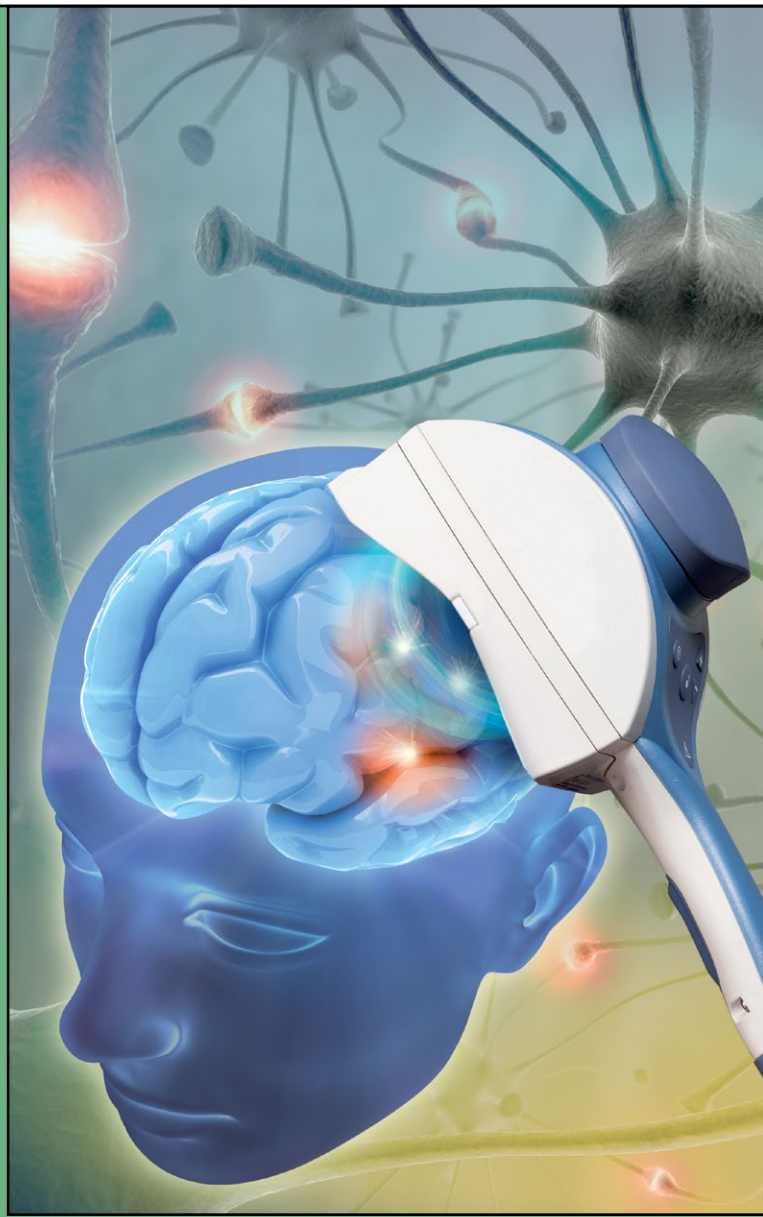
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Transcranial Magnetic Stimulation for Major Depressive Disorder

A PRAGMATIC APPROACH TO IMPLEMENTING TMS IN A CLINICAL PRACTICE



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Introduction
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This supplement is based on a roundtable discussion by psychiatrists experienced in using transcranial magnetic stimulation in their practice. It is sponsored by Neuronetics and was peer reviewed by CURRENT PSYCHIATRY.

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Introduction

Philip G. Janicak, MD

The World Health Organization (WHO) estimates that major depression will be the leading cause of disability by the year 2020.[1] Based on data from the National Comorbidity Survey Replication, it is estimated that each year approximately 14 million adults in the United States experience a major depressive episode.[2] Further, only about half receive a proper diagnosis and less than half adequately benefit from existing first-line therapies (eg, psychotherapy; antidepressant medication).

Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study provide insight into several important issues clinicians struggle with in managing these patients.[3] For example, the primary endpoint chosen by investigators of this landmark National Institute of Mental Health-sponsored trial was remission (ie, minimal to absent symptoms with treatment). The distinction between remission and response is crucial: response often leaves patients with substantial residual symptoms and is more likely to culminate in relapse or recurrence in the months after an acute treatment episode.[4]

Another important observation was that as the number of treatment trials required increased, the chances of achieving remission diminished, and the likelihood of discontinuing treatment because of adverse events increased steadily.[5] Further, as the number of trials needed to achieve remission increased, the risk of relapse rose and the time to relapse shortened.[5] In the second phase of STAR*D, switching or augmenting produced remission in only an additional 25% of patients who did not adequately benefit from an initial aggressive trial of citalopram.[6-8]

What options are available to clinicians for patients with major depression who do not adequately benefit from standard initial treatments? Presently, if a patient is not adequately responsive to or cannot tolerate a first-line antidepressant trial (eg, selective serotonin reuptake inhibitor monotherapy), there are limited FDA-approved options—second-generation antipsychotic (SGA) augmentation or transcranial magnetic stimulation (TMS)—and several approaches supported by clinical studies and experience, such as switching to an alternate antidepressant or augmentation with a second antidepressant. Ironically, the two FDA-approved options were not included in STAR*D because at the time SGA augmentation was not a recognized viable approach and TMS was not yet clinically available.

The disappointing remission rates (approximately 25% to 30%) achieved in both the first and second phases of STAR*D, coupled with the substantial drop off in both the subsequent chances of remission and attenuated durability of effect, argue for an earlier consideration of SGA augmentation or TMS. In this context, the approved indication for TMS is in patients who fail one adequate antidepressant trial during the current episode. Although studies of aripiprazole, quetiapine, and olanzapine augmentation demonstrated efficacy, these agents carry substantial safety and tolerability concerns (eg, neuromotor symptoms; weight and metabolic complications). By contrast, the efficacy and excellent safety and tolerability of TMS argue for its earlier introduction.[9,10] Presently, a variety of factors—such as cost, adverse effects with SGAs, and limited clinical experience with TMS—usually relegate these therapies to third- or fourth-line strategies in most treatment settings.

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A pragmatic approach to implementing TMS in a clinical practice

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Dr. Derstine is a speaker for AstraZeneca, Bristol-Myers Squibb, and Neuronetics, Inc.

Dr. Hutton is a speaker for Wyeth and Neuronetics, Inc.

Dr. Lanocha is a speaker for and consultant to Neuronetics, Inc.

Dr. Wahlstrom is a speaker for and consultant to Neuronetics, Inc., and is an advisor to Sensa Products, LLC.

Another option for managing major depressive disorder (MDD) became available in October 2008 with the Food and Drug Administration's (FDA) market clearance of NeuroStar TMS (transcranial magnetic stimulation) Therapy System. A panel of psychiatrists who have been treating patients with NeuroStar TMS Therapy in their clinics assembled for a virtual roundtable discussion regarding their experiences. In this supplement, the panel addresses the following issues:

- the FDA-cleared indication for use of NeuroStar TMS Therapy
- logistic and staffing considerations in the outpatient setting
- selecting the right patient for TMS Therapy
- talking with patients and family about TMS Therapy.

To give the overview a meaningful context, each panelist shares a personal account of a patient case, describing the treatment course and outcomes achieved with TMS Therapy.

TMS in a psychiatric practice

Timothy Derstine, MD

TMS is a clinical application of electromagnetic induction as described by Michael Faraday in 1839, whereby a time-varying magnetic field induces an electric current that runs perpendicular to the motion of the magnetic field.[1,2] As the brain is an electrochemical structure, it is predisposed to electromagnetic induction. With TMS, an MRI-strength magnetic field induces an electrical current in brain tissues and neurons.[3] Unlike MRI, which uses both pulsed and static magnetic fields to which the whole body is exposed, TMS uses only pulsed magnetic fields that are applied directly to the head, and stimulate only the region of the scalp and cerebral cortex beneath the TMS coil.

