Transcranial Magnetic Stimulation in the Acute Treatment of Major Depressive Disorder: Clinical Response in an Open-Label Extension Trial

David H. Avery, M.D.; Keith E. Isenberg, M.D.; Shirlene M. Sampson, M.D.; Philip G. Janicak, M.D.; Sarah H. Lisanby, M.D.; Daniel F. Maixner, M.D.; Colleen Loo, M.D.; Michael E. Thase, M.D.; Mark A. Demitrack, M.D.; and Mark S. George, M.D.

Background: This report describes the results of an open-label extension study of active transcranial magnetic stimulation (TMS) in medication-resistant patients with major depressive disorder who did not benefit from an initial course of therapy in a previously reported 6-week, randomized controlled study of active versus sham TMS.

Method: Patients with DSM-IV–defined major depressive disorder were actively enrolled in the study from February 2004 through September 2005 and treated with left prefrontal TMS administered 5 times per week at 10 pulses per second, at 120% of motor threshold, for a total of 3000 pulses/session. The primary outcome was the baseline to endpoint change score on the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: In those patients who received sham in the preceding randomized controlled trial (N = 85), the mean reduction in MADRS scores after 6 weeks of open-label active TMS was –17.0 (95% CI = –14.0 to –19.9). Further, at 6 weeks, 36 (42.4%) of these patients achieved response on the MADRS, and 17 patients (20.0%) remitted (MADRS score < 10). For those patients who received and did not respond to active TMS in the preceding randomized controlled trial (N = 73), the mean reduction in MADRS scores was –12.5 (95% CI = –9.7 to –15.4), and response and remission rates were 26.0% and 11.0%, respectively, after 6 weeks of additional open-label TMS treatment.

Conclusions: This open-label study provides further evidence that TMS is a safe and effective treatment of major depressive disorder. Furthermore, continued active TMS provided additional benefit to some patients who failed to respond to 4 weeks of treatment, suggesting that longer courses of treatment may confer additional therapeutic benefit.

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Received July 25, 2007; accepted Dec. 28, 2007. *From the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Harborview Medical Center, Seattle (Dr. Avery); the Department of Psychiatry, Washington University School of Medicine, St. Louis, Mo. (Dr. Isenberg); Mayo Clinic College of Medicine, Rochester, Minn. (Dr. Sampson); the Department of Psychiatry, Rush University Medical Center, Chicago, Ill. (Dr. Janicak); the Brain Stimulation and Therapeutic Modulation Division, Department of Psychiatry, Columbia University/New York State Psychiatric Institute, New York (Dr. Lisanby); the Department of Psychiatry/ECT Program, University of Michigan Health System, Ann Arbor (Dr. Maixner); School of Psychiatry, University of New South Wales, Sydney, Australia (Dr. Loo); the Department of Psychiatry, University of Pennsylvania, Philadelphia (Dr. Thase), and Neuronetics, Inc., Malvern (Dr. Demitrack), Pa.; and the Department of Psychiatry, Medical University of South Carolina, Charleston (Dr. George).*

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Corresponding author and reprints: David H. Avery, M.D., University of Washington School of Medicine, Harborview Medical Center, Box 359896, 325 Ninth Ave., Seattle, WA 98104-2499 (e-mail: averydh@u.washington.edu).

The efficacy of transcranial magnetic stimulation (TMS) has been shown in many sham-controlled studies.[1–6] More recently, a large, multisite trial of TMS administered to patients with treatment-resistant depression demonstrated superiority for TMS over a sham condition in a randomized controlled trial.[7] A unique feature of that trial design allowed nonresponders (defined by prespecified criteria) who had received at least 4 weeks of double-blind treatment the opportunity to enroll in a second extension trial and receive 6 weeks of open-label TMS.

The enrollment of patients who had failed to respond during the blinded, randomized sham-controlled trial into an open-label extension provides additional insights into TMS treatment effectiveness. Specifically, for the subgroup of patients who had received the sham intervention during the previous double-blind study, this second, open-label study represents a partial crossover trial. Furthermore, for the patients who had not responded

to blinded assignment to active TMS during the double-blind study, extension of active TMS for an additional 6 weeks provides clinically relevant information about safety and efficacy of a longer course of TMS therapy. More generally, the optimal duration of all forms of treatment for depression remains a poorly understood variable. The sham-controlled trial that preceded the open-label extension was designed based on what were estimated to be optimal treatment parameters, including the duration of treatment. Thus, the observation of treatment response over the duration of the open-label trial could reveal additional information about the rate of treatment response.

METHOD

Study Overview

This study was conducted as a separate, open-label extension trial accompanying a randomized sham-controlled, clinical trial of TMS monotherapy in patients with unipolar, nonpsychotic major depressive disorder.[7] In the randomized controlled trial, 301 medication-free patients were randomly assigned to active (N = 155) or sham (N = 146) conditions. Sessions were conducted 5 times per week with TMS at 10 pulses/s, 120% of motor threshold, 3000 pulses/session, for 4 to 6 weeks. The outcome variables were the symptom score change as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS)[8] and changes on the 17- and 24-item Hamilton Rating Scale for Depression (HAM-D)[9] and responses and remission rates with the MADRS and HAM-D. Active TMS was significantly superior to sham TMS on the MADRS at week 4 (with a post hoc correction for inequality in symptom severity at baseline), as well as on the HAM-D scores. Response rates were significantly higher on all 3 scales at both 4 and 6 weeks.

Patients who failed to receive benefit from at least 4 weeks of randomized treatment assignment in the controlled trial (i.e., either active or sham TMS) could participate in the open-label trial of TMS. To minimize treatment bias in either study, the specific criterion definition for lack of meaningful benefit was concealed from the investigators and the patients and is discussed in more detail below. Patients and investigators remained blinded to prior randomized treatment assignment upon entry into the open-label extension study.

