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The Efficacy of Transcranial Magnetic Stimulation for Major Depression: A Review of the Evidence

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ABSTRACT

Major depression is a leading cause of disease burden worldwide. Although various treatment approaches exist, including pharmacological (eg, antidepressant agents), psychotherapeutic (eg, cognitive-behavioral therapy), and neuromodulatory (eg, electroconvulsive therapy [ECT]), a substantial number of patients do not adequately benefit from or cannot tolerate these existing options. This has led to a re-emergence of other neurostimulation strategies, the best studied to date being transcranial magnetic stimulation (TMS). This article reviews the rationale for TMS in treating depression with a brief description of the basic principles underlying magnetic stimulation; a discussion of its putative mechanism of action; and its recommended treatment parameters. We then focus on the evidence base to support its use as both a monotherapy and adjunctive therapy for the acute and maintenance treatment of major depression. These data came from controlled trials comparing TMS to a sham procedure and naturalistic outcome studies for acute depression; studies directly comparing TMS to ECT for major depression; and open-label studies, retrospective analyses, naturalistic outcome studies, and case reports that consider the durability of TMS' effect after acute response. The results of these studies have led to a growing use of TMS in clinical practice for treatment-resistant depression. **[*Psychiatr Ann*. 2014; 44(6):284–292.]**

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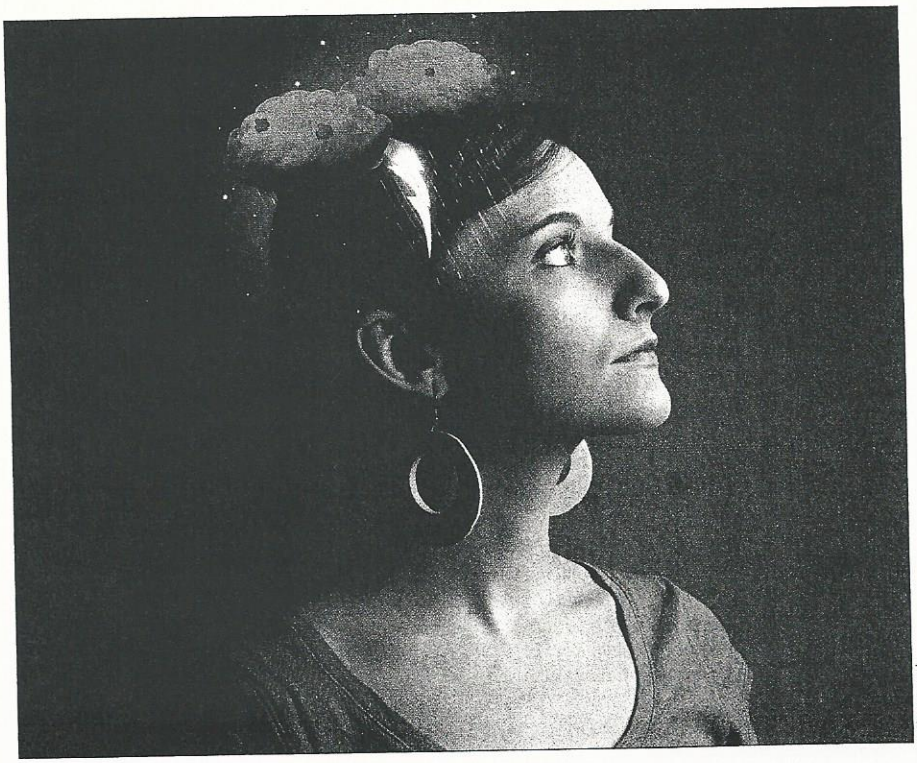

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Major depressive disorder (MDD) is reaching unprecedented levels worldwide and is identified as a leading cause of disease burden and higher health care utilization.[1,2] Further, estimates of insufficient response and/or intolerability to standard antidepressant medications are in the 30% to 50% range.[3] The need for more effective, alternative treatments with improved safety and tolerability profiles is clear. One such approach involves repetitive transcranial magnetic stimulation (rTMS, or simply "TMS"). In this review, we briefly consider the basic principles of TMS, its putative mechanism of therapeutic action in the treatment of MDD, and recommended parameters. We then focus on the data supporting its role for treatment of MDD.

