Deep brain stimulation for refractory obsessive-compulsive disorder: A review and analysis of the FDA MAUDE database

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INTRODUCTION

While most patients diagnosed with obsessive-compulsive disorder (OCD) find therapeutic relief of their symptoms with medication, therapy, or a combination of both, some patients have a form of the disease that is highly resistant to conventional treatment methods called refractory OCD. For this unique subset of patients, an uncommon treatment option is deep brain stimulation (DBS). In 2009, DBS was granted a humanitarian device exemption (HDE)-approval by the Food and Drug Administration after promising preliminary data. Monitoring of long-term safety data through post market surveillance of adverse events has not yet been conducted for DBS in OCD patients. This study aims to address this critical knowledge gap.

ABSTRACT

Background: Deep brain stimulation (DBS) is used as a treatment option for patients diagnosed with a form of obsessive-compulsive disorder (OCD) that is highly resistant to conventional treatment methods. In 2009, DBS was granted a humanitarian device exemption-approval by the Food and Drug Administration after promising preliminary data. Monitoring of long-term safety data through post market surveillance of adverse events has not yet been conducted for DBS in OCD patients. This study aims to address this critical knowledge gap.

Methods: All patient- and device-related (PR; DR) reports from January 1, 2012, to December 31, 2021, were downloaded and compiled from the manufacturer and user facility device experience (MAUDE) database pertaining to DBS for OCD using the product class name “Deep Brain Stimulator For OCD.” Data in this study were examined using descriptive statistics to evaluate for frequency of reporting.

Results: The most frequently reported PR adverse event categories included psychiatric (40%), neurological (19%), other (14%), decreased therapeutic response (10%), and infections (10%). The most frequent DR reports were high impedance (14%), energy output problem (7%), battery problem (7%), malposition of device (7%), and improper/incorrect procedure or method (7%).

Conclusion: The PR and DR adverse events in our study align with the previous findings of adverse events. They also further solidify that DBS for refractory OCD may be a viable option for the right patient population. However, further studies are essential given the limitations of the MAUDE database.

Keywords: Deep brain stimulation, Food and drug administration manufacturer and user facility device experience database, Neuropsychiatry, Obsessive-compulsive disorder
Porwal, et al.: DBS for refractory OCD

Administration (FDA) after promising preliminary data. Since its approval, there have been concerns that the HDE might allow for bypassing of oblige safeguards put in place to ensure the wellbeing of patients. One paper argues that the FDA needs to revisit the HDE-approval granted to DBS so that the device can be tested through the rigors of the FDA’s normal approval process by doing so, patients and providers can be confident that the device is safe to use therapeutically. Monitoring long-term safety data through post market surveillance of adverse events are critical; however, these studies have not yet been conducted for DBS in OCD patients. This study aims to address this critical knowledge gap by characterizing reported adverse events and device problems in refractory OCD patients implanted with DBS systems utilizing real world surveillance data from the FDA manufacturer and user facility device experience (MAUDE) database.

MATERIALS AND METHODS

MAUDE database

This study analyzed post market surveillance data within the FDA MAUDE database. This is a publicly available database maintained by the FDA for tracking adverse events associated with medical devices. Reporting to the database is required by manufacturers, importers, and device user facilities. Reporting is voluntary by health-care professionals, patients, and consumers. Since this database is publicly accessible and consists of de-identified data, no ethics approval was required.

Data mining and classification

All patient- and device-related (PR;DR) reports from January 1, 2012, to December 31, 2021, were downloaded and compiled from the MAUDE database pertaining to DBS for OCD using the product class name “Deep Brain Stimulator For OCD,” revealing a total of 60 reports. Of these, reports were separated into PR and DR reported and those without sufficient information were excluded from the study. This process is represented in Figure 1. PR adverse events were further categorized into categories generated by the authors. Frequencies of each PR and DR report were calculated, along with author generated categories.

