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IN THIS ISSUE

Focus of the Month:
Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation is Approved. Now What?

One year ago we reviewed the status of transcranial magnetic stimulation for depression, and concluded with the following *TCPR* Verdict: "TMS for depression: Approval is highly unlikely."

We were wrong. On October 10, 2008, the FDA approved the Neuronetics Neurostar TMS machine for the treatment of patients with major depression who have failed one prior antidepressant trial.

Did they make the right decision? Or is this a replay of the embarrassing approval of vagus nerve stimulation, which is still not covered by insurance a full 3 ½ years after its approval in July 2005? And if they did make the right decision, how feasible will the device be for office-based psychiatrists?

Efficacy

The Neuronetics FDA application was based on a placebo-controlled clinical trial of 301 patients with various degrees of treatment-resistant depression. These patients were randomly assigned to either fast frequency TMS delivered to the left dorsolateral prefrontal cortex (see this issue's interview with Dr. John O'Reardon for a good explanation of all the TMS jargon) or to sham TMS. As we covered last year, the results were not impressive, with a four week response rate of 18.1% on TMS vs. 11% for sham. This difference was statistically significant, as were most of their other results using various outcome scales, but the clinical significance of an 18.1% response rate is debatable. In fact, two years ago, when an FDA advisory panel looked at this data, the experts were so unimpressed that they recommended that TMS not be approved.

So what happened? Why did the FDA change its mind? Because Neuronetics reanalyzed their data, focusing specifically on the 164 patients who had failed a single prior antidepressant trial (the larger data set included patients who had failed up to four antidepressant trials). Looking specifically at these less treatment-resistant patients, the six week response rate for active TMS was 27.3% vs. 10.5% in the placebo group (see poster with this data at http://www.neuronetics.com/Clinical_Significance_Thase.pdf). Among patients with more than one prior antidepressant trial, there was no significant effect of TMS (Lisanby SH et al., *Neuropsychopharmacology* 2008 August 13, advance online publication).

Thus, when the FDA saw that patients who had failed only one prior trial responded at rates approaching three times the rate of placebo, it relented, and awarded the approval only for these less treatment-resistant patients. While we can appreciate why the FDA was more impressed with these new numbers, it's important to note that this reanalysis was done post-hoc, that is, it was conceived after all the results were in. These post-hoc analyses are exploratory by nature, and never conclusive. The appropriate scientific next step would be to conduct another trial and hypothesize a priori that those who have failed one previous trial will do the best. What are the chances of the company doing such a study, now that they have FDA approval? Can you spell "infinitesimal"?

Nonetheless, we view the treatment more positively than in the past largely

Continued on Page 2

Learning objectives for this issue: Learning objectives for this issue: 1. Describe the indication for which transcranial magnetic stimulation (TMS) has been approved. 2. Evaluate the evidence for the efficacy of TMS for depression. 3. Describe the procedure for the use of TMS. This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Transcranial Magnetic Stimulation

Continued from Page 1

because newer studies of TMS for depression show more benefit than did those on which we based our earlier negative impression. In one meta-analysis, for example, the results of older TMS studies (those published up to January 2002, including 13 studies and 324 patients) were compared with the results of newer studies (December 2005 to November 2006, five studies, 274 patients). While the older studies showed a moderate effect size of 0.35, the newer studies yielded a combined effect size of 0.76, which is considered large (Gross M et al., *Acta Psychiatr Scand* 2007;116:165-173). The authors suggest that later studies used more TMS sessions and larger sample sizes.

Recently, a particularly informative meta-analysis was published in a British journal (Schutter DJLG, P*sychological Medicine* 2008 Apr 30 early online), and reviewed 30 well designed sham controlled trials of TMS. All were trials of patients with non-psychotic depression, and all randomly assigned patients to either high-frequency TMS of the left dorsolateral prefrontal cortex (the LDPFC) or sham TMS.

A total of 1164 patients with major depression were enrolled in these 30 studies, of which 606 received real TMS and 558 received sham. The author reported that the overall weighted mean effect size for TMS treatment was 0.39, a moderate effect size. Such an effect size is comparable to many placebo controlled antidepressant trials, so if you can believe these studies, the treatment looks fairly impressive.

