DEEP BRAIN STIMULATION FOR MAJOR DEPRESSIVE DISORDER

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Abstract

Major Depressive Disorder continues to pose a major public health challenge as up to one-third of patients fail to respond adequately to standard pharmacological and somatic therapies. An improved understanding of the complex circuitry underlying depressive disorders has fostered renewed interest in the development of non-pharmacological approaches to managing these seriously ill patients. Each of these treatments seeks to restore normal brain activity via electrical or magnetic stimulation. In this article, the authors discuss the current status of deep brain stimulation for treatment-resistant depression, including the scientific rationale for re-exploring surgical interventions for MDD, the role of functional imaging in our understanding of the pathophysiology of depression, and the results of clinical trials.

Key Words: Cg25, deep brain stimulation, major depressive disorder, neuromodulation, nucleus accumbens, stereotactic surgery

Declaration of interest: Sanjay Mathew is counsultant with AstraZeneca and received grant funding by Glaxo, Smith Kline, Roche Pharmaceuticals, NARSAO, NIMH

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Introduction

Prior to the introduction of levodopa in the 1960s, therapeutic ablation of various deep brain structures played a central role in the management of Parkinson's disease (PD) and other movement disorders (Benabid et al. 1998). The resounding success of levodopa therapy made ablative surgery for PD virtually obsolete, as it appeared that dopamine replacement would provide a life-long cure for this neurodegenerative disorder. Twenty years later the limitations of chronic dopamine replacement therapy were evident, stereotactic surgery techniques had advanced, and ablative surgery for PD was reborn (Laitinen et al. 1992). Moreover, the development and study of primate models of PD provided a scientific rationale for lesioning various deep brain structures, the benefits of which had been discovered through empiricism and serendipity in prior decades (Bergman et al. 1990). Finally, the development of chronic electrical 'deep brain stimulation' (DBS) as a reversible alternative to neuroablation, and a realization that medications and surgery can work in concert to improve or maintain motor function, has made surgery once again standard of care for select patients with advancing PD, essential tremor, and dystonia (Weaver et al. 2009).

Today, surgery for psychiatric illness is poised to make a similar comeback. In 1957, a medication initially developed to treat tuberculosis fundamentally changed the treatment of Major Depressive Disorder (MDD) when it was found, as a side effect, to elevate mood (Schildkraut 1965). Iproniazid ushered in a new era in which pharmacological therapy gained primacy in the treatment of MDD, relegating ablative surgical interventions to the proverbial 'trash heap' of history. More importantly, the discovery that iproniazid inhibits monoamine oxidase spawned the monoamine theory of depression, which has been the central tenet of depression research and drug development for the last half-century. While monoamine oxidase inhibitors and the tricyclic antidepressants that followed soon after were generally effective for treating depressive disorders, their side effects proved intolerable for many patients. Selective serotonin reuptake inhibitors (SSRIs), which are generally more effective and tolerable, were introduced in the 1980's and yielded the blockbuster drugs fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil). While it was once hoped that these medications would make more aggressive 'somatic' treatments, such as electroconvulsive therapy (ECT) obsolete, it is now clear that a significant proportion of severely affected depressive patients are

Submitted August 2009, Accepted October 2009

refractory to medical therapy and require additional modes of relief. Moreover, advances in functional neuroimaging are beginning to reveal key brain loci involved in the biology of depression, loci that may be targeted for DBS or other emerging therapies. Finally, the success of DBS in the treatment of refractory movement disorders offers the hope that similar or even greater success may be found in psychiatric applications. In this submission we will provide an overview of the current status of DBS for the treatment of MDD. We hope the reader will come away with a deeper understanding of the magnitude of the problem refractory depression poses to public health worldwide, the scientific underpinnings of the current re-exploration of surgical intervention for MDD, and the sensitivity to past abuses with which current endeavors proceed.

