

An Open-Label, Prospective Study of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Long-Term Treatment of Refractory Depression: Reproducibility and Duration of the Antidepressant Effect in Medication-Free Patients

Asli Demirtas-Tatlidede, M.D.; Dawn Mechanic-Hamilton, B.A.; Daniel Z. Press, M.D.; Chester Pearlman, M.D.; William M. Stern, M.A., M.B.B.S.; Mark Thall, M.D.; and Alvaro Pascual-Leone, M.D., Ph.D.

Objective: Several studies have assessed the acute antidepressant effects of repetitive transcranial magnetic stimulation (rTMS), and many have revealed positive results. However, the impact of rTMS throughout the long course of major depressive disorder (MDD) and the efficacy of rTMS in the treatment of depressive relapses still remain to be elucidated.

Method: Sixteen medication-free patients with refractory MDD (diagnosed according to DSM-IV) who initially had clinically significant antidepressant responses to a 10-day course of 10-Hz rTMS were consecutively admitted to the protocol from 1997 to 2001 and were followed for 4 years. The cohort was studied during a total of 64 episodes of depressive relapse. Severity of depression was evaluated with the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) prior to and after completion of each rTMS treatment course. Clinically significant response was defined as a reduction in HAM-D score of at least 50%. Safety was assessed by serial neurologic examinations and neuropsychological evaluations.

Results: Approximately one half of the patients individually sustained a clinically significant response to the repeated courses of rTMS; the mean \pm SD decrease in HAM-D scores was $64.8\% \pm 12.6\%$ ($p < .0001$), and, in BDI scores, $60.4\% \pm 20.6\%$ ($p < .0001$). Despite the lack of adjuvant antidepressant medication, the mean interval between treatment courses was approximately 5 months, and the medication-free period ranged from 26 to 43 months. Transcranial magnetic stimulation was well tolerated, and evaluations regarding the safety of the repeated applications of rTMS revealed no findings of concern.

Conclusions: Repeated rTMS applications have demonstrated a reproducible antidepressant effect in patients with refractory depression who initially showed a clinically significant benefit. The duration of effect varied across patients, but benefits were sustained for a mean of nearly 5 months. Further studies with larger cohorts will be useful in determining the long-term effectiveness of rTMS maintenance therapy.

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Corresponding author and reprints: Alvaro Pascual-Leone, M.D., Ph.D., Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, 330 Brookline Ave., KS-452, Boston, MA 02215 (e-mail: apleone@bidmc.harvard.edu).

Repetitive transcranial magnetic stimulation (rTMS) is a promising therapeutic modality for the treatment of neuropsychiatric diseases.¹⁻³ During the last decade, numerous studies, including several meta-analyses, have indicated the efficacy of rTMS in acute treatment of major depressive disorder (MDD).⁴⁻¹¹ While it is increasingly accepted that rTMS has antidepressant effects, its clinical utility is uncertain as many aspects of this treatment remain incompletely investigated, including the optimal stimulation parameters (intensity and site of stimulation and duration of treatment), the exact mechanism of action of rTMS in depression, and the patient characteristics that might predispose to a strong antidepressant response.

The impact of rTMS throughout the long course of depressive disorders and its efficacy for treatment of relapses also remain to be clarified. There is little evidence regarding the duration and reproducibility of the antidepressant response to rTMS.¹²⁻¹⁴ The efficacy of a second course of rTMS was first documented by Dannon et al.¹² in 4 patients who initially responded to rTMS at 10 Hz over the left dorsolateral prefrontal cortex (DLPFC). Mean \pm SD time between relapses was 6.9 ± 4.8 months. Two of these patients were on antidepressant medications, and 2 were noncompliant with medical treatments.

Table 1. Subject Demographics (N = 16)

Variable	Subjects
Sex, N (%)	
Male	9 (56)
Female	7 (44)
Handedness, N (%)	
Right	13 (81)
Left	3 (19)
Age, mean (range), y	45.8 (18–78)

Subsequently, the same group was able to demonstrate the beneficial effect of a third course of rTMS in a case with refractory MDD.¹³ Finally, Fitzgerald et al.¹⁴ reported on a series of 19 patients who received rTMS for the treatment of depressive relapses in up to 4 episodes. According to the clinical trial that the patients initially responded to, rTMS applications included 3 subgroups: 10 Hz to left DLPFC, 1 Hz to right DLPFC, or a combination of both. The mean relapse time for each round of treatments ranged between 6.0 and 11.6 months. Fifteen patients were on antidepressant treatments, 5 were on mood stabilizers, and 4 were medication-free. The authors concluded that rTMS was of value in the treatment of depressive relapses, with slight reduction in efficacy over time.¹⁴

A greater understanding of the antidepressant efficacy of repeated applications of rTMS as a stand-alone therapy and its potential impact on the long course of MDD is crucial to designing an effective maintenance program using rTMS to treat depressed patients. In this study, we provide further evidence on the efficacy of rTMS after an acute episode of depression in a homogeneous group of patients who are not receiving antidepressant medications and who are all receiving the same rTMS protocol.

