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Can Medication Free, Treatment-Resistant, Depressed Patients Who Initially Respond to TMS Be Maintained Off Medications? A Prospective, 12-Month Multisite Randomized Pilot Study

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (TMS) is efficacious for acute treatment of resistant major depressive disorder (MDD), but there is little information on maintenance TMS after acute response.
Objective/hypothesis: This pilot feasibility study investigated 12-month outcomes comparing two maintenance TMS approaches – a scheduled, single TMS session delivered monthly (SCH) vs. observation only (OBS).
Methods: Antidepressant-free patients with unipolar, non-psychotic, treatment-resistant MDD participated in a randomized, open-label, multisite trial. Patients meeting protocol-defined criteria for improvement after six weeks of acute TMS were randomized to SCH or OBS regimens. TMS reintroduction was available for symptomatic worsening; all patients remained antidepressant-free during the trial.
Results: Sixty-seven patients enrolled in the acute phase, and 49 (73%) met randomization criteria. Groups were matched, although more patients in the SCH group had failed ≥2 antidepressants ($p = .035$). There were no significant group differences on any outcome measure. SCH patients had nonsignificantly longer time to first TMS reintroduction, 91 ± 66 days, vs. OBS, 77 ± 52 days; OBS patients were nonsignificantly more likely to need reintroduction (odds ratio = 1.21, 95% CI .38–3.89). Reintroduction lasted 14.3 ± 17.8 days (SCH) and 16.9 ± 18.9 days (OBS); 14/18 (78%) SCH and 17/27 (63%) OBS responded to reintroduction. Sixteen patients (32.7%) completed all 53 weeks of the study.
Conclusions: Maintaining treatment-resistant depressed patients off medications with periodic TMS appears feasible in some cases. There was no statistical advantage of SCH vs. OBS, although SCH was associated with a nonsignificantly longer time to relapse. Those who initially respond to TMS have a strong chance of re-responding if relapse occurs.

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Introduction

Major depressive disorder (MDD) is a common, chronic, and serious psychiatric illness. Recurrent episodes occur in greater than 50% of patients, and it is this recurrence over the lifetime that contributes to the substantial functional impairment associated with this disorder [1,2]. Additionally, treatment-resistance is common in

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MDD. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated that only one-third of patients achieved remission with a single antidepressant trial of adequate dose and duration, and after multiple trials of antidepressants and multi-drug regimens, only two-thirds of patients achieved remission [3]. STAR*D also reported that 40.1% of patients who achieved remission after failing their first antidepressant experienced a relapse within 12 months of follow up [4]. Although electroconvulsive therapy (ECT) is an effective acute antidepressant treatment, with reports of up to 60% remission in medication resistant patients, there remains a propensity for relapse; in the community setting, over 50% of remitted patients relapse within 6 months [5]. Thus, new approaches are needed for both acute treatment and relapse prevention.

Transcranial magnetic stimulation (TMS) is a safe and efficacious, noninvasive brain stimulation treatment for medication-resistant MDD. To date, the acute efficacy of TMS is supported by multiple double blind, randomized controlled trials [6–8] and a recent meta-analysis [9]. The ideal method for maintaining benefit for a patient who had an adequate response to an acute course of TMS has not been determined. When considering strategies for subsequent treatment with TMS, "reintroduction" of another acute course (typically delivered 5 sessions/week with sometimes fewer treatments in the series) should be distinguished from "maintenance" TMS to prevent symptom recurrence, which involves the use of regularly scheduled TMS treatments over an extended period of time (e.g., weekly, biweekly, or monthly).

Reintroduction of adjunctive TMS in the face of threshold symptomatic worsening was studied systematically in a large (n = 99) prospective trial by Janicak et al. [10], which showed it effectively restored prior level of symptom benefit for approximately 85% of patients. The reintroduction protocol for that study involved TMS delivered twice per week for two weeks, followed by escalation of treatment frequency to 5/week for up to an additional 4 weeks, and termination of the series when the global illness severity rating returned to baseline. Demirtas-Tatlidede et al. [11] reported 4-year outcomes for 16 unmedicated patients who responded to an initial 10-day acute course of TMS. Half benefited from reintroduction of 10-day courses of TMS reintroduced as needed, with an average interval of nearly 5 months between courses.

