Deep brain stimulation for treatment of obsessive-compulsive disorder

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a disabling and potentially chronic mental disorder, affecting approximately 2 to 3 percent of the population, and characterized by anxiety-provoking intrusive thoughts and repetitive behaviors.

Effective treatments for OCD include cognitive-behavioral therapy and serotonin reuptake inhibitors. Even when optimal treatment is provided, however, approximately 10 percent of patients remain severely affected with treatment-refractory OCD [1]. Deep brain stimulation (DBS), a treatment in which implanted electrodes send electrical pulses to specific locations in the brain, may be useful for a small proportion of patients with severe, incapacitating OCD that is refractory to other treatments.

DBS for OCD is discussed here. The epidemiology, clinical manifestations, diagnosis, and treatment of OCD with pharmacotherapy and psychotherapy are discussed separately. OCD in pregnant and postpartum women are also discussed separately.

- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)
- (See "Obsessive-compulsive disorder in adults: Psychotherapy".)
- (See "Management of obsessive-compulsive disorder in adults".)
- (See "Obsessive-compulsive disorder in pregnant and postpartum patients".)

OVERVIEW

Deep brain stimulation (DBS) is a neurosurgical treatment involving the implantation of electrodes that send electrical impulses to specific locations in the brain (figure 1) [2]. Widely used in the treatment of advanced movement disorders, DBS has been investigated for treatment-resistant obsessive-compulsive disorder since the first case reported in 1999 [3]. DBS provides an adjustable and reversible means of neuromodulation. (See "Device-assisted and lesioning procedures for Parkinson disease", section on 'Deep brain stimulation'.)

ANATOMY

The location of deep brain stimulation (DBS) is selected according to the type of symptoms of obsessive-compulsive disorder (OCD) to be addressed. Based on published trials and case studies, it is estimated that a total of approximately 250 patients with OCD have received experimental DBS using the following brain targets [2,4,5]:

- Anterior limb of the internal capsule
- Ventral striatum/ventral capsule
- Nucleus accumbens
- Subthalamic nucleus
- Inferior thalamic peduncle
- Global pallidus interna
- Bed nucleus of stria terminalis
- Medial forebrain bundle

The comparative efficacy of stimulating these different areas is not known. (See 'Efficacy' below.)

MECHANISM

Circuits connecting orbitofrontal cortex (OFC), medial prefrontal cortex, basal ganglia and thalamus are believed to be central to the pathophysiology and treatment response of obsessive-compulsive disorder (OCD) [6].

The mechanism of deep brain stimulation (DBS) is unknown. A widely accepted hypothesis is that OCD is associated with hyperactivity of the cortico-striatal-pallidal-thalamic-cortical network [7]. It is plausible that DBS inhibits or functionally overrides this pathological network hyperactivity [8]. It is most likely that the therapeutic effects of DBS are caused by a

combination of direct and indirect effects dependent on the specific cytoarchitecture of the stimulated brain area. Because the field intensity of the electrode decreases exponentially with distance, neurons are influenced in various ways. Although studies demonstrating the inhibitory characteristics of DBS are sparse, research combining imaging and DBS suggests that hyperactivity in the OFC correlates with the severity of OCD, and that OFC activity normalizes following DBS [9,10]. Studies have suggested that DBS targeted at the nucleus accumbens (NAc) induced striatal dopamine release [11], normalized NAc activity, reduced excessive connectivity between the NAc and prefrontal cortex, and decreased frontal low-frequency oscillations during symptom provocation in OCD patients [12].

Studies using diffusion tensor imaging suggest individual white matter bundle trajectories are associated with DBS response in OCD. Subsequently, tractography-assisted planning has been proposed as a promising technique for individualizing DBS treatment and further improving efficacy [13,14].

INDICATIONS

An investigational/experimental treatment for obsessive-compulsive disorder (OCD), deep brain stimulation (DBS) is typically used in patients who meet each of the following criteria:

- The presence of primary OCD. While some major co-occurring psychiatric disorders are exclusion criteria, OCD patients treated with DBS may have co-occurring depressive symptoms and/or suicidal ideations.

- OCD should be severe and incapacitating, with a severity score on the Yale-Brown Obsessive Compulsive Scale of at least 28 [15,16].

- OCD should be treatment refractory. Treatment refractoriness is generally defined by multiple, unsuccessful trials of an anti-obsessive-compulsive medication (ie, a selective serotonin reuptake inhibitor [SSRI], clomipramine, or venlafaxine) at adequate dosing and duration, as well as a poor response to an adequate trial of behavioral therapy. (See "Management of obsessive-compulsive disorder in adults" and "Obsessive-compulsive disorder in adults: Psychotherapy".)

