Effectiveness of Transcranial Magnetic Stimulation in Clinical Practice Post-FDA Approval in the United States: Results Observed With the First 100 Consecutive Cases of Depression at an Academic Medical Center

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ABSTRACT

Introduction: Transcranial magnetic stimulation (TMS) is a US Food and Drug Administration–approved treatment for major depressive disorder (MDD) in patients who have not responded to 1 adequate antidepressant trial in the current episode. In a retrospective cohort study, we examined the effectiveness and safety of TMS in the first 100 consecutive patients treated for depression (full *DSM-IV* criteria for major depressive episode in either major depressive disorder or bipolar disorder) at an academic medical center between July 21, 2008, and March 25, 2011.

Method: TMS was flexibly dosed in a course of up to 30 sessions, adjunctive to current medications, for 85 patients treated for acute depression. The primary outcomes were response and remission rates at treatment end point as measured by the Clinical Global Impressions-Improvement scale (CGI-I) at 6 weeks. Secondary outcomes included change in the Hamilton Depression Rating Scale (HDRS); Quick Inventory of Depressive Symptomatology, self-report (QIDS-SR); Beck Depression Inventory (BDI); Beck Anxiety Inventory (BAI); and the Sheehan Disability Scale (SDS). Enduring benefit was assessed over 6 months in patients receiving maintenance TMS treatment. Data from 12 patients who received TMS as maintenance or continuation treatment after prior electroconvulsive therapy (ECT) or TMS given in a clinical trial setting were also reviewed.

Results: The clinical cohort was treatment resistant, with a mean of 3.4 failed adequate trials in the current episode. Thirty-one individuals had received prior lifetime ECT, and 60% had a history of psychiatric hospitalization. The CGI-I response rate was 50.6% and the remission rate was 24.7% at 6 weeks. The mean change was −7.8 points in HDRS score, −5.4 in QIDS-SR, −11.4 in BDI, −5.8 in BAI, and −6.9 in SDS. The HDRS response and remission rates were 41.2% and 35.3%, respectively. Forty-two patients (49%) entered 6 months of maintenance TMS treatment. Sixty-two percent (26/42 patients) maintained their responder status at the last assessment during the maintenance treatment. TMS treatment was well tolerated, with a discontinuation rate of 3% in the acute treatment phase. No serious adverse events related to TMS were observed during acute or maintenance treatment.

Conclusions: Adjunctive TMS was found to be safe and effective in both acute and maintenance treatment of patients with treatment-resistant depression.

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Transcranial magnetic stimulation (TMS) was approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of major depression in which the current episode had failed to respond to 1 medication trial, and data from controlled trials and meta-analyses further support its efficacy.[1–5] Recently, Schutter[2] assessed outcomes from 30 randomized controlled trials (RCTs) (n = 1,154) and reported an effect size (Cohen *d*) of 0.39 (95% CI, 0.25–0.54). Lam et al[5] focused on outcomes in patients with treatment-resistant depression (24 RCTs; n = 1,097) and found an effect size of 0.48 (95% CI, 0.29–0.69).

Significant questions remain as to which are the most effective stimulation parameters and which is the most appropriate patient population for TMS in clinical practice. The FDA criterion for approval is also narrow (exactly 1 failed trial in the current episode), leaving the clinician to treat patients with higher levels of treatment resistance off-label. This is the patient group most likely to seek TMS, given its cost and time burden.

We treated outpatients with treatment-resistant depression (n = 100) at an academic medical center. We hypothesized that TMS would be effective in treatment-resistant depression patients from a "real-world" clinical practice setting.

METHOD

Study Participants

This was a retrospective cohort study of 100 consecutive outpatients treated for depression in the TMS Treatment Program at the University of Pennsylvania between July 21, 2008, and March 25, 2011. Subjects had a *DSM-IV* diagnosis of major depressive disorder (MDD), bipolar disorder in a current major depressive episode, or depressive disorder not otherwise specified (NOS).

