THE CARLAT REPORT PSYCHIATRY

A CME Publication

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

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Editor-in-Chief

Volume 13, Number 7&8
July/August 2015
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Interventional Psychiatry

Learning objectives for this issue: 1. Discuss the current neurostimulation options and compare/contrast the effectiveness of available options. **2.** Describe interventional psychiatry treatment options and how to identify which, if any, are most useful for your patients. **3.** Summarize some of the current findings in the literature regarding psychiatric treatment.

Neurostimulation Devices for Depression: An Overview

James Recht, MD, is a psychiatrist based in Cambridge, MA.

Dr. Recht has disclosed that he had no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

When we last reviewed neurostimulation devices 3 years ago, we concluded that there was some promise—but more sizzle than beef. Now there are more devices and more data. But is there more beef? Maybe.

We generally think of neurostimulation as a new technology, but its history is long. Beginning in the 1870s and

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In Summary

- We briefly review six different neurostimulation devices for depression.
- Invasive treatments include vagus nerve stimulation (VNS) and deep brain stimulation (DBS).
- Non-invasive options include repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST), transcutaneous vagal nerve stimulation (tVNS), and transcranial direct current stimulation (tDCS).
- Both rTMS and MST are probably effective for treatment-resistant depression; evidence for the others is less impressive.

Q&A With the Expert

Reflections on the Past and Future of TMS

Mark George, MD

Distinguished University Professor, Layton McCurdy Endowed Chair, Director, Brain Stimulation Laboratory

Dr. George discloses that he is an unpaid consultant to Brainsonix, Brainsway, Cerval/Neostim, Mecta, Neuronetics, NeoSync, Nervive, and Puretech Ventures. Dr. Carlat has reviewed this interview and found no evidence of bias in this educational activity.

TCPR: Dr. George, I guess if there is a "father of TMS" you would be one to potentially qualify for that role. When did you get involved in this research?

Dr. George: There are several modern parents, with Tony Barker inventing the modern machine in 1985, and John Rothwell and Mark Hallett developing the neurophysiological and neurological aspects. In the area of psychiatry, back in 1993 I had this then quite heretical idea that you could noninvasively, nonconvulsively stimulate the prefrontal cortex and ease people's depression. It was heretical because people thought the only way you could stimulate the brain to treat depression was with ECT, and that required a seizure. But nevertheless, we did the early trials, and now, over 20 years later, there are three large randomized controlled trials with Class I evidence showing that TMS is effective for depression. The first was funded by Neuronetics, which got FDA approval around 2008. Then we did a trial without industry funding, the NIH OPT-TMS (optimization of TMS) trial which also found positive results compared to sham

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through the turn of the last century, electrotherapy, adopted enthusiastically in the U.S. and Europe after its introduction by German pioneers, became standard treatment for melancholia, neurasthenia, and related conditions. The most commonly used instruments were, in fact, substantially similar to those used today in transcranial direct current stimulation (tDCS). In light of current debates about the extent of the placebo effect in brain devices, it seems instructive that over 130 years ago, internationally recognized experts convened a symposium to debate the following question: "Are the positive results produced by electrotherapy based on suggestion?" Concerns about observer bias, the absence of a clear explanatory model, and the fact that electrical treatments were "repeatedly suspected of attaining results through suggestion only" led to their eventual fall from favor. By the early 1900s, in fact, electrotherapy had essentially disappeared from mainstream practice.

Thus cautioned, let's sally forth into today's therapeutic "electro-landscape." We'll restrict our focus to the treatment of depression, and specifically (where data are available) to treatment-resistant depression (TRD). Up for your consideration are: transcranial magnetic stimulation (TMS); magnetic seizure therapy (MST); vagus nerve stimulation (VNS); transcutaneous vagal nerve stimulation (t-VNS); transcranial direct current stimulation (tDCS); and deep brain stimulation (DBS).

Transcranial Magnetic Stimulation (TMS)

What is it? Transcranial magnetic stimulation (TMS) is a non-invasive procedure that uses magnetic fields to stimulate nerve cells in the brain. The magnetic coils look different depending on the device used. In the Neuronetics device, the patient reclines in what looks like a dentist chair and a coil is lowered onto the scalp near the forehead. In the Brainsway device, the patient sits in a standard chair and the device is more like a helmet that is put over the entire head. Standard treatments occur once a weekday for six weeks.

How available is it for patients? Many psychiatrists are offering TMS therapy to patients; it is available in most areas.

Does it work? In 2008, the FDA approved rTMS as a treatment for adults with MDD who "have not responded to a single antidepressant medication in the current episode." As recently as early 2014 (Cusin C, Dougherty D, *Biol Mood Anxiety Disord* 2012;2(1):14), meta-analyses generally emphasized the paucity of well-designed trials and the often less-than-overwhelming results. For instance, the one large NIMH-sponsored, randomized, sham-controlled study "showed a statistically significant difference between the treatments, but overall low rates for both response and remission." According to authors Cusin and Dougherty: "Based on published data, the role for TMS in the treatment of TRD is still unclear."

Earlier this year, however, a team at Chapel Hill published the results of a meta-analysis of rTMS in a more narrowly defined population: "patients with major depressive disorder and 2 or more prior antidepressant treatment failures" (Gaynes B et al, *J Clin Psychiatry* 2014;75(5):477–489). They limited their data to "good- or fair-quality studies comparing rTMS with a sham-controlled treatment in TRD patients... published from January 1, 1980, through March 20, 2013." Their results were distinctly more encouraging: "rTMS was beneficial compared with sham for all outcomes... produced a greater decrease in depressive severity (high strength of evidence), and greater response rates (high strength of evidence)… finally, rTMS was more likely to produce remission (moderate strength of evidence); patients receiving rTMS were more than 5 times as likely to achieve remission as those receiving sham (relative risk = 5.07; 95% CI, 2.50 to 10.30)."

