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ORIGINAL RESEARCH

Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study

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Background
Although transcranial magnetic stimulation (TMS) can be an effective acute antidepressant treatment, few studies systematically examine persistence of benefit.

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Clinical trial posted on www.clinicaltrials.gov. Listing No. NCT 00104611.

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Objective
We assessed the durability of antidepressant effect after acute response to TMS in patients with major depressive disorder (MDD) using protocol-specified maintenance antidepressant monotherapy.

Methods
Three hundred one patients were randomly assigned to active or sham TMS in a 6-week, controlled trial. Nonresponders could enroll in a second, 6-week, open-label study. Patients who met criteria for partial response (i.e., >25% decrease from the baseline HAMD 17) during either the sham-controlled or open-label study (n = 142) were tapered off TMS over 3 weeks, while simultaneously starting maintenance antidepressant monotherapy. Patients were then followed for 24 weeks in a naturalistic follow-up study examining the long-term durability of TMS. During this durability study, TMS was readministered if patients met prespecified criteria for symptom worsening (i.e., a change of at least one point on the CGI-S scale for 2 consecutive weeks). Relapse was the primary outcome measure.

Results
Ten of 99 (10%; Kaplan-Meier survival estimate = 12.9%) patients *relapsed*. Thirty-eight (38.4%) patients met criteria for *symptom worsening* and 32/38 (84.2%) *reachieved symptomatic benefit* with adjunctive TMS. Safety and tolerability were similar to acute TMS monotherapy.

Conclusions
These initial data suggest that the therapeutic effects of TMS are durable and that TMS may be successfully used as an intermittent rescue strategy to preclude impending relapse.

Keywords antidepressant; clinical trial; major depression; maintenance of effect; TMS; treatment resistance

Major depression is common, recurrent, frequently chronic and a leading contributor to functional impairment and disability. It is estimated that 20% to 40% of patients do not benefit from or are unable to tolerate standard treatments. In addition, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study reported that 40.1% of patients who achieved remission after failing one adequate antidepressant course experienced relapse (mean time 4.1 months) over 12 months of follow-up.[1] Thus, there is a need for more tolerable, effective, and durable options, especially with initial treatment resistance.

Transcranial magnetic stimulation (TMS) uses briefly pulsed, magnetic resonance imaging (MRI)-strength magnetic fields to induce electrical currents in the cerebral cortex. Two recent, large, multisite, randomized, controlled trials demonstrated the acute antidepressant efficacy of TMS in patients with treatment-resistant, nonpsychotic, unipolar major depression.[2-7] Few studies, however, assess the durability of TMS benefit after achieving acute response (Table 1).[8-12]

We examined the persistence of benefit after successful acute treatment with TMS during two time periods (i.e., the first 3 weeks of tapering and cessation of TMS treatments with transition onto stable maintenance antidepressant monotherapy; and during 24 weeks of long-term follow-up). Our primary outcome measure was the incidence of relapse during this period. We also explored the impact of several pretreatment clinical characteristics on long-term outcome and whether the magnitude of acute clinical benefit predicted long-term durability.

Materials and methods

Study overview

Three hundred one patients participated in a multicenter, randomized, double-blind active versus sham trial examining the acute efficacy and safety of TMS.[2,3] The sham procedure used an aluminum shield embedded within the housing that covered the iron core of the magnetic coil. This permitted delivery of less than 10% of the magnetic pulse intensity produced by the active TMS procedure, while still allowing for some application site sensation during the administration of the sham procedure. Patients who did not improve by at least 25% from their baseline 17-Item Hamilton Depression Rating Scale (HAMD-17) could enroll in a 6-week open trial of TMS.[4] Patients who met the criteria for at least partial response in either the randomized or open-label extension studies were then eligible to be followed in a naturalistic, 24-week durability study, which is the topic of this paper. Individual site investigators and their clinical and research staff were blinded to this criterion as well as the original treatment assignment (i.e., active or sham TMS). Therefore, they were unaware of the details that permitted entry into the open-label extension study.

All eligible patients first underwent a 3-week transition during which time they started on open-label, maintenance antidepressant monotherapy, while gradually tapering off TMS treatments. Similar to clinical practice, the choice of

Table 1 Summary of prior studies assessing the durability of the acute antidepressant effect of TMS

Study	Design	Outcome
Dannon et al.[8]	6-mo follow-up in acute responders to TMS or ECT	• 20% relapse rate in both groups
O'Reardon et al.[9]	Maintenance TMS for major depression over 6 mo to 6 y	• 7/10 received moderate or marked benefit • 3/10 maintained on TMS monotherapy
Fitzgerald et al.[10]	TMS re-introduction in 19 medication-free, TRD patients who initially responded to TMS	• Relapses occurred over 6-12 mo • TMS produced comparable benefit with reintroduction
Demirtas-Tatlidede[11]	16 acute TMS responders followed over 4 y	• 50% benefited from TMS reintroduction • Mean interval between TMS retreatment was 4.9 mo
Cohen et al.[12]	204 initial TMS remitters followed naturalistically	• Median times in remission was 120 d • Younger age and greater number of acute TMS sessions predicted longer-term benefit

maintenance antidepressant was determined by a review of prior treatments, the patient's subjective experience and any information from the referring clinician. Medications used as maintenance pharmacotherapy included duloxetine (26%), venlafaxine (17%), bupropion (19%), and escitalopram (14%). The remaining 24% of patients received medications that included citalopram, fluoxetine, fluvoxamine, mirtazapine, sertraline, and trazodone, (none among this latter list was used by more than 5% of the sample). In the durability study, patients continued on the antidepressant begun during the 3-week transition phase, with only dose adjustments permitted (i.e., no switching or augmentation). Symptom worsening, defined by a Clinical Global Impressions Severity of Illness (CGI-S) score change of at least one point, observed over 2 successive weeks dictated the reintroduction of TMS (i.e., two TMS sessions/week for 2 weeks, followed by five sessions/week for up to 4 additional weeks). TMS was discontinued when the CGI-S returned to baseline and the patient then continued in the durability study.