However, an alternative viewpoint is that this moderate difference between active and sham does not represent a true treatment effect, but rather a placebo effect. While all the studies tried to control for a placebo effect by randomly assigning patients to a sham condition, it is not clear whether patients were always fooled. This is because real TMS produces a clicking sound and causes scalp sensations, whereas sham TMS generally does not. If patients in the real TMS condition were able to guess their assignment, they might have felt more hopeful than those in the sham group, and any difference in depression scores might have been due to expectancy effects alone. Compounding this problem is the potential for investigator bias. In most studies, the researchers actually administering the treatment knew when they were delivering real or fake TMS, and they might have unconsciously communicated their enthusiasm for the new treatment (and lack of enthusiasm for the sham treatment) to patients.

The Schutter meta-analysis reported that of the 30 trials analyzed, six took measures to check the adequacy of the blind, generally by asking patients to guess which treatment they received. In five of those six trials, patients were unsuccessful in guessing their treatment condition, which is reassuring.

What about real life use of TMS? How feasible is it? Unfortunately, the economics of the device remain murky. I called Neuronetics to ask how much the Neurostar machine would cost me if I wanted to set up shop in my office, and I was told that the company "does not have a policy of issuing price quotes publicly." They are planning a "slow roll out," primarily to psychiatrists who already have experience using the device, for example, by having participated in clinical trials.

Reading between the lines, there are some delicate politics involved here. In order for the Neurostar to become successful, insurance companies are going to have to decide to pay for it. They will only pay if they are convinced that it actually works. Presumably, the Neuronetics strategy is to provide the device to psychiatrists who are more likely to achieve good results, and these would be those who have used the device before.

How much are insurance companies likely to reimburse psychiatrists for a typical 40 minute treatment session? The company is hoping for close to $400 per treatment session, which is the rate at which their researchers claim that TMS is as cost-effective as standard anti-depressant treatment (see http://tiny.cc/ENlee for their analysis). If insurance companies believe this analysis, they might reimburse at close to this rate. This may sound like a lot for 40 minutes of work, but you have to factor in various hidden costs. For example, you are going to have to gradually pay off the upfront cost of buying the Neurostar, which may be anywhere from $50,000 to $100,000. You'll need a room for the device, and you'll probably want to hire a nurse or a medical assistant to actually administer the treatments. Otherwise, you'll be spending your days placing magnetic coils on heads and pushing buttons – probably not the work you were hoping for when you went into psychiatry. In addition, you'll have to factor in another expense: about $100/session for a gadget called the "SenStar Treatment Link." These are replaceable sensors that the company says are necessary to ensure good contact with the head and to mitigate scalp discomfort. That may be true, but it's also a lot of extra income for the company – and less money for you.

But the really crucial question, and the one upon which the ultimate success of the Neuro Star device will hinge, is whether psychiatrists will refer patients who have failed only one antidepressant trial for TMS. According to the Star-D trial, the response rates of patients switching from a failed SSRI trial to another antidepressant were on the order of 30%, similar to the TMS 27.3% response (see *TCPR* May 2006). Therefore, it would make sense to try at least two, if not more, antidepressants before trying TMS, which is an inconvenient treatment that requires office visits five days a week for three weeks, and then on a tapering schedule for three additional weeks. If patients have not responded to several trials, then it might be reasonable to go to the next level of treatment. But therein lies the rub. Once patients have been through several meds and are ready to accept a trial of TMS, they fall into the category of highly treatment resistant patients who are unlikely to respond.

TCPR VERDICT: ***TMS: Probably as effective as meds, but feasibility is highly questionable.***

The New Brain Devices in Psychiatry: A Brief Review

By Dhwani Shah, M.D.

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Dr. Shah reports no financial relationships with any commercial companies related to this article.

In this issue of TCPR, we focus on TMS (Transcranial Magnetic Stimulation), which has just been approved for treatment resistant depression. There are also other brain devices in various stages of research and development. Here is a quick run-down of four of them.

