

Research Article

TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR MAJOR DEPRESSION: A MULTISITE, NATURALISTIC, OBSERVATIONAL STUDY OF ACUTE TREATMENT OUTCOMES IN CLINICAL PRACTICE

Linda L. Carpenter, M.D.,^{1*} Philip G. Janicak, M.D.,² Scott T. Aaronson, M.D.,³ Terrence Boyadjis, M.D.,⁴ David G. Brock, M.D.,⁵ Ian A. Cook, M.D.,⁶ David L. Dunner, M.D., FACP⁷, Karl Lanocha, M.D.,⁸ H. Brent Solvason, Ph.D., M.D.,⁹ and Mark A. Demitrack, M.D.⁵

Background: Few studies have examined the effectiveness of transcranial magnetic stimulation (TMS) in real-world clinical practice settings. **Methods:** Forty-two US-based clinical TMS practice sites treated 307 outpatients with Major Depressive Disorder (MDD), and persistent symptoms despite antidepressant pharmacotherapy. Treatment was based on the labeled procedures of the approved TMS device. Assessments were performed at baseline, week 2, at the point of maximal acute benefit, and at week 6 when the acute course extended beyond 6 weeks. The primary outcome was change in the Clinician Global Impressions-Severity of Illness from baseline to end of acute phase. Secondary outcomes were change in continuous and categorical outcomes on self-report depression scales (9-Item Patient Health Questionnaire [PHQ-9], and Inventory of Depressive Symptoms-Self Report [IDS-SR]). **Results:** Patients had a mean \pm SD age of 48.6 ± 14.2 years and 66.8% were female. Patients received an average of $2.5 (\pm 2.4)$ antidepressant treatments of adequate dose and duration without satisfactory improvement in this episode. There was a significant change in CGI-S from baseline to end of treatment (-1.9 ± 1.4 , $P < .0001$). Clinician-assessed response rate (CGI-S) was 58.0% and remission rate was 37.1%. Patient-reported response rate ranged from 56.4 to 41.5% and remission rate ranged from 28.7 to 26.5%, (PHQ-9 and IDS-SR, respectively). **Conclusion:** Outcomes demonstrated response and adherence rates similar to research populations. These data indicate that TMS is an effective treatment for those unable to benefit from initial antidepressant medication. *Depression and Anxiety* 29:587–596, 2012. © 2012 Wiley Periodicals, Inc.

Key words: transcranial magnetic stimulation; depression; clinical trial; observational study

INTRODUCTION

Major Depressive Disorder (MDD) is a disabling and potentially lethal illness. The most recent update from

¹Butler Hospital, Providence, Rhode Island

²Rush University Medical Center, Chicago, Illinois

³Sheppard-Pratt Health System, Baltimore, Maryland

⁴Private Practice, West Chester, Pennsylvania

⁵Neuronetics, Inc., Malvern, Pennsylvania

⁶UCLA Medical Center, Los Angeles, California

⁷Center for Anxiety and Depression, Mercer Island, Washington

⁸TMS Center of New England, Portsmouth, New Hampshire

⁹Stanford University Medical Center, Palo Alto, California

*Correspondence to: Linda L. Carpenter, Butler Hospital/Brown Department of Psychiatry, 345 Blackstone Boulevard, Providence, RI 02906. E-mail: Linda_Carpenter_MD@Brown.edu
Received for publication 16 March 2012; Revised 10 May 2012; Accepted 18 May 2012

DOI 10.1002/da.21969

Published online 11 June 2012 in Wiley Online Library (wileyonlinelibrary.com).

the World Health Organization's Global Burden of Disease (GBD) Study^[1] reported that unipolar major depression alone is the leading cause of disability worldwide. As an illness with onset in the early decades of life, and with a recurrent and sometimes chronic course, the public health implications of depression are profound.

It is estimated that 20–40% of patients do not benefit from, or cannot tolerate, adequate trials of antidepressant medications even after repeated attempts.^[2] Further, the NIMH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study reported that 40.1% of patients remitting after failing one prior adequate antidepressant medication course relapsed during the next 12 months (mean time to threshold relapse of 4.1 months).^[3]

Transcranial magnetic stimulation (TMS) is a non-invasive, nonsystemic device delivering magnetic resonance imaging (MRI) strength, pulsed, magnetic fields to induce an electric current in the cerebral cortex. When used as an antidepressant, TMS produces clinical benefit without the systemic adverse effects associated with medications, and has no adverse cognitive effects.^[4,5] The evidence for the clinical efficacy of TMS in treating major depression spans more than 30 randomized, controlled trials in over 2,000 patients. To date, these data have been examined and summarized in over 10 meta-analyses and two qualitative reviews in the peer-reviewed literature between 2001 and 2011.^[6–19] Overall, these reports represent a comprehensive and consistent literature in which conclusions support the specific use of high-frequency TMS to the left dorsolateral prefrontal cortex in patients who have not benefited from antidepressant medication.

Although the peer-reviewed literature describing the efficacy of TMS in controlled trials is large and includes replications of positive findings, there are no multisite studies characterizing its utility and effectiveness in routine clinical practice. Such data from naturalistic studies are important as they permit the inclusion of subjects with a wider range of symptomatology and comorbidity than those found in controlled trials. The goal of this study was to summarize outcomes experienced by a large population of depressed patients treated with TMS therapy in various clinical settings.