The study included all patients for whom TMS was judged to be appropriate treatment. The only exclusions from TMS treatment were pregnancy or an absolute contraindication to TMS therapy, such as metal within the brain. Patients with a family or personal history of seizures were, in most instances, treated with low-frequency TMS to the right dorsolateral prefrontal cortex (DLPFC).

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Clinical Points

- Transcranial magnetic stimulation is a safe and effective adjunct to medication treatment of major depressive disorder.
- Transcranial magnetic stimulation has here shown additional effectiveness in patients with depressions that are usually more difficult to treat, including those with bipolar disorder, high levels of medication resistance, or past nonresponse to treatment with electroconvulsive therapy.

The study was approved by the University of Pennsylvania Institutional Review Board.

Study Overview

Charts from the first 100 consecutive patients were reviewed. All subjects had an initial evaluation with an attending psychiatrist with expertise in treatment-resistant depression and TMS. Data on demographic and clinical variables were obtained at intake as part of the program's standard evaluation (including the measures selected as primary and secondary outcomes, as described below). A history of previous antidepressant trials was obtained, and the adequacy of prior treatment was assessed via the Antidepressant Treatment History Form.[6]

For inclusion into our analysis of acute TMS efficacy, a minimum level of depression severity was set at ≥ 14 on the Hamilton Depression Rating Scale (HDRS) and/or ≥ 16 on the Beck Depression Inventory (BDI). Existing psychotropic medications were held fixed as long as possible, with TMS applied adjunctively during the 6 weeks of acute treatment and 6 months of maintenance treatment.

In the majority of cases, TMS treatment was off-label, as patients had exceeded 1 failed adequate antidepressant trial in the current episode. Transcranial magnetic stimulation sessions were conducted 5 days per week (Monday–Friday) for a maximum of 30 TMS sessions or 6 weeks of treatment. Data were also collected from patients who continued for up to 6 months of maintenance TMS.

TMS Treatment

A registered nurse and a medical assistant trained in the administration of TMS delivered all TMS sessions. Safety measures consistent with TMS consensus guidelines[7] were applied, including hearing protection and availability of oxygen and anticonvulsant medications. Subjects were queried about adverse effects at each session. Two TMS devices were used for treatment, the MagPro R30 device (Magventure, Inc, Atlanta, Georgia) and the Magstim Rapid^2 (Magstim Ltd, Spring Gardens, Wales, England). Each patient was treated with the same device throughout his or her course.

Transcranial magnetic stimulation was applied over the left DLPFC. Initially, the 5-cm rule was applied to determine the DLPFC target.[8] However, patients treated later in the period reviewed had the F3 electroencephalogram (EEG)-based method.[9] Patients typically began treatment with fast frequency TMS (10 Hz, 5-second train duration, 15-second intertrain interval, with a dose of 4,000 pulses/session at 110% of the observed motor threshold). Patients aged 65 years and older were treated at 120% of the motor threshold to allow for cortical atrophy.[10,11]

Transcranial magnetic stimulation dosing was increased based on clinical progress, up to a maximum of 8,000 pulses per session. Some patients had "slow" TMS at 1 Hz added (1-second train duration), targeting the right DLPFC for 300 to 1,200 pulses per session.

Six patients received 1-Hz right-sided TMS only. Six patients commenced TMS with bilateral stimulation. Thirty-nine of 88 patients (44.3%) treated acutely received right-sided 1-Hz TMS after not responding to fast-frequency TMS.

Patients receiving maintenance treatment were transitioned by means of a taper phase of 6 sessions over 3 weeks (3 sessions in week 1, 2 in week 2, and 1 in week 3). Thereafter, the typical schedule for TMS sessions was 1 per week for 4 weeks, 2 per month for 2 months, and 1 per month for 3 months, but the frequency of sessions could be increased or reduced based on clinician judgment.