As maintenance TMS has not been studied in a systematic manner, there are no protocols to guide when to start maintenance treatments, how often to schedule them, or the optimal number of treatments over time. Evidence that maintenance TMS treatments sustain symptom relief is described in reports from studies that employed observational follow up periods up to six years after successful acute treatment. However, interpretation of long-term efficacy outcomes from the collective body of TMS literature is limited owing to methodological variations across these studies, i.e., all were open-label, few were prospective, some combined maintenance and reintroduction treatments, and most delivered TMS concurrently with antidepressant pharmacotherapy (Table 1). O'Reardon et al. [12] retrospectively reviewed the charts of 10 patients for 6 months to 6 years with maintenance TMS treatments at a nonstandard frequency (typically 1–2 per week) and observed sustained marked benefit in 70%; 3 were maintained on TMS monotherapy. Connolly et al. [13] reported on a retrospective analyses of 42 (unipolar or bipolar) acute TMS responders who went on to receive once monthly maintenance TMS in addition to stable pharmacotherapy. Over 6 months, 62% maintained their level of depressive symptom relief. Fitzgerald et al. [14] conducted a prospective trial of monthly clustered TMS maintenance sessions (5 treatments delivered over two days) in 35 patients who responded to two prior acute courses of TMS. This approach substantially delayed the onset of relapse, relative to the duration of wellness following patients' prior acute TMS series.

Several TMS trials have included a transition from a series of acute daily treatments to a continuation phase. For patients in these studies who had already achieved response during the acute phase, the additional weeks of continuation TMS treatments essentially represented a maintenance regimen. Richieri et al. [15] examined outcomes for acute TMS responders, using propensity analysis to compare a group (n = 22) who did not receive any maintenance TMS with a group (n = 37) who enrolled in a prospective maintenance protocol that provided an extended taper phase (2 once-weekly TMS sessions, followed by 2 bimonthly sessions, followed by 2 once-monthly sessions). There was a statistically significant difference in relapse rate (82% versus 38%) favoring the maintenance TMS group at 20 weeks. Following 20 acute phase TMS sessions, the Levkovitz et al. study [8] transitioned to a schedule of twice per week for 12 weeks. Comparison of week 5 and week 16 remission rates for those who got active TMS (last observed values: 33% versus 32%, respectively) suggest that the continuation regimen was associated with sustained response over time, although there was a significant patient dropout in the follow up phase. Harel et al. [16] transitioned patients to twice-weekly TMS for 8 weeks, followed by once-weekly TMS for 10 weeks. Six of 12 acute responders (50%) in this study remained responders at the end of 22 weeks.

The present study was undertaken as a pilot project to determine the feasibility and efficacy of providing scheduled, once-monthly TMS versus observation only over a one-year period for antidepressant-free subjects who had responded to an acute series of TMS. This design permitted both groups' access to reintroduction treatments if needed for symptom re-emergence. Although in clinical practice most subjects treated with TMS are also receiving antidepressant pharmacotherapy, subjects in this study were antidepressant medication free in order to isolate the effects of TMS from the possible confounding effects of concomitant pharmacotherapy. The frequency of maintenance treatments was chosen based on several factors. First, given the lack of a data on maintenance schedules, we surveyed both academic and private practice TMS providers who provided an expert consensus of once-monthly TMS.

Table 1
Prior studies of continuation or maintenance transcranial magnetic stimulation.

Study	Design	Outcome
O'Reardon et al., 2005 [12]	Retrospective, N = 10, followed 6 months to 6 years	7/10 received moderate or marked benefit; 3/10 maintained on TMS monotherapy
Connolly et al., 2012 [13]	Retrospective, N = 42, followed for 6 months	62% maintained improvements
Fitzgerald et al., 2013 [14]	Prospective, N = 35, monthly series of 5 treatments over two days	Delayed relapse by 6–12 months
Richieri et al., 2013 [15]	Prospective, N = 59, extended taper phase after acute TMS	38% relapse for maintenance group compared to 82% with no maintenance
Harel et al., 2014 [16]	Prospective, N = 26 total, twice per week for 8 weeks then 1 per week for 10 weeks after acute TMS	6 of 12 maintained clinical response at the end of 22 weeks
Levkovitz et al., 2015 [8]	Prospective, N = 159, twice per week for 12 weeks after acute TMS	Remission rates of 33% at week 5 and 32% and week 16

Number of participants indicates those followed in continuation/maintenance phase.

Furthermore, this regimen was chosen to clearly distinguish maintenance TMS from continuation treatment or an extended taper. Most prior TMS maintenance studies (Table 1) used treatments every other week, and as such, made it impossible to evaluate whether observed effects were due to prolonged durability of the acute treatment or maintenance of effect and prevention of depressive relapse.