SUBJECTS AND METHODS

STUDY SUBJECTS

Three hundred thirty-nine patients consented to serial assessments during clinical treatment with TMS. Patients were eligible to participate and considered evaluable for the study data analysis if (1) their primary clinical diagnosis was Major Depressive Episode (single or recurrent episode without psychotic features, consistent with DSM-IV criteria); (2) they did not have medical conditions that would preclude the safe use of TMS therapy; (3) they had not received past treatment with TMS for depression; (4) they met standardized criteria for failure to receive clinical benefit from antidepressant medication treatment in the current illness episode; (5) they had a baseline and at least one post-baseline rating; (6) their attending psychiatrist determined that TMS represented the most appropriate clinical treatment option; and (7)

the attending psychiatrist intended to initiate treatment using the currently labeled TMS treatment parameters. There was no limit on the number of lifetime antidepressant treatment failures in study participants. Treatment resistance was determined with the Antidepressant Treatment Record (ATR, Neuronetics, Inc., Malvern, PA), adapted from and validated against the research version of the Antidepressant Treatment History Form (ATHF).^[20] This naturalistic study design permitted patients to continue concurrent psychiatric medications during treatment with TMS if they were directed to do so by the prescribing psychiatrist. Decisions to administer TMS adjunctively reflected a determination that these agents could not be safely discontinued.

Institutional review board (IRB) approval was obtained at all participating sites. The costs of all treatment sessions and associated direct clinical care were borne entirely by the patient or their insurer. Study physicians were provided a modest financial remuneration by the study sponsor on a contracted basis for study-related document preparation and rating scale completion. Patients were provided a modest remuneration by the study sites for completion of study-specific rating scales. All compensation amounts were reviewed by the study site IRB. After a complete description of the study procedures, written informed consent was obtained from all subjects. The disposition of patients across the acute treatment course is shown in Fig. 1. Thirty-two patients did not meet all eligibility criteria and were not included in the final evaluable population ($N = 307$). Two hundred sixty-five patients (86.3% of the original evaluable population) completed acute treatment and enrolled in a 52-week naturalistic continuation outcome study. Results of this long-term follow-up study are pending and will be reported elsewhere.

STUDY LOCATIONS, TMS DEVICE, AND CLINICAL TREATMENT PARAMETERS

Forty-two clinical practices were included in this study. Thirty-two (76%) were in private clinical practices, seven (17%) were in academic medical centers, and three (7%) were in nonacademic institutional settings. The types and proportions of practice locations participating in this study mirror the distribution of current practice types offering TMS therapy in the United States.

All treatments were delivered using the NeuroStar TMS Therapy system (Neuronetics, Inc., Malvern, PA). Motor threshold (MT) was determined over the left hemisphere at the initial treatment session and used for determination of treatment intensity. An iterative, automatic software-based mathematical algorithm (MT Assist, Neuronetics) is integrated with this system for use in MT determination. External coordinates for placement of the coil over the treatment location are calculated by the device for a site 5 cm anterior from the MT location, along a left superior oblique plane. The standard treatment protocol described in the product user manual specifies stimulation at 120% of MT; pulse frequency of 10 pulses per second; and a cycle of 4 sec on (active stimulation) and 26 sec off (no stimulation). This system provides these default parameters, which generates 75 stimulation cycles, resulting in 3,000 pulses per treatment session. Although all clinicians initiated treatment with left-sided high-frequency stimulation, this default treatment protocol could be modified for tolerability or logistical reasons, or as a consequence of clinician-determined variation in practice technique.

OUTCOME MEASURES

Outcome assessments were obtained at baseline, week 2, at the point of maximal acute treatment benefit, and again at week 6 in cases where the acute course of TMS extended beyond 6 weeks. Efficacy measures included the clinician-reported Clinical Global Impressions-Severity of Illness Scale (CGI-S), and patient-reported Inventory of Depressive Symptoms-Self Report version (IDS-SR), and the 9-Item Patient Health Questionnaire (PHQ-9).