Acute Treatment Outcomes

The primary outcomes for the acute sample were the response and remission rates at treatment end point via the Clinical Global Impressions-Improvement scale (CGI-I).[12] This measure was selected because of its practicality and established validity.[12,13]

Secondary Outcomes

Secondary outcomes were changes in scores from baseline to week 6 on the HDRS[14]; Quick Inventory of Depressive Symptomatology, self-report (QIDS-SR)[15]; and the BDI.[16] Categorical outcomes on these scales were response (a 50% decrease from the baseline score) and remission (≤ 7 on the HDRS, ≤ 5 on the QIDS-SR, and ≤ 9 on the BDI). Other outcomes included changes in score on the Beck Anxiety Inventory (BAI)[17] and functional status per the Sheehan Disability Scale.[18]

Maintenance Outcomes

Patients were followed for 6 months or until they left treatment. Sustained response and remission and reasons for premature discontinuation were recorded.

Data Analysis

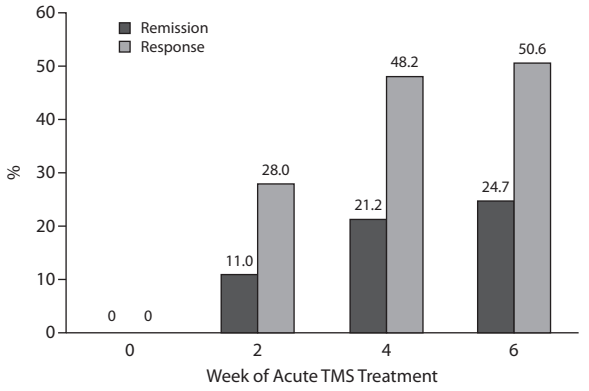
Data were analyzed using SAS statistics software (SAS Institute, Inc, Cary, North Carolina); missing data were imputed via the last-observation-carried-forward method. Statistical significance for a change in secondary outcomes was assessed via 2-tailed, paired samples *t* test, without correction for multiple comparisons. An exploratory analysis was performed using binary logistic regression to identify possible predictors of acute TMS response.

Table 1. Patient Characteristics for Acute Course of Transcranial Magnetic Stimulation (n = 85)

Characteristic	Value
Age, mean (SD), y	50.4 (14.5)
Sex, n (%)	
Male	41 (48.2)
Female	47 (55.3)
MDD, n (%)	65 (76.5)
Bipolar disorder, n (%)	20 (23.5)
Duration of illness (lifetime), mean (SD), y	23.7 (12.4)
Duration of current MDE, mean (SD), mo	42.7 (65.6)
ATHF score (current episode), mean (SD)	3.4 (2.8)
History of ECT, n (%)	31 (35.6)
History of prior hospitalization, n (%)	51 (60.0)
History of prior suicide attempt, n (%)	21 (24.7)
Bipolar disorder subgroup (n = 20)	
Bipolar I, n	11
Bipolar II, n	4
Bipolar NOS, n	5
Duration current MDE, mean (SD), mo	34 (68.8)
No. of failed antidepressants in current episode, mean (SD)	3.4 (2.9)
Prior ECT, n (%)	7 (35.0)
Prior hospitalization, n (%)	17 (85.0)
Prior suicide attempt, n (%)	10 (50.0)
Prior ECT subgroup (n = 31)	
MDD, n (%)	24 (77.0)
Bipolar depression, n (%)	7 (23.0)
Duration of illness (lifetime), mean (SD), y	24.9 (10.65)
Duration current MDE, mean (SD), mo	66.6 (84.9)
ATHF score (current episode), mean (SD)	4.3 (3.3)
Prior hospitalization, %	84
Prior suicide attempt, %	32.3

