



# What's new in transcranial magnetic stimulation

## Recent developments have enhanced the benefits of this treatment

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**T**herapeutic neuromodulation takes advantage of the brain's electrochemical makeup. This allows for treatment devices that modulate neurocircuits relevant to behaviors disrupted in disorders such as major depressive disorder (MDD) (eg, sleep quality, appetite, cognitive, and executive functions). The default mode network (comprised of structures such as the medial prefrontal cortex [MPFC], the posterior cingulate cortex, the hippocampus, and their functional connectivity) serves as a prime example of circuitry that can be targeted by this approach.<sup>1</sup>

For 80 years, electroconvulsive therapy (ECT) has been an important neuromodulation option for patients with more severe illness. Recently, additional neuromodulatory approaches have been FDA-cleared, including transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). Another approach, transcranial direct current stimulation (tDCS), has been extensively studied for its potential clinical utility but is not FDA-cleared. The *Table (page 12)* provides descriptions of these therapies.

Since being cleared by the FDA in 2008, TMS has arguably made the greatest strides in providing an alternate neuromodulation treatment option for patients with MDD, with >1,000 centers nationally and 7 TMS devices FDA-cleared for treatment of depression. In this article, we review recent developments in TMS.

### An evolving therapeutic option

While primarily studied as a monotherapy for MDD, in clinical practice TMS (*Box, page 13*) is typically used as an adjunct to medication and psychotherapy.<sup>2,3</sup> In this context, it has demonstrated efficacy for



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### Clinical Point

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### Table

## Therapeutic neuromodulation for psychiatric disorders

Treatment	Description	Clinical application
Deep brain stimulation	Invasive “functional neurosurgical” procedure that uses electrical current to directly modulate specific areas of the CNS	Depression Dystonia <sup>a</sup> Obsessive-compulsive disorder <sup>a</sup> Parkinson’s disease <sup>a</sup>
Magnetic seizure therapy	Intense, high-frequency magnetic pulses sufficient to induce a seizure	Depression
Transcranial direct current stimulation	Sustained, low-intensity, constant current flow usually passing from anode to cathode electrodes placed on the scalp	Depressed mood Anxiety Other symptoms (eg, attention/concentration problems)
Transcranial magnetic stimulation	Intense high- or low-frequency magnetic pulses produce neuronal excitation or inhibition	Depression <sup>a</sup> Migraine <sup>a</sup> Obsessive-compulsive disorder <sup>a</sup> (DTMS) Posttraumatic stress disorder Schizophrenia Substance use disorders Tinnitus
Vagus nerve stimulation	Intermittent mild electrical pulses delivered to the left vagus nerve, whose afferent fibers affect structures such as the locus ceruleus and raphe nucleus	Depression <sup>a</sup> Epilepsy <sup>a</sup>

<sup>a</sup>FDA-cleared indication  
DTMS: deep transcranial magnetic stimulation

more difficult-to-treat mood disorders with an excellent safety and tolerability profile whether used with or without medication.<sup>4-6</sup>

To further improve the efficiency and efficacy of TMS while maintaining its safety and tolerability, researchers and clinicians have been exploring a few initiatives.

### Altered treatment parameters

One initiative is assessing the feasibility of altering various treatment parameters, such as the total number of treatment sessions (30 to 60 sessions); the frequency of sessions (eg, more than once daily); the total number of magnetic pulses per session (eg, >3,000); the stimulation coil localization (eg, left vs right dorsal lateral prefrontal cortex [DLPFC]; MPFC; and various methods to determine optimal coil placement (eg, EEG F3 coordinate or MRI-guided neuro-navigational methods). Such refinements offer the potential for

enhanced efficacy, shorter treatment sessions, and/or improved tolerability. For example, lower frequency right DLPFC stimulations (eg, 1 Hz) can decrease the risk of seizures and improve overall tolerability. While this has not been studied as extensively as higher frequency left DLPFC stimulations (eg, 5 to 20 Hz), existing evidence supports similar efficacy between these 2 approaches.<sup>7</sup>

**Theta burst stimulation.** Some TMS devices can be adapted to deliver theta burst stimulation (TBS). This produces trains of triple, 50 Hz, pulsed bursts (usually with 200 ms inter-burst intervals occurring at a rate of 5 Hz; at 80% MT) to model naturally occurring theta rhythms. These bursts can be administered in stimulation protocols using intermittent TBS (iTBS) (eg, 10 bursts of triplets over 2 seconds every 10 seconds; 30 pulses per burst; for approximately 3 minutes; totaling 600 pulses) or continuous TBS

(cTBS) bursts given in an uninterrupted train (eg, 40 seconds, 600 pulses). Evidence indicates these protocols facilitate long-term potentiation (ie, iTBS) and long-term depression (ie, cTBS), which in turn can modulate synaptic plasticity.

