From the Emory University School of Medicine

Deep Brain Stimulation for Treatment-Resistant Depression

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Case Presentation, Part 1

Brian is a 27-year-old Caucasian man who presents with signs and symptoms of a severe major depressive episode, including depressed mood, profound anhedonia, decreased sleep with predominant late insomnia, decreased appetite, fatigue, significant psychomotor retardation, feelings of worthlessness and guilt, poor concentration, indecision, and frequent passive suicidal ideation without plan or intent. He denies any history of hypomania or mania. He denies psychotic symptoms. He reports significant somatic and psychic anxiety without any consistent focus. He does not meet criteria for any other major psychiatric illness, including substance use and personality disorder. He is otherwise healthy. This is Brian's fourth clear major depressive episode (by history), and it began approximately 3 years ago.

Brian states that his first major depressive episode occurred "out of the blue" when he was 17 years old following an apparently "normal, happy" childhood and early adolescence. After 4–6 weeks of symptoms, he sought treatment and went into a full remission after 8 weeks of sertraline at 200 mg/day. He stayed on sertraline for 8–9 months, and then discontinued it after high school graduation. He remained well for about two and a half years but developed his second major depressive episode (again without any clear trigger) at age 20 in the fall of his junior year in college, where he was majoring in economics. He again sought treatment and achieved partial remission after about 4 months with a combination of sertraline (200 mg/day), clonazepam (1 mg at bedtime), and supportive psychotherapy. He continued to have residual difficulties with insomnia, mild anhedonia, and mild anxiety but was able to complete the school year without undue difficulty.

He remained in combined treatment but developed a third major depressive episode at age 21 in the fall of his senior year. Bupropion was added to his medication regimen and titrated to 300 mg/day, and he was referred for cognitive-behavioral therapy. He achieved a significant reduction in symptoms, but not remission. Because of residual symptoms, he did not immediately pursue graduate studies and instead went to work for a local bank.

Brian did reasonably well for about 3 years, with occasional worsening of depressive symptoms but generally with good functioning, when he developed his current major depressive episode. This was his most severe episode to date, with active suicidal ideation with a plan (but no immediate intent) to shoot himself. Over the next year, he had a number of treatments, among them multiple antidepressant medications, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, mirtazapine, tricyclic antidepressants, and tranylcypromine, as well as augmentation with lithium, thyroid hormone, buspirone, atypical antipsychotics, anticonvulsants, stimulants, light therapy, and ongoing psychotherapy. No treatment was able to achieve remission or a persistent clinically significant reduction in symptoms.

Given his degree of treatment resistance and continued overall deterioration, including increased suicidal ideation, he was referred for ECT. He achieved a good response (50%–60% symptom reduction) with eight high-dose right unilateral ECT treatments. ECT was delivered concurrently with ongoing medications, and attempts were made to optimize medications during and after ECT. However, Brian relapsed in about 6 weeks, and repeat ECT (including four right unilateral and eight bitemporal treatments delivered concurrently with ongoing medications) was unsuccessful in achieving significant symptom reduction but was associated with notable cognitive impairment.

Treatment-Resistant Depression

Prevalence and Impact

Major depressive disorder is a widespread and costly illness, with a 1-year U.S. prevalence of about 7% (1). A variety of treatments are available, but many patients fail to achieve sustained symptomatic remission. It has been conservatively estimated that 10%–30% of depressed patients will not remit and stay well with adequate therapy (2). Data from the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D) demonstrated that approximately 33% of patients failed to achieve remission despite multiple treatment attempts, and relapse occurred within 6–12 months in approximately 50% of those who remitted (3). Treatment-resistant depression therefore has a U.S. prevalence of 2%–5%. Continued depressive symptoms are associated with ongoing functional impairment (4), increased utilization of health care resources (5), a greater risk of suicide (6), and an overall increased mortality (7).

