

Research Article

IMPROVING THE ANTIDEPRESSANT EFFICACY OF TRANSCRANIAL MAGNETIC STIMULATION: MAXIMIZING THE NUMBER OF STIMULATIONS AND TREATMENT LOCATION IN TREATMENT-RESISTANT DEPRESSION

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Objective: To assess the efficacy of increasing the number of fast left repetitive transcranial magnetic stimulations (rTMS) (10 Hz @ 120% of motor threshold (MT) over the left dorsolateral prefrontal cortex (DLPFC)) needed to achieve remission in treatment-resistant depression (TRD). And, to determine if patients who do not remit to fast left will remit using slow right rTMS (1 Hz @ 120% MT over the right DLPFC). **Method:** Patients were part of a multicenter sham-controlled trial investigating the efficacy of fast left rTMS. Patients who failed to meet minimal response criteria in the sham-controlled study could enroll in this open fast left rTMS study for an additional 3–6 weeks. Patients who failed to remit to fast left could switch to slow right rTMS for up to 4 additional weeks. The final outcome measure was remission, defined as a HAM-D

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3 years. Dr. McDonald is presently an unpaid consultant to NeoStim. Dr. Holtzheimer reports consulting fees from St. Jude Medical Neuromodulation, AvaCat Consulting, and Tetrigenex, and is an unpaid consultant to NeoStim. Drs. McDonald and Holtzheimer are faculty at Emory University which holds a patent on TMS technology. Neither received royalties or is involved in the development or promotion of this patent. Dr. Lisanby reports research grants, speaking fees, or advisory board work with Neuronetics, Advanced Neuromodulatory Systems, Brainsway, and Cyberonics. Dr. Lisanby has a patent application with Columbia University on neuromodulation technology for which she receives no royalties or compensation. Dr. Avery has received research support from Neuronetics and Takeda, has been a consultant for Neuro-netics and has been on the speaker's bureau for Eli Lilly, Takeda and Forest Pharmaceuticals. Dr. Nahas reports past and current research grants, speaking fees or consulting work with Cyberonics, Neuro-netics, MECTA Corporation, and Medtronic. Dr. Nahas has acted as an unpaid consultant for Neuropace. Dr. Sackeim received consultant fees from MECTA Corporation and Cyberonics. Dr. George received consultant fees from PureTech Ventures and reports research grants, speaking fees, or advisory work with Brainsway, Mecta Corporation, Neuronetics, Cephos, NeoStim and NeoSync, Brainsonix, Cyberonics, and Cephos. Dr. George is faculty at MUSC which has two patent applications in Dr. George's name combining MRI and TMS.

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score of < 3 or 2 consecutive HAM-D scores less than 10. **Results:** Forty-three of 141 (30.5%) patients who enrolled in the open phase study eventually met criteria for remission. Patients who remitted during fast left treatment received a mean of 26 active treatments (90,000 pulses). Twenty-six percent of patients who failed fast left remitted during slow right treatment. **Conclusion:** The total number of rTMS stimulations needed to achieve remission in TRD may be higher than is used in most studies. TRD patients who do not respond to fast left rTMS may remit to slow right rTMS or additional rTMS stimulations. *Depression and Anxiety* 28:973–980, 2011. © 2011 Wiley Periodicals, Inc.

Key words: transcranial magnetic stimulation; rTMS; high frequency rTMS; low frequency rTMS; treatment-resistant depression

INTRODUCTION

In two recent multicenter trials, repetitive transcranial magnetic stimulation (rTMS) has been significantly more effective than sham in treating depressive symptoms. However, the magnitude of the effect has been modest and most remitters had low levels of treatment resistance.^[1,2] This study examines strategies for improving the response to rTMS, especially in treatment-resistant patients by evaluating two important treatment parameters: the total number of stimulations and the site and frequency of the stimulation. Increasing the total number of stimulations has previously been demonstrated to improve response to rTMS.^[3,4] However, the studies used in these comparisons have generally come from trials of different lengths or weeks of rTMS treatment and not comparisons of the effect of increasing the number of active rTMS stimulations. The largest multicenter sham-controlled trials to date have studied high frequency (10 Hz) stimulation over the left dorsolateral prefrontal cortex (DLPFC) or *fast left* rTMS and evaluated the primary depression outcome measure after 45,000 pulses over 3 weeks^[1] and 60,000 pulses over 4 weeks.^[2] This study uses a duration-adaptive treatment design^[5] that allows patients to receive up to 12 weeks of fast left rTMS and a maximum of 180,000 pulses. Response to treatment is assessed weekly to determine the number of weeks of treatment (or total pulses) that correspond to a maximal treatment effect.