Magnitude of the problem

Major Depressive Disorder is a significant and growing threat to public health worldwide. According to the World Health Organization (WHO 2009), MDD was the 4th leading contributor to global disease burden in 2000 and is projected to be the 2nd leading generator of Disability Adjusted Life Years (DALYs) by the year 2020 (Mathers and Loncar 2006). The WHO estimates that depression affects 121 million people worldwide. Up to 4% of the population may be affected at any one time and 12-25% may be affected by MDD at some point in their lives (DSM-IV-TR 2000). According to the Centers for Disease Control, MDD and dysthymia may contribute to the development of chronic medical illness, and are the leading causes of suicide in the elderly (Chapman and Perry 2008). Failure to recognize and adequately treat mood disorders has a significant negative impact on public health from both a social and economic perspective (Fava GA et al. 2007).

Limitations of current treatment strategies

Despite the variety of pharmacological therapies available to treat MDD, as many as one-third of patients fail to respond adequately to medications (Rush et al. 2006, Fava M 2003), leaving them severely disabled and at risk of suicide. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was a prospective, multi-center, sequenced therapy trial that sought to assess the ‘real-world’ effectiveness of medical therapy for non-psychotic MDD (Rush et al. 2006). Patients initially received monotherapy with the SSRI citalopram. Patients who did not achieve symptom remission or who could not tolerate this medication were offered several pharmacologic and psychological alternatives in the subsequent steps of the trial, up to four therapies in all. Thirty-seven percent of patients achieved symptom remission with citalopram monotherapy. Subsequent treatment steps yielded lower remission rates of 31%, 14%, and 13% with a cumulative remission rate of 67%. No second line therapy, whether adding an augmentative medication, switching to a new drug either within the same class or of another class, etc., proved more effective than any other. In a follow-up naturalistic study, patients who had participated in the STAR*D trial were followed for an additional 12 months during which they were monitored for relapse (Rush et al. 2006). Relapse rates were greater for those patients who progressed further in the study (ie those who were more treatment resistant). The results of the study, which included more than 3600 patients, suggest that failure to respond to even one SSRI is a poor prognostic indicator, signifying a greater likelihood of treatment resistance and subsequent relapse.

In a complementary study, Souery et al. (2007) sought to delineate those clinical factors that presage treatment resistant depression (TRD). As in the STAR*D trial, poor response to the first antidepressant treatment was associated with future treatment-resistant status; however, of the eleven clinical factors studied, original non-response was the least potent predictor of treatment resistance. Rather, co-morbid anxiety, panic disorder, social phobia, personality disorders, suicidal risk, depression severity, number of hospitalizations, early age at onset, and melancholic subtype, were more significantly associated with TRD. These results support the notion that MDD is heterogeneous in nature with varied responses to treatment; and that additional therapies are required to adequately address this large public health problem.

Non-Pharmacologic therapy for MDD

Electroconvulsive Therapy (ECT)

Traditionally reserved for medically resistant depression, ECT is the oldest continuously practiced somatic intervention in psychiatry, and remains the single most effective treatment available for MDD. Over time, the methods of ECT administration have been refined, though the central therapeutic component (ie elicitation of a seizure) has remained constant. Randomized, prospective, double-blinded studies comparing ECT with sham consistently report a 50% or greater response rate, and studies with more rigorous treatment protocols have reported response rates approaching 90% (Kellner et al. 2006). Yet, despite the unquestioned evidence of ECT’s efficacy, few patients actually undergo the procedure. Only ~100,000 treatments are performed annually in the United States versus an estimated 118 million patients for whom antidepressants are prescribed (Burt et al. 2007, Mathew et al. 2005). The reasons for this limited use of ECT are probably two-fold. The first reason is the continued stigma associated with the use of ECT, which makes patients resistant to accepting the intervention (Dowman et al. 2005) and the second is the concern for cognitive side-effects, particularly from multiple ECT treatments. Short-term memory loss and confusion are often observed in the immediate aftermath of treatment (Sackeim et al. 2000); however, a recent review of ECT practice and success at a set of community clinics found that cognitive outcomes varied across treatment facilities and that differences in technique largely accounted for this variance (Sackeim et al. 2007). In short, while ECT continues to be an important intervention in the treatment of medically resistant depression, significant barriers persist that will likely limit its widespread use for the foreseeable future.