Definition

Despite the growing recognition of the prevalence and public health impact of treatment-resistant depression, a

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consensus definition for this condition has not emerged. Various approaches to staging treatment resistance have been developed (8–10), although studies of treatment-resistant depression continue to vary widely in the operational criteria used (11). That said, failure of at least two antidepressant treatments in the current episode is one of the most consistently appearing definitions in the literature (12), and it appears to have predictive validity. In STAR*D, remission rates in successive stages of treatment were 36.8% in the first treatment, 30.6% in the second treatment, 13.7% in the third treatment, and 13.0% in the fourth treatment (3). The likelihood of remission is substantially lower for patients for whom two adequate antidepressant trials failed than those for whom one adequate trial failed. Notably, the STAR*D data indicated that failure of a trial with one selective serotonin reuptake inhibitor (SSRI) (citalopram) did not substantially diminish the likelihood of responding to a second SSRI (sertraline)—however, failing to respond to two antidepressant treatments (from the same or different classes) did predict subsequent treatment failure.

Current Treatment Approaches

Numerous potential neurobiological targets for pharmacological approaches to treatment-resistant depression have been proposed, but data for agents aimed at these targets are limited or inconclusive (13). Cognitive therapy can be moderately efficacious in patients who did not achieve remission with a single antidepressant medication trial (14) and may be effective in patients for whom a higher number of trials failed (15), although not all studies have been successful (16). Cognitive therapy also may decrease the rate of depressive relapse over time (17–19), although in highly recurrent major depression this effect is somewhat modest (19). Overall, psychotherapeutic approaches have been inadequately tested for treatment-resistant depression, especially compared to somatic interventions (20).

ECT is an effective antidepressant treatment often considered first-line in the management of treatment-resistant depression. ECT may be less effective in treatment-resistant patients, but it is still associated with a remission rate of 50%–60% (21–23). However, ECT can have side effects that limit its clinical use (24), and it is associated with a high relapse rate, especially in patients with treatment-resistant depression (22, 25).

Repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal cortex was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression that has not responded to one antidepressant medication. rTMS is a noninvasive brain stimulation technique that is generally safe and has consistently shown statistically significant antidepressant effects (26–28). However, response rates (defined as a decrease of at least 50% in depression severity) are relatively low: about 15%–20% after 3–4 weeks of treatment and 24% after 6 weeks of treatment (29). Remission rates are even lower: 7%–14% with at least 3 weeks of treatment and less than 18% after 6 weeks of treatment. Furthermore, the utility of this treatment in patients with more resistant depression (those who did not benefit from more than one adequate antidepressant treatment in the current episode) may be limited (30), and the maintenance of benefit over time is largely unknown.

Vagus nerve stimulation (VNS) is FDA approved for the treatment of treatment-resistant depression, defined in this case as depression that has not responded to four or more antidepressant treatments. VNS involves chronic, intermittent, unilateral stimulation of the left vagus nerve through a surgically implanted electrode and pulse generator. The risks of VNS surgery are relatively minor, and long-term treatment is generally well tolerated. However, a sham-controlled study showed statistically nonsignificant antidepressant efficacy for VNS with 10–12 weeks of treatment, with a 15% response rate to active stimulation and a 10% response rate to sham stimulation. Open-label long-term response and remission rates were higher (27% response rate and 16% remission rate after 12 months of stimulation) and statistically significantly greater than 12-month naturalistic outcomes in a nonrandomized treatment-as-usual comparison group not receiving VNS (13% response rate, 7% remission rate) (31–33). In longer-term follow-up studies, 21%–50% of patients who responded to VNS failed to maintain at least a 40% decrease in baseline depression severity over 1–2 years (34, 35). In an open-label European cohort, 56% of patients who had responded during 1 year of VNS relapsed within the next year (36).

In sum, few treatments are currently available for treatment-resistant depression. The most efficacious of these are associated with only modest response and remission rates, and relapse may still be a problem. Transcranial magnetic stimulation may have limited benefit for patients who have failed to benefit from more than one adequate antidepressant treatment, and the pivotal VNS study included only patients who failed to benefit from at least two but no more than six antidepressant treatments in the current episode. Therefore, for patients with a higher degree of resistance (more than six adequate treatments in the current episode, as in the case we present here), there is no available treatment with established short- and long-term efficacy.

