Study Protocol

TITLE: **Long Term Follow-up of Deep Brain Stimulation for Treatment-Resistant Depression (LTF of DBS for TRD)**

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Schema

Recruitment: Patients enrolled in DBS for TRD will be informed of the option to enroll in the naturalistic follow-up study. Patients will be informed of the option during the screening phase of the DBS for TRD study as well as a reminder 2 weeks prior to completion of the study

Study Visits: Assessment by study psychiatrist once per year

1.0 INTRODUCTION

Major Depression is one of the most common and costly of all psychiatric disorders [1]. It ranks among the top causes of worldwide disease burden and is the leading source of disability in adults in North America under the age of 50 [2]. While depression can be effectively treated in the majority of patients by either medication or some form of evidence-based psychotherapy [3], up to 20% of patients fail to respond to standard interventions [4,5]. For these patients, trial-and-error combinations of multiple medications and electroconvulsive therapy are often required [6,7]. For patients who remain severely depressed despite these aggressive approaches, new strategies are needed.

Converging clinical, biochemical, neuroimaging, and post-mortem data suggest depression is unlikely to be a disease of a single brain region or neurotransmitter system. Rather, it is now generally viewed as a systems-level disorder affecting integrated pathways linking select cortical, subcortical and limbic sites and their related neurotransmitter and molecular mediators [8-12]. While mechanisms driving this 'system dysfunction' are not yet characterized, they are likely to be multi-factorial, with important and synergistic contributions from genetic vulnerability, developmental insults, and environmental stressors [13-15]. Treatments for depression can be similarly viewed within this limbic-cortical system framework, where different modes of treatment modulate specific regional targets, resulting in a variety of complementary, adaptive chemical and molecular changes that re-establish a normal mood state [12,16,17].

Functional neuroimaging studies have played a critical role in characterizing these limbic-cortical pathways [17-20]. Previous studies have demonstrated consistent involvement of the subgenual cingulate (Cg25) in both acute sadness and antidepressant treatment effects, suggesting a critical role for this region in modulating negative mood states [21,22]. In support of this hypothesis, a decrease in Cg25 activity is reported with clinical response to different antidepressant treatments including specific serotonin reuptake inhibitor (SSRI) antidepressant medications, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and ablative surgery [23-28]. In addition, Cg25 connections to the brainstem, hypothalamus, and insula have been implicated in the disturbances of circadian regulation associated with depression (sleep, appetite, libido, neuroendocrine changes) [29-33]. Reciprocal pathways linking Cg25 to orbitofrontal, medial prefrontal, and various parts of the anterior and posterior cingulate cortices form the neuroanatomical substrates by which primary autonomic and homeostatic processes influence various aspects of learning, memory, motivation and reward – core behaviors altered in depressed patients [31,34-36].

Recent advances in the surgical treatment of Parkinson's disease have demonstrated that chronic high frequency deep brain stimulation (DBS) in pathologically active brain circuits produces profound clinical benefits [37-39]. It has also been shown that clinically effective DBS in the basal ganglia produces both local and remote changes in neural activity as assessed by positron emission tomography (PET) [40,41].

A second sham-controlled pilot study at Emory University assessed the safety and efficacy of bilateral SCC DBS in 10 TRD patients with major depressive disorder (MDD) and 7 TRD patients with bipolar II disorder (BP). Dr. Holtzheimer was the lead psychiatrist on this study. Rates of response (≥50% decreased in depression severity from baseline) were 41% at 6 months, 36% at 1 year and 92% at 2 years following onset of chronic stimulation. Rates of remission (virtually no depressive symptoms) were 18% at 6 months, 36% at 1 year and 58% at 2 years following onset of chronic stimulation. There was a very modest but statistically significant decrease in depression severity following 4 weeks of sham stimulation, but this was largely accounted for by a decrease in depression severity following surgery but prior to the onset of sham stimulation. In three patients in whom blinded discontinuation was performed after 24 weeks of active stimulation, all had a full return of depressive symptoms within two weeks and antidepressant benefit returned with re-initiation of stimulation. There was only one patient who experienced a serious adverse event (infection requiring removal of the system) related to surgery. There were no adverse events associated with acute or chronic stimulation. In this study, a longer duration of a euthymic (no depression) period since illness onset, fewer adequate antidepressant treatments in the current episode, fewer lifetime psychotropic medications and fewer depressive episodes each predicted response/remission at various time points in the study. It was also demonstrated that functional connectivity of the BA25/SCC region (derived from pre-operative resting state functional magnetic resonance imaging [rfMRI] data) predicted 6 month treatment response. If validated, this would support using clinical variables related to illness stability (number of episodes, time between episodes and number of treatments) as well as pre-operative rfMRI to help with patient selection if SCC DBS is introduced clinically.