Statistical analysis

Data in this study were examined using descriptive statistics to evaluate for frequency of reporting. The FDA suggests MAUDE data cannot be used for inferential statistics or to derive trends due to the nature of spontaneous reporting.

RESULTS

During the study period, a total of 60 medical device reports were extracted. After removing 16 reports with insufficient information and no adverse events or device problems, 44 PR and 37 DR events were recorded. Twenty-two reports had both PR;DR adverse events. Table 1 represents PR adverse events. The most frequently reported PR adverse event categories are represented in Figure 2. These included psychiatric (40%), neurological (19%), other (14%), decreased therapeutic response (10%), and infections (10%). Table 2 represents DR reports with >0.1% reporting frequency. The most frequent DR reports were high impedance (14%), energy output problem (7%), battery problem (7%), malposition of device (7%), and improper/incorrect procedure or method (7%).

DISCUSSION

DBS and OCD

DBS involves placing electrical leads on specific regions on the brain and delivering a high-frequency current to disrupt and reduce the output from that region without resulting in permanent tissue destruction. The history of utilizing DBS began with a successful study in 1998 showing that bilateral stimulation of the subthalamic nucleus in patients with Parkinson’s Disease significantly improved motor dysfunction. With such optimistic results as encouragement, a group of researchers in 1999 decided to apply chronic electrical stimulation to four patients with
severe, refractory OCD; they found that three out of the four patients experienced alleviation of their symptoms. This pioneer study, along with the fact that DBS has comparable efficacy to ablative neurosurgery without the associated permanency, eventually led to the FDA granting DBS a HDE-approval in 2009 for refractory OCD. This special exemption streamlined the approval process without requiring extensive clinical trials of the appropriate size and statistical power. Since the HDE approval, there have been concerns that DBS use for the treatment of refractory OCD was not thoroughly vetted to ensure patient safety. For example, DBS systems are not required to provide the same level of patient follow-

### Table 1: Patient reported adverse events.

| Patient adverse event                          | Count | Percent |
|-----------------------------------------------|-------|---------|
| Psychiatric                                   | 44    | 39.64   |
| Cognitive changes                             | 17    | 15.32   |
| Anxiety                                       | 8     | 7.21    |
| Depression                                    | 7     | 6.31    |
| Emotional changes                             | 7     | 6.31    |
| Irritability                                  | 4     | 3.6     |
| Unspecified mental, emotional, or behavioral problem | 1   | 0.9     |
| Dizziness                                     | 1     | 0.9     |
| Neck pain                                     | 1     | 0.9     |
| Neurological                                  | 21    | 18.92   |
| Electric shock                                | 4     | 3.6     |
| Sleep dysfunction                             | 3     | 2.7     |
| Intracranial hemorrhage                       | 2     | 1.8     |
| Muscular tics                                 | 2     | 1.8     |
| Undesired nerve stimulation                   | 2     | 1.8     |
| Confusion/disorientation                      | 1     | 0.9     |
| Loss of consciousness                         | 1     | 0.9     |
| Neurological deficit/dysfunction              | 1     | 0.9     |
| Dyskinesia                                    | 1     | 0.9     |
| Brain Injury                                  | 1     | 0.9     |
| Seizures                                      | 1     | 0.9     |
| Memory loss/impairment                        | 1     | 0.9     |
| Ambulation difficulties                        | 1     | 0.9     |
| Other                                         | 16    | 14.41   |
| Complaint, ill-defined                        | 5     | 4.5     |
| Inflammation                                  | 1     | 0.9     |
| Fall                                          | 1     | 0.9     |
| Urinary retention                             | 1     | 0.9     |
| Adhesion                                      | 1     | 0.9     |
| Hypoglycemia                                  | 1     | 0.9     |
| Dehydration                                   | 1     | 0.9     |
| Edema                                         | 1     | 0.9     |
| Abscess                                       | 1     | 0.9     |
| Joint dislocation                             | 1     | 0.9     |
| Bone fracture                                 | 1     | 0.9     |
| Tissue breakdown                              | 1     | 0.9     |
| Therapeutic response, decreased               | 11    | 9.91    |
| Infections                                    | 11    | 9.91    |
| Unspecified Infection                         | 8     | 7.21    |
| Postoperative wound infection                  | 2     | 1.8     |
| Bacterial infection                            | 1     | 0.9     |
| Somatic symptoms                              | 7     | 6.31    |
| Pain                                          | 2     | 1.8     |
| Headache                                      | 2     | 1.8     |
| Fatigue                                       | 1     | 0.9     |
| Dizziness                                     | 1     | 0.9     |