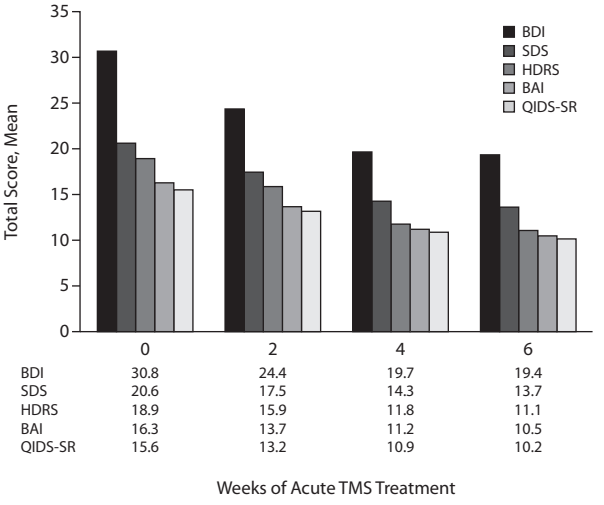
Abbreviations: ATHF = Antidepressant Treatment History Form, ECT = electroconvulsive therapy, MDD = major depressive disorder, MDE = major depressive episode, NOS = not otherwise specified.

Figure 1. Response and Remission Rates on Clinical Global Impressions-Improvement Scale (n = 85)



Abbreviation: TMS = transcranial magnetic stimulation.

Figure 2. Secondary Outcomes by Week (n = 85)



Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology, self-report; SDS = Sheehan Disability Scale; TMS = transcranial magnetic stimulation.

RESULTS

Patient Characteristics

Sixty-five patients were diagnosed with MDD, 20 with bipolar depression, and 3 with depression NOS (n = 88). Individuals diagnosed with depression NOS (n = 3) were excluded from the effectiveness analysis, leaving a total of 85 patients in this analysis (MDD, n = 65; bipolar disorder, n = 20). Eighty percent of patients (n = 68) had at least 1 non-substance–related Axis I comorbidity; 47% (n = 40) had 1 comorbidity, 25% (n = 21) had 2, and the remainder of patients had 3 or more. Data on medication use were collected from 84 of the 85 patients. Of these, 78 (92%) were on at least 1 psychiatric medication at the start of the trial. Twenty-nine patients (34%) had medication changes during their course. Rates of individual medication treatments were as follows: 34 patients (40%) received second-generation antipsychotics; 27 (32%), selective serotonin reuptake inhibitors; 19 (22%), bupropion; 18 (21%), serotonin-norepinephrine reuptake inhibitors; 16 (19%), anticonvulsants; 15 (18%), stimulants/modafinil; 10 (12%), lithium; 9 (11%), monoamine oxidase inhibitors; 6 (7%), tricyclic antidepressants; and 5 (6%), mirtazapine. In addition, 35 patients (41%) received at least occasional treatment with benzodiazepines or benzodiazepine receptor agonists.

In addition, 6 patients switched from maintenance electroconvulsive therapy (ECT) treatment to maintenance TMS, 5 transitioned to maintenance treatment from an RCT of TMS, and 1 patient was included after receiving acute treatment in another clinical trial.[19] All 100 patients were included in the safety analysis. Further, relevant characteristics of the acute treatment sample are presented in Table 1.

Acute Treatment Outcomes (CGI-I response and remission rates)

At the end point of up to 30 adjunctive TMS sessions, the CGI-I response rate was 50.6% and the remission rate was 24.7% (Figure 1). No statistically significant differences were found on χ^2 tests between bipolar and unipolar groups with respect to response or remission rates.

Secondary Outcomes

At acute treatment end point, the mean change in the HDRS score was −7.8 points (SD = 6.5, $P < .001$; Figure 2);

