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REVIEW

Transcranial magnetic stimulation for the treatment of major depression

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Abstract: Major depression is often difficult to diagnose accurately. Even when the diagnosis is properly made, standard treatment approaches (eg, psychotherapy, medications, or their combination) are often inadequate to control acute symptoms or maintain initial benefit. Additional obstacles involve safety and tolerability problems, which frequently preclude an adequate course of treatment. This leaves an important gap in our ability to properly manage major depression in a substantial proportion of patients, leaving them vulnerable to ensuing complications (eg, employment-related disability, increased risk of suicide, comorbid medical disorders, and substance abuse). Thus, there is a need for more effective and better tolerated approaches. Transcranial magnetic stimulation is a neuromodulation technique increasingly used to partly fill this therapeutic void. In the context of treating depression, we critically review the development of transcranial magnetic stimulation, focusing on the results of controlled and pragmatic trials for depression, which consider its efficacy, safety, and tolerability.

Keywords: electroconvulsive therapy, treatment-resistant depression, major depression, transcranial magnetic stimulation

Introduction

Depression is a major contributor to disability worldwide. Further, its management can be a challenge for even experienced clinicians. Problems begin with recognizing and properly diagnosing patients who suffer from this disorder. For example, it is estimated that about half of the individuals in the US who experience a major depressive episode annually are not diagnosed correctly. Of those who are identified and receive treatment (eg, psychotherapy, medications, or various combinations of these therapies), only about half benefit.[1] This is because many patients frequently do not receive an adequate trial of therapy to achieve sufficient symptom reduction, initially benefit but then lose this effect over time, or do not tolerate standard approaches. This problem is highlighted by the results of the National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[2] This large (n=4,040), seminaturalistic clinical trial found that after up to four aggressive treatment strategies, about one-third of patients still had not achieved remission. In summary, there is a critical need to improve the identification of depression in clinical practice and to develop alternate therapies to better manage this disorder.

In terms of alternative treatment approaches, one option is therapeutic neuromodulation, which involves the use of various devices to alter electrical activity in the central nervous system.[3] This approach is based on the premise that the brain is an electrochemical organ and therefore can be modulated by electrical as well as pharmacological

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means. While the therapeutic application of neuromodulation has primarily focused on depression, other neuropsychiatric disorders (eg, bipolar disorder, schizophrenia, pain disorders) may also benefit from this strategy.[4,5]

In the context of depression, various neuromodulation devices appear to impact areas of the brain (eg, mesocortical limbic mood circuit) implicated in its pathophysiology. The prototypic example is electroconvulsive therapy (ECT) which has been available for 75 years. Its use, however, is limited by several disadvantages, including the lack of access in many areas, adverse cognitive effects, substantial relapse rates after a successful acute treatment course, and a negative public image.[6] Further, it is usually reserved for the most severely ill patients encountered in clinical practice. Thus, there are a substantial proportion of depressed patients who are inadequately responsive to first- and second-line treatment approaches and are not ideal candidates for ECT or refuse to consider it as an option. Partly in response to this dilemma, a number of neuromodulation approaches are in development. Two such options presently cleared by the US Food and Drug Administration (FDA) for the treatment of depression are vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS). Although available since 2005, to date VNS is not widely utilized. This is in part because of the need for a surgical procedure to implant the device and the need for prolonged exposure over months to achieve the optimal results.[7] Furthermore, in the US, most insurance companies do not reimburse for this process, and eligible patients usually need to pay out of pocket, with the cost typically exceeding $25,000. In contrast, TMS, which has been clinically available since 2008, is a noninvasive procedure with over 35 randomized, sham-controlled trials supporting its benefit for the treatment of an acute major depressive episode.[8] Of note, TMS produces very few adverse effects and is usually better tolerated than medications or other therapeutic neuromodulation approaches.[9] In addition, relative to VNS and ECT, the cost of an acute treatment course in the US is lower (typically in the $10–$12,000 range); and unlike VNS, insurance companies are increasingly providing coverage.[10]

This review considers the developmental history of TMS as a treatment strategy, its basic principles, purported mechanism(s) of action, and the results of clinical trials for acute and maintenance management of major depression.