This study also examines the efficacy of switching fast left rTMS nonresponders to low frequency stimulation (1 Hz) over the right DLPFC or *slow right* rTMS. Both fast left and slow right rTMS are effective in the treatment of major depression.^[3,4,6,7] However, these studies have randomized patients to either fast left or slow right. This study will compare the therapeutic efficacy of switching from fast left to slow right rTMS in the *same* patient to determine if some patients may respond preferentially to slow right rTMS.

METHODS

Patients were part of a larger sham-controlled trial of the efficacy of daily left DLPFC stimulation in the treatment-resistant depression

(TRD). This study was conducted at four sites (Medical University of South Carolina [MUSC], Columbia University/New York State Psychiatric Institute, University of Washington, and Emory University), with active enrollment taking place from October 15, 2004, through to March 31, 2009. The institutional review board at each center approved the protocol and all the participants provided written informed consent.

All patients met DSM IV criteria for major depression with current episode duration of < 5 years and no evidence of active substance abuse or previous exposure to rTMS. To qualify, patients had to meet severity of illness criteria, including a Hamilton Depression Rating Scale^[8] 24-item score (HAM-D) ≥ 20 and a moderate level of treatment resistance as defined by the Antidepressant Treatment History Form (ATHF);^[9] insufficient clinical benefit to 1–4 adequate medication trials or intolerant to ≥ 3 trials.^[1]

The study included three phases: Phase 1 was a sham-controlled randomized trial of fast left rTMS and is reported elsewhere;^[1] Phase 2 was an open label fast left rTMS trial of patients who did not remit to Phase 1 and is the subject of this article. Patients in Phase 2 received up to 6 weeks of open label fast left rTMS. Patients who did not remit to fast left rTMS were switched to slow right rTMS; Phase 3 was the long-term follow-up of patients who remitted in Phase 1 or 2 and will be the subject of a future article.

In Phase 1, patients underwent a 2-week lead-in period off of all antidepressant (5 weeks for fluoxetine), anticonvulsant, and antipsychotic medication. Using an always active coil, left and right hemisphere motor threshold (MT) was determined weekly by electromyographic measurement (three sites) or visual monitoring (Emory University) of the resting right thumb (abductor pollicis brevis). The standardized treatment location was over the left or right DLPFC, 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. Before the first treatment session, patients underwent head magnetic resonance image (MRI), with fiducials (vitamin E capsules) attached to a swim cap over the left and right motor cortex regions, 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 left or right premotor and prefrontal cortex. In Phase 1, 190 patients were randomized to either sham or active treatment @ 120% magnetic field intensity relative to the patient's resting MT for 10 pulses per second (10 Hz) for 4 sec, with an intertrain interval of 26 sec over the left DLPFC. Treatment sessions lasted for 37.5 min (75 trains) with 3,000 pulses delivered per session.

At the end of 3 weeks in Phase 1, patients were assessed to be either in remission, improving but not remitted, or not improving.

Remission was defined as a HAM-D score of <3 or 2 consecutive weekly HAM-D scores less than 10.^[10] Patients who were assessed to be in remission stopped rTMS treatment and entered Phase 3 for the long-term follow-up. Patients who improved but did not remit (defined as having at least a 30% reduction in HAM-D score from baseline, but without an absolute score meeting remission criteria) continued treatment in Phase 1 for up to 3 additional weeks using a duration-adapted design,^[5] with HAM-D assessments performed twice weekly to monitor for continued improvement. If these patients continued to show improvement (defined as at least a two point drop in the HAM-D per week), then they continued to receive treatment in Phase 1 for up to an additional 3 weeks. If they failed to show continued improvement, they were given the option of entering the open label Phase 2 trial or being followed naturalistically. If they remitted, they entered Phase 3. Patients who did not show sufficient improvement at the end of the fixed 3-week period (defined as a $<30\%$ drop from baseline in HAM-D score) were discontinued from Phase 1 and given the option of crossing over to open treatment (Phase 2) or being followed naturalistically.