VNS (Vagus Nerve Stimulation)

VNS is a surgically implanted device that is FDA-approved for both treatment resistant seizure disorders and treatment resistant depression. VNS is delivered by a pulse generator (like a pacemaker) that sends electrical pulses to the vagus nerve in the left side of the neck. The vagus nerve then transmits these pulses to the areas of the brain that are hypothesized to help with regulation of mood. As covered in previous issues of *TCPR* (Jan 2006, Jan 2008), VNS has had a rocky ride since its 2005 FDA approval for treatment resistant depression. A recent meta-analysis (Daban C, et al., *Journal of Affective Disorders* 2008; 110:1-15,) concluded that the efficacy of VNS to treat depression was modest at best, with only one double blind study demonstrating "rather inconclusive results." Cyberonics also struggled with getting their treatment paid for by major insurance carriers, and currently the device has not gained acceptance from the Centers for Medicare & Medicaid Services for reimbursement, leaving the patient to pay in full for the surgical implantation of the device, which can total over $20,000 (http://pn.psychiatryonline.org/cgi/content/full/42/5/2-a.) Cyberonics is hoping to demonstrate the efficacy of VNS in a large, randomized, double blind, multicenter trial nearing completion comparing VNS therapy at differing doses in treatment resistant depression (http://clinicaltrials.gov/ct2/show/NCT00305565?term=cyberonics&rank=1).

DBS (Deep Brain Simulation)

Psychosurgery has a decidedly checkered history, having received a bad name for itself after Walter Freeman developed trans-orbital prefrontal lobotomy and propagated its use across the United States until the 1950s (for background, see the book *The Lobotomist* by Jack El-Hai). But more sophisticated versions of psychosurgery continue to be used, and DBS is a neurosurgical procedure that can be seen as a 21st century alternative to psychosurgery. In DBS, an electrode is placed at 1 mm accuracy into one of several specific areas of the brain implicated in the neurocircuitry of mood and anxiety disorders. The electrode is connected externally to bilateral subcutaneous generators that can then be adjusted by the clinician. DBS is reversible in that the stimulator can be turned on or off, and the output of the device and stimulation can be controlled. This also allows researchers to create sham conditions that allow for blinded placebo controlled trials, a method that is unavailable for practical and ethical reasons in lesioning operations. However, DBS still requires neurosurgery, and thus has the potential for serious medical and neurological side effects. DBS is currently FDA approved to treat Parkinson's disease and essential tremor. Based on research that an area of the brain named the subgenual cingulate region (Brodmann area 25) is metabolically overactive in treatment resistant depression, Helen Mayberg et al. used this target for deep brain stimulation in six patients with treatment resistant depression. Four out of the six patients had sustained remission from their depression, and the antidepressant effects were associated with changes in their brain PET scans (Mayberg, et al, *Neuron* 2005; 45:651-660). Recently, there has been a flurry of interest and research in DBS for both treatment resistant depression and OCD, targeting specific areas of the brain involved in these disorders, including the anterior limb of the internal capsule, the subgenual cingulate region (extensively researched by Mayberg and colleagues), and the ventral internal capsule/ventral striatum, among others. (For a review paper of DBS in psychiatric disorders, see Larson P.S, *Neurotherapeutics*, 2008; 5:50-58.) Two device companies (Medtronic and St. Jude) are in the process of investigating DBS in severe treatment resistant depression in large scale multicenter, sham-controlled trials that are actively recruiting participants.

The New Brain Devices

Vagus Nerve Stimulation: Approved for treatment resistant depression, but efficacy has been questioned; not covered by insurance.

Deep Brain Stimulation: Deep electrode placement, requires surgery; investigational.

Magnetic Seizure Therapy: Alternative to ECT; seizure induced by magnetic field rather than electrical shock; investigational.

Cortical Stimulation: Electrodes implanted on top of cortex; investigational.

