

**FEATURE**

## Can magnets cure depression?

**Transcranial magnetic stimulation is gaining ground as a therapy for treatment-resistant depression.**

By Kirsten Weir

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Sharon Gray\* has had depression for most of her life. She was first diagnosed at 30, but she believes her depression started much earlier. Now 61, the retired police lieutenant from Columbus, Ohio, has seen clinical psychologists and psychiatrists and taken antidepressant medication for most of the last three decades. The treatments have left her functional, she says, but still mildly depressed. Every so often, she's suffered periods of more severe depression.

In 2007, desperate for a new option, she flew to Atlanta for a therapy that, at the time, was still experimental: transcranial magnetic stimulation, or TMS. Just past the halfway point in the monthlong course of treatment, "I had what I thought were miraculous improvements," Gray says. "I went to sleep on a Tuesday night depressed, and woke up Wednesday morning not depressed."

To celebrate, she went jewelry shopping. If that sounds trivial, think again: "I had not been interested in my appearance for so long," she says.

The following year, in 2008, the Food and Drug Administration (FDA) approved TMS as a treatment for people with major depression who have failed to respond to at least one antidepressant. Initially, the agency approved just one TMS device, called NeuroStar, made by the company Neuronetics. In 2013, the FDA approved a second device, manufactured by Brainsway.

In the years since FDA sanctioned the therapy, TMS treatment centers have been popping up across the country. Slowly, insurance companies have begun to cover the non-invasive, though costly, treatments. But plenty of questions about TMS still linger, including how best to deliver it, which patients make the best candidates and even what, exactly, the device is doing in the brain.

Despite that, the therapy is gaining support from patients and mental health providers alike. "I think it's a promising treatment," says William McDonald, MD, a psychiatrist at Emory University School of Medicine who was involved in the clinical trials that led to the approval of the NeuroStar device. "I'm a skeptic. But if I had significant depression and I had failed one or two antidepressants, I'd have to consider TMS."

### Changing neural networks

TMS is typically administered by a physician or a nurse. The procedure involves a non-invasive machine placed against the scalp. The device sends short but intense magnetic pulses into the brain, where they generate an electric current. The pulses are centered over the left prefrontal cortex, an area that often shows abnormal electrical activity in depressed patients. A typical course of TMS therapy involves 20 to 30 sessions, generally given in three to five treatments per week for four to six weeks. The full course of therapy with the pricey machines can cost \$6,000 to \$12,000. During the treatments, patients remain awake and alert, seated in a chair while a physician or a nurse places the device against the scalp.

TMS has become a promising treatment alternative for the estimated 30 percent to 50 percent of people with depression who don't respond sufficiently to antidepressant medications. One option commonly offered to such patients is electroconvulsive therapy (ECT), a procedure in which electrical currents are sent through the brain to trigger a short seizure. ECT has been available in the United States for more than 70 years. Administered several times per week over three to four weeks, ECT can be effective at alleviating major depressive disorder.

However, ECT has some significant drawbacks. It can cause confusion and memory loss. Plus, it must be administered under anesthesia, which comes with risks of its own and adds preparation and recovery time to each session.

Gray had tried ECT, but her doctor discontinued the treatment after she experienced serious memory loss. "I have no recollection of that entire two-plus weeks," she says. "I live alone, and it was scary."

TMS, by contrast, is administered while patients are awake. "You sit in a chair, it takes about 30 minutes, and then you can get up and drive yourself home," says McDonald. Side effects are minimal; headache and muscle soreness are the most common complaints. Though there is a small risk of seizure, it's reportedly comparable to the seizure risk associated with antidepressant medications. Compared to ECT, Gray says, "TMS is a walk in the park."

But like antidepressant medication and ECT, it's not entirely clear how TMS is acting on the brain. "The theory is that when this stimulation occurs in the left frontal brain, it spreads to the underlying deeper areas of the brain that are involved in regulation of mood. When we do it over and over again, it normalizes the neuronal circuits involved in depression," says Ananda Pandurangi, MD, a psychiatrist at the Virginia Commonwealth University School of Medicine.

Like ECT, TMS appears to reset the system. But instead of jump-starting the entire brain, as ECT does, the magnetic therapy is much more targeted, says Megan Schabbing, MD, a psychiatrist at OhioHealth Riverside Methodist Hospital who treated Gray with TMS. "That's undoubtedly why it's so well tolerated," she says, "but this treatment provides a novel approach to the transformation of neural networks."

### Real-world results

Mark George, MD, a neurologist/psychiatrist at the Medical University of South Carolina and editor of the journal *Brain Stimulation*, has been exploring the use of TMS for depression since the early 1990s. At that time, he says, most neurologists believed brain stimulation was only successful if it induced a seizure, as in ECT.

But George believed that the gentler electric currents generated by TMS could also be effective if they were delivered repeatedly. Small changes add up, he says. Repeated exercise can strengthen a weak muscle. And in depression, psychotherapy can be an effective treatment over time. "You can exercise brain circuits by retraining how you think," George says. "We know repeated minor changes to the system can get the system better."

George was the co-chair of a multisite, randomized clinical trial of TMS sponsored by the National Institute of Mental Health. The study enrolled patients with treatment-resistant major depressive disorder between 2004 and 2009. After three weeks of either active TMS or a sham treatment, all patients were offered an additional three weeks of guaranteed TMS. Those who received TMS were four times as likely to achieve remission as compared with patients who received a sham treatment, the researchers found (*Archives of General Psychiatry*, 2010). The results were fairly modest, however — about a 30 percent remission rate for TMS at the end of the full six weeks, compared with perhaps 60 percent for ECT, George says.