Therefore, patients in Phase 2 were the ones who had failed to achieve remission in Phase 1 and who consented to open label treatment. The initial treatment parameters in Phase 2 were identical to the active treatment in Phase 1 (i.e., fast left @ 120% MT for 3,000 pulses over the left DLPFC). At the end of 3 weeks of open label treatment, patients were assessed to be either in remission, improving but not remitted, or not improving. Patients in remission were moved to Phase 3. Patients who were improving but not remitted continued treatment for up to an additional 3 weeks using the duration adaptive design. Patients who did not show sufficient improvement in Phase 2 were given the option of moving to a 4-week open label trial of slow frequency rTMS over the right DLPFC. The treatment parameters for slow right rTMS were 1 Hz and 120% MT for 30 min or 1,800 pulses per session for up to 4 weeks. The positioning of the coil was determined by moving the TMS coil 5 cm anterior to the MT location along a right superior oblique plane with a rotation point about the tip of the patient's nose.

STATISTICAL ANALYSES

Data were analyzed using a logistic regression model in SAS Version 9.2 (SAS, Cary, NC), to determine if the probability of remission or response during Phase 2 differed between the two treatment arms (active/sham) when controlling treatment resistance (high/low). Remission, as defined above, was an absolute HAM-D score of <3 or 2 consecutive weekly HAM-D scores less than 10. Response was defined as $<50\%$ decrease in the HAM-D score from the baseline HAM-D in Phase 1. Low medication resistance was defined as failing ≤ 1 adequate medication trial in the present episode by ATHF criteria. The primary analysis was conducted using the intent-to-treat population defined as all randomized patients who entered Phase 2 of the study. Baseline demographics were compared using Student's *t*-test for continuous measures and a χ^2 test for categorical measures. All tests were two-sided and assessed at a significance level of 0.05.

RESULTS

The baseline demographic and clinical variables of the 141 patients entering Phase 2 of the study are outlined in Table 1. Of the patients who agreed to participate in Phase 2, 80 had been randomized to sham treatment in Phase 1 and 61 patients randomized to active treatment in Phase 1. Overall, the demographics of the patients who entered Phase 2 were not

significantly different from those of the patients in Phase 1. Phase 2 patients were predominantly female (55%), were an average age of 47.2 years old with a current depression episode duration of approximately 80 weeks, and a mean HAM-D of 26.3 at the start of Phase 1. Phase 2 patients had failed 1.6 adequate antidepressant trials in the present episode and an average of almost 4 antidepressant trials in their lifetime. There were slightly more Phase 2 patients with low antidepressant resistance.

A flow chart of each phase of the study is outlined in Figure 1. Of the original 190 patients enrolled in Phase 1, 92 were in the active arm and 98 were in the sham arm. Thirteen patients in the active arm remitted in Phase 1 and moved to Phase 3 and 5 patients in the sham arm remitted and moved to Phase 3. Thirty-one patients declined to continue into Phase 2 and 141 patients consented to Phase 2a: 61 patients consented to Phase 2a who were originally in the active arm of Phase 1 and 80 patients consented to Phase 2a from the sham arm of Phase 2.

Forty-three of 141 (30.5%) patients in Phase 2 met criteria for remission. Fifty-eight patients (41%) in Phase 2 met criteria for treatment response. Of those patients who remitted in Phase 2, 19/43 (44%) were from the active arm of Phase 1 and 24/43 (56%) were from the sham arm. Treatment assignment (active/sham) in Phase 1 was not statistically associated with remission in Phase 2, for either fast left or slow right treatment (Wald χ^2 0.02; $P = .89$ and $.08$; $P = .78$, respectively). A similar result was found for response in Phase 2 to fast left and slow right (Wald χ^2 0.01; $P = .92$ and $.60$; $P = .44$, respectively).

