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Deep brain stimulation of the subcallosal cingulate gyrus in the treatment of treatment resistant depression

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DEEP BRAIN STIMULATION OF THE SUBCALLOSAL CINGULATE GYRUS IN THE TREATMENT OF TREATMENT RESISTANT DEPRESSION

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ABSTRACT

Objective: a systematic review to determine the efficacy of deep brain stimulation (DBS) targeting the subcallosal cingulate gyrus (SCG) for the treatment of treatment resistant depression (TRD). **Methods:** PubMed database was utilized in a search for clinical randomized control trials that were completed after the year 2000, using the terms deep brain stimulation, treatment resistant depression, and subcallosal cingulate gyrus. **Results:** Three clinical trials were chosen based on specific inclusion criteria as noted in the PRISMA flow chart (Chart 1). The results of the three articles showed various discrepancies. Two of the three studies demonstrated some statistical significance in reduction of scores on the Hamilton Depression Rating Scale (HAM-D). However, in one study, the significance was seen only after long term therapy of over a year compared to 8 weeks of treatment ($df(4)$; $F = 10.691$; $P = 0.031$). The other study showed that treatment was effective after a 6-month study with significantly higher HAMD-17 scores during SHAM versus active stimulation ($\chi 21 = 5.0$, $p = 0.025$). On the other hand, the last study did not demonstrate any statistical significance after a 6 months double blinded controlled phase and 6 months open label trial ($p < 0.05$), with scores based on the Montgomery–Åsberg Depression Rating Scale (MADRS) rating scale. However, unlike results from the MADRS scale, utilization of the Global Assessment of Function score did demonstrate statistical significance after both phases of the trial. **Conclusion:** In summary this systematic review demonstrated that DBS of the SCG shows minimal weak evidence in overall effectiveness of treating treatment resistant depression. Although it is efficacious in some, current data fails to show consistent statistical significance throughout studies and therefore further research should be completed prior to utilizing DBS of the SCG as the main treatment for TRD. At this point in time and until further research is done, it is difficult to state whether or not we would recommend the use of DBS to treat TRD.

INTRODUCTION

Major depressive disorder (MDD) is a debilitating psychiatric disorder that affects the quality of life of individuals and can be characterized by feelings of sadness, emptiness, hopelessness, or diminished interest or pleasure in all activities.[1] It affects people of all ages, genders, and nationalities with a prevalence of 4.7% worldwide and 7% in the United States.[2,3] Treatment for MDD includes both psychotherapy and pharmacotherapy options including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and others.[4] While MDD affects each person differently and with varying intensities, a particularly difficult form of the disorder is treatment resistant depression (TRD). There is no agreed upon definition of TRD, but most research classifies it as MDD that is resistant to at least two different pharmacotherapy trials.[5,6] Numerous treatment modalities for TRD exist including pharmacotherapy, psychotherapy, and electroconvulsive therapy, yet none are 100% guaranteed to relieve patient symptoms and improve overall quality of life. This can leave many patients desperate for other means of relief.

A new and emerging treatment option for TRD is deep brain stimulation (DBS). Deep brain stimulation is an invasive procedure in which one or more electrodes are implanted into specific areas of the brain through utilization of a stereotactic frame and magnetic resonance imaging. A pulse generator with connection to the electrodes is implanted subcutaneously and serves to control stimulation parameters.[7] The subcallosal cingulate gyrus (SCG) is one of the main

surgical targets for DBS in the treatment of TRD. It plays a considerable role in the network that involves cortical structures, the limbic system, thalamus, hypothalamus, and brainstem nuclei, and has shown abnormal increased metabolic activity in patients diagnosed with depression.[8] Conservative treatment interventions including antidepressants, electroconvulsive therapy, and repetitive transcranial magnetic stimulation result in decreased metabolic activity in the SCG, thus proving this location to be a promising target for DBS. It has been predicted that high frequency stimulation of the SCG via DBS could potentially reverse the pathological increased metabolic activity evident in depression.[8] Although DBS has been well known to treat Parkinson's disease, its efficacy in treating psychiatric disorders such as depression is continuing to evolve. This raises the clinical question, in patients with treatment resistant depression (TRD), can deep brain stimulation (DBS) of the subcallosal cingulate gyrus provide symptom resolution as a reasonable alternative treatment to continued pharmacological therapy?

CASE STUDY

R.I. is a 29-year-old male who has been struggling with depression for many years. Despite being prescribed numerous antidepressant medications his depression continues to worsen. Starting at the age of 15, he began experiencing severely depressed moods, debilitating fatigue, difficulty sleeping, and problems concentrating in school to the point his grades started to decline. To this day he still struggles with everyday life, and notes a very low self-esteem. He explains that he has no appetite, feels anxious all the time, and has isolated himself from friends and family. He also states that he occasionally feels a strong urge to harm himself. In addition to the medication use, R.I. has undergone multiple counseling sessions of cognitive behavioral therapy without any improvement in symptoms. There appears to be no resolution to resolving R.I.'s severe mental illness. However, his provider is curious as to whether or not DBS is a safe and effective last resort treatment for R.I.'s apparent treatment resistant depression.