While some clinicians are using TBS off-label, a recent non-inferiority trial (N = 395) reported similar efficacy and safety comparing standard 10 Hz TMS to an iTBS protocol at 120% of resting motor threshold (both over the left DLPFC).<sup>8</sup> This has led to FDA clearance of the TMS device adapted to provide iTBS in this trial.<sup>8</sup>

From a more practical perspective, TBS has the potential to reduce the number of pulses (eg, 600 vs 3,000) and the total number of sessions required, as well as the duration of treatment sessions (eg, 37.5 minutes to <5 minutes). This can accelerate the time to response and decrease patient and staff commitment, with resulting cost savings.<sup>9</sup> Despite this recent progress, ongoing research still needs to clarify issues such as the risk/benefit profile, particularly in younger and older populations, as well as assessment of duration of initial benefit and appropriate maintenance strategies.

### New devices

Another initiative is the development of alternative TMS equipment. For example, newer coil designs with enhanced cooling ability allow for a substantial decrease in the required inter-train interval duration between stimulation trains, thus shortening the total session duration by approximately 50% (eg, from 37.5 to 19 minutes). The use of different coil arrays (eg, the H-coil capable of deeper vs surface stimulation) may allow for more direct stimulation of relevant neurocircuitry (eg, cingulate cortex), possibly improving efficacy and shortening time to onset of benefit. However, in head-to-head comparisons with single-coil devices, enhanced efficacy for depression has not been clearly demonstrated. One caveat is that the increase in depth of magnetic field penetration results in a loss of focality, resulting in the stimulation of larger brain areas. This might increase the risk of adverse effects such as seizures.

#### Box

### Key points: Transcranial magnetic stimulation

- Transcranial magnetic stimulation (TMS) utilizes intense, localized magnetic fields to alter activity in neural circuits implicated in the pathophysiology of depression
- Randomized, sham-controlled acute trials have demonstrated the efficacy of TMS for treatment-resistant depression
- Clinical availability of TMS has grown steadily over the past 10 years as >1,000 centers have been opened and additional devices have been FDA-cleared
- TMS has the potential to avoid safety and tolerability concerns associated with antidepressant pharmacotherapy (eg, weight gain, sexual dysfunction) and electroconvulsive therapy (eg, cognitive deficits)
- Greater sophistication in the choice of stimulation parameters, as well as other ongoing efforts to optimize the benefits of TMS, are yielding better clinical outcomes

### Increasing durability of effect

Because high relapse and recurrence rates compromise the initial benefit of any antidepressant therapy, appropriate maintenance strategies are essential. Several studies have evaluated strategies to maintain the acute benefit of TMS for treatment-resistant depression.

One was a 6-month, open-label TMS durability of effect trial for acute responders (n = 99) in the pivotal registration study.<sup>5</sup> During this study, all participants were given antidepressant medication monotherapy. In addition, with early indication of relapse, patients received a reintroduction of TMS sessions (32/99 patients; mean number of sessions = 14.3). With this protocol, approximately 84% re-achieved their response status. The overall relapse rate was approximately 13%.<sup>5</sup>

In a 1-year naturalistic study, 63% of patients (75/120) who met response or remission criteria after an acute course of TMS still met response criteria after 12 months. These patients received clinician-determined maintenance treatment that included reintroduction of TMS when indicated.<sup>3</sup>

In a prospective, 12-month, multisite, randomized pilot study, 67 patients with

### Clinical Point

**Newer coil designs allow for shortening the total session duration by approximately 50%**



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### Clinical Point

**TMS may achieve similar efficacy as ECT with fewer cognitive adverse effects**

treatment-resistant MDD underwent an antidepressant medication washout and then received 30 sessions of TMS monotherapy.<sup>10</sup> Those who met criteria for improvement ( $n = 49$ ) were then randomized to once-monthly TMS or observation only. All patients remained medication-free but could receive TMS re-introduction if they deteriorated. At the end of the study, both groups demonstrated comparable outcomes, with a trend to a longer time before relapse among participants who received once-monthly TMS. Although these results are preliminary, they suggest that some patients could be treated both acutely and then maintained with TMS alone.

Re-introducing TMS in patients who show early signs of relapse after having an initial response achieves rates of sustained improvement that compare favorably with those of other strategies used to manage patients with treatment-resistant depression.

### TMS vs ECT

The question often arises as to whether TMS is a viable alternate treatment to ECT. I believe the answer is unequivocally yes and no. By this, I mean some patients who in the past only had ECT as their next option when medications and psychotherapy were insufficient may now consider TMS. In support, there is evidence of comparable efficacy between TMS and ECT in a subgroup of patients who were considered clinically appropriate for ECT.<sup>11-13</sup>

How to best identify this group remains unclear, but investigators are exploring predictive biomarkers. For example, a large study ( $N = 1,188$ ), with functional magnetic resonance imaging (fMRI) reported that depressed patients could be divided into 4 neurophysiological "biotypes" based on different patterns of aberrant connectivity in limbic and fronto-striatal networks.<sup>14</sup> The authors further noted that such distinctions were helpful in predicting response in a subgroup of patients ( $n = 154$ ) who received TMS.