Average HAM-D scores by weeks of treatment and randomization assignment for patients that remitted in Phase 2 are shown in Figure 2. There seems to be no difference in the average scores for patients who were assigned to active or sham treatment in Phase 1. Figure 2 shows the average HAM-D scores by weeks of active treatment (i.e., all weeks of treatment minus weeks of sham treatment equals weeks of active treatment). As shown in Figure 3, the average scores seem to have similar slopes, except for the first 3 weeks in the active treatment group which is relatively flat. This initial flat response in the active treatment group is to be expected because patients entering Phase 2 from Phase 1 were enrolled because they showed no improvement in the first 3 weeks of Phase 1.

Sixteen percent ($n = 22/141$) of Phase 2 patients who were administered open label fast left treatments remitted. Active versus sham treatment in Phase 1 was not associated with remission in Phase 2 fast left. The total number of weeks of fast left treatment (combining Phase 1 and 2) did differ between remitters and nonremitters. Remitters received a mean of 5.2 (± 1.9) weeks of active fast left treatment in Phase I and II (median = 5.8 weeks) and nonremitters received a mean of 4.4 (± 1.8) weeks of active treatment (median = 3.8 weeks). Remitters had a slightly lower

TABLE 1. Clinical and demographic data for patients entering Phase II

	Active (N = 61)	Sham (N = 80)	Phase II (N = 141)	P-value
Sex				
Male	22 (36%)	41 (51%)	63 (45%)	.07
Age				
Mean (SD)	47.5 (11.3)	46.9 (12.3)	47.2 (11.8)	.76
Range	22–69	23–69	22–69	
Current episode duration (weeks)				
Mean, Median (SD)	77.2, 56 (62.8)	81.0, 60.5 (66.9)	79.3, 56 (65.0)	.73
Range	8–260	4–260	4–260	
Baseline HAM-D				
Mean (SD)	26.1 (5.3)	26.5 (4.6)	26.3 (4.9)	.62
Range	20–43	20–42	20–43	
Initial phase II HAM-D				
Mean (SD)	24.6 (5.9)	24.5 (6.0)	24.6 (6.0)	.92
Range	13–40	11–39	11–40	
Baseline MADRS				
Mean (SD)	29.9 (6.9)	30.2 (6.2)	30.1 (6.5)	.76
Range	16–43	12–44	12–44	
Initial Phase II MADRS				
Mean (SD)	29.0 (6.7)	30.4 (6.2)	29.8 (6.4)	.25
Range	16–47	17–43	16–47	
Baseline IDS				
Mean (SD)	41.7 (9.2)	39.7 (9.4)	40.5 (9.3)	.22
Range	26–63	18–64	18–64	
Initial Phase II IDS				
Mean (SD)	38.1 (11.4)	38.4 (12.0)	38.3 (11.7)	.87
Range	16–70	11–76	11–76	
Failed antidepressant trials				
Current				
Mean, median (SD)	1.75, 1 (1.39)	1.48, 1 (0.98)	1.60, 1 (1.18)	.18
Range	0–6	0–4	0–6	
Lifetime				
Mean, median (SD)	3.70, 3 (2.97)	3.50, 3 (2.10)	3.59, 3 (2.51)	.65
Range	0–14	0–9	0–14	
ATHF				
Low antidepressant resistance	31 (50.8%)	54 (67.5%)	85 (60.3%)	.05
High antidepressant resistance	30 (49.2%)	26 (32.5%)	56 (39.7%)	
Right motor threshold	n = 60	n = 78	n = 138	
Mean (SD)	56.3 (12.4)	57.9 (11.7)	57.2 (12.0)	.44
Range	36–83	39–85	36–85	
Left motor threshold	n = 61	n = 79	n = 140	
Mean (SD)	58.2 (10.7)	57.2 (10.0)	57.6 (10.3)	.55
Range	36–80	35–76	35–80	

The columns compare those patients entering Phase 2 that were randomized to active versus sham treatment in Phase 1. All numbers are mean values (\pm standard deviation). Baseline values for the measures of psychiatric symptoms (HAM-D or 21-item Hamilton Depression Rating Scale;^[8] MADRS or Montgomery–Åsberg Depression Rating Scale; IDS 30-item Inventory of Depressive Symptoms. Failed antidepressant trials were assessed using the Antidepressant Treatment History Form^[11] and low antidepressant resistance was failing one or fewer antidepressant trials in the present episode of depression. Motor threshold was assessed at baseline and is the mean percent of maximal output over the premotor cortex.

