Deep Brain Stimulation: New Promise in Alzheimer Disease and Depression

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The evolution of deep brain stimulation for various neuropsychiatric disorders results from advances in structural and functional brain imaging, increased understanding of neurocircuitry of the brain, and improvements in neurosurgical techniques and equipment.

Deep brain stimulation (DBS), used in treating Parkinson disease and other movement disorders, has emerged as a promising approach for early Alzheimer disease and for treatment-resistant depression (TRD), according to recent journal articles and key researchers in the neuromodulation field.

The evolution of DBS for various neuropsychiatric disorders results from advances in structural and functional brain imaging, increased understanding of neurocircuitry of the brain, and improvements in neurosurgical techniques and equipment, explained Helen Mayberg, MD, Dorothy C. Fuqua Chair of Psychiatric Neuroimaging and Therapeutics at Emory University School of Medicine, who conducts depression-related DBS research.

As early as 1997, the FDA approved DBS for treatment of essential tremor; this was followed in 2002 by approval for use in advanced Parkinson disease and, in 2003, for dystonia. To date, more than 85,000 patients worldwide have had DBS devices implanted.

In a recent editorial, Andres Lozano, MD, PhD,1 RR Tasker Chair in Functional Neurosurgery at the University Health Network (UHN) in Toronto, wrote that beyond DBS’s “striking clinical benefits” for movement disorders, it may have potential for patients with non-motor neurological and psychiatric disorders.

In 2009, the FDA approved a humanitarian device exemption for DBS therapy (Medtrons’ Reclaim) to suppress the symptoms associated with chronic, severe obsessive-compulsive disorder, said Mayberg.

Possible FDA consideration of DBS for Alzheimer disease and for TRD must await the results of stimulation versus sham trials, said Peter Giacobbe, MD, Assistant Professor at the University of Toronto and Staff Psychiatrist at UHN, where he serves as Head of the ECT service. He also programs DBS devices and provides preoperative and postoperative psychiatric management of patients receiving DBS.

According to a search of open studies listed on www.clinicaltrials.gov and a review article, DBS also is being studied for bipolar disorder, PTSD following combat, obesity, anorexia, addiction, Tourette syndrome, and epilepsy, among other disorders.2 Despite the growing interest in DBS, Hariz and
Hariz recently warned against the testing and touting of DBS for “dubious indications,” such as enhancing normal cognition and treating antisocial behavior.

The DBS procedure
The DBS procedure involves implanting electrodes within specific brain circuits to modulate the circuits’ activity, either to suppress pathological neuronal activity or to drive underactive output, according to Lozano.

“Electrodes are commonly placed with patients fully awake, which allows the surgeon to pinpoint the precise location in the brain using microelectrode recordings of neurons at the target,” he wrote in the editorial. “The surgeon can also gauge the patient’s response to stimulation, which helps guide the final placement of the electrodes. The electrodes are then connected to an implanted pulse generation (along the lines of a standard cardiac pacemaker), which can be programmed to deliver continuous stimulation for several years—batteries last 4 to 5 years or longer with recharging.”

Alzheimer disease
“There have been several failed medication trials for Alzheimer disease recently,” Giacobbe noted. “Our current therapeutics are really only palliative, they don’t address the core issue of plaques and tangles, so there is a great need for some new treatments.”

DBS’s potential for treating Alzheimer disease was discovered “quite unexpectedly” by Lozano’s team while they were using fornix/hypothalamus DBS to treat a patient with morbid obesity. The patient experienced memory improvement. These findings led Laxton, Lozano, and colleagues at the University of Toronto to develop a phase 1 trial of fornix/hypothalamus DBS in 6 patients with early Alzheimer disease who continued to receive medication treatment. The study involved bilateral DBS implantation, detailed neuropsychological and neurological testing, and brain imaging to detect alterations in brain activity induced by stimulation. The patients received continuous stimulation for 12 months.

Increased glucose metabolism was observed in the temporal and parietal cortical areas at 1 month in all patients and was sustained in most of the affected areas at 1-year follow-up. Some patients showed possible improvements or slowing of anticipated cognitive decline at 6 and 12 months based on the cognitive subscale of the Alzheimer Disease Assessment Scale and the Mini-Mental State Examination (MMSE). For example, the rate of decline on the MMSE in the 11 months preceding surgery was 2.8 compared with 0.8 in the 11 months after surgery.

In September’s Archives of Neurology, Lozano’s research team analyzed results for 5 of the 6 patients in the phase 1 trial. The 5 had been studied with the same PET scanner. The scans measured regional cerebral glucose metabolism preoperatively, after 1 month, and after 1 year of continuous DBS.

The researchers’ functional connectivity analysis demonstrated increased cerebral metabolism in cortical-subcortical and cortical-hippocampal networks.

“The persistent cortical metabolic increases after 1 year of DBS were associated with better clinical outcomes in this patient sample and were greater in magnitude and more extensive in the effects on cortical circuitry compared with the effects reported for pharmacotherapy over 1 year in Alzheimer disease,” the team concluded.

Currently, a double-blind, randomized, controlled study is under way at 6 sites in North America to evaluate the safety, efficacy, and tolerability of DBS of the fornix in patients with mild, probable Alzheimer disease.

“We are comparing active stimulation to sham stimulation,” Giacobbe said. The study, he explained, will help answer the questions of whether it is the active stimulation that is helping patients get better or other factors, such as coming to appointments and related nonspecific effects.

Called ADvance, the proof-of-concept study initially involves 20 people aged 55 to 80 years. It will compare the effects of DBS turned on with those observed with the system turned off. The patients will undergo regular physiological, psychological, and cognitive assessments for a year, at which time those patients in the “off” group will be eligible to have the system activated. The study sponsor is Functional Neuromodulation Ltd, of which Lozano is a company co-founder and chair of its scientific advisory board; Medtronic is providing DBS devices.