Conclusion: For carefully diagnosed cases of TRD, it appears reasonable to consider rTMS.

Magnetic Seizure Therapy (MST)

What is it? The patient sits (or lies) in a reclining chair. Small magnetic coils are housed in two round pads attached to a pole that comes out of the main body of the machine. The pads are placed on either side of the scalp, just behind the temples. The operator activates the device and electricity is pulsed into the magnetic coils housed inside the pads. It is similar to the TMS pulse, but the pulses are at a higher intensity and frequency so that they produce a seizure. The patient is under general anesthesia for the procedure. This process directly stimulates the portion of the brain that regulates mood. MST resembles ECT in the number and scheduling of treatments (typically 2–3 per week for 4 to 6 weeks) and the need for anesthesia.

Proponents claim that, compared with conventional ECT, MST can produce a more precise cortical seizure focus. This would have a few advantages. First, it would eliminate the need for the bite block used in ECT because the masseter (jaw muscle) would not be stimulated. Second, and more importantly, the stimulus would

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not reach brain structures important for memory, such as the hippocampus. This would lead to less acute post-ictal confusion, faster recovery times, and a lower risk of cognitive and memory impairment, the chief bugaboos associated with ECT.

How available is it for patients? Not FDA approved; it is available to patients with major depression only through a research protocol.

Does it work? Since 2006, a handful of studies have, with a fair degree of consistency, shown MST to be effective for TRD. A non-industry funded review published earlier this year (Cretaz et al, *Neural Plast* 2015;Epub May 13) describes response rates ranging from 40% to 60% and remission rates ranging from 15% to 30%. The authors were impressed that "most trials were conducted on patients suffering from TRD, who had failed previous therapeutic strategies and therefore had a worse prognosis."

They also found that MST does indeed cause fewer cognitive side effects than ECT—for example, the reorientation time was 2–8 minutes for MST vs. 15–25 minutes for ECT. In addition, MST is much less likely to cause prolonged memory loss. The downside is that MST, while effective, is quite a bit less effective than ECT for TRD. ECT posts remission rates of 50%-70%, at least double the reported remission rates from MST. The authors suggest that MST will gradually become more effective with improvements in lead placement, pulse frequencies, and other parameters.

Conclusion: It's not clear how MST fits into the range of treatments available. It causes fewer side effects than ECT, but it's less effective. And it may not be any more effective than TMS—which is a much less noxious procedure.

Vagus Nerve Stimulation (VNS)

What is it? Vagus nerve stimulation is a neurosurgical procedure. The patient is put under anesthesia, and the surgeon embeds a silver dollar-shaped device—the stimulator—under the skin of the upper chest, just below the collarbone. A second incision is made on the lower left side of the neck where three small electrodes are wrapped around the vagus nerve. The stimulator in the chest sends electrical impulses to the vagus nerve. The frequency and intensity of impulses can be adjusted non-invasively using a wand that interacts with the device remotely.

How available is it for patients? Though FDA approved, it is not widely available.

Does it work? Based on what many felt was lukewarm evidence (see for example *TCPR's* 2006 update), VNS was approved by the FDA in 2005 for treatment-resistant depression. Its invasive nature; potential for messy mechanical problems (for example, any time a battery malfunctions); and side effects (including cough, hoarseness, sore throat, and headache) have resulted in very limited clinical use. One recent review (Cusin C, Dougherty D, *Biol Mood Anxiety Disord* 2012;2(1):14) was a little more bullish, concluding that while the device is not effective for acute treatment of depression, its effect seems to increase over time. In an open-label extension, patients given VNS were followed and had one-year response rates of up to 34% and remission rates of 15%. But there was no control group for comparison.

Conclusion: VNS is almost certainly ineffective for the first 3 months after implantation, but may become effective over time. We need to see more studies to be sure.

Transcutaneous Vagal Nerve Stimulation (tVNS)

What is it? tVNS is like VNS but without the need for surgery. A branch of the vagus nerve supplies a part of the ear, allowing you to stimulate the nerve with an electrode that is simply placed against the ear. In practice, the whole set looks like wearing headphones and listening to an iPhone. You just charge it up and wear the electrodes for the prescribed amount of time. 15 minutes once or twice a day for two weeks, and you have a potential treatment for depression.

How available is it for patients? It is approved in some European countries for the treatment of refractory epilepsy and can be prescribed there.

Does it work? A single pilot study randomly assigned 37 depressed patients to tVNS (worn for 15–30 minutes a day for two weeks) or to sham treatment. Active treatment beat sham on the Beck Depression Inventory but not the HAM-D scale. There were no side effects. (Hein E et al, *J Neural Transm* 2013:120(5):821–827).

Conclusion: tVNS has promise, but it's much too soon to tell.

Transcranial Direct Current Stimulation (tDCS)

What is it? The device involves placing two electrodes—one at each temple—onto the patient's head with an elastic band and flipping a switch. A relatively weak, direct (as opposed to alternating) electrical current is delivered for 20 to 30 minutes, 5 days a week, for 2 to 3 weeks.

How available is it for patients? No FDA approvals. Do it yourself kits are available to anyone. Other, more legitimate devices are available by prescription.