HAM-D score when they started Phase 2 (HAMD for remitters = 22.8 (+5.4); HAMD for nonremitters = 24.9 (+6)), but the relationship between remission and initial Phase 2 HAM-D was not significant.

Approximately 40% of the patients who enrolled in Phase 2 had a high level of medication resistance, yet only 18% (4/22) of patients who remitted in Phase 2 fast left had a high level of medication resistance. Low medication resistance was associated with remission in Phase 2 fast left (Wald $\chi^2 = 4.59$; $P = .03$). The odds

ratio (95% confidence interval) of a low medication resistance patient remitting was 3.5 (1.1, 11.2) times more likely than a high medication resistance patient remitting.

Twenty-six percent (21/81) of patients who were administered open label slow right treatments remitted. Again active versus sham treatment in Phase 1 was not associated with remission in Phase 2 slow right (Wald $\chi^2 = 0.08$; $P = .78$), but the average number of active weeks of treatments in Phase 1 and 2 was again

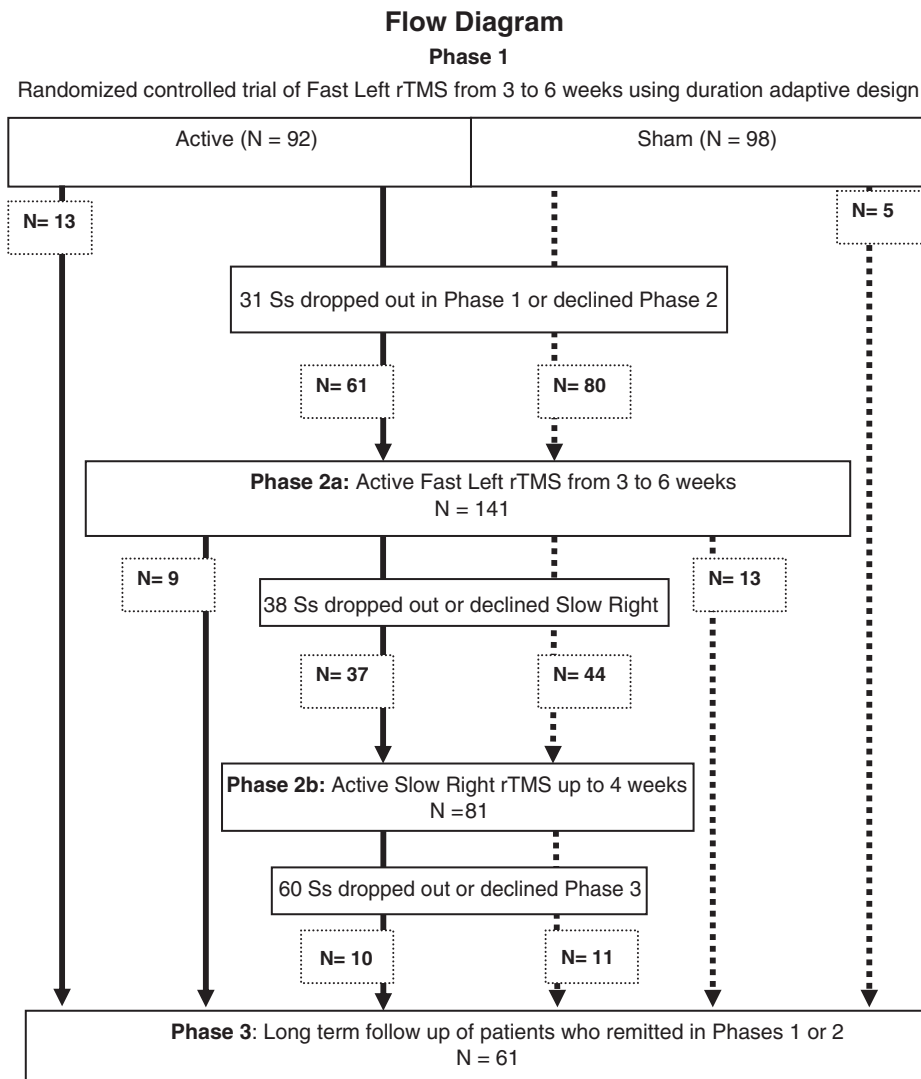


Figure 1. Randomized-controlled trial of fast left rTMS from 3 to 6 weeks using duration adaptive design. Flow diagram of patients participating in OPT TMS trial. rTMS is repetitive transcranial magnetic stimulation. Phase 1 has been described in a previous article.^[1] Phase 2 is the subject of this article and includes both an open label active trial of fast left rTMS trial (Phase 2a) and an open label slow right rTMS trial (Phase 2b). Patients who remitted in each phase are shown moving to Phase 3. Other patients are either included as drop outs or shown moving to the next phase. For example, in Phase 2a (active fast left rTMS), nine patients who were in the active arm in Phase 1 and 13 patients who were in the sham arm of Phase 1 remitted and moved to Phase 3. Thirty-eight patients dropped out or declined further treatment and 37 patients who were originally in