History

Galvani first performed electrical stimulation of muscles and nerve fibers in the late 18th century.[11] Subsequently, Michael Faraday discovered the principles of electromagnetic induction in 1831, giving rise to the possibility of using magnetic fields in lieu of electrical currents to stimulate nervous tissue.[12] There were, however, few attempts in the 19th century to study their effect on the brain, largely due to technological limitations that prevented the reliable generation of powerful and rapidly alternating electromagnetic fields. Thus, there was limited use of this technique in research or clinical settings until the mid-1970s. At that time, Anthony Barker started a research program at the University of Sheffield using ultrabrief magnetic pulses to stimulate the nervous tissue. In 1985, Barker et al[13] designed and built the first practical electromagnetic stimulation device for human use. The initial intention was to stimulate the spinal cord, since these researchers were concerned about the unpredictable effects of TMS on memory (personal communication, George MS. 2013). Nevertheless, TMS was eventually found to be well-suited for exploring cortical function and gained widespread use for this purpose. Mark George, who was a visiting scholar in England, first applied TMS for the treatment of depression after he moved to the National Institutes of Health (NIH) (personal communication, George MS. 2013). In 1995, the first pilot clinical trial was published reporting the results of TMS in six highly treatment-resistant depressed (TRD) patients.[14] This was followed by multiple preliminary and two large trials ultimately leading to FDA clearance of the first TMS device for the treatment of major depression in 2008.[15] A subsequent large trial with a "deep TMS" device led to its clearance in 2013.[16]

Basic principles

Based on the principle of electromagnetic induction, TMS modulates the brain's electrical environment using magnetic fields, which pass through the scalp and skull unimpeded. These fields are produced by passing rapidly alternating electrical currents through a coil with a ferromagnetic core (ie, an electromagnet in lieu of a permanent magnet). The magnetic field strength produced by TMS varies from 1.5 to 3 T and is comparable to an MRI device, except that it focuses on a limited area of the cortex using a circular, figure-eight, conical, or helmet-like coil design (eg, H-coil). TMS can be administered in single pulses or as a brief series of pulses, called a train, for research, diagnostic, and therapeutic purposes. When used clinically, several thousand pulses are usually applied over a period of minutes to hours. This is called repetitive transcranial magnetic stimulation or "rTMS". These pulses can be delivered in a rapid (ie, >1–20 Hz) repetitive fashion, enhancing cortical activity; or in a slow (ie, <1 Hz) repetitive fashion, inhibiting cortical activity. For this review, we will use the term TMS.

Stimulation parameters for major depression

There are several important parameters which can be adjusted when delivering TMS. This includes coil location, which is typically over the left or right dorsolateral prefrontal cortex (DLPFC). Motor threshold (MT) is the intensity of the magnetic field required when the coil is placed over the primary motor cortex to activate skeletal muscles. This threshold has been extensively studied as a basic neurophysiological parameter, and its determination enables practitioners to vary stimulation intensities across individuals with the aim of optimizing efficacy and minimizing adverse effects (eg, seizures).

The magnetic pulses are delivered in stimulation trains that are typically 1–5 seconds in duration. The frequency (Hz) of pulsations over this time period typically varies (eg, <1–20 Hz), with lower frequencies inhibiting and higher frequencies facilitating neuronal depolarization. An intertrain interval is utilized to allow cooling of the coil, recharging of the capacitors for the next train, and decreasing the probability of inducing a seizure.

As the safety of various TMS parameters used for treatment purposes was better understood over time, practitioners have increased the total number of pulses, the duration of the treatment, and stimulation intensities relative to the MT.[17,18] Table 1 lists the most commonly applied parameters that vary based on the specific TMS device and intended impact on neuronal activity.

Table 1 Transcranial magnetic stimulation: common treatment parameters for major depressive disorder

Parameter	Comment
Coil location	Most often: left DLPFC Less often: right DLPFC
MT	Lowest stimulus intensity over primary motor cortex to produce contraction of the abductor pollicis brevis muscle or the first dorsal interosseous muscle, assessed visually or by EMG
Stimulus pulse	
Intensity	90%–120% of MT
Duration of the pulse/	≤1 ms
Interpulse interval	50–100 ms
Frequency	HF =1–20 Hz; LF =<1 Hz; TBS =3 pulses at 50 Hz
Train duration	3–30 s (HF); 5 s–15 min (LF); 40–90 s (TBS)
Intertrain interval	20–60 s (HF); 25–180 s (LF)
Number of pulses	
HF: per session	1,500–6,000
per course	Up to 90,000
LF: per session	120–900
per course	2,400–18,000

Abbreviations: DLPFC, dorsolateral prefrontal cortex; MT, motor threshold; EMG, electromyography; HF, high frequency; LF, low frequency; TBS, theta burst; ms, milliseconds, s, seconds, Hz, hertz.