Magnetic Seizure Therapy (MST)

MST is designed as an alternative to ECT (electroconvulsive therapy). Whereas ECT uses a brief electrical stimulus to induce a seizure, thereby easing depressive symptoms, MST uses a magnetic stimulus to accomplish the same goal. The potential advantage of MST is that it may provide better control of the seizure onset patterns and seizure spread, thereby improving both the tolerability and efficacy of seizure

—*Continued on Page 8*

Q&A With the Expert

This Month's Expert:

Practical Issues in Using Transcranial Magnetic Stimulation

John O'Reardon, M.D.

Associate Professor of Psychiatry
University of Pennsylvania Health System

Dr. O'Reardon has disclosed that he has received research grants from Neuronetics, Cyberonics, Cerex Biopharma, and Pfizer, and is on the speaker's bureaus of Eli Lilly and Bristol-Myers Squibb. Dr. Carlat has found that there is no evidence of commercial bias in this educational activity.

TCPR: Dr. O'Reardon, the FDA recently approved TMS for depression. Can you clarify exactly what this approval was for?

Dr. O'Reardon: They approved a particular device made by Neuronetics (a TMS device manufacturer) to deliver TMS to a certain patient population. And the approved patient population is adults with major depression who have failed one fully adequate anti depressant trial in this episode.

TCPR: How did you personally get interested in TMS?

Dr. O'Reardon: My interest began 10 years ago, when I was doing a fellowship in mood disorders. I was already doing ECT and was interested in treatment-resistant depression. I wanted to find something that would be better tolerated than ECT and my mentor at that time (the late Marty Szuba M.D.) was interested in TMS. We did an initial study that showed that single sessions of TMS, active versus sham, had more than just local effects on the brain. It also had effects on the neuroendocrine system. For example, we showed that TSH (thyroid stimulating hormone) rose in response to active TMS but did not change with sham TMS. This actually replicated a finding that was already established with ECT.

TCPR: Can you talk a bit about the putative mechanism of TMS?

Dr. O'Reardon: The TMS device is an electromagnet which sends out magnetic pulses at frequencies that range from 1 hertz (cycle per second) to 20 hertz. When a dynamic magnetic field reaches the surface of the brain, it induces an electric field. Thus, TMS allows us to induce electrical activity in the brain.

TCPR: Which is ultimately what ECT does as well, right?

Dr. O'Reardon: Yes, but the difference is that a magnetic field passes unimpeded to the surface of the brain, so that it can be targeted, whereas when we pass electricity in ECT, it immediately dissipates. We don't have the option with ECT of focal brain stimulation. With TMS we have the option of basically targeting an area on the surface of the prefrontal cortex that is about 2 centimeters squared.

TCPR: And how do you decide which area of the cortex to target?

Dr. O'Reardon: We generally target the left dorsolateral prefrontal cortex. This came out of neuroimaging studies of patients with depression that were done in the early 90s, and the single most consistent finding was low metabolic activity in the left dorsolateral prefrontal cortex. The simplistic way of looking at this is that we believe that this area of the cortex is not working as hard as it should or is off-line in major depression, so we are using TMS to reactivate those neurons.

TCPR: I've heard about high vs. low frequency TMS. What is the difference?

Dr. O'Reardon: This is a fascinating aspect of TMS. Using low frequency TMS, we seem to primarily be stimulating GABAergic interneurons, so this tends to inhibit the prefrontal cortex. Now what would be the relevance of that to depression? It turns out that another way to do TMS successfully in major depression is to give inhibitory TMS to the opposite side of the cortex (the right side) to dampen what appears to be hyperactivity in the right prefrontal cortex (another imaging finding in major depression).

TCPR: How does one actually do TMS?

Dr. O'Reardon: You start by locating where the left dorsolateral prefrontal cortex is on an individual patient. To do that, we rest the magnet against the scalp at a point about a third of the way between the vertex of the head and the tip of the left ear.

Continued on Page 5

Q & A With the Expert

Continued from Page 4

We give single pulses until we get a twitch in the thumb or index finger, and this tells us we are over the motor cortex. Then, we go forwards 5 centimeters from there and we will end up over the dorsolateral prefrontal cortex.

TCPR: So now you've established where you are going to administer the pulses. What do you next?