BASIC PRINCIPLES OF TMS

TMS involves the application of intense (1.5 to 2.0 T), localized, pulsed magnetic fields to human tissue. These pulses are typically produced by electrical current traveling through coils of conductive material, such as copper wire. As predicted by Faraday's law of physics, these electromagnetic fields induce electrical activity in peripheral and central nervous system tissues located in a perpendicular plane beneath the coil.[4] When a TMS coil is placed on the head and the magnetic energy pulses are delivered with sufficient intensity, they penetrate through scalp and skull tissues to reach the brain cortex.[5] Neuronal depolarization occurs, producing action potentials in targeted areas directly beneath the coil. TMS therapy, whether administered at a rate that is likely to be excitatory (5 to 10 Hz or higher) or inhibitory (≤1 Hz) to neuronal activity, is done with a series of pulses delivered together in a "train" of varying duration (eg, seconds to minutes), followed by a rest period during which no pulses are delivered.[6] In addition to using it as a tool to excite or inhibit regional activity in brain physiology experiments, TMS administered in a series of pulse trains comprises a "treatment session." These sessions are repeated multiple days over a period of several weeks or months and have potential therapeutic applications for several neuropsychiatric disorders.[7]

MECHANISM OF ACTION

Similar to all other treatments for MDD, TMS' therapeutic mechanism of action is unknown. Imaging studies report increased metabolism and blood flow with relatively "high frequency" TMS (HF-TMS; 10 or more pulses per second, or ≥10 Hz) over the left dorsolateral prefrontal cortex (DLPFC).[8] Trans-synaptically, left HF-TMS activates other cortical and subcortical areas (in both the ipsilateral and contralateral hemispheres), including deeper neurocircuits implicated in the behavioral dysregulation characteristic of MDD (eg, sleep-wake cycle, appetite, energy level, ability to experience satisfaction in various activities). It has been proposed that 10-Hz DLPFC TMS works to entrain brain oscillatory rhythms in MDD patients, permitting the resetting of thalamocortical "pacemakers" in key regions where oscillations of electrical activity have become excessively synchronous. Entrainment with TMS may be a critical mechanism for restoring the intrinsic cerebral rhythms required for modulation of regional neuronal activity in response to the demands of one's environment, as required for normal brain function.[9]

TMS FOR TREATMENT OF MAJOR DEPRESSION

Stimulation Parameters

The standard protocol associated with the U.S. Food and Drug Administration (FDA)-cleared, NeuroStar® TMS device (Neuronetics, Malvern, PA) for treatment of depression includes left DLPFC stimulation at 120% of motor threshold (MT), with magnetic field pulses delivered at 10 Hz in 4-second trains (40 pulses), followed by 26-second intertrain rest intervals (ITIs). With this cycle, 37.5 minutes are required for delivery of a total of 3,000 pulses in a single treatment session. Twenty or more, once-daily sessions are typically required to achieve clinical response with an acute treatment course, although some patients respond to fewer than 20 and others benefit from a longer course.[10,11] Consistent with the protocol used in the pivotal clinical trial, a standard course of 30 TMS treatments over 6 weeks, followed by six additional taper treatments spaced over the final 3 weeks, is approved by most third-party payers who cover TMS.[12] Modifications (eg, increasing the number of pulses) of this regimen, however, are often undertaken to optimize the outcome.[13]

Pulsing TMS at a relatively low frequency (≤1 Hz) over the right DLPFC is also associated with relief from depressive symptoms, despite the fact that differential physiological effects appear related to TMS pulse frequency.[14] The effect of "slow" TMS may be inhibitory rather than excitatory on neuronal activity in regions linked through cortical-subcortical networks. Often selected as a strategy for MDD patients with prominent anxiety, 1-Hz treatment on the right decreases regional cerebral blood flow to limbic regions such as amygdala.[15,16] The convention of applying low-frequency (LF-) TMS specifically over the right hemisphere may have arisen from assumptions about cerebral laterality in depressed patients, but recent work suggests 1-Hz stimulation delivered over the left DLPFC may work equally as well for this population.[17]

A typical right-sided 1-Hz treatment session for MDD also involves stimulation over the DLPFC with magnetic field intensities up to 120% MT. Due to the lower risk for inadvertent seizure induction during 1-Hz pulsing, LF-TMS can safely be delivered in trains of relatively long durations, or alternatively as

TABLE 1.