Methods

Study subjects

Patients eligible to participate in the study were antidepressant-free outpatient men or women, aged 18–70, meeting DSM-IV criteria for MDD, single or recurrent type, with current episode duration of at least 4 weeks but no longer than 3 years. Minimum symptom severity for entry was moderate, as measured by the Clinical Global Impressions Severity of Illness (CGI-S) [17] (total score ≥4) and a total score on the 17-item Hamilton Depression Rating Scale (HAMD17) [18] of at least 20. Patients had documented evidence of treatment resistance in the current episode defined as the failure to receive benefit from at least one but no more than four adequate trials of antidepressant medication. Antidepressant resistance was established by the Antidepressant Treatment Record (ATR, Neuronetics, Inc., Malvern, PA), adapted from and validated against the research version of the Antidepressant Treatment History Form (ATHF) [19]. Patients were required to show symptom stability over one week between screening and baseline visits with a minimum total HAMD17 score of 18 and ≤25% reduction from their score at the screening visit.

Exclusion criteria included depression secondary to a general medical condition; history of substance abuse or dependence within the past year; any psychotic disorder or major depression with psychotic features; bipolar disorder; eating disorder (current or within the past year); obsessive compulsive disorder (lifetime); or post-traumatic stress disorder (current or within the past year). Also excluded were individuals with an intracranial implant or any other metal object within or near the head that could not be safely removed; cardiac pacemakers; a clinically defined neurological disorder; an increased risk of seizure for any reason; history of failure to respond to an adequate course of TMS or ECT for a major depressive episode; and history of treatment with vagus nerve stimulation.

Study overview

The study had three phases: a pre-study screening phase of 1 week with no treatment; an acute treatment phase consisting of 30 sessions of TMS administered 5 days per week for 6 weeks; and randomization into a maintenance phase for those who met study-defined response criteria (acute phase endpoint HAMD17 total score <15 and had more than 25% improvement in total score HAMD17 compared with baseline). Investigators were blind to the criterion for eligibility for randomization. Patients were randomized in a 1:1 manner to either: 1) *SCH*: a single TMS session once every four weeks; or 2) *OBS*: observation only at each follow up visit. All randomized patients underwent a three-week TMS taper, consistent with the labeled use of the device (NeuroStar TMS Therapy System User Manual, Neuronetics, Inc., Malvern, PA, USA). All treatments were delivered open-label. Symptoms were assessed at each monthly follow up visit in both SCH and OBS groups, and any patient meeting criteria for symptom recurrence received reintroduction TMS. Symptom recurrence mandating TMS reintroduction included a total score on the HAMD17 ≥16 and ≥25% worsening from the HAMD17 score at entry into the maintenance phase. For patients meeting criteria, TMS was provided in 5-day increments, up to a maximum of 30 TMS sessions (6 weeks). TMS reintroduction was discontinued when a patient's HAMD17 score returned to the value observed at the visit immediately prior to the first observation of clinical deterioration, after which patients resumed their previously assigned maintenance schedule. Patients who did not achieve symptomatic improvement after a complete 6 weeks of TMS reintroduction treatment exited the study. TMS reintroduction could occur as often as clinically required for discrete episodes of symptomatic worsening.

Institutional review board (IRB) approval was obtained at all sites. After a complete description of the study procedures, written informed consent was obtained from all subjects. The cost of treatment sessions and associated direct clinical care were borne by the study site, with material support from the sponsor for treatment related supplies. The sponsor provided study physicians with a modest financial remuneration on a contractual basis for study-related document preparation and rating scale completion. Patients received no direct financial compensation for participation.

Study locations, TMS device and clinical treatment parameters

Six sites with proficiency using TMS and experience in clinical research participated in this study: three academic medical centers, two private clinical practices, and one non-academic institutional setting. All TMS treatments were delivered using the NeuroStar TMS Therapy® system (Neuronetics, Inc., Malvern, PA, USA). Motor threshold (MT) was determined over the left motor cortex at the initial treatment session. An iterative, automatic, software-based mathematical algorithm (MT Assist®, Neuronetics, Inc., Malvern, PA, USA) was used for MT level determination. Coordinates for placement of the coil over the treatment location were calculated by the device for a site 5.5 cm anterior from the MT location, along a left superior oblique plane. The standard treatment protocol was stimulation at 120% of MT; at a pulse frequency of 10 pulses per second; and a cycle of 4 seconds on (active stimulation) and 26 seconds off (no stimulation). A single session contained 75 stimulation cycles, for a total of 3000 pulses. These parameters remained unchanged throughout the study.