Dr. O'Reardon: You determine the motor threshold, which is the energy required to cause that twitch of the thumb. For most patients the motor threshold is somewhere between 50% and 65% of the energy of the device. To actually administer the treatment, instead of giving single pulses, you will be giving trains of TMS at usually 10 pulses per second or 10 hertz. The FDA approval is for 35 minute sessions, though benefits have been found for sessions ranging from 10 to 40 minutes.

TCPR: So are you giving pulses continuously for 35 minutes?

Dr. O'Reardon: No. There is what is called an on and off period. There is a train of TMS that lasts 4 seconds, meaning 40 pulses, and then there is an off period of 26 seconds where you are giving no pulses at all. If you stimulated continuously for a very long train you would have an increased risk of seizure.

TCPR: What is the seizure risk?

Dr. O'Reardon: In the trials that led to the FDA approval there were 10,000 sessions of TMS administered to 325 patients and the seizure rate was zero. So the risk is generally felt to be certainly less than 1 in 1,000 sessions, possibly as low as 1 in 10,000 sessions which translates to 1 in 500 patients treated with TMS. So you are looking at a risk that is less than what would be the case with Wellbutrin. Worldwide, after 13 years of TMS research, the total number of seizures is on the order of 15, and most of those seizures had been where the duration of stimulus was outside the safety guidelines. At our center at Penn, we have been doing TMS since "1997", and we have not had any seizures to date, fortunately.

TCPR: How do patients experience the procedure?

Dr. O'Reardon: They are resting in a kind of armchair and the coil is placed on the scalp. They get about 5 seconds of stimulus every 30 seconds, and they hear the sound of the magnet pulsing, which is a kind of tapping noise. For the first few days they may feel scalp discomfort because 10 hertz is fairly intense and it will stimulate the muscle and the skin nerves as the pulses go through the scalp. After a few sessions they accommodate to that and it goes away. They can read. They can talk to you. When we had some college students in the study, some of them would be reading their novel or doing their reading homework while on the device.

TCPR: How many sessions are there in total?

Dr. O'Reardon: The FDA approval specifies five sessions per week for 20 to 30 sessions, followed by a six-session taper that lasts for three weeks. So an acute course, if you include the taper phase, is anything from seven to nine weeks.

TCPR: Is TMS being reimbursed by insurance companies?

Dr. O'Reardon: I would say it is too soon to expect much on that front. The FDA approval was in October 2008, and it will take six to 12 months before insurance companies develop policies to cover it.

TCPR: Do you think that the insurance companies will eventually cover it?

Dr. O'Reardon: I believe it is likely. Certainly the manufacturer is optimistic that TMS will be reimbursable. The cost advantage of TMS is that it is done in an office rather than a hospital. You don't need the procedure room and the recovery room. Patients have to observed throughout the session, but this can be done by a licensed professional like a nurse or a physician assistant. A psychiatrist needs to supervise the process, but I don't think it is going to be cost effective for most psychiatrists to be doing the treatment themselves.

TCPR: You can't get your secretary to do it?

Dr. O'Reardon: No. I did hear of one psychiatrist in Germany at one time who did do that, but that would definitely not be recommended. The person administering the treatment must have enough medical training to monitor for unexpected adverse effects, and to make sure that there are no indications that the patient is about to have a seizure, such as focal twitching in their hand.

TCPR: Thank you for this brief primer on TMS. We'll check in again in a couple of years and see whether the treatment has gained any traction among psychiatrists.

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Research Updates IN PSYCHIATRY

Section editor, Glen Spielmans, Ph.D.

ANTIDEPRESSANTS

SSRI Discontinuation Linked to Poor Outcomes

In a naturalistic study, researchers identified 87 patients in an outpatient clinic who had taken SSRIs for depression and who were clinically stable for at least five years. After five years, 27 patients elected to discontinue SSRIs, and 60 elected to continue. Patients who chose to stop taking SSRIs were much more likely to experience depressive relapse over a one year period relative to patients who continued on medication (62% vs. 16%). For patients discontinuing SSRIs, the median time to relapse was 10 months, while for those who continued their meds, the median time to relapse was 38 months (three years and two months). Age, gender, number of prior depressive episodes, and SSRI type and dose were not significant predictors of relapse, but presence of residual depressive symptoms did strongly predict relapse (Pundiak TM et al., *J Clin Psychiatry* 2008;69(11):1811-1818).

