Daily Left Prefrontal Repetitive Transcranial Magnetic Stimulation for Acute Treatment of Medication-Resistant Depression

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Daily left prefrontal transcranial magnetic stimulation (TMS) over several weeks was first proposed as a treatment for depression in 1993, with double-blind study beginning in 1997. TMS for the treatment of depression was approved by the U.S. Food and Drug Administration (FDA) in October 2008 (1). More recently, a large trial sponsored by the National Institutes of Health using an innovative sham treatment technique found that a course of active treatment for 3–5 weeks was superior to sham treatment (remission rates were 15% in the active treatment group and 5% in the sham treatment group) and achieved a 30% remission rate in the open-label extension. These findings led to the implementation of the first new Current Procedural Terminology codes for psychiatry since the American Medical Association launched the system in 1966.

In the vignette we describe the case of a 55-year-old woman with treatment-resistant recurrent unipolar depression who was successfully treated with repetitive TMS (rTMS) in each of two episodes 3 years apart. Numerous questions remain on the use of TMS for depression, several of which are raised by the case description. They include how to most effectively deliver rTMS—for example, the appropriate scalp location, the optimal "dose" (frequency, train, number of stimuli per day, and pattern of delivery), its use in combination with medications or talking/exposure therapy, and whether one can use maintenance rTMS to prevent relapse after a patient achieves remission. Daily left prefrontal rTMS reflects a paradigm shift in psychiatry in that it uses noninvasive and nonconvulsive circuit-based physiological processes to treat depression in patients who have not responded to medications or who cannot tolerate them.

Physiological Effects and Evidence Base

The patient described in the vignette is similar to many depressed patients who do not respond to or cannot tolerate antidepressant medications or who respond and then gradually experience a return of symptoms in a tolerance pattern. She failed to respond to sham rTMS during a double-blind study, responded well to open-label rTMS, and maintained her remission for 3 years on medications that had previously been inadequate to treat her acute depression. After a severe relapse, which occurred after FDA approval of TMS, she responded again to rTMS, which could now be offered in a clinical setting as an adjunct to her antidepressant medication. The case illustrates the potential use of rTMS for patients with treatment-resistant depression and the issues associated with this new therapy.

rTMS involves inducing an electrical current within the brain by a pulsating alternating magnetic field generated above the scalp (Figure 2). The essential feature of TMS is the use of electricity to generate a rapidly changing electromagnetic field, which readily crosses the scalp and skull and in turn produces electrical impulses in the brain. A typical rTMS device produces a fairly powerful magnetic field (1.5–3 Tesla), but only very briefly (a fraction of a millisecond for each pulse).

TMS requires a capacitor to store and deliver a charge and an electromagnetic coil (typically in the shape of a doughnut or two round coils side by side and connected in a figure eight) to induce an electrical field in the brain. The system is about the size of a small refrigerator, weighs less than 20 lbs, and can be made portable (4, 5).

Early TMS devices emitted only a single brief pulse. Modern devices can generate a rapid succession of pulses, called repetitive TMS. The typical treatment for depression is a 20- to 40-minute session delivering 3,000 to 6,000 pulses, 5 days a week for 4 to 8 weeks. In order to keep the patient still and the device correctly placed, the patient reclines in a chair and the device is held securely against the head over the left prefrontal cortex. The patient described in the vignette received 3,000 pulses per session in her first treatment course (a total of 105,000 pulses) and 5,000 per session in the second course 3 years later (a total of 220,000 pulses).

Conventional TMS coils generate a magnetic field impulse that can only reach the portion of the cerebral cortex that lies on the brain surface (6), just 2–3 cm below the device (7, 8). A TMS device that penetrates more deeply is in early clinical trials for depression and several other indications (9–11). It has been speculated that complex assem-

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A 55-year-old woman with a long history of recurrent treatment-resistant depression participates in a randomized controlled trial of daily left prefrontal transcranial magnetic stimulation and continues in the study's open-label extension.