Defining the Neurobiology of Treatment-Resistant Depression: Neuroimaging Studies

Over the past several decades, numerous studies have investigated the neurobiology of depression, with structural and functional neuroimaging becoming central to the effort to identify biomarkers for depression and treatment response. Structural neuroimaging studies have identified a number of abnormalities in patients with

depression (37), but studies of treatment-resistant depression are sparse. Smaller medial temporal volumes (primarily the hippocampus but also the amygdala and the entorhinal cortex) have been consistently reported in depressed patients (38–41), and it has been suggested that treatment resistance may contribute to these findings (38, 42–44). However, these studies have generally been limited by one or more factors: not including a treatment-responsive comparison group; using an inadequate definition of resistance (e.g., failure of only one treatment in the current episode); or not controlling for potential medication effects. This last point is critical, since antidepressant medications may offer protection against hippocampal atrophy (45), although it is unclear whether this effect is independent of an antidepressant effect. Zhang et al. (46) showed differences in magnetization transfer ratio in patients with treatment-resistant depression compared to healthy comparison subjects in the right anterior cingulate, insula, caudate tail, and amygdala-parahippocampal regions, suggesting subtle structural/functional dysfunction in these areas; however, voxel-based morphometry failed to identify clear morphological abnormalities, and the study did not include a treatment-responsive comparison group. Taylor et al. (47) found that patients who failed to respond to a single antidepressant medication had higher frontal lobe fractional anisotropy—a diffusion tensor imaging marker of white matter integrity—suggesting better organized white matter in the resistant relative to the responsive patients. Shah et al. (48) showed that patients with treatment-resistant depression had smaller right medial frontal and striatal volumes compared to a group of treatment-responsive patients and comparison subjects. This finding is more specific to treatment-resistant depression, but treatment status was not controlled between the treatment-resistant and treatment-responsive patient groups.

Functional imaging studies of treatment-resistant depression have also been limited. Hornig et al. (49) found that the ratio of amygdalar-hippocampal to cortical blood flow was higher in patients who had at least one prior failed antidepressant treatment compared to patients with nonresistant depression and healthy comparison subjects; all participants were medication free at the time of scanning (and data from the nonresistant depression patients and healthy comparison subjects were combined), so no assessment could be made of differences following adequate treatment. Price et al. (50), using magnetic resonance spectroscopy, found lower concentrations of occipital γ-aminobutyric acid in patients with treatment-resistant depression (defined as failure of at least three antidepressant trials) compared to patients with nonresistant depression and healthy comparison subjects; again, all patients were medication free, so the study could not assess treatment resistance controlling for potential medication effects. Also, because no frontal, striatal, or limbic regions were assessed, the regional specificity of these findings is unknown. Other functional imaging studies have assessed for potential predictors of eventual treatment response or nonresponse (see references 51, 52, for example) or have examined treatment-related functional changes associated with response and nonresponse (53–57), suggesting that "normalization" of brain activity with treatment is required for an adequate antidepressant response—with the corollary conclusion that failure to normalize is an imaging biomarker for treatment-resistant depression and could potentially be used to direct novel treatment development.

Studies of Deep Brain Stimulation for Treatment-Resistant Depression

"Given the invasiveness of the DBS implantation procedure and the risks involved, placebo-controlled data are critical to determining whether DBS may be a clinically effective intervention for treatment-resistant depression."

Deep brain stimulation (DBS) is achieved through stereotactically implanted intracranial electrodes connected to an implanted pulse generator/battery pack (IPG) in the chest wall. High-frequency DBS is currently approved by the FDA for the treatment of medication-refractory Parkinson's disease, essential tremor, primary dystonia, and obsessive-compulsive disorder (OCD) (the last two through a humanitarian device exemption). Generally, DBS offers an alternative to ablative neurosurgical procedures; unlike a lesion, it is potentially reversible (in the case of intolerable side effects), revisable, and adjustable. Serious risks of DBS surgery include intracranial hemorrhage (with the potential for permanent neurological deficits), infection, and death from anesthesia. Side effects from stimulation vary widely with stimulation target. An additional drawback to DBS is the need to avoid certain situations and treatments that may damage the device or heat its components and cause injury to the patient, such as metal detectors, strong magnetic fields, and diathermy. Finally, repeated surgeries are needed over time (anywhere from 6 months to 5 years) to replace the IPG.