Concomitant treatments

All patients were free of antidepressants or other psychotropic medications except limited use of zaleplon, zolpidem, or eszopiclone (1 dose nightly) as needed for treatment-emergent insomnia or lorazepam (up to 2 mg daily) for treatment emergent anxiety. The latter included up to 14 doses during the acute treatment phase, and for up to 10 days on up to 8 occasions during the maintenance phase.

Outcome measures

Clinical assessments were completed at baseline, at the end of the 6-week acute phase, at the end of the 3-week taper, and every four weeks thereafter during the maintenance phase. If TMS reintroduction was required, assessments were obtained at the end of each 5-day block of TMS reintroduction. Efficacy measures included the clinician-reported 24-item Hamilton Rating Scale for Depression (HAMD24) [20], the Montgomery–Asberg Depression Rating Scale (MADRS) [21], the Clinical Global Impressions – Severity of Illness Scale (CGI-S) [17], the patient-reported Inventory of Depressive Symptoms – Self Report version (IDS-SR) [22], and the 9-Item Patient Health Questionnaire (PHQ-9) [23]. Clinical raters were trained in the use of a structured interview for the HAMD24 and MADRS (Sackeim and Demitrack, available on request). The 17-item Hamilton Rating Scale for Depression (HAMD17) was derived from the HAMD24.

Safety was assessed by summary analysis of medically serious, device-related adverse events or device malfunctions during the study. The incidence of such events was compared with the incidence ascertained from routine post-market surveillance data for all NeuroStar TMS Therapy system devices installed in the United States at the time of the study.

Statistical analysis

Primary objective

The primary objective was to evaluate the efficacy of TMS administered every four weeks by examining the proportion of patients who had a sustained response throughout the 12-month maintenance treatment phase. Sustained response was defined as not requiring TMS reintroduction at any observation point during the maintenance phase. The primary efficacy analysis was performed on all patients randomized into the maintenance phase. For this categorical variable, logistic regression was used to model the odds for persistence of response as a function of the assigned maintenance treatment regimen. For continuous variables, analysis of variance was employed with the factor of interest specified as the sole explanatory variable in the model, and survival curves (censored for dropouts) were plotted for time to first reintroduction.

Secondary objectives

Secondary objectives included categorical values for remission (HAMD17 <8, HAMD24 <11) or recovery (MADRS <10) and response (50% or more decrease from baseline score for MADRS, HAMD24, and HAMD17). Other categorical values were the clinician rated CGI-S (remission score <3, response score <4), the patient rated PHQ-9 (remission score <5, response score <10) and patient rated IDS-SR (remission score <15, response >50% reduction in score). Reintroduction utilization was assessed by the number of TMS sessions required, and average time to first TMS reintroduction, compared between the two arms. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated for acute phase remission and response rates, and need for reintroduction.

Results

Demographic and clinical characteristics of the study population

Demographic and clinical features of the study population are shown in Table 2. Sixty-seven patients were enrolled with 49 (73.1%) completing acute treatment and meeting criteria for randomization. There were a greater proportion of patients with higher levels of antidepressant resistance (ATHF ≥ 2) in SCH group. Baseline symptom severity on the HAMD17 was matched between groups, with symptoms in the severe range. Reasons for study discontinuation are shown in Fig. 1.

Table 2
Demographic and clinical characteristics of the study populations.

Demographics	Enrolled N = 67	Randomized		p
		Scheduled TMS N = 23	Observation N = 26	
N (%) Females	42 (62.7)	12 (52.2)	18 (69.2)	.22
Age (years ± SD)	49.1 ± 11.2	48.2 ± 13.3	49.0 ± 9.8	.77
Age range	20–67	24–67	29–66	
Antidepressant treatment history				
ATR ≥ 2, N (%)	28 (41.8)	11 (47.8)	5 (19.2)	.035*
Baseline symptom score				
HAM-D 17 Mean (SD)	23.9 (3.2)	23.5 (3.4)	24.0 (2.9)	.60
IDS-SR Mean (SD)	47.4 (10.4)	46.4 (12.0)	48.3 (8.9)	.52
PHQ-9 Mean (SD)	20.0 (3.94)	19.4 (4.1)	20.5 (3.9)	.34

* $\chi^2 = 4.54$.
ATR, antidepressant treatment resistance.