The study was conducted at 23 study sites in the United States (20 sites), Australia (2 sites), and Canada (1 site), with active enrollment extending from February 2004 through September 2005. Institutional review board approval was obtained at all sites. The study was conducted under an Investigational Device Exemption from the U.S. Food and Drug Administration. All subjects provided informed consent, documented prior to initiation of any study procedures.

The open-label study had 2 phases: a 6-week, antidepressant medication–free acute phase and a 3-week taper phase during which TMS was tapered and a single antidepressant medication was initiated. The antidepressant medications initiated during the 3-week taper phase included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, clomipramine, bupropion, mirtazapine, imipramine, phenelzine, tranylcypromine, or trazodone. During the acute phase, TMS sessions were scheduled daily in a 5-day sequence each week, for a maximum of 30 sessions (6 weeks), and typically administered on a Monday through Friday schedule. During the taper phase, TMS was given 3 times in the first taper week, twice in the second taper week, and once in the third week.

Subjects

One hundred sixty-six subjects were eligible for entry and signed an informed consent statement for study participation. Of those, 158 patients formed the protocol-defined evaluable dataset (patients who entered the study and were present for at least 1 postbaseline observation timepoint). Patients were eligible to participate in the open-label study if they had been enrolled in the previous randomized controlled trial, had participated for at least 4 weeks of treatment in that study, and had shown no meaningful clinical benefit at the time of their exit. Concealment of entry criteria minimized assessment bias for both studies. At the time of eligibility consideration for the open-label study, the investigator reported to the study sponsor central office a summary of baseline and exit clinical rating scores, including HAM-D-24, HAM-D-17, and MADRS total scores and Clinical Global Impressions-Severity of Illness scale (CGI-S)[10] scores. The sponsor then applied an a priori–defined criterion of a HAM-D-17 total score reduction from baseline of < 25%. All subjects whose HAM-D-17 change met this criterion were potentially eligible, and the investigator was so informed.

In addition to the clinical symptom severity criterion, all subjects were outpatients, aged 18 to 70 years, and met DSM-IV diagnostic criteria for major depressive disorder (MDD), nonpsychotic, single episode or recurrent, with a current episode duration of no more than 3 years at the time of enrollment into the entry trial. Prior antidepressant treatment during the current episode was assessed using the Antidepressant Treatment History Form.[11] Patients had failed to receive benefit by Antidepressant Treatment History Form criteria for at least 1 but no more than 4 adequate antidepressant treatments in the current episode. Alternatively, patients were eligible if they had marked intolerance to antidepressants as demonstrated by 4 failed attempts to tolerate an adequate medication trial (lifetime). Patients were free of antidepressant medications at the time of study. Detailed

exclusion criteria for study participation were reported previously.[7]

Study Device Description and TMS Session Procedures

TMS sessions were delivered using the Neurostar TMS Therapy System investigational device (Neuronetics, Inc.; Malvern, Pa.). All efficacy outcome measures were assessed by certified raters who were blinded to a patient's prior treatment allocation in the randomized study. The methods for rater certification are available from the study authors upon request. Efficacy assessments were obtained at baseline (week 0), during the acute phase (weeks 2, 4, and 6), and weekly during the taper phase (weeks 7, 8, and 9).

Treatment was fixed at 120% magnetic field intensity relative to the patient's resting motor threshold, at a repetition rate of 10 magnetic pulses per second, with a stimulus train duration (on time) of 4 seconds and an intertrain interval (off time) of 26 seconds. Motor threshold estimation was repeated weekly by visual observation of thumb or other finger movement[12] using the MT Assist (Neuronetics, Inc.; Malvern, Pa.). This standardized, software-based algorithm provides an iterated estimate of a patient's motor threshold. Stimulation levels were adjusted weekly to the patient's derived motor threshold, although these were relatively stable over the course of therapy. The left dorsolateral prefrontal cortex was the treatment location and was determined by movement of the TMS coil 5 cm anterior to the motor threshold location along a left superior oblique plane with a rotation point at about the tip of the patient's nose.[13] Spatial coordinates were recorded with a mechanical coil positioning system to ensure placement reproducibility.

During the first week of the acute phase only, treatment intensity could be reduced to 110% for tolerability, but was then required to return to 120% from week 2 onward. Each treatment session lasted 37.5 minutes for a total of 3000 magnetic pulses delivered per session.

Concomitant Treatments

All patients were free of antidepressants or other psychotropic medications for depression during the acute treatment phase. Patients were allowed only limited use of either hypnotics or anxiolytics for treatment-emergent insomnia or anxiety, respectively. Up to 14 daily doses of either medication were permitted in the acute treatment phase.

Efficacy Assessments

The primary efficacy outcome was the change in total score on the MADRS from the start of the open-label phase to 6 weeks or study endpoint. Secondary outcome measures included HAM-D-24 and HAM-D-17 total scores and categorical endpoints using the MADRS, HAM-D-24, and HAM-D-17. Response on each of these measures was defined as at least 50% reduction in baseline score. Remission on the MADRS was defined as a score of less than 10, on the HAM-D-24 as a score of less than 11, and on the HAM-D-17 as a score of less than 8.

Global clinical status was assessed using the observer-rated CGI-S. Patient-reported outcomes were obtained using the Inventory of Depressive Symptomatology–Self Report version (IDS-SR)[14] and the Patient Global Impressions-Improvement scale.[10] Quality of life and functional status outcomes were assessed with the Medical Outcomes Study 36-Item Short Form and the Quality of Life Enjoyment and Satisfaction Questionnaire and will be summarized in a separate report.