The first evidence of potential efficacy for DBS in mood disorders came from anecdotal experience of mood changes noted in patients with neurological disorders or OCD receiving DBS (58–60). The first published report of DBS for treatment-resistant depression described a clinically significant antidepressant response in four of six patients with treatment-resistant depression after 6 months

of open-label bilateral DBS applied to the subcallosal cingulate white matter (57); the basis for selection of this target was a converging neuroanatomical database suggesting that the subcallosal cingulate cortex served as a critical node in a distributed mood regulation network involved in depression and antidepressant response (61). This initial study was expanded to include 20 patients followed for 12 months, demonstrating a 60% response rate and 35% remission rate at 6 months and a 55% response rate and 35% remission rate at 12 months (62). Chronic subcallosal cingulate DBS was not associated with any stimulation-related adverse events.

Other targets for DBS in treatment-resistant depression have been proposed, including the inferior thalamic peduncle (63), the anterior limb of the anterior internal capsule (a previous target used for ablative treatment in severe psychiatric disorders) (64), the nucleus accumbens (65), and the habenula (66). DBS of the anterior limb of the anterior internal capsule has been associated with improvement in depressive symptoms in patients with severe treatment-resistant OCD (67), and a recent open-label study in 15 non-OCD patients with treatment-resistant depression showed a 40% response rate and 20% remission rate at 6 months and a 53% response rate and 40% remission rate at last follow-up (68). DBS of the nucleus accumbens was associated with a 50% response rate after 12 months of stimulation in 10 patients with treatment-resistant depression (an average of 24 months [SD=15, range=6–51] after onset of stimulation) (65). With each of these targets, chronic stimulation was not reported to be associated with any notable adverse events, although reversible mood, anxiety, and motor effects were occasionally seen.

To date, only results from small open-label studies and case reports have been published for DBS for treatment-resistant depression. Although large placebo responses might seem unlikely in these carefully selected, severely ill patients (69), it is sobering that a meta-analysis of trials of surgical interventions for Parkinson's disease found a mean placebo response rate of 42% with a range of 29% to 55%—much higher than for other types of interventions despite these studies' inclusion of patients with more severe and treatment-refractory illness (70). Given the invasiveness of the DBS implantation procedure and the risks involved, placebo-controlled data are critical to determining whether DBS may be a clinically effective intervention for treatment-resistant depression. Such data will also help determine the relative efficacy and safety of the various targets under investigation. Additionally, essential questions concerning DBS's mechanism of action remain and should continue to be a major component of future studies.

Case Presentation, Part 2

Brian is seeking participation in an ongoing clinical trial of subcallosal cingulate DBS that was approved by the Emory University Investigational Review Board. After receiving a detailed description of the study, he provides written informed consent for participation. His baseline 17-item Hamilton Depression Rating Scale (HAM-D) score is 25. After a rigorous screening process, he is selected for and consents to surgery. He undergoes neurosurgical bilateral placement of DBS electrodes in the subcallosal cingulate white matter. During testing of individual contacts during surgery, at the third contact tested on the first side, the patient is noted to become spontaneously louder in his responses to questions and states, "I feel like I have more energy, less heavy—if I was home, I feel like I could take the dog for a walk." This effect slowly fades during testing of other contacts. One week after surgery, during initial programming, this effect is not reproducible.

