Deep Brain Stimulation Could Address Suicide Risk in Individuals Resistant to Treatment

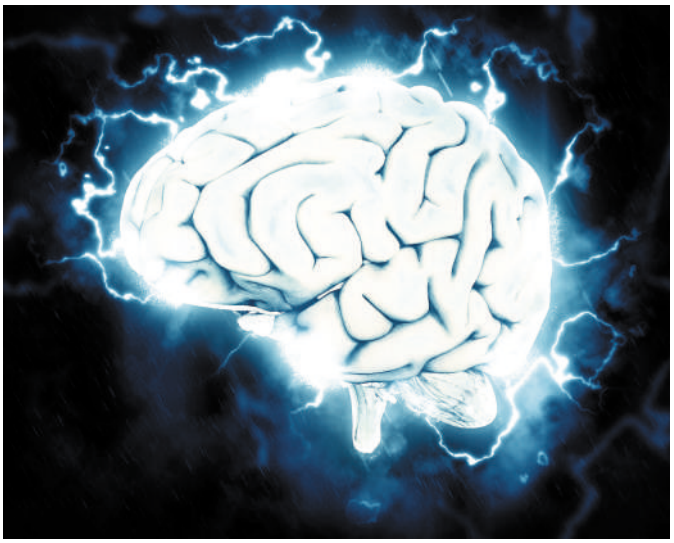
Between 1999 and 2016, the number of suicide attempts in the US increased in most states. According to the Substance Abuse and Mental Health Services Administration, 25 states experienced a >30% increase.[1] In 2018, the US saw 48,344 deaths from suicide, 46,510 of which were adults.

Pharmaceutical and behavioural therapy treatments have successfully helped many patients manage symptoms of mental health conditions, such as major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and schizophrenia, but patients who are refractory to those treatments have few options. The COVID-19 pandemic has only underscored this treatment gap, prompting an increasing number of individuals to seek treatment for depression. Deep brain stimulation (DBS), a treatment that relies on a device and accompanying wires to target certain areas of the brain, may be a solution for some of these individuals.

The Current DBS Landscape

The National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) defines DBS as "a surgical procedure used to treat several disabling neurological symptoms" that "uses electrical stimulation to regulate electrical signals in neural circuits to and from identified areas in the brain to improve movement symptoms."[2] Multiple treatment sites in the brain have been proposed for refractory depression, according to Johns Hopkins University (JHU).[3]

The US Food and Drug Administration (FDA) approved the first DBS device in 1997 for the suppression of tremors in certain patients. Since then, multiple device companies have developed and launched DBS devices for various indications. While DBS is currently only approved in the US to treat Parkinson's disease, essential tremor, dystonia, obsessive-compulsive disorder (OCD), and, most recently, epilepsy, research continues on the use of DBS to treat mental health conditions. OCD was the first – and remains the only – psychiatric indication approved by the FDA for DBS.



Making Untreatable Depression Treatable

MDD affects 15–17% of individuals in the US.[4] The frequency of treatment-resistant depression (TRD) is difficult to quantify due to a lack of standard definitions and criteria, but the incidence of TRD in the literature is reported as 12–55%.[5] In the US, approximately 30% of individuals with TRD have attempted suicide at least once. FDA-approved drug treatment options for TRD include Eli Lilly and Company's Symbyax (olanzapine/fluoxetine; capsule) and Janssen Pharmaceuticals, Inc's Spravato (esketamine; nasal spray). Research is also ongoing into the use of psychedelics (e.g., psilocybin, 3,4-methylenedioxymethamphetamine [MDMA]) to treat TRD.[6]

Eye movement desensitisation and reprocessing (EMDR) can also be used to treat depression and PTSD. Transcranial magnetic stimulation (TMS), a non-invasive form of brain stimulation, is another option, and 50–60% of individuals with depression who do not respond to medication have experienced clinically meaningful response with TMS.[7] In 2005, the FDA approved Cyberonics, Inc's Vagus Nerve Stimulation (VNS) Therapy System, an implantable generator connected to electrodes that deliver electrical signals to the left cervical vagus nerve, for TRD. Despite this long list of treatment options, some patients remain untreatable and are candidates for benefiting from a novel approach.

DBS has been shown through positron emission tomography (PET) imaging studies to reverse pre-treatment blood flow changes in depressed patients, similar to how antidepressants work. In 2013, the FDA approved a premarket approval application (PMA) for the NeuroPace RNS System to treat certain patients with epilepsy. The University of California, San Francisco, is recruiting approximately 12 participants to evaluate the use of the RNS System from NeuroPace, Inc, for treatment-resistant MDD in a randomised, crossover-assignment, two-phase study (PReSiDio). Participants are randomised to an experimental arm or sham comparator arm and receive treatment in three stages. The primary outcome measure of the study, which is estimated to complete in June 2035, is the change in Montgomery-Asberg Depression Rating Scale score.

Emory University, in collaboration with Hope for Depression Research Foundation and the Dana Foundation, is conducting an open-label study to evaluate the use of a new type of DBS device to treat approximately 10 participants aged 18–70 years with TRD. The study is exploring local field potentials (LFPs) with the Medtronic Activa Primary Cell + Sensing (PC+S) "Brain Radio" System, which is not approved by the FDA. This device can record the electrical activity in the brain. Investigators are studying LFP in the brains of individuals with TRD before and during active stimulation and recording the readings for up to three years. The estimated study completion date is September 2023.

Ongoing Research for DBS to Treat Schizophrenia and PTSD

Individuals with schizophrenia and PTSD could also potentially benefit from DBS treatment. JHU is recruiting 3 participants aged ≥22 years for an open-label pilot study to evaluate the use of DBS of the substantia nigra pars reticulata (SNr) in patients with treatment-resistant schizophrenia. Participants are implanted with a DBS therapy system from Medtronic and receive treatment using a method similar to that used in subthalamic nucleus stimulation in patients with Parkinson's disease. The primary outcome measures – change from baseline in the Scale for the Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS), as well as incidence of adverse device effects (ADEs) – are evaluated one year after implantation.

The VA Greater Los Angeles Healthcare System is studying the use of DBS in a difficult-to-treat population – Iraq and Afghanistan war veterans. Approximately 6 veterans aged 25–70 years with PTSD are being recruited for this study based on recent findings that PTSD patients experience abnormal activity in a specific brain region that is likely responsible for core PTSD symptoms. Participants are randomised to two arms to receive DBS through a Medtronic Activa DBS device. The primary outcome measure is the frequency and severity of all adverse events at one year. The estimated study completion date is December 2025.

A Potential Path to Decrease Suicide Attempts and Deaths

Worldwide, the estimated risk of suicidal ideation and suicide attempts in individuals with MDD is 15%.[8] Approximately 18–55% of individuals diagnosed with schizophrenia will attempt suicide in their lifetime,[9] and PTSD is also a risk factor for suicide.[10] As suicide rates continue to increase each year in some locations, the need for an innovative solution for individuals who struggle with suicidal ideation is paramount. The availability of more treatment options each year could show a decreasing trend in suicide attempts and deaths – but these staggering statistics suggest that the time for something new is now.

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