Does it work? At the time of our last review, the available evidence was discouraging: two blinded, sham-controlled studies showed modest symptom improvement, but no significant difference between treatment and control groups (for information, see NIH pages http://1.usa.gov/1gjILX0 and also http://1.usa.gov/1fhBHK9). What's happened since then?

As mentioned in this issue's accompanying piece by Drs. Sahlem and Borckhardt (p. 8), a double-blind 2013 study randomized 120 subjects with MDD to active tDCS, sham tDCS, sertraline, or placebo. Active tDCS was better than sham, and the combination of sertraline and electricity was more effective than either treatment alone. Subsequent meta-analyses, however, have been mixed (of the three, one concluded that tDCS "has promise"; one found "a medium, significant effect size in outcomes"; and one euphemistically described the clinical utility of tDCS as "unclear when clinically relevant outcomes such as response and remission rates are considered").

Conclusion: Larger studies still needed!

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(Borckardt J, *Brain Stimul* 2013;6(6):925–928). And then the most recent large trial was published a couple of months ago and funded by Brainsway (George M et al *Brain Stimul* 2014;7(3):421–431), and their multisite international trial was positive as well and they got FDA approval about a year ago.

TCPR: How effective is TMS?

Dr. George: We've found that across multiple studies the chance of remission in treatment-resistant patients is about 30%, and the chance of response is about 50%–60%.

TCPR: And in terms of length of the effect, how long-lasting do we think TMS is?

Dr. George: We don't have a lot of good data on durability of TMS. We know that ECT has excellent acute efficacy rates, 60%–70%, but the effect is not very durable (George M et al, *Arch Gen Psychiatry* 2010;67(5):507–516). You have over a 50% chance of relapse at six months despite aggressive medication use. So far in the TMS literature, the effects appear to be more durable than ECT and maybe more durable than medications. Neuronetics was required by the FDA to do some long-term studies as a condition of approval. They found that if you are a remitter after the acute course of TMS, a year later you have about a 90% chance of still being a remitter—with the caveat that you have been on medications and sometimes required repeat tune-up sessions of TMS. That study has not yet been published, but the findings have been published in abstract form and they are encouraging. (Links to Neuronetics ongoing research can be found on their site here: http://bit.ly/1TOZXTv.)

TCPR: How often do patients get TMS tune-ups?

Dr. George: That seems highly variable. Our practice here in Charleston is to give people an initial course of TMS, and if they remit we do not automatically do maintenance TMS, but we maintain them on medication. If they do start to relapse we will go back in and do some sessions for a week or two, which often will bring them back to remission. We then talk to them about maintenance TMS. And there are no good rules yet or good studies about how to do maintenance. People are generally tapered to a treatment every week and then every two weeks attempting to try to reduce treatment to once a month. Many patients don't need repeat treatments, but others seem to, and unfortunately we don't have any way right now to predict who is going to need that level of TMS.

"A lot of people can't travel to a doctor's office every day; they live far away from a TMS device. So can you bake the cake faster? Can you get people undepressed faster? Or can you do all the treatments in a day? Different studies are now experimenting with that."

Mark George, MD

TCPR: When I've read the TMS studies, I've always been concerned about whether the treatment is truly double-blinded, because the active treatment causes a clicking and a scalp sensation. The concern is that patients and treaters might guess which is the active treatment arm, leading to a larger placebo effect in that group.

Dr. George: Yes, this was a real problem with the early studies of TMS. The treater is standing right beside the person every treatment session, which might be every weekday for an hour for four weeks, so that is a lot of exposure to a treater. To prevent positive treatment expectations, you have to prevent anybody who comes into contact with the patient from knowing which arm he or she is assigned to. The first Neuronetics trial did not rise to this level of methodology. They tried to keep the coil operators uninformed, but in an informal poll of everybody who was involved in that trial, all treaters figured out which patients were getting real TMS almost immediately. So that was not truly a double-blind trial.

TCPR: And could the patients guess which treatment they were getting as well?

Dr. George: They might have been able to, but in that trial, which was industry sponsored, they did not ask that question. Don't ask, don't tell. With the NIH-funded trial, we worked really hard and we came up with an active sham condition. We put a small ECT pad that was connected to a greatly reduced ECT machine and later a small TENS unit (transcutaneous electrical nerve stimulation) underneath the TMS coil. The patients in the sham condition get a small electrical discharge in those pads underneath the coil precisely at the time of the supposed TMS. So they get the exact same pain sensation as real TMS. In addition, the real versus the fake coils have a different tone to them when they discharge, and so we used noise-dampening ear plugs in the patients and the treaters. And with all of that work we were able to come up with an active sham condition that was truly a sham and was truly blind. And we did ask patients and treaters and raters across the trial what they thought they were getting, and they were not able to guess better than chance. So the first Neuronetics trial wasn't truly double blind by the most rigorous definition; The OPT-TMS was truly double blind, and the Brainsway group built on the technology that we developed in the OPT-TMS, and theirs also was truly double blind.

TCPR: So what do you see happening with the future of TMS?

Dr. George: I'm a bit of a dreamer. When we started all this, we chose some of these ways that we are doing it for no particularly good reason. My boss Bob Post and I had to make a lot of educated guesses. The idea of once a day with weekends off—I just modeled that on ECT. Could we make it more efficient? So, for example, a lot of people can't travel to a doctor's office

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every day; they live far away from a TMS device. So can you bake the cake faster? Can you get people undepressed faster? Or can you do all the treatments in a day? Different studies are now experimenting with that. I just came from a meeting and learned about a study in Korea in which they gave an entire course of TMS—30 treatments—in three days. They randomized people to intensive TMS versus the standard once a day weekdays for six weeks, and found the results were equivalent after 6 weeks.