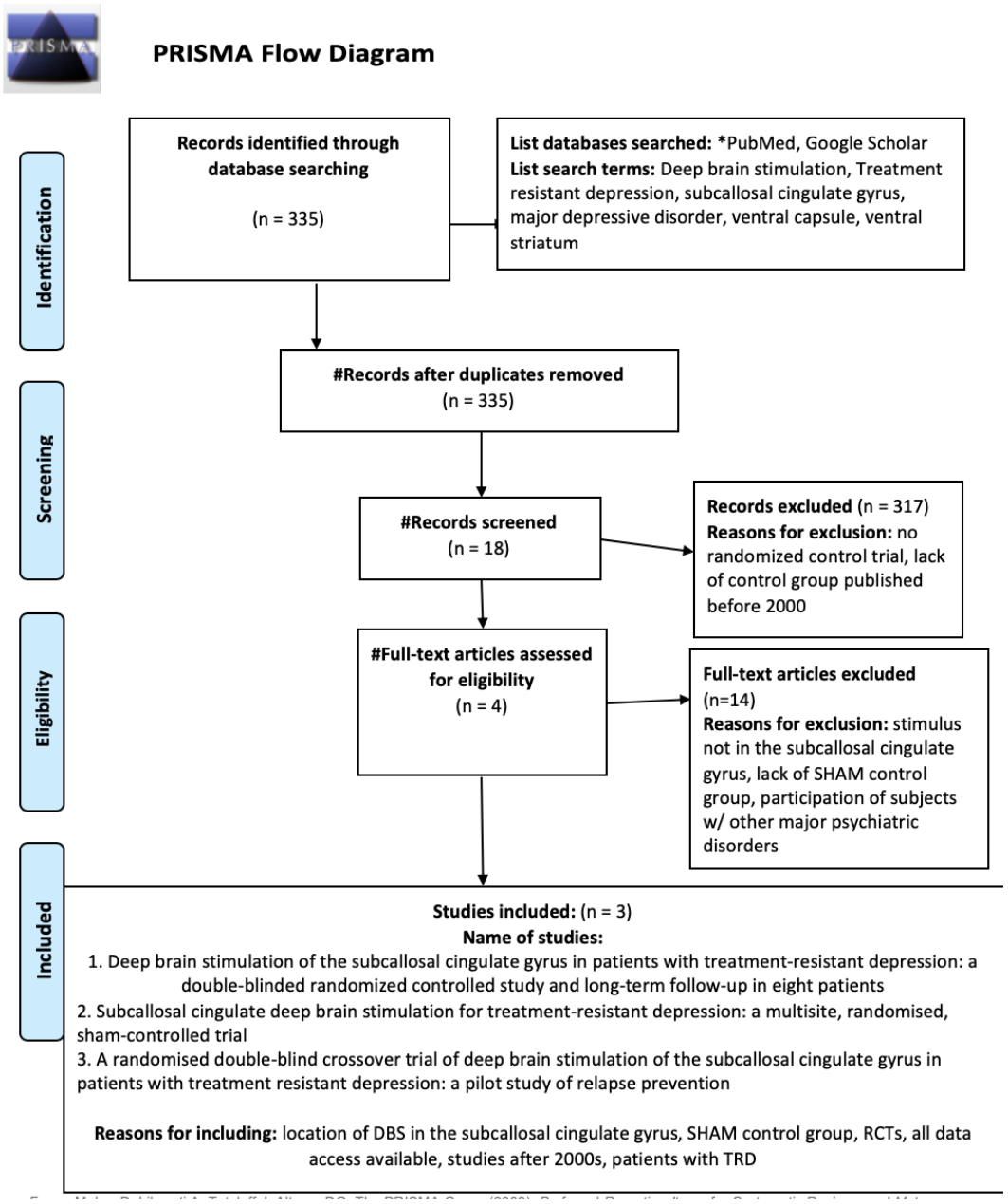
PICO

Population: Male and female adults with treatment resistant depression
Intervention: Deep brain stimulation targeting the subcallosal cingulate gyrus
Control: SHAM controlled DBS
Outcome: Reduction in symptoms or symptom severity of depression

CLINICAL QUESTION

In patients with treatment resistant depression (TRD), can deep brain stimulation (DBS) of the subcallosal cingulate gyrus (SCG) provide symptom resolution as a reasonable alternative treatment to continued pharmacological therapy?

Chart 1. PRISMA FLOW DIAGRAM



METHODS

A preliminary search on the PubMed database was completed using the key terms deep brain stimulation (DBS), treatment resistant depression (TRD), subcallosal cingulate gyrus (SCG), major depressive disorder (MDD), ventral capsule, and ventral striatum. Of the 335 articles identified, 317 were excluded as they did not meet criteria such as they were not randomized control trials, they lacked the appropriate control group, or they were published earlier than 2000. Of the remaining 18 studies, 15 were further excluded due to a stimulus other than the SCG, lack of SHAM control, or participants with major psychiatric disorders other than MDD. Three studies were ultimately selected meeting all criteria of study limitations consistent with randomized controlled trials, studies published after 2000, stimulation solely in the subcallosal cingulate gyrus, and participants without any other comorbid psychiatric conditions. These three studies included (1) *Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a double-blinded randomized controlled study and long-term follow-up in eight patients, (2) Subcallosal cingulate deep*

brain stimulation for treatment-resistant depression: a multisite, randomized, sham-controlled trial, and (3) A randomized double-blind crossover trial of deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment resistant depression: a pilot study of relapse prevention.[9,10,11,12] Summary of the article screening and selection process is shown in the PRISMA Flow Diagram noted as Chart 1.

RESULTS

STUDY 1: Merkl A, Aust S, Schneider G-H, et al. Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: A double-blinded randomized controlled study and long-term follow-up in eight patients. *Journal of Affective Disorders*. 2018;227:521-529. doi:10.1016/j.jad.2017.11.024

Objective

To compare the efficacy of delayed onset (SHAM control) DBS versus non-delayed DBS to improve patient scores on the Hamilton Depression Rating Scale (HAMD-24) (Appendix 1).