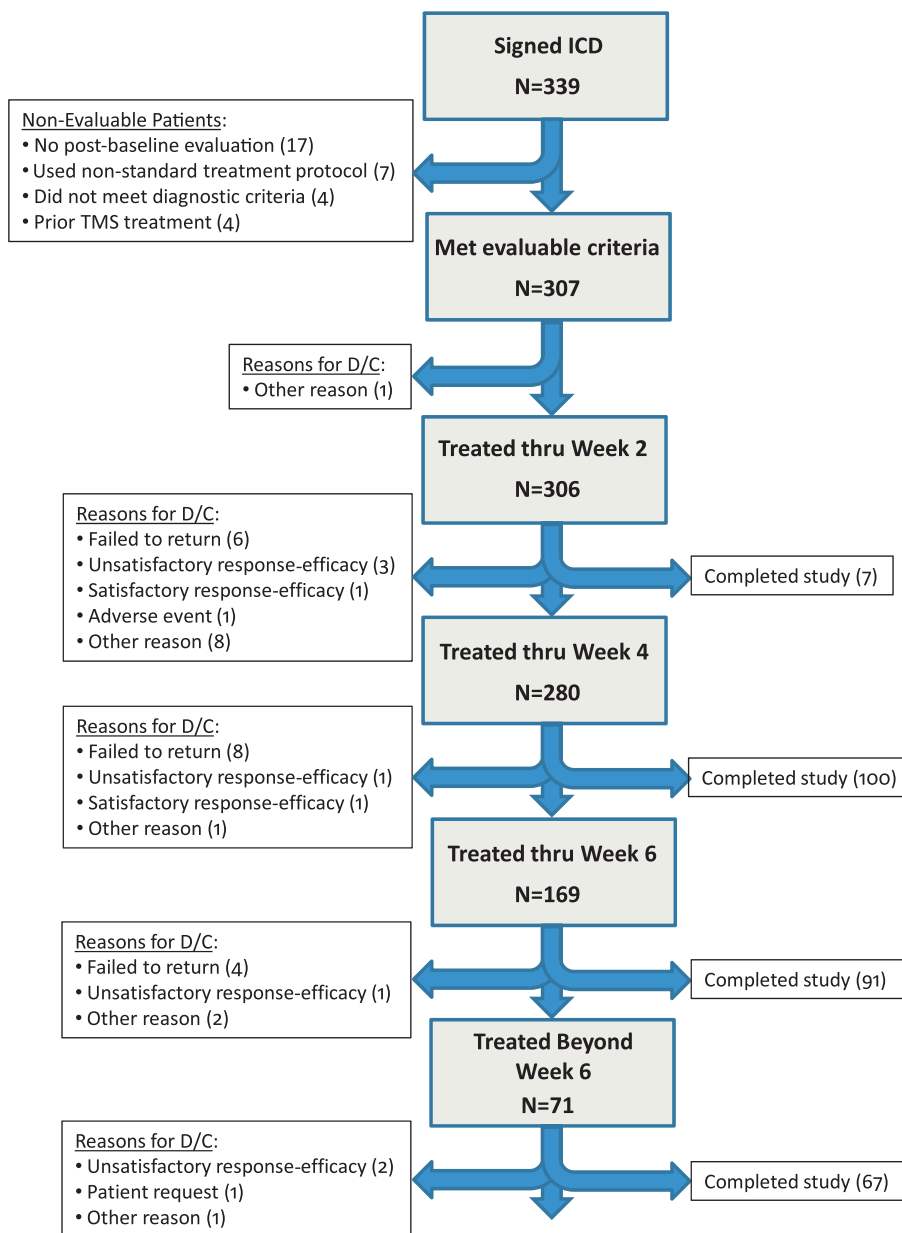


Figure 1. Summary of patient disposition during acute-phase treatment.

The primary outcome measure was the change from baseline to endpoint on the CGI-S. Secondary outcome measures included baseline to endpoint change on the PHQ-9 and IDS-SR scales and various categorical outcomes for each rating scale, as commonly used in prior published studies with these scales. For the CGI-S, response was defined as achieving an endpoint rating of 3 or less (corresponding with “mildly ill” or better), whereas remission on that scale was defined as achieving an endpoint rating of “borderline mentally ill” (2) or “normal/not at all ill” (1).^[21] For the PHQ-9, response was defined as achieving an endpoint score less than 10, whereas remission was defined as achieving an endpoint score less than 5.^[22] Finally, for the IDS-SR, response was defined as achieving a 50% or greater drop in endpoint score compared to the patient’s baseline rating, whereas remission was defined as an

endpoint score of less than 15 (<http://www.ids-qids.org/index2.html#table4>).

Safety was studied by summary analysis of medically serious, device-related adverse events or device malfunctions during this study. Incidence of such events was compared to the incidence of similar medically serious events that occurred in routine postmarket surveillance data for all devices installed in the United States at the time of this study.

STATISTICAL ANALYSIS

An analysis of covariance model examined the change from baseline in reported scores for the acute treatment phase for all

continuous variables. Baseline score, ATR group status (0–1 failures of adequate antidepressant treatment versus 2 or more failures in the current episode), and site were used as covariates. For all continuous efficacy outcome measures, within group testing was performed using the Student's *t*-test for normally distributed data and the Wilcoxon Signed Rank test for non-normally distributed data. Normality testing was evaluated using the Shapiro–Wilk Statistic. All tests were two-sided, at the 5% level of statistical significance. All analyses were conducted in a last observation carried forward (LOCF) manner for both the intent-to-treat population as well as the per protocol study population (i.e. subjects who provided a rating assessment at all evaluation time points). Categorical variables were tested using a chi-square analysis across the time points of the acute treatment phase. Kaplan–Meier survival estimates were used to examine the time course of achieving first remission during the acute treatment phase for the efficacy outcomes. To calculate probabilized estimates of the time to first remission during acute treatment, the Kaplan–Meier function censors observations at each time point representing patients who have not achieved remission. Therefore, as the number of censored or noncontributory observations increases, the probabilized estimate of the time to first remission tends to diverge upward from that seen in the raw observed data.