TCPR's Take: While the sample sizes are modest, the implications to the practicing psychiatrist are profound. Patients often ask us, "Will I have to take medication for the rest of my life?" We typically tell our patients that the longer they are in remission the safer it will be to taper their medications. But this study casts doubt on this clinical wisdom. While patients were not randomly assigned to continuation vs. discontinuation, in some ways this reinforces the results even more. Why? Because patients who naturalistically decided, in consultation with their psychiatrists, to taper their SSRI after five years would be the ones you would expect to have the best prognosis.

The extent to which the advantage for medication continuation represents a true prophylactic effect as opposed to discontinuation effects of the medications is unknown, though medications were slowly tapered in this study. Though not well studied, adding psychotherapy prior to medication discontinuation may help decrease risk of relapse (see research update in this issue).

PSYCHOTHERAPY

Cognitive Therapy Delays Relapse in Youth Depression

A recent trial examined the impact of adding cognitive-behavioral therapy to an existing SSRI regimen in the prevention of relapse in pediatric depression. After showing a treatment response to an open-label trial of an SSRI (usually fluoxetine), participants were then randomly assigned to either augment their medication by adding eight to 11 sessions of CBT or to continue medication at the same dosage. Over the six-month continuation treatment period, 37% of the medication group relapsed compared to 15% of patients in the CBT + medication group, a statistically significant difference. Parents reported greater satisfaction in the CBT + medication group, and a nonsignificant trend favored the combined treatment group in terms of child satisfaction with treatment and depression rating scale scores (Kennard BD et al., *J Am Acad Child Adolesc Psychiatry* 2008;47:1395-1404).

TCPR's Take:This appears to be the first study of its kind with depressed youth. The roughly 40% relapse rate on medication is very similar to rates seen in an earlier study examining long-term antidepressant efficacy in children (Emslie GJ et al., *Am J Psychiatry* 2008;165:459-467). The current study included only 46 participants, but the significant effect seen in favor of CBT suggests that its results are not a fluke. This study's results are consistent with findings from the psychotherapy literature which suggest that maintenance psychotherapy for psychotherapy responders reduces depressive relapse. Providing patients with CBT (or perhaps other psychotherapies) is likely an effective method to improve long-term treatment response.

PRACTICE ISSUES

The Role of Etiquette-Based Medicine

We've all been told from time to time that we should mind our manners. A Boston psychiatrist, Michael Kahn, suggests that manners are not limited to dinner parties; rather, he calls for "etiquette-based medicine." Dr. Kahn is not writing about displaying empathy toward patients (though this is certainly important) – he's talking about simply showing common courtesy and respect. He proposes that to increase patient satisfaction, physicians should seriously consider developing protocols for proper behavior, even creating checklists that remind us how to behave in the presence of patients. For example, he devised a checklist for an initial meeting with a hospitalized patient that included: asking permission to enter the room; introducing oneself; shaking hands; sitting down (smiling if appropriate); explaining one's role; and asking how the patient feels about being in the hospital. Such checklists could be adapted to a wide variety of situations and could be used to help train students and residents (Kahn MW, *N Engl J Med* 2008;358:1987-1988).

TCRP's Take: It is sad to think that physicians need to be reminded to display common courtesy; however, nearly every physician has heard patients complain of another doctor's poor manners. Treating patients with respect is important for many reasons, one of which is that it improves adherence to treatment. Devising some simple professional routines to use during client encounters is likely a good idea; it is hard to see a downside to consistent professionalism.

