

Vagal Nerve Stimulation Versus Deep Brain Stimulation for Treatment-resistant Depression: Show Me the Data

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From its earliest days, neurosurgery for psychiatric disorders has been surrounded by controversy. Walter Freeman (a neuropsychiatrist) and James Watts (a neurosurgeon) were among the first to report on the results of a new procedure for intractable psychiatric disease: frontal leucotomy. Despite their claimed success, presentation of their results provoked an immediate and hostile reaction from the psychiatric community. However, the dismal state of psychiatric care in the late 1930s set the stage for widespread adoption of this controversial procedure. The frequent side effects of dulling of intellect and change in personality were overshadowed by the ability to discharge patients from overcrowded psychiatric hospitals. In fact, the procedure was described as “nothing less than miraculous”.¹⁰ This widespread enthusiasm led Freeman to alter the procedure so that it could be performed in a matter of minutes using a device resembling an ice pick. By 1948, Freeman was traveling around the country performing thousands of leucotomies. The lead story in *Time Magazine*, September 15, 1952, described the procedure thusly: “Carefully manipulating the two ice picks the doctor severed the connection between thalamus and frontal lobes in the patients’ brain. The entire operation took only 10 minutes.” Between 1936 and the mid 1950s, approximately 20,000 frontal lobotomies were performed in the United States.⁶ It soon became generally known that patients who had undergone this procedure frequently suffered significant and often undesirable personality changes. The resulting public backlash against psychiatric surgery was severe. An enduring image of the effects of lobotomy are portrayed by Jack Nicholson in the movie *One Flew Over the Cuckoo’s Nest*. These powerful images of surgical manipulation of our very “personhood” pervade the public consciousness. Any intervention that is aimed at psychological disorders must, therefore, contend with these popular perceptions.

With advances in stereotactic techniques and the development of reversible and adjustable neuromodulatory technologies, such as deep brain stimulation (DBS) and vagal nerve stimulation (VNS), the exploration of surgery for

psychiatric disorders has once again become an area of neurosurgical interest. A recent television program highlighting research in DBS for major depression made ample use of photographs depicting “ice pick” lobotomies and the famous scene from *One Flew Over the Cuckoo’s Nest*. As Kopell, Greenberg, and Rezai wrote in 2004, “Always lurking is the specter that the uncontrolled disaster of lobotomy may once again be reality if psychiatric neurosurgery becomes more widespread before rigorously controlled research trials can establish safety and efficacy data.”⁵

Psychiatric neurosurgery has once again captured the imagination of the popular press, being featured in the *New York Times*, *The Guardian*, *60 Minutes*, and *ABC Primetime*. But, is DBS for depression ready for this type of media scrutiny? Have adequate research studies been performed? What is the evidence that surgical interventions for major depression are effective?

DEEP BRAIN STIMULATION

At the end of 2006, to my knowledge, there has been one published paper and two abstracts focusing specifically on DBS for psychiatric disorders. In 2005, Mayberg et al.⁷ published a report on DBS of the subgenual cingulate gyrus (Brodmann area 25). This intervention was based on previous work showing functional imaging changes in this brain region among depressed patients, which reversed with successful treatment. Six patients with major depression were implanted with bilateral DBS electrodes. Preoperative depression scores measured using the Hamilton Rating Scale for Depression (HRSD) 17 Item Questionnaire (HRSD₁₇) averaged 25, which represents severe treatment refractory depression. “Response” was defined as at least 50% reduction in HRSD₁₇ scores at 6 months. “Remission” was defined as an absolute HRSD₁₇ score of less than 8. At 6-month follow-up, four of six patients were classified as responders, with one partial response and one failure. Two of the six patients met criteria for remission. In one patient, the stimulator was deactivated in a blinded fashion for 4 weeks, with sustained mood improvements, which diminished slightly toward the end of this period. Reactivation of the stimulator recaptured full

benefit. There were no significant side effects, although two patients required explantation because of infection.

The results of this study are very encouraging and have led this investigative team to continue the study with a larger set of patients. Preliminary results of this ongoing study seem to support the initial results. Further follow-up of these patients will be required before DBS of subgenual Area 25 can be deemed a truly effective therapy for depression.

To my knowledge, two abstracts on DBS for depression by other groups have also been presented at major scientific meetings. The first was presented at the American College of Neuropsychopharmacology Meeting in 2004, reporting on five patients with major depression who underwent placement of DBS electrodes into the anterior limb of the internal capsule bilaterally.³ These patients were evaluated with the HRSD 28 Item Questionnaire (HRSD₂₈). Both the patients and raters were blinded to the stimulation condition. At 3-month follow-up, three of five patients experienced greater than 50% improvement in HRSD₂₈. A second abstract, presented at the American Association of Neurological Surgeons Meeting in 2006, reported on six patients with major depression implanted in the anterior limb of the internal capsule.¹¹ Four out of the six patients showed greater than 50% improvement in HRSD scores at a minimum of 6 months follow-up.