  Criteria often used for treatment-refractory OCD in DBS trials include nonresponse to each of the following:

  - Two trials with an SSRI at the maximum dose for three to six months.

    One trial with clomipramine at the maximum dose for three to six months.

- Six months of behavioral therapy that includes exposure under the supervision of a clinical psychologist trained in behavioral techniques.
- At least one trial of an atypical antipsychotic medication used for three months in conjunction with an SSRI or clomipramine.

As an investigational, experimental treatment for OCD, use of DBS should be preceded by fully informed consent, and supported by an interdisciplinary team (including neurosurgery, psychiatry, and neurology) with expertise in diagnosing and treating OCD and able to provide close patient monitoring over time. Pending further evaluation related to patient selection, procedure methods, and treatment outcomes, DBS is not recommended for OCD outside of the research setting.

CONTRAINDICATIONS

- Patients under 18 years of age – Data from long-term study suggest that obsessive-compulsive disorder symptoms often improve over the life of an affected individual [17].
- Intelligence quotient (IQ) under 80 – Patients with an IQ under 80 should be assessed for their capacity to provide informed consent for the procedure.
- Clinically significant and/or unstable neurologic or medical illnesses such as significant brain atrophy, increased bleeding tendency, reduced infection defense, relevant cerebrovascular disease (eg, cerebrovascular accident) or other surgical contraindications.
- Pregnancy.
- Devices generating electrical artifacts, such as cardiac pacemakers and defibrillators.
- Antisocial personality disorder.
- Alcohol or substance abuse during prior six months.
- Acute psychosis (benign hallucinations and/or hallucinations in the past are not exclusion criterion).

IMPLANTATION

The deep brain stimulation (DBS) system consists of three components: an implanted pulse generator (IPG), the lead (with four electrodes at the tip), and the extension cables (figure 1).

The electrical impulses are generated by the IPG, which includes a battery, and is surgically implanted in the chest. The introduction of rechargeable IPGs increased device longevity from 3 years up to approximately 10 to 15 years. An extension cable runs from the IPG, under the skin of the neck and scalp, through a burr hole in the skull, and connects to an electrode surgically implanted in the brain. The precise anatomic position of implantation is calculated beforehand on the basis of magnetic resonance and computed tomography scans. The lead is placed in the brain using a stereotactic head frame attached to the patient's skull under local anesthetic.

In bilateral DBS (most widely performed/studied in obsessive-compulsive disorder), a single pulse generator is placed in the chest with two extension cable outputs.

ADMINISTRATION

The implanted pulse generator used for deep brain stimulation (DBS) contains a microchip, allowing the neurostimulation to be modified. The activity of the electrode can be programmed externally with a portable appliance communicating with the pulse generator through telemetry. These adjustments are usually made by a senior psychiatrist with expertise of the phenomenology of obsessive-compulsive disorder (OCD).

Adjustments can be made to the frequency, intensity, pulse width, and location of neurostimulation. Location is adjusted by activating different electrodes on the lead. Each electrode (usually four) can be stimulated separately. Research suggests that modification of these factors can lead to greater efficacy and fewer side effects in some cases, compared with the results obtained initially [18].

This adjustment phase takes on average 3 to 6 months but may last up to 12 months. When adjustment appears to result in a clinical relevant response, the stimulation is maintained continuously. Parameters are typically adjusted on the basis of an individual patient’s response and reported side effects such as impulsivity, sleeping problems, or tension. Twelve adjustments are needed, on average, with a two-week interval between them before stable settings are arrived at. Among patients who do not appear to respond after adequate adjustment, modification continues until the best outcome is achieved. In very rare cases, in the event of absolute nonresponse and occurrence of side effects, the device is switched off and may eventually be removed.

Typical stimulation parameters for DBS in OCD can vary within the following ranges:

- Frequency between 100 to 185 Hertz (high frequency stimulation)
- Current power between 2 and 10 volts

- Pulse widths between 60 and 150 milliseconds

EFFICACY

Obsessive-compulsive disorder symptoms — Small, randomized trials suggest that deep brain stimulation (DBS) may reduce symptoms of obsessive-compulsive disorder (OCD), but larger trials are needed to confirm these preliminary findings [2,18-21].