Meta-Analyses Considering the Efficacy of TMS for Major Depression

Meta-Analysis	Studies (*N*)	Patients (N)	Outcome	Authors' Conclusions
McNamara et al. (2001)[22]	5	81	NNT = 2 to 3 (1.6 to 4.0)	TMS had demonstrable effects in treating major depression
Holtzheimer et al. (2001)[23]	12	264	ES = 0.81 (0.42 to 1.20)	TMS is statistically superior to sham stimulation for depression
Kozel & George (2002)[24]	12	230	ES = 0.53 (0.24 to 0.82)	TMS produced statistically significant effect sizes and measurable clinical improvement
Burt et al. (2002)[25]	23	432	ES = 0.62	Antidepressant effect is robust statistically; effect sizes are heterogenous
Martin et al. (2003)[26]	14	372	SMD = –0.35 (–0.66 to –0.04)	No strong evidence for benefit
Couturier (2005)[27]	6	91	Weighted mean difference = –1.1 (–4.5 to 2.3)	TMS is no different than sham treatment in major depression; the power within these studies to detect a difference was generally low
Hermann & Ebmeier (2006)[28]	33	877	ES = 0.71 (0.45 to 0.97)	TMS was more effective than sham, but variability was too great to take any single study design as paradigmatic
Gross et al. (2007)[29]	5	274	ES = –0.76 (–1.01 to 0.51)	Recent TMS trials had larger effect sizes compared with earlier trials
Lam et al. (2008)[30]	24	899	ES = 0.48 (0.28 to 0.69) Response: NNT = 6 Remission: NNT = 7	TMS is superior to sham in treatment of acute TRD
Schutter (2009)[31]	30	1164	ES = 0.39 (0.25 to 0.54) ($P < 0.0001$)	HF-TMS over the left DLPFC is superior to sham
Slotema et al. (2010)[32]	34	1383	ES = 0.55 ($P < 0.001$)	HF-TMS superior to sham procedure
Berlim et al. (2013)[33]	8 6	263	Response: OR = 3.35 ($P < 0.007$), NNT = 5 Remission: OR = 4.76 ($P < 0.0001$), NNT = 5	Right LF-TMS is effective for major depression and similar to left HF-TMS
Berlim et al. (2014)[34]	29	1371	Response: OR = 3.3 ($P < 0.0001$), NNT = 6 Remission: OR = 3.3 ($P < 0.0001$), NNT = 8	Left HF-TMS superior to sham procedure

DLPFC = dorsolateral prefrontal cortex; ES = effect size; HF = high frequency; LF = low frequency; NNT = number needed to treat; OR = odds ratio; SMD = standard mean difference; TMS = transcranial magnetic stimulation; TRD = treatment-resistant depression.

a single continuous train of pulses given without any pauses. Published protocols for 1-Hz stimulation describe a wide range of total pulses per session.[14] The largest MDD sample to receive 1-Hz TMS to date was treated with 1,800 pulses per session, at 120% MT intensity.[11] Potential benefits of LF-TMS may include better tolerability and less risk for seizures compared with HF-TMS.[18] Although some data support sequencing right LF-TMS with left HF-TMS in the same session, a recent, sham-controlled trial did not confirm better efficacy of sequenced/bilateral TMS in comparison to left HF-TMS alone.[19]

Currently, the largest database for the therapeutic use of TMS describes treatment of patients with unipolar MDD. Most studies included patients who were moderately to severely depressed and also treatment-resistant or intolerant to standard antidepressant medications. Early, controlled studies found little to only modest differences between active and sham TMS. Later trials, however, consistently reported a significant and clinically relevant benefit favoring active TMS over the sham procedure.[20] This discrepancy is related to several factors, including the use in later trials of larger samples, more aggressive TMS dosing parameters, improved methods for targeting and coil placement, and delivery of a greater number of pulses per treatment session and total sessions

TABLE 2.