### Table 2: Device related reports with a frequency >0.1%.

| Device related problem                         | Count | Percent |
|-----------------------------------------------|-------|---------|
| High impedance                                | 11    | 14.47   |
| Energy output problem                         | 5     | 6.58    |
| Battery problem                               | 5     | 6.58    |
| Malposition of device                         | 5     | 6.58    |
| Improper or incorrect procedure or method     | 5     | 6.58    |
| Break                                         | 4     | 5.26    |
| Premature discharge of battery                | 3     | 3.95    |
| Inappropriate/inadequate shock/stimulation    | 3     | 3.95    |
| Migration or expulsion of device              | 3     | 3.95    |
| Device operates differently than expected     | 3     | 3.95    |
| Patient device interaction problem            | 2     | 2.63    |
| Charging problem                              | 2     | 2.63    |
| Low impedance                                 | 2     | 2.63    |
| Shipping damage or problem                    | 2     | 2.63    |
| Vibration                                     | 2     | 2.63    |
| Electromagnetic compatibility problem         | 2     | 2.63    |
| Pocket stimulation                            | 2     | 2.63    |
| Patient-device incompatibility                | 1     | 1.32    |
| Signal-artifact noise                         | 1     | 1.32    |
| Disconnection                                 | 1     | 1.32    |
| Unintended collision                          | 1     | 1.32    |
| Off-label use                                 | 1     | 1.32    |
| Failure to interrogate                        | 1     | 1.32    |
| Delayed charge time                           | 1     | 1.32    |
| Communication or transmission problem         | 1     | 1.32    |
| Display or visual feedback problem            | 1     | 1.32    |
| Data Problem                                  | 1     | 1.32    |
| Power problem                                 | 1     | 1.32    |
| Peeled/delaminated                            | 1     | 1.32    |
| Impedance problem                             | 1     | 1.32    |
| Positioning problem                           | 1     | 1.32    |
| Low battery                                   | 1     | 1.32    |

Figure 2: Categories of reported patient adverse events.
up and strict, protocolized data collection as other devices that are approved through the normal approval process. In addition, one investigative team found that insurance denial by both government-subsidized and private insurance programs led to a decrease in the proportion of patients implanted with DBS once the HDE came into effect.\textsuperscript{[6]} Therefore, the FDA’s reasoning behind HDE for DBS usage in OCD patients has been shown to be undermined by lack of insurance coverage due to its very approval. We believe that post-market surveillance of adverse events and device problems is essential to ensuring the safety of patients using DBS in refractory OCD and providing insurance companies with data-driven evidence to incentivize coverage.