Mechanism of action

The basic physical principles of TMS and its effect on the brain at molecular, electrophysiological, and neuroimaging levels are extensively studied, and its application in experimental and diagnostic paradigms is well documented.[19] This body of research provides a plausible biological basis for the use of TMS to treat various neuropsychiatric disorders. For example, in the context of depression, there are many similar biological effects associated with response to TMS and response to ECT or antidepressant medications, suggesting that their mechanism of action is similar. As with these other treatment modalities, and in spite of the clinical evidence for efficacy, TMS' mechanism of action in depression is not clearly understood. This gap is largely due to the lack of robust pathophysiological theories of depression as a psychiatric disorder. Further, the validity of the Diagnostic and Statistical Manual of Mental Disorders' criteria for major depressive disorder has been questioned.[20] As a result, the heterogeneity in diagnosing depression contributes significantly to our limited understanding of its underlying cause(s).

The pathophysiology of depression is conceptualized at the levels of neurotransmitter action and cortical and subcortical circuits in the brain.[21] For example, animal and human studies demonstrate that increased dopaminergic transmission occurs in cortical and subcortical areas of the brain after TMS.[22,23] The current hypothesis, that led to the application of high-frequency, excitatory TMS over the DLPFC presumes an unbalanced connection between limbic regions (eg, hippocampus, amygdala, anterior cingulate, and insula) and the prefrontal cortex (PFC).[24] Brain imaging of depressed patients demonstrates decreased activity in the DLPFC, an area implicated in the dysregulation of behaviors consistent with depression (eg, appetite changes, sleep–wake cycle disruption, decreased energy level).[21] In addition, neurophysiological and positron emission tomography (PET) studies of stroke patients generated the "valence theory of emotion". Although later refuted, this hypothesis suggested a lateralization of depression-related emotions to the left hemisphere (happiness, joy, anger) and was influential in the choice to stimulate over the left PFC with high-frequency, excitatory TMS pulses.[25]

The depolarization of cortical neurons with rapid, repetitive TMS temporarily increases blood flow and metabolism in the local area under which the coil is placed. In addition, transynaptic connections impact other cortical and deeper areas of the brain. For example, when higher frequency TMS is applied over the left DLPFC, the mesolimbic "mood

neurocircuit" can be modulated. This may be accomplished through entrainment of cerebral oscillatory rhythms necessary for appropriate regional neuronal activity based on environmental demands. In contrast, selective stimulation of inhibitory interneurons and subsequent hyperpolarization with lower frequency TMS over the right DLPFC could lead to a decrease in local neuronal activity and may also produce antidepressant effects. In this scenario, it is possible that inhibition of linked cortical and subcortical networks may alter blood flow to limbic structures such as the amygdala, an area often implicated in the modulation of anxiety and fear, which are prominent features of many depressive episodes.

Biological markers

More recent research utilizing both brain imaging and TMS points to the connection between the anterior cingulate cortex and the DLPFC.[26] These areas are strongly "anticorrelated" in depression, where overactivity of the anterior cingulate and hypoactivity of the DLPFC occur. In this context, a positive response to treatment with TMS was predicted by this correlation and holds the promise of using imaged-based, individualized treatment parameters in the future.[27]

A comprehensive and detailed review of neurobiological changes observed in animal and human brains caused by TMS is beyond the scope of this article. A recent, systematic review of biological markers in TMS and depression can be found in Fidalgo et al's paper.[28] The authors reviewed more than 50 studies, over half of which utilized neuroimaging methods in addition to clinical outcome measures of depression. They found that neuroimaging studies using various techniques (eg, fMRI, PET, SPECT, MTS) showed the most robust correlations with clinical outcomes, followed by the brain-derived neurotropic factor and cortical excitability studies. Such correlations were not as consistent for other markers such as thyroid stimulating hormone or electroencephalogram (EEG) activity. Contrary to changes observed in TMS animal studies, this review found no significant clinical correlations involving dopamine, serotonin, and saccadic eye movements.

TMS clinical trials for treatment of major depression

Types of trials

Initial studies of TMS for major depression included promising case reports, case series, and small open-labeled trials. This led to more definitive, larger sham-controlled trials with TMS as either a monotherapy or augmentation therapy. The latter is particularly important since a combined approach using different modalities is often required for TRD. In addition, there are several, nonblinded, randomized, and nonrandomized studies which compare the acute effects of TMS versus ECT. Finally, there are a number of pragmatic outcome studies which consider the acute and long-term efficacy of TMS in real-world situations.

