Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder: A Comprehensive Summary of Safety Experience From Acute Exposure, Extended Exposure, and During Reintroduction Treatment

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Background: Transcranial magnetic stimulation (TMS) has demonstrated efficacy in the treatment of major depressive disorder; however, prior studies have provided only partial safety information. We examined the acute efficacy of TMS in a randomized sham-controlled trial, under open-label conditions, and its durability of benefit.

Method: Aggregate safety data were obtained from a comprehensive clinical development program examining the use of TMS in the treatment of major depressive disorder. There were 3 separate clinical protocols, including 325 patients from 23 clinical sites in the United States, Australia, and Canada. Active enrollment occurred between January 2004 and August 2005. Adverse events were assessed at each study visit by review of spontaneous reports with separate reporting of serious adverse events. Safety assessments were also completed for cognitive function and auditory threshold. Assessment of disease-specific risk included the potential for worsening of depressive symptoms. Finally, the time course and accommodation to the most commonly appearing adverse events were considered.

Results: TMS was administered in over 10,000 cumulative treatment sessions in the study program. There were no deaths or seizures. Most adverse events were mild to moderate in intensity. Transient headaches and scalp discomfort were the most common adverse events. Auditory threshold and cognitive function did not change. There was a low discontinuation rate (4.5%) due to adverse events during acute treatment.

Conclusions: TMS was associated with a low incidence of adverse events that were mild to moderate in intensity and demonstrated a largely predictable time course of resolution. TMS may offer clinicians a novel, well-tolerated alternative for the treatment of major depressive disorder that can be safely administered in an outpatient setting.

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The treatment of major depressive disorder is clinically challenging. It is estimated that 20% to 40% of patients do not benefit sufficiently from, or are intolerant to, existing antidepressant interventions, including trials of medication, psychotherapy, and electroconvulsive therapy. Indeed, a substantial proportion of patients ultimately manifest a chronic illness course that is resistant to treatment. Among the clinical challenges in the management of depression is the reality that many of the available treatments are frequently discontinued prematurely because of poor tolerability. Adverse events can range from medically urgent (e.g., cardiac arrhythmias, seizures) to non–life threatening but intolerable physiologic effects (e.g., gastrointestinal disturbances, weight gain, sexual dysfunction). In the recently reported Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the discontinuation rates due to treatment intolerance or adverse events rose steadily across the sequenced levels (i.e., mean = 8.6% at level 1, mean = 23.1% [range, 21.0%–27.2%] at level 2, mean = 35.2% [range, 34.2%–36.2%] at level 3, and mean = 32.1% [range, 21.6%–41.4%] at level 4).[1–6] The need for a new and more diverse choice of effective and tolerable treatment options is clear.

Transcranial magnetic stimulation (TMS) is a method of using powerful, briefly pulsed magnetic fields to induce electrical currents in a focused manner through a

conducting substance. Applied to the brain as a target electrical conductor, TMS differs from other methods of electrical stimulation in that the effects can be directed in a more spatially localized manner. Transcranial magnetic stimulation can be administered as single or repetitive pulses, the latter sometimes referred to as "trains" of short (i.e., several seconds) duration. Most studies of TMS for depression have utilized rapid (i.e., ≥ 1 Hz) frequency stimulation over the left dorsal lateral prefrontal cortex (DLPFC). A smaller number have utilized slow (i.e., < 1 Hz) frequency over the right DLPFC or sequenced the 2 applications.[7] It is now well established that TMS can directly affect brain function in the area of the induced electric currents. Furthermore, these local effects may produce broader, indirect functional effects in areas distant from the site of direct stimulation.[8–10]

These observations have led to studies of the therapeutic potential of TMS in the treatment of major depressive disorder. Most published meta-analyses of this work have concluded that TMS is a statistically and clinically effective antidepressant.[11–17] Similar comprehensive conclusions regarding the broad, commonly expected safety profile of TMS, however, have only been described in a limited manner with a major emphasis on the most uncommon risk (i.e., seizure).[18] The lack of fully detailed information on the broad safety profile of TMS is in part because earlier studies were typically conducted with short treatment exposure intervals and minimal to no follow-up observation periods and used nonstandard methods of adverse event reporting and coding terminology. All limit the ability to compare the safety and tolerability of TMS with other standard approaches to the management of major depressive disorder.

In this report, we discuss the comprehensive acute and longer-term safety data obtained from an integrated program of 3 sequentially conducted studies of TMS for patients with major depressive disorder who had previously failed to receive benefit from antidepressant pharmacotherapy. The first study was a large randomized, multisite, double-blind comparison of active TMS versus sham TMS administered as monotherapy for 6 weeks. We recently reported the results from this study, demonstrating the efficacy of TMS in the treatment of patients with major depressive disorder who failed to receive benefit from previous antidepressant pharmacotherapy.[19] The second study was a 6-week, open-label, acute efficacy study of TMS monotherapy available to all enrolled subjects whose depression had not responded sufficiently during the double-blind study. The third study allowed open-label TMS reintroduction for symptom re-emergence to augment maintenance antidepressant monotherapy over a 24-week period in responders during the first or second study.