The precise location of the treatment and the strength of the magnetic field delivered are individualized for each patient. These determinations are based on a patient's motor threshold, the lowest level of TMS stimulation to the motor cortex that is needed to cause a contraction in the contralateral muscle controlling movement of the thumb (abductor pollicis brevis). Using the motor threshold level as the reference value, the prescribing clinician sets the level of therapeutic stimulation at a percentage of that value (eg, 120%). Patients receive the pulsed stimulation over the left dorsolateral prefrontal cortex. Daily treatments for four to six weeks ordinarily are given, consisting of 75 cycles of 4 seconds each, at 10 pulses per second, with 26-second intervals of rest between cycles, for a total of 3,000 pulses.

The magnetic field of the TMS coil penetrates the skull to a depth of a few centimeters and depolarizes neurons in the superficial cortex, producing local stimulation. Brain mapping and other functional neuroimaging studies have shown that, through neural pathways, this local stimulation causes functional changes in more distant brain regions associated with mood, including the cortical and subcortical regions of the brain, such as the basal ganglia and the limbic system ***(Figure 1)***.[4–6]

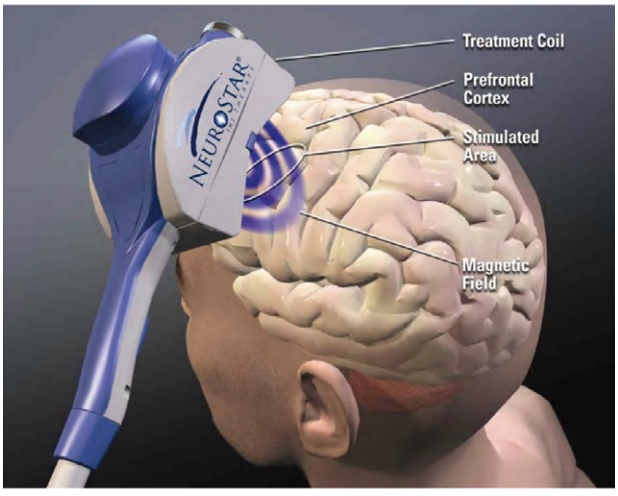
Evolving empirical support for TMS. As knowledge of the brain's functional neuroanatomy increased, experts realized that MDD was a disturbance of brain circuitry as well as brain chemistry. The efficacy of brain stimulation in MDD from electroconvulsive therapy (ECT) suggested that other forms of brain stimulation might be beneficial. Indeed, numerous clinical studies since 1989 have provided empirical evidence for the efficacy and safety of TMS in MDD,[7,8] including advances in knowledge for clinical use.

TMS is ideal for outpatient treatment. Many patients experience an inadequate response to current antidepressant therapies, and there is a clear need for new treatment options. TMS Therapy is such an option, and given its non-invasive approach and relative lack of side effects compared with other treatments for MDD, it is well suited for use in outpatient psychiatric practice. No sedation is involved, and cognition is not adversely affected. A treatment session lasts approximately 37 minutes, during which the patient is continuously monitored by a specially trained health care provider—such as a psychiatrist, a nurse, or qualified technician—for appropriate contact and patient comfort and safety.

The NeuroStar TMS Therapy system is cleared by the FDA for the treatment of adult patients with MDD who have not achieved satisfactory improvement from one pharmacologic antidepressant treatment at or above the minimum effective dose and duration in the current episode.

FIGURE 1

Transcranial magnetic stimulation of the prefrontal cortex has a demonstrable downstream effect in the limbic system circuitry, which is involved in mood regulation.