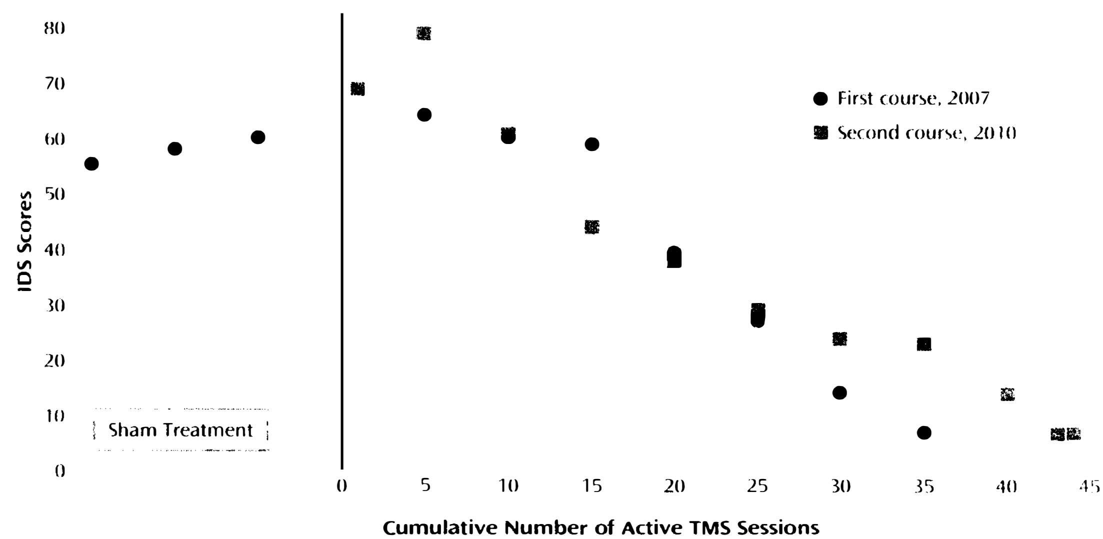
"Mrs. M" is a 55-year-old actress with recurrent unipolar depression. Although she was dysthymic in high school, her first suicide attempt was at age 23 during an episode of depression and bulimia, for which she received counseling and medication. She partially responded but then showed a repeated pattern of partial to complete response to antidepressant medications followed by a gradual loss of efficacy. After a second suicide attempt at age 35, she was hospitalized, and she partially responded to treatment with an antidepressant and psychotherapy. She made a third suicide attempt at age 48; she was hospitalized again, and she partially responded to venlafaxine at 300 mg/day and psychotherapy.

At age 50 Mrs. M relapsed again, and over the next few years she tried the following medications, either alone or in combination: venlafaxine, lamotrigine, olanzapine, trazodone, bupropion, ziprasidone, aripiprazole, oxcarbazepine, lithium, desipramine, imipramine, fluoxetine, sertraline, citalopram, and buspirone. She was offered but refused ECT, citing concerns that the potential cognitive side effects of the treatment could affect her ability to remember her lines as an actress.

In 2007, Mrs. M enrolled in a multisite randomized trial of repetitive transcranial magnetic stimulation (rTMS) (*2*). After being tapered off antidepressant medications, she had an entry score of 31 on the 24-item Hamilton Depression Rating Scale. At randomization she was assigned to receive sham rTMS and was treated daily over the left prefrontal cortex for 3 weeks, with no improvement in her depressive symptoms. She then exited the double-blind phase and was offered open-label treatment with the same TMS settings as were used in the active phase (120% MT, 10 Hz, 4 seconds on and 26 seconds off over 26.7 minutes, 3,000 stimuli per day). Her symptoms improved, and she remitted after 4 weeks (Figure 1). She was then tapered from the TMS (three treatments per week for 2 weeks, then two treatments per week for 2 weeks) and restarted on venlafaxine at 300 mg/day. Although the study protocol suggested that patients be started on venlafaxine with adjunctive lithium or lamotrigine after remitting on TMS, Mrs. M declined use of adjunctive medications.