In both of these prior SCC DBS studies, all patients initially received bilateral stimulation; this decision was made based on previous imaging studies implicating both left and right BA25/SCC in TRD; however, both sides were rarely implicated in the same study. In the Toronto cohort, it was discovered that one patient had a greater antidepressant response with left-sided stimulation only. At Emory, one patient was eventually found to have a greater antidepressant response to right-sided stimulation alone compared to bilateral stimulation. A single case report from an Argentinean group also described antidepressant benefit from right-sided stimulation alone [18]. Further evidence supports differential roles for left- and right-sided brain regions in the pathophysiology of depression [19] but also suggests the nature of this laterality may differ across depressed patients. These data suggest that certain TRD patients may require right-sided stimulation, others may require left-sided stimulation and some may require stimulation bilaterally. If unilateral stimulation is comparable to bilateral stimulation, then this would allow the overall procedure to be safer since the major risk of implantation comes from the potential for an intracranial hemorrhage with each passage of a DBS lead. Additionally, this would speak to both the mechanism of action of DBS and potential neurobiological differences between TRD patients.

This pilot study supports the hypothesis that high-frequency DBS in Cg25 white matter can be used to treat depression, but further data is needed to confirm these findings. The long-term effects of DBS are not known. The following study will evaluate right versus left-sided DBS in Cg25 over the course of ten years. Patients who are enrolled in the DBS for TRD study at DHMC will be given the opportunity to enroll in the ten year follow-up study at the end of the study in which they are currently enrolled.

2.0 OBJECTIVES

We propose to test whether long-term high frequency DBS of the subgenual cingulate white matter (Cg25-DBS) is a safe and efficacious antidepressant treatment in five (5) TRD patients. We will address the following specific aims.

Specific Aim 1. To assess the long term effects including efficacy and safety of Cg25 DBS in patients with Major Depressive Disorder.

3.0 PATIENT SELECTION

Patients who are enrolled in the DBS for TRD study at DHMC will be given the opportunity to enroll in the ten year follow-up study at the end of the DBS for TRD study in which they are currently enrolled. Patients will be informed of the option during the screening phase of the DBS for TRD study as well as a reminder 2 weeks prior to completion of the study. A total of five (5) patients will be enrolled in this study.

3.1 Eligibility Criteria

- 3.1.1 Have received DBS for TRD
- 3.1.2 Ability to provide written informed consent
- 3.1.3 Willing to comply with all necessary study visits

4.0 CLINICAL ASSESSMENTS

During this phase, patients will be evaluated every 12 months by the study psychiatrist (via in-person, phone or video call visit) to assess device functioning, adverse events and current status of depression. This visit will be documented in a note to file. Specific areas to be assessed:

1. Current status of depression and overall functioning
2. Changes in medications
3. Adverse events
4. Status of DBS system including any changes or problems
5. If a patient chooses to have the DBS system explanted or turned off, they will be monitored weekly (by telephone, video call or in person as appropriate) for 12 weeks following explantation for adverse events. After that time, their participation in the study will be concluded.

5.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Data collected in this phase are purely descriptive and no formal analysis is planned.

6.0 DATA SAFETY AND MONITORING

6.1 Data and Safety Monitoring Board (DSMB). We will continue to use the Data Safety Monitoring Board (DSMB) for the Department of Psychiatry as a third-party oversight committee as we have done for the DBS for TRD study.

6.2 Frequency of meetings/review. The frequency of DSMB review for this protocol will follow recommendations from CPHS based on the assessed risk status of the study. Currently, it is expected that the DSMB will meet annually.

6.3 This protocol will be submitted to the DSMB simultaneously with this initial submission to CPHS. The DSMB will review the research protocol and plans for data and safety monitoring. The DSMB will review a report from the study's data manager that includes the following information: the number of participants who signed consent forms for the study and were subsequently randomized to study arms, the number of post-randomization dropouts, the reasons for withdrawal from the study, and any safety concerns, adverse events, an up-to-date consent form, and measures taken to protect confidentiality (e.g., data and tape storage, use of coded ID numbers, etc.). The DSMB will also review the Principal Investigator's summary of any new data or evidence that might alter the risk/benefit ratio for participating in the study (e.g., newly published studies, etc.). After reviewing this information, the DSMB will issue its own report summarizing any serious and unexpected adverse events or other unanticipated problems that involve risk to study participants, and whether these appear related to the study-based interventions or research assessment protocols.

6.4 There will be regular, ongoing communication between the PI, CPHS, and the DSMB. The PI will take responsibility for reporting any serious and unexpected adverse events or other unanticipated study problems to CPHS within 24 hours, according to standard regulations. A copy of each report will be sent to the DSMB. Actions taken by CPHS in response to adverse event reports will be immediately reported to the DSMB, which will review all serious adverse events as they arise. DSMB reports will be shared with CPHS.

6.5 A Serious Adverse Event (SAE) in this study will be defined as an event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity. The degree of probable relation between study procedures and the SAE will be carefully evaluated and documented.

6.6 Unexpected adverse events in this study will be defined as any adverse events for which the nature and severity are not consistent with expected adverse events resulting from the surgery, pre- or post-operative evaluation, or deep brain stimulation.

6.7 The DSMB will have the authority to stop the study at any point.

7.0 REFERENCES

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