Study Design

This was a randomized control trial including 8 patients recruited from the Departments of Psychiatry of the University Hospital Cologne and Charié hospital Berlin between October 2007 and March 2015. Study inclusion criteria is noted in Table 1. In this study, treatment-resistant depression was defined as "failure of at least 2 different classes of second-generation antidepressants, 1 trial of tricyclic antidepressant, 1 trial of a tricyclic antidepressant with lithium augmentation, 1 trial of monoamine oxidase inhibitor, and 6 or more sessions of unilateral ECT." After written consent was obtained, all 8 participants received quadripolar electrodes implanted in the SCG bilaterally with target planning performed with MRI or MRI/CT fused images. After correct electrode placement was confirmed, the pulse width was set to 90 μs and the frequency to 130 hz. The 8 patients were randomized equally into either the immediate stimulation-onset group, who had stimulation switched on after a mean of 7 days (SD = +/1 2.09, range 4-9), or the delayed-onset group, with stimulation switched on after 4 weeks. All 8 patients completed the double-blind trial period, 6 were followed for 28 months, and 2 were followed for 4 years. Out of the 8, 2 requested early removal of the electrodes after 11 and 20 months due to no response and inconvenient symptoms including sensation of tingling at the neck and sensation of a foreign body due to the external cable implanted subcutaneously on the patient's neck.

Patients completed the Hamilton Depression Rating Scale-24 (HAMD-24) (appendix 1) before DBS electrode implantation to obtain baseline measurements. At the end of the study, response to DBS was defined as a 50% reduction in the patient's HAMD-24 score, whereas partial response was a 25% reduction in score. Full remission was defined as a HAMD-24 score of less than 24. Secondary measurements were also obtained with the Beck's Depression Inventory (BDI) and the Montgomery-Asberg Depression Rating Scale (MADRS) (appendices 2, 3). These measurements were taken weekly until 3 months after the electrodes were implanted, and then at periodic follow up timepoints. The clinical data was analyzed using non-parametric methods and per-protocol analysis. Specifically, the Wilcoxon test (2-tailed) and mixed effects ANOVA were used to calculate mean scores and standard deviations for the HAMD-24, BDI, and MADRS over chosen time points. These time points were baseline at inclusion, upon completion of the 4 weeks, 8 weeks and 3, 6, 12 and 24 months. First, mean scores were calculated regardless of randomization. Next, a mixed effects ANOVA was performed with one main factor, time, and one factor group, randomization, to further analyze the results. The significance level was set at $p < 0.05$. Furthermore, at the end of the study 5 of the participants completed a patient satisfaction questionnaire designed by the researchers.

Table 1. Patient Inclusion Criteria for Study 1

- Primary diagnosis of treatment-resistant major depressive disorder
- Illness duration > 2 years
- Score of 20 or higher on the 12-item Hamilton Depression Rating Scale
- Treatment resistance as indicated with antidepressant Treatment History Form score for adequacy of 3 or above
- No significant psychiatric comorbidity

Study Results

In regards to the primary outcome, this study showed no statistically significant differences in patient HAMD-24 scores at the end of the 8-week randomized phase. However, after 6 months, 3 of the participants showed response (50% reduction) in HAMD-24 scores with one patient reaching full remission. At 12 months, while there were apparent reductions in the raw HAMD-24 scores compared to baseline for all participants still receiving treatment, these decreases were not statistically significant in the two-sample t-test ($T(6) = 1.789$; $P = 0.124$). However, at 24 months, the mean decrease in HAMD-24 scores was statistically significant compared to baseline ($T(5) = -2.735$; P - 0.41).

As stated earlier, there was no statistically significant difference between SHAM or immediate stimulation patient symptom HAMD-24 scores at the 4 week follow up. However, a statistically significant difference in BDI scores were shown between the 2 groups at the 4 week mark, ($F(6) = 47.44$; $P = 0.006$). These trends stayed consistent at the 8 week follow up for HAMD-24 and BDI scores. Overall, for the participants still receiving treatment at 24 months (6), statistically significant reductions in HAMD-24 scores were seen for each individual participant (df(4); $F = 10.691$; $P = 0.031$). However, there was no statistical difference between the SHAM and active group scores at the 24 month follow up.

Results were mixed for the secondary outcomes measured (BDI and MADRS) as well. A reduction in patient BDI scores was observed at 6, 12, and 14-months when compared to baseline scores. Additionally, for the 6 participants still receiving treatment at 24 months, their average BDI score reduction was statistically significant ($T(5) = 2.994$; $P = 0.048$). Of these, 2 patients reached full BDI remission with a score < 10 at 24 months. In contrast, there were no statistically significant reductions in patient MADRS scores at any of the follow up visits.

For qualitative data collection, at the end of the study, 5 of the 8 participants returned the patient questionnaire. All 5 endorsed the use of DBS for treatment in other patients, 3 patients responded with ambivalent attitudes toward the side effects of DBS, and 2 responded with strong negative attitudes regarding the efficacy of the treatment.

Participant Safety

While there were no major adverse effects reported by the patients, 2 requested early removal of the device due to lack of efficacy and bothersome sensations. Additionally, all patients reported headaches, scalp tingling, dizziness, and sore throat due to anesthesia after the implantation surgery. This is comparable to other documented DBS-electrode surgeries. Additionally, each participant experienced a hypomanic episode from days 2-4 after the initial surgery, which resolved without any further treatment.