the active arm of Phase 1 and 44 patients who were in the sham arm of Phase 1 consented to start Phase 2b (active slow right rTMS). Phase 3 will be detailed in a manuscript under review and is the long-term follow-up of patients on a standardized medication trial to evaluate relapse rates after rTMS. Of the patients who remitted in either Phase 1, Phase 2a, or Phase 2b, 61 patients consented to participate in Phase 3.

slightly higher in patients who remitted (7.9 (± 3.0) weeks of treatment versus 7.4 (± 2.1) weeks of treatment for nonremitters). Similar to fast left patients, the patients who remitted during Phase 2 slow right had a lower absolute HAM-D score entering this phase than the nonremitters (HAM-D for remitters = 17.9 (+7.2); HAM-D for nonremitters = 22.9 (+7.9)). Unlike the patients in Phase 1 and 2 fast left, the Phase 2 slow right patients did not show a relationship between medication resistance and remission (Wald $\chi^2 = 0.02$; $P = .88$)

ADVERSE EVENTS

There were no seizures or suicides in the open label treatment phase of the study. One patient had increased suicidal ideation in fast left treatment. This patient had received sham treatment in Phase 1. One other patient in fast left treatment had a significant worsening of depression and three patients in slow right treatment reported significant worsening of depression. Many of these patients would have been in the study and off of all mood stabilizers for weeks.

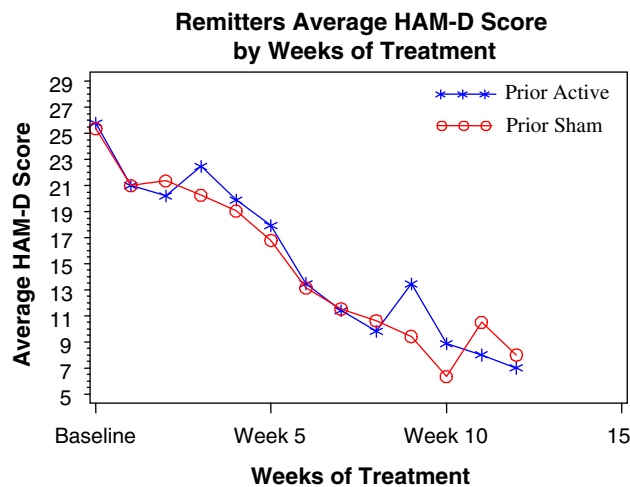


Figure 2. Remitters average HAM-D score by weeks of treatment. The graph depicts the number of weeks of treatment in the study including Phase 1 and 2 and showing the average Hamilton Depression Scale Score (HAM-D) only for patients who remained in the study. The x-x-x line depicts patients who received active treatment in Phase 1 (prior active) and the o-o-o line depicts patients who received sham treatment in Phase 1 (prior sham).