The information obtained in these studies provides the largest and most comprehensive safety dataset yet reported for the use of TMS in adults with major depressive disorder in a single clinical program. This exposure dataset involved treatment parameters administered at a maximum feasible dose under currently accepted guidelines for the safe use of TMS. Further, it also included a longer acute treatment exposure duration (e.g., for some patients as long as 12 weeks of continuous daily TMS) than has previously been described. These data are also reported using currently accepted standards for adverse event collection and coding of verbatim terms. Since TMS was administered as a monotherapy and in conjunction with antidepressant pharmacotherapy, we also present information regarding the potential interactions of TMS with medications. Finally, these studies provided data over a long-term follow-up interval with the opportunity for repeat exposure to TMS in the same patients. This longer follow-up provides a unique opportunity to observe the time course of acute adverse events, whether these events dissipate over time, whether the common adverse event profile is predictable, and, finally, whether there are any late-appearing adverse events that may not have been obvious in earlier, shorter-duration clinical trials.

METHOD

Overview of Clinical Development Program

The clinical development program included 3 separate protocols that were temporally sequenced. The studies were conducted at 23 clinical sites in the United States (N = 20), Australia (N = 2), and Canada (N = 1). Active enrollment occurred between January 2004 and August 2005. Study protocol and informed consent were reviewed and approved by each site's institutional review board. All subjects provided written informed consent prior to any study procedures. Study 101 was a randomized, controlled clinical trial designed to examine the efficacy of the Neuronetics NeuroStar TMS Therapy System (Malvern, Pa.) compared with a sham TMS treatment condition.[19] For the active and sham TMS arms, application in all subjects was limited to stimulation over the left DLPFC. Additional details of the method of treatment localization are described elsewhere.[19] Study 102 was an open-label trial that followed the same treatment sequence as the randomized, controlled trial and was available upon request for all patients who had participated in the first study for at least 4 weeks and had not received significant clinical benefit from their randomized assignment (D. H. Avery, M.D.; K. E. Isenberg, M.D.; S.M.S.; et al., manuscript submitted, 2007). The criterion defining failure of clinical benefit in study 101 was applied in a blinded manner (i.e., investigators or patients were unaware of the criterion for eligibility for study 102 enrollment). The specific criterion to determine eligibility for entry into the open-label extension study was failure to

achieve at least a 25% improvement in total score on the 17-item Hamilton Rating Scale for Depression[20] (HAM-D-17) compared with baseline assessment.

A 3-week period of treatment transition, or taper phase, was included at the conclusion of the acute phases of study 101 and study 102. The purpose of this taper phase was to determine whether the acute response to TMS could be maintained without abrupt loss of effect and to allow for clinically appropriate transition to maintenance treatment on a known active antidepressant medication. Choice of medication initiated during the taper phase was restricted to antidepressant monotherapy only. Medications selected by the treating clinicians included selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), serotonin and norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, duloxetine), or other agents (bupropion, mirtazapine, and trazodone).

Study 103 was an open-label, 24-week, durability-of-effect study (P.G.J.; Z. Nahas, M.D.; S.H.L.; et al., unpublished data, 2007). All patients who participated in either study 101 or 102 were eligible if they had shown at least a ≥ 25% improvement in HAM-D-17 score at exit compared with baseline assessment, with this criterion again applied in a blinded manner for entry into study 102. Upon entry into study 103, patients continued taking the open-label antidepressant pharmacotherapy chosen during the taper phase of study 101 or 102. During the entire clinical program, the blinded treatment assignment received in study 101 was not revealed until all patients had completed all studies.

In addition to ongoing pharmacotherapy, active open-label TMS was permitted in study 103 as a rescue add-on treatment for symptom breakthrough. This was defined as deterioration in the Clinical Global Impressions-Severity of Illness scale[21] score of at least 1 point observed over a 2-week period. If this criterion was established, the study protocol required that TMS was initiated as an add-on to the current antidepressant medication regimen. Patients were discontinued from the study and referred for appropriate clinical management if they met full DSM-IV criteria for a major depressive episode or if they received a complete 6-week reintroduction course of TMS rescue without symptom improvement.

Subjects

A complete description of the inclusion and exclusion criteria for participating patients is described elsewhere.[19] In general, patients met DSM-IV diagnostic criteria for unipolar, nonpsychotic major depressive disorder confirmed by a structured psychiatric interview. Patients were moderately to severely ill by symptom measures at baseline and moderately to severely resistant to pharmaceutical antidepressant treatment in the current illness episode as measured by the Antidepressant Treatment History Form (ATHF).[22] A history of seizures was an important exclusion criterion.

Definition of TMS Treatment Parameters

A TMS treatment session consisted of a fixed-dose parameter set involving stimulation at 120% of the patient's observed motor threshold, with a repetition rate of 10 pulses per second. Stimulation trains were grouped with a 4-second on time and a 26-second off time, for a total of 40 pulses for each pulse train. Seventy-five pulse trains, or a total of 3000 pulses, were delivered in each treatment session. Thus, patients initially assigned to active TMS could potentially receive a total of 216,000 pulses if they participated in both study 101 and study 102, including the taper phase. Additional exposure could occur with reintroduction to TMS in study 103. A complete summary of the TMS treatment exposures for the differing study populations is summarized in the Results. Motor thresholds were performed per protocol procedure at the beginning of each treatment week or when indicated in the opinion of the clinical investigator.