Acute clinical outcomes

Of the 49 randomized patients, 23 were assigned into the SCH group and 26 patients to the OBS group; 19/23 (82.6%) patients in the SCH group and 23/26 (88.5%) in the OBS group met HAMD17 remission criteria at time of randomization. The proportion of patients who met response and remission criteria at randomization was similar when using other rating scales (90.6%, 90.6% and 73.5% responders, and 81.3%, 59.4% and 44.9% remitters, on the CGI-S, PHQ-9 and IDS-SR, respectively), with an equal distribution of responders and remitters assigned to each group. Odds of achieving remission in the acute phase did not differ between groups (OR = .62, 95% CI 0.12–3.12). Because all participants in the OBS group met criteria for clinical response, calculation of the OR for response was not possible.

Maintenance therapy outcomes

Efficacy results for the continuous and categorical outcomes on the HAMD17 across the maintenance phase are shown in Table 3, and survival curves (censored for dropouts) are displayed in Fig. 2. Of the 49 randomized patients, sixteen (32.7%) completed all 53 weeks of the study. There were no statistically significant group differences in the primary outcome variable (i.e., the number of patients who did not require TMS reintroduction), 9/23 (39%) in the SCH group versus 9/26 (35%) in the OBS group ($p > 0.1$), or on any other outcome variable. The odds of needing TMS reintroduction were nonsignificantly greater in the OBS group compared to the SCH group (OR = 1.21, 95% CI 0.38–3.89). Survival curves also found no significant differences in time to first retreatment (log-rank $\chi^2 = 1.01$, df = 1, $p > 0.1$). There were no statistically significant group differences in the number of patients who did not require TMS reintroduction: 9/23 (39%) patients in the SCH group vs. 9/26 (35%) in the OBS group ($p > 0.1$). There was a mathematical, but not statistically significant, difference in rates of study completion, with 10/23 (43%) in the SCH group and 6/26 (23%) in the OBS group ($p > 0.1$). Efficacy analysis using outcomes with the IDS-SR and PHQ-9 were similar to those on the HAMD17, with no statistically significant group differences (data not shown).

TMS reintroduction outcomes

TMS reintroduction was similar between groups during the maintenance phase (Table 4). Mean ± SD duration of time from the end of the acute treatment series to first reintroduction was 91.2 ± 65.8 days for the SCH group and 77.1 ± 51.7 days for the OBS group. When removing the taper phase following end of acute treatment series from the calculation, the duration of initial benefit until first reintroduction was 69.9 ± 64.5 days for the SCH group and 56.0 ± 49.6 days for the OBS group. The number of retreatment TMS sessions received by individual patients across the maintenance phase was 14.3 ± 17.8 in the SCH group and 16.9 ± 18.9 in the OBS group. When including the taper phase treatments and regularly scheduled once-monthly treatments along with all reintroduction treatments during over the maintenance phase, the mean treatments per patient was 25.3 ± 16.7 for the SCH group and 27.5 ± 16.9 in the OBS group. The reintroduction success rate (defined for each patient as return to the HAMD17 score they reached at the end of acute treatment, or better) was 14/18 (78%) for the SCH group versus 17/27 (63%) for the OBS group. An exploratory analysis of demographic and clinical characteristics, including age, gender, ATHF status, baseline HAMD17 score and end of acute treatment HAMD17 score was not predictive for patients who required reintroduction TMS (data not shown).