Study Critique

The strengths of this study include that it was a blinded, randomized control trial implementing both active and SHAM controlled DBS periods. Neither the patient nor the rating clinician was aware if the stimulation was active or SHAM during the 8-week blinded-phase. Additionally, for participants to be included they must have tried a variety of antidepressant medications from nearly all classes of available medications, thus showing they truly were treatment resistant. The primary outcome was the HAMD-24 depression scale, which is widely used in clinical trials, thus making these study results easily compared to others. Finally, 6 patients were able to be followed for 28 months with 2 allowing follow up for 4 years, which allowed some long-term data to be collected. However, this study does have several weaknesses. First, the study only included 8 participants, which is a small sample size. Of the 8 participants, 2 requested the device be removed early, which is a 25% drop out rate. Additionally, there was no crossover period, so an individual participant's responses to both active and SHAM stimulation could not be determined for every participant. Furthermore, the participants were allowed to receive changes to their pharmacotherapy during the study, making it difficult to establish if the results seen were due to the DBS or medication changes.

STUDY 2: Holtzheimer PE, Husain MM, Lisanby SH, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression; a multisite, randomised, sham-controlled trial. *The Lancet Psychiatry.* 2017;4(11):839-849. doi:10.1016/S2215-0366(17)30371-1

Objective

To determine the safety and efficacy of DBS of the subcallosal cingulate white matter in the treatment of chronic unremitting treatment resistant depression

Study Design

In a multicenter prospective, randomized, double blinded, SHAM-controlled trial, participants with TRD were implanted with a DBS system that targeted bilateral subcallosal cingulate white matter and then randomized to 6 months of active or SHAM DBS, followed by 6 months of open label subcallosal cingulate DBS (12-month study). This study took place between April 10th, 2008 and November 21st, 2012. A total of 90 participants were selected with the inclusion and exclusion criteria listed in table 2A and 2B, respectively. 60 participants were assigned to active stimulation and the remaining 30 participants were assigned to SHAM stimulation. Randomization was computer generated with a block size of three at each site. The outcome was measured based on frequency of response which was defined as a 40% or greater reduction in depression severity from baseline, and averaged over 4-6 months of the double-blind phase. At the end of the 12-month study, a subset of patients was followed up for up to 24 months.

After a series of baseline visits, a neurological battery was administered to assess attention, working memory and other executive functions. A high-resolution MRI scan was completed for presurgical evaluation. The DBS consisted of two leads, extension wires, and an implantable pulse generator. Each of the two leads consisted of a four-electrode array with 3 mm electrode at the tip and three 1.5 mm electrodes separated by 1.5 mm. Two experts were noted to select an optimal target region. Implantation took place 2-4 weeks post baseline evaluation. Impedance of the system was tested intraoperatively but no stimulation was delivered during surgery. Post op CT was ordered to assess for ICH and lead localization. Two weeks after device implantation, participants were randomly assigned active stimulation (stim group) or 6 month delayed stimulation (SHAM group) in a 2:1 ratio. Those in the stimulation group received monopolar stimulation at 130 Hz, 91 microsecond pulse width, 4 mA. Those in the control received a programming session but no stimulation.

Participants were randomized to three at each site prior to start of study, with a DBS programmer informed of the allocation and the rest of the team members masked.

Participants were evaluated at weeks 4, 6, and 8 and then monthly until the 6-month endpoint utilizing a series of evaluations (MADRS; Systematic Assessment for Treatment Emergent Effects (SAFTEE); DBS programming form; Inventory of Depressive Symptomatology – Clinician Rated (IDS-C30); Quick Inventory of Depressive Symptomatology – Self Rated (QIDS-SR); Work and Social Adjustment Scale (WSAS); Global Assessment of Functioning (GAF); Clinical Global Impression (CGI); Patient Rated Global Impression (PGI); Hamilton Anxiety Rating Scale (HAM-A); and Columbia-Suicide Severity Rating Scale (C-SSRS). At the 3-month and 6-month visits, the following additional evaluations were completed: HRSD-17; YMRS; QOL; and HLQ. See appendix 3 for an example of the primary scale, MADRS. The neuropsychological battery was repeated at the 6-month visit. During this initial phase of the trial, participants were permitted to continue current stable psychotherapy and medication regimen and were allowed to have minor changes in sedative, hypnotic, and anxiolytic medications. However, further medication changes were not allowed. After the 6-month double blind phase, participants were then involved in a 6-month open label phase in which all participants including the SHAM control group received stimulation. The same evaluations as above were made and the neuropsychological battery test was performed again at the 12-month visit.

Table 2A. Patient Inclusion Criteria for Study 2

- Men and women aged 21-70 years old
- Unipolar, non-psychotic major depressive disorder that was diagnosed before age 45 with a current episode at least 12 months in duration
- Lack of antidepressant response to a min of four adequate antidepressant treatments including three different medications from three different classes, evidence-based psychotherapy, or electroconvulsive therapy
- Lack of sustained response to a course of psychotherapy
- Montgomery-Asberg Depression Rating Scale (MADRS) was utilized and participants that were included scored > 22 at three separate baseline visits (with absence of notable improvement (< 20% lessening of MADRS score) between visits
- Global Assessment of Function score < 50 and MMSE < 24
- Medication free or current AD or psychotropic medication regimen stable for 4 weeks prior to start, along with written informed consent

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Table 2B. Patient Exclusion Criteria for Study 2