Important Characteristics of Recent Large Controlled TMS Studies for Major Depression

Study	N[a]	Gender Breakdown	Treatment Resistance	TMS Procedure	Sham Procedure and Coil Placement	Primary Outcome
O'Reardon et al. (2007)[12]	301	Active: 69 men/86 women Sham: 2 men/74 women	1 to 4 failed adequate AD trials or intolerant to 4 trials (M = 1.5 failed trials)	HF-TMS (10 Hz) to left DLPFC 4-sec train; 26-sec ITI 3,000 pulses/session—up to 30 sessions (90,000 pulses) Limited rescue medications	Metal insert in coil to block magnetic field 5-cm rule for coil placement	MADRS change score at week 4
George et al. (2010)[35]	190	Active: 4 men/58 women Sham: 48 men/50 women	1 to 4 failed adequate AD trials or intolerant to ≥3 trials (M = 1.5 failed trials)	HF-TMS (10 Hz) to left DLPFC 4-sec train; 26-sec ITI 3,000 pulses/session—up to 30 sessions (90,000 pulses) Limited rescue medications	Metal insert in coil to block magnetic field Scalp electrodes to deliver matched somatosensory sensations 5-cm rule for coil placement with MRI-guided adjustment	Proportion of remitters at week 6 based on the HDRS-24
Brainsway Deep TMS System[36]	233	Active: 108[b] Sham: 121[b]	1 to 4 failed adequate AD trials or intolerant to ≥2 trials	HF-TMS (18 Hz) to medial and lateral PFC 120% MT 1,980 pulses/session—total of 20 sessions (29,600 pulses) DTMS H-coil	Electric currents traveling opposite directions in coil's double wires produce negligible magnetic field Broad field/large coil windings enclosed in helmet	HDRS-21 change score at week 4

AD = antidepressant; DLPFC = dorsolateral prefrontal cortex; DTMS = deep transcranial magnetic stimulation; HDRS = Hamilton Depression Rating Scale; HF = high frequency; ITI = intertrain rest intervals; MADRS = Montgomery–Åsberg Depression Rating Scale; MT = motor threshold; MRI = magnetic resonance imaging; PFC = prefrontal cortex; TMS = transcranial magnetic stimulation.

[a] *Number in intent-to-treat sample.*

[b] *Breakdown by gender not available in published documents.*

per course of therapy. Earlier work reflects a more conservative application of pulsed magnetic fields to human brain as safety data were gradually emerging, whereas more recent trials incorporating greater "doses" of TMS (likely, with better penetration to key anatomical structures) were associated with more robust antidepressant effects. In addition, safety and tolerability issues using these more aggressive TMS parameters were clarified and generally found to be less problematic than medications or electroconvulsive therapy (ECT).[21] Studies involving TMS for depression can be divided into:

- Randomized, controlled trials (RCTs) of TMS as monotherapy or adjunctive therapy versus a sham procedure.
- Studies of TMS versus ECT.
- Naturalistic, observational outcome studies that consider the acute and sustained benefits of TMS.

Randomized, Sham-Controlled, TMS Trials for Major Depression

There are now more than 35 randomized, double-blind, sham-controlled TMS trials for depression reported in the literature. Owing to the requirement for a safe and conservative approach to the development of a novel modality for therapeutic brain manipulation (ie, using energy fields produced by investigational devices), the trajectory of TMS research over time has been incremental and reflects implementation of trial designs that prioritized the safety of depressed patients. Notable limitations characterize some of the published controlled trials, including modest sample sizes, inclusion of patients on stable concurrent pharmacotherapy, use of suboptimal sham procedures, and inclusion of both unipolar and bipolar depressed patients. Further, relatively few captured follow-up data regarding maintenance of effect after completion of an acute treatment

series. Despite these limitations, several meta-analyses concluded that HF-TMS over the left DLPFC demonstrates a statistical and clinically relevant acute benefit compared with a sham procedure (**Table 1**).[22-34]

The most recent meta-analysis included 29 RCTs involving 1,371 patients with MDD.[34] After an average of 13 TMS sessions (range = 10 to 30), response and remission rates were 29.3% and 18.6%, respectively, with active TMS. By contrast, those rates were 10.4% and 5%, respectively, with the sham procedure. The pooled odds ratio (OR) for both response and remission rates was 3.3 ($P < 0.0001$) and the number needed to treat (NNT) was 6 and 8, respectively. Of note, the authors reported no difference when TMS was used as a monotherapy or augmentation approach; when used in mixed samples involving both unipolar and bipolar depressed patients; or when delivered as either left HF-TMS or right LF-TMS. Further, dropout rates were similar between the active and sham arms (ie, 7.5% versus 7.6%).