Adverse Event Reporting

Adverse events were obtained at each treatment visit by spontaneous verbatim report from the patient and coded by body system and preferred term using the current version of the *Medical Dictionary for Regulatory Activities*[23] (MedDRA). All adverse events were assessed by the investigator with regard to their potential causal relationship to the study device (5-tiered assessment) and also by their clinical severity (3-tiered assessment). All serious adverse events were separately described.

Assessment of Auditory Threshold

During active stimulation, the operation of the device produces an audible clicking sound. All patients and investigative personnel present in the treatment room were required to use ear plugs meeting a minimum standard of 30dB protection. Air conduction auditory threshold was assessed utilizing the Earscan Audiometer (Micro Audiometrics Corp., Murphy, N.C.) at baseline, week 4, and week 6 during the acute treatment phases of study 101 and study 102 and again at the conclusion of study 103.

Assessment of Cognitive Function

Cognitive function was assessed for global cognitive function, immediate and delayed recall, and long-term memory. The instruments used were the Mini-Mental State Examination,[24] the Buschke Selective Reminding Test,[25] and the Autobiographical Memory Interview-Short Form.[26] These measures were obtained at baseline, week 4, and week 6 during the acute treatment phases of study 101 and study 102 and again at the conclusion of study 103.

Methods of Data Summary and Statistical Analysis

In general, the data obtained from the overall study program were summarized to address several major areas of safety interest.

Acute exposure (study 101: active TMS vs. sham). This comparison provides the core summary of the acute adverse event profile observed with active TMS treatment when compared with a within-study control treatment condition.

Acute exposure (study 102: extended active TMS vs. sham to TMS groups from study 101). This comparison provides confirmatory evidence of the acute adverse event profile observed in controlled study 101 and also permits an analysis of any potential late-appearing adverse events in patients who may have received an extended course of acute TMS exposure (i.e., received active TMS in both study 101 and study 102).

Reintroduction exposure (study 103: all continuing-treatment groups from either study 101 or study 102). A summary of the safety profile in these groups provides confirmatory evidence that the acute adverse event profile observed in studies 101 and 102 is predictable upon later TMS reintroduction. The extended period of observation also permitted sufficient follow-up assessment for late-appearing adverse events and provided safety data regarding TMS combination treatment with antidepressant medications.

In addition to these summary data, additional analyses were performed. These analyses included assessment of the time course of selected adverse events to determine whether there was evidence of accommodation to the more commonly occurring problems such as headache or treatment discomfort. Because it has been speculated that antidepressant treatment may be associated with worsening of depression in some patients, specific evidence of treatment-emergent disease exacerbation was also examined using item 3 (i.e., suicidality) of the HAM-D.

Data are reported using descriptive statistical summaries in most instances. Where inferential comparisons are appropriate, the specific analytic methods are noted in the relevant data tables or figures.

RESULTS

Demographic and Clinical Characteristics of the Study Population

Three hundred twenty-five patients were randomly assigned to a treatment condition in study 101 (active TMS: N = 165, sham TMS: N = 160). Two patients left the study prior to receiving their first treatment and were not included in the safety data tables (both had been randomly assigned to sham TMS). Of this population, 158 patients did not receive sufficient clinical benefit from their randomized treatment assignment in study 101 and were enrolled in open-label study 102. Finally, 136 patients received sufficient clinical benefit from their treatment in either study 101 or 102 and were enrolled in study 103.

Table 1. Baseline Demographic Features, Illness History, and Symptom Measures in the Overall Study Population

Variable	Active TMS (N = 165)	Sham TMS (N = 160)	p Value
Demographic			
Female, N (%)	91 (55.2)	80 (50.0)	.375
Age, mean (SD), y	48.2 (10.9)	48.3 (11.1)	.887
Ethnic origin, N (%)			
White	156 (94.5)	143 (89.4)	
Other	9 (5.5)	17 (10.6)	.103
Clinical			
Recurrent illness course, N (%)	158 (95.8)	150 (93.8)	.463
Duration of current episode ≥ 24 mo, N (%)	24 (15.0)	38 (23.0)	.068
No. of antidepressant treatments in current episode, mean (SD)	5.5 (3.4)	5.5 (4.0)	1.000
No. of fully adequate antidepressant treatments in current episode, mean (SD)	1.6 (0.8)	1.6 (0.8)	1.000
Baseline symptom severity			
MADRS total score, mean (SD)	32.6 (5.3)	33.0 (5.7)	.479
24-Item HAM-D total score, mean (SD)	30.7 (3.9)	30.6 (4.4)	.836
17-Item HAM-D total score, mean (SD)	22.7 (2.4)	22.9 (3.1)	.466
CGI-S score, mean (SD)	4.7 (0.6)	4.7 (0.7)	.595
Motor threshold, mean (SD)	55.1 (9.7)	56.7 (10.1)	.168

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, TMS = transcranial magnetic stimulation.

During study 101, the adherence rate to the study protocol through the primary efficacy time point was high. Through week 4, the "all-cause" discontinuation rate was similar in the active (7.7%) and sham TMS (8.2%) groups. Discontinuation due to adverse events was also similar across treatment conditions (i.e., 4.5% in active TMS vs. 3.4% in sham TMS patients).