Safety Assessments

Safety was assessed at every treatment visit by recording spontaneous adverse event reports, which were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Additional safety evaluations included targeted assessment of air-conduction auditory threshold at baseline, week 4, and week 6. Cognitive function was assessed at the same timepoints using the Mini-Mental State Examination, the Buschke Selective Reminding Test, and the short form of the Autobiographical Memory Interview. A more detailed review of the auditory threshold data and cognitive function outcomes will be the subject of a separate report.

Statistical Methods

The subjects participating in this open-label extension trial are not a randomized sample because of their differing treatment assignment in the preceding randomized controlled trial. Indeed, we hypothesized that because of the efficacy of active TMS, the prior treatment allocation would have differentially sorted the patients participating in this study. In particular, we presumed that patients previously allocated to active TMS in the randomized trial would be a less treatment-responsive group during the open-label treatment because all of the easier to treat members of that group had been preferentially retained in the preceding randomized trial. Based on these considerations, results in this report are always shown separately for the study populations based on their prior randomized treatment assignment. Also, since these 2 groups were not fully randomized, in general, we present the data as descriptive statistical summaries. Categorical outcomes are always computed using the total enrolled sample for the specific treatment group at study entry as a constant denominator. We specifically note where inferential comparisons are made, for example, for selected within-group comparisons, and provide justification in the text or footnotes of the relevant table or figure.

Table 1. Demographic Features, Illness History Variables, and Symptom Severity of Study Population

Variable	Treatment Group: Extended TMS (N = 73)	Treatment Group: Sham-to-TMS (N = 85)	p Value[a]
Demographic variables			
Female, N (%)	38 (52.1)	40 (47.1)	.63
Age, mean (SD), y	47.8 (11.2)	50.0 (10.1)	.22
Ethnic origin, N (%)			
White	71 (97.3)	78 (91.8)	
Other	2 (2.7)	7 (8.2)	.18
Clinical variables			
Recurrent illness course, N (%)	69 (94.5)	81 (95.3)	1.00
Duration of current episode ≥ 24 mo, N (%)	19 (26.0)	11 (12.9)	**.04**
No. of antidepressant treatments in current episode, mean (SD)	5.5 (2.8)	5.4 (2.9)	.83
No. of adequate antidepressant treatments in current episode, mean (SD)	1.7 (0.9)	1.7 (0.8)	1.00
Baseline symptom severity, mean (SD)			
MADRS total score	35.7 (5.9)	35.0 (5.2)	.46
HAM-D-24 total score	30.5 (5.5)	30.0 (5.8)	.49
HAM-D-17 total score	22.5 (3.8)	22.6 (3.8)	.91
CGI-S score	4.9 (0.8)	4.8 (0.8)	.68
IDS-SR total score	40.1 (14.9)	40.8 (13.9)	.75
Motor threshold, mean (SD)	51.1 (9.6)	55.5 (9.9)	**.01**

[a]Significant values are indicated by boldface type.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, IDS-SR = Inventory of Depressive Symptomatology–Self Report version, MADRS = Montgomery-Asberg Depression Rating Scale, TMS = transcranial magnetic stimulation.

RESULTS

Subject Characteristics

Demographic features, illness history variables, and symptom severity at baseline are shown in Table 1. Despite their differing treatment histories prior to entry, the 2 groups began the open-label portion of the study with comparable levels of depression. Patients were moderately to severely symptomatic, with moderate to severe levels of antidepressant treatment resistance in the current episode.

Patient Disposition

One hundred fifty-eight patients formed the evaluable dataset (met study inclusion criteria, received at least 1 active TMS treatment, and were present for a scheduled posttreatment follow-up assessment). Seventy-three patients had been allocated to active TMS in the preceding randomized study (extended TMS group), while 85 patients had been allocated to sham TMS in the preceding randomized study (sham-to-TMS group). Figure 1 shows the flow of subjects through the 6 weeks of the protocol and the taper phase. Adherence to the study protocol was excellent. The all-cause discontinuation rate through the end of the acute treatment phase for the entire study population was 17.7%. The treatment was well tolerated. Through the end of the acute treatment phase, no patients discontinued the study due to adverse events in the extended TMS group, while 9.4% (N = 8) did so in the sham-to-TMS group.

The median number of TMS sessions administered during the acute treatment phase was 29 (range, 2–30) and was identical in the extended TMS group and the sham-to-TMS group.