Other treatment modalities

Additional modalities for the treatment of MDD that are under active investigation include transcranial magnetic stimulation (Loo et al. 2008), transcranial direct current stimulation (tDCS), vagus nerve stimulation (Daban et al. 2008) and Ketamine infusion therapy (Price et al. 2009). Discussion of these modalities is beyond the scope of this review, but the fact that these modalities are under investigation further highlights the short-comings of current treatment paradigms for MDD.

Deep brain stimulation

If on-going prospective, double-blinded trials confirm the findings of preliminary open-label trials, deep brain stimulation (DBS) will become the first therapy for depression directly informed by our evolving understanding of the neural circuitry of depression. Although we are far from a complete understanding of the complex neurobiology of depression, much progress has been made over the last decade. It is now generally believed that depression has a complex genetic, developmental, and environmental etiology, and its manifestations lie at a systems level within the corticostriatothalamic circuitry (Rauch 2003, Mayberg 2003). Neuroimaging studies have elucidated a number of brain regions that behave abnormally in depressed patients. In particular, the finding that neural activity in Brodmann's area 25 (ie the ventral cingulate cortex; Cg25) is elevated in patients who are actively depressed and normalizes in patients whose symptoms abate, regardless of the reason (ie spontaneous remission, medications, etc.); and that direct stimulation of this brain region can alleviate depression in treatment resistant patients, has demonstrated for the first time the potential of functional neuroimaging to guide targeted therapies for the treatment of complex brain disorders (Mayberg 2003).

DBS Surgery

Deep Brain Stimulation involves the implantation of stimulating electrodes (called leads) into one or more specified brain regions and connecting those leads to programmable pulse generators that are implanted beneath the skin of the chest wall or abdomen, similar to a cardiac pacemaker (**Figure 1**). The therapeutic region of interest is targeted employing standard stereotactic techniques, and the leads are implanted via burr holes that are created in the frontal skull, just anterior to the coronal suture. Implantation of the stimulating leads typically is performed under local anesthesia (ie the patient is awake), which facilitates the performance of intraoperative neurophysiological recordings, when necessary, and allows the treating physicians to monitor the acute beneficial and adverse effects of stimulation prior to securing the stimulating lead in place. The only DBS systems currently approved by the FDA are manufactured by Medtronic, Inc. St. Jude Neurological, Inc. produces a DBS system that is currently approved for use in Europe and is being evaluated by the FDA for approval in the U.S.

Each one of the four contacts on the implanted lead can be activated independently at the physician's discretion. The stimulation parameters including stimulus amplitude, frequency, and pulse width, as well as active contacts, are adjusted telemetrically. Stimulation is continuous, in contrast to VNS, which is cycled. Optimal stimulation parameters are determined empirically for each target and may vary from patient to patient. Optimal settings may be determined easily in some disorders such as essential tremor, in which tremor represents an objective, measurable symptom, and clinical benefit is obtained on the order of seconds. The programming process is much more challenging in psychiatric disorders because the clinician must rely more on subjective patient responses and a considerable lag time exists (on the order of hours, weeks, or months) between the induction of stimulation and clinical benefit.