The two largest MDD published studies to date included 491 patients ($n = 301$ and $n = 190$, respectively) randomized to either active or sham TMS.[12,35] These two trials used less conservative stimulation parameters for acute treatment of MDD with left HF-TMS (**Table 2**). Both studies entered only treatment-resistant, nonmedicated, nonpsychotic, unipolar major depressive patients and used the same device, the first of its kind to receive FDA clearance for treatment of depression. Critical parameters included stimulation over the left DLPFC with pulse intensity of 120% MT, at a frequency of 10 Hz (4-second pulse train and 26-second ITI) for up to 30 sessions (90,000 pulses) delivered once daily over 6 weeks, followed by six taper treatments during weeks 7 to 9. Relative to earlier trials, greater attention was given to blinding in both studies, including use of more appropriate sham coils. The George et al.[35] study optimized sham treatment through use of an electrical stimulator that delivered weak, pulsed currents to surface electrodes on each subject's face and head during TMS sessions to mask the sensations produced by the active TMS device. The primary outcomes from this second, large, sham-controlled trial using standard depression assessments confirmed the findings reported by O'Reardon et al.[12] For example, remission rates were approximately 15% for active and 5% for sham TMS in both trials based on the 24-item Hamilton Depression Rating Scale (HDRS-24) scores.

Remission rates were approximately 15% for active and 5% for sham TMS in both trials based on the 24-item Hamilton Depression Rating Scale scores.

Recently, a large double-blind, multicenter RCT ($n = 233$ intent-to-treat; $n = 181$ efficacy sample) was conducted by the manufacturers of a new TMS device thought to deliver stimulating pulses which penetrate more deeply into the cortex.[36] In contrast to the iron-core coil used by the NeuroStar TMS device, an "H-coil" with air core and complex windings placed over a larger surface area of medial and lateral prefrontal cortex characterizes the Brainsway® (Jerusalem, Israel) "deep TMS" (DTMS) approach. This coil received FDA clearance for treatment of adults with MDD in January 2013.[36] In the double-blind, sham-controlled TMS trial conducted with the H-coil and Magstim Rapid® stimulators (Whitland, Wales, UK), TMS sessions (ie, 2-second trains, 20-second ITIs, at 18 Hz, 120% MT, 55 trains, 1,980 pulses per session, session duration of 20.2 minutes) were delivered 5 days per week for 4 weeks. The acute phase was followed by a maintenance phase in which subjects were treated twice weekly for another 12 weeks. Acute phase DTMS therapy was associated with a 6.39-point decrease on the 21-item HDRS, compared with 3.11 points in the sham group ($P < 0.008$). These results were corroborated by statistically significant improvements in the Clinical Global Impression of Improvement scores at week 5, which were also maintained through week 16. Similar to clinical trials conducted with the predicate TMS device, no negative cognitive effects were associated with the Brainsway DTMS treatment. The main side effects of active DTMS included jaw and stimulation site pain. One seizure was reported.

Randomized Trials of TMS versus ECT for Major Depression

The potential role of TMS relative to ECT considers different scenarios. For example, there are preliminary data that TMS may be sequenced with ECT to achieve similar benefit but minimize adverse cognitive effects, or that TMS may be used as a maintenance strategy after a successful acute course of ECT.[37-39] The largest database, however, considers whether TMS may be an alternative to ECT for an acute MDD episode. This is of importance given the adverse effects associated with ECT are typically absent with TMS. Further, the pending decision by the FDA for categorizing ECT devices may limit its use in the future.

There are currently nine published trials (seven randomized, two open-label) of left HF-TMS and one trial of right LF-TMS versus ECT in the literature (**Table 3**).[40-50] All involved depressed patients who were deemed appropriate candidates for ECT. Each of these trials, however, has significant limitations. These include small samples, nonblinded assessments, and no sham procedure. In most studies, the total number of TMS sessions was low and

TABLE 3.