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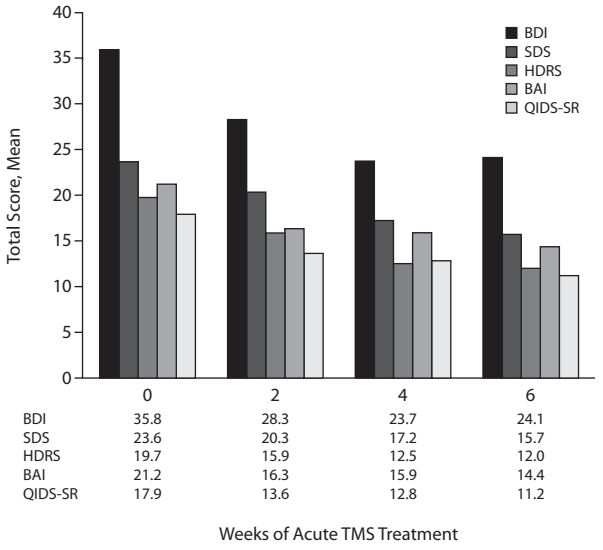
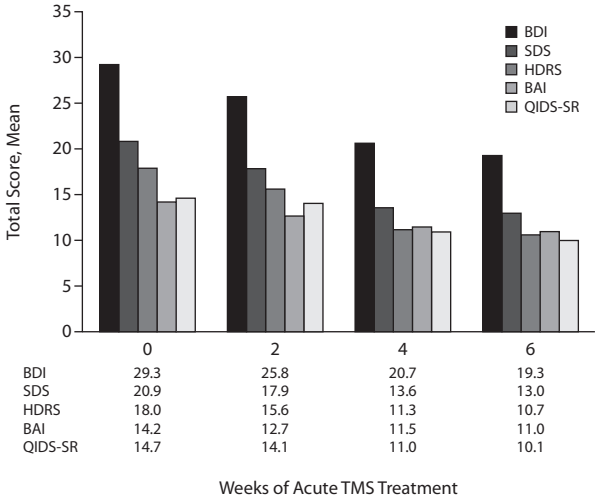
Figure 3. Secondary Outcomes by Week—Bipolar Subgroup (n = 20)



	0	2	4	6
BDI	35.8	28.3	23.7	24.1
SDS	23.6	20.3	17.2	15.7
HDRS	19.7	15.9	12.5	12.0
BAI	21.2	16.3	15.9	14.4
QIDS-SR	17.9	13.6	12.8	11.2

Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology, self-report; SDS = Sheehan Disability Scale; TMS = transcranial magnetic stimulation.

Figure 4. Secondary Outcomes by Week—Prior Electroconvulsive Therapy Subgroup (n = 31)



	0	2	4	6
BDI	29.3	25.8	20.7	19.3
SDS	20.9	17.9	13.6	13.0
HDRS	18.0	15.6	11.3	10.7
BAI	14.2	12.7	11.5	11.0
QIDS-SR	14.7	14.1	11.0	10.1

Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology, self-report; SDS = Sheehan Disability Scale; TMS = transcranial magnetic stimulation.

change in QIDS-SR score was −5.4 points (SD = 6.4, $P < .001$); change in BDI score was −11.4 points (SD = 13.1, $P < .001$); change in BAI score was −5.8 points (SD = 9.0, $P < .001$); and change in Sheehan Disability Scale score was −6.9 points (SD = 8.5, $P < .001$). Response and remission rates on the HDRS were 41.2% and 35.3%, respectively. Response and remission rates on the BDI were 35.3% and 20%, respectively. Response and remission rates on the QIDS-SR were 38.8% and 24.7%, respectively.

Exploratory Analysis

Using binary logistic regression to explore predictors of response or remission (including number of comorbidities, type of medication, and number of medication failures, as well as the characteristics from Table 1) yielded no statistically significant predictors of the primary outcome. Among secondary outcomes, increasing duration of the current episode was *negatively* correlated with QIDS-SR response (OR = 0.67, $P = .04$) and HDRS response (OR = 0.98, $P = .05$).

Outcomes With 1-Hz and Sequenced Bilateral (left plus right side) TMS

Of the 6 patients who had only right-sided 1 Hz TMS, 3 responded (of which 2 remitted). Thirty-nine patients had right-sided slow-frequency (1 Hz) TMS added to left-sided fast-frequency TMS because of insufficient improvement (defined as < 25% reduction in the baseline QIDS-SR score after 2 weeks of treatment or 10 sessions of left-sided TMS). Sixteen of these patients (41%) responded by week 4, with improvement maintained at week 6.

By comparison, the 34 patients who did not receive slow TMS had a 43.5% response rate (CGI-I score ≤ 2) by 10 sessions and a 65.6% response rate at weeks 4 and 6 (ie, after 20–30 sessions). Patients who received bilateral TMS from the start of treatment (n = 6) had a 0% CGI-I response rate at 10 sessions and a 33.3% response rate after 20–30 sessions.