For now, experience indicates certain clinical factors may provide some guidance. Patients are usually better served by ECT if they:

- have depressive episodes of longer duration (eg,  $>3$  years)
- have a high risk of suicide
- have psychotic or catatonic features associated with their depression
- have difficulty maintaining their physical well-being
- have bipolar depression.

Although existing evidence supports a possible benefit with TMS for bipolar depression (used in combination with a mood stabilizer), the lack of a definitive trial (precluding FDA clearance for this indication) and the lack of insurance coverage both limit the routine use of TMS for this indication.<sup>15</sup>

One potential advantage of TMS over ECT is a lower cost.<sup>13</sup> Transcranial magnetic stimulation also may make it possible to achieve similar efficacy as ECT with fewer cognitive adverse effects when used in combination with ECT to reduce the number of acute ECT treatments required or as part of a maintenance strategy after a patient experiences an acute response to ECT.<sup>13</sup>

### Magnetic seizure therapy (MST) vs ECT.

An experimental treatment, MST uses a TMS device capable of producing more intense magnetic fields sufficient to induce a seizure.<sup>16</sup> The advantage of MST over ECT-induced seizures is better control of intra-cerebral current path and density, thus avoiding deeper cortical areas associated with memory (eg, hippocampus) and minimizing cognitive adverse effects. As with ECT, however, anesthesia and muscle relaxation are required. Presently, MST remains investigational.

### Other potential indications

In addition to MDD, TMS is also being studied as a potential treatment for other neuropsychiatric disorders.

### Obsessive-compulsive disorder (OCD).

A recent double-blind study that evaluated a deep TMS (DTMS) device reported a significantly better outcome based on the Yale-Brown Obsessive-Compulsive Scale score with active high-frequency (20 Hz) DTMS ( $n = 18$ ) vs a sham control ( $n = 15$ ).<sup>17</sup> The

initial benefit persisted up to 1 month after the end of treatment. The authors speculated that this benefit may be due to direct modulation of the anterior cingulate cortex. These results led to the first FDA clearance of a deep TMS device for treating OCD.

**Cognition.** Because TMS does not require a seizure to produce its antidepressant effect and does not require anesthesia, the risk of neurocognitive disruption is low. In fact, evidence suggests TMS may have beneficial cognitive effects.<sup>18</sup>

In an effort to take advantage of this benefit, researchers have explored providing psychoeducation and psychotherapy sessions (eg, behavioral activation) during TMS treatments (“online”).<sup>19,20</sup> The rationale is that neurocircuitry subserving various cognitive functions may be in a heightened state of receptivity during a TMS treatment, which would allow patients to assimilate and better utilize the therapeutic information provided.<sup>19,20</sup>

Researchers are also looking at the use of TMS to treat patients with mild cognitive impairment or early dementia. These patients often experience comorbid depression, and TMS could potentially improve memory via both its pro-cognitive and antidepressant effects.<sup>1</sup> The lack of effective treatments for dementia supports pursuing TMS as a therapeutic option for these patients.

**Other neuropsychiatric disorders.** In addition to early-onset cognitive problems, other neurologic indications with promising data for TMS include chronic pain syndromes, Parkinson’s disease, tinnitus, and migraine headaches (a hand-held FDA-cleared device is now available for treating migraines). In addition to OCD and bipolar

## Related Resources

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depression, other psychiatric indications with promising data include schizophrenia (eg, refractory auditory hallucinations, negative symptoms), posttraumatic stress disorder, and various addictive disorders.<sup>21</sup> Because results have been mixed for most of these disorders, definitive trials are needed to clearly characterize the potential role of TMS.

## An ongoing evolution

Neuromodulation is undergoing a renaissance spurred on by the need for more effective treatments to manage some of our most challenging illnesses. Transcranial magnetic stimulation and other forms of therapeutic neuromodulation are welcome additions for managing treatment-resistant depression, OCD, and possibly other disorders. But perhaps their greatest value is as a bellwether for what’s to come. In addition to the ongoing refinements to existing neuromodulation devices, newer modulation approaches (eg, temporal interference stimulation) and the search for reliable biomarkers may dramatically expand and enhance our clinical options.<sup>14,22</sup>

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continued

## Clinical Point

**TMS is being studied as a potential treatment for bipolar depression, schizophrenia, PTSD, and addictive disorders**

## Bottom Line

Transcranial magnetic stimulation (TMS) continues to evolve as a nonpharmacologic treatment for mood disorders, obsessive-compulsive disorder, and potentially for other indications. Recent developments, including altered treatment parameters, new devices, and strategies for increasing the durability of antidepressant effects, have enhanced the benefits of TMS.



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Newer modulation approaches and the search for reliable biomarkers may expand our clinical options

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