“All sites are actively recruiting patients,” said Dan O’Connell, company co-founder and chief executive officer. The 6 sites are Toronto Western Hospital; Johns Hopkins Bayview Medical Center in Baltimore; the Banner Alzheimer’s Institute in Phoenix; the University of Florida Center for Movement Disorders and Neurorestoration at Gainesville; the University of Pennsylvania; and Brown University in Providence, RI.

The 20 patients should be enrolled and implanted with the device by the second quarter of next year, O’Connell said, noting, “If all goes well and DBS is found to be reasonably safe and effective,
the study may be expanded to 40 patients.”

Asked about informed consent concerns, Giacobbe said the sites are recruiting patients with early Alzheimer disease only, because of the complexities of consent and because intervening early in the disease’s course will facilitate maximization of patients’ functioning.

**Treatment-resistant depression**

DBS has been studied in a small number of clinical trials to treat patients with TRD. Estimates are that 10% of all depressed patients will become resistant to available treatments, including ECT, so “new options are needed,” Mayberg told *Psychiatric Times.

Based on preliminary observations that the subgenual cingulate region (Brodmann area 25 [BA25]) of the brain is metabolically overactive in TRD, Mayberg and colleagues in Toronto studied whether DBS to modulate BA25 could reduce the elevated activity and produce clinical benefit for 6 patients with refractory depression. In a study supported by a NARSAD grant, chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with “a striking and sustained remission of depression in 4 of 6 patients” at the end of 6 months, without changes in concurrent medications.

Following the original study, the Toronto team expanded the sample to 20 patients and reported on 12-month outcomes. The response rate was 60% (with response defined as a decrease of 50% or greater in total score on the 17-item Hamilton Depression Rating Scale [HAM-D]) and the remission rate was 30% (with remission defined as a HAM-D score of 7 or less). In 2011, the researchers reported on the extended follow-up of the patients with data from 3 to 6 years after implantation. “The cumulative duration of follow-up was 70 patient years,” Giacobbe said. The percentage of patients who responded was 62.5% after 1 year, 46.2% after 2 years, 75% after 3 years, and 64.3% at the last follow-up visit. More than one-third of patients were in remission at year 3 and at last follow-up.

“We also looked at their quality of life,” said Giacobbe. “Not only their mental health quality of life, but their physical well-being, such as vitality and energy, seemed to improve over time.” Three of the 20 died—1 of cancer; 1 a likely suicide; and 1 a sudden unexplained death, which was considered a possible suicide.

“We have to be extremely vigilant, because this is a group that has been extremely depressed for a very long time. Even 5 to 6 years later, they still need active psychiatric and neurosurgical follow-up,” Giacobbe said.

At the UHN, he added, psychotherapy is offered after DBS. Patients seem to benefit more from post-DBS psychotherapy than pre-DBS psychotherapy. Many patients, he said, feel their “cognitive cloudiness” is lifting and they are no longer actively depressed, so they want to re-enter psychotherapy to sort out job issues, inter-personal relationships, and other difficulties.

In a pilot study sponsored by St Jude Medical, Lozano, Giacobbe, and several others conducted a prospective open-label trial of subcallosal cingulate DBS for 12 months in patients with TRD. The Canadian study involved 21 patients at 3 centers—Vancouver, Montreal, and Toronto. Overall, at 6 months, 48% of the patients responded (50% reduction in the 17-item HAM-D), and at 12 months, 29% responded. Published this year, the study results demonstrated that clinical effects of DBS for TRD are reproducible across centers, Giacobbe said.

Also testing subcallosal cingulate DBS is the BROADEN (BROdmann Area 25 DЕep brain Neuromodulation) study to evaluate the safety and effectiveness of DBS in treatment-resistant severe MDD. This 6-month, blinded, sham-controlled clinical trial sponsored by St Jude Medical is under way at some 20 sites in North America.

At Emory University, Mayberg and colleagues are conducting further studies to examine sub-callosal cingulate efficacy and mechanisms in various subgroups, including unipolar and bipolar depressed patients.

This year, Holtzheimer and colleagues reported their first results of a DBS trial that included a 4-week sham stimulation phase; a 24-week, open-label, active-stimulation phase; and an observational follow-up phase.

Performed under a physician-sponsored investigational device exemption and supported by grants from the Dana Foundation, the Stanley Medical Research Institute, and the Woodruff Foundation, the study involved 17 patients, 10 with MDD and 7 with bipolar II who were experiencing depression. After 2 years of chronic stimulation involving 12 patients, Holtzheimer and colleagues found patient response and remission rates were high (92% response, and 58% remission). In addition, patients who achieved remission did not experience a spontaneous relapse, efficacy was similar for MDD and bipolar II patients, and no patient experienced a hypomorphic or manic episode during the study. Beyond BA25, other brain targets are being evaluated in both open-label DBS trials and controlled
clinical trials. These areas include the nucleus accumbens, ventral capsule/ventral striatum, lateral habenula, and anterior thalamic peduncle. DBS trials for depression are also being conducted in Europe.

Risks
Like any other brain surgery, DBS includes risk of stroke, hemorrhage, seizure, and infection, according to Mayberg and Giacobbe. There are also risks with general anesthesia and with possible equipment malfunction or breakage.

“DBS surgeons quote about a 5% risk of a serious event occurring during the procedure,” Giacobbe said.

Regarding continued trials of DBS for depression, both Giacobbe and Mayberg remain highly committed and optimistic. For Giacobbe, it’s the possibility of advancing treatment options and being “on the cusp of making some meaningful changes.” For Mayberg, it is “seeing that our research can make a difference” and “seeing patients get their lives back.”

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