Logistics and staffing for TMS in the office setting

Carl Wahlstrom, MD

The TMS Therapy system requires a room at least 15 feet by 11 feet to provide adequate space in which staff can maneuver. Room temperature must be maintained at a comfortable level with adequate ventilation. Given the level of noise produced by the device, soundproofing is desirable, depending on location of the treatment room relative to other office space. Hearing protection is required during treatments for the patients and clinical staff in the treatment room.

Treatments can be administered throughout normal office hours. We allow an hour for each patient. When proper scalp contact is maintained, the procedure lasts about 37 minutes. Extra time is needed before starting treatment to accurately position the patient, during treatment if scalp contact with the coil is lost, and at the end of the session to give the patient time to collect any belongings and exit the treatment area.

Our usual treatment plan is daily treatment Monday through Friday for four to six weeks—ie, 20 to 30 treatments. In research studies used to seek FDA approval of NeuroStar TMS Therapy, researchers followed the end of the acute treatment phase by tapering the number of weekly treatment sessions over three weeks from three treatments weekly to two and eventually to one. In our office-based treatment, we also taper treatment at the end of the acute phase of therapy as appropriate, based on patient response and clinical judgment.

FIGURE 2

The noninvasive NeuroStar TMS Therapy system comfortably positions patients to receive pulsed magnetic-field stimulation without sedation or anesthesia.



The NeuroStar TMS Therapy system ***(Figure 2)*** can be sold only to psychiatrists practicing in the United States, who prescribe and supervise its use. Assistants can participate in treatment once they have received thorough training in the use of the NeuroStar TMS Therapy system. Given the manufacturer's recommendations regarding medical education and experience, I chose two registered nurses (RNs) to work with me on a part-time basis. RNs are accustomed to monitoring patient status, managing emergencies, and making clinical progress notes. Utilizing RNs is not a requirement; however, I reasoned that there would be advantages for both me and my patients, which has proven to be true. The nurses assist me in determining the patient's proper positioning, the motor threshold, and the treatment intensity, and they review each day's treatment sessions with me. I evaluate each patient initially, reviewing his or her psychiatric history to determine if TMS treatment is indicated, and then every two weeks (or more often if indicated) to monitor the patient's progress.

Identifying patients who can benefit from TMS

Todd M. Hutton, MD

The FDA-cleared indication for NeuroStar TMS Therapy is for the treatment of MDD in adult patients who fail to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode.

Patients to consider for TMS. TMS Therapy needn't be reserved for treatment-resistant patients. It is extremely benign, safe, and well tolerated. It is far more benign than ECT, which can cause memory loss and requires that patients undergo anesthesia. Both patients who have and have not benefited from a course of ECT have requested TMS as a treatment option. Patients can drive themselves home after TMS treatment, go to work, and not feel any ill effects during the day.

I have used TMS for patients who tolerated their antidepressant medication but achieved only a partial response. Throughout TMS Therapy, my patients almost always continue taking their medications. This may account for the higher response rates I see compared with the original Neuronetics studies or other studies in which patients were antidepressant-free during the acute treatment phase.

I also consider TMS treatment for some patients for whom specific safety and efficacy data are unavailable, but for whom the expected benefit of TMS outweighs the negligible known risk. Such patients include women who are pregnant or nursing and do not want to take an antidepressant medication, and those who have responded to medication but cannot tolerate the drug side effects.