TMS sham-controlled monotherapy trials

There are now several sham-controlled trials that vary in terms of their quality, which consider TMS monotherapy in the management of TRD. Multiple systematic reviews and meta-analyses have summarized their results (Table 2). Most recently, Gaynes et al[29] identified 18 trials (n=1,970) which met their criteria for good or fair quality. They reported that active TMS was superior to the sham procedure on all three of their major outcomes: severity of depressive symptoms; response rate; and remission rate. Thus, active TMS averaged more than a 4-point greater decrease in Hamilton Depression Rating Scale (HDRS) scores compared with the sham procedure. Further, those receiving active TMS were three times more likely to achieve response and five times more likely to achieve remission compared with the sham group. The authors concluded that for patients with major depression who have failed two or more adequate antidepressant medication trials, TMS represents a reasonable, effective alternative. They also recommend comparative studies with alternate treatments such as ECT or medication combinations to further clarify the role of TMS in TRD. Finally, they recommend longer maintenance trials to assess the durability of acute TMS benefit.

TMS sham-controlled augmentation trials

Liu et al[30] also recently published the first meta-analysis of studies that used TMS as an augmentation strategy in TRD. They identified seven randomized sham-controlled trials which met their criteria for inclusion. The total sample size was 279 (171 in the TMS group; 108 in the sham group). The pooled response rates for active TMS compared with the sham procedure were 46.6% and 22.1%, respectively (OR =5.12; 95% CI =2.11–12.45; z =3.60; $P<0.0003$). Active TMS was also superior to the sham procedure in terms of change in baseline HDRS scores (ie, pooled standardized mean difference was 0.86; $P<0.00001$). The authors concluded that TMS augmentation was significantly superior to a sham condition for TRD. However, given the small number of studies and heterogeneity in subgroup analyses,

Table 2 Meta-analyses assessing the efficacy of TMS for major depressive disorder

Author(s)	N = studies	n = patients	Results	Study conclusions
McNamara et al[59]	N=5	n=81	NNT =2–3 (1.6 to 4.0)	TMS had demonstrable effects in treating major depression
Holtzheimer et al[60]	N=12	n=264	ES =0.81 (0.42 to 1.20)	TMS is statistically superior to sham procedure for depression
Kozel et al[61]	N=12	n=230	ES =0.53 (0.24 to 0.82)	TMS produced statistically significant ES and measurable clinical improvement
Burt et al[62]	N=23	n=432	ES =0.62	Antidepressant effect is robust statistically; effect sizes are heterogeneous
Martin et al[63]	N=14	n=372	SMD =–0.35 (–0.66 to –0.04)	No strong evidence for benefit
Couturier[64]	N=6	n=91	Weighted mean difference =–1.1 (–4.5 to 2.3)	TMS is no different than sham procedure in MD; the power within these studies to detect a difference was generally low
Hermann and Ebmeier[65]	N=33	n=877	ES =0.71 (0.45 to 0.97)	TMS was more effective than sham procedure, but variability was too great to take any single study design as paradigmatic
Gross et al[66]	N=5	n=274	ES =–0.76 (–1.01 to 0.51)	Recent TMS trials had larger effect sizes compared with earlier trials
Lam et al[67]	N=24	n=899	ES =0.48 (0.28 to 0.69) Response: NNT =6 Remission: NNT =7	TMS is superior to sham procedure in treatment of acute TRD
Schutter[68]	N=30	n=1,164	ES =0.39 (0.25 to 0.54) ($P<0.0001$)	HF-TMS over the left DLPFC is superior to sham procedure
Slotema et al[69]	N=34	n=1,383	ES =0.55 ($P<0.001$)	HF-TMS is superior to sham procedure
Berlim et al[70]	N=8	n=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 MD and similar to left HF-TMS
Berlim et al[71]	N=29	n=1,371	Response: OR =3.3 ($P<0.0001$); NNT =6 Remission: OR =3.3 ($P<0.0001$); NNT =8	Left HF-TMS was superior to sham procedure
Gaynes et al[29]	N=18	n=1,970	4.53 point differential decrease in HDRS; NNT =5 for remission and 9 for response OR =5.07 (*P*-value NR; 95% CI =2.5–10.3)	Active monotherapy TMS was superior to the sham procedure on all three major outcomes
Liu et al[30]	N=7	n=279	46.6% (active) versus 22.1% (sham) response rates	Active adjunctive TMS led to a 2-fold higher response rate that was significantly better than the sham procedure

Abbreviations: NNT, number needed to treat; TMS, transcranial magnetic stimulation; ES, effect sizes; SMD, standardized mean difference; MD, major depression; TRD, treatment-resistant depression; HF-TMS, high frequency TMS; OR, odds ratio; LF-TMS, low-frequency TMS; HDRS, Hamilton Depression Rating Scale; NR, not reported; CI, confidence interval, DLPFC, dorsolateral prefrontal cortex.

they suggest more rigorously designed trials are needed to confirm this observation.