TMS treatment parameters

All treatments were delivered using the Neuronetics Model 2100 TMS Clinical Research System (Neuronetics, Malvern, PA). Protocol-specified parameters were the same as in the active treatment arm of the double-blind study and included stimulation at 120% of motor threshold (MT); pulse frequency of 10 pulses per second; and a cycle of 4 seconds on (active stimulation) and 26 seconds off (no stimulation interval) for 75 cycles, resulting in 3000 pulses. MT was determined using an iterated automatic, software-based, maximum-likelihood estimation method, mathematical algorithm to ensure standardization across study sites (MT Assist,® Neuronetics). Treatment location was determined by external landmarks at a site 5 cm anterior to the optimal site for motor response, placing the coil over the region of the left dorsolateral prefrontal cortex (DLPFC). Reproducibility from session to session involved a mechanical positioning system that maintained a record of the three-dimensional spatial location of the coil relative to the patient's head.

Subject description

Three hundred one patients met DSM-IV diagnostic criteria for unipolar, nonpsychotic major depressive disorder, confirmed by the Structured Clinical Interview for the DSM-IV.[13] A complete description of the inclusion and exclusion criteria and efficacy and safety results for the acute treatment outcomes are described elsewhere.[2-4] A recurrent course of illness was reported in over 95% of patients who were moderately-to-severely ill by symptom measures at baseline (i.e., HAMD-17 baseline score of ≥ 20) and moderately to severely treatment resistant (i.e., failure to benefit from one to four antidepressant trials of adequate dose and duration) during the current episode (Table 2 provides further details on level of symptom severity and treatment resistance). Adequacy of each treatment attempt was determined with the Antidepressant Treatment History Form (ATHF), a reliable and validated method of assessing treatment resistance.[14] There was no limit on lifetime treatment failures for study entry.

Institutional review board approval was obtained at all sites. After a complete description of the study, written informed consent was obtained from all subjects before undergoing any procedures.

Subject disposition

Disposition of the 301 patients and their treatment paths in the current analysis are shown in Figure 1. Of the original sample, 142 achieved partial response (i.e., $\geq 25\%$ improvement from their baseline HAMD-17 score) by the end of their active TMS course in either the randomized or open-label study. Ninety-nine of these patients successfully transitioned from TMS to antidepressant maintenance monotherapy and agreed to participate in the durability study.

Table 2 Comparison of demographic and clinical characteristics among the original randomized study patient population: patients who participated in long-term durability of effect analysis (n = 99) versus patients who did not participate in long-term durability of effect analysis (n = 202)

	Participated in long-term follow-up (n = 99)	Did not participate in long-term follow-up (n = 202)	*P* value
Demographic variables			
N (%) females	53 (53.5)	107 (53.0)	>.99
Age (y ± SD)	49.1 ± 10.3	47.9 ± 11.0	.565
Ethnic origin, N(%)			
White	92 (92.9)	185 (91.6)	
Other	7 (7.1)	17 (8.4)	.822
Disease history			
Recurrent illness course n (%)	96 (97.0)	189 (93.6)	.281
Duration of current episode in months, mean (SD)	12.7 (9.3)	13.6 (9.8)	.459
N (%) of population with current episode ≥ 2 y	16 (16.2)	42 (20.9)	.355
N (%) of population with comorbid anxiety disorder	29 (29.3)	72 (35.6)	.300
Prior antidepressant treatment			
Number of antidepressant treatment attempts in current illness episode (mean, SD)	5.5 (3.3)	5.4 (3.6)	.497
Number of dose/duration adequate antidepressant treatments in current episode (mean, SD)	1.6 (0.7)	1.7 (0.9)	.908
Baseline symptom scores			
MADRS total score (SD)	32.9 (6.2)	33.5 (5.7)	.359
HAMD17 total score (SD)	22.4 (3.4)	22.8 (3.4)	.339
HAMD24 total score (SD)	29.7 (5.0)	30.6 (4.9)	.146
CGI –Severity (SD)	4.7 (0.6)	4.8 (0.7)	.199
IDS-SR total score (SD)	42.3 (9.7)	42.9 (9.6)	.662

Categoric variables examined using Fisher's exact test, continuous variables tested using Student t test.

Of patients originally randomly assigned to sham TMS, 36 (24.7%) achieved partial response. Among this group, 21 successfully completed the transition phase and participated in the durability study. Note that patients from the sham and active TMS groups were no longer fully randomized at the time of entry into the durability study; therefore inferential statistical analyses are not appropriate between these two groups at these later time points. Nevertheless, all data are included in the patient disposition table and in the long-term survival graphs for completeness of reporting.