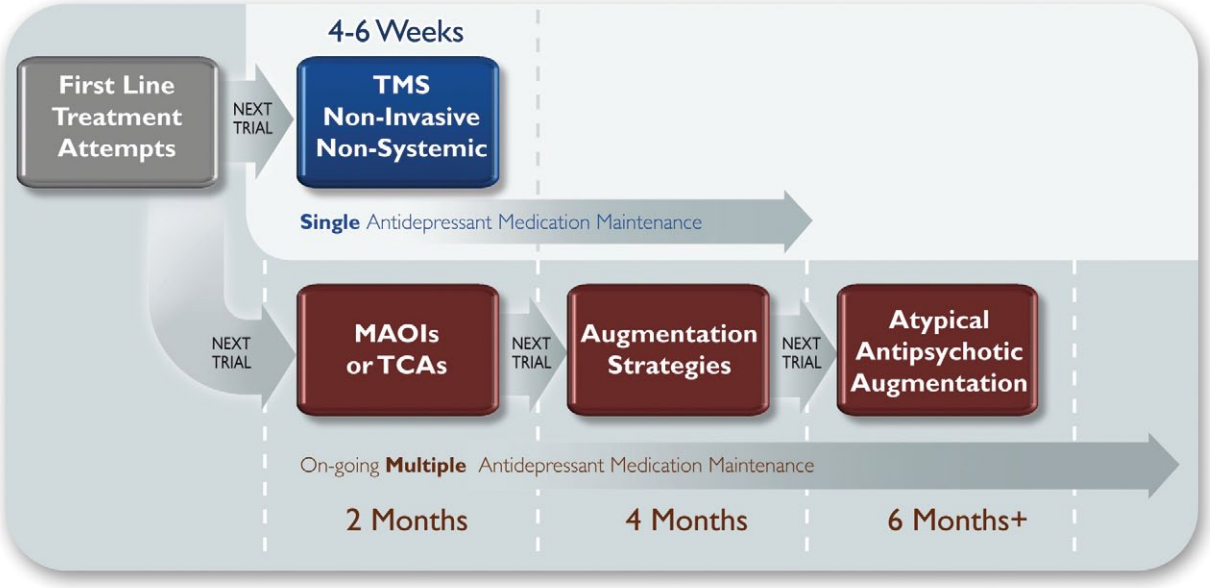
Contraindications. TMS Therapy is contraindicated in patients who have ferromagnetic metal within 30 centimeters (1 foot) of the coil. This is within the head and neck region for most patients. The NeuroStar TMS System should be used with caution in patients with an implantable device, such as a pacemaker, controlled by physiologic signals.

Karl Lanocha, MD

At present, most patients seeking TMS Therapy have struggled with depression for a long time. They have tried multiple medications or other treatments. But TMS Therapy deserves to be considered at an earlier point in the treatment plan, certainly before ECT and possibly even before tricyclic antidepressants (TCAs), atypical antipsychotics, or monoamine oxidase inhibitors (MAOIs). I believe that TMS could be considered between TCAs and selective serotonin

ALGORITHM

The role of TMS in the treatment of depression: An important treatment option when initial acute phase treatment fails



MAOIs: monoamine oxidase inhibitors; TCAs: tricyclic antidepressants; TMS: transcranial magnetic stimulation

Source: Adapted from American Psychiatric Association. Practice Guidelines for Treatment of Patient's With Major Depressive Disorder. 3rd ed. 2010.

reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) and TCAs—ie, after a patient has tried one or two first-line pharmacologic treatments. The findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[9] are instructive as it demonstrated that only 30% to 40% of patients achieve full remission with the first antidepressant they try, and the likelihood of achieving remission decreases steadily with each new treatment failure. After a patient has tried three antidepressants without success, the likelihood of achieving remission with a subsequent round of pharmacotherapy was only a little more than 10%. More than 15% of patients never achieve remission regardless of how many medications they try. TMS may be effective for this last 15%; however, TMS is not a treatment of last resort and it should be considered as an option much earlier in the management algorithm given its safety profile (***Algorithm***). The recently published American Psychiatric Association practice guidelines for treating patients with major depressive disorders include TMS as a treatment option for patients who have failed to benefit from initial acute phase treatment of their depression.[10]

Presenting TMS to patients

Karl Lanocha, MD

Depressed persons often have difficulty processing new information, so I encourage them to bring their spouse or another family member to the initial consultation. Based on the volume of information to be reviewed, I use visual aids and handouts to explain the TMS procedure. I show patients the TMS treatment room and give them an opportunity to sit in the chair and view the TMS system. I briefly explain how the device works.