Critical studies

Among the randomized sham-controlled studies, four stand out due to their size and clinical implications. The first two studies used a research version of the Neuronetics device and included 491 patients (301 and 190, respectively). Both involved only nonmedicated TRD patients who were randomized to either active or sham TMS.[31,32] These studies also differed from others in their use of more aggressive treatment parameters based on the safety record obtained from previous trials and earlier analyses suggesting that these parameters improved clinical outcomes. The most relevant of these parameters were coil placement over the left DLPFC; a frequency of 10 Hz; stimulation intensity at 120% MT; 4-second pulse trains; 26-second intertrain intervals; and up to 90,000 pulses delivered over 30 sessions. Moreover, blinding was improved in both the studies by designing and using more convincing sham treatments. For instance, the NIH-sponsored study also included electrical stimulation of the scalp to mask any differences in sensations produced by the active and sham TMS procedures.[32] The results of the two trials aligned surprisingly well. For example, based on improvement in the HDRS-24 scores, rates of remission were approximately 5% for the sham procedure and 15% for active TMS in both trials. Further, tolerability and safety were comparable between the two studies (eg, no suicides,

no seizures, no cognitive adverse effects, low dropout rates due to adverse effects).

The third large (n=212) RCT utilized a novel coil design (ie, H-coil) coupled to a Magstim stimulator.[33] This system produces strong magnetic fields that penetrate deeper into the brain.[34] The results of this study were presented to the FDA which cleared this system for the treatment of major depressive disorder in patients who failed at least one adequate antidepressant medication trial.[16] In this double-blind, sham-controlled study, coil placement was over the medial and lateral PFC and treatment parameters included an 18 Hz frequency, stimulation intensity of 120% MT, 1,980 pulses per session given over a 20.2 minute duration, and administration 5 days a week with a total of 20 sessions. The sham procedure involved the use of inverse currents, which produced negligible magnetic fields. After the acute treatment phase, patients were treated twice weekly for an additional 12 weeks during a maintenance phase. Based on HDRS-21 change scores, TMS significantly separated from the sham procedure (ie, a 6.39- versus a 3.28-point decrease; $P<0.008$). Further, the response rates (37.0% versus 27.8%; $P<0.03$) and remission rates (30.4% versus 15.8%; $P<0.016$) were significantly different between active and sham coil treatments. Common adverse effects were stimulation-site pain and jaw pain. One seizure (confounded by heavy alcohol use) was reported, and no cognitive adverse effects were observed.

Finally, the fourth large (n=170) multicenter sham-controlled trial conducted at 18 sites in France compared low-frequency TMS to venlafaxine (VEN) for TRD.[35] The study included three arms: active TMS plus VEN, active TMS plus placebo tablets, and sham TMS plus VEN. The active TMS group received daily stimulations over the right DLPFC at 1 Hz frequency; 120% MT intensity; 8.5 minute durations; and a total of 360 pulses per day for 2–6 weeks. The mean VEN dose was 179.0 (±36.6) mg per day. Based on the primary outcome, all groups achieved a comparable number of remitters. Since TMS alone was comparable to the combination and VEN-only groups, the authors suggested it may be a useful alternative in this population.

TMS versus ECT

ECT is considered the most effective treatment available for more severe episodes of depression. There are, however, a number of limitations associated with ECT, including a lack of availability in many areas, significant short-term cognitive adverse effects, poor durability of effect in a substantial proportion of acute responders, patients' reluctance to accept this treatment, and its cost. In this context, TMS is often considered as a potential substitute for or a complementary treatment with ECT.

There are several trials directly comparing these two approaches, primarily for patients deemed clinically appropriate for ECT (Table 3). In this context, two recent systematic reviews and meta-analyses considered the randomized trials comparing the relative benefit of TMS with ECT for the acute management of more severe depressive episodes.

Micallef-Trigona[36] reported the first meta-analysis of such a comparison which included nine trials (n=384). The author found that this primarily treatment-resistant group of patients experienced significant reductions in depressive symptoms from baseline as measured by the HDRS. Specifically, the TMS group had an average reduction of 9.3 points and the ECT group, an average reduction of 15.4 points. When comparing the two treatment modalities, however, the ECT group experienced a significantly greater point reduction ($P<0.011$). Overall, the mean effect size was 1.33 for TMS and 2.14 for ECT. The authors concluded that while ECT was superior to TMS, at least some patients who might otherwise be referred for ECT could potentially benefit from TMS as an alternative. Further, they opined that the ultimate role for TMS in more severe depression depends in part upon technological and logistical advances in its administration.