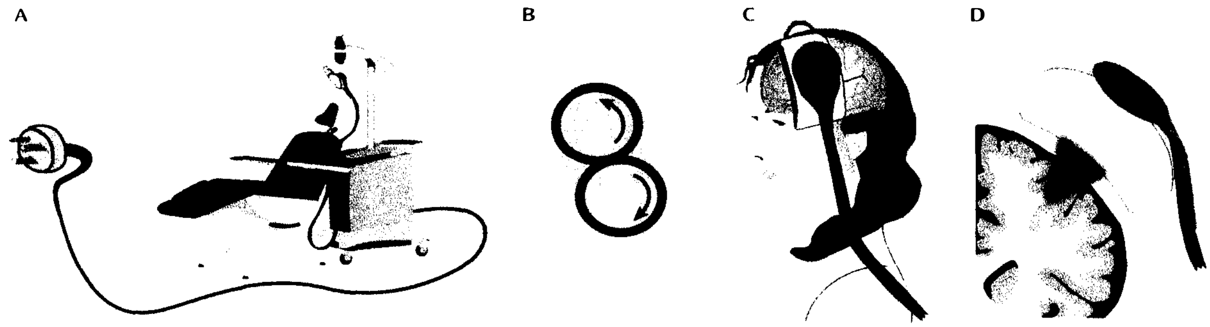
Mrs. M remained in remission from depression on venlafaxine for 3 years. She resumed her acting career and remarried. At age 58, in January 2010, without changing or stopping medications, she gradually noted the return of her core depressive symptoms and recontacted our group to request another course of rTMS. Her score on the Inventory of Depressive Symptoms (IDS) was high (69 out of a possible 84 points). She then received 45 treatments of daily left prefrontal TMS for the second time, but this time while continuing to take venlafaxine. After 6 weeks of daily TMS, her IDS score was 24 (65% improvement). While being tapered from the TMS over the next 2 weeks, she was started on duloxetine at 30 mg/day, and the venlafaxine was tapered. She was then referred back to her treating psychiatrist with an exit IDS score of 7.

FIGURE 1. Depression Scores and Course of Improvement for a Patient Participating in a Trial of Repetitive Transcranial Magnetic Stimulation (rTMS)[a]



[a] Scores on the Inventory of Depressive Symptoms (IDS) are graphed for the first and second courses of TMS. In the first trial, in 2007, the patient initially received sham TMS, the results of which are shown to the left of the y-axis. Over 6–7 weeks, the patient responded to TMS and even remitted. The two courses were 3 years apart and had other differences, but the clinical response was similar.

FIGURE 2. Components of a TMS Device[a]



[a] The TMS system is about the size of a small refrigerator (panel A). The device uses a capacitor that stores an electric charge and then discharges it through an electromagnetic coil, typically in the shape of a doughnut or two round coils side by side and connected in a figure eight (panel B), resting on the scalp over the prefrontal cortex (panel C). This powerful but brief pulse induces electrical currents to flow in the cortex (panel D), depolarizing neurons locally and sending signals to distant areas, including deeper limbic regions. TMS does not involve a seizure, and patients are awake and alert during their daily sessions, which typically last an hour. Figure modified from Higgins and George (3).

blies of coils could be built to summate and stimulate deep within the brain while sparing the superficial cortex (12).