Similarly in study 102, the adherence rate during open-label TMS treatment was high through week 6 of the acute treatment phase. The all-cause discontinuation rate was 17.7% and similar regardless of prior study 101 treatment assignment. Discontinuations due to adverse events were none in the extended active TMS group and 9.4% in the sham to TMS group.

Finally, through 24 weeks of durability-of-effect follow-up in study 103, the all-cause discontinuation rate was 34.6%, with 2.2% discontinuing due to adverse events.

Baseline demographic features, illness history variables, and symptom measures for the overall study population are shown in Table 1. There were no clinically meaningful differences in the active and sham TMS groups on any variable. In general, patients were moderately to severely ill with a largely recurrent course of illness. A review of overall antidepressant treatment history

Table 2. Transcranial Magnetic Stimulation (TMS) Treatment Session Exposure Summary for All Studies

Variable	Study 101, Acute Exposure (6 wk) (N = 91)	Study 102, Acute Exposure (6 wk) (N = 92)	Study 101 and 102, Extended Acute Exposure (12 wk) (N = 74)	Study 103, Reintroduction Acute Exposure (6 wk) (N = 53)
No. of TMS treatment sessions, mean	2396	2624	4021	1053
No. of TMS treatment sessions per patient, mean (SD)	26.3 (13.0)	28.5 (11.8)	54.3 (10.9)	19.9 (13.2)
Median (range)	34 (1–37)	35 (1–36)	56 (18–72)	18 (3–51)

in the current episode found that patients received a median of 5 antidepressant treatments in their current episode (range, 1–23 treatment attempts). Of these treatments, nearly half of all patients had failed to benefit from exposure to 2 or more definitive antidepressant treatments (i.e., fully adequate dose and duration, as assessed by the ATHF).

TMS Treatment Exposure Summary

Across all 3 studies, a total of 10,094 TMS treatment sessions occurred. A summary of the treatment exposure is displayed in Table 2 showing the number of patients who experienced up to 6 weeks of acute treatment and 3 weeks of taper in either study 101 or study 102; those who experienced up to 12 weeks of acute treatment across studies 101 and 102; and those who experienced additional reintroduction treatment cycles of TMS in study 103. A total of 268 patients received at least 1 session of active TMS in 1 or more of the studies. Motor threshold, however, was attempted in all subjects.

Overall Summary of Adverse Event Profile (acute TMS treatment, extended acute TMS treatment, and reintroduction of TMS treatment)

Across all 3 studies, no deaths or seizures were reported. Twenty-three serious adverse events were reported during controlled study 101. Of these, 20 were assessed by the investigator as not related to the study device, and 3 were assessed as probably related. These latter 3 serious adverse events were all due to a specific malfunction arising from a manufacturing defect in a component of the study device. None of these events led to treatment discontinuation. Twelve serious adverse events were reported in study 102. Of these, 10 were assessed as not related, 1 was reported as probably related, and 1 was reported as related to the study device. This last serious adverse event involved the gradual onset of left-sided facial numbness in 1 patient, which was present in a sensory distribution consistent with irritation of the maxillary branch of the trigeminal nerve. A subsequent neurologic examination was normal with the exception of a discrete region of diminished touch and temperature sensation at the tip of the nose and in the left upper and lower lip, spreading up the left cheek. A magnetic resonance image was normal. Treatment was discontinued, and the event was fully resolved. In study 103, 6 serious adverse events were reported, and all were assessed as not related to the study device. Table 3 summarizes these events.

During acute treatment in the randomized, controlled trial, the most common adverse event was headache occurring equally in both the active and sham TMS treatment groups (i.e., 58.2% and 55.1%, respectively). Headache was assessed by the study investigator as "severe" in 4.2% of active TMS patients and in 5.1% of sham TMS patients. Study investigators classified the headache as "probably or definitely" related to the study device in 27.9% of the active and 19.6% of the sham groups. Analgesics (aspirin, nonsteroidal anti-inflammatory drugs [NSAIDS]) were permitted for headaches or other treatment-related discomfort, but clinical outcomes were not recorded.

Among those adverse events that occurred with an excess incidence in the active TMS treatment condition (i.e., ≥ 5% and twice the incidence in the sham TMS group), the most commonly reported was application site pain (Table 4). This adverse event was reported by 35.8% in the active TMS group compared with 3.8% in the sham TMS group. The investigator characterized the pain as "severe" in 6.1% of patients in the active TMS group and in none of the sham TMS group. Study investigators classified all instances of application site pain as "probably or definitely" related to the study device in both groups. *Application site pain* is the standardized, MedDRA-defined, adverse event term used to group the verbatim descriptions provided by the patient or clinician. As such, this term subsumed a variety of reports, including words describing pain or discomfort occurring under the magnetic coil or at the general location of the treatment stimulation site (e.g., "tingling" or "scalp pain"). As with headaches, use of over-the-counter analgesics was permitted prior to a treatment session. Topical anesthetics were helpful in a few patients to allow continuation of the treatments. In addition, when clinically indicated, the study protocol permitted reduction of treatment intensity to 110% of motor threshold during the first week only. This adverse event was limited to the time of stimulation and did not interfere with patients' daily activities.

