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Transcranial magnetic stimulation for depression

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Only 28% to 33% of patients with major depression experience remission after their first antidepressant treatment, according to results of the Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial.[1] Therapeutic options include switching to an alternate antidepressant, augmentation with a second antidepressant, psychotherapy, mood stabilizers, or second-generation antipsychotics.

In October 2008, the FDA approved a new option: transcranial magnetic stimulation (NeuroStar TMS Therapy), a neuromodulation approach indicated for patients with major depressive disorder (MDD) who failed 1 adequate antidepressant trial in the current episode (***Table 1***).

FDA approves a new option for patients who fail 1 antidepressant trial

How it works

TMS delivers intense intermittent magnetic pulses produced by an electrical charge into a ferromagnetic coil. The intensity of the pulse is similar to that of MRI (1.5 to 2 tesla); however, in MRI the magnetic field is constantly on, whereas in TMS the field is exceptionally brief (milliseconds).

For depression treatment, the coil is usually placed on the scalp over the left dorsolateral prefrontal cortex (DLPFC). Pulses are delivered in a rapid, repetitive train, causing neuronal depolarization in a small area of the cerebral cortex and distal effects in other neurocircuits.

For depression, standard outpatient treatment consists of 5 daily sessions per week for up to 6 weeks. Each session takes approximately 40 minutes, and patients typically return to normal daily activities without difficulty. Initially, NeuroStar TMS will be available in a limited number of treatment centers (see ***Related Resource, page 29***).

Intensity of treatment is individualized by adjusting parameters that affect delivery of the magnetic pulses. Motor threshold (MT) is the level of stimulation required to

Table 1

Transcranial magnetic stimulation: Fast facts

Brand name: NeuroStar TMS Therapy
Class: Class II medical device
Indication: Treatment of major depressive disorder in adults who failed to achieve satisfactory improvement from 1 prior antidepressant medication at or above the minimal effective dose and duration in the current depressive episode
Approval date: October 7, 2008
Availability: Limited number of treatment centers; see www.NeuroStarTMS.com
Manufacturer: Neuronetics, Inc.
Recommended dose: 75 10-Hz, 4-second trains; 26-second intertrain interval; administered over the left dorsolateral prefrontal cortex; 5 days a week, up to 6 weeks

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Table 2

TMS depression treatment parameters

Parameter	Definition	Recommended treatment level
Motor threshold	Level of stimulation required to produce contractions in the contralateral target muscle (abductor pollicis brevis, which causes contraction of the thumb)	120%
Frequency of stimulation	Measured in cycles per second or hertz (Hz)	10 Hz
Stimulation train	Duration of the stimulation	4 seconds
Intertrain interval	Time between stimulation trains	26 seconds
Site of stimulation	Where in the brain the stimulation will occur	Left dorsolateral prefrontal cortex
Number of treatments	How many times the patient receives stimulation/treatment	5 days per week for up to 6 weeks
Total stimulation time	Number of stimulations given in a session	3,000 stimulations per session

TMS: transcranial magnetic stimulation

Clinical Point

Compared to sham procedure, TMS produced a significant decrease in depressive symptoms

produce movement in a contralateral target muscle, such as the abductor pollicis brevis that causes contraction of the thumb. Once this level is determined, pulses are administered at an intensity relative to the MT (such as 120%). Single TMS pulses are used to find the relevant area of the motor cortex, whereas repetitive pulses are applied over the left DLPFC for therapy.

Frequency of stimulation is measured in cycles per second or hertz (Hz). Stimulation train is the duration during which pulses are administered, and the intertrain interval (ITI) is the time between stimulation trains. Other parameters include site of stimulation and number of treatments per day, week, and course. Recommended treatment levels appear in ***Table 2***.

Efficacy

George et al[2] first reported TMS for depression in 1995. Initial small, open-label studies examined a variety of treatment intensities, durations, and stimulation sites. Several sham-controlled studies further refined treatment parameters. These studies generally found TMS efficacious, but questioned the robustness of the clinical effect.