Outcome in Depressed Patients Randomized or Assigned to TMS or ECT

	Outcome		
Randomized Studies	**ECT (%)**	**TMS (%)**	**Comments**
Grunhaus et al. (2000)[40]	16 of 20 (80%)	9 of 20 (41%)	Response rate: HDRS-17 (≥50%); GAS (≥60) TMS comparable to UND/BL ECT in nonpsychotic major depression
Pridmore et al. (2000)[41]	11 of 16 (69%)	11 of 16 (69%)	Remission rate: HDRS-17 (≤8) UND ECT
Janicak et al. (2002; 2005)[42,43]	6 of 14 (43%)	7 of 17 (41%)	Response rate: HDRS-24 (≥50%; ≤8) BL ECT
Grunhaus et al. (2003)[44]	12 of 20 (60%) 6 of 20 (30%)	11 of 20 (55%) 6 of 20 (30%)	Response rate: HDRS ≥ 50%; <10; GAS ≥60) Remission rate: HDRS ≤8) HDRS-17 UND ECT
Rosa et al. (2006)[45]	6 of 15 (40%)	1 of 20 (50%)	Response rate: HDRS-17 (≥50%) UND/BL ECT
Eranti et al. (2007)[46]	13 of 22 (59%)	4 of 24 (17%)	Remission rate: HDRS-17 (≤8) UND/BL ECT
Keshtkar et al. (2011)[47]	68% improvement from baseline ($n = 40$)	29% improvement from baseline ($n = 33$)	HDRS-21 HF-TMS (total pulses = 4,080) BL ECT
Hansen et al. (2011)[48]	26% higher rate of partial remission with ECT ($P < 0.04$)		HDRS-17 LF-TMS ($n = 30$) UND ECT ($n = 30$)
Nonrandomized Studies			
O'Connor et al. (2003)[49]	62% mean improvement from baseline ($n = 14$)	10% mean improvement from baseline ($n = 14$)	HDRS-17 UND ECT
Schulze-Rauschenbach et al. (2005)[50]	6 of 14 (46%)	7 of 16 (44%)	Response rate:HDRS-17 (≥50%) UND ECT

BL = bilateral; ECT = electroconvulsive therapy; HDRS = Hamilton Depression Rating Scale; HF = high frequency; GAS = Global Assessment Scale; LF = low frequency; TMS = transcranial magnetic stimulation; UND = unilateral, nondominant.

would be considered subtherapeutic by today's standards. Further, most did not measure durability of effect beyond the acute treatment phase. With these limitations in mind, one recent meta-analysis of seven randomized left HF-TMS trials concluded that ECT was superior to TMS, with 50% and 30% of patients achieving remission, respectively.[51] Another meta-analysis of data from nine trials also found ECT to be superior to TMS, particularly for patients with psychotic depression.[52] Among nonpsychotic patients, however, both HF-TMS and LF-TMS were as effective as ECT.

Although TMS therapy as it is currently delivered should not replace ECT for all MDD patients, the two treatment modalities may be complementary with either preferable for specific subgroups of depressed patients. The ideal study design for investigating the comparative efficacy of TMS and ECT requires a larger sample, better baseline matching, longer follow-up period, and a more intensive treatment protocol than used in past studies. As pointed out by another group who conducted a meta-analysis of these data, standardization of TMS stimulus parameters may play an important role in clarifying its efficacy relative to ECT.[53] The ongoing development of new TMS coils and the application of therapy with different stimulation parameters at alternate sites (eg, DMPFC, ventromedial prefrontal cortex) creates additional challenges for conducting properly controlled investigations to compare the relative effectiveness of TMS with ECT.