In accordance with the clinical trial protocol, all psychotropic medications are held stable during the 24-week open stimulation period; Brian's regimen includes duloxetine, 60 mg/day; mirtazapine, 60 mg/day; buspirone, 90 mg/day; aripiprazole, 20 mg/day; dextroamphetamine, 20 mg/day; and clonazepam, 2 mg at bedtime. After 4 weeks of active bilateral stimulation (130 Hz, 91 μsec pulse width, 6 mA, monopolar stimulation), Brian begins to note a slight decrease in his level of suicidal ideation and a subtle increase in motivation; his HAM-D score is 17. He reports no adverse events related to the surgery or chronic stimulation. Over the next 8 weeks, he notes a decrease in negative mood, a slight improvement in sleep quality and quantity, and better concentration. At his 12-week follow-up visit, his HAM-D score is 13. Asked about his slow but consistent improvement, he remarks, "It's like my hair: day to day, it's hard to tell it's growing, but after a month, it's clearly a lot longer. That's the way it is with the depression getting better." He continues to report no side effects associated with stimulation.

At his 16-week visit, Brian's HAM-D score is 18. He reports a sense of guilt that he is not engaging in more productive activities, he continues to have occasional suicidal ideation, and he does not feel "happy." He reports that he has been reading the business section of the newspaper on a regular basis (for the first time in over 3 years) but feels that he is just a spectator rather than the active participant in the business world that he perceived himself to be before this episode of depression. He also describes feeling lonely, stating that he lost contact with most of his friends during this episode of depression because he did not return phone calls or respond to e-mail or requests to get together. He continues to emphasize that his depression is much improved but expresses concern that this might be "as good as it will get."

At his 24-week visit, Brian reports doing much better, and his HAM-D score is 9. He continues to have a moderate decrease in libido (possibly secondary to medication side effects), occasional fleeting suicidal ideation (usually situational), and some mild sleep disturbance, for which he continues to take clonazepam. However, he has started reconnecting with old friends and is planning to take a class at a local community college. He intends to look for a part-time job and hopes to return to graduate school in the next year or two. He begins a slow taper of his duloxetine (presumed to be contributing to his decrease in libido), and 3 months later completely discontinues this medication, with no return of depressive symptoms and

a substantial increase in libido. His other medications remain unchanged.

Approximately 2 years after surgery, Brian calls the DBS investigators to report that his depressive symptoms have gradually returned over the past 4 weeks; he continues on his previous medications with no interval changes. On examination, it is discovered that his IPG is no longer active—the battery has been depleted. Within the next week, he receives a replacement IPG and is encouraged to check the status of the battery every 1–2 weeks. Four weeks after the battery replacement, he reports that he is doing much better but is concerned about starting graduate classes in the fall because of a fear that his depression may return.

Discussion

The patient we present in this case experienced a dramatic and mostly sustained antidepressant response to chronic subcallosal cingulate DBS without any adverse events. It is critical for clinicians to recognize, however, that DBS remains a purely investigational treatment for treatment-resistant depression; available data are limited to small, open-label, noncontrolled, unblinded studies. When adverse events related to surgery are considered, DBS represents the riskiest treatment currently being investigated for use in patients with treatment-resistant depression. A single case clearly cannot confirm the safety and efficacy of a treatment; large, randomized, placebo-controlled studies of DBS for treatment-resistant depression are necessary. Our purpose here is to inform our colleagues of the state of development of this treatment approach, not to advocate its use.

In many ways Brian represents a prototypical patient enrolled in our ongoing study of subcallosal cingulate DBS for treatment-resistant depression, in terms of demographic characteristics, clinical characteristics, and treatment response over time. Of the first 13 patients in the study, 10 (77%) had an excellent response to a previous—often their first—antidepressant treatment. Only later in the course of illness did these patients develop confirmed treatment resistance. Patients who show a significant decrease in depressive symptoms associated with chronic subcallosal cingulate DBS typically describe a gradual, subtle, but largely consistent change over months rather than a dramatic improvement over days or weeks. This is true even in patients who experience an acute effect with initial stimulation (as in this case and as previously reported [57]). Brian's notable worsening (as reflected in his HAM-D score) at 16 weeks of treatment is consistent with what was seen in an earlier cohort of patients receiving DBS of the subcallosal cingulate (62). Although there may be other explanations, this case suggests that some patients may show a worsening of symptoms as they begin to reengage the outside world—a behavioral change made possible by an overall decrease in depression severity. Finally, the gradual return of depressive symptoms Brian experienced after battery depletion is consistent with a previous report (57). Thus depression is not "cured" in these patients—ongoing treatment is necessary.