- Bipolar or Psychotic disorder
- Obsessive Compulsive Disorder
- Post-traumatic stress disorder
- Panic disorder
- Bulimia or anorexia nervosa
- Generalized anxiety disorder as primary diagnosis during depressive episode
- Substance use disorder (including caffeine or nicotine) within the past 12 months
- Borderline or antisocial personality disorder
- Substance risk of suicide
- ECT within 3 months prior to enrollment
- Likely to require ECT during study
- CNS disease impairing motor, sensory or cognitive function or requiring intermittent or chronic medication
- Fibromyalgia, chronic fatigue syndrome, or condition requiring narcotics
- Unstable or uncontrolled medical illness
- Past ablative or other intracranial surgery
- CI to MRI scanning
- CI to general anesthesia or DBS surgery
- Pregnant, intending to get pregnant, or breastfeeding
- Involvement in another investigational device, drug, or surgical trial
- Unable to comply with study schedule

Study Results

The criteria for determining response was defined as a 40% or greater reduction in MADRS and no worsening in GAF (Global Assessment of Function) score from baseline to the average scores at months 4, 5, and 6 (appendices 3, 4). Secondary measures of efficacy included changes from baseline to endpoint for HRSD-17, IDS-C30, QIDS-SR, WSAS, PGI, CGI, QOL, and HAM-A. During the 6 month open label trial response was defined as 40% or greater reduction in MADRS from baseline to average score to the score at follow up including 12 months, 18 months, and 24 months, and finally remission was defined as a MADRS score < 10 (appendix 3). The clinical data was analyzed using per-protocol analysis.

An estimated sample size of 201 participants contributed to a hypothesis of response in 40% of active stimulation and 20.7% of SHAM participants. The p-value was set at < 0.05. Patients in both groups showed a statistically significant improvement in depression and global functioning over 6 and 12 months. However, at the endpoint for the 6 month blinded controlled phase there was no statistically significant difference between the groups with only 20% (12/60) of patients showing response in the stimulation group compared to 17% (5/30) in the control group. The same lack of statistical significance was also noted in terms of remission with 5% (3/60) in the stimulation group, and 7% (2/30) in the control group. In the SHAM group, the open label trial of 6 months of stimulation did not result in additional antidepressant efficacy. Furthermore, by the 12 month visit, although numerically responses (in terms of number of participants with improved scores), increased in both groups with 30% or 18/60 in the stimulation group, and 27% or 8/30 in the SHAM control group, this level of response was not considered statistically significant. The same was concluded for remission with a stable or slight increase to 18% or 11/60 in the stimulation group and 7% or 2/30 in the SHAM control group. In summary, although both stimulation and SHAM control groups showed some improvement, 6 months of active DBS in comparison to SHAM stimulation did not demonstrate statistical significance in the primary efficacy of DBS resulting in antidepressant effects based on the MADRS scoring system. However, on average both groups

demonstrated statistically significant difference improvement from baseline in depressive symptoms and global functioning over 6 and 12 months. Based on these results, the number needed to treat was calculated to be 8.57.

Participant Safety

Throughout the duration of the clinical trial, a total of 10 participants exited the study. 6 participants left the study due to adverse events consisting of one worsening depression, one suicide attempt, one increased suicidal ideation with failed rescue, two deaths by suicide, and one due to head pain. 3 participants withdrew from the study due to patient preference, one due to the sponsor closing the study, and 4 participants made the decision to have the device fully explanted. In total 28 patients experienced 40 serious adverse effects with 8 of these adverse effects (experienced in 7 patients) considered related to the study device or DBS surgical procedure. Adverse events included suicidal ideation or behavior, unanticipated medical treatment for psychiatric reasons, device related events, and hospital admission due to worsening depression. The number needed to harm was calculated to be 3.75. A more detailed list of serious and non-serious adverse events is listed below in Table 2C.

Table 2C. Serious and Non-Serious Adverse Events

Serious Adverse Events	Non-serious Adverse Events
• Increase in depressive symptoms • Infection • Anxiety • Suicidal ideation • Suicide or suicide attempt • Seizure or convulsion • Headache • Postoperative discomfort • Hearing and visual disturbance • General erosion or local skin erosion over the pulse generator • Hospital admission • Elective admission to hospital • Death (unknown cause)	• Headache • Postoperative discomfort or pain • Persistent pain or redness at the implantable pulse generator site or the surgery site or extension • Anxiety • Pulling sensation along extension site • Hearing and visual disturbance • Increase in depressive symptoms • Nausea or vomiting • Sleep disturbance • Paresthesia • Infection • Disequilibrium • Skin disorder • Neuralgia

Study Critique

The strengths of this study include that it was a randomized control trial and double blinded, with a single unblinded DBS programmer who was informed of treatment allocation and the remaining team members and participants masked. This helped to limit potential underlying bias as well as limiting the power of suggestion in the study. Furthermore, strict inclusion and exclusion criteria as noted in Table 2A and 2B, also limited the potential compounding factors that may have influenced study outcomes. The study also had a fairly large sample size of 90 participants. Additional strengths include the fact that the participants were followed throughout a reasonable period of 24 months, the study was completed in the United States at the St Jude Medical Center in Plano, TX, and there were no significant differences between the stimulation and SHAM control groups in terms of demographics or clinical factors. One final major strength was the fact that two different scoring systems were used, both of which revealed conflicting statistical significance. This demonstrates the major discrepancies that exist when utilizing two different scoring systems to

determine statistical significance of the outcomes of DBS therapy. On the other hand, one weakness of the study included that there was a relatively moderate dropout rate, although author did account for the reason behind why participants dropped out (as noted above under Participant Safety). Another weakness of the study was the unequal allocation of participants in the stimulation vs control group. As a result of the participants being stratified into a 2:1 ratio of 60:30, results may have been skewed with an increased chance of seeing a greater number of significant results in the stimulation group as opposed to the SHAM control group. Furthermore, another setback in the study was due to the permittance of medication and psychotherapy changes in the 6 month open label phase (as opposed to allowing only minimal changes in medication regimens in the initial phase of the trial). In such circumstances, improvements in depressive symptoms may be inaccurately attributed to the DBS during this phase of the study, when in reality symptomatic relief may be due to altering medication and psychotherapy regimens.

