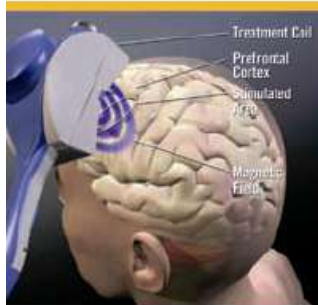


Depression



Neuromodulation Offers New Options for Treatment-Resistant Depression

STORY HIGHLIGHTS

Trigeminal nerve stimulation delivers low-energy electrical stimulation to specific areas of the brain associated with epilepsy, depression, attention deficit hyperactivity disorder and post-traumatic stress.

Transcranial magnetic stimulation uses magnetic energy to stimulate parts of the brain that regulate mood.

A major clinical trial has shown that only about one-third of adults with major depression will respond after their first medication trial, and the likelihood that similar therapies will succeed declines with each new attempt, leaving about 20-to-30 percent of patients with treatment-resistant depression (TRD). However, newer neuromodulation therapies, along with refinements in older ones that deliver electrical impulses to specific areas of the brain, can help to restore normal function and improve outcomes.

Mental disorders, including depression, affect an estimated one-in-four adults in the United States each year, and for many patients the first line of treatment is medication. But for those who are unable to tolerate the side effects from prescribed medicines or have tried without success many different drugs, so-called neuromodulation offers the hope of meaningful benefit, says Ian Cook, MD, director of the Depression Research & Clinic Program at UCLA.

"With neuromodulation, we can use noninvasive or minimally invasive techniques to change the levels of activity within targeted circuits of the brain that are important for treating illness, while providing clinically significant benefits, with fewer side effects," Dr. Cook explains.

One of the newest neuromodulation strategies, trigeminal nerve stimulation (TNS), delivers low-energy electrical stimulation through a patch placed on the forehead to specific areas of the brain that are associated with epilepsy, depression, attention deficit hyperactivity disorder (ADHD) and post-traumatic stress (PTS). TNS was invented at UCLA, by Dr. Cook, neurologist Christopher DeGiorgio, MD, and their colleagues, for treatment of drug-resistant epilepsy, and later has been studied for treatment-resistant depression. Although it is approved in Canada and Europe for those conditions, TNS must still be evaluated in U.S. clinical trials before being considered for FDA-approval. In preliminary studies, TNS has

been associated with reduced seizures in patients with epilepsy and improvements in behavior and cognitive function in children with ADHD and in trauma-associated symptoms in adults with PTS.

Another approach, transcranial magnetic stimulation (TMS), uses magnetic energy to stimulate parts of the brain that regulate mood. It is currently used in one-of-two ways: by stimulating the outer layers of the brain or by targeting deeper brain structures. Dr. Cook's program has been treating patients with an FDA-approved TMS system since 2009.

"It is hard to find a one-size-fits-all treatment with a condition like depression, so we approach it using different pathways," Dr. Cook says. TMS is FDA-approved as a stand-alone treatment for depression that is unresponsive to medications, but in practice it is often used as a complementary treatment strategy, added on to medications or psychotherapy.

"We still have no clear idea how it all works," says Alexander Bystritsky, MD, PhD, director of the Anxiety Disorders Program at UCLA. "We need more studies to explore TMS as a stand-alone therapy in patients without prior drug treatments and to investigate how TMS potentially interacts with prescribed medicines and therapy."

Researchers are just beginning to understand the parameters and pathways through which TMS and other neuromodulation strategies may be used for specific psychiatric disorders, according to Dr. Bystritsky. For example, deep-brain stimulation (DBS) is a surgical procedure that involves implanting a pacemaker-like device in the chest wall and placing electrodes in the brain to send out electrical impulses to specific regions of the brain. Although DBS is commonly used to treat the symptoms of Parkinson's disease and related neurological disorders, severe obsessive-compulsive disorder (OCD) is the only psychiatric condition for which DBS is FDA-approved (under a humanitarian-device exemption). At UCLA, researchers are conducting studies to explore the potential of DBS for treating OCD and depression and other conditions.

The researchers are also exploring noninvasive methods to stimulate deeper structures within the brain, such as deep magnetic brain stimulation (DrTMS) and low-intensity focused ultrasound pulse (LIFUP). Currently Dr. Bystritsky is

conducting a study of DrTMS in bipolar disorder.

"Bipolar disease is a tricky disorder to treat because antidepressants can trigger patients into a manic state or make them very anxious," Dr. Bystritsky explains. "A single course of DrTMS combined with mood stabilizers may potentially be effective in quickly treating depression in bipolar patients." The DrTMS technique was recently approved by the FDA for the treatment of unipolar depression.

In patients with hard-to-treat depression, DBS research is attempting to delineate the dysfunctional brain circuits that are most critical to alleviating depressive symptoms and to determine when DBS is indicated given the inherent risks involved.

"The surgical risks are quite low when DBS is performed by an experienced team, but there are risks associated with stimulation, such as increased anxiety, restlessness and mood changes" says Randall Espinoza, MD, MPH, director of the Electroconvulsive Therapy Program at UCLA. In current trials, DBS has been associated with a 40-to-50 percent response rate for patients who have not previously responded to other available treatments, with 30 percent of patients achieving remission of depressive symptoms and 90 percent of patients opting to continue DBS long-term, which speaks to general safety, tolerability and low occurrence of side-effects. DBS is also being studied for PTS, chronic-pain management, schizophrenia and severe OCD.

The oldest neuromodulation technique, electroconvulsive therapy (ECT), continues to be both widely used in clinical practice and investigated in research studies. "ECT is one of the most robust treatments we have for psychotic, suicidal, catatonic or medication-refractory depression, but we are investigating ways to increase the response rate and lessen associated cognitive side-effects," Dr. Espinoza says.

He adds that an important goal of neuromodulation research is to identify biosignatures of antidepressant response that will enable better matching of patients with appropriate treatments. "Then," Dr. Espinoza says, "we could avoid much of the suffering patients experience as they go through multiple trials of medications or psychotherapy before getting to the right treatment."

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