I inform the patient that the known side effects are those associated with the magnetic pulses as they pass through the scalp and other tissues. The most common side effects are scalp pain or discomfort. I further describe the scalp sensation they may experience from the stimulation, and explain that most patients adjust to the sensation over a week or so. I also explain that TMS does not have the systemic side effects associated with antidepressant medications because it works at the level of the brain and does not circulate or affect the rest of the body.

Additionally, I inform patients that there is a remote risk of seizure with TMS, although the rate is

extremely low. No seizures occurred during the 10,000 treatments administered in the Neuronetics TMS studies,[11] and since the device was cleared by the FDA, only one seizure has been reported in more than 60,000 additional treatments. I always screen patients for a history of epilepsy. A history of epilepsy is not an absolute contraindication to the use of TMS; however, if a patient is taking anticonvulsant medication, the drug can affect the motor threshold level and, therefore, the optimal TMS treatment level.

Another unique aspect of TMS is that, unlike pharmacologic antidepressants, it carries no "black-box" warning for a potential worsening of depression or precipitating suicidal thinking for adults. Since "black-box" warnings for antidepressant medications were initiated for children and adolescents, I have used TMS with three adolescents age 16 to 17 years old. In all instances, the parents preferred TMS as a treatment option, based on the warnings of worsening or emergence of suicidal thinking with continued exposure to antidepressant medication. All three of these patients responded to TMS therapy.

I discuss with potential patients that TMS is not a cure for depression but does have a very high success rate. I have used TMS with patients who were treatment-resistant to medications; most of them experienced improvement with TMS and many achieved remission. Additional treatment for these patients will likely be necessary because of the chronic and recurring state of MDD.

Case studies

All of the panelists have used TMS Therapy to treat patients with MDD. Some, but not all, of their patients are similar to those who participated in the NeuroStar TMS registration studies. Other patients were searching for an option besides medications or conventional nonpharmacologic modalities. In the view of the treating physician, the potential benefit from TMS Therapy outweighed the potential risks of TMS treatment. All potential risks were reviewed with patients before receiving TMS Therapy.

Linda

Timothy Derstine, MD

Linda, a 48-year-old woman who was referred to me, had a 20-year history of moderately severe, recurrent MDD and generalized anxiety disorder. Her depressive symptoms had responded reasonably well to pharmacologic treatment. Because of the side effects she experienced, the medication dosages were reduced, and depressive symptoms returned. This also occurred subsequently with different antidepressant medications. She had frequent crying spells that she could not control. She had never been hospitalized for her depression, although she did undergo a brief course of psychotherapy. She had been diagnosed and treated for hypothyroidism by her primary care clinician.

When she presented, Linda had been taking sertraline, 50 mg/d, and bupropion, 300 mg/d, for more than a year. Higher doses of sertraline brought more symptom relief but caused problematic sexual side effects. She was also unable to tolerate higher doses of bupropion. Previous medication trials included paroxetine, 40 mg/d; citalopram, 60 mg/d; escitalopram, 20 mg/d; fluoxetine, 40 mg/d; and venlafaxine, 150 mg/d—many of which were given for an inadequate period of time, but all of which caused unacceptable side effects. In the remote past, other antidepressants were tried but failed to provide adequate responses.

I administered 24 sessions of TMS, five times per week, then tapered treatment to six sessions over three weeks. During the first and second weeks, she had some difficulty tolerating the TMS treatment because of irritation at the site of application. She was determined to proceed, however, and continued the treatment for the rest of the treatment cycle. The treatment site discomfort resolved without any intervention. She benefited clinically, having exhibited a Patient Health Questionnaire-9 score of 14 before TMS treatment and a score of 1 after treatment completion. She has returned to her psychiatrist for follow-up regarding her illness.