METHOD

Patients

Sixteen patients diagnosed with MDD were included in this open-label, prospective study. All of the patients had initially participated in double-blind, sham-stimulation-controlled trials of rTMS in medication-refractory depression at Beth Israel Deaconess Medical Center. Those who had demonstrated a clinically significant response to initial rTMS treatment were consecutively admitted to the present protocol from 1997 to 2001 and were then followed for a period of 4 years. Major depressive disorder was diagnosed by a board-certified psychiatrist through review of psychiatric records and assessment with the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).¹⁵ Clinically significant response was defined as a reduction in the Hamilton Rating Scale for Depression (HAM-D) score of at least 50%.

Patient demographics. Patient demographics are described in Table 1. The mean duration of MDD diagnosis

was 15.3 years. All patients were suffering from refractory depression, having failed at least 3 trials of therapeutic doses and durations of different antidepressants lifetime prior to receiving rTMS. Fifty-five percent had been hospitalized for their depression in the past, 25% had a history of suicide attempts, and 73% had previously undergone electroconvulsive therapy (ECT). These patients were therefore at the severe end of the spectrum of MDD.

Requisites for repeated rTMS treatment. Each patient, with his or her treating psychiatrist's clinical input, was encouraged to contact the TMS laboratory upon noticing any signs or symptoms of recurrent depression. Repeated applications of rTMS were offered when the patient felt the need for it, provided that the HAM-D score was ≥ 18 and the patient had remained free of antidepressants, benzodiazepines, and neuroleptics since the previous rTMS course. All patients were required to continue follow-up with their treating psychiatrists throughout involvement in the study to assure their safety and well-being.

The study was approved by the local Institutional Review Board and the Scientific Advisory Committee of the General Clinical Research Center at Beth Israel Deaconess Medical Center, Boston, Mass. All participants gave written informed consent before being enrolled in the study.

Clinical Assessments

In order to evaluate the degree of symptomatic improvement, the 28-item HAM-D¹⁶ and the Beck Depression Inventory (BDI)¹⁷ were administered prior to and within 2 weeks after the completion of each rTMS course.

In addition, to assess the safety of repeated rTMS exposure, prior to each rTMS course, patients underwent a brief neuropsychological evaluation and full neurologic examination by a board-certified neurologist. The battery of neuropsychological tests was designed to be short and easy to administer but sufficiently sensitive to detect subtle deficits. It included the following tests¹⁸: (1) simple and choice reaction time, (2) Rey Auditory-Verbal Learning Test (immediate and delayed recall), (3) Digit Span (forward and backward), (4) Spatial Span (forward and backward), (5) Letter-Number Sequencing, and (6) Transient Events Test.

Transcranial Magnetic Stimulation Applications

All patients underwent 10-day rTMS treatment courses, with application of rTMS to the left DLPFC. Each treatment course consisted of 1 day of evaluations followed by 9 daily treatment sessions.

A Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Dyfed, U.K.) was employed for rTMS treatment. A commercially available figure-of-8 coil (each wing measuring 7 cm in diameter) was held 45° tangentially to the scalp. Resting motor threshold was ascertained before each treatment session for the contralateral (right) first dorsal interosseous muscle

Table 2. Mean Treatment Intervals and Percent Change in HAM-D and BDI Scores for Each Study Subject and for Total Sample (N = 16)

Sample	No. of Treatment Courses	Mean Treatment Interval (mo)	Mean Percent Change in HAM-D Score ^a	Mean Percent Change in BDI Score ^a
Individual Results				
1	2	24.0	-65.4	-63.4
2	2	3.0	-69.4	-73.0
3	4	5.0	-67.5	-70.0
4	3	4.5	-52.4	-65.5
5	3	8.5	-87.6	-81.1
6	3	5.5	-85.0	-79.7
7	3	9.5	-59.7	-60.5
8	9	3.0	-68.2	-53.2
9	4	4.0	-53.5	-26.7
10	10	3.8	-64.7	-60.2
11	2	3.0	-53.3	-71.8
12	5	6.3	-60.8	-52.7
13	4	5.0	-58.7	-51.1
14	4	5.3	-68.0	-73.3
15	3	1.5	-54.1	-59.2
16	3	2.5	-51.8	-39.9
Group Results				
Mean (SD)	4.0 (2.3)	4.9 (3.8)	-64.8 (12.6)	-60.4 (20.6)
Range	2 to 10	1 to 24	-44.4 to -97.1	-100 to 8.7

^aMeans include only treatment courses that allowed patients to return for subsequent treatment.

Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression.

following the guidelines of the International Federation for Clinical Neurophysiology.¹⁹ Left DLPFC, determined anatomically to be 5 cm anterior to the hand representation in the primary motor cortex, was the area of stimulation for the whole group.⁴ Each session consisted of 20 blocks of rTMS with a 52-second rest period between each block. Each block of stimulation was done at 90% of motor threshold and at 10 Hz for 8 seconds, for a total of 80 stimuli per block and 1600 stimuli per session; therefore, the total number of stimuli that patients received throughout a course was 14,400.

Statistical Analysis

Efficacy of each treatment course, as well as maintenance of initial gains of treatment through each subsequent course, was determined by analysis of pretreatment and posttreatment HAM-D and BDI scores using paired *t* tests. Pretreatment HAM-D scores were also analyzed to assess consistency of pretreatment level of depression throughout patient participation in the study. The intervals between treatment courses within and among patients were analyzed to ascertain possible trends. Differential response by sex, age, and handedness was also examined using an analysis of variance test to identify possible effects of demographic differences on outcome.

RESULTS

Outcomes

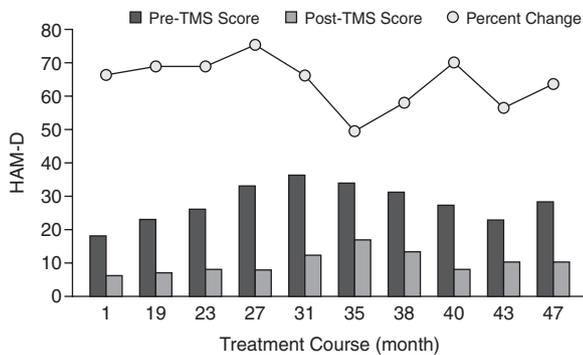
The number of rTMS treatment courses completed by each of the 16 patients is summarized in Table 2. Patients

completed a mean of 4 (range, 2–10) rTMS treatment courses. The mean interval between treatment courses was 4.9 months overall (range, 1–24 months). Those patients who continued to return for treatment began their next treatment course between 3.0 and 5.3 months after the previous course. The number of treatment courses revealed no consistent or significant effect on the duration of the interval between rTMS courses across the group of patients.

Of the 16 patients included, 1 opted to discontinue treatment because of the difficulty of traveling to the lab and 1 was lost to follow-up after having completed participation in 3 rTMS courses. Therefore, 14 patients completed the study. Seven of these (50%) sustained a clinically significant antidepressant response to rTMS and were allowed to continue in the study. Three of these patients required no further TMS following either their third or fifth treatment course because of an adequate and persistent reduction in depressive symptoms that lasted for 13 to 31 months. These 7 patients remained medication-free for a mean of 33 months (range, 26–43 months) after their first rTMS treatment. The mean \pm SD decrease in HAM-D scores for treatment courses was 64.8% \pm 12.6% ($p < .0001$), while the mean \pm SD decrease in BDI scores was 60.4% \pm 20.6% ($p < .0001$).

The remaining 7 patients obtained a HAM-D score of less than 18 within one of the rTMS courses and did not qualify to continue in the study; this occurred in the second ($N = 3$), third ($N = 1$), fourth ($N = 2$), or fifth ($N = 1$) treatment course. Four of these patients were not able to continue despite their desire to do so. Three decided to

Figure 1. Hamilton Rating Scale for Depression (HAM-D) Scores and Percent Change in Score Before and After Each Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment Course: A Case Study



return to medications or ECT because they were not satisfied with the magnitude of the antidepressant effect of rTMS.

The effect of gender, age, or handedness on the mean percent change in HAM-D was studied, and none of these variables revealed a significant interaction with HAM-D changes.

Figure 1 follows the progress of HAM-D scores and their percentage decrease for a patient who completed 10 rTMS courses over the course of 4 years. This patient had a mean \pm SD decrease in HAM-D scores of $64.7\% \pm 7.7\%$ (range, 50.0%–75.8%; $p < .0001$) and a mean \pm SD decrease in BDI scores of $60.2\% \pm 16.0\%$ (range, 34.8%–81.1%; $p < .0001$). The mean \pm SD interval between treatment courses was 3.8 ± 1.1 months (range, 2–6 months). There were no trends for increase or decrease in treatment interval or for change in magnitude of antidepressant effects over the 4 years of treatment.