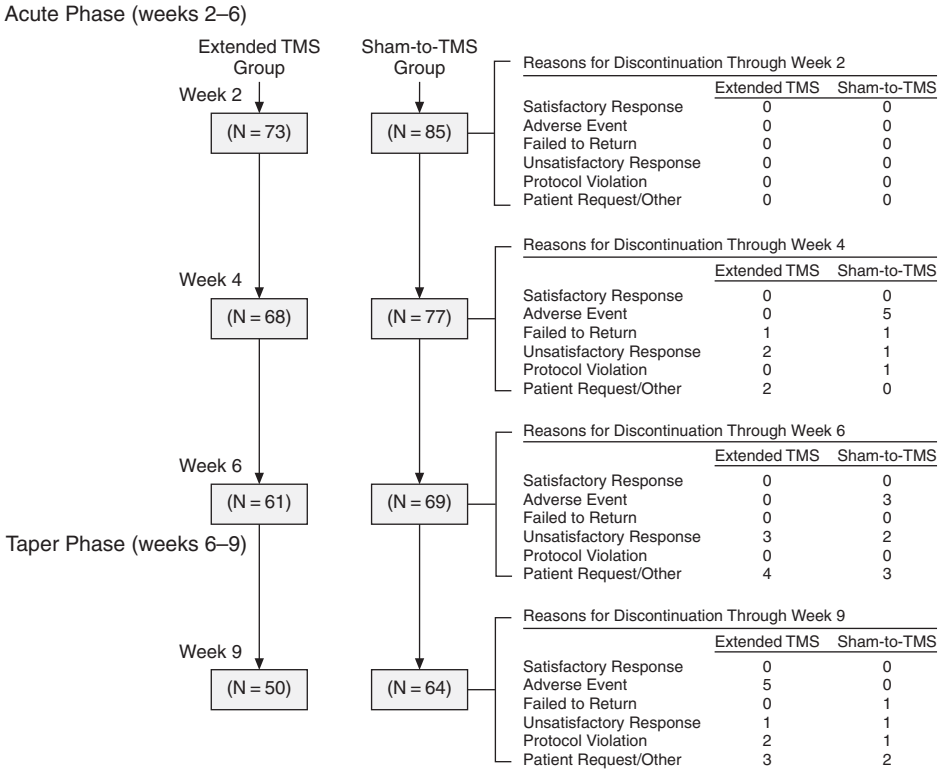
Effectiveness Outcomes

Improvement was observed in all efficacy assessments in both groups over the 6-week acute treatment phase and through the end of the 3-week taper phase. Mean changes from baseline for both the MADRS and HAM-D-24 total scores are shown in Figures 2A and 2B. Statistically significant improvement from baseline within group is shown on both scales from week 2 onward ($p < .001$). Factor scores for the HAM-D were also examined (core depression, Gibbons factor, Maier factor, anxiety/somatization factor, retardation factor, and sleep factor) and showed statistically significant ($p < .05$) improvement from baseline within group from week 2 onward (data not shown).

Categorical efficacy outcomes (response and remission) for the MADRS and HAM-D-24 are shown in Figure 3 over the 6-week acute treatment phase and through the end of the 3-week taper phase. As was observed for the continuous outcome measures on these scales, during the 3-week taper phase, clinical improvement did not plateau, but continued to improve further. At the conclusion of the taper phase, in the sham-to-TMS group, 44.7% of patients achieved response criteria on the MADRS, and 30.6% achieved remission. In the same group, 45.9% achieved response on the HAM-D-24, and 36.5% achieved remission. Similar observations were observed in the extended TMS group; at the end of the taper phase, 34.2% of patients achieved response criteria on the MADRS, and 17.8% achieved remission. In the same group, 31.5% achieved response on the HAM-D-24, and 19.2% achieved remission. In all instances, the sham-to-TMS group had superior clinical outcomes, consistent with the hypothesis that the extended TMS group represents a less treatment-responsive patient population.

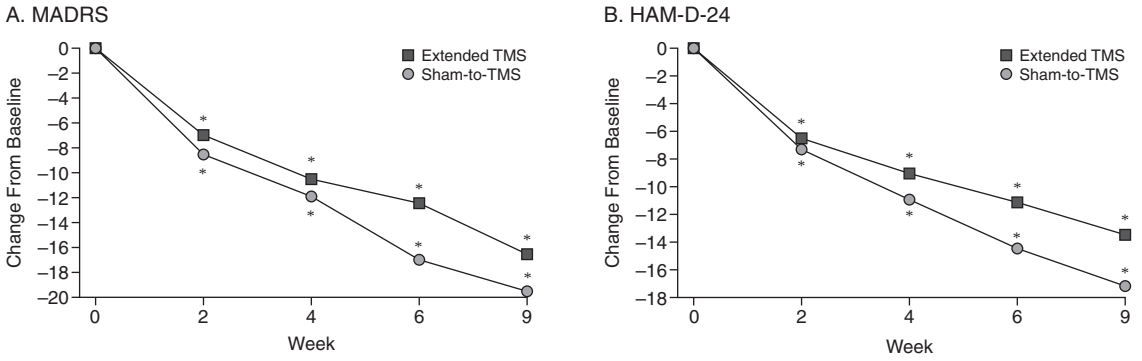
The outcomes described above in the extended TMS group indicate that a longer treatment course of TMS may ultimately prove beneficial, even when no clinical benefit was evident at the end of an acute treatment course of 6 weeks. In order to understand if the benefit from extended treatment reaches a plateau, the cumulative sustained response rate (HAM-D-17) was examined for the total population of patients who were randomly assigned to active TMS in the initial blinded TMS study (N = 155),

Figure 1. Patient Disposition and Reasons for Study Discontinuation Across All Study Phases



Abbreviation: TMS = transcranial magnetic stimulation.

Figure 2. Mean Change From Baseline in Continuous Outcome Measures (MADRS and HAM-D-24 total scores): Acute Treatment and Taper Phases