Arthur

Karl Lanocha, MD

Arthur is a 55-year-old man who owns a nurse placement agency. He is successful in his professional career, with clients around the country. He has struggled with depression throughout his entire adult life and it has been more prominent since the death of his wife a couple of years ago. Some mornings, his business partner has had to come to his house, drag him out of bed, throw him in the shower, and drive him to the office. He has had daily thoughts of suicide and a well-thought-out plan. Only his devotion to his adult children has kept him from following through with his plan.

He has been seeing a psychologist and a psychiatrist for ongoing treatment during this current episode. At the urging of his psychologist, Arthur came to see me and underwent a

course of 30 TMS treatments over a period of six weeks. He tolerated them very well and did not experience any discomfort at the treatment site. Within the first week, there was a noticeable improvement in his sleep quality. In the second week of treatment, he abruptly stopped smoking after 40 years of nicotine dependence. He was surprised by this result because he had attempted to stop smoking many times without success.

Before treatment, his score on the Beck Depression Inventory (BDI) was 55; at the end of treatment, he was in complete remission with a BDI score of 0. He was on antidepressant medication at the time he started TMS treatment, and continued to take the medication at the same dose throughout his treatment. I have contacted the patient since completion of treatment and he continues to do well.

Jeff

Carl Wahlstrom, MD

Jeff is a 45-year-old executive with MDD whose first major depressive episode occurred in 1999. Treatment with bupropion and clonazepam and supportive therapy resulted in full remission after three months. He remained symptom free until 2008, when he relapsed and was not responding to his medication treatment. At this time, he was determined clinically to be severely depressed, with depressed mood, loss of usual interests, hopelessness, feelings of guilt, and frequent suicidal thoughts. His low maintenance dose of bupropion XR, 150 mg/d, was increased to 300 mg/d but his depression continued to worsen. I switched his antidepressant medication to mirtazapine, which was titrated from 15 mg/qhs to 45 mg/qhs. After four weeks, he had a partial response with a BDI score of 31. His family was concerned with his level of depression and we discussed TMS as a therapeutic option.

In February 2009, I started Jeff on daily TMS treatment at 3,000 pulses/d, which continued for six weeks. He was continued on his medications, mirtazapine and low-dose clonazepam. After six weeks of treatment at five sessions per week, I tapered his treatment over three weeks, with three treatments the first week, two the second week, and one in the final week. Over the six-week course of NeuroStar TMS Therapy, his BDI score went from 31 to 8, and his improvement was sustained for three months. He now receives one monthly TMS treatment, and for an additional nine months this approach has sustained his response. He mentioned that after each booster treatment, he feels young again—in his words, "like 20 years old." He says that things about his life that once would bother him just fade into the background now. I continue to monitor him clinically on a monthly basis.

Leah

Todd M. Hutton, MD

Leah is a 52-year-old divorcee and former RN. She presented with an extremely severe course of bipolar disorder with psychotic features, primarily depressive episodes and only minor manic episodes. She had 11 psychiatric hospitalizations in the prior two years, and had been aggressively treated with medications, including TCAs, MAOIs, various mood stabilizers (including lithium), and high-dose antipsychotic medications (including haloperidol). None of the treatments stopped her auditory hallucinations or stabilized her mood. During this episode, she did respond to a course of ECT, but relapsed within about four months.

After discussing TMS with her, I started her on therapy. Her BDI score at this point was 45. At the end of the first week, she baked a cake and did a pile of laundry that had been sitting on her floor for four months. After four weeks of TMS, her BDI score went down to 13, indicating just mild depression. She said this was the best she had felt in 20 years. She continues to receive TMS treatments once or twice a month, and she's been able to stay out of the hospital for 10 months now. Her auditory hallucinations have stopped and she is taking much lower doses of medication.