Safety

The most important adverse effect of rTMS is induction of a seizure.²⁰ The rTMS parameters used in this study were compliant with the published safety guidelines for rTMS.²¹ Out of the 576 sessions of rTMS application within this protocol, no seizures occurred and no other serious side effects were recorded.

Serial neurologic examinations were performed prior to each rTMS course. To check for possible cognitive impairment, all participants were assessed by neuropsychological evaluations prior to and after each course of rTMS. None of these evaluations revealed any findings of concern regarding the safety of the repeated applications of rTMS.

DISCUSSION

In this report, repeated applications, as a monotherapy, of 10-Hz rTMS to the left DLPFC were shown to lead to a

consistently robust and reproducible antidepressant response in depressed patients who previously had shown response to rTMS therapy for MDD. Similar to the time course of response to antidepressant medications, changes in HAM-D and BDI scores after rTMS treatment were not fully evident until 2 weeks after the treatment course in most patients. Fifty percent of the patients who remained in the study and continued to respond to rTMS courses were medication-free for a mean of 33 months. The intervals between treatment courses consistently neither increased nor decreased, indicating that the length of the antidepressant effect remained stable, albeit somewhat variable, over time. The reproducibility of the antidepressant effect of repeated rTMS treatment is exemplified by the case study that follows 1 patient over 4 years and 10 courses of rTMS (Figure 1). This patient showed a reproducible, predictable, and striking response within 2 weeks of the conclusion of each treatment course. These beneficial effects were not associated with any undesirable effects of rTMS.

The time between the treatment courses varied within and across patients. Patients consistently returned for another treatment course when their HAM-D score was approximately equal to previous pretreatment scores, often well beyond the 18 points required to initiate another rTMS treatment course. In order to help patients maintain a consistently higher level of functioning, a monthly HAM-D assessment could facilitate prophylaxis of severe depressive episodes and allow for true maintenance of the TMS effect. It would also be beneficial to collect information on the prevalence of Axis II disorders to obtain a clearer picture of how clinical symptomatology may affect outcome in our treatment-refractory population; comorbidity of personality disorders with MDD has been shown to decrease the rate and intensity of response to both ECT and antidepressant medication.^{22–24}

Two patients who had been treatment-resistant prior to rTMS returned to medications or ECT after an unsatisfactory response to rTMS and subsequently found relief from depressive symptoms. Further investigation of the nature of this response may be helpful in assessing the usefulness of rTMS as an augmentation strategy or, possibly, a complementary or concomitant modality of antidepressant treatment with medication or ECT. Indeed, rTMS has been shown to be effective as an add-on treatment in patients with medication-resistant MDD, whereas this effect could not be confirmed in patients with nonresistant MDD.^{25,26} Pridmore,²⁷ in a randomized, single-blind, controlled study, concluded that substituting 4 rTMS treatments following 1 ECT treatment for 2 consecutive weeks in mostly medicated, depressed patients demonstrated no loss of antidepressant effect and possibly fewer side effects.²⁷ Some preliminary data additionally suggested that ECT might be an effective treatment following rTMS for 40% of the patients who failed to respond to rTMS treatment.²⁸

Regarding our methodology, clinically significant signs of relapse were required for repeating rTMS treatment, as the current data on treatment of relapses are very limited. Consequently, 4 patients who benefited from rTMS therapy were disqualified from the study despite their desire to continue, as they scored below 18 on the HAM-D. Such patients would have been included in a maintenance protocol due to advisability of treating at the first signs of relapse. This study also has limitations due to its open-label design. Obviously, in the cohort of patients reported here, the level of motivation was very high, as all knew that they had responded to the initial rTMS course. However, the findings are most encouraging and suggest a sustained clinical utility of rTMS as a monotherapy in those patients who initially respond to it.

This study provides substantial evidence for the efficacy and safety of rTMS in the long-term treatment of refractory depression. Our results support and extend prior reports on the treatment of depressive relapses with rTMS^{12,14} by demonstrating the reproducibility of rTMS effects even after 10 depressive relapses in the absence of adjunct medications. While important, treatment of relapses seems clinically less desirable than true maintenance of the antidepressant effects of rTMS. Available data on maintenance, though still limited, suggest a sustained benefit from 1 to 2 sessions of weekly rTMS for periods from 6 months to 6 years.²⁹ Further studies with larger cohorts of patients and true double-blind maintenance protocol designs (with or without medication adjuncts) are required and seem warranted given the demonstrated safety and efficacy of the repeated rTMS applications in our patients.

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