

Development of Deep Brain Stimulation for the Treatment of Resistant Depression



Major depression is the most common of all psychiatric disorders [Wang PS. *JAMA* 2003] and the leading cause of disability in North America among adults under 50 years of age [World Health Organization 2001]. Although a variety of treatments are available, less than 40% of patients achieve remission with their first treatment [Rush AJ et al. *Am J Psychiatry* 2006], and approximately 10% becomes treatment-resistant over time. Although electroconvulsive therapy (ECT) is effective for many patients, those who have failed to respond to 4 previous antidepressant treatments are likely to relapse (CORE). New treatments are needed for patients who remain depressed despite having tried all available therapies.

Helen Mayberg, MD, Emory University, Atlanta, GA, has been investigating the use of deep brain stimulation (DBS) as a treatment for patients with chronic, treatment-resistant depression who have failed all other therapies. According to Dr. Mayberg, "It is now clear that depression cannot be viewed as simply a chemical "shortage" but rather as a more complex disorder of dysfunctional brain circuits." The emerging evidence, made possible in large part by advances in imaging technology, indicates that depression is a "systems-level disorder affecting integrated pathways linking select cortical, subcortical, and limbic sites and their related neurotransmitter and molecular mediators" [Mayberg HS et al. *Neuron* 2005].

Although there are several circuits that might be targeted to produce clinical benefit in patients with treatment-resistant depression, Dr. Mayberg and her colleagues are particularly interested in the subgenual cingulate region of the brain (Cg25). Studies have indicated that Cg25 may play a role in modulating negative mood states [Mayberg HS et al. *Am J Psychiatry* 1999; Seminowicz DA et al. *Neuroimage* 2004], and a decrease in Cg25 activity has been shown in response to select SSRIs, ECT, repetitive transcranial magnetic stimulation (rTMS), and ablation [Mayberg HS et al. *Neuron* 2005]. It also has been suggested that certain Cg25 connections may be involved in the sleep, libido, appetite, and neuroendocrine disturbances that are associated with depression [Mayberg HS et al. *Neuron* 2005], as well as have an effect on other core behaviors that are affected by depression (eg, learning, memory, motivation, and reward).

The use of chronic high-frequency DBS has been shown to be effective in the treatment of Parkinson disease. Using that knowledge and evidence from worldwide studies that have shown that DBS produced local and remote changes in neural activity when applied to the basal ganglia, Dr. Mayberg and her colleagues continue to study the effect of DBS that is targeted to the Cg25 white matter of chronically depressed patients who do not respond to standard therapies.

DBS is accomplished using three-dimensional magnetic resonance imaging to guide the bilateral placement of very small wires deep into the brain. Patients are awake during this part of the procedure and have their skull secured in a special frame that allows very precise placement. The wires contain 4 contacts that span the areas to be stimulated. Once inserted, the contacts are tested to ensure that they are properly placed and to determine the appropriate level of stimulation. Following this, the patient is put to sleep, and the other end of the wire is connected to a small cable under the skin in the neck and then to a small battery pack. Ongoing stimulation is accomplished using a magnet and a small external control box (Figure 1).

Highlights from the
American Psychiatric Association
2008 Annual Meeting

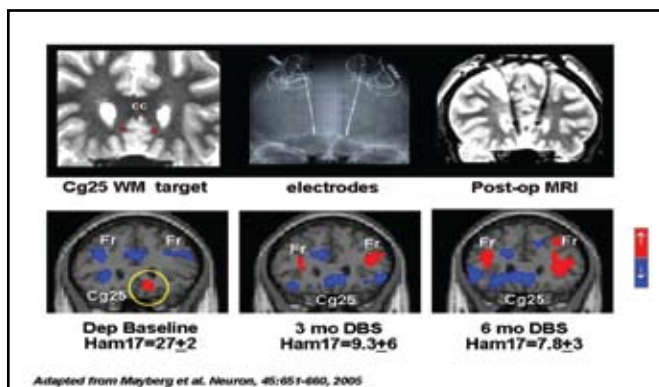
Figure 1. Deep Brain Stimulation.



Photo courtesy of Medtronic.

In 2005, Dr. Mayberg and colleagues published the preliminary results of a pilot study of DBS in 6 patients with chronic, treatment-resistant depression [Mayberg HS et al. *Neuron* 2005]. In this study, patients showed progressive improvement over several weeks, and by 3 months, the investigators were able to distinguish between those patients who would go on to do well and those who would not. Four of the 6 patients achieved a good clinical result at 6 months (Figure 2). Follow-up continues on all patients, and the initial 4 responders continue to do well more than 4 years out with continuous DBS. As of 2008, 20 patients have received DBS implants as part of the original pilot study. Approximately 50 patients worldwide have been implanted in this same brain target, and placebo-controlled studies are now underway. Final results of the original 20-patient pilot project are now in press. Although these studies clearly offer hope to patients who have not responded to other treatments, Dr. Mayberg cautioned that “behavioral rehabilitation is still needed for patients after DBS.”

Figure 2. 6-Month Results.



In closing Dr. Mayberg said, “The combination of deep brain stimulation and advanced imaging capabilities have given us new insights into the pathogenesis of depression that are laying the foundation for a whole new approach to the treatment of psychiatric disorders.”

APA 2007 Survey Explores Efficacy of Current Antidepressants

The American Psychiatric Association (APA) survey on the treatment of depression was undertaken to gain insight into the challenges that physicians face when treating individuals with major depression (MD) and identify the issues that inhibit effective treatment. A 6-question multiple-choice survey was administered to 1066 physician attendees at the APA’s 2007 annual meeting. Results were reported by region where there were notable differences; US respondents and rest of world (ROW):

What are the top three symptoms that lead you to a diagnosis of depression? Top responses:

- depressed mood (30%)
- diminished interest (23%)
- feelings of worthlessness (US 13.5%; ROW 9.1%)
- fatigue (US 9.2%; ROW 12.9%)

What is your primary treatment goal?

The most commonly cited goal for MD treatment was long-term prevention of relapse (US 78%; ROW 59%), while only a minority of respondents considered acute efficacy, meaning short-term response or remission, as the priority.

How effective are prescription medications in meeting your treatment goal?

ROW physicians rated current medication as very effective (ROW 20.8%; US 14.9%) or effective (ROW 56.8%; US 50.3%) more often than domestic physicians.

What are the main obstacles to achieving your treatment goal?

- drug-related sexual function (23%)
- weight gain (17%)
- inadequate efficacy (16%)

How often do you switch medications, and why?

Half of all respondents indicated that each month, >20% of their patients switched because of tolerability issues, and approximately the same number of respondents indicated that >20% of the patients switched due to lack of efficacy.

The survey investigators concluded that the key barriers to reaching treatment goals are adverse events and treatment efficacy, adding emphasis to the need for the development of better treatment options.