Subgroup Analysis: Patients With Bipolar Depression

Twenty patients (13 male subjects) in the acute sample were treated for a bipolar depressive episode. The CGI-I response rate for these patients at week 6 was 35% and the remission rate was 15%, less than that observed with unipolar patients. The mean change in the HDRS score was −7.7 points (SD = 6.4); in the QIDS-SR, −6.7 points (SD = 6.5); in the BDI, −11.7 points (SD = 15.5); in the BAI, −6.8 points (SD = 10); and in the Sheehan Disability Scale, −7.9 points (SD = 7.4). Secondary outcomes by week are presented in Figure 3.

Subgroup Analysis: Patients With a History of ECT Treatment

Thirty-one patients (19 male subjects) in the acute sample had a lifetime history of ECT treatment, 24 with MDD and 7 with bipolar depression. All patients reported that prior ECT treatments either had failed or had been intolerable; further detail of ECT course was, in most cases, unavailable. In this group, the CGI-I showed a response rate of 47% and a remission rate of 20% at week 6. The mean change in the HDRS score was −7.3 points (SD = 6.5, Figure 4); in the QIDS-SR, −4.6 points (SD = 6.3); in the BDI, −10.0 points (SD = 12.7); in the BAI, −3.2 points (SD = 9.1); and in the Sheehan Disability Scale, −7.9 points (SD = 8.4).

Forty-one percent of the ECT subgroup discontinued TMS because of a lack of efficacy. Secondary outcomes by week are presented in Figure 4.

Maintenance Treatment

Forty-two of 85 patients (49% of the acute treatment sample) went on to maintenance TMS treatment. An additional 6 patients entered the maintenance phase following treatment of a major depressive episode in an industry-funded TMS trial using a different device (Neurostar [Neuronetics Inc, Malvern, Pennsylvania]). The same stimulation parameters were used as in the acute phase, and medications were kept fixed as much as clinically feasible. Twenty-six of 42 patients (62% of those entering maintenance) maintained their response at 6 months.

Adverse Events

There were no serious adverse events during acute TMS treatment. The most commonly reported adverse effects were headache (27%; n = 23) and scalp discomfort (17.6%; n = 15). Two patients (2.4%) reported a transient increase in anxiety. One patient each reported nausea, dizziness, and transient insomnia. Three patients (3%) discontinued the treatment due to an exacerbation of preexisting headaches. No cases of switching to hypomania or mania were observed.

Reasons for Discontinuation

Three patients discontinued treatment for adverse effects as described above, 10 discontinued treatment due to logistical difficulties, principally the cost of treatment or the demands of traveling for treatment multiple times per week. The remainder (27 patients) stopped for lack of efficacy or were lost to follow-up.

DISCUSSION

Transcranial magnetic stimulation was effective and safe in the acute and maintenance treatment of 100 consecutive outpatients recruited from clinical practice. Acute response and remission rates at 6 weeks on the CGI-I scales were 50.6% and 24.7%, respectively. On the HDRS, outcomes were similar, with a response rate of 41.2% and a remission rate of 35.3%. Other scales (BDI, BAI, and QIDS-SR) also showed significant improvements. Functional improvement also occurred, as evidenced by a significant reduction of 7 points on the Sheehan Disability Scale, moving the treatment group from a level of severe impairment in functioning at baseline to one of mild impairment at 6 weeks. Most of the improvement occurred in the first 4 weeks.

Patients who entered 6 months of maintenance TMS did well. The large majority (62%) were still responders at the end of their maintenance treatment. In most cases, the frequency of TMS sessions could be reduced to as little as 1 session per month while maintaining the response.