A second systematic review and meta-analysis by Ren et al[37] included nine trials (n=425). The authors reported that ECT was superior to high-frequency TMS when psychotic depressed patients were included, both in terms of response ($P<0.03$) and remission ($P<0.006$); but that ECT and high frequency TMS were comparable in the nonpsychotic depressed group. Of note, overall discontinuation rates were low (ie, ~9%) and did not differ between the two treatment groups. Adverse cognitive effects (eg, visual memory, verbal fluency) were more common in the ECT group. The authors called for more good quality trials to assess the long-term outcome between these two treatments, especially in terms of cognitive effects. They also noted that more work is needed to optimize the stimulus delivery with TMS.

One positive, pilot study also found TMS in combination with ECT (versus ECT alone) for acute treatment of depression reduced the number of ECT sessions required, thus minimizing adverse effects (eg, cognitive).[38] Preliminary data and increasing clinical experience also suggest a potential maintenance role with TMS after a successful acute trial of ECT.[39]

Table 3 Randomized clinical trials comparing ECT and TMS

Author(s)	Results by primary outcome		
	ECT (%)	TMS (%)	Primary outcome and comments
Randomized			
Grunhaus et al[72]	16/20 (80%)	9/20 (41%)	Response criteria: HDRS-17 (≥50%); GAS (≥60) TMS comparable to UND/BL-ECT in nonpsychotic MD subgroup
Pridmore et al[73]	11/16 (69%)	11/16 (69%)	Remission criteria: HDRS-17 (≤8) TMS at 100% MT given in unlimited numbers was comparable to UND-ECT
Janicak et al[74,75]	6/14 (43%)	7/17 (41%)	Response criteria: HDRS-24 (≥50%; ≤8) TMS was comparable to BL-ECT in patients with MD or bipolar depression
Grunhaus et al[72]	12/20 (60%) 6/20 (30%)	11/20 (55%) 6/20 (30%)	Response criteria: (HDRS-17 ≥50%; GAS ≥60) Remission criteria: (HDRS-17; ≤8) TMS comparable to UND-ECT in nonpsychotic MD
Rosa et al[76]	6/15 (40%)	10/20 (50%)	Response criteria: HDRS-17 (≥50%) No difference in response rates between TMS and UND/BL-ECT in nonpsychotic MD
Eranti et al[77]	13/22 (59%)	4/24 (17%)	Remission criteria: HDRS-17 (≤8) UND/BL-ECT superior to TMS (mean number of 14 treatment sessions)
Keshtkar et al[78]	68% (n=40)	29% (n=33)	HDRS-24: percentage improvement from baseline BL-ECT and HF-TMS (total pulses per course =4,080) significantly improved baseline depression scores, but ECT was superior to TMS
Hansen et al[79]	26% higher (n=30)	(n=30)	HDRS-17: percentage achieving at least partial remission UND-ECT significantly better than LF-TMS ($P<0.04$)

Abbreviations: ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale; GAS, global assessment scale; UND-ECT, unilateral nondominant ECT; BL-ECT, bilateral ECT; MT, motor threshold; MD, major depression; HF-TMS, high-frequency TMS; LF-TMS, low-frequency TMS.

TMS outcomes studies

These trials were conducted to assess the durability of antidepressant benefits after a successful, acute TMS course. They can be divided into follow-up studies after response to acute TMS in controlled trials or follow-up studies after response to acute TMS in clinical practice settings. Of note, these studies employed reintroduction of TMS sessions when required, in addition to standard maintenance therapies involving medication and psychotherapy.

The first, large-scale, semi-controlled outcome study involved patients who were considered at least partial responders (ie, at least a 25% decrease in their baseline HDRS scores) after acute treatment in the pivotal trial that led to FDA clearance of the first TMS device for treatment of depression.[40] In this study, patients (n=99) were initially tapered from their 5-day-per-week TMS schedule over a 3-week period, while simultaneously being titrated up on a single antidepressant medication for maintenance purposes. Over the next 6 months, they were regularly assessed for early signs of depression relapse. If this occurred, they then received additional TMS treatments to regain mood stability. At the end of the 6-month trial, 10 (13%) of the patients had relapsed. Thirty-eight (38%) met criteria for symptom worsening and were retreated with reintroduction TMS sessions (mean ~14 additional treatments). Thirty-two (84%) of this pending relapse group were able to reachieve symptomatic stability. In a second follow-up study, 50 patients who had achieved remission during the acute phase of the NIH-sponsored optimised TMS trial were then followed for 3 months.[41] After TMS taper and either continued pharmacotherapy or naturalistic follow-up, 29 (58%) maintained remission; two (4%) maintained partial response; and one (2%) relapsed.