CME Post-Test

To earn CME or CE credit, you must read the articles and complete the quiz below, answering at least four of the questions correctly. Mail a photocopy or fax the completed page (no cover sheet required) to **Clearview CME Institute, P.O. Box 626, Newburyport, MA 01950**; **fax (978) 499-2278**. For customer service, please call (978) 499-0583. Only the first entry will be considered for credit and must be received by Clearview CME Institute by December 31, 2009. Acknowledgment will be sent to you within six to eight weeks of participation. This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of the Clearview CME Institute. Clearview CME Institute is accredited by the ACCME to provide continuing medical education for physicians. Clearview CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Clearview CME Institute maintains responsibility for this program and its content. Clearview CME Institute designates this educational activity for a maximum of one (1) AMA PRA Category 1 Credit™ or 1 CE for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

Please identify your answer by placing a check mark or an X in the box accompanying the appropriate letter. Note: learning objectives are listed on page 1.

1. Transcranial Magnetic Stimulation has been approved by the FDA for the treatment of: (Learning Objective #1)

[ ] a. Depression with psychotic features.
[ ] b. Depression which has failed one adequate antidepressant trial.
[ ] c. Depression which has failed up to four adequate antidepressant trials.
[ ] d. Depression which has failed one trial of ECT.

2. An FDA advisory panel initially recommended nonapproval TMS because: (L.O. #2)

[ ] a. There was an unacceptably high rate of seizures.
[ ] b. TMS was less effective than MAOI antidepressants.
[ ] c. TMS was ineffective for patients in the trial.
[ ] d. The TMS advantage over placebo was statistically significant but not robust.

3. Among less treatment resistant patients, the TMS response rate was nearly triple the placebo rate. (L.O. #2)

[ ] a. True [ ] b. False

4. A typical course of TMS requires: (L.O. #3)

[ ] a. Three weeks of daily visits, followed by a three week tapering phase.
[ ] b. Six weeks of daily visits.
[ ] c. Inpatient treatment three days a week for one month.
[ ] d. Inpatient treatment for one week, followed by 5 weeks of office-based treatment.

5. According to Dr. O'Reardon, TMS works by increasing levels of serotonin. (L.O. #3)

[ ] a. True [ ] b. False

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Your evaluation of this CME/CE activity (i.e., this issue) will help guide future planning. Please respond to the following questions:

1. Did the content of this activity meet the stated learning objectives? L.O.#1: [ ] Yes [ ] No L.O.#2: [ ] Yes [ ] No L.O.#3: [ ] Yes [ ] No
2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity? [ ] 5 [ ] 4 [ ] 3 [ ] 2 [ ] 1
3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice performance in a manner that improves your patient care? Please explain. [ ] Yes [ ] No

4. Did you perceive any evidence of bias for or against any commercial products? Please explain. [ ] Yes [ ] No

5. How long did it take you to complete this CME/CE activity? ___ hour(s) ___ minutes
6. **Important for our planning:** Please state one or two topics that you would like to see addressed in future issues.

Continued from Page 3

treatment. Like ECT, MST is performed under general anesthesia in a medical suite. Clinical trials and several case reports have already indicated that MST may cause less cognitive impairment than ECT, though it is not yet clear if it will be as effective as ECT (Lisanby et al., *Neuropsychopharmacology*, 2003; 28:1852-1865).

Cortical Stimulation

In cortical stimulation, electrodes are implanted on top of the brain's cortex; these electrodes are then connected with a wire to a neurostimulator implanted subcutaneously in the patient's chest (www.northstarneuro.com). The amount and frequency of the stimulation can be controlled by the clinician using a handheld device. A recent multicenter randomized controlled trial for improving the recovery from stroke demonstrated the treatment is safe, but failed to show efficacy (http://www.forbes.com/markets/feeds/afx/2008/01/22/afx4557007.html). The company is now focusing on using the device to treat depression. In October, the FDA granted conditional approval for a feasibility trial evaluating cortical stimulation for the treatment of treatment resistant major depressive disorder.

TCPR VERDICT: ***The research looks promising, but these devices still need to prove a benefit for our patients in large scale trials.***

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This Month's Focus: **Transcranial Magnetic Stimulation**

Next Month in *The Carlat Psychiatry Report*: An update on the use of psychotropics in pregnancy, including an interview with perinatal psychiatry expert Victoria Hendrick, M.D.