Transcranial magnetic stimulation was flexibly dosed. Treatment was commenced at 4,000 pulses per session and titrated up depending on clinical response to a maximum of 8,000 pulses per session. This high dose was based on a recent report of safety and effectiveness of TMS that used 2,700–10,000 pulses per session.[20] The addition of right-sided 1-Hz frequency TMS was operationalized clinically in the sense that patients who had not improved on the QIDS-SR by at least 25% after 10 sessions were augmented with slow TMS to the right DLPFC for 300–1,200 pulses per session. Patients who were already improving with 10-Hz TMS at 2 weeks (> 25% reduction in QIDS-SR score after 10 sessions) had a 65.6% response rate by week 6 (20–30 sessions). The group that did well with left unilateral TMS also seemed to be fast responders with, 43.5% meeting criteria for response (CGI-I score ≤ 2) after as little as 10 sessions (2 weeks).

The addition of 1-Hz TMS to the right DLPFC for slow responders (< 25% reduction in QIDS-SR at 10 sessions) appears to have been beneficial, though in uncontrolled conditions. This group (46% of the acute sample, n = 39) had a 0% response rate by 10 sessions. By 4 and 6 weeks, the response rate rose to 43.5%. This suggests that a switch from unilateral to bilateral TMS after 10 sessions may be an effective augmentation strategy for slow responders, much like a switch to bilateral ECT after insufficient response to unilateral treatment. This area is important for future study as attempts are made to further improve TMS outcomes in treatment-resistant depression patients.

Transcranial magnetic stimulation was very safe in this clinical cohort. Only 3 patients stopped treatment for adverse effects, all due to a worsening of preexisting headaches. No seizures or other serious adverse events related to TMS occurred during acute or maintenance treatment. One patient committed suicide during maintenance treatment, which was judged to be due to a worsening of his disease state and not related to TMS treatment.

The acute outcomes observed here are similar to those reported by Avery et al[21] in an open-label study that found an HDRS response rate of 42.4% and remission rate of 27.1% at the end of 6 weeks of treatment (up to 30 sessions). Our remission rate with clinical TMS was higher (35% vs 27%). The clinical cohort treated here, however, was clearly more treatment resistant. The mean number of failed adequate medication trials in the current episode was 3.4 (versus 1.6 in the trial by Avery et al[21]), and mean duration of the current episode was 42.7 months, or 4 years, compared to 13 months in the Avery et al[21] study. Thirty-six percent of our patients had received ECT in their lives (versus 0% in Avery et al[21]). In addition, 60% of patients in our study had a history of psychiatric hospitalization and 24.7% had previous suicide attempts.

This study also differs from the Avery et al[21] study by its inclusion of bipolar disorder in addition to major depression. Additionally, in the Avery et al[21] study, TMS was administered as a stand-alone monotherapy, versus adjunctive treatment here. Finally, a different method of targeting the prefrontal cortex was used in the patients in the treatment program: namely, the EEG-based F3 method, for some

patients (n = 24, 27% of the sample) rather than a "one-size-fits-all" method with the standard 5-cm rule. For patients treated with the F3 targeting approach, the mean distance from the motor threshold point was, in fact, 6.5 cm. After allowance for variance, this means that 95% of individuals would fall into a range of 5.5–7.5 cm. This implies that the F3 method results in a more anterior prefrontal cortical target in the large majority of cases. The 5-cm rule may result in a significant amount of treatment to the premotor area rather than prefrontal cortex.

In the bipolar subgroup (n = 20), the response rate was 35% and the remission rate was 15% at 6 weeks. These results were numerically lower than the response and remission rates observed with unipolar depression. Two previous small trials have shown therapeutic effects of TMS in bipolar depression. Dell'Osso and colleagues,[22] in an open-label study (n = 11), demonstrated improvement in bipolar depression after 3 weeks of slow (1 Hz) TMS, and Dolberg et al[23] found active TMS to be superior to sham in a 2-week trial (n = 20). Nahas et al,[24] however, in another 2-week trial, reported only a trend for a difference between active and sham TMS over the left DLPFC (n = 23). In this study, the lower response rate in bipolar depression than in the unipolar patient group is most likely due to their higher level of treatment resistance (4.3 failed trials in the bipolar subgroup vs 3.4 in the full group). Across samples, medication resistance appears to be the strongest predictor of response to TMS, with better outcomes in patients with fewer failed antidepressant trials.[25,26]