Prior research suggests that there are several clinical variables that influence a patient's response to treatment.^[11,23–25] Therefore, additional secondary analyses were conducted to identify potential moderators of treatment outcome with TMS. The candidate pretreatment variables and their method of stratification included baseline symptom severity (as a continuous variable), ATR status at baseline (baseline ATR ≤ 1 versus ≥ 2), the presence of a secondary anxiety disorder diagnosis (Yes/No), gender (M/F), age (age ≤ 55 years versus >55 years), and the presence of a prior psychiatric hospitalization for depression (Yes/No). We first used an analysis of variance model to explore the candidate moderator variables, with the criterion that a potential moderator variable should demonstrate a main effect at a $P < .10$ and its influence should be consistently present across all three outcome measures (i.e. CGI-S, PHQ-9, and IDS-SR) during the acute phase. Because the decision regarding the actual duration of TMS treatment in the acute phase was governed by the psychiatrist's estimate of the time point of maximum benefit, we also examined whether any specific candidate predictor variables systematically varied as a function of treatment duration. We hypothesized that, if outcome varies by treatment duration, then potential moderator variables should similarly vary in the population.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY POPULATION

General demographic and clinical descriptive information at study enrollment is shown in Table 1. A recurrent course of illness was reported in over 90% of patients. By CGI-S criteria, baseline depression severity was rated as moderately ill or worse (CGI-S ≥ 4) in 99% (303 of 307) of the population. Patients had received a mean (*SD*) of 2.5 (*SD*: 2.4) attempts at an adequate dose and duration, as defined by ATR criteria. Over 54% of patients met ATR criteria for resistance to two or more antidepressant trials during the current episode.

SUMMARY OF TMS TREATMENT PARAMETERS

The average number of TMS sessions across the acute phase was 28.3 (*SD*: 10.1, Range: 2–94), corresponding

TABLE 1. Demographic and clinical characteristics of study population (*N* = 307)

Demographic variables	
<i>N</i> (%) females	205 (66.8)
Age (years, mean \pm <i>SD</i>)	48.6 \pm 14.2
Age range	18 – 90
Disease history	
Recurrent illness course, <i>N</i> (%)	285 (92.8)
Comorbid anxiety disorder, <i>N</i> (%)	46 (15.0)
History of inpatient hospitalization for depression, <i>N</i> (%)	134 (43.6)
History of prior treatment with ECT, <i>N</i> (%)	16 (5.2)
Antidepressant treatment history	
Number of overall antidepressant treatment attempts in current illness episode, mean (<i>SD</i>) (Range)	3.6 (3.1) (0 – 21)
Number of dose/duration adequate antidepressant treatments in current episode, mean (<i>SD</i>) (Range)	2.5 (2.4) (0 – 14)
Baseline symptom scores	
CGI-Severity, mean (<i>SD</i>)	5.1 (0.9)
IDS-SR total score, mean (<i>SD</i>)	45.7 (11.0)
PHQ-9 total score, mean (<i>SD</i>)	18.3 (5.2)

to an average duration of treatment of 42 days (*SD*: 14.2, Range: 2–130). Two hundred eighty (91.2%) patients received treatment over the left dorsolateral prefrontal cortex only. The average number of pulses per session was 3216 (*SD*: 466). The baseline MT was 1.1 standard motor threshold (SMT) units (*SD*: 0.2, Range: 0.6–1.8).

ACUTE-PHASE TREATMENT OUTCOMES: CONTINUOUS VARIABLES

There was a statistically significant improvement from baseline in CGI-S total score (-1.9 ± 1.4 , $P < .0001$) (Table 2). A similar pattern and magnitude of clinical improvement was observed in the two patient self-reported outcome measures, the PHQ-9 and the IDS-SR (Table 2.)

ACUTE-PHASE TREATMENT OUTCOMES: CATEGORICAL VARIABLES

Examination of categorical outcomes reflected the improvement on the continuous outcome measures (Table 2). Categorical response and remission rates were consistent in clinical magnitude on all three outcome measures (i.e. CGI-S, PHQ-9, and IDS-SR). More than half of patients achieved responder status at the end of acute treatment, and approximately one third of patients achieved remission. For example, on the primary outcome measure (i.e. CGI-S) 58.0% of patients were categorized as responders with an end of treatment score of mildly ill or better (CGI-S ≤ 3), whereas 37.1% of patients reached remission (an endpoint score of 1 [normal, not at all ill] or 2 [borderline, mentally ill]) (Table 2).

TABLE 2. Summary of acute-phase outcomes—final acute treatment determined by clinician assessment of maximum improvement

	Baseline	Week 2	End of acute phase
Clinical rating			
CGI-Severity of Illness			
Total score, mean (SD)	5.1 (0.9)	4.4 (1.1)	3.2 (1.5)
Change from baseline, mean (SD)		-0.7 (0.9)	-1.9 (1.4)
<i>P</i> -value		<.0001	<.0001
Response rate, <i>N</i> (%)	-	52 (16.9)	178 (58.0)
Remission rate, <i>N</i> (%)	-	12 (3.9)	114 (37.1)
PHQ-9 Self-Rating Scale			
Total score, mean (SD)	18.3 (5.2)	12.7 (6.3)	9.6 (7.0)
Change from baseline, mean (SD)		-5.6 (5.9)	-8.7 (7.2)
<i>P</i> -value		<.0001	<.0001
Response rate, <i>N</i> (%)	-	101 (32.9)	173 (56.4)
Remission rate, <i>N</i> (%)	-	31 (10.2)	88 (28.7)
IDS-Self Rating Scale			
Total score, mean (SD)	45.7 (11.0)	35.0 (13.2)	27.4 (15.8)
Change from baseline, mean (SD)		-10.7 (10.0)	-18.3 (14.9)
<i>P</i> -value		<.0001	<.0001
Response rate, <i>N</i> (%)	-	38 (12.5)	127 (41.5)
Remission rate, <i>N</i> (%)	-	26 (8.6)	81 (26.5)

Note: All data are computed in a last observation carried forward (LOCF) analysis. *P*-values reflect comparison of change from baseline between baseline score and subsequent outcome time points performed using Student's *t*-test.