Measurement of efficacy outcomes and durability of acute antidepressant benefit

Blinded raters determined symptomatic and clinical efficacy using the Montgomery-Asberg Depression Rating Scale (MADRS), the 24-Item version of the Hamilton Depression Rating Scale (HAMD24), and the CGI-S. Subjective outcomes were determined using the Inventory of Depressive Symptoms–Self-Report version (IDS-SR). Efficacy was assessed weekly during the 3-week transition period from TMS to maintenance antidepressant. During the 24-week durability of effect study, evaluations were conducted weekly for the first month, and every 4 weeks thereafter. Patients who experienced deterioration were seen weekly to evaluate criteria for TMS reintroduction.

Relapse was the *primary outcome measure*, and was defined as a recurrence of full DSM-IV criteria for major depression for 2 consecutive weeks; or failure to achieve symptomatic improvement as defined above despite a 6-week reintroduction course of TMS.

Secondary outcome measures included baseline to endpoint change score and percent change from baseline on the various efficacy rating scales. For the 99 active TMS patients who benefited from their acute treatment and enrolled in the durability study, response was defined as a 50% or greater reduction in total baseline score on the MADRS or HAMD24 scales. Remission required an endpoint score of <10 on the MADRS, or <11 on the HAMD24.

Statistical methods

All active TMS treated groups were pooled to increase the sample size for the overall analyses of long-term outcome. Relapse was examined using Kaplan-Meier survival estimates (SAS Institute, Cary, NC). Secondary outcome measures were examined in an *observed case analysis*, comparing endpoint with the baseline scores observed at entry into either of the two study phases using Student *t* test.

An exploratory analysis for pretreatment predictors of outcome during the durability study was performed on the active treated TMS group, using a logistic regression model. The explanatory pretreatment variable was the

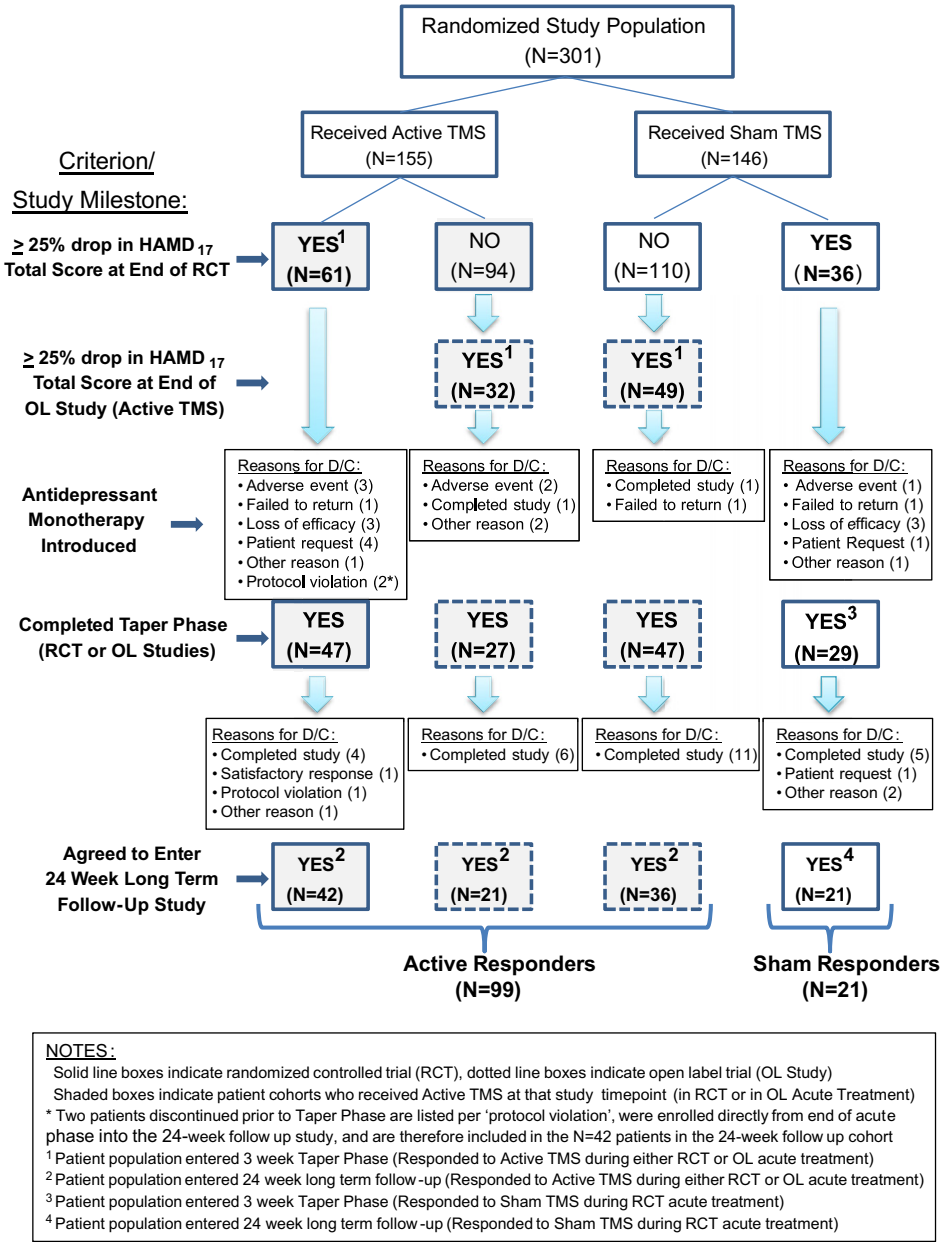


Figure 1 Disposition of original patient population across the randomized and open-label extension studies into the immediate (n = 142) and long-term (n = 99) durability follow-up population cohorts.