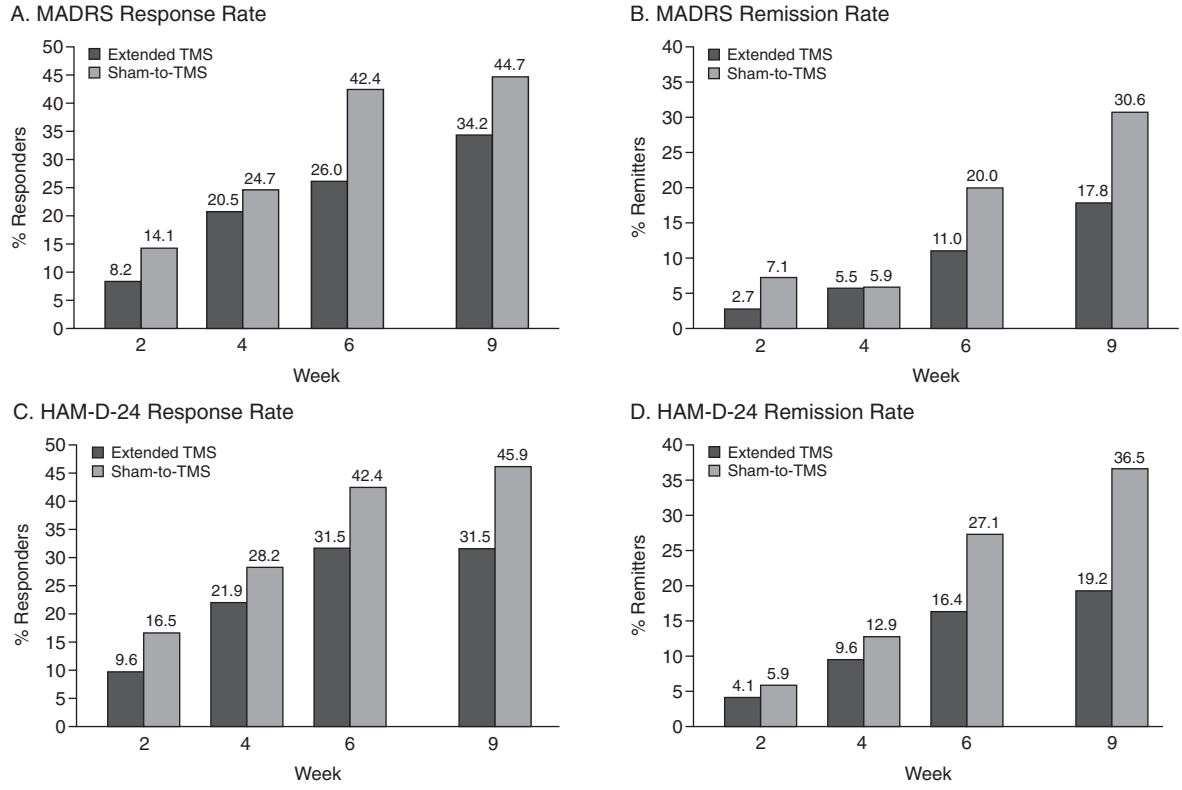


*p < .001 for within-group comparison of change from baseline.
Abbreviations: HAM-D-24 = 24-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, TMS = transcranial magnetic stimulation.

including those patients who did not respond initially and continued in the open-label TMS study. For this analysis, sustained response (HAM-D-17) was defined as achieving a ≥ 50% reduction in total score compared to baseline, with all subsequent scores remaining ≥ 25% reduced compared to baseline score. These data are summarized in Figure 4, where it can be seen that the potential benefit for late responders does not plateau across the 12 weeks of treatment, and clinical benefit was apparent in some patients even through the last treatment visit of the acute phase in the open-label study.

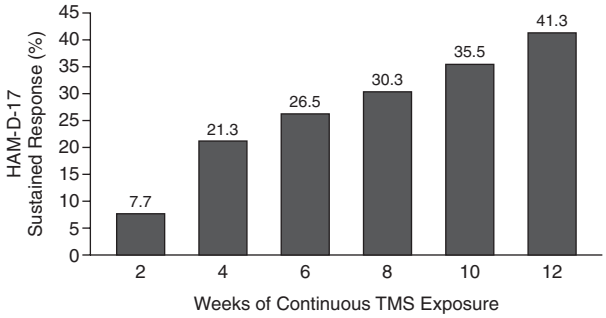
Finally, for both treatment groups, we examined whether any pretreatment clinical features were associated with greater likelihood of achieving a MADRS

Figure 3. Categorical Clinical Outcomes (response and remission) for MADRS and HAM-D-24: Acute Treatment and Taper Phases[a]



[a]Rates computed based on total enrolled sample for each group. MADRS response = 50% or greater reduction from baseline total score, MADRS remission = total score < 10, HAM-D-24 response = 50% or greater reduction from baseline total score, HAM-D-24 remission = total score < 11.
Abbreviations: HAM-D-24 = 24-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, TMS = transcranial magnetic stimulation.

Figure 4. Cumulative Incidence of Sustained Response[a] (HAM-D-17) for Subjects Allocated to Active TMS Through the Combined Acute Treatment Phases of the Randomized Controlled Trial and Open-Label Extension



[a]Sustained response = achievement of 50% or greater reduction from baseline score and 25% or greater reduction from baseline maintained at all subsequent timepoints.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, TMS = transcranial magnetic stimulation.

response at the end of 6 weeks of acute treatment. Variables examined included age, gender, duration of current episode, presence of a comorbid anxiety disorder, employment status, and baseline symptom severity (MADRS, HAM-D-24, and HAM-D-17 separately). In the sham-to-TMS treatment group, a statistically significant benefit in week 6 outcome was evident based on history of treatment failure, with those patients who had failed 1 fully adequate antidepressant treatment in current episode having a greater likelihood of favorable outcome compared to those who had failed to receive benefit from more than 1 adequate treatment (Table 2). In contrast, this benefit was not evident in the extended TMS group. On the other hand, in the extended TMS group, female gender was associated with a statistically significantly greater likelihood of response at week 6.

Table 3 summarizes the remaining efficacy outcome measures for the HAM-D-17, CGI-S, IDS-SR, and Patient Global Impressions-Improvement scale.