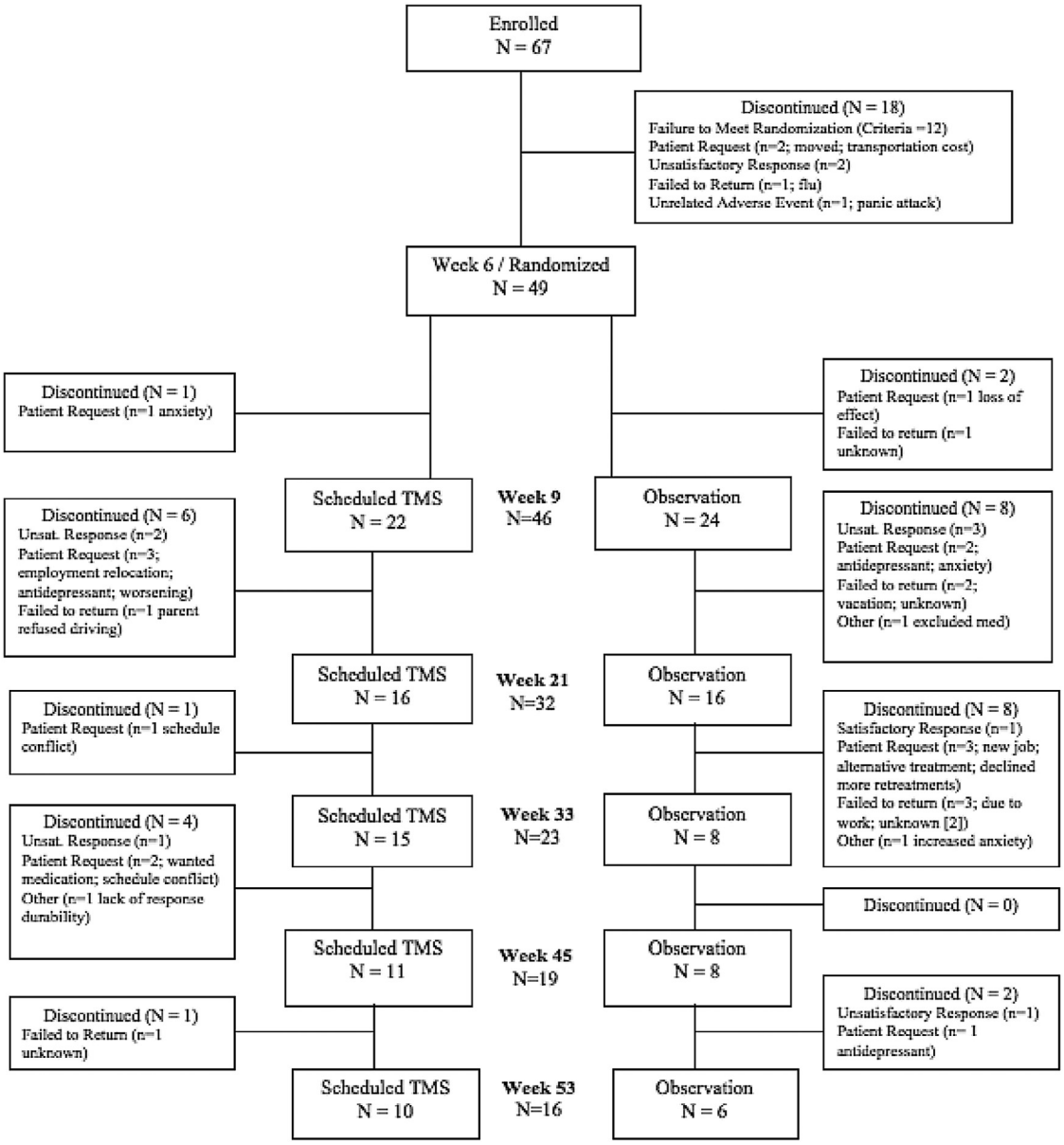

Figure 1. CONSORT diagram: Patient disposition across acute treatment and maintenance phase.

Safety

There were no serious device-related adverse events, no seizures, no hospitalizations, and no suicide attempts reported during the study. The risk of emergent suicidal ideation was evaluated post-hoc for the acute and maintenance phases using Item 3 (Suicidality) of the HAMD by determining the proportion of patients who increased from a value of 0 or 1 at start of the phase to a value of 3 or 4 at any time during the phase. One patient overall had a transient increase in suicidality associated with worsening of depressive symptoms during the post-acute treatment taper consistent with loss of treatment benefit, which responded to TMS reintroduction.

Discussion

This pilot study in antidepressant-free patients with treatment-resistant MDD who responded to an initial acute course of TMS therapy involved an open-label, randomized design comparing two maintenance regimens: once-monthly TMS versus observation only, with all participants eligible to receive reintroduction TMS for protocol-defined symptomatic worsening. We did not find an advantage for once-monthly maintenance TMS treatments over observation, since it did not significantly delay the time until reintroduction TMS was needed or reduce the proportion of patients who needed retreatment. While the experience of symptom re-emergence by the majority of patients in this study may not be unexpected given the severity and pharmacoresistence of depressive illness characterizing the patient sample, we were able to confirm feasibility of using TMS monotherapy over the course of one year. Even in the context of symptom re-emergence during the one year of follow-up, medication free, treatment-resistant, depressed patients who initially responded to TMS were maintained off medications safely as there were no suicide attempts or hospitalizations, and only a single patient had a transient increase in suicidal ideation.