In general, the data from study 102 demonstrated a safety profile consistent with the results observed in study 101 (Table 5). Based on their prior treatment assignment in study 101, there were 2 treatment groups in study 102

Table 3. Serious Adverse Events Experienced Across the 3 Studies of TMS Exposure[a]

Serious Adverse Event	Study 101			Study 102, Open-Label Active TMS[b]	Study 103, Open-Label Adjunctive Active TMS[c]	Relationship of Serious Adverse Event to TMS Device
	Prior to Randomization (lead-in phase)	Sham TMS	Active TMS			
Worsening depression only	3	2	0	1	0	Not related
Suicidal ideation only	1	2	2	1	0	Not related
Worsening depression and suicidal ideation	1	0	0	2	1	Not related
Operator error (exceeded maximum specified treatment duration)	0	0	5	4	1	Not related
Device malfunction/first-degree burn	0	0	2	0	0	Probably related
Suicide attempt	0	1	0	0	0	Not related
Device malfunction/severe pain at treatment site	0	0	1	0	0	Probably related
Lower lobe pneumonia	0	1	0	0	0	Not related
Bowel obstruction	0	1	0	0	0	Not related
Shortness of breath and increased heart rate	1	0	0	0	0	Not related
Left-sided facial numbness	0	0	0	1	0	Probably related
Tinnitus	0	0	0	1	0	Probably not related
Atrial fibrillation	0	0	0	2	1	Not related
Coronary artery disease (catheterization and stent placement)	0	0	0	0	1	Not related
Bladder tumor (surgical removal)	0	0	0	0	1	Not related
Hip pain	0	0	0	0	1	Not related

[a]Numbers in each cell represent the number of reports of the specified event term.
[b]All study 102 patients were receiving only active TMS under open-label study conditions.
[c]All study 103 patients were receiving antidepressant pharmacotherapy as a maintenance treatment per protocol.
Abbreviation: TMS = transcranial magnetic stimulation.

(i.e., those patients previously assigned to active TMS [extended active TMS group] and those patients previously assigned to sham TMS [sham to TMS group]). The sham to TMS group provides additional evidence in an open-label cohort, confirming the pattern of adverse events seen in study 101. The extended active TMS group provides data for patients treated with active TMS on a continuous acute schedule for durations of approximately 12 weeks.

As in study 101, headache and application site pain were also the 2 most frequently reported adverse events in both treatment groups. In this study, insomnia occurred at the same rate in both groups; however, for only 1 patient in the sham to TMS group was it reported as related to the TMS treatment. Headache occurred with similar incidence in both treatment groups. The extended active TMS group reported a 47.9% incidence, and the sham to TMS group reported a 45.9% incidence. These events were characterized by the study investigator as "severe" in 6.8% of the extended active TMS group and in 5.9% of the sham to TMS group. Study investigators classified the headaches as "probably or definitely" related to the study device in 24.7% of the extended TMS group and 18.8% of the sham to TMS group. In contrast to headache, fewer patients in the extended active TMS group experienced the adverse event of application site pain (11%) compared with those in the sham to TMS group (31.8%). This adverse event was characterized as "severe" in none of the extended TMS group and in 9.4% of the sham to TMS group. The investigators classified all instances as "probably or definitely" related to the study device.

Table 4. Adverse Events Experienced During Acute Treatment With Active TMS in the Randomized, Controlled Trial (study 101)[a]

Adverse Event, N (%)	Sham TMS (N = 158)	Active TMS (N = 165)
Eye disorders		
Eye pain	3 (1.9)	10 (6.1)
Gastrointestinal disorders		
Toothache	1 (0.6)	12 (7.3)
General disorders and site administration conditions		
Application site discomfort	2 (1.3)	18 (10.9)
Application site pain	6 (3.8)	59 (35.8)
Facial pain	5 (3.2)	11 (6.7)
Musculoskeletal and connective tissue disorders		
Muscle twitching	5 (3.2)	34 (20.6)
Skin and subcutaneous tissue disorders		
Pain of skin	1 (0.6)	14 (8.5)

[a]Adverse events experienced at a rate of ≥ 5% and at least twice that of sham TMS.
Abbreviation: TMS = transcranial magnetic stimulation.

As in study 101, the greatest incidence of headache and application site pain occurred during the first week and then decreased, suggesting a rapid accommodation (Figures 1A, 1B, 2A, and 2B) to either event. Acute treatment with aspirin or another NSAID was permitted per protocol.

Finally, study 103 provides further insight into the adverse events appearing during longer-term follow-up and the predictability of the commonly occurring adverse events observed during recurring acute treatment courses of TMS. A total of 53 patients met protocol-

Table 5. Adverse Events Experienced During Acute Treatment With Active TMS in the Open-Label Trial (study 102)[a]