Safety Outcomes

There were no deaths and no seizures. Twelve serious adverse events were reported. Eleven were assessed by the

Table 2. Summary of Relationship Between Pretreatment Clinical Features and MADRS Responder Status at Week 6 of Acute Treatment[a]

	Extended TMS (N = 73)			Sham-to-TMS (N = 85)		
Variable	Week 6 Responder (N = 19)	Week 6 Nonresponder (N = 42)	p Value[b]	Week 6 Responder (N = 36)	Week 6 Nonresponder (N = 33)	p Value[b]
Age of 55–70 y	4 (21.1)	13 (31.0)	.42	13 (36.1)	11 (33.3)	.81
Female	14 (73.7)	17 (40.5)	**.02**	20 (55.6)	12 (36.4)	.11
Duration of episode > 2 y	3 (15.8)	8 (19.0)	.76	5 (13.9)	2 (6.1)	.43
Any comorbid anxiety disorder	5 (26.3)	17 (40.5)	.29	9 (25.0)	12 (36.4)	.31
Recurrent course	16 (84.2)	41 (97.6)	.09	36 (100.0)	32 (97.0)	.48
> 1 Adequate antidepressant treatment in current episode	10 (52.6)	21 (50.0)	.85	13 (36.1)	22 (66.7)	**.01**
Not employed	8 (42.1)	23 (54.8)	.46	18 (50.0)	19 (57.6)	.44
Baseline symptom severity, mean (SD)						
MADRS total score	34.8 (5.4)	36.6 (6.1)	.27	35.8 (5.8)	34.1 (5.9)	.22
HAM-D-24 total score	31.2 (5.7)	30.7 (5.8)	.77	30.5 (5.5)	30.3 (4.6)	.89
HAM-D-17 total score	23.0 (3.8)	22.6 (3.8)	.72	23.2 (3.9)	22.7 (3.3)	.55

[a]Values shown as N (%) unless otherwise specified.
[b]Significant values are indicated by boldface type.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, TMS = transcranial magnetic stimulation.

study investigator as not related to the study device. One patient experienced a serious adverse event of gradual onset of left-facial numbness, which was present in a sensory distribution consistent with irritation of the maxillary branch of the trigeminal nerve. Treatment was discontinued, and the event fully resolved.

There were no changes in auditory threshold or cognitive function. These data will be the subject of a separate report. Nonserious adverse events occurring in 5% or more of either treatment group are shown in Table 4. These events were generally mild to moderate in intensity and followed a pattern consistent with those observed in the preceding randomized controlled study,[7] with headache and cutaneous discomfort representing the most commonly reported events. As previously reported, there was evidence of rapid accommodation to the cutaneous discomfort as shown by the reduced incidence of this adverse event in the extended TMS group compared to the sham-to-TMS group.

DISCUSSION

These open-label data support the efficacy and safety of TMS in the treatment of major depressive disorder. In this study, TMS therapy was associated with a significant reduction in depression, as demonstrated across a variety of self-report and clinician-administered rating scales.

The response and remission rates observed at the end of 6 weeks of acute treatment (42.4% and 20.0%, respectively, on the MADRS) seen in the sham-to-TMS group were clinically superior when compared with the response and remission rates on that same instrument seen in the group randomly assigned to active TMS in the controlled study (23.9% and 14.2%, respectively).[7] As in any open-label study, the response and remission rates are probably higher because both the treating clinicians and patients know that an active therapy is being provided, hence amplifying the placebo effect via higher expectations for benefit.

In the absence of a within-study control condition, how can the clinical significance of the categorical efficacy outcomes be assessed? To address this question, it is instructive to compare the results observed here with similar open-label treatment results reported with the same clinical outcome methods. In fact, the remission rates seen using the HAM-D-17 remission outcome of a total score < 8 in this TMS study compare favorably to the remission rates on the same outcome metric that were observed in another open-label clinical study of major depressive disorder, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[15] The STAR*D study recruited patients who had no evidence of having failed to receive benefit from any of the antidepressant medications offered in the first 2 levels of that study and then examined the remission rates to several commonly used antidepressant monotherapies and augmentation strategies. When the initial treatment trial failed, sequential treatments were prescribed in a semi-naturalistic, sequential algorithm. The STAR*D results clearly show that, if patients have not benefited from at least 2 antidepressant trials, the likelihood of remission with subsequent trials decreases. As STAR*D was a multisite study providing open-label trials of antidepressant therapy, it is of some interest to compare those results with the results observed in the current study. Specifically, in STAR*D, remission rates after 1 and 2 unsuccessful courses of antidepressant therapy were 21% and 16%, respectively.[16] In the current study of TMS, the HAM-D-17 remission rates after 1 and 2 unsuccessful courses were 25.6% and 17.9%, respectively (Figure 5). Such similar remission

Table 3. Summary of Mean Change From Baseline Score (95% CI) for Clinician- and Patient-Rated Efficacy Outcome Measures