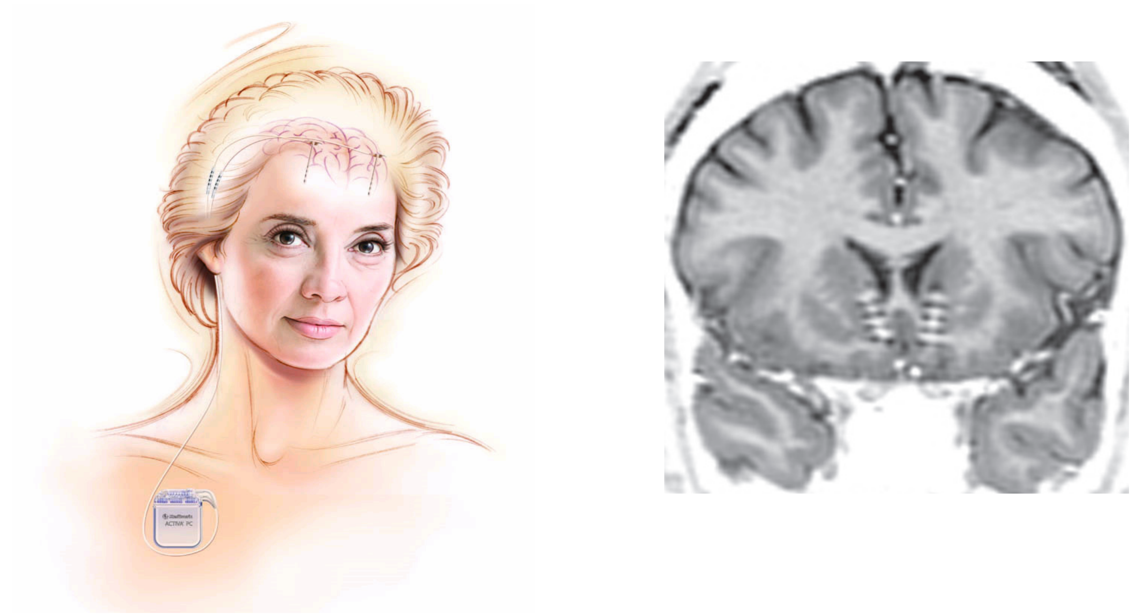
Risks Associated with DBS

Generally, DBS is considered to be safe with very low rates of neurological complications. There are, however, some serious risks that need to be addressed when DBS surgery is discussed with patients, including the possibility of intracranial hemorrhage, seizure, infection, and hardware malfunction/breakage (Anderson and Lenz 2006). Stimulation-induced side effects such as paresthesia, muscle contraction, dysarthria, and diplopia are target-related and usually temporary and/or reversible (Eitan and Lerer 2006). It should be remembered that to date only a handful of MDD patients have received DBS so it is difficult at this time to know fully the risks in this patient population.

Use of DBS in Major Depressive Disorder

The safety and efficacy of DBS in MDD is currently under active investigation in the U.S., Canada, and Europe. Two pivotal industry-sponsored U.S. trials have been initiated, one investigating the efficacy of stimulation at the ventral anterior internal capsule/ventral striatum, including the Nucleus Accumbens (VC/VS) and the other at Cg25. Additional targets that are in more preliminary stages of investigation include the inferior thalamic peduncle (Jimenez et al. 2005), the rostral cingulate gyrus (Sakas and Panourias 2006), and the lateral habenula (Sartorius and Henn 2007)

The potential application of DBS at VC/VS for MDD derives from studies of DBS at this target for the treatment of medically refractory Obsessive Compulsive Disorder (OCD), an indication for which the FDA granted the Medtronic Reclaim™ DBS system a Humanitarian Device Exemption in 2009 (United States Food and Drug Administration). In the course of studying DBS in OCD, investigators noted that patients



A B

Figure 1. *Deep Brain Stimulation Device*

(A) The Deep Brain Stimulation Device consists of one or two stimulating leads that are implanted stereotactically within a specified deep brain target via burr holes that are drilled in the pre-coronal frontal bone. The leads are then connected to a subcutaneously implanted pulse generator via extension cables that are tunneled subcutaneously. Stimulation parameters are programmed telemetrically. (B) Coronal MRI demonstrating bilateral DBS leads implanted in the white matter subjacent to Brodmann's area 25 (Cg25).