In a meta-analysis that included eight randomized trials of 85 subjects with refractory OCD, DBS was found to have a greater response rate (defined as >35 percent reduction in the Yale-Brown Obsessive Compulsive Scale [Y-BOCS]) than sham treatment (51 versus 18 percent; relative risk 2.4, 95% CI 1.3-4.3) [22]. The mean difference between sham and active stimulation was 7.8 points on the Y-BOCS. Among these randomized trials, as well as 38 observational studies, there was an average decrease of 15 points from baseline on the Y-BOCS and an average response rate of 58 percent by the end of follow-up. No differences were found between limbic and nonlimbic targets and no consistent predictors of response were found. Adverse effects were mild and transient. (See 'Adverse effects' below.)

In the largest clinical cohort study to date, 70 subjects with OCD received DBS directed at the ventral part of the anterior limb of the internal capsule (vALIC) [23]. At 12-month follow-up, 52 percent had responded to treatment (>35 percent decrease in Y-BOCS) while 17 percent had a partial response (>25 percent decrease in Y-BOCS).

The effects of DBS in the treatment of OCD appear to be long-lasting. In a longitudinal study, 50 patients with treatment-refractory OCD were treated with DBS targeting the vALIC showed improvement of symptoms over 3 to 13 years. [24]. At last follow-up, 50 percent of the patients responded (defined as >35 percent reduction in Y-BOCS) with an average reduction in the Y-BOCS of 39 percent. Forty percent of patients either stopped or lowered medications, although this included nonresponders as well as responders.

Quality of life — DBS for OCD has been linked to improved quality of life [24]. A longitudinal study of 16 patients with treatment-refractory OCD found DBS to be associated with improved quality of life (as measured with the World Health Organization Quality of Life Scale – Brief Version) after eight months of stimulation, compared with pretreatment [25]. The improvement was sustained on follow-up after three to five years of active stimulation. Gains were seen in the general score as well as in physical, psychological, and environmental domains.

Concurrent antidepressant effects — DBS has been associated with reduction of depressive symptoms in patients with OCD and comorbid depression, a common comorbidity. Studies have

reported improvement in mood after stimulation of the nucleus accumbens, anterior limb of the internal capsule, and ventral striatum/ventral capsule [18,20,24]. Antidepressive effects seem to be related to DBS of the ventral striatum in particular; no mood improvement was observed following stimulation of the subthalamic nucleus [19]. (See 'Anatomy' above and "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis", section on 'Epidemiology'.)

Preliminary studies have been conducted on DBS for treatment-resistant depression without co-occurring OCD [26,27]. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Safety'.)

ADVERSE EFFECTS

Deep brain stimulation (DBS) is associated with different types of adverse events [2]:

- Complications related to surgical implantation of the device
- Device or hardware-related problems
- Undesired effects caused by stimulation or cessation of stimulation

Surgical complications — As an invasive procedure, DBS implantation can be associated with surgical complications. However, serious adverse effects have been infrequent in obsessive-compulsive disorder (OCD) and in DBS treatment of movement disorders, which have been more extensively studied and involve devices and implantation procedures similar to those for OCD. A review of 360 patients who underwent DBS implementation for movement disorders experienced a mortality rate of 0.6 percent and a rate of adverse effects with permanent neurological sequelae of 2.8 percent [28]. Surgical complications that did not lead to permanent effects included infection, hemorrhage, confusion, and seizures. (See "Device-assisted and lesioning procedures for Parkinson disease", section on 'Complications and adverse effects'.)

Hardware complications — Hardware problems after DBS implantation, including device malfunction, lead migration, and infection, are not uncommon, with aggregate reported rates of approximately 11 to 17 percent [28]. (See "Device-assisted and lesioning procedures for Parkinson disease", section on 'Complications and adverse effects'.)

Stimulation-related complications — Stimulation-related complications vary widely by type and may be specific to the area of the brain that is stimulated. Optimizing the parameter settings of the neurostimulator can reduce stimulation adverse effects; they are usually reversible by cessation of stimulation [2]. (See 'Anatomy' above.)

Severe depression and anxiety — Acute cessation of DBS in OCD may result in severe rebound effects of depression and anxiety, and relapse effects of obsessions and compulsions [20]. These can be reversed by reactivation of the stimulation.

Risk of suicide — Studies have reported the emergence or worsening of suicidal ideation and behavior associated with DBS in patients who received the treatment for Parkinson disease [29] and for major depressive disorder [30]. One patient who reportedly committed suicide had received DBS for OCD [22]. (See "Device-assisted and lesioning procedures for Parkinson disease", section on 'Complications and adverse effects' and "Unipolar depression in adults: Treatment with surgical approaches", section on 'Safety'.)