	Extended TMS Group (N = 73)				Sham-to-TMS Group (N = 85)			
Variable	Week 2	Week 4	Week 6	Week 9	Week 2	Week 4	Week 6	Week 9
Primary Outcome Measure (clinician-rated)								
MADRS	–7.0 (–5.1 to –8.8)	–10.5 (–8.4 to –12.7)	–12.5 (–9.7 to –15.4)	–16.6 (–13.1 to –20.1)	–8.5 (–6.6 to –10.4)	–11.9 (–9.7 to –14.1)	–17.0 (–14.0 to –19.9)	–19.3 (–15.8 to –22.7)
Secondary Outcome Measures								
Clinician-rated								
HAM-D-24	–6.7 (–5.1 to –8.3)	–9.0 (–7.0 to –11.0)	–11.1 (–8.6 to –13.5)	–13.6 (–10.7 to –16.6)	–7.4 (–6.0 to –8.9)	–11.0 (–9.2 to –12.8)	–14.5 (–12.3 to –16.8)	–17.1 (–14.4 to –19.8)
HAM-D-17	–4.9 (–6.1 to –3.8)	–6.4 (–7.9 to –5.0)	–8.2 (–10.0 to –6.4)	–10.0 (–12.1 to –7.8)	–5.7 (–6.8 to –4.6)	–8.2 (–9.6 to –6.9)	–10.8 (–12.5 to –9.0)	–15.0 (–14.8 to –10.7)
CGI-S	–0.5 (–0.7 to –0.3)	–0.8 (–1.0 to –0.6)	–1.3 (–1.6 to –0.9)	–1.8 (–2.2 to –1.4)	–0.6 (–0.8 to –.0.5)	–1.1 (–1.4 to –0.9)	–1.8 (–2.1 to –1.5)	–2.1 (–2.5 to –1.7)
Patient-rated								
IDS-SR	–4.3 (–8.2 to –0.4)	–6.8 (–11.0 to –2.6)	–9.9 (–14.8 to –5.1)	–15.3 (–20.3 to –10.4)	–5.6 (–8.4 to –2.8)	–11.4 (–14.7 to –8.1)	–16.8 (–21.2 to –12.4)	–19.8 (–24.6 to –15.0)
PGI-I	–1.1 (–1.4 to –0.7)	–1.3 (–1.7 to –0.9)	–1.6 (–2.0 to –1.2)	–2.0 (–2.4 to –1.6)	–1.0 (–1.3 to –0.7)	–1.5 (–1.9 to –1.2)	–2.0 (–2.3 to –1.6)	–1.8 (–2.2 to –1.4)

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, IDS-SR = Inventory of Depressive Symptomatology–Self Report version, MADRS = Montgomery-Asberg Depression Rating Scale, PGI-I = Patient Global Impressions-Improvement scale, TMS = transcranial magnetic stimulation.

rates suggest that the efficacy of TMS is at least comparable to that of second- or third-line pharmaceutical strategies.

The patients in the current study were required to discontinue their current antidepressant before starting the protocol. It is possible that concomitant antidepressant medication might add to the clinical benefit of TMS and that therefore the current study might underestimate the potential efficacy of TMS in clinical practice. In fact, some TMS efficacy studies that have allowed concomitant medication have reported remission rates higher than the rates usually seen when antidepressants are not added. At least 2 controlled TMS studies allowing medications have found remission rates of 50% in medication-resistant depressed patients.[6,17] Interestingly, Haskett and colleagues[18] found that ECT patients randomly assigned to receive either nortriptyline or venlafaxine concurrently with ECT had better response rates than those randomized to receive placebo medication during ECT.

The design of this study, with the inclusion of extended TMS group and sham-to-TMS group results, also allows unique insights into the potential for an extended course of TMS to ultimately provide clinical benefit in patients who have had a modest or no response to a standard course of up to 6 weeks of acute treatment. The greater proportion of patients resistant to more than 1 fully adequate antidepressant trial in the current episode among the nonresponders compared to responders in the sham-to-TMS group suggests that higher levels of medication resistance may be a poor prognostic sign early in the course of TMS. However, the level of medication resistance was not associated with nonresponse in the extended TMS group, suggesting that the predictive value of medication-resistance history may lessen as the number of TMS sessions increases.

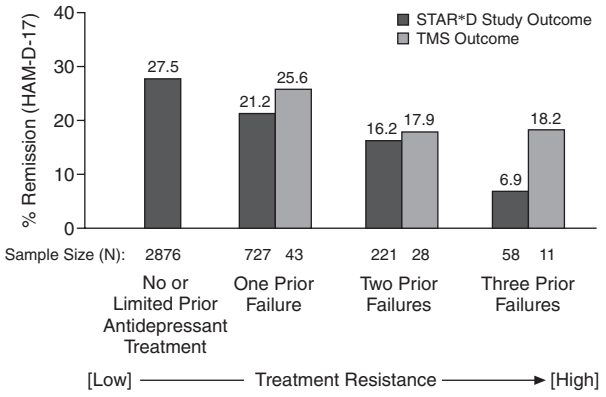
The continued increase in response and remission rates in both treatment groups during the 3-week TMS taper phase is also notable. The increase in the MADRS remission rate of 10.6% (from 20.0% at week 6 to 30.6% at week 9) in the sham-to-TMS group is similar to the increase of 6.4% in the active group of the double-blind portion of the study and clearly greater than the 3.4% increase seen in the sham group during the taper phase of that study.[7] A similar pattern was also seen when remission was assessed using either the HAM-D-24 or HAM-D-17. It is unlikely that the increase in remission rates seen in the TMS groups during the taper phase of this study could be explained by the passage of time or the start of medication treatment given the relative lack of change in remission rates in the sham group using the same protocol during the taper phase of the previous blinded, randomized study. Whether this improvement during the taper phase is a delayed effect of the 5 session per week TMS schedule; the effect of the continued, but less frequent TMS sessions during taper; or the addition of an antidepressant is unclear.