Responder defined as: score of ≤ 3 (CGI-S), score of <10 (PHQ-9), or $\geq 50\%$ decrease in score compared to baseline (IDS-SR).

Remitter defined as: CGI-S score ≤ 2 , PHQ-9 score <5 , or IDS-SR score <15 .

In order to examine the sensitivity of CGI-S clinician ratings for measurement of response and remission outcomes, we conducted an exploratory analysis whereby categorical “responder” status was defined by a requirement for improvement on CGI-S score by two or more levels from baseline, in addition to the requirement that endpoint CGI-S rating correspond with an overall severity level with “mildly ill” or better. With application of this more stringent criterion, the CGI-S response outcome is 50.2% ($N = 154$ patients); 24 patients (7.8% of the total study population) previously considered responders were no longer categorized as such. Similarly, use of a more stringent definition for “remitter,” which requires both improvement by two or more CGI-S levels together with a final severity rating of “borderline mentally ill” or “normal/not at all ill,” reveals a remission rate of 36.5% ($N = 112$) and reclassifies two patients as nonremitters.

The Kaplan–Meier estimate for the cumulative remission rate across the acute treatment phase was 69.2,

49.3, and 54.7%, as measured by the CGI-S, PHQ-9, and IDS-SR, respectively (Fig. 2). Similarly, the mean time ($\pm SD$) to first remission was 54 days ($SD: 1.2$), 49 days ($SD: 1.0$), and 60 days ($SD: 1.6$), as measured by the CGI-S, PHQ-9, and IDS-SR, respectively.

ACUTE-PHASE TREATMENT OUTCOMES: ANALYSIS OF MODERATORS OF TREATMENT OUTCOME

In the overall population, baseline score (as a continuous variable) and age (age ≤ 55 years versus >55 years and older) each showed a significant main effect on outcome at the criterion level described above (data not shown). Treatment benefit was better in patients with lower pretreatment baseline scores, and in the younger age cohort. In general, ATR status had only a modest influence on treatment outcome, with the more treatment-resistant cohort (ATR ≥ 2) demonstrating a modest reduction in the percentage of patients achieving remission as compared to the less treatment-resistant cohort (Fig. 3).

SAFETY SUMMARY

There was one medical event considered probably or definitely related to the device and that was filed with the FDA as a Medical Device Report. This event was a generalized tonic-clonic seizure that occurred in a female patient during her 10th TMS treatment session. The patient had no prior history of seizure, however she had several clinical factors that may have contributed to altering her seizure threshold. Specifically, the evening before her treatment she had completed a night shift of work, and was therefore sleep-deprived at the time of the TMS session. In addition, she was also taking bupropion, sertraline, and dextroamphetamine/levoamphetamine at the time of her TMS acute-phase participation. The patient recovered fully from the event without neurologic sequelae.

Seizure is a known, but rare, medical risk associated with TMS. In the entire postmarketing experience with this system, there have been six reports of seizure filed as MDRs to the FDA. Based on this experience, the estimated risk of seizure is approximately 0.003% per treatment exposure, and $<0.1\%$ per acute treatment course. Therefore, the safety experience of the study population is consistent with the larger postmarket safety experience with this system.

DISCUSSION

The main findings suggest that during the first few years after FDA approval clinicians in a variety of practice settings are delivering TMS therapy in a manner largely consistent with published research protocols. Moreover, patients are experiencing clinical results that match those reported in controlled research trials. Observations from this sample of 307 patients receiving acute course TMS therapy include a highly significant

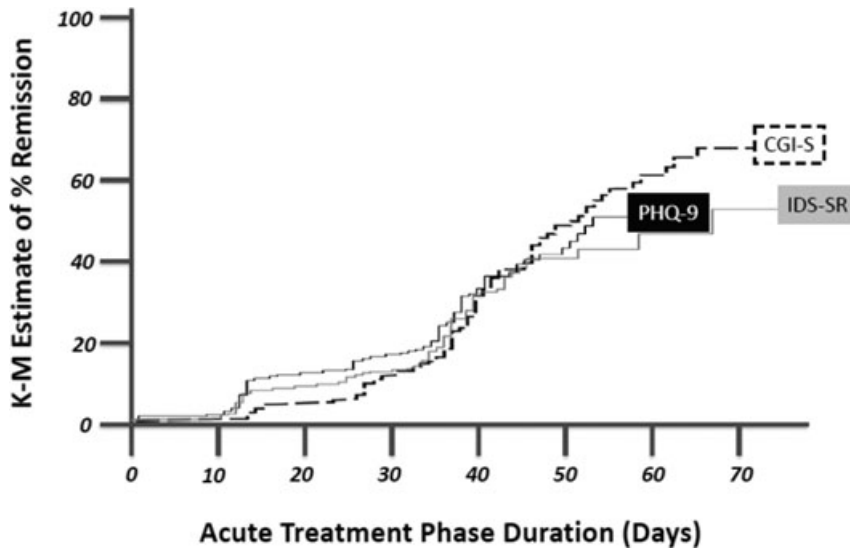


Figure 2. Kaplan–Meier survival estimate of time to first remission (CGI-S, PHQ-9, and IDS-SR outcomes).

improvement in depression severity at endpoint, alongside categorical response and remission rates consistent with efficacy outcomes seen in the open-label extension phase of two large sham-controlled studies.^[26–30] Additionally, these data confirm that TMS therapy with the approved device for MDD is safe and well tolerated in a nonresearch population.