STUDY 3: Puigdemont D, Portella MH, Perez-Egea R, et al. A randomized double-blind crossover trial of deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a pilot study of relapse prevention. *Journal of Psychiatry & Neuroscience.* 2015;40(4):224-231. doi:10.1503/jpn.130295

Puigdemont D, Perez-Egea R, Portella MJ, et al. Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. *International Journal of Neuropsychopharmacology.* 2012;15(01):121-133. doi:10.1017/S1461145711001088

Objective

To confirm the efficacy of DBS of the SCG in treatment-resistant depression and to determine the effect of withdrawing stimulation on patient relapse.

Study Design

This was a randomized, double blind, crossover study including 5 patients recruited between February 2008 and December 2009 at the Department of Psychiatry of the Hospital de la Santa Creu i Sant Pau in Barcelona, Spain. Inclusion criteria can be found in Table 3. In this study, 8 participants were considered who had treatment-resistant depression and had already received DBS of the SCG. 5 were selected for this study after showing stable clinical improvement in their HAMD-17 scores (appendix 5). The 5 patients recruited were then randomized into 1 of 2 groups. Group 1 (Off-On), consisting of 2 participants, received SHAM stimulation for 3 months, followed by active stimulation for 3 months. Group 2 (On-Off), consisting of 3 participants, received active stimulation for 3 months followed by SHAM stimulation for 3 months. This process was blinded (by sealing the information in an envelope) to everyone except the investigator who manipulated the stimulation. During active stimulation the stimulation was set as follows: Frequency 130-135 Hz, amplitude 3.5-5V and pulse width 120-240 ms. During the SHAM stimulation, patients were monitored by frequent HAMD-17 evaluation (appendix 5). For the 2 occasions the scores were higher than 14 during SHAM stimulation, the patient was withdrawn from the study and the stimulation was turned on.

Patient response was measured through monthly evaluation with the HAMD-17 (appendix 5). The 3 measurements during the SHAM period were averaged together and the 3 from open stimulation were averaged together to consolidate each patient response into 2 overall HAMD-17 scores (appendix 5). Remission was defined as a HAMD-17 score less than 8 and relapse as a HAMD-17 score greater than 14. Statistical analysis was completed with intention to treat analysis and the Friedman nonparametric, repeated-measures analysis of variance (ANOVA) to compare the active

vs SHAM stimulation. Additionally, areas under the curve for the SHAM and active stimulation were calculated with the trapezoid method. Significance was set at $p < 0.05$.

Table 3. Patient Inclusion Criteria for Study 3

- Men and Women age 18-70
- Diagnosed with a major depressive episode according to the DSM-IV-TR criteria
- Resistant to pharmacological treatment
- At least a stage IV of the Thase-Rush scale
- Lack of efficacy to ECT or partial efficacy to ECT treatment
- Admission score on 17-item HAMD $\geq$ 18
- Not pregnant
- No contraindications to undergoing DBS surgery
- No acute, serious, or unstable comorbid neurological or medical illness
- No current or past non-affective psychotic disorder
- No severe personality disorder that could impact tolerance or compliance during the study
- No current substance abuse or dependence (except nicotine)

Study Results

Of the 8 considered patients, 5 completed the trial. The other 3 were excluded because they did not originally achieve full remission. Additionally, 1 participant withdrew before the 6 weeks were completed due to experienced relapse. At the end of the study, statistical analysis showed the treatment was effective with significantly higher HAMD-17 scores during SHAM compared to active stimulation ($\chi 21 = 5.0$, $p = 0.025$). Moreover, the AUC results showed overall HAMD-17 scores for patients in the On-Off group be 13.9 during active stimulation and 20.8 during SHAM stimulation. For the Off-On group, the AUC was 16.3 during SHAM and 5.0 during active stimulation. During the active stimulation 4 out of the 5 patients maintained remission scores and none completely relapsed. However, while they maintained remission, there was a moderate worsening in scores observed during the initial period for the patients in the ON-OFF arm. The researchers attributed this to potential anxiety about being in the trial or a possible “nocebo” effect where patients had negative expectations of receiving SHAM stimulation initially. However, in contrast to this, during the SHAM stimulation only 2 patients maintained remission while 2 experienced relapse and 1 showed progressively worsening scores while never fully hitting relapse. For the 2 patients who did not relapse when in their OFF period, the researchers attributed this to a maintenance effect of DBS in which some patients experience long lasting effects of the DBS after stimulation has been removed. However, this is simply a theory and was not further studied by the researchers. The number needed to treat for this study was calculated to be 2.

Participant Safety

There were no major adverse effects reported throughout this study. Immediately after the implantation surgery, 2 patients reported cephalalgia and 3 reported neck pain at the site of the subdermal cable. These are consistent with expected mild adverse effects from the DBS surgery. However, as previously stated, 1 participant did experience severe relapse during the OFF phase and had to be withdrawn from the study for their own safety.