TCPR: Have there been any other studies looking at this kind of accelerated treatment?

Dr. George: We recently published a study of patients who were admitted to the hospital for suicidality. We randomly assigned patients to either 15 sessions in three days vs sham and we found that the active group had their suicidal ratings cut in half on the first day.

TCPR: Is accelerated TMS off-label?

Dr. George: It depends on how you interpret the FDA label, which focuses on the number of treatments; the timing is kind of secondary. So someone can argue that it is not really off-label; it is just a different dosing schedule.

TCPR: What about TMS for patients who come into the office with their first episode of depression? Has that been studied?

Dr. George: It has not been formally studied, but yes, we have recently treated a cohort of new onset nontreatment-resistant depression and we had a 100% remission rate. There was one person in that group who had been wrongly diagnosed as having Alzheimer's disease, and when I took a history I found a pattern of chronic recurrent untreated mood disorder. When we treated him, his dementia turned out to be pseudodementia and it went away. So people are using it in depression in the setting of cognitive decline and with good results. Unlike ECT, it doesn't have any potentially negative cognitive side effects.

TCPR: I want to touch on an ethical issue. Psychiatrists who lease these expensive machines have a strong financial incentive to refer patients to the treatment. Other specialists have long wrestled with those kinds of issues, but not psychiatrists. Do you have any thoughts about that?

Dr. George: That's an important issue, and the level of conflict of interest depends to some extent on your treatment model. In one model treaters view themselves as referral centers, and most of the patients that they treat are not their patients. And in that model I think there is less of a conflict of interest, because the incentive is for the psychiatrist to do their best job with TMS so they will get future referrals. That is the way ECT has commonly occurred; there are usually one or two ECT providers in a town, and then different psychiatrists will refer to that ECT practice and so there is less self-referral. Now, if you have a small practice and you own or lease the device and you self-refer your own patients, that could be more problematic. At the minimum, you would certainly need to inform your patients about the potential economic incentives so that they are aware of it. You might also consider a policy in which someone else who is not economically linked to the decision should chime in to say yes or no.

TCPR: Seeing TMS being adopted so widely must be pretty satisfying to you after all the fundamental work you did on it.

Dr. George: In psychiatry we don't have many good examples of rags to riches, taking a far out idea into a clinically usable technique. TMS for depression is thus unique. So I have been very satisfied with the way it has gone and I think the future is promising. But what I say to everybody is that I would love in 20 years to come back and find that no one is using TMS and that we have figured out something else that is even better. And that TMS as a technology was just a bridge to even more effective ways of modifying the brain therapeutically. So I am not necessarily wedded to TMS at all; it is one technology and it may become a bridge to even more effective ways of modifying neural circuits and helping people who are suffering.

TCPR: Thank you, Dr. George.

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Deep Brain Stimulation (DBS)

What is it? In this invasive form of treatment, electrodes are surgically implanted in deep brain structures, including the subgenual cingulate cortex (SCC; also known as Brodmann area 25, ref: Drevets et al, *CNS Spectr* 2008;3(8):663–681) and the ventral striatum/ventral cortex, that have been implicated in depression.

How available is it for patients? Available with proper consultation and assessment by doctors. This may require consults with multiple specialists, including psychiatrists, psychologists, neurologists, and neurosurgeons, to determine if the device is appropriate.

Does it work? After a series of very impressive open-label trials showing robust responses and few side effects, several large, multi-center randomized, sham-controlled studies were launched, accompanied by fanfare and great expectations. Disappointment has followed: At least two of these, one sponsored by Medtronic (http://bit.ly/1Hqsk1G) and the other by St. Jude Medical (http://www.sjm.com/broaden), have reportedly been shut down due to lack of measurable benefit in the treatment arms. According to one review author, "researchers involved remain hopeful that modifications of inclusion criteria and technique might ultimately result in a demonstrable clinical benefit for some subset of patients..." (http://bit.ly/1fCL7jE)

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Q&A With the Expert

The Practice of Interventional Psychiatry

Nolan Williams, MD

Instructor, Psychiatry and Behavioral Sciences, Stanford University

Dr. Williams has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: You have written about this new breed of psychiatry and psychiatrists, interventional psychiatrists, and you are certainly one of very few in the country that is actually doing it. What is interventional psychiatry?

Dr. Williams: In some sense we are all "interventional" psychiatrists because we provide interventions of various kinds to help our patients. But I use the term in a way that's similar to how it's used in cardiology and radiology and other specialties. These are doctors who have specific training to perform procedures that are typically more invasive than standard practice.

TCPR: What do you mean by more "invasive"? Does that mean some kind of surgical procedure?

Dr. Williams: Not necessarily. Some of the devices, like transcranial magnetic stimulation, don't entail breaking the skin, but others, such as deep brain stimulation, do. There's a continuum of invasiveness with the many devices available. What separates interventional psychiatry from psychopharmacology or psychotherapy is that these are pieces of hardware that interact with the brain in some way. You could also call this "device psychiatry" but "interventional psychiatry" is more consistent with how the term is used in the rest of medicine.

TCPR: What are the devices that fall within the purview of interventional psychiatry?