When the TMS device produces a pulse over the motor cortex, descending fibers are activated and volleys of electrical impulses descend through connected fibers into the spinal cord and out to a peripheral nerve, causing a muscle to twitch. The minimum amount of energy needed to produce contraction of the thumb is called the "motor threshold" (MT) (13–16). Because it is easy to generate and varies widely across individuals, the MT is used as a measure of general cortical excitability. Most TMS studies, both research and clinical, report the TMS intensity or dose as a function of individual MT, not as an absolute physical value (17). In general, a stronger, more intense TMS pulse—for example, 110%–120% of MT—results in greater activation of the CNS tissue as well as a wider and deeper area of activation (18–22).

The manipulation of the frequency of stimulation is more complex. In general, frequencies of less than 1 per second (<1 Hz) are inhibitory (23). This may be because low frequency TMS more selectively stimulates inhibitory γ-aminobutyric acid neurons. This frequency resembles the frequencies used in animal and cell studies that produce long-term depression. One particular TMS sequence builds directly on the neurobiological studies of long-term depression and uses short bursts of TMS at theta frequencies (24, 25). Conversely, higher-frequency stimulation is excitatory (26). Interestingly, high-frequency TMS over some brain regions can, in some instances, temporarily block the function of that part of the brain (27, 28).

Putative Mechanisms of Action

TMS can produce different brain effects depending on the brain region being stimulated, the use parameters (intensity, frequency, duty train), and whether the brain region is engaged or "resting." Thus, TMS may have several different mechanisms by which it improves mood. In general, however, a single pulse of TMS at an intensity at or above MT over a cortical region like the motor cortex causes large neurons to depolarize. That is, the powerful transient magnetic field induces current to flow in neurons in the superficial cortex. Both modeling and simple testing have shown that the fibers that are most likely to depolarize are those that are perpendicular to the coil and bend within the gyrus (16, 29–32). Some lower TMS intensities do not cause large neuron depolarization but can still affect resting membrane potentials and thus alter brain activity and behavior.

The most striking positive phenomena that TMS can produce are motor twitches (thumb, hand, arm, or leg movement) when applied over motor cortex regions and "phosphenes" when applied over the occipital cortex. TMS does not produce acute memories, thoughts, or sensations or percepts such as those typically induced by intracerebral stimulation.

rTMS over some cortical regions can produce a disruption of behavior. This is most striking when the coil is placed over Broca's area, where one can produce a transient expressive aphasia or speech arrest. Much interest is focused on whether TMS can produce short-term or even longer-term changes in plasticity (26, 33). Simple studies in motor and visual systems clearly indicate the potential for this approach (34), which is now being applied in studies of poststroke recovery and other forms of rehabilitation (35, 36).

Coupling TMS with electrophysiological measures allows one to use TMS as a measure of motor cortex excitability and then measure how behavior, medications, or other interventions change that excitability. This technique is being used to investigate new CNS-active compounds (26, 37–39).

Brain imaging techniques (positron emission tomography [PET], single photon emission computed tomography, functional MRI [fMRI], and blood oxygen-level dependent fMRI) allow one to directly access the changes generated by rTMS (40, 41). With respect to the neuropsychiatric uses of TMS for depression or pain, TMS is known to have many molecular effects similar to those seen with ECT, such as increased monoamine turnover, increased brain-derived neurotrophic factor, and normalization of the hypothalamic-pituitary-adrenal (HPA) axis.

The initial use of daily prefrontal TMS to treat depression was based on the theory that clinical depression involves an imbalanced relationship between prefrontal (cortical) and limbic regions (insula, cingulate gyrus, amygdala, and hippocampus) involved in mood regulation and that in many patients the prefrontal cortex was hypometabolic (42). The basic hypothesis in 1993 was that repeated subconvulsive stimulation of the prefrontal cortex would activate circuits involving regulatory pathways interacting with the limbic system (42, 43). Such circuits had been described in motor, sensory, and prefrontal systems (44).

Early work showed that single sessions of prefrontal rTMS in healthy adults had no side effects but produced evidence of HPA interaction (serum thyroid levels) and slight mood changes (45), clearing the way for case series in treating depression (46), followed by a double-blind trial (47).