clinical predictor (categorical or continuous) and the dependent outcome variable was the dichotomous clinical status of the patient during the follow-up study (i.e., TMS reintroduced, TMS not reintroduced). Categorical variables included age (i.e., greater or less than 55 years); gender; duration of current episode (i.e., greater or less than 2 years); the presence of comorbid anxiety disorder; course of illness (single episode versus recurrent); treatment resistance status in the current episode (i.e., one ATHF failure or two to four failures); employment status; and the presence of an atypical depression. Continuous variables included MADRS baseline total score, number of TMS sessions during acute treatment, and baseline MT.

Results

Demographic and clinical characteristics

One hundred forty-two patients achieved at least partial response from active TMS in the randomized or open-label studies and entered into the 3 week transition phase (Figure 1). One hundred twenty-one patients (121/142 or 85.2%) completed the transition phase successfully. Ninety-nine patients (99/121 or 81.8%) among those who successfully transitioned from active TMS to maintenance antidepressant monotherapy agreed to follow-up for an additional 24 weeks. The reasons for refusing the follow-up study are shown in Figure 1.

Table 3 Summary of continuous clinical ratings during the 3-week transition from TMS to stable antidepressant maintenance monotherapy (n = 142)

	Transition phase study period				
	Pretreatment baseline score (Week 0)	End of acute TMS treatment score (Week 6)	Week 7	Week 8	Week 9
Clinical rating					
Sample size (N)	142	142	123	121	123
MADRS total score (SD)	33.7 (6.1)	13.3 (8.3)	13.4 (9.0)	12.8 (9.2)	10.5 (8.5)
Change from baseline (SD)			0.3 (6.4)	0.0 (7.1)	−2.5 (7.1)
P value			.567	>.99	.0002
Sample size (N)	142	142	123	121	123
HAMD24 total score (SD)	30.0 (5.1)	12.1 (6.7)	12.1 (7.0)	11.5 (7.6)	9.9 (6.9)
Change from baseline (SD)			0.3 (5.1)	−0.2 (5.8)	−1.9 (5.7)
P value			.585	.729	.0003
Sample size (N)	142	142	122	122	124
CGI –Severity (SD)	4.7 (0.7)	2.6 (1.0)	2.5 (1.2)	2.3 (1.1)	2.2 (1.1)
Change from baseline (SD)			−0.1 (0.8)	−0.2 (0.9)	−0.4 (1.0)
P value			.379	.031	<.0001
Sample size (N)	142	142	122	117	119
IDS-SR total score (SD)	41.0 (12.0)	19.4 (10.3)	18.9 (11.2)	18.4 (11.1)	16.4 (10.0)
Change from baseline (SD)			−0.2 (6.9)	−1.1 (8.4)	−3.3 (7.8)
P value			.734	.176	<.0001

P values reflect comparison of change from baseline between end of acute treatment score and subsequent outcome time points performed using Student *t* test. Some variation in sample size is due to missing values at some time points.

Table 2 summarizes the demographic and clinical characteristics of the original randomized sample (n = 202) who did not participate in the durability study and the final cohort of active TMS treated patients (n = 99) who did. In the latter group, an analysis of the baseline demographic and clinical features across the various treatment pathways showed no statistical or clinical differences between groups based on whether they received active TMS treatment in the randomized or open-label study (data not shown). At entry into the randomized study, these 99 partial responders had averaged 5.5 antidepressant treatment attempts (SD: 3.5, range 1-23) during the current episode of illness. By ATHF criteria, however they received an average of 1.6 (SD: 0.7) adequate trials (based on dose and duration) in the current episode.

Of note, 21 of the 99 patients (21.2%) in the durability study had received up to 12 weeks of active TMS (i.e., up to 6 weeks in the randomized study and up to an additional 6 weeks in the open-label extension study). This group showed no difference in long-term outcomes compared with the other groups (data not shown). This indicates that pooling of all groups provided the most comprehensive and informative approach in the descriptive analyses presented in this report.

Persistence of acute benefit during transition to maintenance antidepressant treatment

A summary of the clinical ratings and disposition of the 142 patients who achieved at least partial response is shown in Tables 3 and 4, and Figure 1. One hundred twenty-one (85%) of these patients completed the transition phase successfully.

Persistence of acute benefit during long-term follow-up and incidence of relapse

Of the 99 patients who successfully transitioned from active TMS onto maintenance antidepressant monotherapy, relapse occurred in 10 (Kaplan-Meier survival estimate = 12.9%, Figure 2) with a mean time of 164 (± 4) days after entry into the durability study.