	Extended Active TMS		Sham to TMS	
Adverse Event, N (%)	Overall (N = 73)	Related (N = 73)	Overall (N = 85)	Related (N = 85)
Gastrointestinal disorders				
Nausea	10 (13.7)	2 (2.7)	6 (7.1)	0
Toothache	2 (2.7)	1 (1.4)	6 (7.1)	3 (3.5)
General disorders and site administration conditions				
Application site discomfort	7 (9.6)	7 (9.6)	8 (9.4)	8 (9.4)
Application site pain	8 (11.0)	8 (11.0)	27 (31.8)	27 (31.8)
Facial pain	0	0	5 (5.9)	4 (4.7)
Pain	4 (5.5)	1 (1.4)	3 (3.5)	1 (1.2)
Musculoskeletal and connective tissue disorders				
Muscle twitching	15 (20.5)	15 (20.5)	18 (21.2)	15 (17.6)
Nervous system disorders				
Dizziness	6 (8.2)	1 (1.4)	7 (8.2)	2 (2.4)
Headache	35 (47.9)	18 (24.7)	39 (45.9)	16 (18.8)
Paresthesia	5 (6.8)	3 (4.1)	4 (4.7)	1 (1.2)
Psychiatric disorders				
Anxiety	11 (15.1)	0	12 (14.1)	1 (1.2)
Insomnia	22 (30.1)	0	22 (25.9)	1 (1.2)
Skin and subcutaneous tissue disorders				
Pain of skin	1 (1.4)	1 (1.4)	5 (5.9)	5 (5.9)

[a]Overall incidence of adverse events occurring in ≥ 5% of either group and specific incidence of events assessed by the investigator as probably or definitely related to the study device.
Abbreviation: TMS = transcranial magnetic stimulation.

Figure 1. Time Course of Incidence of Headache in the Randomized, Controlled Trial (study 101) and in the Open-Label Trial (study 102)

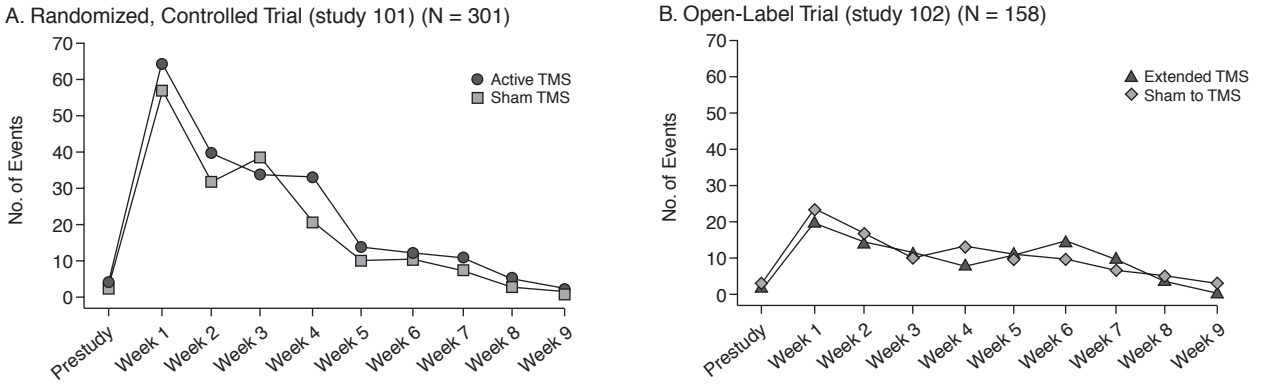

Figure 2. Time Course of Incidence of Application Site Pain in the Randomized, Controlled Trial (study 101) and in the Open-Label Trial (study 102)

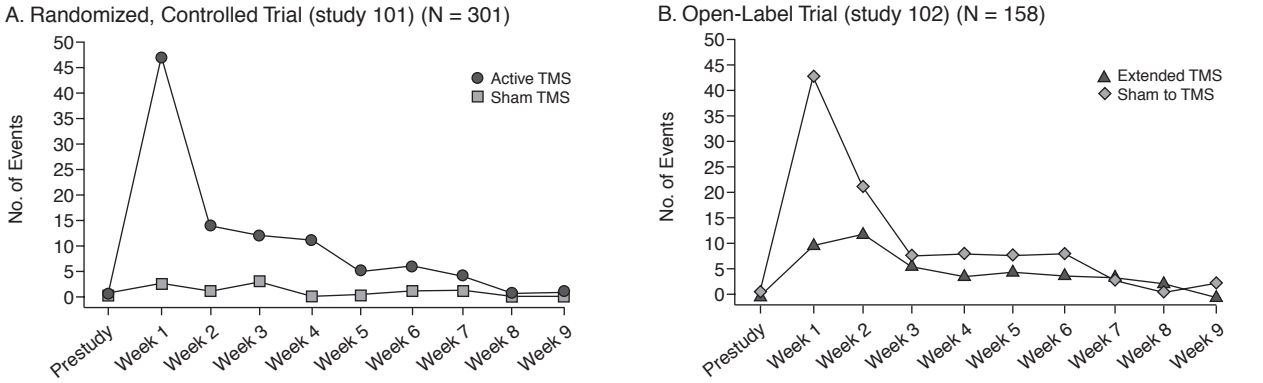

Table 6. Adverse Events Experienced During Acute Reintroduction of TMS Treatment in the Maintenance-of-Effect Trial (study 103)[a]