Study Critique

Similar to the other 2 studies analyzed, this was a double-blind, randomized control study. The assignments were placed in a sealed envelope, allowing only the researcher in charge of manipulating the stimulation to know the patient assignments. Furthermore, this study included a SHAM-controlled crossover period which allowed each participant results to be compared to both other participants and within themselves during their own crossover periods. An additional strength of this particular study is that all participants included had previously achieved remission with DBS. This study then looked at the effect of stopping active stimulation on relapse and repeat remission rates for the participants. Again, a version of the HAMD rating system was used, which helps this study gain comparability to other DBS trials. Another strength of this study is that all other antidepressant medication was stopped during the trial and restarted after completion. This eliminated the confounding variable of medication interfering with the DBS results. Contrarily, a major weakness of this study was the very small sample size. While 8 patients originally received DBS, only 5 achieved full remission and were enrolled in this crossover trial. Furthermore, 1 of the 3 participants assigned to the ON-OFF arm dropped out during the off phase due to serious remission, making the sample size 4 at the end of the study. Additionally, since all participants in the study had previously achieved remission, there is a possibility that positive results were due to selection bias.

DISCUSSION

This review focused on the clinical significance and safety of deep brain stimulation targeting the subcallosal cingulate gyrus as a sustainable treatment option to reduce depressive symptoms for patients with treatment resistant depression. Overall, the current studies demonstrate conflicting results over the efficacy of DBS of the SCG in reducing depressive symptoms from treatment resistant depression. Table 4 summarizes the 3 studies with their main results.

Table 4: Summary and Results of Research Studies

	Study 1 **Merkl, et al.[9]**	**Study 2** **Holtzheimer, et al.[10]**	**Study 3** **Puidgemont, et al.[11,12]**
Objective	To compare the efficacy of delayed onset DBS versus non-delayed DBS to improve patient depression scores.	To determine the safety and efficacy of DBS in the treatment of chronic, unremitting treatment resistant depression	To confirm the efficacy of DBS in treatment-resistant depression and to determine the effect of withdrawing stimulation of patient relapse
Study Type and stimulation protocols/ overview	**Randomized control trial**; immediate stimulation vs delayed stimulation. All participants had active DBS after 4 weeks.	**Prospective, randomised, double blind, sham-controlled trial.** Sham vs active stimulation lasted 6 months. At 6 months, all participants received active stimulation	**Randomized, double blind crossover study** looking at relapse rates in patients who had already achieved remission with DBS. ON-OFF vs OFF-ON
Sample Size	8	90	5
DBS location	SCG	Subcallosal cingulate white matter	SCG
Depression Scale	Primary: HAMD-24 Secondary: BDI, MADRS	Primary: MADRS, GAF Secondary: SAFTEE, DBS programming form, IDS-C30, QIDS-SR, WSAS, CGI, PGI, HAM-A, C-SSRS	Primary: HAMD-17
Follow Up	6 participants were followed for 28 months and 2 were followed for 4	All participants were followed for a total of 12 months	6 months

	years		
Results/ Conclusion	HAMD-24 -4 weeks: **No significance** found between delayed and immediate stimulation groups -8 weeks: no significance seen -12 mo: **no significant** decrease in scores -24 mo: **significant** score reduction seen for all participants. **No significance** comparing dealayed vs active group. BDI -4 weeks: **significant** decrease between 2 groups -6, 12, 14 mo: **significant** reduction in individual patient scores MADRS -**No significance** seen at any follow up visit (*p<0.05)*	MADRS -6 mo: **no significance** seen between groups -12 mo: moderate reduction in scores seen in both groups, but overall **not significant** GAF -6 and 12 mo: **statistically significant** improvement in depression and global functioning	HAMD-17 -3, 6 mo: **significant** difference in scores was observed at the end of both 3 and 6 months comparing the ON groups to the OFF groups.
NNT	N/A	8.57	2
NNH	N/A	3.75	N/A

The 3 studies analyzed in this review were similar in several aspects, but contain key differences that make it difficult to compare their efficacy. While all 3 were randomized control trials, they each had a unique study design. They study by Merkle et al. involved DBS treatment naive patients and enrolled them in a 4-week blinded SHAM vs active stimulation trial, followed by all participants receiving 4 years of active DBS.[9] The Holtzheimer et al. study also involved DBS treatment naive patients but observed a 6 month SHAM vs active stimulation period.[10] After this, all participants received a minimum of 6 months of active stimulation. The Puigdemont et al. study differed by looking at participants who had already achieved remission with DBS, thus introducing a considerable amount of selection bias into their results.[11,12] This study also specified the "experiment treatment" was turning the DBS off, to see if patients relapsed, whereas studies by Merkle et al. and Holtzheimer et al. considered the "experimental treatment" turning the DBS on for the treatment naive participants.[9-12] Another considerable difference between the 3 was the depression scale used to score patient symptoms. While Merkel et al. and Puigdemont et al. used a version of the HAMD as their primary outcome, Holtzheimer et al. used the MADRS (see appendices 1, 2, and 3).[9-12] Each of these scales uses a different number of symptoms to assess depression severity, and that must be considered when looking at the raw data. Thus, the use of different scoring systems may serve as an imperative reason as to why some studies showed statistical significance whereas others did not.