While interpretations should be tempered by consideration of the population studied, the relatively limited sample size, attrition

Table 3
Summary of HAM-D 17 total score, response and remission rates during the maintenance phase.

HAMD17 randomized population	Baseline	Week 6 (End of Acute)	Week 9 (End of Taper)	Week 13	Week 17	Week 21	Week 25	Week 29	Week 33	Week 37	Week 41	Week 45	Week 49	Week 53
Arm A – Scheduled (N)	23	23	22	21	18	16	15	14	13	14	13	10	11	10
Mean (SD)	23.5 (3.4)	6.4 (3.6)	8.0 (6.3)	8.1 (5.9)	9.2 (6.4)	8.3 (4.6)	10.3 (6.9)	9.3 (7.2)	8.8 (5.7)	7.6 (5.7)	8.0 (5.7)	4.5 (3.0)	5.3 (4.5)	4.3 (4.0)
Response N (%)		22 (95.7)	16 (69.6)	16 (69.6)	13 (56.5)	12 (52.2)	10 (43.5)	10 (43.5)	10 (43.5)	11 (78.6)	10 (43.5)	9 (39.1)	10 (43.5)	10 (43.5)
Remission N (%)		19 (82.6)	12 (52.2)	11 (47.8)	9 (39.1)	7 (30.4)	5 (21.7)	6 (26.1)	6 (26.1)	8 (34.8)	7 (30.4)	7 (30.4)	7 (30.4)	9 (39.1)
Arm B – observation (N)	26	26	24	21	18	16	14	10	8	8	7	8	7	6
Mean (SD)	24.0 (2.9)	6.2 (3.2)	8.8 (3.7)	11.4 (5.6)	11.6 (7.2)	10.9 (7.1)	10.0 (7.8)	11.9 (7.0)	10.6 (7.0)	8.6 (5.7)	13.4 (11.4)	12.9 (7.6)	8.6 (7.7)	6.7 (8.1)
Response N (%)		26 (100.0)	19 (73.1)	12 (46.2)	11 (42.3)	10 (38.5)	10 (38.5)	6 (23.1)	5 (19.2)	7 (26.9)	4 (15.4)	4 (15.4)	6 (23.1)	5 (19.2)
Remission N (%)		23 (88.5)	9 (34.6)	5 (19.2)	5 (19.2)	7 (26.9)	6 (23.1)	2 (7.7)	4 (15.4)	4 (15.4)	3 (11.5)	3 (11.5)	3 (11.5)	4 (15.4)

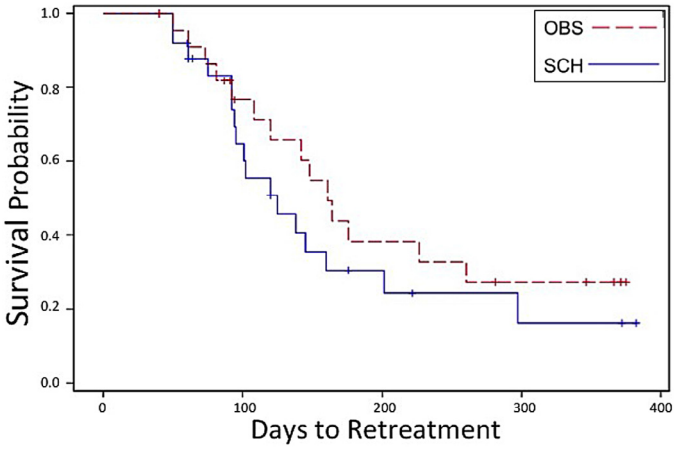

Figure 2. Survival curves for time to first retreatment. Kaplan–Meier survival curves for time to first retreatment. Log-rank $\chi^2 = 1.01$, df = 1, $p > 0.1$. Key: OBS, observation-only group; SCH, scheduled TMS group. + indicates participant drop outs.

rate and open-label design, we point to several numerical differences suggesting greater benefit from the SCH maintenance strategy compared to OBS that may suggest a possible signal. Though remaining off all maintenance pharmacotherapy following initial response to TMS may be a seldom-chosen strategy for this type of patient receiving care in a naturalistic practice setting, for those who may pursue such a strategy, our results indicate a maintenance TMS schedule of only one treatment per month is not sufficient to prevent return of depressive symptoms within the year.