	Study 101 Active		Study 101 Active/ Study 102		Study 101 Sham/ Study 102		Study 101 Sham	
Adverse Event, N (%)	Overall (N = 44)	Related (N = 44)	Overall (N = 27)	Related (N = 27)	Overall (N = 42)	Related (N = 42)	Overall (N = 23)	Related (N = 23)
Gastrointestinal disorders								
Constipation	0	0	5 (18.5)	0	2 (4.8)	1 (2.4)	0	0
Dry mouth	1 (2.3)	0	4 (14.8)	0	5 (11.9)	1 (2.4)	2 (8.7)	0
General disorders and site administration conditions								
Application site pain	3 (6.8)	3 (6.8)	2 (7.4)	2 (7.4)	2 (4.8)	2 (4.8)	6 (26.1)	6 (26.1)
Musculoskeletal and connective tissue disorders								
Arthralgia	8 (18.2)	1 (2.3)	4 (14.8)	0	8 (19.0)	0	2 (8.7)	0
Muscle twitching	5 (11.4)	2 (4.5)	1 (3.7)	1 (3.7)	4 (9.5)	3 (7.1)	4 (17.4)	3 (13.0)
Nervous system disorders								
Headache	16 (36.4)	3 (6.8)	9 (33.3)	1 (3.7)	14 (33.3)	1 (2.4)	10 (43.5)	2 (8.7)
Psychiatric disorders								
Anxiety	8 (18.2)	0	2 (7.4)	0	7 (16.7)	1 (2.4)	3 (13.0)	0
Insomnia	13 (29.5)	0	10 (37.0)	0	15 (35.7)	1 (2.4)	7 (30.4)	0

[a]Overall incidence of adverse events occurring in ≥ 5% of any group and specific incidence of events assessed by the investigator as probably or definitely related to the study device.
Abbreviation: TMS = transcranial magnetic stimulation.

defined criteria for symptom worsening and required reintroduction of open-label active TMS during this study. For those patients who received coadministration of TMS with their assigned antidepressant medications, the overall pattern of adverse events was consistent with that observed during active TMS treatment administered alone (i.e., headache and application site pain) (Table 6). Patients were exposed to medications plus TMS during the taper phases of the acute trials (101 and 102) and in the maintenance of effect trial (103). Further, 34 patients were treated with bupropion per protocol during either the taper phases or the maintenance of effect study and tolerated concurrent adjunctive TMS administration without a seizure incident.

Treatment-Emergent Suicidal Ideation

Treatment-emergent disease exacerbation was also examined in the randomized, controlled trial. Given the severity of the clinical condition in the patient population recruited, exacerbation of depression comprised the most commonly reported serious adverse events. The majority of these events were reported in the sham treatment condition, including suicidality (1.9% with sham vs. 0.6% with active TMS), exacerbation of depression (1.9% with sham vs. 0.6% with active TMS), and a single suicide attempt (overdose of prescription anxiolytics) occurring in the sham treatment group. To characterize this risk using a more sensitive indicator, emergent suicidal ideation was assessed using item 3 (suicidality) of the HAM-D. This was defined as the proportion of patients in either group who had an item 3 value of 0 or 1 at baseline that increased to a value of 3 or 4 at any time point during the acute treatment phase. Overall, 10 events meeting this criterion were observed in the sham TMS group compared with only 1 event in the active TMS group.

Auditory Threshold Summary

There was no evidence of change in air conduction threshold across the observation time points in all 3 studies. Both right and left ears were assessed across a frequency spectrum ranging from 500 to 8000 Hz.

Cognitive Function Summary

No change in cognitive function was observed on any of the measures, reflecting stability on indices of global cognitive function, short-term and delayed recall, and retrieval of long-term autobiographical memory. A more detailed consideration of these data will be the basis of a separate report.

DISCUSSION

Our data represent the most comprehensive and largest experience to date regarding the safety and tolerability of rapidly pulsed TMS for the treatment of major depressive disorder. Further, the parameters used were aggressive compared with previous studies, underscoring the safety of the procedure when delivered to the left DLPFC. Our safety results, however, may not generalize to use of this device with different parameters delivered to other brain locations. In addition to the size of the population included in these studies, the data are important because they examined the safety of TMS administered for a longer acute treatment duration than previously reported in the literature. Further, these studies provided the unique opportunity to examine the safety profile of TMS in the same patients treated with repeated courses of TMS at separate points in time. Finally, to our knowledge, this summary provides the first report of information on the safety profile of continuous daily TMS administered to patients for periods of up to 12 weeks.

It is useful to place these results in context relative to the tolerability and safety of other antidepressant treatment options. From this perspective, the incidence of adverse events and discontinuation rates due to tolerability of TMS compare quite favorably to the experience with current antidepressant medications. For example, in a recent large meta-analysis, the all-cause discontinuation rate in randomized, controlled trials of standard antidepressants was 37%.[27] By comparison, the all-cause discontinuation rate due to adverse events for the treatment-resistant TMS-treated patients in study 101 was 8% at week 4, the primary efficacy time point.

Similarly, in the STAR*D study with the initial level 1 treatment option (i.e., open-label treatment with citalopram, mean final dose averaging 41.7 mg/day for up to 14 weeks), the discontinuation rate due to adverse events was 8.6%. For comparison, in the TMS open-label study 102, 9.4% of patients in the sham to TMS group and none in the extended TMS group discontinued due to adverse events through the end of the acute treatment phase.

In addition, the data reported here support the view that TMS can be safely administered in an outpatient setting. Adverse events observed with acute, extended, or repeated courses of TMS were generally mild to moderate in severity. Headache and treatment discomfort during the TMS session itself were the most common events. The occurrence of these adverse events was predictable over repeated courses of treatment, and there was clear evidence of adaptation to these events in most patients. Interestingly, the incidence of application site pain was greater in the sham to TMS group compared with the extended active TMS group. This finding is consistent with the view that application site pain is more directly related to the treatment itself and also that rapid accommodation to this event can be expected.