Other aspects of the 3 studies to note are the technical features of the DBS electrodes and the settings for the pulse width and frequency. One common factor between the 3 is that all electrode placements were confirmed with either CT or MRI, ensuring correct placement in the SCG.[9-12] However, Merkle et al. set the pulse width to 90 μs and the frequency to 130 hz.[9] Holtzheimer et al. was very similar with a pulse width of 91 μs and frequency of 130 hz.[10] However, the study by Puigdemont et al. differs drastically with a pulse width of 120-240 ms (depending on the participant) and a frequency of 130-135 hz.[11-12] While the articles do not discuss the reasoning certain pulse widths were chosen, it is interesting to note the study showing the most statistically significant findings used the highest pulse width. Furthermore, another key difference of the three studies is whether the participants took other antidepressant medications during the study periods. In studies by Merkle et al. and Holtzheimer et al., participants were not only taking antidepressant medications, but their

physicians were allowed to change their medication regimen throughout the study.[9,10] This makes it difficult to assess if the differences in depression scores observed were from the DBS alone, medication alone, or a combination of the two. However, Puigdemont stopped all medication before the study began and resumed them when the study was over.[11,12]

A major weakness of studies by Merkle et al. and Puigdemont et al. is the small sample size.[9,11,12] While this is a rare experimental treatment and it is difficult to obtain participants, these small sample sizes bring question to the validity of the findings. In contrast, the study by Holtzheimer et al. had a larger sample size of 90.[10] It is important to note that studies by Merkle et al. and Puigdemont et al. showed some statistically significant findings whereas the study by Holtzheimer et al., with the largest sample size, showed zero statistically significant findings based on the MADRS scaling system.[9-12] A strength of the study by Merkle et al. is the long follow up time.[9] While this study did not show statistical significance in the short term follow up, all participants achieved a statistically significant reduction in their own HAMD-24 at 24 months.[9] This could indicate that DBS is efficacious over several years, rather than several months. A strength of the study by Puigdemont et al. is that the findings showed that withdrawing DBS from patients previously in remission caused relapse, indicating that the DBS itself truly does have an effect on patients' depressive symptoms.[11,12] Additionally, this study used intention to treat analysis whereas the other 2 used per protocol analysis.[9,10,11,12] However, another weakness of this study is that it used the HAMD-17 as the sole depression rating scale. The researchers acknowledge that HAMD scores may not be able to accurately measure other clinically important endpoints such as increased emotional expression, sociability, or the increase of daily activities.[11,12] Studies by Merkle et al. and Holtzheimer et al. are superior to the study by Puigdemont et al. in the aspect of using multiple depression rating scales to obtain a more holistic measure of patient symptoms.[9-12]

While DBS is a new and experimental treatment for TRD, it has been used for over 20 years in the treatment of Parkinson's related tremors.[13] Therefore, the major and minor adverse events of the surgery have been widely studied. For example, up to 25% of patients may experience hardware related adverse effects such as lead fractures or lead migrations.[14,15] The most severe adverse effect, intracranial hemorrhage, is seen in about 3.9%.[16] However, some of the most common adverse effects from DBS include mild paresthesia, dysarthria, and manic/hypomanic episodes.[16,17] An overall strength of the studies listed in this systematic review is the lack of major adverse events and the presence of well-known minor adverse events, showing these studies are comparable to previous literature in regards to patient safety.

Overall, the major limitations of this systematic review include the different depression scales used and their contribution to the lack of consistent statistical results, the limited sample sizes in 2 studies, the use of concurrent medications and CBT during 2 studies, differing treatment and follow up times between all 3 studies, and the different stimulation parameters. While the 3 studies are an effective start to review DBS as a treatment option for TRD, it is difficult to determine the clinical efficacy based on this systematic review.

CONCLUSION

Among patients with treatment resistant depression (TRD), can deep brain stimulation (DBS) of the subcallosal cingulate gyrus provide symptom resolution as a reasonable alternative treatment to continued pharmacological therapy?

Not many treatment options currently exist for patients with unrelenting major depressive symptoms, many of which have been refractory to antidepressant medication use or recurrent cycles of cognitive behavioral therapy. Although some studies have shown moderate benefit of DBS in the subcallosal cingulate gyrus, based on this systematic review, further studies are necessary to determine the overall efficacy and long-term benefits of DBS as treatment for TRD. In

terms of current clinical application, at this point in time and until further studies are done, it is difficult to state whether or not we can definitively recommend or reject DBS as a potential last resort treatment for TRD. However, we can most certainly state that it is important to weigh the risks and the benefits of DBS and individualize treatment therapy.

Despite this being an invasive procedure with some risk associations, DBS may provide significant relief for patients such as R.I., who are greatly restricted in their everyday lives by this debilitating mental illness, in addition to those experiencing unremitting suicidal ideations. Such treatment would be further justified by the limited side effects involved in DBS including mild paresthesia of the neck, dysarthria, as well as potential manic and hypomanic episodes. Therefore, in cases such as R.I., deep brain stimulation of the subcallosal cingulate gyrus may prove to be beneficial in terms of alleviating depressive episodes and providing patients with an overall increased quality of life. In conclusion, although some evidence exists that deep brain stimulation may be an effective option for treating TRD, it is important to consider such therapy with caution, based on the individual patient, the severity of symptoms, and ultimately the patient's quality of life. Therefore, it is presumed that DBS may serve as a probable option in patients in whom antidepressant medications and cognitive behavioral therapy have been ineffective for treating major depressive symptoms.

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APPENDICES

Appendix 1.

Hamilton Depression Rating Scale- 24 (HAMD-24): http://www.medafile.com/cln/HDRS.html

Appendix 2.

Beck's Depression Inventory: https://www.ismanet.org/doctoryourspirit/pdfs/Beck-Depression-Inventory-BDI.pdf

Appendix 3.

Montgomery–Åsberg Depression Rating Scale (MADRS): https://www.mdcalc.com/montgomery-asberg-depression-rating-scale-madrs

Appendix 4.

Global Assessment of Functioning Scale: https://www.albany.edu/counseling_center/docs/GAF.pdf

Appendix 5.

Hamilton Depression Rating Scale-17 (HAMD-17): https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-DEPRESSION.pdf