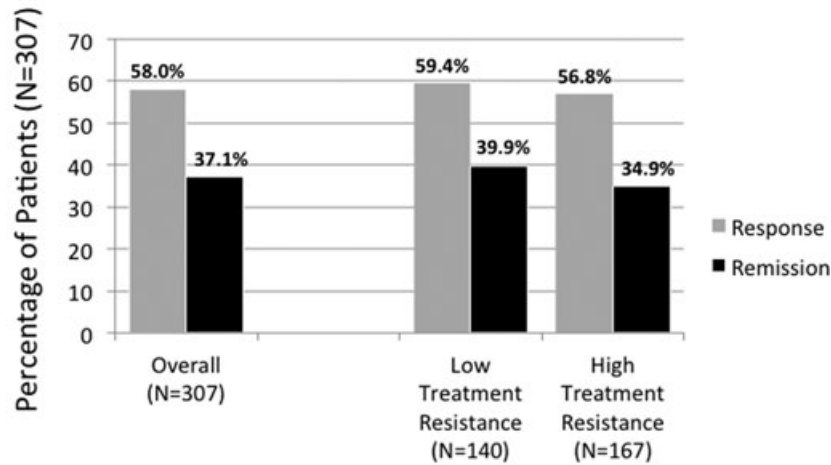
Naturalistic study results assist in bridging findings from the evidence obtained with more narrowly defined patient populations to the anticipated effects of a treatment when used on a larger scale in nonresearch patients. The application of stringent inclusion and exclusion criteria for generation of research samples in typical phase III clinical trials does not reflect the broader illness morbidity associated with depression and may overestimate the clinical outcomes that can be expected in routine practice. Retrospective analysis of the STAR*D data done with the study population stratified according to conventional enrollment criteria for a phase III clinical trial found that the subset of patients meeting these criteria had relatively shorter durations of illness and lower rates of family history of substance abuse, prior suicide attempts, and anxious or atypical symptom features.^[31] The subgroup of phase III research-level STAR*D patients experienced more favorable outcomes compared to the remainder of the study population. Similarly, the patient sample described in the present report also have several clinical characteristics suggesting greater illness morbidity compared with the patients studied in the controlled trials of this device.^[26,28,29] In particular, our naturalistic outcomes sample experienced a nearly fourfold higher incidence of prior inpatient psychiatric hospitalization for depression, and the average number of failed, adequate-exposure antidepressant trials was greater in this community sample than in the phase III research study population. Nevertheless, in contrast to the differ-

ential outcomes seen in the STAR*D retrospective analysis noted above, it is striking that the outcomes here indicate that clinical benefit obtained with TMS treatment under conditions of general clinical use rivals that seen in the research setting.

Our exploratory analysis of potential moderators of TMS clinical outcomes showed few specific clinical characteristics that predicted a beneficial effect of treatment. Among these, patients who were younger and had a lower baseline symptom severity had a modestly better outcome; features that have been reported as positive moderators of antidepressant treatment in general.^[23] In prior research studies, the level of antidepressant treatment resistance was a robust predictor of benefit from TMS treatment. Interestingly, in this population staging of antidepressant treatment resistance level using a validated method of assessment (ATR) revealed only a modest effect on acute outcome. In fact, 54% of the patients in the study population met criteria for resistance to more than one adequate antidepressant medication trial during the current illness episode, and patients who had failed a minimum of one adequate antidepressant trial were as likely to be TMS responders as those who had failed two or more trials in the current episode. Furthermore, the remission rate seen among patients with relatively “high” levels of pharmacoresistance was only slightly less than the remission rate for those with relatively “low” pharmacoresistance. In general, the benefits of TMS therapy appeared to be consistent across a range of clinical features including the presence of a comorbid anxiety disorder, or a history of prior psychiatric hospitalization.

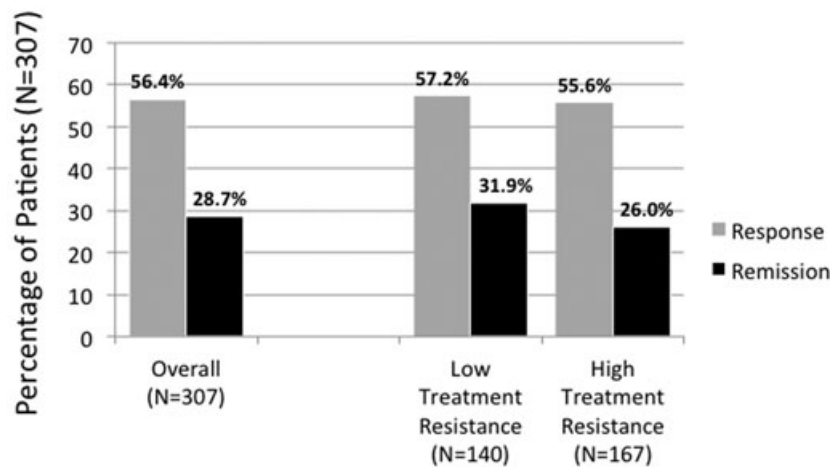
The suggestion that TMS may be effective across a broad range of treatment resistance and illness morbidity is generally consistent with the larger body of controlled clinical trial evidence.^[26,29] It is also worth noting that