Figure 1A courtesy of Medtronic, Inc.

with co-morbid depression experienced improvement in both their depression and OCD after the onset of stimulation (Gabriels et al. 2003, Aouizerate et al. 2004, Abelson et al. 2005, Greenberg et al. 2006). Interestingly, the respective improvements in OCD and depression exhibited different time courses, with mood improving weeks to months before the improvement in OCD symptoms. These divergent response times are consistent with the clinical responses of both mood and OCD to medications, and suggest that the improvement in mood is a direct effect of stimulation and not a secondary effect of alleviating the symptoms of OCD.

In the largest published examination of long-term outcomes from DBS for OCD, Greenberg et al. (2006) reported on 10 OCD patients, eight of whom had co-morbid MDD. The mean 24-item Hamilton Scale for Rating Depression ($HSDR_{24}$) decreased 30%, from 21.1 ± 1.5 at baseline to 14.7 ± 2.1 after 3 months of therapy, thereafter remaining stable, with a mean score of 15.4 ± 2.6 after 36 months. Adverse effects included a small asymptomatic intracerebral hemorrhage, a single intraoperative generalized tonic-clonic seizure (with no further recurrence during the 3-year follow-up period), a superficial surgical wound infection in a diabetic patient, and various stimulation-dependent changes in mood and motor function that were reversible within seconds to minutes of stimulation cessation.

Encouraged by these results, these investigators initiated a prospective, open-label feasibility trial examining the safety and efficacy of VC/VS DBS in MDD (Malone et al. 2008). Fifteen patients were studied, 14 who met DSM-IV criteria for MDD and one with bipolar depression. Study participants had been treated with an average of six different anti-depressant medications, six augmentation/combination trials, and a mean of 30.5 ECT treatments. The patients were severely depressed as evidenced by a mean baseline $HSDR_{24}$ score of 33.1 ± 5.5. Patients were followed for a mean of 23.5 months (range: 6-51 months). Both the mean $HSDR_{24}$ and Montgomery-Asberg depression rating scale (MADRS) scores were reduced by ~45% six months after the onset of stimulation. In patients who responded, scores improved steadily over the initial six-month period and were maintained for up to three years in those who had been followed that long. Approximately half of the patients were categorized as responders (defined as a 50% or greater reduction in the $HSDR_{24}$ and/or MADRS) and approximately one third were categorized as achieving remission (defined as an absolute MADRS or $HSDR_{24} < 10$). Overall, the DBS procedure was well-tolerated, though one patient experienced two stimulation-related episodes of hypomania. Two patients required revision surgery for device-related complications. Of note is that the mean stimulation amplitude was 6.7 ± 1.8 volts with a correspondingly short average device life of just 10.6 months.

Schlaepfer et al. (2008) treated a series of three patients (including a pair of monozygotic twins) with DBS in the VC/VS region, but with the main focus of stimulation within the nucleus accumbens. They noted specific improvement in anhedonia, which is consistent with the role of this brain region in reward processing. Within 60 seconds of blinded stimulation onset, patients spontaneously reported the desire for a new pleasurable activity without reporting an improvement in depression. Both $HDRS_{24}$ and MADRS scores decreased significantly within a week of stimulation onset and were significantly correlated with blinded on/off stimulation status and stimulation strength.