Electroconvulsive therapy still appears to be superior in overall efficacy to TMS, as shown by meta-analyses[27] demonstrating effect sizes of 0.91 (large) for ECT and 0.48 (medium) for TMS when evaluated with the same depression outcome scale (HDRS). These effects might imply that, if ECT were not helpful to a patient, then TMS certainly would not be. However, among patients previously treated with ECT, we observed surprisingly high response (47%) and remission (20%) rates. These results may be explained by the inclusion of some patients who were intolerant rather than resistant to ECT treatment. The effectiveness may also be related to the use of more intense stimulation parameters than found in prior studies. The findings above suggest, then, that a trial of TMS may still be a reasonable option for patients with a prior history of either intolerance or resistance to ECT.

There are several limitations in this study that should be considered in the interpretation of the results. Treatment was open-label and adjunctive to existing medications. Thus, at least part of the improvement is quite likely related to the combination of TMS plus medications rather than TMS alone. Detailed characterization of prior ECT trials was not possible nor was it feasible to review pharmacy and medical records to more accurately ascertain the Antidepressant Treatment History Form score. The absence of a control group and the sample size derived from a single treatment center are also limitations in generalizing these results to clinical TMS treatment more generally.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), lithium (Lithobid and others), mirtazapine (Remeron and others), modafinil (Provigil).

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REFERENCES

1. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007;62(11):1208–1216.
2. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med*. 2009;39(1):65–75.
3. Schutter DJ. Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. *Psychol Med*. 2010;40(11):1789–1795.
4. Gross M, Nakamura L, Pascual-Leone A, 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(3):165–173.
5. Lam RW, Chan P, Wilkins-Ho M, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *Can J Psychiatry*. 2008;53(9):621–631.
6. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10–17.
7. Rossi S, Hallett M, Rossini PM, et al; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120(12):2008–2039.
8. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry*. 1997;154(12):1752–1756.
9. Beam W, Borckardt J, Reeves S, et al. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulat*. 2009;2(1):50–54.
10. Nahas Z, Teneback CC, Kozel A, et al. Brain effects of TMS delivered over prefrontal cortex in depressed adults: role of stimulation frequency and coil-cortex distance. *J Neuropsychiatry Clin Neurosci*. 2001;13(4):459–470.
11. McConnell KA, Nahas Z, Shastri A, et al. The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biol Psychiatry*. 2001;49(5):454–459.
12. Guy W. *ECDEU Assessment Manual for Psychopharmacology–Revised*. US Department of Health, Education, and Welfare publication (ADM 76-338). Rockville, MD: National Institute of Mental Health; 1976:218–222.
13. Leon AC, Shear MK, Klerman GL, et al. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. *J Clin Psychopharmacol*. 1993;13(5):327–331.
14. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
15. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.

16. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4(6):561–571.
17. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56(6): 893–897.
18. In Sheehan DV. *The Anxiety Disease*. New York, NY: Charles Scribner; 1983:151.
19. O'Reardon JP, Cristancho P, Pilania P. et al. Patients with a major depressive episode responding to treatment with repetitive transcranial magnetic stimulation (rTMS) are resistant to the effects of rapid tryptophan depletion. *Depress Anxiety*. 2007;24(8):537–544.
20. 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.
21. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry*. 2008;69(3): 441–451.
22. Dell'Osso B, Mundo E, D'Urso N, et al. Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. *Bipolar Disord*. 2009;11(1):76–81.
23. Dolberg OT, Dannon PN, Schreiber S, et al. Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. *Bipolar Disord*. 2002;4(suppl 1):94–95.
24. Nahas Z, Kozel FA, Li X, et al. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disord*. 2003;5(1):40–47.
25. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009;34(2):522–534.
26. Fregni F, Marcolin MA, Myczkowski M, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. 2006;9(6):641–654.
27. Slotema CW, Blom JD, Hoek HW, et al. 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.

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