In our clinical experience, OCD patients presenting for DBS often report suicidality **prior** to DBS treatment, typically associated with co-occurring depression, which is common in these patients. Such suicidal ideation frequently appears to diminish in response to DBS in our experience, in conjunction with improvement in other depressive symptoms. (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis", section on 'Comorbidities'.)

Hypomania — Transient hypomania is the most commonly seen side effect of DBS for OCD [20]. Hypomania seems to occur frequently (in 50 to 67 percent of cases) in association with stimulation in the ventral striatum/ventral capsule-nucleus accumbens region, but has also been seen with DBS administered to other brain areas, including the globus pallidus, subthalamic nucleus (4 to 8 percent of cases), and the anterior limb of the internal capsule-nucleus accumbens regions [20].

Cognitive dysfunction — Studies of patients with OCD who received neuropsychiatric testing have reported varied findings:

- DBS targeting the ventral internal capsule/ventral striatum
  - Transient, diminished concentration and verbal perseveration in 26 patients with an average duration of treatment of 31.4 months [20].
  - No cognitive decline in 10 patients with an average duration of treatment of 8.91 months [31].
- DBS targeting the nucleus accumbens
  - Sixteen patients with treatment-refractory OCD treated with DBS at the nucleus accumbens were compared with a control group of 14 patients with treatment-refractory OCD treated with care as usual. Three weeks postoperatively, DBS showed a

significantly reduced performance on measures on verbal fluency and visual organization as well as trend towards reduced performance on measures of visual memory and abstract reasoning. After eight months of active stimulation, reduced performances persisted, except for a significant improvement in verbal fluency. Subsequently, the observed minor reduced cognitive performances were possibly associated with the surgical intervention [32].

CONCURRENT TREATMENT

Patients with obsessive-compulsive disorder (OCD) often continue to take antidepressant and antipsychotic medications while receiving deep brain stimulation (DBS).

There are no trials that have specifically studied the efficacy of medication or psychotherapy in combination with DBS treatment for OCD. In one small trial, however, investigators noted that cognitive-behavioral therapy (CBT) administered concurrently with DBS appeared to be particularly effective in decreasing compulsive behavior and avoidance, and that gains appeared to be lost after stimulation was discontinued.

In the absence of data to guide practice, remaining depressive, OCD or anxiety symptoms during DBS could reasonably be treated with a serotonergic antidepressant, benzodiazepine, or CBT.

ALTERNATIVE INTERVENTIONS

Alternative, experimental interventions for severe, treatment-refractory OCD include ablative neurosurgical techniques and transcranial magnetic stimulation [6,33].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Obsessive-compulsive disorder and related disorders".)

SUMMARY AND RECOMMENDATIONS

- Deep brain stimulation (DBS) is a neurosurgical treatment involving the implantation of electrodes that send electrical impulses to specific locations in the brain (figure 1). An

effective treatment for selected patients with advanced Parkinson disease, DBS is an investigational treatment for incapacitating, treatment-refractory obsessive-compulsive disorder (OCD). (See 'Overview' above and "Device-assisted and lesioning procedures for Parkinson disease".)

- Although the mechanism of DBS is unknown, a widely accepted hypothesis is that OCD is associated with hyperactivity of the cortico-striatal-pallidal-thalamic-cortical network. It is plausible that DBS inhibits or functionally overrides this pathological network hyperactivity. (See 'Mechanism' above.)

- The frequency, intensity, pulse width, and location of the neurostimulation can be adjusted over the course of treatment; this may increase effectiveness and reduce side effects of DBS treatment. (See 'Administration' above.)

- The efficacy of DBS for OCD has not been established, but preliminary trials, either uncontrolled or inadequately controlled, have shown promising results. Of 63 patients with treatment-refractory OCD who have received DBS, 34 experienced a reduction of symptoms of 35 percent or more. (See 'Efficacy' above.)

- DBS implantation is an invasive procedure that can cause infection, hemorrhage, confusion, or seizures. Severe adverse effects are uncommon; the mortality rate has been estimated at 0.6 percent. Hardware malfunctions, which can generally be corrected, are more common. Stimulation-related complications are usually reversible by adjusting the stimulation. Large randomized trials are needed to determine the treatment's efficacy and safety. (See 'Adverse effects' above.)

- DBS is an experimental procedure that has been used to treat incapacitating and treatment-refractory OCD. Given the invasive nature of DBS and the relative lack of efficacy data, we suggest that patients with OCD only be treated with DBS in the context of a clinical trial (**Grade 2C**). (See 'Efficacy' above and 'Adverse effects' above.)

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