As the study of DBS for treatment-resistant depression progresses, several challenges must be considered. First, it is highly probable that adjunctive psychotherapy or rehabilitation may be necessary to maximize the benefits associated with DBS in patients with treatment-resistant depression—arguably, Brian may not have experienced his worsening at 16 weeks and might have achieved maximal response sooner if he had been receiving directed psychotherapeutic intervention concurrently with chronic DBS. The addition of psychotherapy to chronic DBS may strike some as degrading the scientific quality of the clinical trial, given the propensity toward placebo response in depressed patients and the addition of a second treatment perceived as having antidepressant efficacy in and of itself. However, failing to add adjunctive psychological rehabilitation to chronic DBS for treatment-resistant depression may be akin to not providing physical and occupational therapy after a hip replacement or cardiac rehabilitation after coronary artery bypass surgery—especially since the eventual desired outcome is functional recovery, not just symptomatic improvement.

Second, there is a potential for interaction with ongoing pharmacotherapy, such that chronic DBS may work better for patients on certain psychotropic medications, whereas other agents could potentially interfere with DBS's efficacy or contribute to adverse events. It will be important to learn whether DBS is effective in patients who are not taking any medications and whether some form of pharmacotherapy is needed for maximal benefit (as is common with DBS for Parkinson's disease). This will be difficult to assess in current, ongoing studies, in which most patients are maintained on their pre-DBS medication regimens. Also, because any interaction effects noted may differ with different DBS targets, results with one target should only cautiously be extrapolated to other targets.

Third, it is critical that investigators work carefully to identify appropriate patients for participation in ongoing clinical trials. Brian's candidacy was relatively straightforward, as he had no significant psychiatric or medical comorbidities. However, it is well established that many patients with treatment-resistant depression have significant psychiatric or medical comorbidity. What level of comorbidity should be permitted in pilot and pivotal trials is a subject of debate. On the one hand, it would seem appropriate to have the study population reflect the target population so that the results could be generalized more broadly. On the other hand, the presence of significant comorbidity may reflect a different neurobiological basis for treatment resistance that may obscure the antidepressant signal associated with DBS. In addition, if psychosocial adjustments are required for maximal efficacy, the presence of certain comorbidities (such as personality disorders) may make this more difficult and further reduce the observed effect.

Fourth and finally, the relative safety and efficacy of various DBS targets are as yet unknown and cannot be estimated from the small data sets currently available. Additionally, it remains unclear whether there are subtypes of treatment-resistant depression that may respond better with DBS at one or another target—and again, such treatment specificity may not transcend all possible DBS targets. Until large comparative studies are conducted (similar to studies of various targets in movement disorders), these questions will remain unresolved.

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Dr. Mayberg has a consulting agreement with St. Jude Medical, Inc., which has licensed her intellectual property to develop subcallosal cingulate deep brain stimulation for the treatment of severe depression (US 2005/0033379A1, co-inventor, Andres Lozano, M.D., Ph.D.). The terms of these arrangements have been reviewed and approved by Emory University in accordance with their conflict-of-interest policies. Dr. Mayberg has received grant funding from the Dana Foundation, NARSAD, NIMH, Stanley Medical Research Institute, and Woodruff Foundation. Dr. Holtzheimer has received grant funding from the Dana Foundation, Greenwall Foundation, NARSAD, NIMH (grant K23 MH077869), NIH Loan Repayment Program, Northstar, Inc., Stanley Medical Research Institute, and Woodruff Foundation and has received consulting fees from AvaCat Consulting, St. Jude Medical Neuromodulation, and Oppenheimer & Co.

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