The results of a recent controlled maintenance trial is reported only in abstract form presently.[42] A medication-free TRD group (n=67) received an acute course of TMS. Responders were then randomized to 12 month follow-up assessments with or without a scheduled prophylactic TMS session at each visit. Patients in either group could also receive acute reintroduction TMS treatments if they met predefined criteria for worsening. About two-thirds of these patients achieved remission during the acute TMS treatment phase. After 1 year, based on the proportion of patients without symptomatic worsening, there was a trend favoring the monthly TMS prophylactic treatment group. These preliminary results indicate that TMS monotherapy for both acute and maintenance purposes may be a viable strategy in some patients.

Several studies report the outcome in depressed patients who received an acute trial of TMS in routine clinical practice and were then assessed after varying periods of time for ongoing benefit. For example, one trial (n=59)

followed TRD patients who benefited from an acute course of TMS for 20 weeks.[43] Thirty-seven of these patients received maintenance TMS and 22 received no additional TMS treatments. At the end of this period, 82% of patients without TMS maintenance treatment had relapsed versus only 38% who received maintenance TMS ($P<0.004$). In another retrospective report, the authors assessed 42 patients who initially responded or remitted after an acute trial of TMS for their unipolar or bipolar depressive episode.[44] In this group, 62% experienced continued benefit over a 6-month period while receiving adjunctive maintenance TMS.

In the largest pragmatic study to date, Dunner et al reported the outcome in 257 TRD patients who successfully completed an acute TMS course and agreed to follow-up over 52 weeks.[45–47] Patients received ongoing maintenance medication as per clinician's discretion and also had the option to receive reintroduction TMS if they demonstrated worsening of symptoms. Of the 120 patients who met response or remission criteria at the end of their acute TMS treatment course, 75 (62.5%) continued to meet response criteria throughout the 1-year period. The authors concluded that TMS demonstrated both a statistical and clinically meaningful durability of acute benefit over 12 months.

Patient selection for TMS

Based on the results of the aforementioned clinical trials as well as existing clinical experience, the optimal patient for TMS appears to be someone whose depressive episode has lasted 3 years or less; has failed between one and four adequate antidepressant trials (both medication and psychotherapy); and does not have psychotic features.

TMS safety and tolerability

The overall effectiveness of any treatment must consider both its efficacy as well as any safety and tolerability issues. In this context, TMS appears to be a relatively safe and reasonably well tolerated treatment.[9,18] Adverse effects associated with this therapeutic approach involve a number of localized problems at the site of the coil placement. The most common problem includes application site discomfort or pain. This occurs as a result of the intense magnetic pulses applied over the DLPFC. While approximately 50% of patients will experience this problem, most acclimate in a relatively short time period. To help patients manage this discomfort, various parameters can be adjusted, usually temporarily. This includes lowering the stimulation intensity, altering the coil rotation or angle, or slightly changing its location. Because of the rich innervation in this area, stimulation of certain nerve branches (eg, trigeminal nerve) can cause contraction of the muscles around the eye, sensations in the nose and the teeth, or tearing. These occur while the stimulations are being delivered and rarely persist afterwards. Due to muscle contractions, tension-like headaches also occur in about half of patients. Typically these are mild-to-moderate in severity and gradually subside over the first several treatment sessions. The use of analgesics (eg, aspirin, acetaminophen, ibuprofen) as a pretreatment may preclude the headaches or be used to manage them when they occur.

The most serious potential adverse effect is an inadvertent seizure. The incidence appears to be approximately 0.1% over an entire course of TMS treatments. This compares favorably to the incidence of seizures with many medications used to manage depression. Reported seizures have always occurred while the patient was receiving a treatment, resolved spontaneously with supportive therapy, and did not result in any long-term neurological or medical complications. In the two largest studies to date, which used aggressive treatment parameters, no seizures occurred.[9,31,32] In the deep TMS study, one seizure incident was reported.[33] As a result, a prior history of seizures is a relative contraindication to the use of TMS. Further, care must be taken to avoid situations where multiple medications which can lower the seizure threshold are combined with TMS treatments to assure that the coil is placed sufficiently anterior to the motor cortex, to avoid periods of sleep deprivation, to minimize the use of alcohol or other substances, and to minimize any significant changes in diet and fluid intake which could alter the MT.

Future directions

In addition to investigating biological markers of TMS response as mentioned earlier, there are several ongoing projects to further refine the application of TMS to achieve therapeutic enhancement. Below we summarize some of these developments.