Overall, 70 (70/99 or 70.7%) patients who previously benefited from active TMS completed the entire 24-week study. Table 5 summarizes the reasons for study discontinuation and Tables 6 and 7 provide the ratings observed during this period. Most patients experienced satisfactory clinical benefit, with approximately 75% maintaining full response and >50% maintaining remission based on either the MADRS or HAMD24 scores.

Incidence of TMS reintroduction during long-term follow-up

Thirty-eight (38/99 or 38.4%) patients had symptom worsening and received reintroduction TMS. The majority (32/38 or 84.2%) benefitted from TMS reintroduction and continued in the study. The Kaplan-Meier survival estimate for symptomatic worsening requiring TMS reintroduction was 40.6% (Figure 3). The mean time to first reintroduction was 109 (± 5) days. The mean number of TMS reintroduction sessions was 14.3 (SD = 9.3).

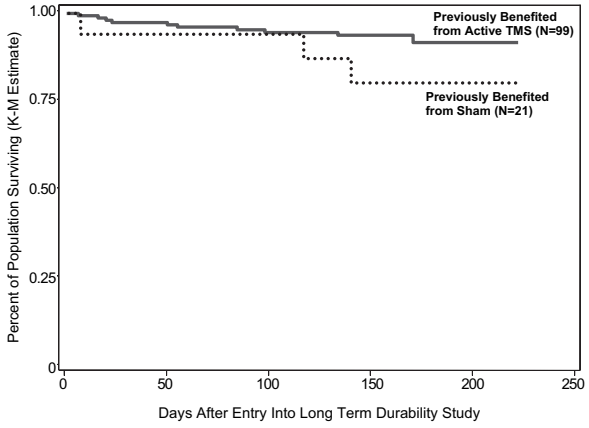
Table 4 Summary of categorical clinical ratings during the 3-week transition from TMS to stable antidepressant maintenance monotherapy (n=142)

	Transition phase study period			
	End of acute TMS treatment (Week 6)	Week 7	Week 8	Week 9
Clinical rating				
Sample size (N)	142	123	121	123
MADRS				
Responder rate (%)	62.0	64.1	64.8	70.4
Remitter rate (%)	31.7	36.6	36.6	44.4
HAMD24				
Responder rate (%)	64.8	63.4	65.5	70.4
Remitter rate (%)	42.3	40.8	44.4	51.4

All categoric are outcome percentages at each time point are computed based on the total sample size at entry as the denominator. Some variation in sample size is due to missing values at some time points.

There was no limit to the number of TMS reintroduction courses, and 15 and 5 patients experienced a second or third period of symptom re-emergence, respectively. There were not enough patients, however, to draw meaningful clinical conclusions.

At the point of entry into the study, 77/99 (77.8%) patients had achieved full response or greater benefit (i.e., at least 50% or greater reduction of HAMD-17 total score from baseline). This cohort was compared with the remainder of the population (22/99 or 22.2%) who had only achieved partial response (i.e., 25-49% reduction in the HAMD-17 baseline score). Partial responders were more likely to require TMS reintroduction (Kaplan-Meier survival estimate = 48.9%) compared with patients who achieved full response or greater benefit (Kaplan-Meier survival estimate = 38.2%) (Figure 4).



NOTE: Both groups are shown for contrast, however, because these groups are no longer fully randomized samples at entry into the durability of effect follow up study, inferential comparisons are not statistically appropriate (please see text for details).

Figure 2 Kaplan-Meier survival curve estimate of relapse during the 24-week, long-term durability of effect study for patients previously benefiting from acute treatment with active TMS (n = 99) and for patients previously benefiting from sham treatment (n = 21).

Table 5 Reasons for discontinuation during the 24-week long-term durability of effect study (n = 99)

	Number (%) of patients
Reason for discontinuation	
Completed study	70 (70.7)
Adverse event	2 (2.0)
Failed to return	7 (7.1)
Unsatisfactory response-efficacy	7 (7.1)
Protocol violation	4 (4.0)
Patient request unrelated to study	4 (4.0)
Other	5 (5.1)

We conducted an exploratory analysis to determine the impact of several pretreatment, clinical variables related to the need for TMS reintroduction in the active TMS treatment cohort. None demonstrated a significant ability to predict the likelihood of symptom worsening requiring TMS reintroduction (data not shown). Further, there was no difference in short- or long-term clinical outcome based on choice of antidepressant.

Incidence of relapse and TMS reintroduction in sham responders

Twenty-one patients who benefited from sham treatment in the controlled trial successfully transitioned to maintenance antidepressant monotherapy and entered the durability study (Figure 1). Relapse occurred in three of these patients (Kaplan-Meier survival estimate = 16.0%, Figure 2). Eleven of 21 (i.e., 52.4%) patients required reintroduction TMS, and 5/11 (45.5%) benefited and continued in the follow-up study. The Kaplan-Meier survival estimate for symptomatic worsening requiring TMS reintroduction was 66.4% in this group (Figure 3). The mean time to first reintroduction was 116 (± 13.2) days. The mean number of TMS sessions was 15.2 (SD = 7.0).