"The data now demonstrate that daily left prefrontal rTMS for at least several weeks treats acute depression in a subset of moderately but not extremely treatment-resistant patients with unipolar illness."

There is now accumulating support, primarily from brain imaging studies (18, 38, 48), that prefrontal rTMS in depressed patients is changing cortical and limbic activity and regulatory circuits. No one has yet linked these changes directly to the antidepressant effects of the treatment, although an important recent study using a serotonin PET ligand in depressed patients undergoing rTMS (49) found that a prefrontal serotonin deficiency at baseline normalized after several weeks of treatment.

Safety and Side Effects

In general, rTMS appears to be safe and to have no enduring side effects. There have been no reported lasting neurological, cognitive, or cardiovascular sequelae. A recent international conference on TMS safety updated the guidelines for use (50, 51). Inducing a seizure remains the primary safety concern with TMS. There have been fewer than 20 reported cases of seizures induced with TMS, with a sample size of several thousand patients and healthy volunteers exposed to TMS. The risk is probably less than 0.5%.

Published safety tables concerning the proper intensity, frequency, and number of stimuli have helped minimize the numbers of seizures (50). Of the reported seizure cases, the majority were in healthy volunteers who were receiving TMS to the motor cortex—the most epileptogenic region of the cortex—and were receiving trains of stimulation outside of the limits now suggested. All of the seizures were self-limited, without need for medications or other interventions, and occurred during TMS administration when the subjects were sitting down and near an investigator. There are no reports of any recurrences among these individuals. These cases and the few that have occurred in patients suggest that TMS-induced seizures will remain a small but significant adverse event in patients without histories of seizures, even when rTMS is used within the suggested guidelines. For these reasons, TMS needs to be supervised by a physician in a facility capable of quickly responding to a potential seizure (52, 53).

Studies in rabbits as well as some human studies suggest that the loud click accompanying the TMS discharge can cause hearing loss, and therefore study subjects, patients, and operators should wear earplugs (54, 55). One patient reported a temporary hearing loss after rTMS. However, an extensive study of auditory threshold before and after 4 weeks of rTMS in more than 300 patients in the pivotal TMS depression study found no changes.

Headaches are the most common complaint after TMS, although there was no difference in headache frequency between TMS and sham treatment in the recent large trials (1, 2). Repeated analysis of neurocognitive functioning of TMS patients has not revealed any enduring negative effects from the procedure (56, 57). Immediately after an rTMS session, patients are able to drive home or return to work. The rTMS procedure itself can cause some scalp pain, which is usually worse during the first few sessions and then largely disappears, although a few patients drop out of studies because of this discomfort (58, 59).

Clinical Studies in Depression

Largely because of its noninvasiveness, rTMS has been investigated in a plethora of neuropsychiatric conditions. Until recently, there has not been a device industry to promote or perform this work, and thus much of the initial clinical work was conducted at single sites with relatively small sample sizes.

Depression has been the most widely studied condition with rTMS. Three initial studies in Europe in the early 1990s used TMS over the vertex as a potential antidepressant (60–62). In the United States in the mid-1990s, George et al. performed an open study and then a double-blind controlled trial of rTMS for 2 weeks (45–47). This work has now dramatically grown, but without much change in many of the initial treatment parameters (coil location, frequency, dosing). Several meta-analyses have been published, most of them concluding that left prefrontal TMS provided statistical superiority over sham treatment for

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Clinical Guidance: Transcranial Magnetic Stimulation (TMS) for Medication-Resistant Depression

TMS is recommended by George and Post for moderately depressed patients who have failed to respond adequately or did not tolerate initial treatment of an acute episode of depression with an antidepressant, accompanied by a targeted psychotherapy. Typical stimulation parameters for 5 days per week, 4 to 8 week treatment are presented in the article itself. The treatment is not recommended for more seriously ill or refractory patients for whom ECT remains the treatment of choice.