In this study, we demonstrated that patients implanted with DBS for the treatment of OCD experienced a myriad of adverse events associated with both device implantation and stimulation. This finding was not abnormal or unexpected. According to current literature, there are several risks associated with DBS usage in general, many being mild and reversible.\textsuperscript{[14]} Due to the surgery itself, patients may experience a stroke or brain hemorrhage, infections, headaches, seizures, and cardiovascular problems. However, these rare complications of DBS are likely more predominant in older patients treated for Parkinson’s Disease rather than the younger population for OCD. While being actively stimulated by DBS, patients may experience tingling in their face or limbs, confusion, difficulty concentrating, seizures, worsening mental or emotional state, or lack of therapeutic benefit. In terms of adverse events associated with DBS in OCD patients specifically, one study looked at 40 articles published to date on the use of DBS for OCD and found both surgical and stimulation-induced side effects.\textsuperscript{[19]} Intracranial hemorrhage was the most serious adverse event associated with surgical implantation of DBS, with frequency rates low in most studies but as high as 4.8% and 7.7% in others. Seizures were also commonly seen. However, these rates are not specific to DBS for OCS. The most common adverse event due to direct DBS stimulation was hypomania; other adverse events included sleep disturbances, increased anxiety, weight gain, and cognitive problems.\textsuperscript{[19]} Another study that looked at nine patients implanted with DBS for OCD found intracerebral hemorrhage and superficial infection as adverse results of the implantation surgery.\textsuperscript{[13]} During active stimulation, patients experienced acute changes in their emotional state, both positive and negative, as well as motor effects, such as a unilateral smile contralateral to the side of stimulation and tightness in their jaw muscles. These adverse effects either resolved spontaneously or were easily reversed by discontinuing or changing the parameters of the stimulation. This particular study did not find any patients becoming suicidal or experiencing changes in cognition due to DBS.\textsuperscript{[8]} However, Medtronic states that patients receiving Medtronic DBS therapy have reported depression and suicidality.\textsuperscript{[8]}

Overall, our results align with the previous findings of adverse events associated with DBS in OCD patients. In our review, the most common category of adverse events reported by patients was psychiatric in nature, with 15% of patients experiencing cognitive changes, 7% experiencing anxiety, and 6% reporting depression and emotional changes. Decreased therapeutic response and infections were also seen in almost 10% of patients. Neurological adverse events, such as electric shock, sleep disturbances, and intracranial hemorrhage, were seen in a small percentage of patients. Uniquely, our study also looked at adverse device reports and found that high impedance was the most common complaint, followed by energy output, and battery problems. This supports that fatal malfunction of these devices are uncommonly reported. The PR and DR adverse events in our study further solidify that DBS for refractory OCD may be a viable option for the right patient population. However, further studies are essential given the limitations of the MAUDE database.

**OCD epidemiology and pathophysiology**

The national institute of mental health defines OCD as an illness, where a person experiences uncontrollable, reoccurring thoughts, known as obsessions, and/or the urge to repeat behaviors, known as compulsions. OCD is a chronic condition with an estimated lifetime prevalence of 2.3%, impacting a higher proportion of individuals than schizophrrenia.\textsuperscript{[27]} At least 50 million individuals worldwide suffer from this debilitating disorder.\textsuperscript{[30]} The mean age of onset is 19.5 years, and females have a higher lifetime risk of developing OCD compared to males.\textsuperscript{[8]} Many patients with OCD show comorbidities with anxiety disorders, mood disorders, and substance use disorders.\textsuperscript{[30]}

While the exact cause of OCD is still unknown, it is widely accepted that a complex interplay of neurobiology, genetics, and environmental factors play a role. In terms of pathophysiology, several studies involving positron emission tomography, single-photon emission computed tomography, and functional magnetic resonance imaging have displayed abnormal levels of activity in the orbitofrontal cortex, the anterior cingulate cortex, and the dorsolateral prefrontal cortex in patients diagnosed with OCD.\textsuperscript{[10]} The orbitofrontal cortex is essential to decision-making since it assigns significance to the consequences of a particular action;\textsuperscript{[3]} dysfunction in this region in OCD could contribute to the patient’s perception of grave consequences if they do not repeat and resolve their compulsions. The anterior cingulate cortex is activated in situations, where there are conflicting options and a high likelihood of making a mistake.\textsuperscript{[13]} Essentially, this region of the cortex is hypothesized to detect and perceive mistakes. Hyperactivity in the anterior cingulate cortex seen in OCD patients can contribute to an abnormal perception
of errors or an excessive preoccupation with correcting the perceived error. The dorsolateral prefrontal cortex is involved in executive control and how the brain processes relevant information; the reduced activation of this region seen in OCD patients may be contributing to their inability to control and respond appropriately to intrusive obsessions and compulsions. Furthermore, while these three regions of the brain have their own specific, individualized functions, they also work in concert to create excitatory and inhibitory effects on behavior. The orbitofrontal and dorsolateral prefrontal cortex are a part of the orbito-fronto-thalamic circuit, an excitatory positive feedback loop that is thought to be abnormally excited in OCD patients, leading to obsessions and compulsions. The orbitofrontal cortex is also a part of the cortex- striatum-thalamus-cortex loop (CSTC), which is believed to have an inhibitory effect to counteract the effects of the orbito-fronto-thalamic circuit; an abnormally decreased level of activity in the CSTC leading to decreased inhibition by the CSTC could also lead to OCD symptoms. Finally, the communications between the anterior cingulate gyrus and the limbic system are thought to contribute to affective anxiety symptoms of OCD. While the degree these changes in subcortical regions have in the emergence of OCD is unknown, neurobiological dysfunction is integral to the presentation of the disease.