The published literature describing scheduled maintenance TMS for preventing recurrence of major depressive episodes is relatively sparse (reviewed above in Table 1). While results arising from this body of work indicates maintenance TMS is effective, their interpretation is hindered by use of a variety of factors in both the acute and maintenance phases that make it difficult to determine whether specific parameters, scheduling intervals, or other aspects of their protocols led to positive outcomes. Importantly, nearly every one of these used concurrent TMS with antidepressant pharmacotherapy. Therefore, it is equally plausible to attribute their reported outcomes to the enduring effects of the initial course of TMS, to effects of antidepressant medications, or to the combination thereof. A clear advantage of the current study was that it used a well-established, effective, left prefrontal, high frequency TMS protocol prospectively and systematically delivered to a medication-free population, allowing the observed outcomes to be uniquely attributable to the TMS interventions. It is notable that in our study, TMS reintroduction was successful in rescuing most patients with threshold deterioration and returning them to their prior level of depressive symptom relief. This is an important observation given the chronic and relapsing nature of pharmacoresistant major depression and absence of definitive data suggesting that re-treatment with

Table 4
TMS reintroduction utilization by group, randomized population.

Number of independent reintroduction periods per patient, N (%)	Scheduled TMS	Observation
0	10 (43.5)	10 (38.5)
1	9 (39.1)	8 (30.8)
2	3 (13.0)	7 (26.9)
3	1 (4.3)	0 (0.0)
4	0 (0.0)	0 (0.0)
5	0 (0.0)	1 (3.8)
Total number of individual TMS reintroduction sessions, mean (SD)	26.0 (18.1)	22.3 (19.3)

previously effective medications is capable of doing the same. On this issue, our results provide support for a long-term treatment strategy that incorporates retreatment with TMS for patients who showed positive response to an initial acute course.

While not the *a priori* focus of this investigation, we noted a high rate of remission (61.2%) from an acute series of TMS for the larger sample of all enrolled antidepressant-free participants (prior to randomization). For comparison, under similar open label treatment conditions, Avery et al. [24] reported a 27.1% remission rate, and the OPT-TMS study [25] reported a 29.6% remission rate. The patient sample recruited in the current investigation was comparable with regard to baseline depression scores and level of treatment resistance to those who participated in these two trials, using the same device and stimulation parameters. The current study required a full 6 weeks of acute treatments delivered five times per week, even if remission occurred prior to treatment 30. Possible reasons behind our observed acute phase outcomes include protocol-required completion of a fixed six-week acute course of TMS treatments, or factors related to the open-label design of the study where physician and participants likely knew that some degree of clinical improvement was required to participate in the continuation portion of the study.

The data we gathered regarding durability of positive response to the initial acute course of TMS (measured as days until threshold symptom deterioration) produced results that were consistent with prior TMS studies [10,26] and continue to suggest that approximately one-third of patients require reintroduction TMS treatments during the year following successful acute treatment. Although diminished somewhat by a more stringent criterion for success (defined as HAMD17 total score <15 and >25% improvement) and the absence of maintenance pharmacotherapy in this trial, the data we generated are in line with previous work [10] showing the majority of TMS responders benefit from TMS again if they relapse.

This study had several limitations. Most importantly, this pilot study was powered not to be a definitive study but rather to provide preliminary data that could inform future maintenance TMS study designs. Another limitation was the significant attrition through the 12 months of follow-up, which may be expected in a longitudinal study of medication-free MDD patients with treatment-resistant illness. On the other hand, it is informative that 32% of randomized patients completed the study despite an otherwise poor prognosis. This study also had an imbalance in the distribution to the randomized groups, with the scheduled treatment arm including a greater proportion of treatment resistant subjects. This might have created a more difficult-to-treat population in the monthly maintenance treatment arm. Another limitation was the use of medication-free patients. While this was by design, conducted to characterize long-term TMS outcomes in the absence of the confounding presence of antidepressant medications, it nonetheless limits the generalizability of these findings to clinical populations who are rarely antidepressant free.

In summary, results from this study indicate that once-monthly TMS is not superior to “watchful waiting” for antidepressant-free MDD patients who responded to an acute TMS course. These results suggest that TMS may require different, sequenced approaches for maintenance. For example, this might include observation at first, moving to prophylaxis or more frequent maintenance treatments as a second stage and perhaps reserving combination with pharmacology as a last step.

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