DURABILITY OF ACUTE TMS ANTIDEPRESSANT EFFECTS

Although numerous RCTs are assessing the acute efficacy of TMS for MDD, results from controlled trials specifically describing its durability of effect have yet to be published. A number of case series and open studies, however, rendered consistent findings, particularly when "booster" treatments with TMS are available to "rescue" patients showing evidence of clinical deterioration. In one study, 59 treatment-resistant depressed (TRD) patients who responded to an acute course of TMS were followed for 20 weeks (37 receiving maintenance TMS and 22 no additional TMS treatments).[54] At study endpoint, there was a statistically significant difference in relapse rates favoring the maintenance TMS group (ie, 38% versus 82%; hazard ratio = 0.288; confidence interval [0.124, 0.669]; $P < 0.004$). Another trial ($n = 35$) found that prophylactic "cluster" TMS sessions (ie, five treatments delivered over 2 days each month) given to patients who had responded to two prior courses of TMS (initial therapy and subsequent retreatment delivered in the face of depressive relapse) substantially increased the period of wellness and delayed the onset of future relapse.[55] A retrospective, cohort study followed 42 patients who met response or remission criteria after an acute trial of TMS for a major depressive episode (either unipolar or bipolar).[56] The authors reported that 62% maintained their acute clinical benefit over 6 months with adjunctive maintenance TMS. In a third trial, after achieving remission in the randomized controlled phase, durability of clinical benefit was assessed over 3 months following a protocol-specified TMS taper and either continued pharmacotherapy or naturalistic follow up.[57] At the end of 3 months, 29 of 50 (58%) continued in remission, 2 of 50 (4%) were partial responders, and 1 of 50 (2%) had relapsed. As a follow up to the Neuronetics' pivotal TMS study, a group of 99 patients with MDD who met criteria for at least partial response (ie, ≥25% decrease in HDRS-17 baseline score) after an acute course of TMS were transitioned to a single maintenance antidepressant medication and followed for 6 months.[58] Ten of 99 (13%) patients relapsed. Thirty-eight of 99 (38%) met prespecified criteria for symptom worsening and began retreatment with TMS. Of these, 32 of 38 (84%) re-achieved symptomatic benefit. In a 6-month, retrospective naturalistic study ($n = 204$), younger age and increased number of TMS sessions were associated with longer periods of remission.[59] In an open-label, prospective study, 16 unmedicated TRD patients initially responded to an acute course of TMS.[60] Over 4 years, this group experienced a total of 64 relapses with approximately half sustaining a clinically significant response to repeated courses of TMS. The duration of benefit from each course of TMS persisted for an average of nearly 5 months. Finally, after acute response, 10 depressed adults were provided maintenance TMS treatments with a session frequency of 1 to 2 per week, ranging from 6 months to 6 years. Seven of 10 (70%) experienced sustained marked or moderate benefit without any serious adverse events.[61]

An important issue is whether symptomatic improvement from TMS translates into higher functioning and a better quality of life.

Three other ongoing studies are also relevant. In conversation with D.L. Dunner, MD (March 2014), a 12-month, naturalistic outcome study involving 257 patients who had responded to acute TMS therapy in "real-life practice settings" was recently completed; the results are currently in press. In a second ongoing, randomized maintenance-of-effect study, unmedicated patients who responded to an acute course of TMS are receiving monthly follow-up assessments for 1 year. In addition, one group is randomized to receive a single booster TMS session each month. Either group can also receive re-introduction TMS if clinical worsening occurs. The results of this trial are also pending per conversation with D.G. Brock, MD (March 2014). Finally, a Chinese study is in progress that acutely stabilizes patients with MDD using venlafaxine and then randomizes them to three different maintenance strategies (ie, venlafaxine only; venlafaxine plus active TMS; venlafaxine plus sham TMS) over 12 months.[62]

The data reported thus far add to the evidence that individuals who initially benefitted from an acute course of TMS therapy are able to respond to TMS retreatment delivered in the context of clinical deterioration or episode recurrence at some point after completion of the acute treatment series. The ideal TMS maintenance schedule for supporting optimal durability of acute treatment response, however, has yet to be defined.

FUTURE DIRECTIONS

Although much progress has been made toward optimizing left HF-TMS as a treatment option for patients with MDD, the beneficial effects of this novel, noninvasive brain stimulation treatment can still be enhanced. Promising new strategies to improve efficacy of TMS will require verification from naturalistic trials. An important issue is whether symptomatic improvement from TMS translates into higher functioning and a better quality of life. In this context, recent outcome studies support the use of TMS for MDD.[56,63-65] Additional strategies, which may enhance the efficacy of TMS, include optimized coil placement, delivery of stimulation over alternate brain targets, further refinement of treatment parameters, deeper penetration of TMS electromagnetic fields into the cor-

tex, and development of biomarkers to predict responsivity (eg, brain-derived neurotrophic factor; functional magnetic resonance imaging).[66-68]

CONCLUSION

The results of studies with HF-TMS stimulation over the left DLPFC support a clinically relevant, acute antidepressant benefit with the first FDA-cleared TMS device for MDD when compared with a sham procedure. Preliminary data suggest that next-generation devices with alternative coil designs will be as good or better at bringing about relief of depressive symptoms. In preliminary trials, TMS' durability of effect after acute response appears substantive and is associated with improvement in functioning and quality of life. In support of the clinical utility of TMS for MDD, groups such as the New England Comparative Effectiveness Public Advisory Council have reviewed the peer-reviewed published evidence for TMS in TRD, concluded TMS was as good or better than "treatment as usual," and that TMS represents a reasonable value.[69]

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