SPEAKER NOTES

Advances in TMS Therapy: Treatment-Resistant Depression and Beyond

Summarized by Thomas T. Thomas

Transcranial Magnetic Stimulation (TMS) therapy is an alternative treatment for patients suffering from Major Depressive Disorder (MDD) who have not achieved satisfactory improvement with prior antidepressant treatments. This revolutionary technology has long been studied but was only introduced to the market with FDA approval as a treatment for major depression in 2008. Since then, TMS has provided impressive results as a non-invasive, non-systemic alternative for treatment-resistant patients who do not respond well to medications.

RICK TRAUTNER, MD

Our speaker at the July 25 meeting was **Rick Trautner, MD,** who is a founder and Medical Director at Bay-TMS, with clinics in Berkeley and San Rafael. He is also Director of Mental Health Services at Alta Bates Summit Medical Center and serves on the board of directors of the Clinical TMS Society.

Dr. Trautner noted that 17 million adults in the United States suffer from MDD, and the incidence worldwide is 4.7%. Starting about 100 years ago, the standard treatment was psychotherapy, originating with Sigmund Freud, which now takes about a hundred different forms. And then psychopharmacology came in the 1950s with the first antidepressants.

He reported that the largest and longest study of depression treatment, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study funded by the National Institute of Mental Health, found that medications don't work that well, and that they become increasingly less effective with each new medication that the patient tries. Response rates drop from 27.5% to 6.9% after several rounds of treatment. At the same time, patients become increasingly likely to stop taking a new medication, from 8.6% in the first round up to 41.6% in later rounds, primarily due to lack of response and side effects.

Neurostimulation in the form of Electroconvulsive Therapy (ECT) was introduced in 1938. Similar therapies such as Vagus Nerve Stimulation and Deep Brain Stimulation came along in the 1980s, but these are off label for MDD, while Repetitive TMS was first demonstrated in 1985, first used to treat depression in 1995, and received FDA approval for treatment-resistant depression (TRD) in 2008.

"Think of the brain as an electrochemical organ," Dr. Trautner said. "You can change it with psychotherapy, with chemicals, and with neurostimulation through

electric current."[1] He noted that British scientist Michael Faraday showed in 1831 that alternating magnetic fields create an electric current in conductive substances. TMS repetitively applies these alternating fields to target areas in the brain, mostly in the prefrontal cortex and the deeper brain systems associated with them. Nerves communicate through electrical signals in neurons and the chemical signals between them at the synapses. A magnetically induced current depolarizes electrical activity in the neuron and changes the post-synaptic receptors that absorb neurotransmitters.

Six or seven different devices can be used to apply the TMS treatment, and BayTMS uses three: the NeuroStar, Magvita, and Brainsway Deep TMS.

In treatment, a technician measures the patient's head from nose to back of skull, from earlobe to earlobe, and circumference of the skull. These measurements are entered into a formula that shows how to mark treatment locations and place the device. The device activates the motor strip running up the side of the brain from the ear to the top of the cortex to establish a "motor threshold," indicated by twitching of the patient's hand. This helps set the level of stimulation required for treatment.

The device then delivers 3,000 pulses of a magnetic field to identified targets. The field typically alternates at 10 cycles per second (10 Hertz) over a twenty-minute period. This treatment is repeated five times a week for six weeks, or a total of 30 sessions.

The process is non-invasive, generally painless, requires no anesthesia, and creates no cognitive impairment—unlike ECT. Still, the technician checks for the patient's comfort and safety during treatment. The field strength is 1.5 to 3 Tesla, similar to an MRI scanner. There is a small risk of seizure—less than 0.001%—although BayTMS has never experienced this in approximately 22,000 treatments.

Dr. Trautner noted that, based on their observations, the left frontal part of the brain is under-active in depression, and so the treatment excites or stimulates it with pulses of 10-20 Hertz. In cases of depression with anxiety disorder, the right frontal cortex may be over-active, and it can be inhibited or slowed down with pulses of 1 Hertz.

Studies of TMS therapy versus sham controls—that is, placebo equipment set up to do everything but deliver a magnetic pulse—showed TMS as performing better than all outcomes with the controls.

BayTMS has analyzed their first 500 patients, including 63% females to 37% males, representing 95% cases of major depression and 5% cases of bipolar disorder with depression. They found that 33% of cases reported remission; 29% reported a response of greater than 50% improvement; 20% reported partial response (25-50% improvement); and 13% had no response, while 5% withdrew from treatment. These results were based on both an interviewer's assessment and the patient's self-assessment.

One of the benefits of TMS therapy, Dr. Trautner said, is that effects are long

[1] Dr. Trautner differentiated TMS treatments from "cranial electrotherapy stimulation," which uses electric current and pads attached to the skin, and is often confused with TMS.

lasting. This has been shown by animal studies of synaptic plasticity. The one contraindication of the therapy is any ferrous metal in and around the head, such as a metal plate, although dental work does not affect the treatment.

TMS has been compared with Electroconvulsive Therapy, and for psychotic symptoms ECT is still considered preferable. But ECT requires three treatments per week for four weeks, followed by maintenance treatments. ECT also requires anesthesia for each treatment, creates cognitive impairment during the course of treatment, and has poor durability—that is, it has a "robust" relapse rate.

Dr. Trautner reported new directions in TMS therapy: experiments with Theta Bursts, or ultra-high frequency; treatments in new locations including the dorsomedial prefrontal cortex and right suborbital frontal cortex; and synergy with the antidepressant ketamine.

Emerging indications—that is, conditions for which TMS may eventually be approved—include bipolar disorder, which has a depression component; adolescent depression; anxiety disorders such as obsessive-compulsive (OCD) and post-traumatic stress disorder (PTSD); auditory hallucinations and tinnitus; autism, based on John Elder Robison's *Switched On: A Memoir of Brain Change and Emotional Awakening*; attention deficit hyperactivity disorder (ADHD); Alzheimer's, cardio-vascular accidents (CVA), epilepsy, and other neurological disorders; chronic pain; and substance abuse and addiction.

During the course of his talk, Dr. Trautner took questions. Here are some responses.

Q. Do you take the patient off medication before and during TMS treatments?

A. The patient should stay on his or her meds. The effects are more durable with medication, and TMS can be thought of as an augmentation of medication, especially for patients who are not achieving a good response with medication alone. If TMS renders a good response, the patient can then consider discontinuing medication.

Q. What if the patient resists taking anything

A. To qualify for insurance coverage of the TMS therapy, the patient usually has to have failed with at least one medication. Some insurance requires a previous history of failure with three or four different medications.

Q. What does a typical TMS therapy cost?

A. The cost is $10,000, but that includes all the psychological evaluation as well as TMS treatments.

Q. How long does the TMS therapy last?

A. BayTMS follows patients for two years. Most patients report benefits for at least a year, using the two rating scales. Symptoms are reported and rated at the beginning, during treatment, and at the end.

Q. Do you do brain imaging before treatment?

A. Typically, you don't. But you can use functional MRI to see how the brain acts in a depressed state and when not depressed.

Q. What are the results with schizophrenia?

A. So far there's no data. TMS has been used to treat auditory hallucinations—the magnetic field is applied to the auditory cortex at a low frequency for an

inhibitory effect—but not for visual hallucinations or other symptoms of schizophrenia. Of four patients so treated, one reported full remission and two had improved function.