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. 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 neuro-modulation approach indicated for patients with major depressive disorder (MDD) who failed 1 adequate antidepressant trial in the current episode (Table 1).

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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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.

### Table 2

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

TMS: transcranial magnetic stimulation

To better assess the antidepressant effect of TMS, studies employed larger samples and more aggressive treatment parameters. Avery et al. 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. 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.

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**Clinical Point**

Compared to sham procedure, TMS produced a significant decrease in depressive symptoms.
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 al6 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 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.

**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 Wasserman7 published consensus guidelines on the safe use of TMS in 1996.

Janicak et al8 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

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**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.
Out of the Pipeline

continued from page 29

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.

References