Dr. Williams: We're witnessing an explosion of magnetic and electrical devices to treat different problems, so the list is expanding rapidly, and there are many experimental devices being tested, probably dozens. But to stick with those for which we have the most evidence, on the less invasive end of the continuum, you have transcranial direct current stimulation (tDCS—not approved by the FDA), transcranial magnetic stimulation (TMS—approved for MDD), magnetic seizure therapy (MST, not approved by the FDA), and of course electroconvulsive therapy (ECT). On the more invasive end, meaning that they require neurosurgical procedures, there is deep brain stimulation (approved by the FDA under the humanitarian device exemption for OCD), vagus nerve stimulation (approved by the FDA for MDD), and epidural prefrontal cortical stimulation (EpCS—not approved by the FDA). [Editor's Note: This month's lead article describes most of these devices as well as the evidence for efficacy.]

TCPR: What kinds of patients get referred to you?

Dr. Williams: Typically, the depressed patients I see are at the end of the road. They have failed essentially every major approved psychiatric intervention and some experimental less invasive ones. They are very desperate.

TCPR: Can you give us an example?

Dr. Williams: I took care of a middle-aged woman, a professional in the medical field, who had chronic depression, had failed six to eight antidepressants, had forty treatments of ECT, and had tried the vagal nerve stimulator, but was still chronically suicidal. She tried to hang herself in the emergency room one time, and was hiding razor blades in the house to kill herself.

TCPR: And what treatment did you offer her?

Dr. Williams: This was the cortical stimulation device, which is experimental for depression. It involves a burr hole through the skull but not actually piercing the brain tissue. An electrode is placed between the skull and the brain, usually on the dura mater, and this stimulates the dorsolateral prefrontal and frontopolar cortices, which we believe has low activity in depression. The patient had a dramatic turnaround. She did not return fully to her job, but she is currently working as a medical writer. She hasn't had a suicide attempt in a very long time. She is largely not depressed and stays remitted. Every once in a while—once a year or something—she will have an episode for a couple of weeks, but she is largely okay.

TCPR: When you discuss these treatments with your patients, what do you say? I mean, I'm a fairly skeptical person, and I could imagine myself thinking, so you are going to be putting an electrode on my brain and you'll be stimulating some neurons, but do you really know what's happening in there other than that the brain is going to get reset in some way?

Dr. Williams: Certainly you should be skeptical, and I tell you this as a skeptic myself. The first question a lot of folks have is what is this device—whether it's TMS or a device requiring surgery—going to do to me? And just as we don't know with any certainty how therapy or medication works, I can't tell you absolutely how our devices work. What I can tell you is that we can use functional neuroimaging to identify certain neural circuits that are characteristic of depression, and that when we stimulate

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those circuits there seems to be a downstream effect in how different regions of the brain communicate with one another. We use something called diffusion tensor imaging that allows us to look at the white matter tracts that connect brain regions.

TCPR: That makes sense, but aren't patients still quite reluctant to actually have neurosurgery?

Dr. Williams: It is actually not a huge jump for somebody who has gone through 40 ECT treatments, has had anesthesia 40 times, and has had some trouble with cognitive symptoms. We are saying that we are going to give you anesthesia one more time. And in the case of cortical stimulation, you just introduce a small stimulation paddle between the dura and the skull and have a pacemaker-sized battery implanted into the chest under the skin. That is not necessarily a foreign idea by the time they get to me, and many times these people are expecting something like this.

There is a 1% risk of a hemorrhage with DBS, which is real and needs to be thoroughly discussed. There is somewhere between 3%-5% risk of infection, generally in the pocket around the battery under the skin of the chest, but it can also be around the lead in the brain, and that is a major concern for any person contemplating an implanted device, but particularly for patients with OCD who have contamination concerns. So there is an extensive discussion about surgical technique and that sort of thing, and they have to accept that risk before we proceed.

"In some sense we are all 'interventional' psychiatrists because we provide interventions of various kinds to help our patients. But I use the term in a way that's similar to how it's used in cardiology and radiology and other specialties. These are doctors who have specific training to perform procedures that are typically more invasive than standard practice."

Nolan Williams, MD

TCPR: I'm assuming that the patients you see for OCD have pretty significant symptoms.

Dr. Williams: Yes—for example, I saw a gentleman with OCD who had multiple symptoms. He had a worry that he had killed his parents. At its worst, this became almost a delusion and he needed to have his parents call him to convince him that he did not actually kill them. He also had unusually severe contamination fears. He would take two-hour showers and would have to pay a sitter to watch him to make sure he didn't scrub his skin away. He also had elaborate ritual about food. After shopping, he would transfer all of his groceries from plastic containers to glass containers because he viewed that as less contaminated. He would have to put the food outside the house to ensure that it was pure. This ritual took so long that often the food would spoil before he ate it. He would then eat only sugar and drink only water for a while until his obsessions diminished enough to go back to the store.

TCPR: What treatment did he receive?

Dr. Williams: He received deep brain stimulation, and that didn't cure him, but it brought his symptoms down to a level where he could participate in therapy like somebody with mild to moderate OCD.

TCPR: When you talk to these patients, very treatment resistant, how do you go about deciding on which interventional treatment to use? There are so many of them.

Dr. Williams: It depends on the diagnosis. But for this patient with severe OCD, I said to him, "Your symptoms are very severe. You meet criteria for deep brain stimulation, but I am going to have this clinical trial of TMS coming down the pike the next few months. The open-label data suggest that about a quarter of the people who get TMS have the same degree of improvement that some people get with deep brain stimulation, so do you want to go through a less risky intervention—TMS—or do you want to skip forward to DBS that would involve having something implanted permanently?" This gentleman was severely suffering and didn't want to spend any more time trying other things. So he decided to go straight to surgery. Other OCD patients that I've talked to want to take lower-risk interventions first, so they would do something like TMS.