Multiple magnets (Cervel Neurotech)

This investigational device has multiple coils that utilize a spatial summation technology to directly stimulate deeper structures and achieve higher circuit-level specificity in the brain. Although unpublished, the company reports that the pilot clinical trials to date have produced positive statistical and clinically relevant results.[48,49]

Theta burst stimulation

Rather than a different magnet design or configuration, this is a modification of pulse parameters utilizing high and low frequencies in the same stimulus train by applying a very high (50 Hz) frequency magnetic field in a very brief burst, which has its own frequency of 4–7 Hz (hence, theta) (ie, three 50 Hz bursts delivered five times a second). This is modeled after animal studies, exploring the firing patterns of hippocampal neurons and long-term depression and long-term potentiation mechanisms. When administered continuously (ie, cTBS), this stimulus pattern is similar to slow TMS (1 Hz), and when delivered intermittently (ie, 8 second pauses between bursts), it is similar to rapid TMS (10–20 Hz). Pilot clinical studies in humans for the treatment of depression have generated initial positive results.[50,51] Although there are no direct comparison studies yet, TBS may provide the same clinical benefits as TMS but with shorter treatment sessions and lower magnetic intensities.[52]

TMS phase and frequency coupled to EEG (Neosync)

This device utilizes low magnetic fields produced by rotating spherical, rare earth magnets that synchronize with the patient's frontal alpha EEG frequency as measured by the device.[53] Hypothetically, this can entrain the oscillatory rhythm of the mood-related brain circuitry.

Improved consistency and precision of coil placement with structural MRI

Current TMS treatment protocols determine the coil placement over the DLPFC based on approximate measurements, which rely on the primary motor cortex homunculus or 10–20 EEG coordinate standards. There are TMS devices, however, which incorporate sophisticated MRI-based navigation within their designs and are used in preneurosurgical mapping of the cortex (motor and speech centers).[54] The role of individualized and enhanced precision of coil placement is as yet unknown and may not be critical for treatment efficacy with the current protocols. This approach, however, may gain importance in the treatment of much younger individuals and when more focal coil designs are accomplished in the future.

Direct comparison of TMS modalities and devices

While different coil designs, devices, and treatment parameters continue to evolve, clinicians will be challenged in making risk–cost–benefit analyses to decide which treatment modality is optimal. While difficult to perform, direct comparisons of these modalities will be critical to understand the differences and similarities of these devices in clinical practice. This type of research may also improve our understanding of the mechanisms of action and subtypes of depression.

In this context, there are several small studies comparing high frequency, left-sided TMS with low frequency, right-sided TMS.[55] They suggest these two modalities are beneficial without a dramatic difference in efficacy. To date, however, the largest sham-controlled studies involve the use of high frequency left-sided treatment. Based on the existing data, low frequency right-sided treatment may be preferred in patients at higher risk for seizures. These studies also suggest that the session duration could be shortened with low frequency right-sided treatment.

Direct inhibition of anterior cingulate cortex

Several imaging studies suggest that overactivity of the anterior cingulate is highly correlated with major depression. Current devices barely reach this region and likely affect it indirectly through synaptic connections. This brings up the testable hypothesis that directly inhibiting the activity of the anterior cingulate cortex with TMS coils which can reach and focus on this region may improve clinical outcomes.

Simultaneous combination with active (psychotherapy, task performance) and/or other passive treatments (bright light therapy, ketamine)

TMS is a passive treatment from the point of view of the patients. Vedeniapin et al[56] published a case report indicating that CBT during TMS for depression is feasible and may produce an additive effect. In addition, in a sham-controlled single-blind trial, Hoy et al[57] exposed ten healthy study participants to affective stimuli while they were being administered a single session TMS, which suggested that short duration TMS did not alter the mood of healthy subjects. In addition to active tasks, other passive treatments such as light therapy and ketamine infusions could be combined with and potentially enhance the antidepressant effects of TMS.

A multisite study is also currently under way for the treatment of Alzheimer disease.[58] This trial combines domain-specific task performance with TMS over different regions of the cortex.

Serial combination with other neuromodulation treatments (ECT, tDCS)

Another combination strategy may be to sequentially perform other brain stimulation treatments such as ECT[38] or transcranial direct cortical stimulation (tDCS) with TMS.

Conclusion

In summary, TMS is a promising, novel antidepressant treatment still relatively early in its development. Its efficacy and safety have improved significantly with continued research and clinical experience. The effect size for TMS antidepressant efficacy is at least comparable to those of antidepressant medications even though studies included only treatment-resistant or treatment-intolerant depressed patients. To date, this evidence base satisfies the critical thresholds for FDA clearance and approval of coverage by most third-party payers in health care. Further, there is a signal that TMS may benefit certain subgroups of patients who previously would be referred for ECT. Finally, the durability of TMS' antidepressant benefit and safety and tolerability profile make it an attractive treatment option for selected patients. Although TMS is labor intensive compared with medications, its efficacy, safety, and tolerability for depression and possibly other disorders are driving additional research to refine and improve its therapeutic potential.

Disclosure

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