CGI-S Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

PHQ-9 Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

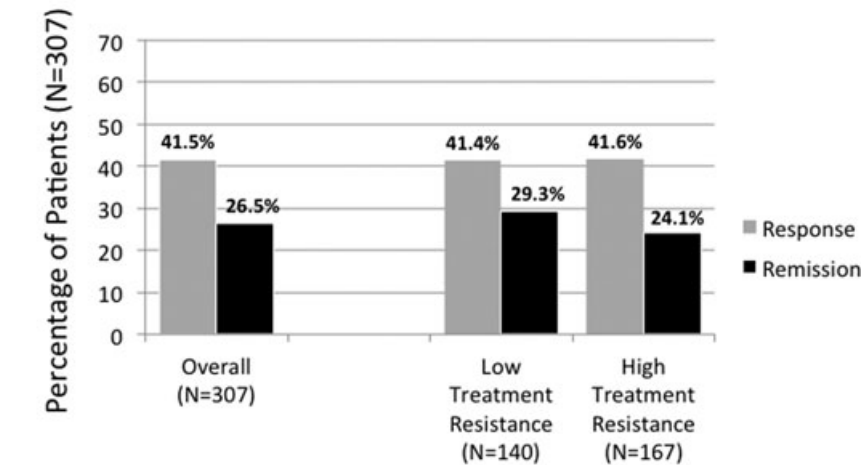
Figure 3. (Continued on next page.) Categorical response and remission outcomes (CGI-S, PHQ-9, and IDS-SR)—stratified by baseline level of treatment resistance (low versus high).

nearly all of the patients in this observational study continued on their previously ineffective antidepressant regimens during the acute course of TMS. The potential for an adjunctive benefit of TMS when used in combination with pharmacotherapy cannot be definitively answered by the present report.

Of considerable interest to both clinicians and reimbursement authorities is the question of the optimal treatment parameters for TMS therapy. Although preliminary uncontrolled studies point to accelerated on-

set of response and larger size effects associated with increased number of pulses per session^[32,33] and with a greater number of acute-phase treatment sessions,^[10] the vast majority of patients in our sample were given a standard course of 30 treatments over 6 weeks, mirroring the protocol used in registration trials with this system. A small subset of patients (6.5%), who were characterized by the highest mean depression severity scores at baseline, ended their acute course of TMS therapy in 2 weeks or less (corresponding with a mean \pm SD of

IDS-SR Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Figure 3. Continued.

only 10.9 ± 2 treatment sessions). There was no evidence of symptom worsening during TMS in this subset, but their categorical outcomes were inferior to those generated by other patients treated for at least 4 weeks. Unfortunately, the design of this study does not permit a complete understanding of the reasons for abbreviated treatment courses. Another minority subset (22%) of our sample, also characterized by relatively greater baseline depressive severity, was comprised of individuals treated beyond 6 weeks' duration. We speculate that this cohort reflects the clinical application of findings from published data demonstrating that an extension of the acute treatment phase may be beneficial for some patients with more difficult-to-treat illness courses,^[27,30] as there were no specific guidelines for treatment duration associated with this study protocol.

Most, but not all, of our sample were treated exclusively with TMS over the left prefrontal cortex. The exceptions we observed may signal early adoption by some psychiatrists of published TMS treatment protocols providing preliminary efficacy and safety data for sequential bilateral stimulation^[34] or for switching to right-sided stimulation following nonresponse to left-sided treatment.^[30] The inclusion of data from a few patients prescribed TMS despite pretreatment ratings of "borderline" or "mild" severity of illness likely reflects a variety of real-world scenarios (such as TMS treatment at the earliest threshold of depressive episode relapse, or initiation of TMS for targeting low-level residual or persistent symptoms) where a safe and effective nonpharmacological intervention outweighs the relative inconvenience and cost of the therapy. However, it is not possible to know how the availability of insurance reimbursement or financial resources accessible by patients to pay for their treatment impacted the treatment

duration statistics gathered by this study (or the option to fully pursue what might be considered an "optimized" course of TMS therapy).

Finally, although not specifically designed to address questions about TMS tolerability, the high adherence rate (83%) and paucity of medically serious adverse events reported during this naturalistic study underscore the benign safety profile associated with the treatment. There was one case of seizure induction in this study. Comparison with data collected via postmarketing report leads us to conclude that the safety experience observed in this study cohort mirrors the safety experience of the larger general patient population treated with TMS therapy at the same time.

In conclusion, this naturalistic study observed clinical response and adherence rates similar to those reported in open-label clinical trials in research study populations. These data validate the TMS efficacy reported in published controlled trials, and further support TMS as an effective and well-tolerated therapy for those who have failed to benefit from antidepressant medication.