TCPR: This is a fascinating time for psychiatry.

Dr. Williams: Absolutely. It is a very interesting time. We have forever tried to change the brain using therapy, and we can at least temporarily change the way the brain is working in psychiatric conditions with psychopharmacology. With interventional psychiatry, it looks like we can induce long-term changes with brain stimulation that persist if the brain stimulation approach is continued.

TCPR: Thank you, Dr. Williams.

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Fisher Wallace and Alpha-Stim for Depression? Claims vs Evidence

Gregory L. Sahlem, MD, clinical instructor of Psychiatry and Behavioral Sciences at the Medical University of South Carolina

Jeffrey J. Borckardt, PhD, associate professor and director of the Biobehavioral Medicine Division, Brain Stimulation Laboratory and Biobehavioral Medicine Division at the Medical University of South Carolina

Both Drs. Sahlem and Borckhardt have disclosed that they have no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

Carly Simon swears by it. The daytime show "The Doctors" gave it a glowing review. Ads for it seem to be invading psychiatrists' Google search results. We're talking, of course, about the Fisher Wallace Stimulator, touted by the manufacturer as being an effective treatment for depression, anxiety, insomnia, and pain (http://www.fisherwallace.com/). The Alpha-Stim device makes similar claims (http://www.alpha-stim.com/). How do these devices work? Are they actually effective? And where do they fit into the rapidly expanding array of neuromodulators?

If you want to understand these devices, it's best to start by learning about their simpler cousin process, transcranial direct current stimulation (tDCS). Picture a battery with a wire attached to the negative end (the anode) going into a light bulb and returning to the battery's positive end (the cathode). Electrons flow through the wire, heating the lightbulb's filament to create light. This one-way electrical circuit is called direct current (DC).

Now, imagine that the lightbulb is replaced with your skull, and the wires from the battery go to conductive pads that are kept on either temple by a headband. You are now picturing a simple tDCS device. A small charge will flow to your temple and will stimulate the part of your cortex under the electrode. If we're talking about, say, the left dorsolateral prefrontal cortex, which is thought to be hypoactive in depression, this stimulation will theoretically increase electrical activity there and ease your depression.

It makes sense, and it may actually work—according to a recently published randomized sham-controlled trial. In the study, 120 mildly treatment-resistant patients with MDD were randomized to tDCS alone, tDCS combined with sertraline, sertraline alone, or placebo, and followed for 6 weeks. Both tDCS and combined tDCS and sertraline worked better than placebo alone or sertraline alone, and the combined treatment posted the best outcomes of all (Brunoni AR et al, *JAMA Psychiatry* 2013;70(4):383–391). It's not a huge study, and we'd like more data, but we can at least say that this technology looks promising—and the side effects are almost non-existent.

How are the Fisher Wallace Stimulator and the Alpha-Stim devices related to tDCS? They're very similar except that the current going to the skull is alternating current (AC) instead of direct current (DC), and for that reason they are categorized as tACS (transcranial alternating current stimulators). In DC, the flow of electrons is constant and in one direction, but in AC, the flow changes direction frequently. AC is how electricity is transported to households, and in that context it has the advantage of being more efficient and cheaper to deliver.

Why would AC have any advantage over DC for brain stimulation? It's not clear. The theoretical advantage of AC is that the brain has its own natural oscillations, and with alternating current you can either try to match the brain's ongoing frequency by stimulating at that frequency, or disrupt it with alternate frequencies. Both the FWS and Alpha-Stim

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Some Useful Facts about Transcranial Stimulators

How can patients get the devices?

- A prescription is required for both the Fisher Wallace Stimulator and Alpha-Stim.
- tDCS devices are readily available on the internet without a prescription.

How much do they cost?

- The Fisher Wallace Stimulator costs $699, discounted to $599 for Medicaid, Medicare, veterans, and first responders (police, fire, EMT, etc.).
- The Alpha-Stim AID (for anxiety, depression, insomnia) costs $795; and the Alpha-Stim M (for acute, chronic, and post-traumatic pain) device is $1,195.
- tDCS devices can be had for less than $50, but variations can go up over $400 (https://thebrainstimulator.net/, http://tdcsplacements.com/tdcs-devices-market/).

Are they covered by insurance?

- According to the Fisher Wallace website, the device is not in-network with any insurance providers at this time.
- Some plans that cover durable medical equipment (a class of medical equipment that is used in the home, such as nebulizers and wheelchairs) will pay for Alpha-Stim. Patients should speak with their insurance providers.
- tDCS is not covered by most insurance companies.

Are the devices safe?

- Fisher Wallace: 1 in 500 patients experience headache upon using, and 1 in 250 patients have experienced increased wakefulness after using. A small number of patients have experienced skin irritation at electrode sites (http://www.fisherwallace.com/pages/published-research).
- Alpha-Stim: According to the company's website, clinical studies have found only minor side effects, such as headaches, and skin irritation at electrode sites has been reported by a tiny fraction of users (http://www.alpha-stim.com/healthcare-professionals/clinical-research/).
- tDCS: There have been some reports of headaches, dizziness, or irritation around the electrode sites reported. There are no studies on the long-term effects of repeat sessions of tDCS stimulation.

Which TMS Device Should You Buy?

Daniel Carlat, MD, Editor-in-Chief, Publisher, The Carlat Psychiatry Report

So let's say you've decided to take the TMS plunge. With three devices currently FDA cleared, you have some decisions to make. The following table brings together some information you might find useful. I focused on Neuronetics and Brainsway, with a blurb at the end about Magstim, the latest device to be approved. Material for this comparison came from various sources, including company websites and interviews with community practitioners. The TMS business is competitive and fast-moving, and companies often adjust pricing and improve products—so contact the manufacturers for updated info.