Table 4. Summary of the Overall Incidence of Adverse Events Occurring in 5% in Either Group and the Specific Incidence of Events Assessed by Investigator as Probably or Definitely Related to the Study Device[a]

	Extended TMS (N = 73)		Sham-to-TMS (N = 85)	
Body System[b]	Overall	Related	Overall	Related
Gastrointestinal disorders				
Nausea	10 (13.7)	2 (2.7)	6 (7.1)	0
Toothache	2 (2.7)	1 (1.4)	6 (7.1)	3 (3.5)
General disorders and site administration conditions				
Application site discomfort	7 (9.6)	7 (9.6)	8 (9.4)	8 (9.4)
Application site pain	8 (11.0)	8 (11.0)	27 (31.8)	27 (31.8)
Facial pain	0	0	5 (5.9)	4 (4.7)
Pain	4 (5.5)	1 (1.4)	3 (3.5)	1 (1.2)
Musculoskeletal and connective tissue disorders				
Muscle twitching	15 (20.5)	15 (20.5)	18 (21.2)	15 (17.6)
Nervous system disorders				
Dizziness	6 (8.2)	1 (1.4)	7 (8.2)	2 (2.4)
Headache	35 (47.9)	18 (24.7)	39 (45.9)	16 (18.8)
Paresthesia	5 (6.8)	3 (4.1)	4 (4.7)	1 (1.2)
Psychiatric disorders				
Anxiety	11 (15.1)	0	12 (14.1)	1 (1.2)
Insomnia	22 (30.1)	0	22 (25.9)	1 (1.2)
Skin and subcutaneous tissue disorders				
Pain of skin	1 (1.4)	1 (1.4)	5 (5.9)	5 (5.9)

[a]Values shown as N (%).
[b]Coded using MedDRA coding thesaurus body system and preferred terms.
Abbreviation: TMS = transcranial magnetic stimulation.

Figure 5. Remission Outcomes With TMS Therapy Compared to STAR*D Levels 1 Through 4, Stratified by Prior Antidepressant Treatment Failure



Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, STAR*D = Sequenced Treatment Alternatives to Relieve Depression, TMS = transcranial magnetic stimulation.

TMS was safe and well tolerated.[19] During the acute treatment phase of this study, cutaneous discomfort at the site of application was present in 31.8% of the sham-to-TMS group and only 11% of the extended TMS group. Discontinuation due to adverse events was greater in the sham-to-TMS group. Presumably, those who were unable to tolerate TMS in the preceding sham-controlled study dropped out and did not enter this study, leaving only patients who tolerated TMS. The discontinuation rate due to adverse events seen in this study ranged from 0% to 9.4% (depending on prior randomized treatment exposure), rates that compare favorably to the STAR*D discontinuation rates due to intolerance or adverse events, which ranged from 23.1% to 41.4%.[16,20] As in the sham-controlled study, there was an absence of systemic side effects such as weight gain or sexual dysfunction.

It is also worth noting that compared to the sham-to-TMS group, those in the extended TMS group had a significantly lower motor threshold at entry to this study. However, the reasons for this are not clear and cannot be answered in a definitive manner by either the controlled or open-label study designs. In the preceding blinded, randomized study, the TMS and sham treatment groups began with similar motor thresholds. However, in the active TMS condition, those who responded to TMS were more likely to have had higher baseline and within-study motor thresholds. The better response in the controlled trial may have been related to the higher intensity of stimulation delivered to those with higher motor thresholds. On the other hand, a similar apparent predictive relationship between baseline motor threshold and later treatment response was not seen in the open-label study results. In neither the controlled nor the open-label study did motor threshold change with treatment. It is unlikely that the initial differences in the motor threshold levels unblinded the investigators to the assignment in the initial sham controlled study. This motor threshold difference between the extended TMS group and the sham-to-TMS group was not found until after completion of the entire study. Therefore, neither the administrators of the TMS nor the raters were aware of any significance of the motor threshold in relation to group assignment. A further analysis and discus-

sion of the motor threshold findings is beyond the scope of this article and will be the subject of another report.

This study has several limitations. As noted above, the lack of a control treatment condition limits the interpretation of the data, but overall the efficacy was consistent with that seen in sham-controlled studies of TMS. We used a probabilistic surface anatomy approach targeting 5 cm anterior to the motor threshold location. While commonly used, this approach may not optimally target the dorsolateral prefrontal cortex.[21,22]

In conclusion, these open-label data are consistent with TMS efficacy in a predominantly treatment-resistant group of patients with unipolar, nonpsychotic major depressive disorder and indicate a good tolerability profile. These results provide further support for the use of TMS as a novel alternative in the treatment of major depressive disorder.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

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REFERENCES

1. Avery DH, Holtzheimer PE III, Fawaz W, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 2006;59(2):187–194
2. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta-analysis. Int J Neuropsychopharmacol 2002;5(1):73–103
3. 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
4. Loo CK, Mitchell PB. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. J Affect Disord 2005;88(3):255–267
5. Fitzgerald PB, Benitez J, de Castella A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 2006;163(1):88–94
6. Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. J Clin Psychiatry 2005;66(7):930–937
7. O'Reardon JP, Solvason HB, Janicak PG, et al. 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
8. Montgomery SA, Asberg MC. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
9. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
10. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
11. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62(Suppl 16):10–17
12. Pridmore S, Fernandes Filho JA, Nahas Z, et al. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. J ECT 1998;14(1):25–27
13. George MS, Wassermann EM, Williams WA, et al. Daily repetitive

transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6(14):1853–1856
14. Rush AJ, Carmody TJ, Reimitz PE. The Inventory of Depressive Symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. Int J Methods Psychiatr Res 2000;9:45–59
15. Rush AJ, Trivedi MH, Wisniewski SR, et al. 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
16. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006;354(12):1231–1242
17. Rossini D, Lucca A, Zanardi R, et al. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. Psychiatry Res 2005;137(1–2):1–10
18. Haskett RF, Rosenquist PB, McCall WV, et al. The role of antidepressant medications during ECT: new findings from OPT-ECT. J ECT 2007;23(1):56
19. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure and extended exposure and during reintroduction treatment. J Clin Psychiatry 2008; 69:222–232
20. McGrath PJ, Stewart JW, Fava M, et al. 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
21. 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
22. Herwig U, Padberg F, Unger J, et al. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 2001;50(1):58–61