Financial Disclosures

Linda L. Carpenter: *C-Path Institute (Board member); Abbott, Johnson&Johnson, Takeda, Hellcon (Consultant); NIMH, Cyberonics, Medtronic, NeoSync (Grant support); Neuronetics (Sponsored present study)*

Philip G. Janicak: *Neuronetics (Grant, Sponsored present study); Neuronetics (Consultant, Expert Testimony, Speaker); Cervel Neurotech (Grant)*

Scott Aaronson: *Neuronetics (Grant, Sponsored present study, Speaker); Genomind (Board member); Sunovion, Eli Lilly, Astra Zeneca (Speaker)*

Terrence Boyadjis: *Neuronetics (Grant, Sponsored present study, Speaker)*

David G. Brock: *Neuronetics (Employee, Stock options)*

Ian Cook: *Neuronetics (Grant, Sponsored present study); Pfizer, Bristol Myers Squibb (Board member); US Department of Justice, NIH (Consultant); Department of Defense (Unpaid consultant)*

David L. Dunner: *Neuronetics (Grant, Consultant, Sponsored present study); Eli Lilly, Pfizer, Cervel Neurotech, Jazz (Board member); Samiarabow (Consultant); Cyberonics (Grants); Astra Zeneca, Pfizer (Speaker)*

Karl Lanocha: *Neuronetics (Grant, Sponsored present study, Speaker)*

H. Brent Solvason: *Neuronetics (Grant, Sponsored present study)*

Mark A. Demitrack: *Neuronetics (Employee, Stock options); Johnson&Johnson (consultant)*

REFERENCES

- World Health Organization. (2008) The Global Burden of Disease, 2004 Update. Geneva, Switzerland: WHO Press. Available at: http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html. Retrieved 28 December, 2009.
- Kessler R, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289(23):3095–3105.
- 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;163:1905–1917.
- Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation (TMS) in the treatment of major depression: a comprehensive summary of safety experience from acute and extended exposure and during reintroduction treatment. *J Clin Psychiatry* 2008;69(2):222–232.
- Guse B, Falkai P, Wobrock T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. *J Neural Transm* 2010;117:105–122.
- Aarre TF, Johansen JB, Kjonniksen I, et al. Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence. *Nord J Psychiatry* 2003;57:227–232.
- Allan CL, Herrmann LL, Ebmeier KP. Transcranial magnetic stimulation in the management of mood disorders. *Neuropsychobiology* 2011;64:163–169.
- Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol* 2002;5:73–103.
- Couturier J. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. *J Psychiatry Neurosci* 2005;30(2):83–90.
- Gross M, Nakamura L, et al. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand* 2007;116:165–173.
- Herrmann L, Ebmeier K. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. *J Clin Psychiatry* 2006;67:1870–1876.
- Holtzheimer PE, et al. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bulletin* 2001;35:149–169.
- Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation to treat depression. *J Psychiatric Prac* 2002;8:270–275.
- Lam RW, Chan P, Wilkins-Ho M, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *Canad J Psychiatry* 2008;53(9):621–631.
- Loo C, Mitchell P. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *J Aff Disorders* 2005;88:255–267.
- Martin JLR, Barbano MJ, Schlaepfer TE, et al. Transcranial magnetic stimulation for treating depression (review). *Cochrane Library* 2003;(4)
- McNamara B, Ray JL, Arthurs OJ, et al. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychol Med* 2001;31:1141–1146.
- Schutter DJLG. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Medicine* 2009;39:65–75.
- Slotema CW, Blom JD, Hoek HW, Sommer IEC. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A Meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry* 2010;71(7):873–884.
- Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 2001;16:10–17.
- Bandelow B, Baldwin DS, Dolberg OT, Andersen HF, Stein DJ. What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder. *J Clin Psychiatry* 2006;67:1428–1434.
- Katzelnick DJ, Duffy FF, Chung H, Regier DA, Rae DS, Trivedi MH. Depression outcomes in psychiatric clinical practice: using a self-rated measure of depression severity. *Psychiatric Services* 2011;62(8):929–935.
- Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. *J Clin Psychiatry* 2001;62(Suppl 16):18–25.
- Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. *Arch Gen Psychiatry* 2008;65(8):870–881.
- Berlanga C, Heinze G, Torres M, Apiquian R, Caballero A. Personality and clinical predictors of recurrence of depression. *Psychiatric Services* 1999;50(3):376–380.
- O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multi-site randomized controlled trial. *Biol Psychiatry* 2007;62:1208–1216.
- Avery DH, Isenberg KE, Sampson SM, et al. TMS in the acute treatment of major depression: clinical response in an open-label extension trial. *J Clin Psychiatry* 2008;69(3):441–451.
- Demitrack MA, Thase ME. Clinical significance of transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant depression: synthesis of recent data. *Psychopharmacol Bulletin* 2009;42(2):5–38.
- George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010;67(5):507–516.
- McDonald WM, Durkalski V, Ball ER, et al. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment

- location in treatment-resistant depression. *Depress Anxiety* 2011;28(11):973–980.
31. Wisniewski SR, Rush AJ, Nierenberg AA, et al. Can phase III trial results of antidepressant medications be generalized to clinical practice? A STAR*D report. *Am J Psychiatry* 2009;166:599–607.
 32. Hadley D, Anderson BS, Borckardt JJ, et al. Safety, tolerability, and effectiveness of high doses of adjunctive daily left prefrontal repetitive transcranial magnetic stimulation for treatment-resistant depression in a clinical setting *J ECT* 2011;27(1):18–25.
 33. Holtzheimer PE 3rd, McDonald WM, Muftic M, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. *Depress Anxiety* 2010;27(10):960–963.
 34. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 2006;163(1):88–94.