The most significant medical risk associated with the use of TMS is the inadvertent induction of a seizure. The risk of this event was identified early in the research literature with TMS. Even prior to the introduction of more specific parameter guidelines for the use of TMS, however, the reported incidence was low. In 1996, when the National Institute of Neurologic Disorders and Stroke consensus safety guidelines were presented, only 6 instances of seizure with TMS had been recorded in the world experience.[18] Since that time, we are aware of at least 7 additional case reports of seizure.[28–34] In most reports, the seizures were self-limited without evidence of lasting neurologic sequelae; typically, there was eventual normalization of the postictal electroencephalogram when studied. Currently, it is presumed that the 2 most critical parameters that may contribute to an increased seizure risk are (1) the duration of the TMS pulse train at a given frequency and magnetic field intensity[18] and (2) the duration of off time between trains.[33,35] With the publication of suggested safety limits for the use of TMS, the reported incidence of seizures appears to have been reduced in studies strictly adherent to these parameter limits. It is worth noting that a history of a seizure disorder is not an absolute contraindication to the use of TMS.[36–37] In fact, a number of research centers have suggested that TMS may have specific anticonvulsant properties with certain parameter sets.[38–40]

During the extensive exposure reported here, using a clinically definitive set of TMS treatment parameters and a standardized clinical screening methodology for seizure risk, no seizures were reported in over 10,000 active outpatient TMS treatment sessions. These data are consistent with the reported experience of inadvertent seizure incidence with TMS in the published literature and underscore the previous estimates that the actual incidence is likely to be low. The use of an appropriately worded informed consent procedure, adequate pretreatment clinical screening for potential seizure risk, clinical monitoring of the TMS treatment sessions, appropriate training of attending clinical personnel with regard to "first responder" seizure clinical skills, and attention to existing recommendations for TMS treatment parameter limits appears to minimize the risk of this medical event. The data reported here add to our understanding of the safety profile of TMS in the treatment of patients with major depressive disorder and indicate that the basic clinical processes noted above can be successfully implemented in an outpatient setting.

Prior to the data reported here, the existing literature had described the specific safety profile of TMS for continuous acute treatment durations of 2 to 3 weeks for a total of up to 30,000 magnetic pulses. More recently, a report has described the safe administration of up to 12,960 pulses in a single daily treatment for up to 3 days over 1 week in healthy men.[41] Our own report extends these data and provides consistent evidence that the acute safety profile of TMS is similar to prior literature reports. Further, there was no evidence of late-appearing adverse events with extended exposure or upon subsequent acute courses. Safety data in such a group have not been previously reported and inform our understanding about the cumulative effects or late-appearing events that may occur with extended courses of TMS.

Nevertheless, the question regarding whether even more extended courses of acute TMS exposure would introduce additional safety risks has not been specifically examined. Thus, the safety information that has been obtained from the extensive published literature on the use of pulsed magnetic fields in the context of magnetic resonance imaging technology is relevant to this issue.[42,43] In this regard, TMS utilizes a magnetic field that is clinically comparable to the pulsed gradient field used in magnetic resonance imaging. These fields are comparable with regard to the peak field intensity and have similar field switching times.[44] As a result, they produce comparable

levels of induced current density in conductive tissue. With this type of pulsed magnetic field, it is established that there is clinically negligible tissue heating, no histopathologic evidence of cellular change, and no evidence of mutagenesis.[45–46] With regard to total pulsed field exposure, 2 standard magnetic resonance imaging sessions would result in approximately 10×10^6 pulses compared with 0.45×10^6 pulses across 150 TMS treatment sessions as conducted using the parameter set described here.

There are limitations of the conclusions that can be drawn from this dataset. Most important, the results described here are likely to be specifically related to the magnetic coil design used in this work and may not fully generalize to the safety of other coil designs, in which the volume of tissue stimulated or other biophysical characteristics of the magnetic pulse may vary. Further, our results refer to stimulation over the left DLPFC and may not generalize to other application sites or different delivery parameters. In addition, we limited the extent of treatment resistance in the current episode in our study population and therefore the safety in more treatment-resistant patients is not known. Other important exclusions included unstable medical illnesses, seizure disorder, and patients with active or emergent suicidal ideation.

This large, multisite, clinical development program found TMS to be safe and generally well tolerated. This finding is underscored by the low and similar overall discontinuation rate due to adverse events through the primary efficacy time point in study 101 for both the active and sham TMS groups (i.e., 4.5% vs. 3.4%, respectively). A likely contributing factor to the low discontinuation rate was the rapid accommodation to these events with a substantial reduction in the incidence of headache and application site pain after the first week of exposure. This is particularly important in light of the treatment parameters utilized and also given the potential for extended exposure in many of the patients. A comparison of the adverse event profile associated with TMS to that observed with various medication strategies and device-based therapies indicates a favorable tolerability profile for TMS, relatively speaking. Coupled with the growing body of evidence supporting its antidepressant efficacy, TMS may become an important treatment consideration for patients who have failed prior therapeutic options for major depressive disorder.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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