Risk factors for OCD

Genetics are thought to contribute to the emergence of OCD. It has been reported that the morbid risk of OCD was significantly greater in the first-degree relatives of OCD patients than those of healthy subjects. According to the National Institute of Mental Health, the risk is even higher if first-degree relative's age of onset of the disease was <19. Moreover, several twin studies have shown that the concordance rate for monozygotic twins, who are genetically identical, was much higher compared to that of dizygotic twins, who only share half the same genetic material. Further, research regarding the genetic component of the etiology of OCD can improve understanding and may lead to the development of better treatment options.

Environmental factors, particularly trauma during childhood and adolescence, have also been linked with the development of OCD. One study found that monozygotic twins who scored highly on a questionnaire asking about obsessive-compulsive symptoms reported more experiences of sexual assault than monozygotic twins who scored low on the questionnaire; all victims of sexual assault were women, which could be a possible explanation for the higher incidence rate of OCD in women as compared to men. However, more research is necessary to better understand this relationship between trauma and OCD.

Treatment options for nonrefractory OCD

Current treatment options for OCD attempt to address these complex elements contributing to the disease's etiology and presentation. One of the predominant treatments for OCD is cognitive behavioral therapy (CBT), specifically a form known as exposure and response prevention (ERP) therapy. ERP therapy is based on Mowrer's two-factor theory on fear and avoidance. In OCD, various situations can trigger anxiety-provoking obsessions in affected patients. To resolve the anxiety that they experience due to these intrusive thoughts, patients will perform compulsions or practice avoidance behaviors. These responses work to reinforce the patients' fear as well as further strengthen the obsessions and compulsions. In ERP therapy sessions, patients are presented with stressful, anxiety-provoking stimuli to recreate real-world scenarios and then taught to tolerate the distress without engaging in their compulsions or avoidance behaviors. By doing so, patients learn that there are not any negative consequences to resisting their compulsions, which serves to challenge their usual fear response. Studies have shown that two-thirds of patients who underwent ERP therapy experienced an improvement in their symptoms, while one-third of patients were considered completely recovered. ERP therapy even produced better outcomes than other forms of CBT and is currently one of the first-line treatments.

In addition to behavioral therapy, pharmacotherapy of OCD has also been proven to be effective in controlling the debilitating symptoms of the disease. In the 1960s, drug therapy for the treatment of OCD symptoms began with the efficacious results of clomipramine, a tricyclic antidepressant (TCA) that most specifically inhibits serotonin reuptake. The next development in OCD pharmacotherapy occurred in the 1980s with the initiation of selective serotonin reuptake inhibitors (SSRIs) use. One particular SRI, fluvoxamine, was shown to reduce short-term symptoms in OCD patients and have a more tolerable profile than clomipramine. While clomipramine is still widely used to this day, SSRIs have become first-line treatments over TCAs since TCAs can cause more serious side effects in patients. Finally, the therapeutic effects of pharmacotherapy agents such as SSRIs have been shown to be further enhanced when used in combination with ERP therapy.