TMS Showdown: NeuroStar vs Brainsway

	Neuronetics NeuroStar (neurostar.com)	**Brainsway Deep TMS (www.brainsway.com/us/depression-treatment-use)**
Date cleared by FDA	**2008**	**2013**
Efficacy	• Recent meta-analysis reported 18.6% remission rate vs. 5% for sham (Berlim et al, *Psychol Medicine* 2014;44:225–239). • Easier to adapt for off-label uses, because adjusting location of coils to stimulate or inhibit different parts of brain is easier than Brainsway helmet.	• High remission rate (32.6% vs. 14.6%) in company-sponsored trial (Lefkowitz et al, *World Psychiatry* 2015;14:64–73), but no head-to-head trials (so to speak) have been done. • Being marketed as "deep TMS" as opposed to Neuronetics' "repetitive TMS."
Provider experience	• Excellent customer service, help with getting insurance coverage, help with setting up TMS practice. • Larger device and less portable, so requires a dedicated room. • Can store stimulus parameters in computer with device, which is convenient when a patient returns.	• Smaller and more portable, can move to different rooms (though most busy practitioners will maintain a dedicated room regardless). • No ability to store stimulus parameters, so must enter them manually each time patient returns.
Patient experience	• More comfortable coil. Some scalp sensation, but rare to have sensation in mouth. • Takes longer: 40-minute treatments five times a week for 4 to 6 weeks. • More ability to talk during treatment because ratio of non-stimulus to stimulus is higher.	• Helmet coil. Deeper and wider penetration leads to more facial movement and jaw pain. Many patients must wear a bite guard. • Quicker treatment: 20-minute treatments five times a week for 4 to 6 weeks. • Less ability to talk because higher proportion of time involves stimulus, and stimulus often leads to jaw movement.
Cost to provider	• About $75,000 upfront cost to purchase device, then $100/treatment. Can buy treatments in bulk to pay closer to $75/treatment. • Device not cooled, so can treat only one to two patients per hour, depending on dose required (thus you make less money).	• Leased by the year, about $50,000-$70,000/year. Lease usually covers cost of unlimited treatments in first year, then it is about $75/treatment. • Device is air cooled, so can treat up to three patients per hour (thus you can make more money).
Cost to patient	No clear differences. Cost to patient is usually $300-$400 per session, total treatment cost varies from $7,000-$14,000 depending on number of sessions, office fee schedules, etc… Many insurance companies reimburse at least some of the cost.	
Bottom line	Brainsway: More lucrative for provider, possibly more effective, but more side effects. NeuroStar: More comfortable for patients, better customer service for provider, can do psychotherapy during treatment.	

Magstim TMS: A game changer?

- Magstim is a new rTMS device that was cleared by the FDA in May 2015.
- Rumor has it that it will be offered for sale to physicians at about $60,000, and that there may be NO per-treatment charges, which would make the whole package *much* cheaper than either NeuroStar or Brainsway. If so, expect both established companies to scramble quickly to change their pricing structure. Magstim's coil will be air- or fluid-cooled, and will be capable of theta bursts (six-minute treatments).
- More information can be found at www.magstim.com.

Research Update IN PSYCHIATRY

FOOD AND COGNITION

Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial

(Valis-Pedret C et al, *JAMA Intern Med* 2015. 11.doi:10.1001/jamainternmed.2015.1668. Epub ahead of print.)

Background:

As our patients age, they often worry about their memory and ask us if we can prescribe them something to either improve their memory or to prevent memory loss in the future. Unfortunately, we don't have much to offer in terms of medications. Acetylcholinesterase inhibitors are somewhat helpful for those already diagnosed with dementia, but don't seem to prevent cognitive decline. What about diet? Some observational studies have hinted that specific foods might protect against cognitive decline. This study was a randomized clinical trial conducted to determine if a Mediterranean diet (an antioxidant-rich cardioprotective dietary pattern) does indeed delay cognitive decline.

Methodology:

- 447 cognitively healthy men and women from Barcelona, Spain (mean age 66.9 years) were enrolled in this trial. They all had cardiovascular risk factors, but no actual heart disease (this was part of a larger study about the effects of diet on heart disease).
- They were randomly assigned to one of three intervention groups: a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advised to reduce all dietary fat). Everyone had neuropsychological testing and Hamilton depression scale testing both at the beginning of the study and at the end. They were followed for a median of 4.1 years.

Results:

- A lot of participants dropped out of the study before getting their second neuropsych tests—113, or 25.3% of the group. Those who dropped out had somewhat lower MMSE scores, and were more likely to have the ApoE allele, a risk factor for dementia. This means that the results of the study are more likely to apply to elderly people who are sharper and who don't have the ApoE allele.
- Participants assigned to the Mediterranean diet plus olive oil significantly outperformed those on the control diet in two of the three composite scores: frontal cognition and the global cognition. Those assigned to the Mediterranean diet plus nuts outperformed control on the memory composite score. Over the study period, 37 people developed mild cognitive impairment, with no significant difference among the different diets. The intervention had no effect on depression scores.