Yet it now seems that TMS may be more effective than the initial trials suggested. Linda Carpenter, MD, a psychiatrist at Brown University School of Medicine, and colleagues studied TMS as it's used in the real world. Across 42 TMS clinics in the United States, they found that 58 percent of patients showed improvement, including 37 percent who achieved full remission (*Depression and Anxiety* (<http://www.ncbi.nlm.nih.gov/pubmed/22689344>), 2012).

Anecdotally, many practitioners appear to be pleasantly surprised by the treatment's success. While the NIH-sponsored trial found about two in 10 patients experienced remission

following TMS. George, Pandurangi, and Schabbing all say they've seen higher remission rates among the patients they've treated. "It has really exceeded my expectations," Schabbing says.

The strict protocols in the clinical trials probably account for some of the difference. Trial participants were required to stop taking medications during the course of TMS treatment. They could continue their psychotherapy, but they couldn't increase the frequency of their sessions.

Patients receiving TMS in the real world have many more options, says Pandurangi. They can continue taking medications to which they may have had a partial response, and they can see therapists whenever they'd like. Those options appear to improve patient outcomes. "We mix and match anything and everything we have to make the patient feel better," he says.

## Everything's a question

While TMS shows promise, it's certainly no miracle cure. Some of the patients who responded positively to TMS have experienced remissions lasting months or even years, but follow-up booster sessions every few weeks or months may help prevent a relapse.

About six months after her incredible improvement in 2007, Gray says, her depression began to resurface. She underwent a second course, this time at a clinic in Vancouver, Canada. While she felt better, her improvement was more modest the second time around.

Gray had paid out of pocket for the pricey therapy and was quickly burning through her retirement savings. She couldn't afford another round, even after her depression resurfaced months later. "So I puttered along until a few years ago, when I had another deep depression," she says.

By then the treatment had been approved by the FDA. Still, it took Gray multiple applications over several years before her insurance company agreed to cover the treatment. She finally underwent a third course of TMS in 2014. "I feel pretty good," she says. "I've had two pretty bad pieces of news in the last couple weeks and I didn't crumble."

Now Gray is planning to have a maintenance course of TMS every month or so, in hopes that it will keep her depression at bay. She's still not sure if her insurance will pay for those booster sessions — and that's not the only thing that remains unclear about maintenance TMS.

French researchers recently reported that patients who received maintenance TMS were significantly less likely to relapse than those who did not receive boosters (*Journal of Affective Disorders*, 2013). But the study was small, and the best way to administer such treatments is far from settled. "The protocols for maintenance boosters don't exist. Nothing has been approved by the FDA, so we devise our own protocols," Pandurangi says.

In fact, he adds, when it comes to TMS, "almost everything is a question." What's the best frequency and intensity of the magnetic pulse? How many total treatments should patients receive, over how many days or weeks? Where on the scalp should the current be directed?

Researchers are a long way from fine-tuning the technique, George agrees. "All the things we did in the first studies used a good first approximation, and it turned out that it worked," he says. "However, it would be inconceivable that the first approximations were also the best approximations."

There's some evidence the total amount of brain stimulation is what matters, rather than the number of calendar days spent in treatment, George says. In a recent pilot study, George and his colleagues tested TMS as a treatment for patients hospitalized during a suicidal crisis. Patients received nine TMS treatments in just three days. They experienced no serious side effects from the rapid-fire course of treatment, George says, and those who received TMS showed more improvements on the first day than did control subjects who received a sham treatment (*Brain Stimulation* (<http://www.sciencedirect.com/science/article/pii/S1935861X14001211>), 2014).

"They got unsuicidal very quickly," George says — though he acknowledges that more research and larger samples are required to fully test the approach.

While many questions remain, scientists who study the device say it's a valuable tool for psychologists to keep in mind when referring patients with difficult-to-treat depression. "Psychologists should know it's a good treatment option for patients who have failed to respond to or tolerate antidepressant medication," Schabbing says.

## Fire together, wire together

As magnetic brain stimulation continues to be tested in the real world, researchers are considering whether to expand its use. Psychotherapy and antidepressants are highly effective treatments for many people with depression. They're also more convenient and less expensive, so TMS is unlikely to become a first-line therapy for depression that responds to other treatment. But it has potential for treating other conditions.

Researchers have found that TMS could be effective in treating vascular depression following stroke, for example (*Archives of General Psychiatry* (<http://www.ncbi.nlm.nih.gov/pubmed/18316673>), 2008). Others are studying TMS as a possible treatment for disorders including schizophrenia, attention deficit-hyperactivity disorder and post-traumatic stress disorder. "Following the success with depression, almost everybody who treats brain diseases is thinking about whether you could use TMS," George says.

So far, however, the results are mixed. "The one exception is in the treatment of pain," George says. Data suggests TMS could be helpful in treating both acute pain and chronic pain conditions such as fibromyalgia — but to date, no companies have sought FDA approval for that use, he adds.

Meanwhile, scientists are also exploring how to engage patients in order to maximize the effectiveness of TMS during treatment for depression. "There's a concept that says 'neurons that fire together wire together,'" says George. According to this theory, brain cells might be more receptive to treatments when they're actively engaged in some task.

For instance, preliminary research suggests patients might experience greater improvements if they receive TMS while simultaneously undergoing cognitive-behavioral therapy, George says. If this line of research pans out, psychologists could play an important role by providing psychosocial therapy while patients are in the TMS chair.

And TMS may be just the beginning. Scientists are exploring other methods of stimulating the brain, including pulsed ultrasound and optogenetic stimulation. The research could open up important new avenues for treating mood disorders and mental illness, Pandurangi says. "It's exciting to see what's coming next."

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*\*Not her real name.*

## Further reading

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