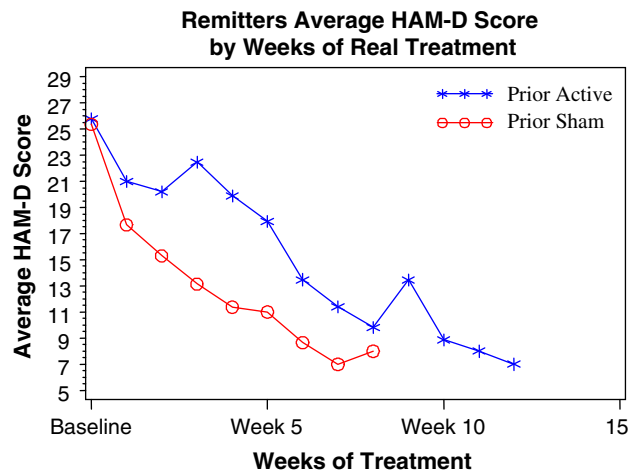


Figure 3. Average HAM-D score by weeks of active treatment. The graph depicts the number of weeks of treatment in the study, including Phase 1 and 2, and showing the average Hamilton Depression Scale Score (HAM-D) only for patients who stayed in the study for the entire 12 weeks. The x-x-x line depicts patients who received active treatment in Phase 1 (prior active) and the o-o-o line depicts patients who received sham treatment in Phase 1 (prior sham). Real treatment is defined as the total number of weeks of treatment minus the number of weeks of sham treatment (or 4 weeks during Phase 1 for those patients randomized to sham).

The most common spontaneous adverse events are reported in Table 2. The spontaneous adverse events were very similar to those reported for active TMS in the Phase 1 study. For example, in Phase 1 the

TABLE 2. Spontaneous adverse events in open label fast left and slow right rTMS

Adverse event	Number of unique subjects	Percent of total subjects
Headache	36	26
Discomfort at stimulation site	26	18
Insomnia	15	11
Worsening of depression	14	10
Muscle aches	9	6
Gastrointestinal	7	5
Fatigue	6	4
Other	44	31

rTMS, repetitive transcranial magnetic stimulation. Adverse events were code in a MedDRA-modified manner similar to a recent rTMS depression trial.^[2]

most common adverse events in the active arm were headache, discomfort at the stimulation site, and insomnia, which were reported by 32, 18, and 7.6% of patients, respectively.

Table 3 reports the number of subjects in each arm who reported spontaneous adverse events. None of these patients had any sequelae (e.g., development of chronic headaches or pain on their scalp) that was noted when they were in the study or in our follow-up phases.

DISCUSSION

This article reports on an open phase extension of a multicenter sham-controlled trial of fast left rTMS in TRD.^[1] The remission rate of patients receiving open label rTMS in this study (30.5%) was more than double the remission rate of patients receiving active treatment in the sham-controlled trial (14.1% active rTMS versus 5.1% sham; $P < .02$). These remission rates are encouraging given the fact that patients enrolled in this study had failed an average of 1.6 medication trials in their present episode of depression. In patients who have failed two medication trials, open label studies of pharmacotherapy have shown that less than 20% of patients remit with another medication trial or augmentation. In patients with three failed medication trials (the lifetime average of this group), remission rates are between 10 and 20%.^[12-14] The safety data are also encouraging given the fact that some patients may have received multiple weeks of active rTMS with few significant adverse events, no reported seizures, and no long-term sequelae. This study supports rTMS as an important therapy for TRD.

This study examined two variables that are potentially related to this treatment response: optimizing the number of rTMS treatments and changing the treatment site. In the multicenter sham-controlled trial (Phase 1),^[1] no patient received more than 5 weeks of rTMS treatment because patients who did not meet minimal response criteria (e.g., a 30% decrease in the

TABLE 3. Spontaneous adverse events in open label fast left rTMS versus slow right rTMS

	Fixed fast left (<i>n</i> = 141)	Variable fast left (<i>n</i> = 27)	Slow right (<i>n</i> = 81)
Adverse event			
Headache	24 (17%)	2 (7%)	10 (12%)
Discomfort at stimulation site	20 (14%)	2 (7%)	4 (5%)
Insomnia	11 (8%)	1 (4%)	3 (4%)
Worsening of depression	11 (8%)	0	3 (4%)
Muscle aches	6 (4%)	0	3 (4%)
Gastrointestinal	4 (3%)	0	3 (4%)
Fatigue	5 (4%)	0	1 (1%)
Other	27 (19%)	4 (15%)	12 (15%)

rTMS, repetitive transcranial magnetic stimulation. Adverse events are reported as percent of unique number of subjects reporting adverse event in each group with the percent of these subjects in each group reported in parentheses. Adverse events were code in a MedDRA-modified manner similar to a recent rTMS depression trial.^[2]

baseline HAM-D at 3 weeks with continued response in weeks 3–5) were dropped from Phase 1. Yet, the average weeks of treatment for remitters in the open phase extension of active fast left rTMS (i.e., Phase 2) was 5.2 weeks of active treatment. Clearly, some patients needed more than 5 weeks of active rTMS and the criteria for patients to remain in Phase 1 and receive additional treatment (i.e., a decrease of $\geq 30\%$ in the HAM-D at 3 weeks with continued improvement on biweekly HAM-D measurements) may have been overly restrictive and artificially decreased the remission rate for active treatment.