Refractory OCD and surgical intervention

While CBT and/or pharmacotherapy significantly improve the quality of life in OCD patients and should be considered first-line treatments, few patients diagnosed with OCD experience complete remission of symptoms. Furthermore, some patients find no significant alleviation of symptoms with these forms of treatment and are considered
to have a form of the disease known as treatment-resistant or refractory OCD. Without the therapeutic effects of ERP therapy and medication, it is believed that up to a fourth of patients with refractory OCD will attempt suicide.\(^{[15]}\) Due to the debilitating nature of severe, untreated OCD, there are neurosurgical interventions currently available as a last resort.

Neurosurgery was used extensively in the 1940s and 1950s for the treatment of psychiatric disorders before being almost completely abandoned due to public criticism, ethical concerns, and the emergence of effective pharmacotherapy in the mid-1950s.\(^{[12]}\) In the 1990s, neurosurgery once again emerged as a treatment method for mental disorders, with capsulotomies and cingulotomies proposed as “last resort” treatments for refractory OCD. In patients with OCD, a capsulotomy involves placing lesions in the anterior limb of the internal capsule. The orbito-fronto-thalamic circuit involves bidirectional, excitatory communication between the orbitofrontal and dorsolateral prefrontal cortex, and the thalamus through the anterior limb of the internal capsule; surgically interrupting the fibers involved in this positive feedback loop may decrease the excessive excitation inducing OCD symptoms. Conversely, a cingulotomy involves placing lesions bilaterally in the anterior cingulate gyri, which as mentioned before, has been shown to be hyperactive in OCD patients, leading them to abnormally perceive errors or have an excessive preoccupation with correcting the perceived error.\(^{[20]}\) The anterior cingulate gyri are also thought to be responsible for the affective anxiety symptoms of OCD. Therefore, a cingulotomy may target the erroneous perception of, and preoccupation with mistakes and decrease the anxiety associated with obsessions in OCD patients.\(^{[31]}\)

While both capsulotomy and cingulotomy procedures have been shown to be effective in decreasing the severity of symptoms in refractory OCD, these procedures are associated with a substantial risk of adverse side effects.\(^{[17,20]}\) In addition, the permanent nature of ablative neurosurgery, and the corresponding irreversibility of potential adverse effects, has served as an impetus to consider DBS as another treatment option for refractory OCD.

**Limitations**

The limitations in this study relate to the inherent limitations of the MAUDE database. Data are reported spontaneously; therefore, no conclusions can be made about incidence or causality since there is no information on the total number of devices or patients. MAUDE data merely reflect reporting frequency which may allow for detection of the possibility of an adverse event occurring, without revealing risk. Per the FDA, MAUDE data are not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices. In addition, there is minimal awareness of the database by health-care providers, leading to likely underreporting of adverse events. Although there are inherent limitations to the MAUDE database, our results highlight some important PR and DR complications that can help optimize patient counseling, management, and drive essential future research.

**CONCLUSION**

Our study of the post market surveillance data of DBS devices for refractory OCD using the MAUDE database aligns with previous findings of adverse events. In our review, the most common category of adverse events reported by patients was psychiatric in nature, with 15% of patients experiencing cognitive changes, 7% experiencing anxiety, and 6% reporting depression and emotional changes. Decreased therapeutic response and infections were also seen in almost 10% of patients. Neurological adverse events, such as electric shock, sleep disturbances, and intracranial hemorrhage, were seen in a small percentage of patients. Uniquely, our study also looked at adverse device reports and found that high impedance was the most common complaint, followed by energy output, and battery problems. This supports that fatal malfunction of these devices are uncommonly reported. The PR and DR adverse events in our study further solidify that DBS for refractory OCD may be a viable option for the right patient population. However, further studies are essential given the limitations of the MAUDE database.

**Declaration of patient consent**

Patients’ consent not required as patients’ identities were not disclosed or compromised.

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**Conflicts of interest**

There are no conflicts of interest.

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