Safety and tolerability of TMS reintroduction

Table 8 summarizes the most commonly reported adverse events in the 99 patients who benefited from active TMS and were followed in this study and highlights specific events determined by the investigator to be causally related to reintroduction TMS. Concurrent administration of TMS and antidepressant medication produced an overall pattern of adverse events similar to active TMS monotherapy.[3]

Discussion

The majority of patients who benefited from active TMS for a major depressive episode maintained this benefit over 24-weeks while on maintenance antidepressant monotherapy. Only 10/99 (10%) met criteria for relapse during this

Table 6 Summary of continuous clinical ratings during the 24-week durability of effect study (n = 99)

	Long-term durability of effect period (week of follow-up)									
	End of acute TMS treatment	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Clinical rating										
Sample size (N)	99	99	97	94	87	92	86	80	73	70
MADRS total score (SD)	9.8 (7.9)	10.8 (8.4)	11.1 (9.3)	11.4 (9.4)	10.7 (9.1)	11.2 (8.7)	11.0 (9.5)	11.1 (10.2)	10.7 (8.9)	9.6 (9.2)
Change from baseline (SD)		1.0 (10.3)	1.3 (7.3)	1.6 (7.9)	0.7 (9.0)	1.6 (8.6)	1.6 (9.1)	1.9 (9.9)	1.8 (9.5)	0.9 (8.8)
P value		.162	.081	.050	.449	.076	.115	.100	.107	.378
Sample size (N)	99	99	97	94	87	92	86	80	73	70
HAMD24 total score (SD)	9.1 (6.2)	10.7 (7.5)	10.9 (7.5)	11.0 (7.4)	10.5 (7.3)	10.7 (7.2)	10.2 (7.5)	10.3 (7.8)	10.5 (7.3)	9.0 (7.1)
Change from baseline (SD)		1.5 (6.2)	1.8 (6.0)	1.9 (6.0)	1.1 (7.1)	1.7 (6.9)	1.4 (7.4)	1.4 (7.9)	1.8 (7.8)	0.5 (6.8)
P value		.015	.004	.003	.152	.020	.086	.112	.049	.537
Sample size (N)	99	98	97	93	80	92	86	80	73	70
CGI –Severity (SD)	2.1 (1.1)	2.1 (1.1)	2.1 (1.2)	2.3 (1.2)	2.2 (1.2)	2.2 (1.1)	2.2 (1.3)	2.1 (1.2)	2.0 (1.1)	1.8 (1.1)
Change from baseline (SD)		0.0 (0.7)	0.0 (0.9)	0.1 (1.0)	0.0 (1.0)	0.1 (1.0)	0.1 (1.3)	0.0 (1.2)	0.0 (1.2)	−0.1 (1.2)
P value		.892	.738	.160	.735	.539	.411	.857	.638	.340
Sample size (N)	96	97	95	89	84	92	86	79	73	69
IDS-SR total score (SD)	15.4 (9.7)	16.0 (9.7)	16.6 (11.0)	16.6 (10.5)	15.8 (10.9)	15.7 (10.5)	16.1 (10.8)	16.8 (10.6)	16.8 (10.9)	14.6 (10.0)
Change from baseline (SD)		1.0 (5.6)	1.8 (8.2)	2.0 (7.8)	0.6 (9.2)	0.7 (9.2)	1.4 (10.2)	2.2 (10.5)	2.5 (9.7)	0.4 (8.8)
P value		.078	.032	.019	.537	.452	.211	.062	.033	.692

All data are computed in an observed case analysis. Some variation in sample size is due to missing values at some time points. *P* values reflect comparison of change from baseline between end of acute treatment score and subsequent outcome time points performed using Student *t* test.

Table 7 Summary of categorical clinical ratings during the 24-week durability of effect study (n = 99)

Long-term durability of effect period (week of follow-up)									
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Clinical rating									
Sample Size (N)	99	97	94	87	92	86	80	73	70
MADRS									
Responder rate (%)	77.8	75.8	72.7	81.8	76.8	70.7	70.7	74.7	74.7
Remitter rate (%)	47.5	50.5	49.5	48.5	50.5	50.5	51.5	46.5	50.5
HAMD24									
Responder rate (%)	73.7	71.7	70.7	75.8	73.7	69.7	70.7	69.7	72.7
Remitter rate (%)	53.5	54.5	50.5	55.6	54.5	60.6	59.6	55.6	59.6

All categoric outcome percentages at each time point are computed based on the total sample size at entry as the denominator. Some variation in observed case sample size is due to missing values at some time points.

period compared with 3/22 (13.6%) in the sham treated group. Of the 38/99 (38.4%) who met criteria for symptom worsening after active TMS, 32/38 (84.2%) reachieved mood stability with reintroduction TMS. Results from the sham treated group suggest a less robust outcome (i.e., 11/21 or 52.4% met criteria for symptom worsening, and 5/11 or 45.5% reachieved mood stability). Notably, patients with a more robust acute response to active TMS were less likely to relapse or require TMS reintroduction than those with a partial response. This is consistent with other data suggesting a better prognosis in those who demonstrate greater acute antidepressant benefit. Also of interest, our exploratory analysis did not identify any factors that might predict outcome over 24-weeks of follow-up. This contrasts with the results of a similar analysis by Lisanby et al.,[5] which identified level of treatment-resistance as a critical predictor for acute TMS benefit in this study population; and the results of Cohen et al.,[12] which identified younger age and number of treatments as independent predictors of long-term benefit. Possible explanations for these differences are that predictors of short-term outcome may not be the same as those factors that may predict long-term outcome; and, given the relatively small sample size, there is a greater possibility of missing an effect.