The other DBS target actively being investigated for the treatment of MDD is the subgenual cingulate cortex (Cg25). Mayberg et al. (2005) chose this region as a target for DBS on the basis of neuroimaging studies, which suggested that hyperactivity of Cg25 is associated with MDD and that normalization of Cg25 activity is associated with alleviation of symptoms whether in response to pharmacotherapy (Mayberg et al. 1999), rTMS (Mottaghy et al. 2002), or ECT (Nobler et al. 2001). Six months after the onset of stimulation, four of the initial six patients treated with Cg25 DBS exhibited a positive response to stimulation defined by the authors as a 50% or greater reduction the 17-item Hamilton Depression Rating Scale score ($HSDR_{17}$). Two of the four responders were classified in remission, defined as a $HSDR_{17}$ score <8. In a larger open-label trial, Lozano et al. (2008) extended these findings in 20 patients with severe treatment resistant depression. They report that, six months after surgery, 60% of patients were classified as responders to Cg25 DBS and 35% met criteria for remission. These results remained stable for up to one year. Of note is that stimulation amplitude in responders ranged from 3.5 to 5.0 volts, significantly less than that reported in studies of DBS at VC/VS.

Functional imaging of DBS response

Neuroimaging studies comparing pre- and postoperative cerebral blood flow demonstrate that DBS effectively alters the circuitry involved in depression. Three months following the onset of DBS in at Cg25, there was a marked decrease in cerebral blood flow in this region and in the orbital frontal cortex, two areas with known involvement in the pathophysiology and treatment response of depression (Rauch 2003). In addition, only the patients who responded to DBS exhibited decreased metabolic activity in the hypothalamus, anterior insula, and medial frontal cortex and increased activity in the dorsolateral prefrontal cortex, dorsal anterior and posterior cingulate cortices, and the pre-motor and parietal cortices. Chronic (3–26 months) stimulation in the VC/VS decreased activity in the subgenual anterior cingulate cortex (Cg25), the right and left dorsolateral prefrontal cortex, and the right anterior insula (Van Laere et al. 2006). Improvement in depression severity was inversely correlated with a decrease in activity in the left hippocampus and positively correlated with a decrease in activity in the right dorsolateral prefrontal cortex. Interestingly, activity in the ventral striatum, which was found to be hyperactive in these patients preoperatively and was a target of the stimulation, was not suppressed. In fact, a negative correlation was found between a lowered metabolic rate in the ventral striatum and an improvement in clinical scores. Thus, while DBS at the subgenual cingulate cortex may improve depression by inhibiting the target region, effective DBS at the VC/VS seems to work via a different mechanism, perhaps one of altered activation patterns or neural jamming. Complicating the matter further is the finding that acute bilateral stimulation of the VC/VS in OCD patients activates the right orbital frontal cortex primarily (Rauch et al. 2006). In summary, it appears that VC/VS stimulation directly activates the OFC and striatum, but over time, this activation may alter the circuitry so as to cause the OFC to become less active than at baseline, while striatal activity remains roughly unchanged.

Conclusion

Major Depressive Disorder is one of the most significant causes of disability worldwide. Medical therapy, predominantly with SSRI's, remains the first-line treatment of MDD; however, approximately one third of patients may respond inadequately to even multiple medications including augmentative therapies. Electroconvulsive therapy remains the most effective treatment for severe depression, but is reserved for severe patients who do not respond to medications. Moreover, ECT may be underutilized due to the social stigma attached to the therapy and concerns of cognitive decline after multiple treatments. Investigational therapies include vagus nerve stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, intravenous ketamine therapy, and deep brain stimulation.

Pivotal trials of DBS at the VC/VS and Cg25 are currently underway in the United States. The VC/VS target was discovered serendipitously when it was observed that the mood of OCD patients being treated with DBS at this target improved *before* their OCD symptoms did. In contrast, the decision to attempt DBS at Cg25 was based on multiple functional neuroimaging studies, which indicated that this brain region is intimately involved in the neurobiology of depression. Feasibility studies of DBS at both targets suggest that DBS may be efficacious in a significant proportion of treatment resistant patients, patients who are at significant risk of suicide and for whom there are few other options. Complications have thus far been acceptable. It is hoped that the reported response and remission rates for DBS at these targets are realized in the on-going double-blinded trials. If so, DBS will represent a major break-through in the treatment of MDD with the potential to relieve the suffering of countless patients worldwide.

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