Clinician discussion and questions answered

Dr. Derstine: Maintenance of effect after acute TMS and use of periodic TMS treatments seem to be part of the TMS treatment plan. Please comment on your experience.

Dr. Lanocha: I use TMS treatments for maintenance of the antidepressant benefit gained with TMS Therapy. In my experience, the durability of the effects of TMS is impressive. Most of my patients remain in remission for six to nine months, but at least 10% do show some signs of symptom breakthrough. When this occurs, I usually prescribe two TMS treatments, given one week apart. If there is not too much delay after symptoms begin to appear, my patients have returned to remission. If a second symptom breakthrough occurs, I start these patients on treatment five times a week and then gradually increase the time interval between treatments. One patient who is now receiving a single treatment every six weeks is maintaining remission.

Dr. Hutton: I also use TMS treatments to maintain symptom response after acute TMS Therapy. At this point, there are no long-term study results to indicate what proper maintenance protocols should be. In looking at the Neuronetics studies that followed patients out to six months, most patients sustained their remission, but perhaps 30% required a varying number of follow-up TMS treatments.[12] About 85% of those who received these TMS treatments were able to regain the effect. With longer periods after acute treatment, it is expected that patients will present with worsening symptoms and need additional treatments. One of my patients successfully used TMS after failing an acute course of ECT.

Dr. Lanocha: Three of my patients did well with an acute course of ECT, but at the same time experienced fairly significant cognitive side effects that were intolerable. They chose to receive maintenance TMS in place of maintenance ECT. With TMS, patients can drive themselves to and from their treatments, do not have to depend upon family members, and do not have to experience repeated sessions of general anesthesia.

Dr. Wahlstrom: Since February 2009, 29 patients have received acute TMS treatment at our outpatient practice. This represents 900 to 1,000 single TMS sessions. Of those patients, about one-third have returned after six to nine months for re-treatment sessions. No one has required more than a few sessions to restore the initial effect. When a patient starts experiencing depressive symptoms beyond the ups and downs of everyday life—eg, ongoing depressed mood, loss of interest, hopelessness—we inform him or her that they should come into the office to discuss re-treatment options. Two of my patients come in every four to six weeks for a single session. The other patients come in as needed, usually for one or two sessions in the same week and then one additional session the following week.

One patient decided she was doing so well following TMS that she no longer needed her antidepressant medications. Most of my patients receiving NeuroStar TMS Therapy, however, have remained on their medications, although dosage adjustments or changes are made as clinically indicated. In my clinical experience, I believe the chemical actions of medications are augmented by the electrical effects of the TMS treatments.

Final thoughts from the participants

Dr. Derstine: Any final thoughts about the use of TMS Therapy for treating depression?

Dr. Wahlstrom: TMS Therapy is a genuine advance in depression treatment. It doesn't eliminate the need for medication but it's a truly innovative and effective option for treatment-resistant depressed patients.

Dr. Hutton: TMS is a treatment modality that is here to stay. We're still learning where it best fits into the overall treatment algorithm and about all its possible uses. There's tremendous potential yet to be realized, but I'm already convinced I'll be using it long into the future.

Dr. Lanocha: Not only is TMS a breakthrough in the treatment of depression, I also think it marks the beginning of a new era in the treatment of neuropsychiatric illness in general. I believe that in the coming years, we will see a number of applications of TMS extending beyond unipolar depression.

Dr. Derstine: One of the exciting things for me in using TMS is the hope it gives patients. We all work with patients who work hard to adhere to their prescribed treatments but still cannot get to the point of remission or even adequate reduction of symptoms. In other words, their treatments fail them. I've even had new patients tell me they believed their previous physician had given up hope for them. It's very gratifying, then, to see patients who have suffered a long time with depression exhibit a real reduction in their symptoms. Even if they don't achieve full remission, the reduction in symptoms gives them the ability to function better and enjoy their lives. If some patients decide not to take that course of treatment immediately, it still offers them hope for the future.

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NEURONETICS