An important related question is whether TMS could be safely reintroduced in combination with medication. Our results did not reveal additional safety or tolerability issues with TMS augmentation compared with TMS monotherapy.[3]

The relapse rate in this trial compares favorably to a recent meta-analysis of 11 maintenance antidepressant treatment trials in unipolar depressed patients.[15] Over 1 year, the authors reported a significant difference in relapse rates favoring active drug (i.e., 23%) versus placebo (i.e., 51%). Our findings also compare favorably with reports with maintenance strategies after acute response to ECT.[16-18] In this context, it is important to note that the ECT populations are not comparable in certain respects to those treated with TMS in our study. Thus, although the level of treatment-resistance in the ECT population is generally similar as shown in the Prudic et al.[17] report; the ECT trials were largely conducted in patients who required hospitalization for initial treatment,

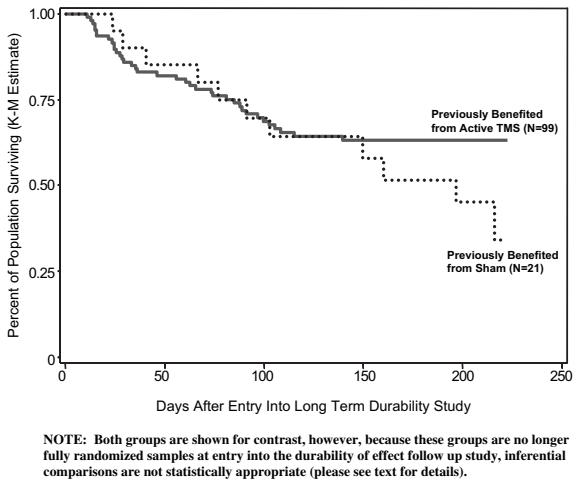


Figure 3 Kaplan-Meier survival curve estimate of time to first reintroduction of TMS during the 24-week, long-term durability of effect study for patients previously benefiting from acute treatment with active TMS (n = 99) and for patients previously benefiting from sham treatment (n = 21).

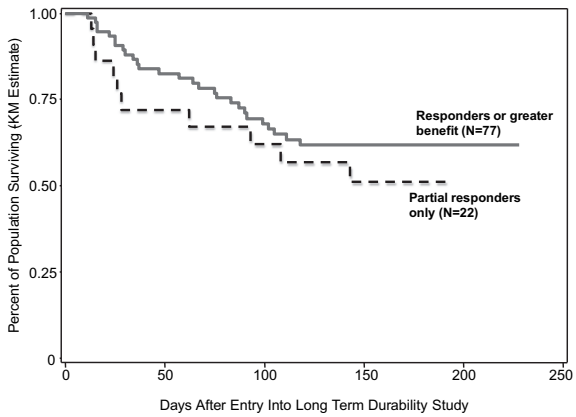


Figure 4 Kaplan-Meier survival curve estimate of time to first reintroduction of TMS during the 24-week, long-term durability of effect study for patients previously benefiting from acute treatment with active TMS: comparison of full response or greater cohort (n = 77) with the partial response only cohort (n = 22).

Table 8 Summary of overall and device-related adverse events during the 24-week durability of effect study

Adverse event	Active TMS treated study population (n = 99)	
Body system - preferred term	Overall incidence n (%)	Device-related n (%)
Gastrointestinal disorders		
- Dry mouth	8 (8.1)	1 (1.0)
- Nausea	8 (8.1)	0 (0.0)
- Constipation	6 (6.1)	1 (1.0)
- Diarrhea	6 (6.1)	0 (0.0)
General disorders and administrative site conditions		
- Fatigue	11 (11.1)	0 (0.0)
- Application site pain	6 (6.1)	6 (6.1)
Infections and infestations		
- Upper respiratory tract infection	11 (11.1)	0 (0.0)
- Nasopharyngitis	5 (5.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
- Arthralgia	18 (18.2)	1 (1.0)
- Back pain	10 (10.1)	0 (0.0)
- Muscle twitching	8 (8.1)	7 (7.1)
- Myalgia	7 (7.1)	0 (0.0)
- Pain in extremity	5 (5.1)	0 (0.0)
Nervous system disorders		
- Headache	33 (33.3)	4 (4.0)
- Dizziness	7 (7.1)	0 (0.0)
Psychiatric disorders		
- Insomnia	35 (35.4)	1 (1.0)
- Anxiety	14 (14.1)	0 (0.0)
- Libido decreased	8 (8.1)	0 (0.0)
- Depressive symptoms	6 (6.1)	0 (0.0)
- Irritability	5 (5.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders		
- Pharyngolaryngeal pain	5 (5.1)	0 (0.0)

Overall incidence of adverse events shows those events that were reported in >5% of the patient population, regardless of relationship to the study device; Device-related incidence shows those events within the Overall incidence that were determined by the study investigator to be probably or definitely related to the TMS device.