TCPR Take:

- The bad news: There were methodological problems with this study. (1) This was a post-hoc analysis of a subsample of data from a larger clinical trial. (2) There was substantial dropout rate, limiting the generalizability of the findings. (3) The subjects were not blinded to their treatments (eg, their diets). (4) The sample size was not big enough to be really confident in the findings.
- The good news: Nonetheless, the researchers did show that randomly assigning people to Mediterranean diets leads to measurable cognitive improvement relative to people asked simply to reduce dietary fat.
- Practice implications: Since the Mediterranean diets have been shown to improve heart health, and given these positive findings on cognitive functioning, go ahead and recommend this diet to your elderly patients. You can find more specifics about the diet from the National Center for Biotechnology Information site: http://1.usa.gov/1PFcsw5.

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Fisher Wallace and Alpha-Stim for Depression? Claims vs Evidence

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have patented frequencies (sometimes called "waveforms"), which the manufacturers say are the keys to how their devices modulate neuronal activity.

Regardless of the theoretical mechanism, the key issue is whether the contraptions actually help your patients. The company websites make prominent mention of the fact that their devices have been "cleared" by the FDA for depression and other conditions. But for those not steeped in FDA regulatory policy, this is a potentially misleading statement. the FDA "clears" a device, it does not mean that it has been "approved," nor does it mean that the agency has reviewed any efficacy data. Instead, it means that the FDA has determined that the device is similar to other devices previously approved, often for indications completely different from the one being marketed. Nonetheless, the company websites state that the devices are proven to be effective treatments for depression.

To dig deeper into these claims, we reviewed both the company-cited publications (http://bit.ly/1BhuAKg) and any other data we could find via standard databases such as PubMed. We were not able to find any published large-scale (meaning 200-400 subjects) randomized, controlled trials for the treatment of MDD. The data that both companies cite as demonstrating efficacy are derived from small studies (none have enrolled more than 70 patients, and most enrolled about

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CME Post-Test

This CME post-test is intended for participants seeking *AMA PRA Category 1 Credit*™. For those seeking ABPN self-assessment (MOC) credit, a 25 question pre- and post-test must be taken online. For all others, to earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by August 31, 2016. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on p. 1.

1. Of the following neurostimulation treatment options, only _____ is an invasive procedure. (Learning Objective #1)
   [ ] a) Transcranial magnetic stimulation (TMS) [ ] b) Magnetic seizure therapy (MST)
   [ ] c) Vagus nerve stimulation (VNS) [ ] d) Transcranial direct current stimulation (tDCS)

2. Which of the following neurostimulation treatment options is FDA approved for treatment-resistant depression? (LO #1)
   [ ] a) Deep brain stimulation (DBS) [ ] b) Repetitive transcranial magnetic stimulation (rTMS)
   [ ] c) tDCS [ ] d) MST

3. In a recently published trial, 120 patients with depression were randomized to treatment with tDCS, tDCS with sertraline, sertraline alone, or a placebo. The most effective treatment was: (LO #2)
   [ ] a) tDCS [ ] b) tDCS with sertraline [ ] c) sertraline alone [ ] d) placebo

4. Both the Fisher Wallace Stimulator and the Alpha-Stim devices are categorized as _____ because of the type of current they use. (LO #2)
   [ ] a) DBS [ ] b) rTMS [ ] c) tDCS [ ] d) tACS

5. TMS was found to be effective for treating depression in _____ large randomized controlled trials. (LO #3)
   [ ] a) Two [ ] b) Three [ ] c) Four [ ] d) Five

6. The chance of relapse with ECT at six months is _____. (LO #3)
   [ ] a) 15% [ ] b) 30% [ ] c) 50% [ ] d) 70%

7. Deep brain stimulation is currently approved by the FDA HDE (Humanitarian Device Exception) for which condition? (LO #2)
   [ ] a) Anxiety disorder [ ] b) Binge eating disorder
   [ ] c) Depression [ ] d) Obsessive compulsive disorder

8. The risk of hemorrhage with DBS is ____ and should be discussed with the patient. (LO #3)
   [ ] a) 1% [ ] b) 3% [ ] c) 5% [ ] d) 10%

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO PAID SUBSCRIBERS

Fisher Wallace and Alpha-Stim for Depression? Claims vs Evidence

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20) focusing on other conditions (such as substance use and anxiety disorders) or on mixed pathologies. Some of these studies included a depression measure, but none specifically targeted MDD. The company websites also cite anecdotal evidence from clinicians. However, none of these sources of evidence, either alone or in aggregate, rise to the level that we usually require when deciding on treatments for our patients. At best, they suggest possible efficacy.

What about tDCS? The evidence for tDCS in depression is stronger (we referenced an impressive result above), although smaller studies have been contradictory (http://bit.ly/1IfSqZk). No tDCS device has yet been FDA cleared for any psychiatric indication, though patients can buy such devices very cheaply from the internet.

The bottom line is that both tACS and tDCS devices suffer from a shortage of good evidence for efficacy in depression. While we did not thoroughly review the evidence for other indications, such as anxiety or insomnia, it appears that the company-cited studies for these are also quite small and methodologically weak.

TCPR VERDICT: Fisher Wallace and Alpha-Stim for depression: They probably can't hurt, but they may not help either.

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This Month's Focus:
Interventional Psychiatry

Next issue of *The Carlat Psychiatry Report:* Sleep Disorders

Neurostimulation Devices for Depression: An Overview

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but for now, DBS remains an experimental form of treatment.

TCPR VERDICT:

Overall Verdict on Brain Stimulation for Depression

We have significantly more data now than we had just 3 years ago. And based on this evidence, the following conclusions seem reasonable.

- rTMS is effective for depressed patients who have failed one or more trials of an antidepressant.
- MST may have similar efficacy as rTMS.
- VNS, tVNS, tDCS, and DBS are interesting, but it's still too soon to tell.