In summary, the medical literature is presently very limited regarding DBS for major depression. Only 12 patients have been implanted, with 6 patients reported in one published manuscript and 6 patients described in two abstracts. Follow-up is short and there is insufficient statistical power to draw any firm conclusions. However, the early results are certainly promising. DBS for depression is clearly still in its infancy and represents a promising but unproven therapy.

VAGAL NERVE STIMULATION

A companion therapy to DBS, which is less invasive and likely of lower risk, is VNS. VNS was initially used for the treatment of medically refractory epilepsy. It was observed that some epilepsy patients being treated with this modality experienced elevations in their mood. This led Rush et al.¹² to study VNS in a population of 30 patients with treatment-resistant depression. These patients suffered from severe depression with mean HRSD scores of 38. "Response" was defined as at least 50% reduction in the HRSD scale at 12 weeks. Forty percent of patients in this study were classified as "responders." There were no adverse events. However, it should be noted that this was an early phase study without a control group, performed in an open-label fashion.

Given the encouraging results of this initial study, a prospective, randomized, controlled, double-blind study was designed to definitively answer the question of efficacy of VNS in treatment-refractory depression.¹³ Two hundred and sixty six participants were enrolled, with 235 patients im-

planted. The mean HRSD₂₄ score in these patients was 29, again representing a severely depressed group of patients. Fifty-three percent of patients had received electroconvulsive therapy at some point during their treatment, and 36% had received electroconvulsive therapy during the current depressive episode. "Response" was once again defined as at least 50% reduction in HRSD scale score at 10 weeks. This was defined as the primary outcome measure. The study was powered to detect a difference of 17% between the treatment group and the placebo group. Patients were randomized to receive either 20-Hz stimulation at up to 3.5 mA with an on/off cycle of 30 seconds on and 5 minutes off. The placebo group received sham stimulation, in which the device was programmed but not activated.

In the treatment group (consisting of 112 patients), the response rate was 15.2%. In the control group (consisting of 110 patients), the response rate was 10%. This difference failed to reach statistical significance, with a *P* value of 0.25. In fact, clinical response as measured by three of the four measurement scales used in this study did not reach statistical significance. This study did not, therefore, achieve its primary outcome measure, and could be interpreted as demonstrating a failure of the therapy.

Despite this failure to achieve the primary outcome measure in the pivotal study of VNS, the United States Food and Drug Administration (FDA) subsequently approved it for the treatment of medically refractory depression. There was some controversy surrounding the FDA's decision to approve VNS. In a report authored by the Committee on Finance of the United States Senate, Charles Grassley and Max Baucus reported that:

*The FDA approved the VNS therapy system for TRD based upon a senior official overruling the comprehensive scientific evaluation of more than 20 FDA scientists, medical officers and management staff who reviewed Cyberonics' application over the course of about 15 months. The official approved the device despite the conclusion of the FDA reviewers that the data provided by Cyberonics and support of its application for a new indication did not demonstrate a reasonable assurance of safety and effectiveness sufficient for approval of the device for TRD.*²

It is possible that the director for Center for Devices and Radiological Health of the FDA considered the open-label extension of this randomized trial, which suggested that, at 12 months, the response rate doubled to 27% and there was a 15% rate of remission. Or perhaps he was influenced by other studies, which also reported a positive effect of VNS for the treatment of depression.^{1,4,8,14}

At approximately this time, a favorable review of VNS for treatment-resistant depression was published in the *Journal of Neuropsychopharmacology*.⁹ The lead author of this paper, Charles B. Nemeroff, was also the editor-in-chief of the *Journal of Neuropsychopharmacology*. Unfortunately,

there was no financial disclosure attached to this manuscript, despite the fact that all of the authors had financial ties to Cyberonics, the manufacturer of the VNS device. The *Wall Street Journal*, on July 18, 2006, stated that:

Charles Nemeroff, one of the nation's most prominent psychiatrists, edits the Journal of Neuropsychopharmacology which this month favorably reviewed a controversial new treatment for depression. Yesterday the Journal said it plans to publish a correction because it failed to cite the ties of the article's 8 academic authors to the company that makes the treatment, including the article's lead author: Dr. Nemeroff.

The following day, *Blumberg News* quoted Bernard Carroll, former Chairman of Psychiatry at Duke University, as saying, "This is about as classic an example as you'll ever find of conflict of interest and manipulation by thought leaders who are beholden to corporations."

CONCLUSIONS

Neurosurgical interventions for psychiatric disorders remain as controversial as ever. Media hype, differing opinions regarding therapeutic efficacy, and allegations of conflict of interest all contribute to this murky picture, which will require considerable scientific study to clear up. The data for the use of DBS and VNS in depression is not strong enough at the present time to clearly guide clinical decision making. Each practitioner must use his or her own best judgement in deciding which therapies provide sufficient benefit to balance the risks in patients who may be desperate for any form of relief.

DBS for depression should currently be considered an experimental procedure and should only be performed under Institutional Review Board-approved research protocols at academic centers. VNS for depression has been demonstrated to have moderate effectiveness in several open-label studies, but is no better than placebo in the one prospective, randomized, controlled trial powered to demonstrate its effectiveness. VNS is FDA approved, and, although the efficacy is questionable, it should be available as a last-ditch treatment for severe, intractable depression.

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