some manifested psychotic features, and as a group would generally be considered more severely-ill.[16-18] The comparison may still be instructive, however, because the ECT literature is the best available description of long-term outcome in a treatment-resistant population. This literature indicates that although ECT usually produces a robust acute treatment effect, optimization of effective maintenance strategies remains elusive. For example, Tew et al.[19] reported on 73 unipolar depressed patients who remitted with acute ECT and were randomized to maintenance treatment with nortriptyline monotherapy, nortriptyline plus lithium or placebo for up to 6 months. The combination medication group experienced a 39% relapse rate versus 60% for those on nortriptyline only and 84% on placebo. These results were virtually identical to an earlier report by Sackeim and colleagues[16] in a group of 83 unipolar depressed patients followed for up to 24 weeks after achieving remission to an acute course of ECT. Finally, the Consortium for Research in Electroconvulsive Therapy (CORE) reported the relapse rates over 6 months in 201 acute ECT responsive, unipolar depressed patients maintained on either continuation ECT (i.e., 37.1%) or continuation medication (i.e., lithium plus nortriptyline; 31.6%).[18] To provide as direct a comparison as possible of the long-term outcomes after successful acute response to TMS with those previously reported for ECT, we compared the 24-week clinical outcome in the remitter-only subset (n = 56) of the larger patient cohort (n = 99) to the remitter-only population reported in the CORE Study dataset (Table 9). Mindful of the slight differences in study designs and the differences in the study populations noted previously, the durability of outcome for patients who achieved remission during acute treatment with TMS compared favorably with the outcomes observed for ECT.

Strengths of this report include it being the only prospective, follow-up study of the durability of the acute antidepressant effects of TMS in which the regimen of maintenance antidepressant monotherapy was standardized. Secondly, the population was well characterized, particularly with regard to level of treatment resistance in the current episode. *Limitations* include the lack of a controlled comparison. We did,

Table 9 Comparison of long-term clinical outcomes (HAMD24) of TMS or ECT after benefit from acute treatment

Outcome	TMS (n = 56)	Outcome	ECT - combination pharmacotherapy[18] (n = 95)	ECT - continuation ECT[18] (n = 89)
% Early discontinuation[a]	16.1%	% Early discontinuation[q]	22.1%	16.8%
% Disease recurrence[b]	10.7%	% Disease recurrence[b]	31.6%	37.1%
% Total not achieving remission by study completion	*26.8%*	*% Total not achieving remission by study completion*	*53.7%*	*53.9%*
% In remission by study completion[c]	**73.2%**	**% In remission by study completion[c]**	**46.3%**	**46.1%**

All patients in TMS sample had achieved categorical remission (HAMD-24 total score of $\leq$10) by end of acute treatment. All patients in ECT sample had achieved categorical remission ($\geq$60% reduction in baseline HAMD-24 total score + HAMD-24 total $\leq$10 on two separate occasions) by end of acute treatment. For TMS sample, ***relapse*** was defined as discontinuation due to lack of efficacy at any time point or reintroduction of TMS up to 6 wk without benefit, and ***remission*** was defined as a HAMD-24 score of $\leq$10. For ECT sample, ***relapse*** was defined as two consecutive HAMD-24 ratings of 16 or more and a minimum increase of 10 points from baseline score at entry to long-term follow-up, and remission was defined as $\geq$60% reduction in baseline HAMD-24 total score + HAMD-24 total $\leq$10 on two separate occasions.

[a] Discontinued study for reasons other than relapse of illness.

[b] Discontinued study due to relapse or completed study and were not in remission at study endpoint.

[c] Met protocol criteria for remission at study endpoint as described above.

however, include the outcomes of those patients who continued on in a blinded manner from their acute response to sham TMS. It is noteworthy that this group had a relapse rate of 14%, compared with 10% with active TMS. The sham responders were also more likely than the active responders to experience symptom worsening and require TMS reintroduction during the follow-up period, (i.e., 52.4% versus 38.4%, respectively). Unfortunately, because these two groups were no longer fully randomized after entry in the long-term trial, inferential statistical comparisons are not appropriate. Further, all patients, regardless of whether they benefitted from active or sham TMS during acute treatment, were continued on antidepressant medication monotherapy as a primary maintenance strategy during the 24-week follow-up. Hence, the acute sham responder group was not followed as a "pure" sham responder (or no treatment) extension cohort, because these patients may have received clinical benefit from the introduction of antidepressant medication. This potential must be considered in the interpretation of the outcomes between the treatment groups. The method of coil positioning used in this study was the so-called "5 cm rule." This method is a reproducible and easy-to-use approach in clinical practice, and has resulted in safe and effective use of TMS in the treatment of depression in replicated clinical studies. Recent research questions whether this approach can be improved through the use of methods that account for natural variations in head circumference, or use more sophisticated methods of neuronavigation.[20] Whether such advances will result in improvements in clinical outcome, however, is unclear at the present time.

We believe this report informs clinicians about potential approaches to patient management in the aftermath of successful acute treatment with TMS. Thus, our monotherapy antidepressant medication relapse prevention strategy, combined with reintroduction TMS for symptom re-emergence, provides guidance for the use of intermittent TMS as a clinically meaningful rescue intervention. In addition, these data further support the safety and tolerability of TMS as an augmentation to antidepressant medication.

In conclusion, these data expand our understanding of the clinical durability of acute benefit with TMS, and describe the results of a clinically plausible, effective, and safe strategy for maintenance of acute benefit in clinical practice. Moreover, they provide a framework for the design of future controlled maintenance or relapse prevention trials with TMS.

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Supplementary data

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