, Madan A, Sackeim H, George MS. Development and evaluation of a portable sham TMS system. *Brain Stimulat*. 2008;1(1):52-59.
58. Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, Long J, Sackeim HA, George MS. Focal electrical stimulation as a sham control for rTMS: does it truly mimic the cutaneous sensation and pain of active prefrontal rTMS? *Brain Stimulat*. 2008;1(1):44-51.
59. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10-17.
60. Borckardt JJ, Nahas Z, Koola J, George MS. Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: a computer simulation evaluation of best methods. *J ECT*. 2006;22(3):169-175.
61. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Bassar P, Hallett M, Post RM. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport*. 1995;6(14):1853-1856.
62. George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Bassar P, Hallett M, Post RM. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. *J Neuropsychiatry Clin Neurosci*. 1996;8(2):172-180.
63. Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr*. 2003;16(2):95-99.
64. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. *Biol Psychiatry*. 2001;50(1):58-61.
65. Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F, Haynor D, George MS, Nahas Z. More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. *Biol Psychiatry*. 2009;66(5):509-515.
66. Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, Ninan PT, Thase ME, Gelenberg AJ, Kupfer DJ, Regier DA, Rosenbaum JF, Ray O, Schatzberg AF; ACNP Task Force. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*. 2006;31(9):1841-1853.
67. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, Gilmer W, Marangell LB, Aaronson S, Daskalakis ZJ, Canterbury R, Richelson E, Sackeim HA, George MS. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009;34(2):522-534.
68. Epstein CM, Evatt ML, Funk A, Girard-Siqueira L, Lupei N, Slaughter L, Athar S, Green J, McDonald W, DeLong MR. An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. *Clin Neurophysiol*. 2007;118(10):2189-2194.
69. Anderson B, Mishory A, Nahas Z, Borckardt JJ, Yamanaka K, Rastogi K, George MS. Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. *J ECT*. 2006;22(1):49-53.
70. Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry*. 2008;65(3):268-276.
71. Sackeim HA, Dillingham EM, Prudic J, Cooper T, McCall WV, Rosenquist P, Isenberg K, Garcia K, Mulsant BH, Haskett RF. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry*. 2009;66(7):729-737.
72. Fava M, Rush AJ, Wisniewski SR, Nierenberg AA, Alpert JE, McGrath PJ, Thase ME, Warden D, Biggs M, Luther JF, Niederehe G, Ritz L, Trivedi MH. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR\*D report. *Am J Psychiatry*. 2006;163(7):1161-1172.
73. Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, Alpert JE, Warden D, Luther JF, Niederehe G, Lebowitz B, Shores-Wilson K, Rush AJ. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR\*D report. *Am J Psychiatry*. 2006;163(9):1519-1530, 1665.
74. Wisniewski SR, Fava M, Trivedi MH, Thase ME, Warden D, Niederehe G, Friedman ES, Biggs MM, Sackeim HA, Shores-Wilson K, McGrath PJ, Lavori PW, Miyahara S, Rush AJ. Acceptability of second-step treatments to depressed outpatients: a STAR\*D report. *Am J Psychiatry*. 2007;164(5):753-760.
75. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, Thase ME, Davis L, Biggs MM, Shores-Wilson K, Luther JF, Niederehe G, Warden D, Rush AJ. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR\*D report. *Am J Psychiatry*. 2006;163(9):1531-1541, 1666.
76. Funk AP, George MS. Prefrontal EEG asymmetry as a potential biomarker of antidepressant treatment response with transcranial magnetic stimulation (TMS): a case series. *Clin EEG Neurosci*. 2008;39(3):125-130.
77. Li X, Nahas Z, Anderson B, Kozel FA, George MS. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depress Anxiety*. 2004;20(2):98-100.
78. O'Reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimiento PC. Long-term maintenance therapy for major depressive disorder with rTMS. *J Clin Psychiatry*. 2005;66(12):1524-1528.
79. Nahas Z, Oliver NC, Johnson M, Molloy M, Hughes PL, Ballenger JC, Rischia SC, George MS. Feasibility and efficacy of left prefrontal rTMS as a maintenance antidepressant. *Biol Psychiatry*. 2000;47(8)(suppl 1):S156-S157.
80. Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT, Heart KL, Demitrack MA. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry*. 2008;69(2):222-232.
81. Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry*. 2003;53(4):324-331.
82. Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals: preliminary report. *Biol Psychiatry*. 2002;51(8):687-690.