These results are congruent with a previous multi-center sham-controlled trial of fast left rTMS, which did not find a significant difference in remission rates between active fast left rTMS and sham treatment until week 6.^[2] In the open phase extension of that trial, Avery et al. analyzed patients who received active treatment in the blinded randomized trial separately from patients who initially received sham treatments.^[15] The patients who were treated with active treatment in the randomized blinded phase then open label active treatment had a 20% remission which was significantly higher than those who received sham then open label active (14.2% remission rate).

The results of this study are, however, limited by the fact that the patients were in an open label trial. Although the active sham coil used in Phase 1 was effective in masking patients and treaters from determining active from sham treatments in Phase 1,^[1] the more difficult task would be for patients who had experienced sham stimulus to change to active stimulus (i.e., within, as opposed to between subject blinding) and not notice a qualitative difference. If a patient could distinguish a difference in sensation in the sham and active conditions (e.g., the active conditions was qualitatively different with more scalp sensations than the sham condition), then patients switching from sham to active conditions would “expect” to have a higher rate of response because they experienced a more tactically intense treatment. In this study, there were no differences in response or remission rates in

Phase II for patients who had received sham or active treatment in Phase 1.

The patients entering Phase 1 and 2 were similar in their demographic and clinical variables and the differences in remission rates do not appear to be due to a difference in patient characteristics. Eighty-two percent of eligible Phase 1 patients (141/172) consented to Phase 2 and the demographic and clinical data of the patients entering Phase 1 and 2 were not significantly different. Therefore, patients who eventually remitted in Phase 2 may have been showing some response to Phase 1 treatment, although not enough to meet the minimal response criteria to remain in Phase 1.

Finally, medication resistance was an important clinical variable in remission in both Phase 1 and 2 fast left with medication-resistant patients remitting at lower rates. The relationship of treatment response to medication resistance has been found in other randomized rTMS trials.^[2] In Phase 2, the remission rate for patients with high medication resistance on the ATHF was low (only 18% of remitters had high medication resistance) as it was in Phase 1 (16.7% of patients who remitted in Phase 1 and were assessed as having a high level of medication resistance^[1]).

The remission rate to slow right rTMS (26%) was higher than would have been expected, because the patients in this group had already failed fast left rTMS. Unlike responders to fast left, the slow right remitters did not show a relationship of medication resistance to remission rate.^[1,2] Patients who do not remit with fast left rTMS, particularly TRD patients, therefore, may benefit from changing to slow right.

The other possibility is that these TRD patients may have benefited from additional rTMS pulses. In the open label extension by Avery et al.^[15] patients continued to have improvement in their depression scores over the entire 9 weeks which included the 6-week open phase and the 3-week taper. Avery et al. also found that the more active treatments a patient received, the less important treatment resistance was in determining response.

Slow right remitters received an average of 7.9 weeks of active treatment. In fact, Phase 1 baseline HAM-D

scores were similar for remitters and nonremitters to slow right, but the remitters had lower HAM-D scores before starting slow right, supporting the hypothesis that remitters to slow right may have been starting to respond and needed additional treatments. The difference was not statistically significant and future research is needed to determine the clinical variables that should be used to continue treatment in patients who do not remit.

The results of this study are limited by the open label design and practical considerations. The finding that some patients may need 6–9 weeks (~90,000 or more total pulses) is a practical problem in both study design and clinical practice. Recent advances in rTMS administration demonstrate the safety and efficacy of providing accelerated treatments (i.e., 15,000 pulses administered over 2 days)^[16] and future studies should focus on delivering more treatments and evaluating the efficacy of slow right rTMS particularly in TRD.

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