To better assess the antidepressant effect of TMS, studies employed larger samples and more aggressive treatment parameters. Avery et al[3] randomized 68 patients to 15 sessions of active or sham TMS over the left DLPFC. Each treatment consisted of 32 10-Hz, 5-second trains at 110% MT with a 25-second ITI. At 1 and 2 weeks after treatment, 31% of subjects in the active treatment group showed a significant decrease in symptoms—defined as ≥50% reduction in Hamilton Depression Rating Scale (HDRS) score—versus 6% in the sham group. In addition, 20% of subjects in the active TMS group achieved remission (defined as HDRS score <8) versus 3% in the sham group.

The largest trial of TMS monotherapy (N=301) for moderately treatment-resistant major depression was completed in 2007.[4] This 3-phase study began with a 4- to 6-week, randomized, double-blind active-versus-sham TMS procedure, followed by 6 weeks of open-label TMS in initial non-responders. The third phase reintroduced TMS over 6 months as needed to augment maintenance antidepressant medication.

This trial used the most aggressive treatment parameters to date: 75 10-Hz, 4-second trains at 120% MT with a 26-second ITI, delivering 3,000 pulses per treatment

over an average of 26 sessions. To maintain an adequate blind, the study utilized sham and active coils with similar appearances, placement, and acoustic properties. The sham coil had an embedded aluminum shield, which limited the magnetic energy reaching the cortex to ≤10% of the active coil. Although there was no assessment of the adequacy of the blind in this trial:

- subjects were naive to TMS in the sham-controlled phase
- TMS operators did not assess efficacy
- TMS operators and subjects did not discuss the treatment experience with the efficacy raters.

Compared with those who received the sham procedure, subjects who received active TMS showed significantly better response rates on the Montgomery-Åsberg Depression Rating Scale (MADRS) at weeks 4 and 6. Similar results were found for the 17- and 24-item HDRS. At 6 weeks, the remission rate (defined as a MADRS score <10) was significantly higher in the active treatment group (14.2%) compared with sham procedure (5.5%).

A post-hoc analysis found that the greatest benefit occurred in patients who had only 1 failed adequate antidepressant trial (effect size = 0.83).[5]

TMS vs ECT. Dowd et al[6] summarized 8 published trials that compared TMS with electroconvulsive therapy (ECT) for severe depression:

- 5 reported equivalent efficacy
- 1 found unilateral ECT (UL-ECT) and bilateral ECT (BL-ECT) superior to TMS
- 1 reported UL-ECT superior to TMS
- 1 found UL-ECT plus medication superior to TMS monotherapy in patients with psychosis but comparable in efficacy to TMS in the absence of psychosis.

These results need to be interpreted with caution because of the studies' diverse designs, nonblinded assessments, and small sample sizes.

Related Resource

- For availability information, contact the manufacturer, Neuronetics, at (877) 6000-7555 or www.NeuroStarTMS.com.

Disclosures

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Tolerability and safety

The most frequently reported adverse effects of TMS are headache and pain at the site of stimulation. Seizures had been reported in early trials, but the extremely low occurrence has been much lower since Wasserman[7] published consensus guidelines on the safe use of TMS in 1996.

Janicak et al[8] examined safety data from the 3-phase trial mentioned above, which included >10,000 cumulative treatment sessions. TMS was well-tolerated, with a low discontinuation rate associated with adverse effects: 4.5% in the active treatment group versus 3.4% in the sham TMS procedure group. No deaths, seizures, or cases of treatment-emergent mania occurred. The most commonly reported adverse effects were transient headache and discomfort at the stimulation site. Most patients acclimated

Clinical Point

The most common adverse effects of TMS are headache and stimulation site pain

Bottom Line

Transcranial magnetic stimulation (NeuroStar TMS Therapy) is a new option for patients with major depression who fail to respond to 1 adequate antidepressant trial. This noninvasive procedure delivers intense intermittent magnetic pulses in a rapid, repetitive train, causing neuronal depolarization in a small area of the cerebral cortex. TMS has shown a lack of systemic side effects, but administration is time-intensive.

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to these effects in the first week. No changes were seen in cognitive functioning or auditory thresholds.

As in previous studies, TMS was safely combined with antidepressants in the third phase of this trial; however, patients at risk for seizure or on medications that could lower the seizure threshold were excluded. Thus, risk of seizure may be increased under these conditions. TMS is contraindicated for patients with implanted metallic devices or nonremovable objects in or around the head, except for dental hardware or braces.

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